THE 8TH INTERNATIONAL WORKSHOP ON INNOVATIVE SIMULATION FOR HEALTH CARE

SEPTEMBER 18 – 20, 2019
LISBON, PORTUGAL

EDITED BY
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Dear I_WISH attendees,

Over the past decade health sciences have achieved enormous advances in human capabilities, and life span expansion is pushing boundaries beyond the conventional limits. For the first time, gene therapies and technological advances are saving lives and bringing cure for previously untreatable disorders. Overall, there has been remarkable success on several fronts, but many areas of disease burden remain. Life-style related diseases remain high on the list of all causes of death worldwide, such as heart disease, cancer, chronic lower respiratory disease, Alzheimer's disease and diabetes. Chronic health conditions remain the primary health-care related expenditure. Wearable technologies now enable easier monitoring of these conditions, earlier diagnosis and facilitate patient management.
New technologies and simulators have become an integral part of medical education and training. Modeling and simulation of ambulatory and institutional care delivery, planning and execution is essential to overcome limitations, mitigate the errors and deliver high quality care at the lower cost. Utilization of new technologies such as wireless sensor monitoring, artificial intelligence, simulation and modeling approaches will soon enable better designs of care delivery, diagnostic and individualized treatment approaches.
IWISH workshop provides a multidisciplinary platform to explore new ideas and methodologies in many areas of medicine and health care to facilitate individual and institutional care and further improve overall quality of life worldwide.

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The IWISH 2019 International Program Committee (IPC) has selected the papers for the Conference among many submissions; therefore, based on this effort, a very successful event is expected. The IWISH 2019 IPC would like to thank all the authors as well as the reviewers for their invaluable work.
A special thank goes to all the organizations, institutions and societies that have supported and technically sponsored the event.

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CFD ANALYSIS OF PERIPHERAL ECMO CANNULATION

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ABSTRACT

ECMO (Extra Corporeal Membrane Oxygenation) is a technique supporting vital functions through extracorporeal circulation, by raising blood oxygenation, reducing the blood values of carbon dioxide (CO2), increasing cardiac output and acting on body temperature. In conditions of severe respiratory and/or cardiac insufficiency, it allows to rest heart and lungs while performing their ventilation and pump functions.
The most common sites for establishing peripheral ECMO are femoral artery and vein. The main goal of ECMO cannulation is to provide the least traumatic and most durable and simplified method for delivering the blood to and from the circuit.
There are several ways to connect ECMO to the venous/arterial system. The present study's aim is to analyse one connection by anastomoses and another one by cannula through a Computational Fluid Dynamics (CFD) model.

Keywords: Femoral cannulation, CFD, ECMO, hemodynamics

1. INTRODUCTION

Basically, ECMO is made up of a pump, an oxygenator and a blood heater. The extracorporeal tecnique is performed by the cannulation of central (usually internal or femoral jugular) veins and artery. Thus, it is possible to distinguish between two main types of Ecmo, even if others exist:

- VV-ECMO (veno-venous): it supports lung function by ventilation and oxygenation of the blood. It is usually performed through vascular accesses in the internal jugular vein and femoral vein. Moreover, it can be used in conditions of severe respiratory failure only if cardiac function is preserved, not providing any hemodynamic – if not indirect - support.
- VA-ECMO (veno-arterial): it also supports the heart pump function. Through vascular accesses in the femoral artery and vein, it supports circulation as well, having a direct hemodynamic action, acting on cardiac output and, therefore, on blood pressure directly; it is indicated in the management of severe systemic hypoprofusion pictures and in cardiopulmonary resuscitation.

The most frequent complication of the method is arterial hemorrhage in va-Ecmo, followed by hemolysis and thrombocytopenia depending on pump speed with consequent mechanical damage, thrombotic and thromboembolic problems, sepsis and gas embolism; in va-Ecmo the risk of ischemia of the lower limb is very high, due to the large caliber of the cannula positioned in the femoral artery.
The new investigation techniques and the need to organize and interpret an increasing amount of biological information and data represent a remarkable opportunity for the use of computational and statistical methods and models, in biological and biomedical research and in the understanding of medical problems (diagnostics, epidemiology, clinical medicine…)
Analysis and numerical simulation of mathematical models in the more general context of life sciences is slowly emerging as an additional investigative tool to be used alongside other experimental or theoretical methods. Indeed, there are several studies in the fields of biomechanics, hemodynamics, artificial organs and prosthesis design (Pascoletti 2018, Zanetti 2013, Zanetti 2017, Aldieri 2018, Caruso 2015, Ambrogio 2015, Campobasso 2018).
Even if the survival rate is high, cerebrovascular injury and/or lower limb pathologies may be important complications. In fact, the significant changes in circulation that happen during induction of ECMO (compared with the previous state - patient is hypoxemic for hours) are often responsible for irreversible damage (Papademetriou 2011). Although several studies were carried out to investigate the position of the cannulae (Mazzitelli 2016) or to analize the flow through the cannulae (De Bartolo 2011), there are no studies that analize the differences between the insertion of a cannula and the realization of an anastomosis for the use of ECMO.
A computational approach was employed to carry out the investigation on a 3D patient-specific femoral artery model by means of Computational Fluid Dynamics (CFD) simulations. In our model we compared the blood flow distribution of the interposition graft for VA ECMO simulating a connection by means of cannula and an anastomosys.

2. MATERIALS AND METHODS

During VA ECMO assistance, the ECMO system is connected to the patient's vascular system through the femoral artery (Fig.1).

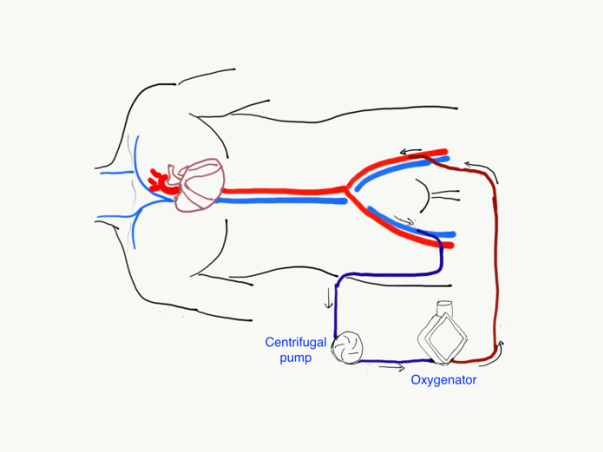
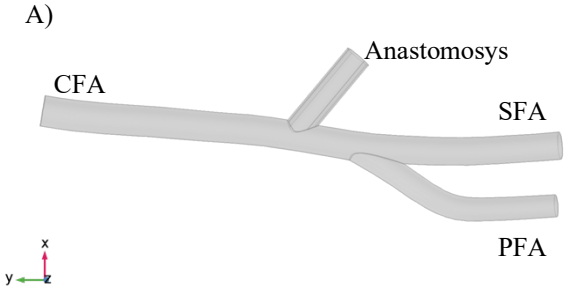


Figure 1: ECMO connection scheme

In the present study finite element models were analyzed to verify haemodynamic behaviour when either a cannula (Case A) or an anastomosis (Case B) is used to connect the femoral artery.

2.1. Geometrical Model

The geometrical model was realized by means of commercial CAD Software starting from anatomical data (vessel caliber and lenght) (Czyżewska 2012). The cannula was created using reverse engineering techniques, whereas the arteries were reconstructed starting from DICOM images. The model reproduced Common Femoral Artery (CFA), Superficial Femoral Artery (SFA), and Profound Femoral Artery (PFA) as showed in Figure 1. The diameter of the anastomosis is 8 mm, whereas the cannula has a diameter of 16 Fr and ends with a curved tip. The results may be influenced also by other factors, such as the angle and position of the cannula and anastomosis. In this work the same angle and position values were used for both the cannula and the anastomosis, so as to evaluate only the difference between the two solutions.



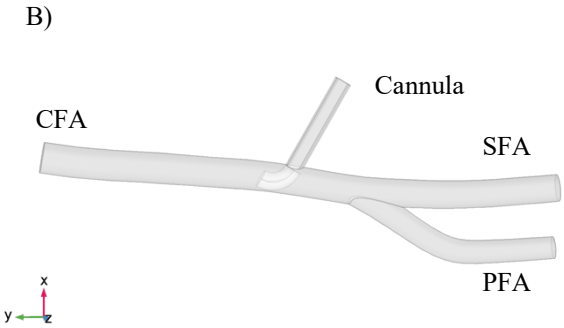


Figure 2: a) Geometrical model for a) anastomosis and b) cannula connection.

2.2. Mesh

The domain was discretized with tetrahedral, pyramidal, triangular and prismatic element (table1), with an amount of ~ 2,000,000 elements for each model, as shown in Figure 2. Boundary layer mesh elements have been used along the no-slip boundary.

Table 1: Mesh statistics

	Case A	**Case B**
Minimum element quality	0.001823	0,001704
Average element quality	0.5191	0.5197
Tetrahedral elements	284835	331160
Pyramid elements	1454	3298
Prism elements	1433306	1660420
Triangular elements	25456	30254
Quadrilateral elements	732	648
Edge elements	947	1201
Vertex elements	20	32

The number and distribution of the mesh elements was optimized to give a 10^{-5} error under any investigated condition, generally obtained with a number of elements in excess of $2.5 \cdot 10^{6}$. The mesh was optimized by analyzing the error trend as a function of calculation time.

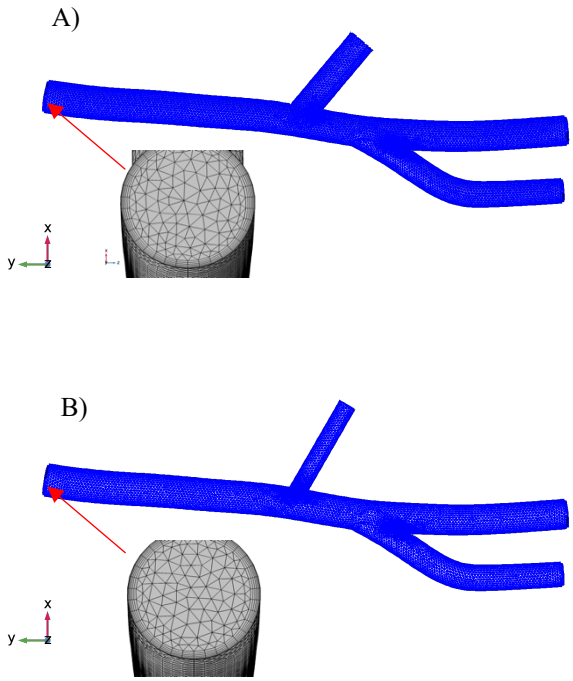


Figure 3: Model mesh for a) Case A and b) Case B

2.3. Boundary conditions

As boundary condition, the same mean inlet flow of about 2.5 L/min was applied in the two cases, whereas zero-pressure conditions were set as outlets in all vessels, as in similar comparative studies (Caruso et al. 2017, Karmonik et al. 2012, Lawford 2008).

2.4. Simulations details

Numerical computations were performed using the steady three-dimensional Reynolds-averaged Navier-Stokes (RANS) equations and the low-Reynolds k-ω turbulence model. Turbulence effects are modeled using the Wilcox revised two-equation *k*-ω model with realizability constraints (Wilcox 2002). That model solves for the turbulent kinetic energy, k, and ω is the dissipation per unit turbulent kinetic energy:

$$\rho\frac{\partial k}{\partial t}+\rho\mathbf{u}\cdot\nabla k = P_k-\rho\beta_0^{*}k\omega+\nabla.\left(\left(\mu+\sigma_k^{*}\mu_T\right)\nabla k\right),$$

$$\rho\frac{\partial \omega}{\partial t}+\rho\mathbf{u}\cdot\nabla \omega = \alpha\frac{\omega}{k}P_k-\beta_0\rho\omega^2+\nabla.\left(\left(\mu+\sigma_\omega\mu_T\right)\nabla \omega\right).$$

where u is the velocity field, p the pressure, k Turbulent kinetic energy and ω is the specific dissipation rate. α, σ_ω, σ_κ^{*}, β_0, β_0^{*} are the auxiliary parameters for Wilkox revised k-w. The turbulent viscosity is defined as:

$$\mu_T = \rho\frac{k}{\omega}$$

Blood can be approximated with a Newtonian and incompressible fluid (Caruso 2017, Condemi 2016, Gaudio 2017).

COMSOL 5.4 (COMSOL Inc, Stockholm, Sweden), a commercial software package based on finite elements method, was used to carry out the computational studies, for the postprocess and to visualize the results.

Because simulations were performed on a Workstation equipped with a 64 GB RAM and two Intel Xeon E5-2630 v3 2.40 GHz processors, the computational time for each CFD analysis was approximately 3 hours.

3. RESULTS

Streamlines of the flow distribution with velocity magnitude on the CFA, SFA and PFA are illustrated in Figures 4 and 5.

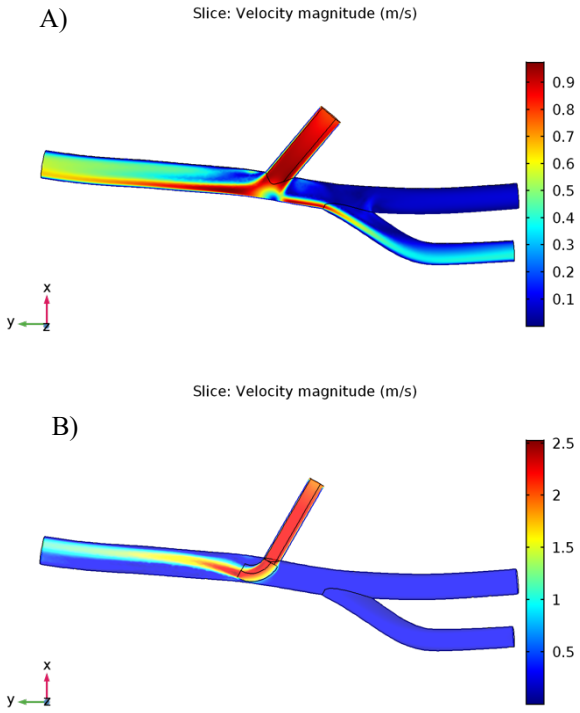


Figure 4: Velocity Magnitude a) Case A b) Case B.

Both in Case A and in Case B, blood flow from the ECMO system is mainly oriented towards the upper part of the body, even if in Case B a small direct flow towards the lower limbs, and particularly in the Profound Femoral Artery, can be noticed.

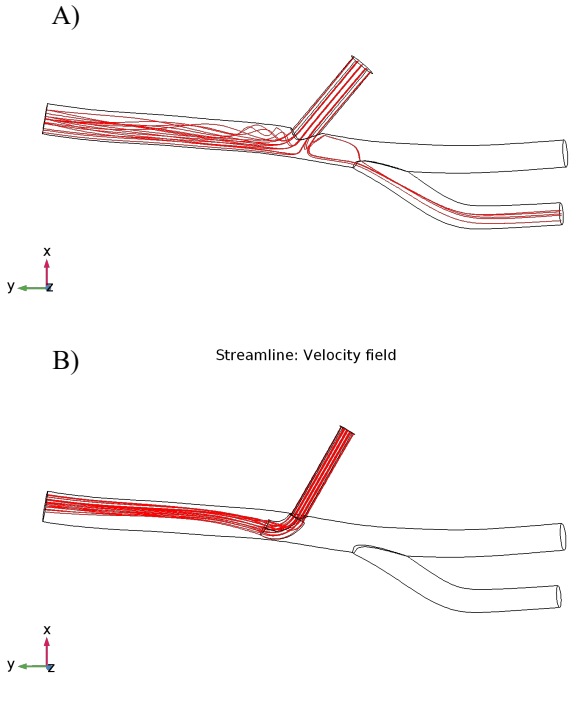


Figure 5: Streamlines a) Case A b) Case B.

Table 2 shows the percentage distribution of the flows in the arteries considered in the model. Also this table highlights quantitatively how the flow from the pump is mainly directed towards the upper part of the body.

Table 2: Comparison between Case A and Case B in terms of flow rates.

	Case A	**Case B**
Common Femoral Artery	74,0%	99,7%
Superficial Femoral Artery	6,0%	0,2%
Profound Femoral Artery	20.2%	0,1%

Moreover, to better understand the influence of ECMO on femoral artery hemodynamics, the wall shear stress (WSS), which is the friction force created by blood motion on vessel walls, was evaluated according to equation reported in Caruso et al. (2015).

The physiological level of WSS is about 1.5-2.0 Pa, (Malek et al. 1999), whereas values less than 0.481 Pa are considered as low and correlated to atherosclerotic place formation (Lee et al. 2008).

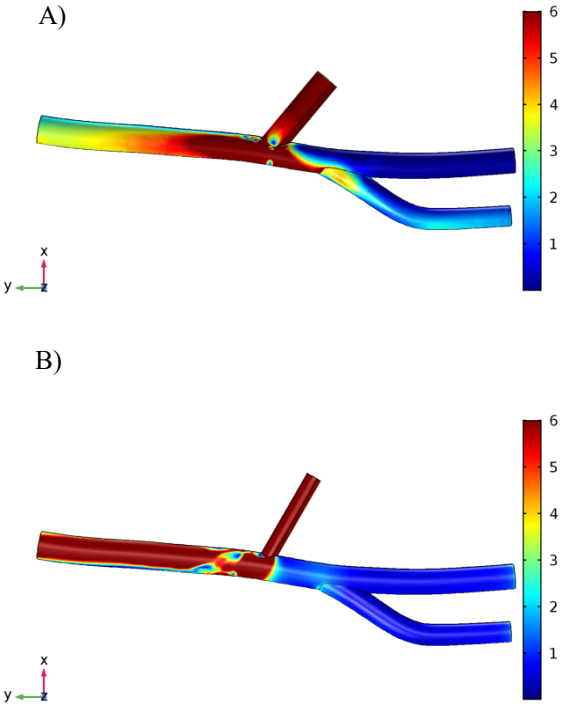


Figure 6: Viscous stress (Pa) a) Case A b) Case B.

4. DISCUSSIONS

During peripheral VA ECMO, one of the complications of retrograde flow into femoral artery is lower limb ischemia. The results show that when using anastomoses (Case A) the flow can be distributed both towards the upper part of the body and towards lower limbs (Figures 4a and 5a), whereas when using a cannula the flow is almost completely directed towards the upper part (Figures 4b and 5b).

Particularly, if the connection is made by anastomoses, 74% of the flow from ECMO flows towards the upper part of the body, whereas 26% is directed towards the lower limbs (20% through SFA and 6% through PFA). In the case of anastomoses (Case A), it is possible to vary the angle between the duct coming from the pump and the femoral artery so as to vary the flows towards the lower part of the body (in the case in question we considered a 60° angle). When a cannula was used (Case B) for connection to the pump the flow was almost completely oriented towards the upper part of the body (more than 99%), whereas from SFA and from PFA the flow was almost zero. In this configuration, even varying the inclination of the cannula with respect to the axis of the femoral artery, no significant variations of flow rates would be obtained. In fact, most of the flow would be oriented towards the upper part of the body anyway, which might cause some problems both in the lower limbs (hypoperfusion) and in the brain (hyperperfusion).

The femoral artery surface in both Case A and Case B had a similar WSS distribution. In detail, the CFA

vessel is subjected to high WSS (>5 Pa), whereas the surfaces around SFA and PFA presented a very low value (≈ 0 Pa).

Starting from these results it can be seen how using an anastomosis it is possible to better modulate the fluid by seeking an optimal distribution of the flow between the upper and lower parts of the body. Furthermore, it is possible to make the correct flow flow exactly in the various districts by creating artificial occlusions to the SFA and PFA (i.e. by means of clamps).

5. CONCLUSION

The use of interposition graft allows limb perfusion but with significant blood loss central perfusion. A better central blood flow support can be achieved by varying the anastomosis insertion angle so as to correctly distribute the flow towards the lower limbs in oder to avoid unwanted effects.

From the analyzed results it can also be deducted that if an accidentally erroneous tilt angle of anastomosis is used cerebral blood flow or lower limb perfusion will decrease, thus creating potential problems for the patient. Therefore, since many patients suffer from impaired autoregulation, this study can support diagnostic tools (Lu 2014, Caruso 2015), helping to optimize support conditions based on patient-specific assessment and thereby improving the patient's outcome. Future developments might also include analyzing the influence of cannula and anastomosis positions and the validation of the model with clinical data.

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EVALUATING KINECT V1 AND V2 FOR CHEST WALL SURFACE SCANNING AND ASSESSMENT

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ABSTRACT
Optical scanning has proven to be advantageous to objectively assess the severity of chest wall deformities and the effectiveness of its treatment. By potentially eliminating the need for computed tomography (CT) scanning and superseding manual measurements that are subject to errors, a system that utilizes optical scanning presents great value to patients and practitioners. This work aims to investigate and evaluate the performance of two off-the-shelf optical scanning sensors in the context of their utility and accuracy to measure the severity of chest wall deformities. An in-vitro experiment and a human study are conducted utilizing both sensors to collect data and report the findings.

Keywords: Chest deformities, surface scanning, Kinect sensor

1. INTRODUCTION

Pectus Excavatum (PE) is a chest wall deformity characterized by a depression of the sternum and accounts for nearly 90% of all congenital chest malformations (Williams & Crabbe, 2003). Commonly diagnosed in early adolescence, the severity of the deformation determines a patient's candidacy for surgical (e.g., Nuss procedure (Nuss, Robert E. Kelly, Croitoru, & Katz, 1998)) or conservative nonsurgical treatment (e.g., Vacuum Bell (Haecker, 2011)).

Severity, as well as treatment progress, is commonly determined by rudimentary techniques such as simple linear measurements using dowel-shaped rulers (Brigato, Campos, Jatene, Moreira, & Rebeis, 2008) or through expert evaluation of indices (Haller Index (Haller, Kramer, & Lietman, 1987) or Correction Index (Peter et al., 2011)) calculated from the patient's computerized tomography (CT) image. However, CT is expensive and results in extensive exposure to harmful ionizing radiation, while manual techniques can be inaccurate and inherently subjective.

Recent hardware and software advancements in 3D imaging have led to the rise of low-cost, portable, and mass-market 3-dimensional scanning devices. These tools capture the surface geometry of objects and have shown great potential in recording, quantifying, and tracking chest wall deformity (Glinkowski et al., 2009; Poncet et al., 2007).

To mitigate misdiagnoses and monitor PE treatment, we developed an imaging system that uses Microsoft Kinect Version 1 (Figure 1-a) to obtain surface scans of the pectus deformity and provide informative metrics of the target area (Kelly et al., 2018). Our technique was verified to measure distances from the probe accurately and was found to be sufficient for the application (Obeid, Kidane, et al., 2016; Obeid, Obermeyer, Kidane, Kelly, & McKenzie, 2016; Zeng et al., 2016). Nonetheless, scanning technology is evolving rapidly, raising the challenge of selecting a suitable scanning device that can further enhance the usability of our systems.

This paper aims to compare two versions of Microsoft Kinect (V1 and V2), in the application of evaluating the severity and treatment of chest wall deformity. A three-fold experiment was conducted involving four different types of targets to be scanned: (1) a flat white surface, (2) male and female mannequin torsos, (3) a 3D-printed pectus phantom, (4) and nineteen healthy individuals. The results are validated against the ground truth (GT) of anatomical landmark distances recorded with Vernier caliper and a tape measure, as well as, in the flat test object case, mathematical plane surface. Other comparative studies (F. Redaelli, Gonizzi Barsanti, Fraschini, Biffi, & Colombo, 2018; Pöhlmann, Harkness, Taylor, & Astley, 2016; Sarbolandi, Lefloch, & Kolb, 2015) have explored the characteristics and differences between these devices for computer vision and healthcare applications (e.g., Orthopedic (Pöhlmann et al., 2016)), but to the best of our knowledge, no study has been conducted assessing the accuracy and application of these two sensors for pediatric chest wall deformity.

This paper is organized as follows: Section II will summarize background information on the sensors, while Section III will present the methods for comparison and data collection. Section IV will highlight experimental results and subsequent sensor selection for the relevant work. Finally, Section V will discuss conclusory remarks and propose potential future work.

2. BACKGROUND

The first-generation Kinect (V1) has two cameras colored RGB (Red, Green, Blue) and a monochrome NIR Near-infrared camera, as well as a NIR projector with a laser diode of 850 wavelengths (F. Redaelli et al., 2018). Depth determination is conducted based on structured light. The device starts by releasing infrared light onto an object which is then broken into a pattern by a diffraction grating. Patterns are sectionalized into neighborhoods and analyzed. Depending on the object's distance from the sensor, the light becomes distorted, and a 3D triangulation technique is used to compute the depth of the object (Pöhlmann et al., 2016). However, the device may produce inaccurate data in the event an object with challenging geometry is scanned, due to the disruption inflicted upon the neighborhood, making it difficult to determine between distorted and undistorted patterns.

The second generation of Kinect (V2) is composed of a 512 x 414 depth image sensor, where each 10 µm x 10 µm pixel incorporates a Time-Of-Flight (TOF) detector that operates using the Quantum Efficiency Modulation (F. Redaelli et al., 2018; Wasenmüller & Stricker, 2017). Depth evaluation of a Kinect V2 is determined through a TOF technology. The device measures the total time it takes for infrared light to make a round trip journey from the device to the object and back. The phase shift is analyzed by comparing the incoming signal to four phase-shifted control signals (Pöhlmann et al., 2016). An object's reflectiveness may skew data showing higher depth values due to the noise presented into the depth measurement.

(a) (b)

Figure 1: Microsoft Kinect (a) V1 and (b) V2.

Table 1: Comparison of Kinect sensors for surface scanning.

	Kinect V1	**Kinect V2**
Release	2010	2013
Technology	Struct. light	Time-of-flight
Depth image (pxls)	320 x 240	512 x 424
FOV (degrees)	54 x 43	70 x 60
Range (m)	Up to 6	Up to 4.5

3. METHODOLOGY

3.1. Experiments

Experiment A: The purpose of this experiment is to determine the spatial uncertainty for different operating distances. Each depth sample collected by the sensor is comprised of (1) actual measured values, (2) unavoidable random error due to environmental conditions such as thermal or electronic noise, and (3) a systematic error due to device miscalibration or incorrect use (Guidi, Gonizzi Barsanti, & Micoli, 2016). The precision of the sensor is limited by the random error, which can only be statistically modeled and noted as the device's intrinsic limitation. The accuracy, on the other hand, is influenced by the systematic error, which is difficult to detect but can be minimized with proper calibration. The combinations of these two errors represent global spatial uncertainty.

Following a similar approach used by (F. Redaelli et al., 2018; Guidi et al., 2016), global spatial uncertainty for the two sensors in this study was evaluated by scanning a flat test object (Figure 2-a) and measuring the deviation of the scanned reference surface from an ideal plane. For each flat surface scan, acquired at four different operating distances, we estimated the deviation of the observed 3D surface against a best-fitting mathematical plane model. Additionally, a low-pass filter was used to remove the high-frequency random error component and highlight systematic distortion.

Experiment B: In this experiment, we evaluated the dimensional accuracy of the sensors by comparing known landmark distances of selected rigid physical objects against their virtual counterparts (3D models collected by scanning the objects with the two sensors). For this purpose, we used plastic mannequins and a 3D printed PE replica with fiducial markups (Figure 2b-d). The geometric details on the mannequins mimic the human body, albeit in a rigid way; whereas the 3D-printed PE replicated the anticipated patient morphology. Fiducial markers were placed on the belly button/navel (N), sternal notch (S), nipples (Rp & Lp), center chest line, and upper chest area. However, for ground truth, only the "sternal notch to navel" (S-N) and "right nipple to left nipple" (Rp-Lp) linear (Euclidean) distance were recorded using a Vernier caliper. The same distances were digitally measured on the acquired 3D surface using a virtual ruler (Figure 6).

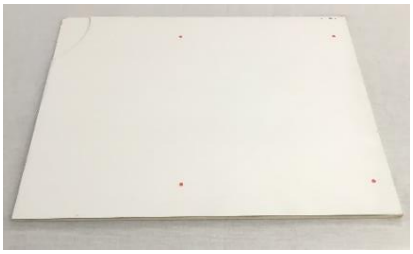
Experiment C: The final experiment investigated the accuracy of the two sensors to capture dimensions on human subjects. In a clinical setting, landmarks show relative displacements due to the patient's change in posture and skin or soft tissue movement due to breathing. In a fashion similar to the test conducted in experiment B, a trained nurse placed fiducial markers on the navel, sternal notch, and nipples. For ground truth, "sternal notch to navel" (S-N) and nipple (Rp-Lp) distances were measured manually on the subjects. However, in this case, surface distance instead of linear

distance was recorded using a flexible tape measure. The mean deviation between the digital (Figure 8) and hand-measured values of the distances quantifies the dimensional accuracy used to compare the two sensors.

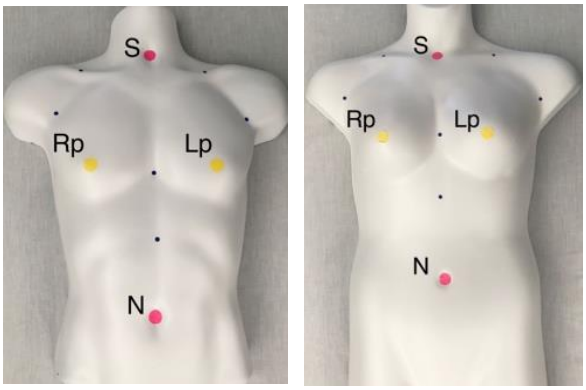
3.2. Test Objects

The study involved four different test objects. Similar to (F. Redaelli et al., 2018; Guidi et al., 2016), a float glass was selected as a flat reference surface due to the smooth and close approximation of a theoretical plane. The glass (Figure 2-a) had a dimension of 58 cm x 48 cm and a thickness of 0.05 cm. It was painted matte white to be sensed by the devices, and four markers were placed to create a region of interest.

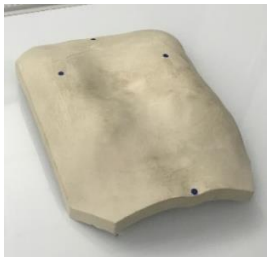
In addition to the object described above, three other objects emulating human chest profile were used to evaluate dimensional accuracy. The first two consisted of male and female plastic mannequins with fiducial markups (Figures 2-b and 2-c). The third object was a physical replica of real PE patient obtained by scanning a patient before undergoing the Nuss procedure surgery and 3D-printing the model (Figure 2-d). The PE phantom had dimensions of 27 x 21 cm with the deepest point of deformity at 25 mm.



(a)



(b) (c)



(d)

Figure 2: Objects used for experiment: (a) glass, (b) male mannequin, and (c) female mannequin, and (d) 3D-printed pectus chest.

3.3. Subjects

Nineteen healthy individuals (all males, age: 11 ± 2 years, height: 155. ± 14.7 in.) with no chest deformity participated in this study. The Eastern Virginia Medical School ethics committee approved the study (EVMS IRB# 14-10-EX-0214), and all subjects signed consent forms before data collection (Figure 3-b).

3.4. Data Acquisition

3D surfaces were acquired using ReconstructMe (Heindl & Kopf., 2012) for Kinect V1, and Microsoft Kinect Fusion SDK (Microsoft, 2014) for Kinect V2. For ReconstructMe, the volume bounding box was fixed to 1 x 1 x 1 m at an offset of 0.1 m – 0.50 m from the camera. Similarly, for Fusion SDK, volume voxels per meter were set to 768 with the voxel resolution of 512 x 512 x 512. The depth threshold was fixed at 0.5 m in front of the camera with a bounding box size varying from 1.00 m ~ 2.0 m in order to fully capture the torso.

Scans were collected utilizing a supine test subject/object position/posture. The sensors were fixed on a curved platform which was mounted on a movable overhead frame, as shown in Figure 3, allowing for stable arc motion.

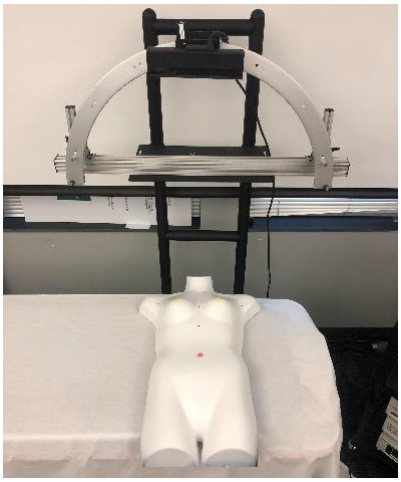
The test objects were scanned at four different distances from the sensors: 0.7 m, 0.8 m, 0.9 m, and 1.0 m. It is important to note that the objects were placed on the table with the sensor height adjustment occurring by sliding the overhead platform with increments of 0.1 m (Figure 3-a). All four items were scanned using the two sensors individually before moving to scan at the next height. Both snapshot (sensor is stationary) and continuous (moving the sensor on the curved frame) scanning approaches were used to capture full sides of the figure. The data acquisition was stopped after 5 seconds for snapshot and 30 seconds for continuous scanning.

Unlike the test objects, the human subjects were scanned with the sensor mounted at a distance of 0.9 m from the subject. The camera was rotating 130° around the subject to capture the front and sides of the torso. Both Kinect V1 and V2 were running simultaneously for comparison (Figure 3-b).

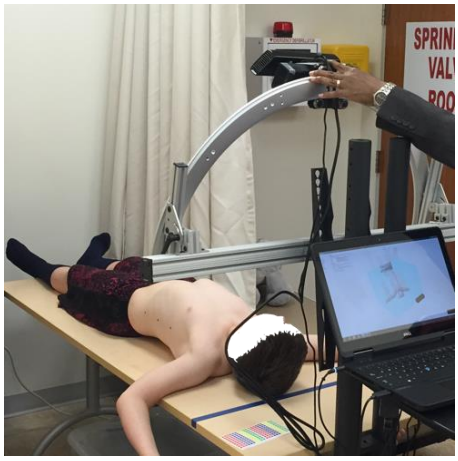
3.5. Data Processing

After the scanning procedure, raw 3D data was saved as a colored polygon (.ply format) mesh file. All further processing steps are done on the opensource MeshLab (Cignoni et al., 2008), and GOM inspect (GOM, 2013) software applications. The mesh data is used as provided by the sensors with minor pre-processing such as removal of artifact points or undesired background objects. For Kinect V2, the 3D model was scaled by a factor 1000 to convert to millimeter units.

The flat glass surface was cropped into 20 x 20 cm area, and the Taubin filter (λ = 0.95, μ = -0.98 with 50 iterations) was also utilized in MeshLab to remove high-frequency components from the global error and highlight systematic error (Taubin, 1995).



(a)



(b)

Figure 3: the scanning procedure: (a) scanning a mannequin and (b) scanning a healthy subject.

4. RESULTS AND DISCUSSION

4.1. Experiment A

Spatial uncertainty is reported as the standard deviation (SD) of the 3D surface from the fitted mathematical plane model. Table 2 and Figure 4 illustrate the global uncertainty/error (σ_u) for both sensors. Similar to (F. Redaelli et al., 2018; Guidi et al., 2016) systematic error (σ_s) is deduced by applying Taubin filter. Lower values indicate better device performance. The first-generation Kinect (V1) had a higher global error (SD ≤ 1.5 mm) for the tested sensor range. The error did not exceed 0.5 mm for Kinect V2, and it remained stable over the operating distances. Trends were within the expected interval and consistent with other comparative studies (F. Redaelli et al., 2018; Guidi et al., 2016; Pöhlmann et al., 2016).

Table 2: SD of the point-to-plane distance for the float glass test object at different sensor distance

	Global (σ_u) and Systematic (σ_s) Errors [mm]							
	0.7 m		0.8 m		0.9 m		1.0 m	
Device	σ_u	σ_s	σ_u	σ_s	σ_u	σ_s	σ_u	σ_s
V1	1.10	1.07	1.25	1.21	1.45	1.39	1.48	1.44
V2	0.41	0.41	0.44	0.39	0.39	0.34	0.34	0.31

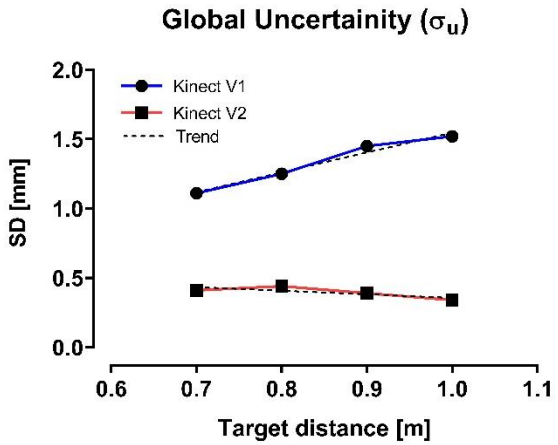
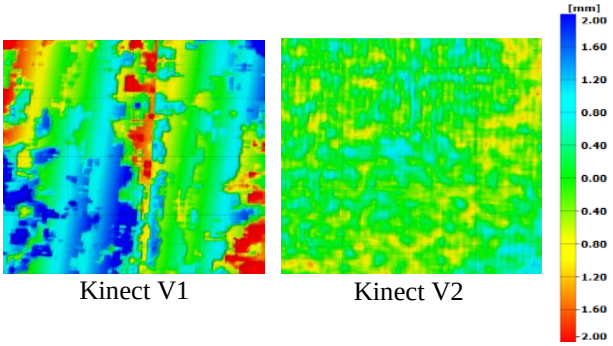


Figure 4: Standard deviation of measurement error to fitted plane at different sensor distances.

Compared to Redaelli et.al (F. Redaelli et al., 2018), we observe lower error values for both sensors, which may be explained by the different methods used to fit the ideal plane; we used a best-fit method while they used Iterative Closest Point (ICP). Figure 5 shows the point to plane deviation at sensor distance 0.8 m. For Kinect V1, approximately 45% of the observed deviation was below 1.0 mm, and 0.82% were within 2 mm. For Kinect V2, 80% of observed deviation was below 0.5 mm and 97% was under 1.0 mm. This result is similar to one reported by (Pöhlmann et al., 2016).



Kinect V1 Kinect V2

Figure 5: Color-mapped point-to-plane deviation of the 3D cloud from the fitted ideal plane for data collected with both sensors at 0.8 m operating distance.

4.2. Experiment B

As previously mentioned, the ground truth is the caliper/tape manual measurement. Therefore, a deviation from that measurement was computed for all scanned objects. Figure 6 shows an example of a virtual measurement obtained for the male mannequin object. Figure 7 shows the dimensional accuracy plot for all 3 objects, for both S-N and Rp-Lp distances, and for both sensors; it presents the millimeter difference box plot.
Kinect V2 showed better results for both Rp-Lp (right nipple to left nipple) and S-N (sternal notch to navel) distances than V1. A one-sample t-test was conducted to determine whether the virtual measurements were different from the ground truth, comparing the mean error score to zero. All virtual measurements passed

Shapiro-Wilk's normality test ($p > 0.05$). The S-N distance deviation of the female mannequin (1.5, 95% CI, -3.19 to 6.18) and PE phantom (-1.38, 95% CI, -3.6 to 0.89) was not significantly different from zero. The Rp-Lp distance deviation for the male mannequin (0.75, 95% CI, -.049 to 1.98) and PE phantom (-0.87, 95% CI, -2.19 to 0.35) was also found to be not statistically significant. However, on Kinect V1, only mean deviation from the female mannequin was found to be not significant (S-N = 1.5, 95% CI, -3.19 to 6.18 and Rp-Lp = -1.38, 95% CI, -3.6 to 0.89); whereas all other measured values were found to be significantly larger or smaller ($p < 0.05$) than measured ground truth.

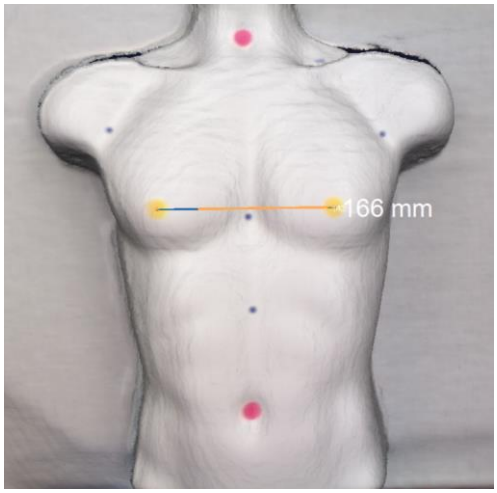


Figure 6: Illustration of obtaining virtual measurements (in this case for object: male mannequin).

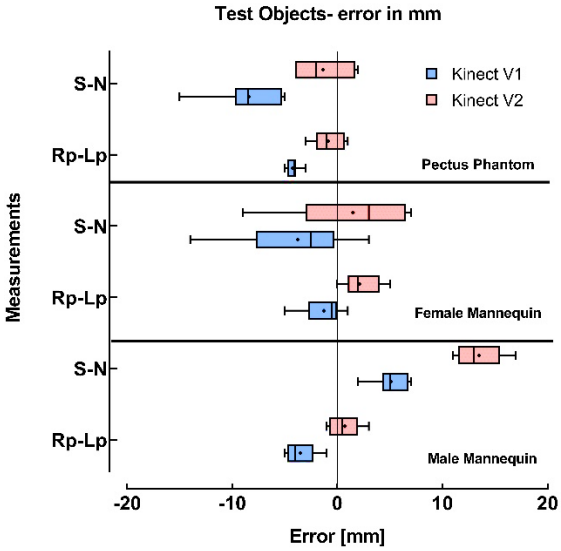


Figure 7: Test object millimeter difference error box plot.

4.3. Experiment C

The purpose of the final experiment was to validate the sensors in a clinical setting. We evaluate the hypothesis that distances measured from Kinect V1 and Kinect V2 data are equivalent to the real measurements obtained from a human participant's chest surface using a tape measure. Figure 8 shows an example of a virtual measurement for one of the participants.

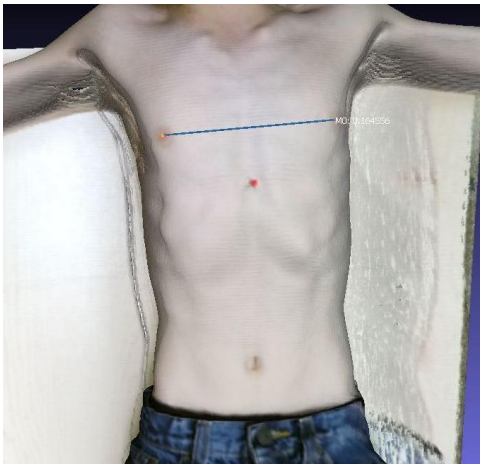


Figure 8: Illustration of obtaining virtual measurements for a real healthy subject.

The equivalency analysis assesses whether mean variations are small enough to be deemed acceptable. The discrepancy (Δ) values for Rp-Lp and S-N were selected to be 1.4 cm and 4.5 cm, respectively. We derive these values from the average anthropometric diameter of the nipple and navel (Kawale et al., 2013; Tanini & Lo Russo, 2018).

The nipple diameter (areola) for males ranges from 0.5 - 1.0 cm, with a mean value of 0.7 cm (Tanini & Lo Russo, 2018). Therefore, $\Delta = 1.4$ is acceptable as it is equivalent to 2x an average nipple diameter, representing negligible variation when using different measurement techniques (e.g., inside or outside the nipple-nipple distance).

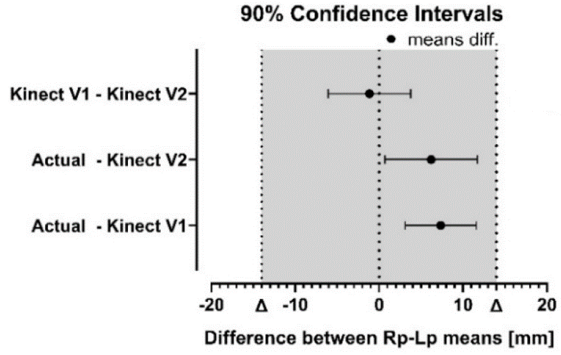
Similarly, the average navel diameter varies from 1.5 to 2.5 cm, the average sternal notch width is 5 cm, and the average sternal notch to navel distance is 40-45 cm (Kawale et al., 2013). Therefore, we choose Δ to be 4.5 cm, which is 10% S-N distance. Figure 9 shows the 90% confidence interval and the zone of indifference.

Digitally measured Rp-Lp distances showed acceptable agreement with the manual measurements. Both sensors were found to be equivalent, with the 90% CI falling inside the indifference zone. It should be noted that for a two-sided t-test, only actual-vs.-Kinect V2 outcome (6.21, 95% CI, -0.02 to 12.61) was not statistically different from zero ($p = 0.58$). However, for S-N measurement, all actual-vs.-Kinect groups were statistically different from zero and not equivalent.

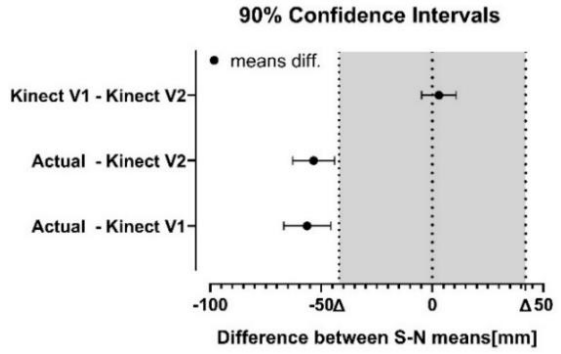
4.4. Discussion

Spatial uncertainty was evaluated by scanning a flat test object at a range of 0.7 m - 1.0 m and measuring deviation to a fitted mathematical plane model. This range is suitable for clinical PE chest scanning application. Our results showed lower global uncertainty for Kinect V2 with 97% of deviation below 1 mm; the error remained stable for the operating distances. The device performance obtained from the simple flat surface is only a preliminary indication of the sensor's performance and may vary in a real clinical setting.

When evaluating linear dimensional accuracy using rigid objects, Kinect V2 outperformed V1, but both devices exhibited errors for the larger linear distance (S-N).
Dimensional accuracy was also assessed in a clinical setting. Although both sensors showed acceptable agreement with manual measurements for the Rp-Lp distance, Kinect V2, in particular, showed an error not statistically different from zero ($p = 0.058$). However, all digital measurements performed worse for S-N distance in human subjects. A plausible explanation for the relatively large error maybe the size of the anatomical landmarks. Higher variability is expected when manually annotating large anatomical landmarks such as the sternal notch as it allows more room for inconsistency and human error. Furthermore, the digitally defined surface path between the two points may be different from the manual measurement.



(a)



(b)

Figure 9: 90% confidence interval and zone of indifference for (a) Rp-Lp means and (b) S-N means.

5. CONCLUSION

Recent advancements in imaging have led to the rise of low-cost 3-dimensional scanning devices. While the technology is evolving rapidly, a challenge of selecting a suitable device for medical applications rises.
This paper compares two generations of Microsoft Kinect (V1 &V2) scanning sensors that use two different technologies (structure light and time-of-flight) in the context of assessing chest wall deformities. This was done by conducting a 3-fold experiment to investigate the spatial uncertainty as well as the linear dimensional accuracy of the two devices. Kinect V2 showed a level of accuracy that exceeded that of V1 and allows the capturing of small anatomical features in a clinical setting. For assessing chest wall deformities such as pectus excavatum, this study shows that V2 can provide a more reliable evaluation of the condition (than V1) and can better inform on treatment progress.

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TOWARDS AN ADAPTIVE DECISION-SUPPORT SYSTEM FOR TYPE I DIABETES TREATMENT BASED ON SIMULATION AND MACHINE LEARNING

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ABSTRACT
Diabetes is one of the most prevalent chronic diseases in the world, especially in middle- and low-income countries. Inter- and intra-patient variability greatly hinders the establishment of effective treatments by clinicians, even among those most experienced. This variability also prevents health administrations to establish adequate controls that guarantee the application of the most cost-effective interventions. In this work, we propose a decision support system that uses simulation and machine learning as tools to provide the clinician with information adapted to the patient on the best intervention for a patient in terms of effectiveness and cost-effectiveness.

Keywords: clinical decision-support system, cost-effectiveness, diabetes, machine learning, simulation

1. INTRODUCTION

Diabetes mellitus is a chronic disease that can be caused by a malfunction of the pancreas, which does not produce enough insulin (the hormone that regulates blood glucose), or the body, which is not able to use the insulin produced. In the long term, hyperglycemia affects the organs of the body, which leads to develop all kinds of chronic complications (cardiovascular and eye diseases, nephropathy, neuropathy...) with extremely negative effects on the patient's health and with an enormous economic impact in health systems.

Approximately 425 million adults have diabetes worldwide, and this figure is expected to increase to 629 million by 2045, with a special incidence in low- and middle-income countries (International Diabetes Federation, 2017). The precise diagnosis of diabetes is quite complex, although three main types are currently accepted: type 1 (T1DM), type 2 (T2DM) and gestational.

More specifically, T1DM is an autoimmune disease, which results in the body producing little or no insulin. Although its cause is not fully understood, it is known to be associated with genetic factors and certain environmental triggers. Typically, T1DM develops in childhood or adolescence. In high-income countries, T1DM is estimated to be between 7% and 12% of all cases of diabetes.

The adequate management of the disease relies on a constant and frequent monitoring of the blood glucose level, as well as other risk factors; accompanied by a treatment with adequate doses of insulin, and diet and healthy habits. In this way, it is possible to delay or avoid most of the worst consequences of the T1DM.

Despite the existence of clinical practice guidelines and the increasing training of health professionals, great uncertainty surrounds the potential effectiveness of a treatment in a particular patient. Hence, it is still necessary to have systems that improve the decision making of the clinicians. Furthermore, in this decision-making process, not only the effectiveness of the interventions should prevail. In the current context in which we live, the sustainability of public health systems is in question, so the cost of interventions should also be considered when recommending a treatment. Cost-effectiveness analysis is a type of economic evaluation that allows assessing both the cost and the effectiveness of a new health intervention. This type of evaluations is increasingly used in contexts where the availability of resources is limited, and respond to the need to have tools that objectively value the benefits for the population of a health technology against its cost (Briggs, Claxton, and Sculpher 2006). Specifically, in Spain, Royal Decree-law 16/2012, of 20 April, determines that the economic evaluation of health interventions is a necessary instrument to decide whether the National Health System should finance a new drug, therapy or health technology.

The rest of this paper is organized as follows. Section 2 presents a review of the state-of-the-art in terms of decision support systems for the treatment of diabetes. Section 3 highlight the main modelling frameworks

available for the economic assessment of new interventions for diabetes. Section 4 proposes a new approach that intends to incorporate economic factors into decision-making, and advance in the adaptation to the patient of the simulations by means of machine learning techniques. Within this section, special emphasis is made on the simulation model. Finally, Section 5 draws some conclusions and further research.

2. CLINICAL DECISION SUPPORT SYSTEMS FOR DIABETES TREATMENT

The creation of computerized clinical decision support systems (CDSS) in diabetes is not recent. Salzsieder et al. (1988) proposed a CDSS to predict the effect of different treatment regimens in patients with T1DM. The system was based on a simulation model that predicted the patient's metabolic evolution based on the glucose-insulin ratio.

In the 90s, a number of CDSSs based on rule-driven expert knowledge systems appeared. For example, DIABETEX was a CDSS for patients with T1DM focused on helping non-expert clinicians. The system was manually fed with follow-up data from patients. With this information, DIABETEX calculated the best insulin dose for the patient (Zahlmann et al. 1990). Carson et al. (1990) and Deutsch et al. (1990) present similar proposals.

Much more recently, Salzsieder et al. (2011) developed KADIS, a patient-centered and model-based CDSS to provide clinicians with evidence-based recommendations. KADIS uses a model of the physiological system of glucoregulation, which can be adapted to individualized patient profiles. This model provides a reference to analyze the impact of different therapies on the individual and recommends insulin guidelines. Currently, KADIS is part of an European project, called Power2DM.

METABO is another project that monitors the pharmacological and lifestyle factors that may affect the blood glucose levels of a patient. This monitoring leads to structured information that helps patients and caregivers to make decisions. The core of METABO is a compartmental model that provides immediate information to patients about how their lifestyle or treatment affects their glucose level. Clinicians benefit from the information gathered by METABO thanks to 1) the identification of rules that relate lifestyles, treatments and metabolic data; 2) the creation of groups ("clustering") of patients based on criteria hidden in the data, using machine learning tools; and 3) the classification of new patients in the identified groups based on their characteristics (Fico et al. 2015).

METABO is a clear example of the current trend, where the use of machine learning techniques stands out among other strategies. Contreras and Vehi (2018) and Kavakiotis et al. (2017) present revisions on these last approaches, of which we highlight some in the following paragraphs.

OntoDiabetic is a CDSS based on a series of ontologies, extended by rules to model clinical practice guidelines. These ontologies allow evaluating the patient's risk factors and providing treatment suggestions. This approach does not include any type of patient simulation (Sherimon et al. 2016).

The approach of Chen et al. (2017) is a CDSS for clinicians that uses multicriteria decision-making techniques for prioritizing among treatments for T2DM. Their approach also applies a fuzzy logic model to take into account patient's disposition in the decision-making process.

Caballero-Ruiz et al. (2017) present a web platform that has a CDSS for patients in relation to their diet and insulin dose. A clinician should always review the insulin dose before approval. A rule-based knowledge system, which combines the output of two finite automata to determine the patient's metabolic status, generates the recommendations.

Kang (2018) proposes a system for predicting the effectiveness of treatments for patients with T2DM based on recurrent neural networks. Neural networks incorporate information about the sequence of treatments prior to the inference process, which, according to the author, improves the accuracy of the prediction.

3. ECONOMIC MODELS FOR HEALTH INTERVENTIONS ON DIABETES

None of the aforementioned proposals incorporates elements to assess not only the effectiveness, but the cost of health interventions. In diabetes, the economic evaluation of new treatments is usually carried out with the support of models that reflect the evolution of the disease throughout the patient's life, so that the impact on both the long-term health of the patient, and the use of health resources can be quantified. Many of these models are created *ad hoc* to evaluate a specific intervention in a specific context but the complexity of this disease has led to the creation of some large commercially available generic models.

The Core Diabetes Model (CDM) of IQVIA is probably the most widely used of these models (Palmer et al. 2004a). The CDM is able to simulate the progression of T1DM and T2DM from the levels of glycosylated hemoglobin (HbA1c), blood pressure, lipids, weight and hypoglycemia. With these characteristics, it can predict life expectancy, quality-adjusted life expectancy, time to presentation of complications, and costs. CDM has been widely validated and is in continuous development (Palmer et al. 2004b).

The Prime Diabetes Model (PDM) is a similar alternative to CDM, and it is also widely validated (Valentine et al. 2017).

Both the CDM and the PDM are commercial models. Other models developed from the academic environment are the Michigan model for diabetes (Zhou et al. 2005), and the model for T1DM at the University of Sheffield (Thokala et al.2013).

All these models focus on the evaluation of new technologies, but its use as a framework for the decision making of the clinician with the existing treatments has not been considered until now.

4. A NEW APPROACH FOR SUPPORTING THE DECISIONS OF CLINICIANS ON DIABETES TREATMENT

Figure 1 shows a schematic diagram of a new CDSS based on simulation and machine learning techniques, which has three main components:

- The simulation model core
- The parameter adaptation system
- The CDSS interface

4.1. Simulation model core

Currently, the simulation model core is a highly modular discrete event simulation (DES) model that characterizes the progression of T1DM for a patient for a lifetime horizon. We selected this kind of model above other alternatives (Markov models, decision trees…) to allow the inclusion of individual characteristics to model the progression of the disease, to faithfully represent non-linearity of hazard ratios with patient characteristics, to easily include acute complications, and to avoid the explosion of states due to the multiple comorbidities that patients concurrently suffer. The model is implemented by using a Java-based DES library that incorporated all the tools for managing events and obtaining results (Castilla, García, and Aguilar 2009).

The developed model comprises, as well as other previously published studies, four groups of chronic complications of T1DM: cardiovascular disease, nephropathy, neuropathy and retinopathy (Health Quality Ontario 2018; Thokala et al. 2013). In addition, it incorporates episodes of severe hypoglycemia. The risk of progression of these complications depends, fundamentally, on the HbA1c level of each individual, though age or duration of diabetes may serve as predictors too. As shown in Figure 2, the model starts by assigning some characteristics to the individuals, such as age, HbA1c level and intervention group. HbA1c, together with the other initial characteristics, serve as a predictor of the time it will take the individual to develop each of the complications.

The onset of a chronic complication is handled as an event that modifies the patient's condition. These modifications can lead to increasing the risk of other complications, which, in turn, may shorten the time of the complication onset. Similarly, the risk of patient mortality increases with many of these complications, which may reduce their life expectancy. The manifestation of each chronic complication can be accompanied by a cost for the acute treatment of the problem, and then contribute to the annual burden of the disease with a fixed treatment and follow-up cost per year.

The model contemplates only the first event for cardiovascular disease, be it an angina, a stroke, a heart failure or a myocardial infarction.

Nephropathy involves three phases: an initial phase of microalbuminuria, i.e., with very mild or nonexistent clinical manifestations; a phase of macroalbuminuria, where the manifestations are moderate; and a final phase that is expressed as end-stage renal disease.

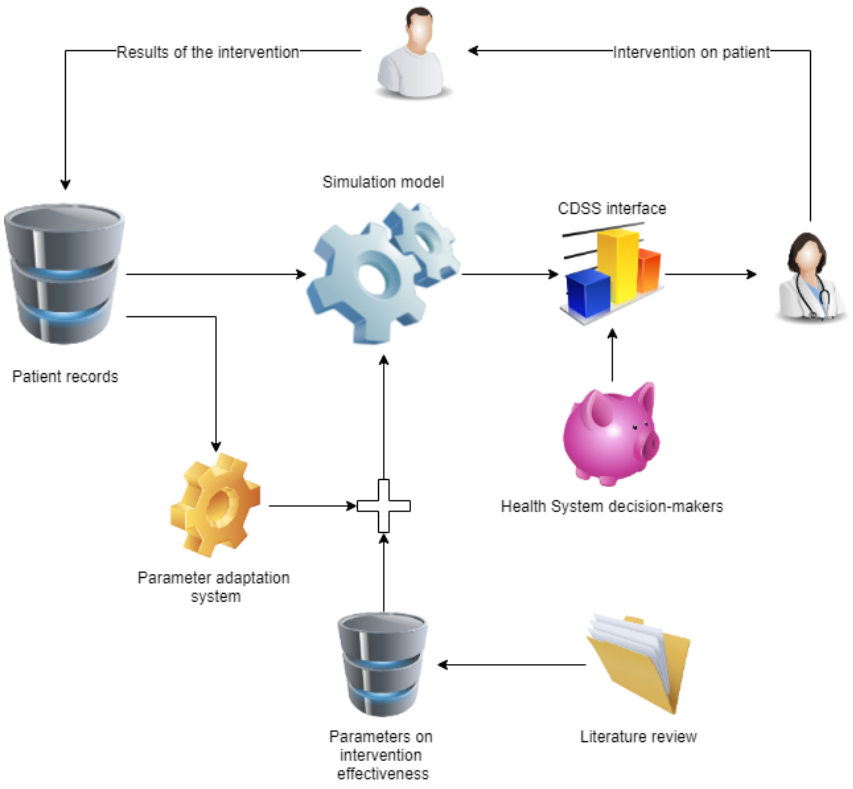

Figure 1: Simplified schema of the solution

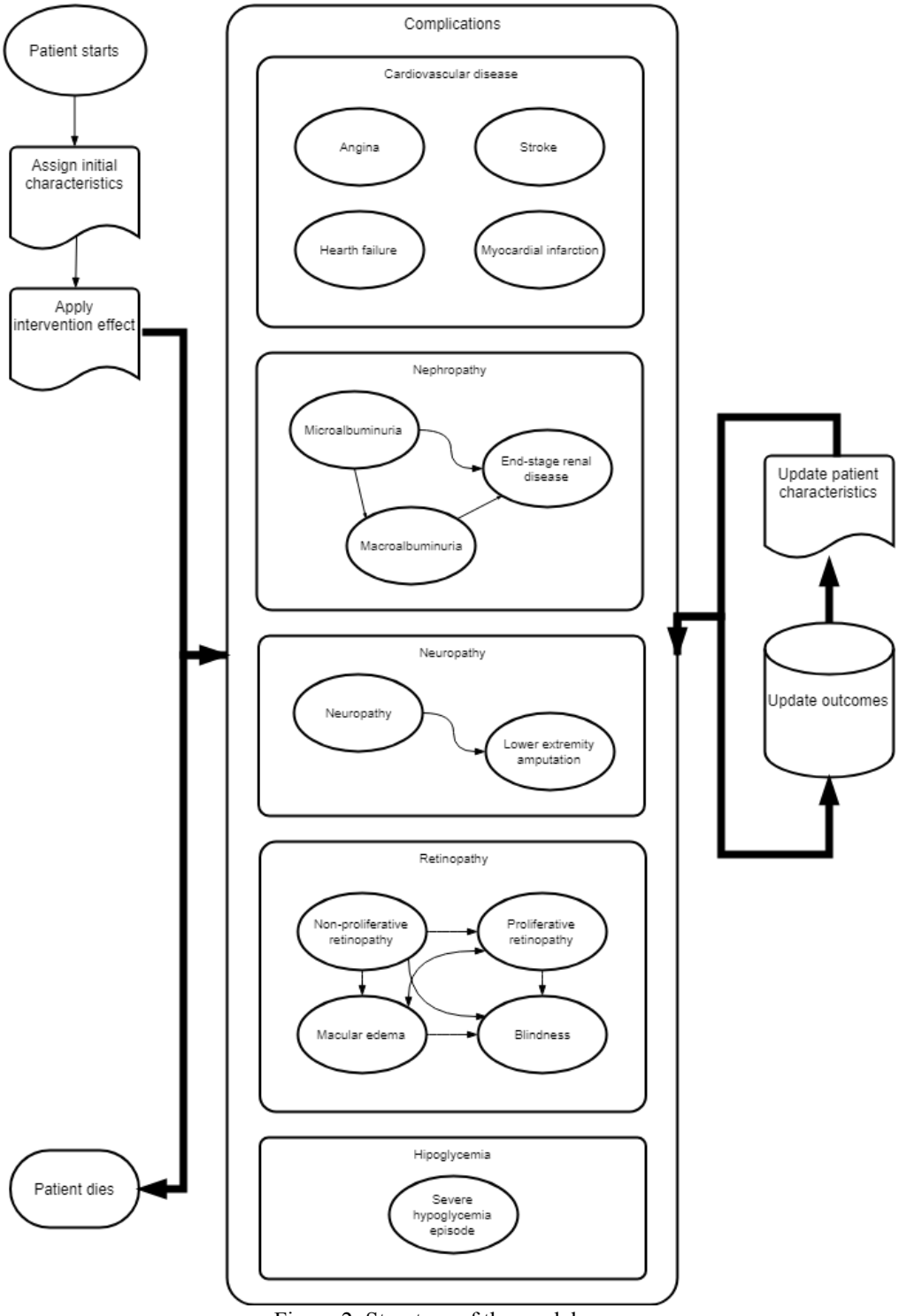

Figure 2: Structure of the model

Neuropathy considers two possibilities of evolution: a mild or moderate neuropathy, and the amputation of a lower limb as the most severe consequence, which, in turn, would lead to a marked decrease in quality of life.

For retinopathy, the model recognizes two stages of progression (non-proliferative and proliferative). At the same time, the patient can develop a diabetic macular edema. From any of these states the patient could lose sight completely.

The model handles episodes of severe hypoglycemia slightly differently. When suffering from severe hypoglycemia, patients suffers a decrease in their quality of life and have an associated probability of dying from the episode.

The parameters of the model are based on different sources. The time to develop complications is adapted from annual transition probabilities published in a

number of former economic evaluations (Health Quality Ontario 2018; Thokala et al. 2013).

We performed several validation tasks to increase the confidence in the results of the model. These tasks included the comparison with the accumulated incidence of background retinopathy, microalbuminuria and neuropathy at 9 years described in the Diabetes Control and Complications Trial (DCCT), as posed by The Mount Hood Challenge 4 Modeling Group (2007); and the parameterization of the model to reproduce the model from Health Quality Ontario (2018).

With respect to the validation with the DCCT results, we must consider the results on microalbuminuria and neuropathy as an internal validation of the model, since the probabilities used in the model were adapted from this study. Conversely, the comparison with the results for retinopathy is an external validation.

Table 1 shows the results of the validation against DCCT. The internal validity of the model is satisfactory, especially for the progression of the population in intensive treatment, which presents very low errors. For conventional treatment and the same complications, the relative error is higher, although always lower than 3 percentage points.

As regards background retinopathy, the absolute error in the intensive intervention is less than 5 percentage points. However, the discrepancy with the results of the conventional intervention is remarkable. This discrepancy could have its origin in differences due to other clinical factors between the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) population (used as a source for our model) and the DCCT population. It could also be partly explained by the way HbA1c reduction is applied to the population with intensive intervention: the behavior of the incidence of retinopathy with respect to the level of HbA1c is not linear, so the accumulated incidences are highly influenced not only by the average value of HbA1c but because of its dispersion. From the DCCT study, it was possible to obtain that the reduction of HbA1c was 1.5% on average, with a standard deviation of 1.1. However, there was not enough information to characterize this reduction in detail. In any case, although we calibrated the model to mimic the progression of DCCT in sensitivity analysis, the results remain robust.

Table 2 shows the results of the validation against the model from Health Quality Ontario (Health Quality Ontario 2018). Our model faithfully reproduced the life expectancy of the population, with relative errors lower than 2.5%. Results in quality-adjusted life expectancy also obtained low relative errors (<5%). The greatest discrepancy occurred with the costs, and could stem from the structural differences between the models: the model from Health Quality Ontario had absorbing states for amputation, end-stage renal disease or blindness, while the discrete event simulation used in this report allows an individual to suffer all those complications at the same time. Therefore, the former model may be underestimating the costs associated with treating multiple complications as the disease progresses.

The simulation model handles the effectiveness of the interventions in several ways. An intervention may reduce the HbA1c of the patient, hence increasing the time to suffer most complications. Other interventions may directly reduce the risk of a specific complication. The application will include a set of predefined interventions, characterized according to an exhaustive review of the literature; but the user will be able to create his/her own interventions too, by posing a tentative effectiveness and observing the expected evolution of the patient.

Table 1: Validation of the model against the cumulative incidence of complications in DCCT

Intervention	Complication	DCCT	Our model	Relative error	Absolute error (pp)
Conventional	Microalbuminuria	27.30%	25.52%	6.52%	1.78
	Background retinopathy	52.20%	21.62%	58.58%	30.58
	Neuropathy	21.30%	18.74%	12.02%	2.56
Intensive	Microalbuminuria	16%	16.16%	1.00%	0.16
	Background retinopathy	14.30%	9.94%	30.49%	4.36
	Neuropathy	10%	10.26%	2.60%	0.26

pp: percentage points

Table 2. Validation of the model against the model from Health Quality Ontario

Intervention	Item	Canada model	Our model	Relative error
SMBG plus multiple daily injections	Cost	$125,586.00	$180,090.03	43.40%
	QALY	18.812	17.962	4.52%
	LY	26.411	26.688	1.05%
SAP	Cost	$258,306.00	$332,805.05	28.84%
	QALY	18.944	18.417	2.78%
	LY	26.564	27.170	2.28%

LY: Life years; QALY: Quality-adjusted life years; SAP: sensor-augmented pump; SMBG: self-monitoring of blood glucose

4.2. Parameter adaptation system

As the volume of available data increases, we want to add new input variables to the system. It is possible that, by increasing the complexity of the model, the simulation will no longer properly represent the underlying relationships in the new data. At this point, we want to continue using the simulation to predict the estimated times to develop each of the pathologies depending on the current input variables under study (such as HbA1c and age), since that model has been obtained from large volumes of data and represents the relationship that exists between the input and output variables at a population level. However, these generalist predictions may not fit properly at the individual level, especially when new information is available. Therefore, we want to complement this model, with a system based on Machine Learning that predicts the estimated times to develop T1DM-related complications by using new input variables. These new input variables may include information on the presence of comorbidities, current treatment, and physiological or biochemical characteristics of the patient, both punctual estimates and time series. As the volume of available data increases, this system will learn new patterns in the data that serve to particularize predictions at the individual level. We will try different machine learning techniques such as neural networks, decision trees, probabilistic methods such as Naive Bayes or logistic regression, or kernel-based methods such as Support Vector Machines.

4.3. CDSS interface

The CDSS interface actually represents two different interfaces for two different audiences.

The clinician requires a clear interface that presents the simulation results. The interface allows a clinician to select a patient, preselect among different treatment strategies or interventions, and ask the system for prioritizing such interventions.

The second audience are health system decision maker. In this case, the interface becomes a dashboard to monitor the use of interventions and to track their actual effectiveness. The dashboard also shows a set of indexes on the use of cost-effective interventions by clinicians. Therefore, health system decision makers could economically incentivize clinicians to adhere to cost-effective interventions, and then track the achievement of the objectives.

5. CONCLUSIONS AND FURTHER WORK

Health care for diabetes requires the best support tools to improve not only the health of the patient, but also the sustainability of the public health systems. We have presented the first step towards an ambitious project on a decision-support system for clinicians that will help choosing the best treatment for T1DM patients. “Best” here refers to effectiveness of treatment, but also to cost-effectiveness. This second dimension will allow the managers of the public health systems to incorporate incentives for the use of the most cost-effectiveness treatments.

Up to now, a first version of the core simulation model is ready, which has been validated against well-known studies. We have already prepared a prototype of a standard intervention with insulin pump.

With the validated simulation model, we have a robust basis for parsimoniously incorporating Machine Learning techniques that will improve the model fitting to individual patients, and thus will move towards predictions that are more precise.

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A MULTI-MODAL DATA MODEL FOR MORPHOLOGICAL SEGMENTATION IN 3D DOSIMETRY

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ABSTRACT

Patient specific dosimetry established during the last decade in modern radio-therapy. Usually, tracer kinetics in main compartments of observed metabolism is assessed from anterior and posterior whole body scans. The effective doses for each organ, derived by the MIRD scheme, provide evidence for following radio-therapeutic treatment and helps to meet vital dose limits for critical organs, e.g. kidneys. The calculation of individual dose in a three-dimensional context leads to more accurate dose estimates, as was proven by intensive research, but is still on the cusp to clinical application.

In this work, a statistical approach, based on multi-modal image and feature data, is presented, to overcome manual segmentation, the most time consuming step, in 3D based dose calculation. 3D data volumes from a hybrid SPECT study, comprising SPECT and CT data, covering main compartments of metabolism, build the image features of a Gaussian classifier. From prior segmentations organ-specific membership maps are derived, and substituted as additional feature into the segmentation procedure. Centroids, eccentricity and principal axes of organ models are registered to a rough thresholded image of the SPECT component, and define membership coefficients of the voxels.

The new approach yields accurate results, even with real patient data. The new method needs minimal user interaction during selection of some sample regions, thus showing high potential for implementation in a clinical workflow.

Keywords: medical internal dosimetry, image registration, segmentation

1. INTRODUCTION

Radiotherapy is a strongly evolving branch in modern nuclear medicine. In contrast to tele-therapy, it affects the lethal impact, by transfer of the radioactive particles directly into the tumour. Accumulation processes in the tumour-tissue, utilizing specific bindings of trace-molecules, shall reduce the region of lethal effects to the target region and protect surrounding tissues, specifically essential organs, from radiation stress.

Nuclear medicine therapy came always along with radiation protection. First attempts were made using static phantoms, built from bottles (Bush 1949), yielding rough dose estimates, for each radiopharmaceutical and therapy application under consideration.

Consideration of patient scans leads to individual dose planning. Exposure data, measured from organ scans, are combined with Monte-Carlo dose calculations, based on standardized phantom geometries. Standardized tabulated values exist for each therapeutic isotope, applied to various different human models, e.g. pediatric, female, pregnant, and male body phantoms. Results for all relevant body compartments are published in the ICRP reports. The principles are implemented in the software package MIRDOSE (Stabin 1996), the clinical standard until 2004, before OLINDA was deployed (Stabin and Siegel 2003).

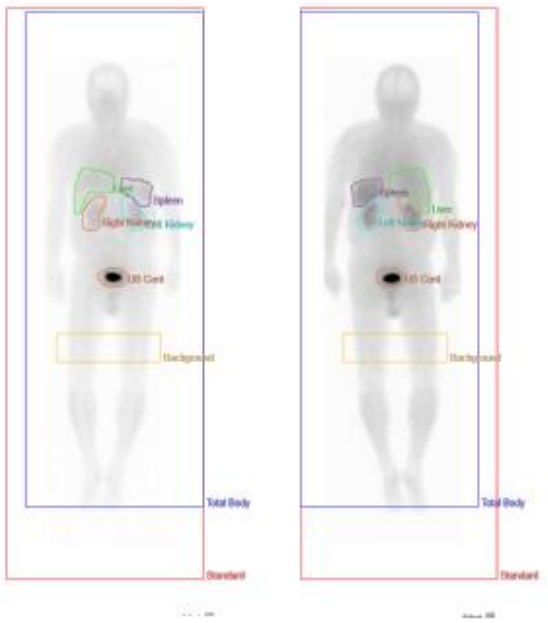

Figure 1: Manually drawn regions used for dose calculation. Regions are drawn over whole body scans, displayed in anterior and posterior view: kidneys (brown, cyan), liver (green), spleen (purple), bladder (ocher), body background (gold), total body (blue), and the reference standard (orange).

With the further development of imaging modalities, anthropomorphic models are refined towards realistically shaped organs. These models are derived from segmentation of measured 3D data (Schläger 2011).

Individual dose planning focuses on the assessment of pharmacokinetics and accumulation of the radioactive isotope in every single patient. Most therapeutic radiopharmaceuticals are mainly beta emitters and have

no or only weak gamma lines in their emission spectra, inhibiting assessment of radioactive uptake. In this case an isotope with similar pharmacokinetics but strong gamma spectrum is substituted to perform the dose estimation scans. Time activity curves for all relevant organs, providing the essential information for the following dose calculation, are estimated from emitted cumulative counts. Regions of interest (ROIs) are drawn manually over the whole body images and evaluated at each point in time, cf. Fig1. To correct for the latter applied therapeutic isotope the summed counts are modified, reflecting the physical half-life-time of the therapeutic isotope (Mirzarei et al 2013).

Projection may lead to overlapping ROIs in 2D scans making accurate rating of concerned TACs very difficult. Approaches with factor analysis were made for distinguishing overlapping regions, utilizing small differences in tracer dynamics (Backfrieder et al. 1996, Backfrieder and Zwettler 2015, Sámal et al. 1987, 1989)

Recent approaches of individual dose planning are based on hybrid tomography data, SPECT-CT or PET-CT, in combination with 2D whole body data series for estimation of temporal evolution dose distribution (Lee 2015, Backfrieder 2018), but until now costly image acquisition and data processing in 3D are drawbacks in clinical application of 3D dosimetry.

In the current approach a method for automated segmentation in 3D based on bi-modal SPECT-CT Data is developed, substituting a statistical membership map as further feature to a standard Gaussian discrimination process to improve segmentation, thus fostering 3D dosimetry in clinical procedures.

2. MATERIALS

Imaging protocol for dose estimation in nuclear medicine radiation therapy comprises multiple patient studies. A three dimensional SPECT scan, together with a low dose CT scan, provide general information about specific uptake in a 3D context, and the CT allows attenuation correction for further improvement estimating true source counts. Temporal behavior is derived from a series of planar whole body images.

Data from six patients, three male and three female, age ranging from 52 to 79 years, are examined. Each patient study comprises a SPECT and CT volume image, and six planar whole body scans.

2.1. Whole body scans

After administration of 60 MBq In-111, whole body scans are acquired 20 min, 90 min, 24h, 48h, 72h, and 96h after injection. Image data are acquired with a double-headed gamma camera, Philips BrightView. Detectors are in 180 degree position. Anterior and posterior data are captured on a 1024x512 image matrix, 2.8mm pixel-size and scan-speed 10cm/min. Figure 2 shows the full whole body series in anterior view.

Images are scaled to individual data ranges. In early images, the content of the urinary bladder dominates the image dynamics, thus diminishing organ contrast. In latter frames, kidneys show higher relative intensity indicating the washing out of radioisotopes from blood. Uptake of liver and spleen is increasing; urinary bladder shows still substantial filling. The following frames show main residence of the radioactive substances in liver, spleen and kidneys. The residence times in spleen and liver are slightly higher than in kidneys, indicated by higher count rates. Accumulation in these organs is responsible for main dose stress.

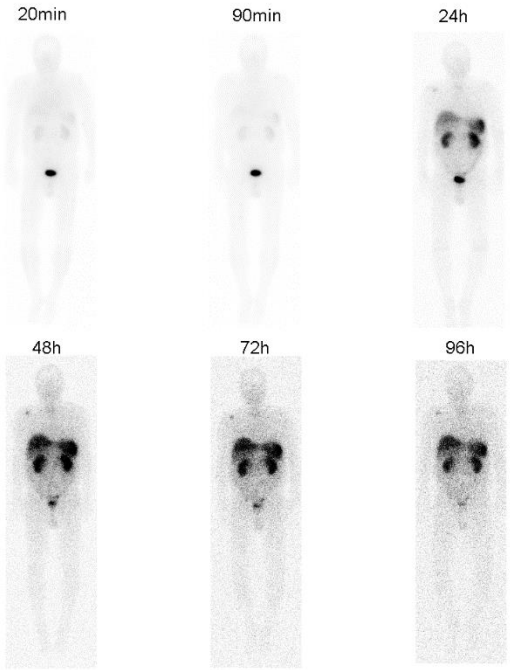

Figure 2: Anterior projection data set. The series of whole body scans shows the dynamic processes, six scans cover a period of 96 hours. Projection images are acquired on a 1024 by 512 matrix, with 10cm/min scan speed. The intensity window is scaled to 45% of the maximum in each individual frame.

2.2. Volume scans

SPECT and CT data are taken directly after the 90 min planar whole body scan. SPECT projections are acquired on an elliptical, body approaching orbit with 3 degrees rotational increment, 20s acquisition time on a 130x130 matrix, with a squared FOV of 605mm length. A series consists of 90 slices, with thickness 4.66mm. Images are reconstructed with an OSEM algorithm and attenuation corrected. CT data are on a 512x512 matrix with isotropic voxel-size of 1mm. The volume comprises 406 slices. Figure 3 shows an identical slice from both SPECT (a) and CT (b).

3. METHODS

The MIRD approach leads to an estimate of effective doses for each organ, respectively compartment, considering it as mutual source and target for all others (Snyder et al. 1975). To obtain realistic dose values, estimates need reliable measurements of emitted radiation. In standard clinical procedures, regions are manually drawn over the whole body scans and accumulated counts build the samples for the time

activity curves (TACs), yielding the total counts over this region. However, this approach suffers from general information loss in 2D projection images. For proper consideration of attenuation effects and correction of overlapping regions, three-dimensional segmentation is inevitable. Manual segmentation by drawing regions slice by slice is very time consuming and besides scientific case studies, it is not likely to take place in a clinical workflow.

Global thresholding of the SPECT image volumes is not sufficient, since organs aggregating radiation touch each other, e.g. liver and kidney, or liver and spleen, and no sufficient discrimination is achievable. Manual post-processing needs roughly the same efforts as manual segmentation.

A full data set for preparation of radio-therapy comprises, besides the planar whole body studies, a SPECT and a CT volume scan, as described in the materials section. The mutual information from SPECT and CT is the basis for segmentation, since CT images comprise detailed morphological information. Both volumes build a multivariate data model, each pixel has a SPECT and CT feature value. Gaussian discrimination is intended to obtain accurate segmentation. CT data are actually acquired for attenuation correction, hence weak x-ray intensity keeps additional patient dose low, but causes low contrast in image data. The reduced contrast resolution is not sufficient for accurate differentiation between considered tissues. As a further dimension, a membership feature is substituted, representing a flexible model build from former segmentations.

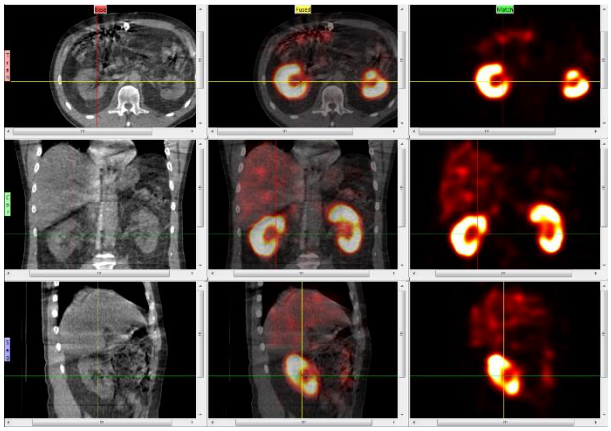

Figure 3: Co-Registration of CT and SPECT image volumes. Primary registration inherent to the hybrid camera (Philips BrightView) is further refined by MI voxel based registration. Columns show CT, CT-SPECT overlay, and SPECT images in transversal, coronal, and sagittal slice orientation.

3.1. Thresholding

Segmentation is a workflow comprising many steps. During the first step, scan data are prepared for segmentation. Double thresholds are applied to the CT and the SPECT image volumes to exclude all voxels, outside the limits, from further consideration. All the segmented voxels are subject to multispectral classification. In this process, voxels with similar features are grouped together. The features are its respective intensity value in the specific modalities and the value from the probability map, defining a fuzzy membership to a tissue type. Exact registration of the scans is an inevitable requirement for successful registration.

3.2. Registration

Mutual information is a statistical measure from information theory; it describes the relation of symbols in two coherent data sets, respective tissues or morphologies. It is extensively used in image registration of multimodal data, where correlation methods are not applicable to modality specific manifestation of tissue. In perfectly registered images, mutual information is maximized (Studholme et al. 1996, Hill et al. 1998, Crum et al. 2003).

For aligment of two-dimensional images, X and Y, the global maximum in a three-dimensional variable space, one rotational and two translational degrees of freedom, is determined. Mutual information of both images is maximized by steepest gradient search

$$MI(X;Y) = \sum_{y \in Y} \sum_{x \in X} p(x,y) \log\left(\frac{p(x,y)}{p(x)\,p(y)} \right). \qquad (1)$$

In the above equation $p(x,y)$ denotes the joint probability of images X and Y, the probabilities of both single images are represented by $p(x)$ and $p(y)$.

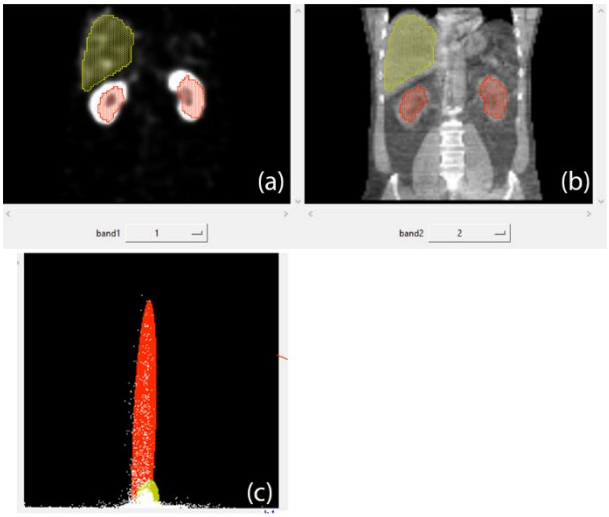

Figure 4: Feature images with samples for liver (green-yellow) and kidneys (red). Regions for sampling are drawn simultaneously on, both the SPECT image (a) and CT image (b). The distributions derived from the samples are drawn over the scattergram (c).

3.3. Multi-spectral classification

Co-registered data build the base features of the multispectral classification procedure. Intensity values of a specific tissue type or organ, in respective modality, build clusters in feature space, i.e. the scattergram. Each voxel is an object in feature space, and its position is determined by the intensity values along the axes. In this work we us a simple Gaussian data model for clustering

(Kaufman and Rousseeuw 2005). But the approach can easily refined by substituting another clustering technique.

In this model, each tissue type is described by a multivariate Gaussian distribution.

$$f(\vec{x}) = \frac{1}{\sqrt{(2\pi)^p \|\Sigma\|}} \exp\left(-\frac{1}{2}(\vec{x}-\vec{\mu})^T \Sigma^{-1}(\vec{x}-\vec{\mu})\right) \quad (2)$$

The $\vec{x}$ is the object or voxel with the image values from each modality and the rest of the *p* features describing the object-characteristics, $\vec{\mu}$ is the mean of the distribution, and Σ the covariance matrix.

For first estimates for the parameters $\vec{\mu}$ and Σ, regions are drawn manually over the tissues, and the estimates are calculated, based on these. Figure 4 shows an example for these regions. Regions are displayed over the feature images, too. The application allows choice of any feature as image slice in two canvases. The regions are displayed in different colors, selected voxels are colored in the scatergram, displayed at the bottom. After selecting samples the first estimate of the distributions are calculated. The distributions are limited by an α value, to achieve optimal segmentation. In the example shown in Figure 4.c a value of 0.03 is chosen.
These initial distributions are the starting points for an iterative procedure to refine segmentation. The distributions are used for segmentation of the whole image volume in each step. The intermediate segmentations are the samples for the next iteration, providing new estimates for mean and covariance and updated distributions for the next iteration. In this approach, a fixed number of 5 iterations is applied.

3.4. Topological membership map

A topological membership map is built to further support segmentation, since SPECT and CT values provide sometimes weak differentiation between tissue types. The map is based on prior segmentations. Relevant features as centroids, principal axes, eccentricity and some statistical moments are estimated from these data sets. Each new segmentation updates this parameter, leading to a steadily improving prior model. The model is globally registered against the preliminary segmentation after thresholding, to provide an initial position. The single organs are further adapted to local shape of the given segment. For each organ, a topological map is substituted as artificial feature to the multispectral classifier.

4. RESULTS

As a proof of concept for the elaborated segmentation method, anonymized clinical data from patient studies are processed. Topological membership maps provide useful information to employ Gaussian clustering for meaningful automated segmentation. Segmentation of liver and kidney based solely on SPECT and CT data is shown in Figure 6.a. Samples are drawn, as shown in Figure 4.a and 4.b, on representative slices, of the coronary cut. Regions are drawn on the adjacent slices, also, to reach sufficient sample size. The distributions calculated by classification on a confidence interval of 97% are displayed over the scattergram, cf. to the bottom row of Figure 4.c. The resulting classification is shown in Figure 6.a. Identified soft tissue voxels are colored, liver is shown as green-yellow and kidneys are labeled red. To keep comparability in Figure 6 the same slice is displayed as in Figure 4. As clearly seen, clustering based on CT and SPECT data, without any position information, provides very poor segmentation. Most of the classifications are wrong. The method, without any further improvement, is not applicable for segmentation, as shown in Figure 6.a.

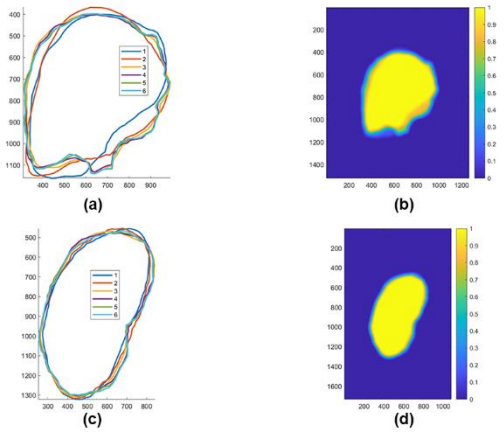

Figure 5: Standardized topological membership maps generated from most significant PCs. Topological models are calculated for liver (top row) and kidney (bottom row). Figures (a) and (c) show the cumulative contours from PC1 up to PC 6. The maps in (b) and (d) show the probability maps for membership based on these PC-curves.

Topological membership maps substitute the required position information. A principal component model of a priori known outer contours gathered from former segmentations is built. The contours are registered to each other and resampled on an equally spaced angular grid, to provide point correspondence for PCs. The resulting PC models are shown in Figure 5 on the left column. The curve of the first, most significant PC represents the average shape of all captured contours. All further contours represent the deviations from the prior curves. The plot shows the curves for liver and right kidney reconstructed from 1 up to 6 components, cf. Figure 5.a and 5.c. These curves are converted to probabilities by accumulation of the regions surrounded by the PC curves. Figure 5.b and 5.d display the maps for liver and right kidney. Substitution of topological membership maps provides the additional position information to achieve proper segmentation. Figure 6.b shows the improved results. Kidneys are clearly visible and accurately distinguished from surrounding tissue. Liver is slightly over-segmented, but superior to the segmentation before. Post-processing with morphological operations may further improve results. The proposed method of topological membership maps is self-learning. Each new segmentation is added to the

data pool, providing new variability and diversity of contours. By the way, the PC model is further refined.

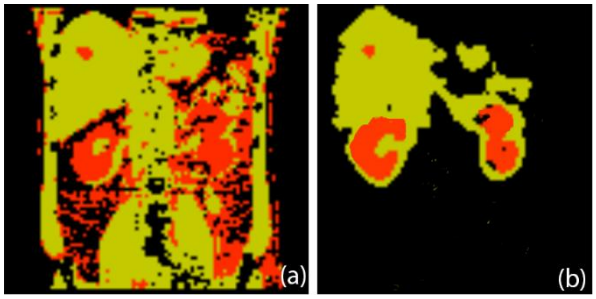

Figure 6: Automated segmentation based on multispectral classification. Liver (green-yellow) and kidneys (red) are classified. (a) Classification based on SPECT counts and CT units, solely, yield weak results. Substitution of topological membership maps improves segmentation substantially (b).

5. DISCUSSION

Internal dosimetry raises its importance with the increasing availability of a great variety of tracer molecules, enabling individual tumor therapy. Ethic and legal constraints put focus on reliable and accurate dosimetry. With common whole body scintigraphy, problems of overlapping organs in projections and deterioration of counts by attenuation are inherent to the method. The installation of modern 3D imaging modalities allow a three dimensional sight of the problem, at the cost of at least two additional scans and some very time consuming data processing. This work proposes a reasonable approach for mainly automated definition of 3D VOIs with little user interaction collecting representative sample data, in contrast to manual drawing organ ROIs.

The method is promising for establishing 3D dosimetry as standard in clinical daily routine, but it still needs improvement by further post processing and careful testing with clinical data.

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TRAINING SYSTEM FOR FIRST RESPONSE MEDICAL EMERGENCY GROUPS TO GUIDE TRIAGE PROCEDURES

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ABSTRACT

The work presents training system which provides a structured, simple and practical approach to triage training, for first response paramedic and emergency medical services personnel, as implementation of the triaging procedures in mass casualty accidents. The proposed training system allows to train the procedures at all three levels of hierarchical chain of strategic, tactical and executive command management. It provides reliable connectivity at the scene based on Bluetooth Low Energy standard or Internet connection with the use of mobile 4G LTE communication networks infrastructure. In training system we use simulators of vital human signs based on mobile devices, which generate so-called the victim's life cycle chart, consisting of the heartbeats and respiratory rates, systolic and diastolic blood pressure, and capillary refill time, used as the basis for triage categorization. Presented training system increases trainees competence level in executive as well as control and governance skills.

Keywords: triage procedures, mass casualty incident, medical emergency group training

1. INTRODUCTION

First response medical emergency groups are services that are called to any accidents involving people. After arriving at the scene of the accident, they evaluate the scale of the event. If the number of victims and the scale of its injuries is so large that it is not possible to provide assistance at the level required by standard procedures, (when there are insufficient resources for medical care of everyone at once) then medical categorization (triage) procedure is necessary. As a result of this procedure, the victims obtain priority related to its injuries, time of assistance, and evacuation (Super 1984, Wallis 2006).

Triaging algorithms are not very sophisticated, they are rather straightforward, and easy to use (Navin 2010a, Jenkins 2008, Lerner 2013). However, they can allow for over or under triaging depending on the situation. Therefore, the idea of performing trainings which impose the desired behaviours, as reflex actions realizing required procedures. This is especially important when mass casualty incidents happen so rarely that first response medical staff forgets details of the required procedures.

According to study conducted with medical rescue staff (Wilk 2015) 28% of respondents had no real experience in medical rescue at mass events. 38% had never participated in training in this field, and 7% had never received professional training at their workplace.

Trainings are obviously not the same as working in real emergency, but it make effective a certain habits, that in real situations allow to maintain a high efficiency of action (Navin 2010c).

1.1. Organization of rescue management

Rescue operations during a mass casualty incident consist of three levels (Fig.1):

- ***strategic level,*** Health Service Commander in Crisis Management Centre coordinates all emergency services with the necessary number of medical resources as dedicated medical staff and medical facilities that are necessary for highest efficiency of rescue operation.

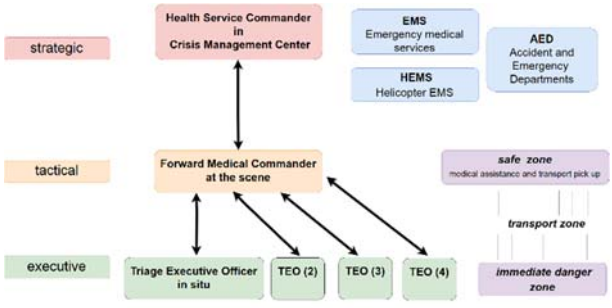

Figure 1: Hierarchy of Rescue Management. Chain of Strategic, Tactical and Executive Command

- ***tactical level,*** Forward Medical Commander, who operate on site of the mass casualty incident, controls the work of all Triage Executive Officers at the scene. He maintain reliable and continuous communication with

Health Service Commander and recognise the actual situation at the scene and notify it the Health Service Commander.

- ***executive level,*** Triage Executive Officers, who cooperate with first responder medical services at the scene of the incident, e.g. physicians, paramedics, nurses, rescue and fire-fighting units.

The rescue operation site is organised in 3 zones (Fig.1):

- ***safe zone,*** which provide the dedicated medical staff and equipment necessary for saving injured victims and prepare them for transport to the hospital. It consists of: casualty collection point, categorized treatment areas, patients loading area. Here the secondary medical segregation (re-triage) is carried out.

- ***transport zone***, there are designated corridors that are used to transport victims to safe zone. For people who can walk independently, separate escape routes are designated.

- ***immediate danger zone,*** determined by the State Fire Service commander who, as the first, arrived at the site of the accident.

1.2. Triage procedures - issues of concern

Triage procedure we use to prioritize emergency care and identify victims who need immediate medical attention because of the nature or severity of their injury. Triage possibilities vary depending on the zone in which the victims are located. Within the immediate danger zone rescuers usually work in protective clothing which limit the possibility of a detailed examination of the victim. So, basically a quick assessment of the victim in terms of the urgency and rationality of evacuation to the safe zone, is required.

Re-triage is carried out within the safe zone, where qualified medical staff in a safe environment can assess the victim condition on the basis of a larger number of parameters.

Finally, the last re-triage takes place in the phase of removing the effects of accident in emergency departments or hospital trauma centres. There, it is possible to re-assess the condition of the victim after a significant time from the first triage procedure performed by the first response medical emergency personnel.

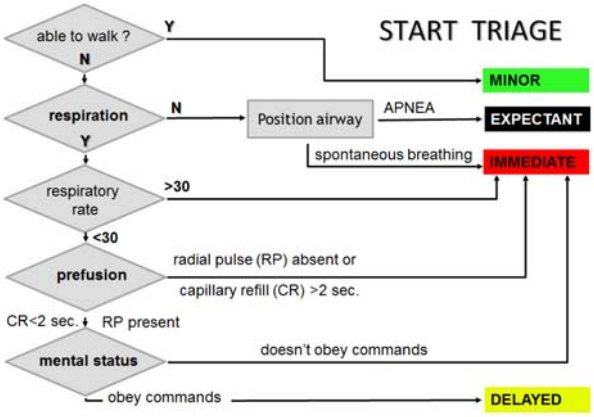

Figure 2: Simple Triage And Rapid Treatment Procedure

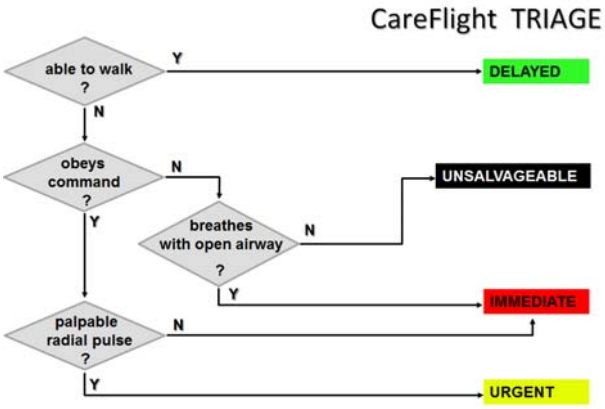

Figure 3: CareFlight Triage Procedure

All data collected by Triage Executive Officers are transferred to the Forward Medical Commander, person guided in situ a medical rescue operations. Based on that information, he has the possibility of combining the victims with the division into the urgency of their evacuation to the safe zone.

Forward Medical Commander has direct communication (usually via a radio or mobile network) with the Health Service Commander. This allows the flow of information on the number of victims, the possibilities of their admission to the specific hospitals and the allocation of the victims to specific medical facilities.

On executive level (Fig.1), triaging algorithms are rather simple, straightforward, and easy to use. To prove that, it suffices to analyse the most-popular procedures such as: Simple Triage And Rapid Treatment (Fig.2) (Kahn 2009), Care Flight Triage (Fig.3), Triage Sieve (Fig.4), Sacco Triage or Sort, Assess, Lifesaving Interventions, Treatment (Navin 2010b).

All triage procedures are based on a common set of 3-4 screening questions. Triage consists of life-saving procedures like; open airway, control haemorrhaging, make chest decompression and then answer the screening question about: mental status, walk ability, respiration, perfusion.

On strategic and tactical levels (Fig.1) triaging procedures ensure excellent strategy and effective tactics to support the implementation of activities on site of the accident. Tactic engaged with strategy results in synergy, but requires good team cooperation on all three levels. Proposed training system doesn't provide genuine hands-on experience, but it can be a complement to the disaster preparedness plan which can ultimately help to save human lives.

2. ARCHITECTURE OF TRAINING SYSTEM

Triage simulation training has been consistently shown to improve triage performance of technical, as well as co-operational teamwork skills (Garner 2001).

The poor communication and cooperation are common-

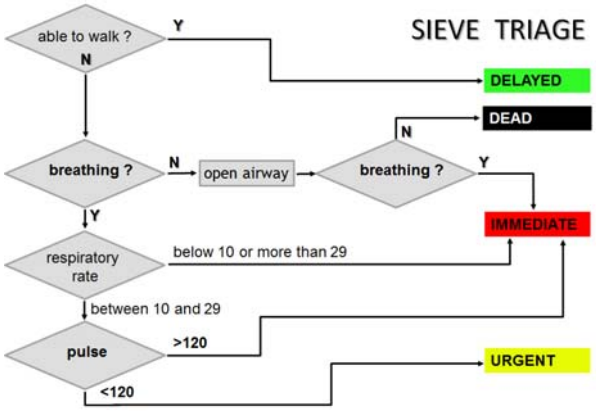

Figure 4: Sieve Triage Procedure

est falling of management effectiveness during mass casualty incident (Gao 2007), that's why our training system provides reliable connectivity at the scene based on Bluetooth Low Energy standard and software which forces the use of procedures specified in mass casualty accident operation guideline manuals.

Despite proven benefits of simulation, current training standards for first response medical services personnel consist primarily of education lectures that do not adequately address the reality of providing triage in a real, emergent in disaster setting. Specifically, simulation has proven effective for training a realistic response while emergency staff working in a stressful environment.

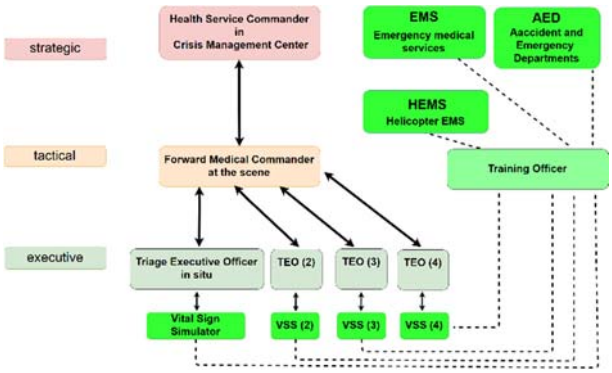

Figure 5: The Structure of Proposed Training System

The proposed training is conducted by the Training Assistant, who prepares tasks and governs exercises (Fig.5). Preparation of tasks consists in:

- specifying the number of injured people and work schedule for Vital Sign Simulators for each victim,
- defining the availability schedule for operating facilities and surgical nursing staff, in a crowded medical facility, emergency ambulances, paramedics or other skilled personnel.

2.1. Simulating of human vital signs

Modern technology offers a whole range of sensors that enable measurement and monitoring of selected physical quantities (Baheti 2009). The development of the wearables technology allowed to miniaturize the systems that monitor vital human activities using non-invasive methods (Stetson 2004). The latest information technologies provide software that integrates various technical solutions and combines them into a single measurement and local communication system, to capturing and transmitting patient data (Niswar 2015).

Wearable and IoT technologies offer more in this area (Yao 2005). The stick-on sensor called VitalTag (Dolon 2018) is fixed to a victim's sternum and wirelessly transmit real-time vital sign measurements such as heart and respiration rates, blood pressure, shock index, blood oxygen saturation etc.

In training system we use simulators of vital human signs based on mobile devices (Fig.6). These devices generate so-called the victim's life cycle chart, consisting of the values (heartbeats and respiratory rates, systolic and diastolic blood pressure, and capillary refill time) used as the basis for triage categorization

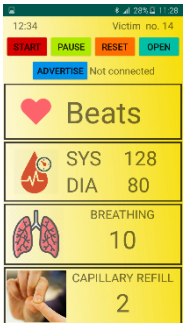

Figure 6: Human Vital Sign Simulator, (Burik 2019)

The victim's life cycle chart simulate victim behaviour for consecutive 20 minutes, and vital signs are broadcast with a 10 seconds period. It is played periodically every 20 minutes (unless the dead/unsalvageable status is reached before).

2.2. Organization of training teammates in triage procedures

Some number of Vital Signs Simulators (mobile devices with running life cycle chart) are placed on the selected training area. The team of first responders arrive on the scene with no foreknowledge how many are injured and how is the nature and extent of their vital signs (simulated by mobile device).

Due to the hierarchical chain of command (strategic, tactical and executive) triage procedures, we stimulate the following person activities (Fig.5):

- *Health Service Commander* in Crisis Management Center, who uses a desktop computer and internet communication channel to link with Forward Medical Commander working at the mass casualty incident area.
- *Forward Medical Commander* at the scene, who uses a tablet device (provided with application) to

communicate with Triage Executive Officers working at the scene.

- *Triage Executive Officers* at the scene categorizing victims according to triage procedures, communicating with both; Forward Medical Commander – as uplink and human Vital Signs Simulator as downlink, using data and advertising channels.

2.3. Team work coordination in triage procedures

The proposed training system allows to train the procedures at all three levels of hierarchical chain of strategic, tactical and executive command management (Fig.5). Wilk (2015), argues that 60% of medical rescue staff indicated organisational difficulties pertaining predominantly to coordinating actions during genuine or simulated mass casualty incidents. 66% of the respondents claimed that the leaders of rescue were chaotic. In order to improve the team work, it is necessary to define a chain of command (strategic, tactical and executive) and identify any actual and potential scene hazards.

On the executive level, the objective of our training exercise is to stage on scene, realistic triage simulation with participation of many victims. Triage Executive Officers organize an appropriate triage, identify and stabilize victims without unnecessary delays. They should correctly categorize patients according to severity of injury and evacuate them from the immediate danger zone. On this level, proposed training system can improve the communication and teamwork skills of the first response personnel and the efficiency with which the team performs challenging triage in a high-stress situation.

On the tactical level, Forward Medical Commander is the main (and only) person who manages all medical activities on accident area. He coordinates the activities of the rescuers. He sizes-up incident, estimates extent of impact area, and number and severity of victims. He creates an aggregative card of the current state of rescue action and based on it, he determines resources required. Effective management is crucial at this level. It is obligatory to co-ordinate activity of 4 types of team (Fig.1); three rescue groups operating in different zones and an vehicles of emergency medical services that provide transport from accident pick up area to emergency departments facilities. Regardless of various disruptions (deterioration of victims condition, deadlocks within transport zone, delays of ambulance arrival), smoothness of the flow of victims from the immediate danger zone to medical facilities needs to be ensured (with guaranteed level of medical services).

On the strategic level, Health Service Commander using an aggregative card of the current state of rescue action focuses on safe zone (where medical assistance (followed by re-triage) is provided, and staff prepare victims for safety transport). The effective coordination of vehicles to transport patients to medical facilities is definitely his management duty.

Because the triage is dynamic process, so it must be repeated at every stage of casualty evacuation chain to detect changes of victim's vital signs. After completing the one victim triage, Triage Executive Officer communicates (using Bluetooth data channels) his decision to the Forward Medical Commander (on Fig.7 *Connection* data channel) and continues the search activity in the scene of the accident. From that moment, the proposed software allows Forward Medical Commander take over the monitoring of vital signs function (Sakanushi 2011), using Bluetooth advertisement channels (on Fig.7 *Scanning-Advertising* data channel). This continuously gathered information is useful to determine the needs and adequacy of subsequent re-triage (Albahri 2018).

3. PROPOSED HARDWARE AND SOFTWARE

Creating a training system (Fig.1) we tended to minimize the difference between the training and the genuine action to be as small as possible. That's why the equipment used during training and the software requirements are similar to those used in real-life actions. Triage Executive Officers use smartphones/tablets and software running under the Android system. Forward Medical Commander uses a tablet/notebook and software running under Android/Windows. Health

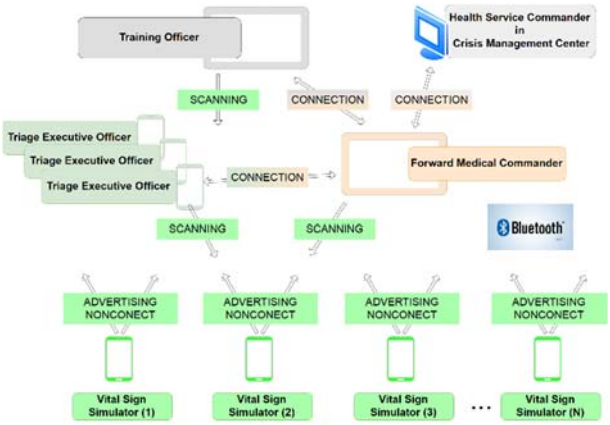

Figure 7: The Communication Structure based on Bluetooth Low Energy 5.1 Standard

Service Commander uses desktop computer and internet or wireless communication channel. Training Officer uses a tablet with bidirectional wireless communication.

In the scope of victim simulations, we propose two options: a simulator based on smartphone either medical phantoms, both providing wireless broadcast of vital human life parameters.

Proposed communication links between the training participants provide; directed one-way and bi-directional as well as broadcast, type connections. The basic variant of the communication is wireless Bluetooth Low Energy (BLE). Another version is the Internet connection with the use of mobile 4G LTE communication networks infrastructure (in the future 5G). Both variants provide sufficient bandwidth and number of channels, alike in rooms and open environment (in range circa120 m).

3.1. Triage Executive Officers software

Current methods of mass casualty incidents victims triage use such categories of optical markers as coloured bands or emergency Triage Tags fasten on the wrist. Triage Executive Officer, after examine the victim's vital signs (obtained from simulator or phantom), decides to which category the victim belongs to, and attaches to it the appropriate colored marker. Preserving mentioned above rules, we equip Triage Executive Officer (trainee) with Android smartphone and software providing the following functionalities:

- enter the trainee ID and triage method ID, once at start of training session,
- determine the GPS position and ID of the triaged victims,
- collect wirelessly broadcasting information about the victim's status,

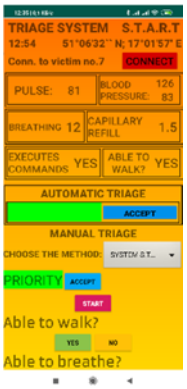

Figure 8: Triage Executive Officers Application, Display Screen, (Burik 2019)

- maintain log for on-site triage activity, stamp in the device memory; time, triage decisions, and life parameters that was the basis for the decision,
- transmit to Forward Medical Commander record with triage results (trainee ID, triage method ID, GPS position, victim's ID, time and triage decision).

The basic requirement for the user interface of Triage Executive Officers application (Fig.8), is to be minimalistic in terms of functionality. Displaying a huge number of different data and information introduces confusion and chaos, which usually is already in excess at the place of the mass casualty accident. Therefore the user interface is simple, transparent and user friendly.

3.2. Forward Medical Commander software

Organisational difficulties of Forward Medical Commander, pertaining predominantly to coordinating actions during mass casualty incidents appears to be largely a result of necessity of two-way cooperation (upwards with Health Service Commander and downwards with Triage Executive Officers), combined with concurrent information processing. The Forward Medical Commander management currently based on paper-used, manual methods of data acquisition.

Preserving mentioned above rules, we introduce Android tablet as smart devices to enhance management process. Proposed software provides the following functionalities:

- enter the trainee ID, his GPS position and triage method ID, once at start of training session,
- maintain log for on-site management activity,
- track the Triage Executive Officer's movement,
- receive from Triage Executive Officers records with triage results (trainee ID, triage method ID, GPS position, victim's ID, time and triage decision),
- present graphically the current triage situation at the place of the mass casualty accident,
- receive from qualified medical staff (working at treatment area located in safe zone, Fig.1) records with re-triage results (staff ID, triage method ID, GPS position, victim's ID, time and triage decision),
- present graphically the current triage situation at the treatment area located in safe zone,
- monitor on-line, the broadcasted vital signs, and collect it wirelessly for all already triaged/re-triaged victims of accident,
- alert the situation of critical changes in vital signs,
- display charts of vital signs, for chosen, already triaged/re-triaged victims of accident,
- transmit information to Health Service Commander about the number and severity of victims,
- transmit periodically to Health Service Commander an aggregative card of the current state of rescue action and information about resources required,
- receive information from Health Service Commander about the number of available EMTs, destinations and medical facilities.

The user interface of Forward Medical Commander application (FMC) is much more sophisticated than it was with the Triage Executive Officers (TEO) application. This FMC application is an intelligent re-transmitter between the Triage Executive Officers (downwards) and the Health Service Commander (upwards), supported Forward Medical Commander.
This application focuses on triage results, the actual condition of the victims, available rescuers, emergency medical service ambulances, and transporting patients to the medical facilities. That's why its appearance of a desktop, consists of many display screens with graphics, decision buttons and the drop down windows.

4. CONCLUSION

Proposed training system provides a structured, simple and practical approach to triage training, for first response paramedic and emergency medical services personnel, as implementation of procedures of the triaging in mass casualty accidents.
Many of emergency medical staff (EMS) (Wilk 2015, argues that about a third) had no real experience in medical rescue at mass casualty accidents. Those EMS,

who had training the triage procedures as well as those who once had acting during realistic response to mass casualty incidents, (it does not happen often) simply forget required procedures. Maintaining of the trained skills efficiency requires their repetition every now and then.

Presented training system increases trainees competence level in executive as well as control and governance skills.

Triage in mass casualty accident is carried out as team work under high psychological pressure for emergency medical personnel. The mobile devices (Windows notebooks, Android smartphones, and tablets) used in training system are exactly the same as had been used during genuine mass casualty incidents. Triage in real conditions, it's just one more varieties. This significantly reduces the level of stress.

Emerging technologies and their potential application yield new contenders. The stick-on sensor called VitalTag (Dolon 2018) is fixed to a victim's sternum and wirelessly transmit real-time vital sign measurements.

A soft, stick-on patch (DGIST 2017) fixed to a victim's sternum, which collects, analyzes and wirelessly, via Wi-Fi channel, transmits a vital signs to a smartphone.

We should not become complacent with this state of affairs. Our system may not be as poor as some currently used systems (e.g. these using booklets, pencils and cardboard tags), which look almost laughable to our modern information technology perspective, but there is still plenty of room for improvement. We intend to provide this training system for emergency medical staff to test and formulate comments that allow to improve this issue.

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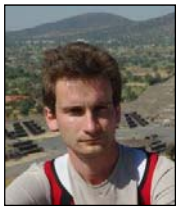

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COST ANALYSIS OF ELECTROCARDIOGRAPHIC SCREENING IN A POPULATION OF NON-COMPETITIVE ATHLETES

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ABSTRACT

To quantify the costs for each situation at risk of sudden death identified by ECG screening using a Telecardiology system.

ECGs received at the Telecardiology Center (Telemedico Srl, Genoa) for non-competitive sports, in the September-November 2018 period were analyzed.

A total of 4360 non- competive athletes (2113 women, 48.5%) were evaluated between the ages of 3 and 40 years (mean ± SD: 17.3 ± 10.6). The average cost per ECG was € 9.2.

An ECG pattern at risk of sudden death has been identified in 319 (7.3%) subjects, respectively 259 (5.9%) at low risk and 60 (1.4%) at medium-high risk.

The cost of ECG screening to identify a risk situation was € 125.74 and rose to € 668.53 in the identification of a medium-high risk situation of sudden death.

The low costs of the ECG performed by Telecardiology justifies its use in the screening of heart disease at risk of sudden death even in subjects practicing non-competitive sports.

Keywords: athlete; electrocardiogram; pre-participation screening; sudden cardiac death

1. INTRODUCTION

It's known that medical evaluation of athletic populations before competition offers the potential to identify asymptomatic athletes with potentially lethal cardiovascular abnormalities and to prevent sudden death through disqualification from competitive sports.

Since 2012, also the practice of a non-competitive sport requires, in Italy, the execution of at least one electrocardiogram (ECG) in order to identify situations at risk of sudden cardiac death.

Telemedicine allows health care professionals to evaluate, diagnose and treat patients at a distance using telecommunications technology. Furthermore its applications are increasingly important in many areas of health education and training.

Among the wide range of medical specialties in which telemedicine has been successfully applied, cardiology can be considered as one of the most important fields of application. Through the transmission of clinical data and the electrocardiogram, telecardiology allows access to a real-time assessment (teleconsultation) without any need to travel for both patient and cardiologist. Telecardiology has three different settings of application. Pre-hospital telecardiology has proved to be useful either in the clinical management of remote patients with acute coronary syndrome or in supporting the decision-making process of general practitioners. In the setting of in-hospital telecardiology, most of the applications refer to real-time echocardiography transmissions between rural small hospitals and tertiary care centres, particularly for the diagnosis or exclusion of congenital heart disease in newborns. Finally, many trials show that post-hospital telecardiology improves outcomes and reduces re-admissions or outpatient contacts in patients with heart failure, arrhythmias or implantable devices.

Recently, telecardiology has been used as a preparticipation screening method for the evaluation of sport subjects.

Purpose of this study was to quantify the costs for each situation at risk of sudden death identified by ECG screening using a Telecardiology system.

2. METHODS

ECGs received at the Telecardiology Center (Telemedico Srl, Genoa) for non-competitive sports, in the September-November 2018 period were analyzed.

2.1. ECG recording and transmission

For each athlete, a 12-lead ECG was recorded using Cardiette Microtel 1 or Cardiette Microtel 2 electrocardiographs at a sampling rate of 500sps and with a frequency response range of 0.05-150Hz. ECGs were recorded by general practitioners, pediatricians, sport physicians, nurses or pharmacists practising all over the Italian territory, trained to correctly using the devices. ECG signals were transmitted in real time over the internet (Cardiette Microtel 1) or by phone (Cardiette Microtel 2) to the Telecardiology Center, where one or more cardiologists are on duty 24 hours a day, as previously reported [1-4].

2.2. ECG measurements

The digitally stored ECGs were processed and analysed using a well-validated ECG computer program (Cardioline Record, IT Medical Devices SpA).

2.3. Exclusion criteria

Pre-existing heart disease and / or intake of any pharmacological substance in the previous 48 hours.

Based on the ECG report, the following conditions were considered:

• subjects at medium-high risk: presenting expressive or suspected ECG patterns for genetically determined ion channelopathies, congenital cardiac conduction abnormalities, idiopathic disease of the ventricular myocardium, acquired cardiomyopathies;

• subjects at low risk: minor conduction disorders, 1st or 2nd degree atrio-ventricular blocks, supraventricular or ventricular extrasystoles;

• normal subjects: no ECG abnormalities outside the normal juvenile pattern.

3. RESULTS

A total of 4360 non- competive athletes (2113 women, 48.5%) were evaluated between the ages of 3 and 40 years (mean ± SD: 17.3 ± 10.6).

An ECG pattern at risk of sudden death has been identified in 319 (7.3%) subjects, respectively 259 (5.9%) at low risk and 60 (1.4%) at medium-high risk. Abnormal ECG patterns are listed in table I. Among subjects with ECG abnormalities at low risk of sudden death, three presenting right bundle branch block resulted affected by arrhythmogenic right ventricle cardiomyopathy and 2 subjects with left bundle branch block by dilated cardiomyopathy. Ionic channel diseases such as Brugada Syndrome or long/short QT syndrome have been found very rarely in our population (only in 0.3% of subject) while the finding of Wolff-Parkinson-White Syndome has been more frequent either in the persistent (Figure 1) or intermittent pattern (Figure 2).

The total cost of the screening was € 40.112. The average cost per ECG was € 9.2±0.9 .

The cost of ECG screening to identify a risk situation was € 125.74 and rose to € 668.53 in the identification of a medium-high risk situation of sudden death.

4. DISCUSSION

A nationwide systematic preparticipation athletic screening was introduced in Italy in 1982. The impact of such a program on prevention of sudden cardiovascular death in competitive athletes was positive and in the following years the mortality trend significantly decreased while remained unchanged the mortality in non-competitive athletes. On this bases a new program regarding non-competitive athletes (the so-called decreto Balduzzi) was applied since 2012.Our study refers to this kind of athlete subjected to ECG screening by means of a Telecardiology system. As expected the most athletes (92.7%) showed a normal ECG pattern. Sixty non-competitive athletes (1.4%) were stopped because of a clear ECG pattern of cardiac disorder with high risk of sudden death, i.e. ECG abnormalities suggestive for ischemic heart disease, Wolff-Parkinson-White Syndome, Brugada Syndrome, Long or Short QT Syndrome. In the remain 5.9% of cases further investigations, such as echocardiography, stress test, magnetic resonance imaging, were necessary to reach a final decision.

Many authors have previously reported that telecardiology is more cost effective than routinary care in different cardiology settings, nevertheless at the state of art does not exist a study about costs of an ECG screening.

The major limitation of this study is that we do not have a control with the cost of ECG performed in a hospital environment. However, we know the patient's participation in health care costs to perform an ECG that is about € 20.

On this basis we suggest ECG screening using a Telecardiology system.

5. CONCLUSIONS

The low costs of the ECG performed by Telecardiology justifies its use in the screening of heart disease at risk of sudden death even in subjects practicing non-competitive sports.

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TABLES

Table 1

Abnormal ECG pattern in 319/4360 Subjects	
Subjects at low risk of S.D., n (%)	**259 (5,9)**
Incomplete/complete RBB, n (%)	123 (2,82)
Incomplete/Complete LBB, n (%)	25 (0,57)
Negative T waves*, n (%)	93 (2.13)
Hypertrophic Cardiomyopathy,n (%)	7 (0.16)
I/II degree AV Block, n (%)	11 (0.25)
Subjects at medium-high risk of S.D., n (%)	**60 (1.4)**
QT interval exceeding age corrected normal limits, n (%)	6 (0,14)
QT interval shorter than age corrected normal limits, n (%)	4 (0,09)
Type I or II Brugada pattern, n (%)	3 (0,07)
Wolf Parkinson White pattern, n (%)	35 (0,80)
Ischemic changes, n (%)	12 (0,28)

S.D.= Sudden Death
* in peripheral leads other than V1 to V3.

FIGURES

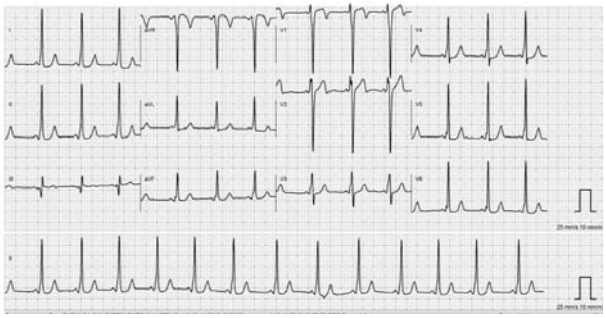

Figure 1: Typical ECG persistent pattern of Wolff-Parkinson-White Syndrome in a 22 years-old subject

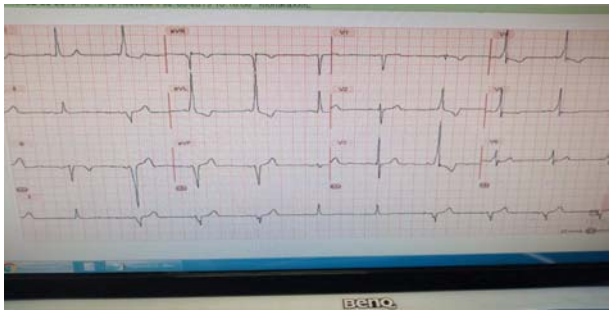

Figure 2: ECG intermittent pattern of Wolff-Parkinson-White Syndrome in a 13 years-old subject

PUPPET MENTORING: A NEW SIMULATION SCENARIO FOR LEARNING SURGICAL ABILITIES

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ABSTRACT

Surgical simulators are now able to teach in a way that the learning curve of young surgeons can progress in a lab faster than when using other teaching models (cadaveric or animal) or real patients. The impact of surgical simulators is confirmed by the fact that, in the US, standardized training courses are needed to acquire the Board of Surgery certification. The virtual simulator set up at the University of Genoa (eLaparo4D) is based on two key features: a convincing haptic feedback and a limited cost. Nevertheless, the main issue of eLaparo4D is the "simplicity" of the virtual scenario. To improve it, a new model of simulation is proposed in this project: the "puppet mentoring", that might enhance its characteristics. The "puppet mentoring" is based on the recording of the movements of the surgeon in the real clinical scenario, that are transferred to the virtual machine. The apprentice, in his learning session, could be led through the operation by the simulator itself, in a scenario and in a way is the same of the real one.

Keywords: Surgical Simulator, Virtual Reality, Training, Haptic Feedback, Validation

1. INTRODUCTION

The European Society for Translational Medicine (EUSTM) defines Translational Medicine (TM) as an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community. The aim of TM is to enhance prevention, diagnosis, and therapy (Cohrs 2015). Translation describes "translating" laboratory results into potential health benefits for patients. Research on medical education contributes to translational science because its results enrich educational settings and improve patient care practices. Simulation-Based Medical Education has demonstrated its role in achieving such results (McGaghie 2012).

In April 2004, the Food & Drug Administration became involved in the discussion about the didactics of young surgeons, demanding the development of a learning program based on simulators that were primarily tested and validated by industry experts, thus sanctioning the start of the "Simulation era" (Roberts 2006; https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-12-2018-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting). Surgery requires learning in a simulated and safe area before operating on the patient (Grantcharov 2008; ACGME Program Requirements for Graduate Medical Education in General Surgery. Revised Common Program Requirements effective: July 1, 2016), also to respect ethical and social implications. For these reasons, the Accreditation Council for graduate medical education decided that all accredited facilities for surgical teaching must include simulation (Bjerrum 2017).

At present, many medical training centers are equipped with simulation areas, but there is still significant disagreement about how to develop training programs: efforts are needed to standardize these training paths (Kurashima 2017; Tavakol 2008; Alaker 2016; Kostusiak 2017; Zendejas 2013; Nagendran 2013; Vapenstad 2013). To this purpose, in the United States, standardized training courses (e.g. FLS - Fundamentals of Laparoscopic Surgery) are needed to acquire "American Board of Surgery" certification (Bjerrum 2017). The new Italian medical specialization teaching system was approved in 2017, but the integration of simulation into training programs is not mentioned. Despite this gap, many surgeons are aware that proper simulation training is of mainstream importance for the education of young surgeons: to this purpose, dedicated programs are being set up, but only in a few settings (Stefanidis 2010; Shanmugan 2014). These programs can be supported following two main paths: 1) using devices that are already on the market (the more expensive option) and/or 2) with research projects aiming to develop custom-built surgical simulators (Kowalewski 2017; King 2016; Belykh 2017).

Two main simulator models are currently available: physical and virtual platforms. Physical simulators (box trainers) were the first to be introduced. They are cheap, and the haptic feedback is authentic. They reproduce basic gestures but do not allow to reproduce entire surgical procedures or intraoperative complications. These restrictions have been overcome by the introduction of virtual platforms that allow to simulate, in addition to basic skills, more complex and realistic surgical scenarios (Munz 2004; Mohammadi 2010; Loukas 2012).

Several studies have shown the effectiveness of virtual platforms on surgical training, but their high costs and unrealistic haptic feedback do not allow their diffusion in the departments involved in teaching programs. Haptic feedback is a key feature of a mixed physical/virtual simulator because its realism is essential for the correct learning of laparoscopic gestures. Nevertheless, it is often the most neglected part of the system mostly because of the lack of a suitable algorithm able to estimate the best force feedback during the interaction with virtual organs and tissues.

To improve the surgical training program, a team of general surgeons and engineers of the University of Genoa developed a mixed (virtual/physical reality) robotized surgical simulator (eLaparo4D) focused on two essential features: the lowest possible cost and a realistic haptic feedback (Frascio 2016; Mandolfino 2016; Perino 2015; Sguanci 2015; Sguanci 2014a; Sguanci 2014b). As established by the FDA's protocol, the validation study performed to verify if the simulator was able to discriminate surgical abilities demonstrated that eLaparo4D allowed to differentiate young surgeons (residents with limited surgical experience) from students that had no experience in laparoscopic surgery (Minuto 2018; Stabilini 2013; Fornaro 2009; Fornaro 2008). The eLaparo4D has been patented in 2018.

The main implementation of eLaparo4D, and the focus of this project, is a totally new approach to teach surgical gestures, inspired from what happens in a real surgical setting, where the teaching surgeon "moves" the hands of his apprentice to favor the movements the way he prefers. The "Puppet Mentoring" is a scenario where a virtual machine can record the movements of the surgeons and the assistants in a real surgical operation and is able to reproduce and "induce" them in a simulated environment, driving the young surgeon toward a correct performance of his movements and, finally, of his surgery. Fine motion tracking of each surgical act is possible within a controlled area (the simulated operational scenario) where kinematic and dynamic data of tools, instruments and people involved in the scenario are collected using an IoT (Internet of Things) based low-cost infrastructure.

2. MATERIAL AND METHODS

The eLaparo4D system is composed of hardware and software components that interact to simulate the environment, its physical and visual rendering, and its haptic feedback.

2.1. Software

a. The simulation system. The backend system is based on a server developed with a Node.js application that allows interactions among the visual system, the different components of the hardware and the database containing the user data. The server technology works as a "gate" among all the elements of the system (hardware or software). The user interacts with the system through an web-based real-time user interface based on the Unity multiplatform game engine, a largely used software for videogames and 3D/VR applications development. The use of a web page interface was chosen because of its standardized data exchange and because, being inherently multi-user, it might permit quick interactions with another user or a supervisor (e.g., a tutor).

b. The rendering system. The meshes were shaped, starting from real and artificial data, using 3D Studio Max®, developed by Autodesk© (2016 Autodesk Inc) [30], and then imported in Unity together with texture and UV maps. Finally, different visual effects (e.g., the shader effect) have been added to the meshes in Unity to create deformable objects with the most realistic result possible. Physical modeling was developed using more dynamic parametric protocols to avoid system overloads.

2.2. Hardware

c. The haptic feedback system. The key feature of the simulator is obtained through an innovative device (a robotized simulator of a standard laparoscopic instrument and the endoscopic camera) based on low-cost off-the-shelf electronics (potentiometers, vibrating engines, and other sensors/actuators), connected to three Geomagic Touch® (formerly known as Phantom Omni®) haptic devices, and managed by the Arduino electronic card.

d. The real-time control board. The Arduino card is essential for the real-time control of the realistic simulated scenario; it limits the grip of a forceps when tissue is grabbed, and it allows the vibration of the tissues that are being manipulated or cut to be felt. The three haptic devices are directly connected to the handpieces of the surgical instruments and are used to simulate the resistance of the tissues while moving the instruments or pulling the different tissues and to render limitations from the surrounding structures (e.g., simulating collisions). During the training session, the ELaparo4D hardware interacts with the software component through instruments that are made using real laparoscopic surgery instruments.

2.3. Simulated scenario setting

To improve eLaparo4D's current limits, the idea behind the Puppet Mentoring relies on a preliminary robust analysis of the standardized procedures of competence build-up and skill assessment of those professions that use the virtual simulation as a focal part of their training (e.g. aviation, military, engineering).

A preliminary analysis will include stress-tests and data acquisition of the performances of surgeons during their real surgeries, recording data from both young and experienced operators. An evaluation of the results obtained from the two groups of surgeons will be then performed. The Puppet Mentoring is based on the acquisition of a video stream from a real laparoscopic operation and the synchronized recording of sequence of movements of the hands/upper limb (positions/velocities/accelerations) of both the surgeon and his assistant. This acquisition could be obtained with the use of low-cost miniaturized IMUs - Inertial Measurements Units - embedded/weared into the surgical gowns of the surgeons. On the surgical side, hands gestures, upper and lower limb movements, camera tracking, the forces applied on the instruments and their directions (e.g. the movements in the 3D space: rotation, extraction, insertion of the instruments) will be recorded (allowing to measure the haptic feedback), as well as the position of the patient. These all are the kinematic/dynamic data that will be re-elaborated by the Puppet Mentoring system, and will be added to the eLaparo4D machine. The engineers of the research team will analyze, organize, and build up a software that might fit this entirely new simulating scenario. All the data will be used to reproduce the video and the relative movements of both surgeons and could be replicated on the enhanced Laparo4D platform: the trainees can therefore exercise in the real environment, performing the surgery under the guide of the machine. In this way, the student and/or the resident, grasping the instruments of the simulator that autonomously reproduces the sequence of the real movements performed by the surgeons during their same operation, could be led, as a "puppet", throughout all the phases of the real operation, following on the monitor the real anatomic situation, as seen by the surgeon.

3. DISCUSSION

Over the past several decades, surgical learning has been based on three different models: the traditional triad "see one, do one, teach one", the cadaveric model and the animal one. According to the first method, the young surgeon needs to initially learn from the more experienced colleague's surgical movements, reproduce the same gestures under a gradually decreasing level of supervision, and then teaches them to less experienced trainees: this model has no economic impact, but needs a long time for trainees, especially in complicated and rare operations. The cadaveric and animal models are focused mainly on the acquisition of gestures repetitively performed on human cadavers (in a real, although bloodless, surgical field) and/or live animals (in a surgical field that is similar to that of a human, but with a real hemorrhagic risk). These learning strategies are associated with ethical, legal and economic issues, and are currently not easily available in Italian academic or teaching environments.

The simultaneous upgrade of both technology and surgery has allowed the development of surgical simulators, focused mainly on training the laparoscopic branch of surgery. Simulators allow the basic surgical techniques to be learned in a lab before being transferred to a patient in the operating room, allowing a faster learning for the trainees. The surgical simulators that are currently available on the market are indeed extremely appealing from a graphic point of view, look realistic, but are still far from a real surgical experience. Their major limits are organs reconstruction and virtual anatomy scenario, as well as the haptic feedback that is unreliable. These limits make the virtual simulators closer to an extremely expensive videogame than to a machine that allows the reproduction and the teaching of a real surgical gesture. It should also be added that a virtual machine, without the guide of a tutor, cannot lead an apprentice through the sequence of the many different movements (that could be performed in many correct ways, and in a few wrong ones) that might drive the surgery to its final completion and success. In fact, the virtual reconstruction of the anatomical details, although often enjoyable from a graphic point of view, is still too coarse, simplified and "clean" compared to a real surgical scenario (it is always easy to orientate in the virtual scenario and recognize the different structures, organs, tissues, and to understand the task of the virtual surgery). All the same, the basic surgical gestures (e.g. dissection, traction) are not adequately reproduced yet (e.g. the adhesions between organs simply "disappear" with the simple contact of the virtual dissector).

Further on, the current simulators allow the apprentice to perform his movements in total freedom and autonomy, but do not teach a correct sequence of body movements that are needed in a real surgical environment: this is composed of a patient (in a due position), of three nurses, the anesthesiologists, and two or more surgeons. It is therefore important to teach and tutor the young surgeon in his movements and posture, so that, in a correct sequence of movements, he/she can be able to help and not to hinder the surgeon or the other actors in this setting during the different phases of a surgical procedure.

Using the current simulators, the trainees performing the virtual exercises, could learn and acquire wrong sequences of movements that may not be recognized as wrong or useless by the software, but could be dangerous if carried out on the patient or hinder the movement of the other surgeons during the operation. In fact, one of the major problems for the young surgeons is to learn the ability to calibrate the movements, the force and the manipulation of the different organs and

tissues (e.g. the epiploon, the fatty tissue covering the peritoneal organs can be handled differently from the more delicate tissue of the liver or from the intestine) and the correct sequence of movements to always be synchronized with the other surgeons, especially the use of the non-dominant hand.
The student should be at first guided passively by the simulator in carrying out the correct sequence of movements to be performed for acquiring in a good way all phases of different operations. This is of mainstream importance to avoid the problem of a possible wrong learning due to a lack of guidance regarding the learning of the various phases of the surgical intervention on the simulators. To support this hypothesis, there is the practical and real evidence that in the operating room the hands of the residents are often positioned and corrected by the hands of the experienced surgeon. In this way he actively guides the trainees in the correct movement sequences, in the position of the instruments, in the direction and in the traction force on the organs.
The "puppet mentoring" is a new strategy for teaching and learning surgical gestures, that takes inspiration from what happens in those professions where a simulation has been already proved to be effective (e.g. in aviation), but also from what happens in a driving school, where the apprentice can use the help of the tutor only when and if needed. The main point of this project is not only to allow trainees to learn the basic and advanced skills of surgery, in a setting that is the reproduction of a patient with his real clinical scenario and peculiar characteristics, but also train the experienced surgeons to upgrade their surgery in a clinical and surgical scenario that can be that of a difficult or complicated case, allowing a continuous exchange of clinical situations that are not standardized, because obtained from the recordings of different surgeries. In the immediate future, it can be foreseen that these records can be annotated and classified in order to build an "experiential" virtual knowledge base: a repository that can be used for different purposes. It could be queried and explored by apprentices and by experienced surgeons before a critical surgery, but it can be also mined and used by surgeons and researchers in general to plan new patterns, strategies, or techniques.
To our knowledge, this approach has never been applied to surgical teaching, representing then a completely new field in the development of surgical simulators.
The social impact of this project would be the faster and safer evolution of young surgeons that would be mature and ready for their tasks in a shorter time, and without the need of developing the first part of a learning curve on a real patient, thus allowing also to avoid undesired morbidity and complications, that are costly for the national health system.
The setup of the simulator would lead to further studies aimed at validating it as an effective trainer of surgical abilities, and also at verifying its impact on the learning curve of surgical trainees. If its efficacy will be demonstrated, the possibility of exchanging real surgical cases and scenarios might lead to its possible use in the certification of the Italian Board of Surgery.
The new learning method proposed by the Puppet Mentoring aims to overcome these problems inherent to the graphic and gestural realism and sequence of movements of surgical simulation during the different phases of the operation.
Our multidisciplinary team (composed of medical doctors, engineers, informatics) already realized and validated a low cost virtual surgical simulator, with a reliable haptic feedback (e-Laparo4D, patent pending).
The results of the validation study showed that the simulator still has some flaws.
Mainly there were:
- the lack of real and consistent reality of the all environment, that is limited to a machine that although forged with real surgical instruments is limited because located in a lab;
-the computer graphic although acceptable, is not comparable to the real surgical situation;
- the haptic feedback was not totally satisfactory.
The focal point of this virtual simulation is the possibility that the trainees have to interact with a surgical scenario that not only adheres or reproduces a real one, but is in fact a real clinical situation, with its intraoperative peculiar findings. The machine can then drive the trainees in different ways and at different levels, starting from an almost complete assistance for the younger and less experienced surgeons, to an extremely limited help for the more experienced ones.
Another important feature is that, in the simulated environment, there is the possibility of playing the role of the assistant surgeon at first, and, only after the acquisition of the due skills, switch to the position of the first surgeon. Of notice, as in a real situation, the training includes the necessity of synchronizing with the instruments of the assistant surgeon, or, at the beginning of the training, with the instruments of the first surgeon, a peculiarity that is not reproducible with other virtual simulators, where a trainee works alone. It is also important to mention the opportunity of recording the performances and review them after the practical training, to visualize, focus, and discuss the mistakes that are made during the virtual procedures with the tutors. The Puppet Mentoring thus assumes the ambitious didactic role of implementing the classic triad "see one, do one, teach one" in the new sequence "see one, do a driven (puppeted) one, do a real one, teach one". The main goal of the puppet mentoring is indeed to impact the learning curve of young surgeons, but, with an extended vision, also to allow experienced ones to refine their skills and exchange their most difficult surgical cases. The Puppet mentoring would then allow to learn and improve the basic and advanced surgical skills, acquire the right operative times in synchrony with the movements of the other operators and the various phases of the surgical intervention previously performed by more experienced surgeons. This would allow to learn more realistically the various surgical

techniques and phases of operation in a laboratory on a surgical simulator and not directly on the patient in the operating room.

This would have a positive impact on the safety and benefits in terms of patient's outcome and it also could reduce the learning curves of surgeons, allowing to reduce the overall costs of the operative room.

This new method of surgical training, based on the puppet mentoring, would allow the young surgeons to effectively acquire a faster and progressive autonomy of surgical gestures, in a real surgical scenario, but also in the safety of a lab.

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A MODEL OF PILOT STUDY TO ASSESS THE RISK OF EXPOSURE TO SURGICAL SMOKES FOR OPERATING ROOM PERSONNEL

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ABSTRACT

During the last decades the exposure to surgical smokes has been a long-standing concern both in open and laparoscopic surgery. The aim of this project is to assess the health risks for medical operating room (OR) personnel associated with surgical plumes derived from laparoscopic procedures.

The purpose of this model is to check the correlation between the concentration of toxic elements derived from electrosurgical procedures in the operating setting air and the concentration of the same substances in urine and plasma of patients and operating staff. Moreover, it will be considered also the correlation between toxic concentration and time of exposure.

The results of the study could be relevant to indicate if individual protection devices are efficacious to make the surgical procedure safe for patients and staff or if any adequacy has to be considered.

Some unexpected difficulties delayed the expected results.

Keywords: surgery risk, surgical smoke, laparoscopic procedures, electrosurgical procedures.

INTRODUCTION

Surgical smoke (otherwise known as plume) is a dangerous by-product generated from the use of lasers, electro-surgical pencils, ultrasonic devices, and other surgical energy based devices.

During the last decades the exposure to surgical smokes has been a long-standing concern both in open and laparoscopic surgery (Fornaro 2008; Stabilini 2013; Fornaro 2009).

As surgical energy based instruments cauterize vessels and destroy (vaporize) tissue, fluid, and blood, a gaseous material known as surgical smoke plume is created. It is estimated that approximately 95% of all surgical procedures produce some degree of surgical plume (Ulmer 1998).

Laser and electrosurgical devices commonly used in surgical theatre cause targeted cells to heat to the point of rupturing the cellular membrane and spewing cellular contents into the air as surgical smoke. Through continuous exposure, the inhalation of surgical smoke can be harrmful to the surgical team members.

Estimations note that approximately 350,000 health care workers are exposed to surgical smoke each year, thus creating an unsafe work environment. More than 30 years ago (Tomita 1981) delivered laser energy to 1 gram of tissue: the plume, when inhaled, was shown to be comparable to smoking 3 unfiltered cigarettes.

When using an electrosurgical device on 1 gram of tissue, inhaling the plume was equivalent to smoking 6 unfiltered cigarettes.

Recent evidences show that the chemical component of surgical smoke plume contains over 80 different toxic chemicals and by-products; some which have documented harrmful health effects.

The chemical compounds previously isolated from surgical smokes is listed in Table 1, according to IARC classification.

For example, plumes can also be hazardous to patient during laparoscopy since the contaminants of surgical smoke are absorbed into the patient's vascular system.

Several studies already demonstrated that carboxyhemoglobinaemia and methaemoglobinaemia concentrations rise after a laparoscopic procedure (Wu 1997; Ott 1998; Chowdhury 2011).

The physical components from surgical smoke plume consist of particulate that ranges from <0.01 microns to >200 microns with a majority up to 0.3 to 0.5.

Particles smaller than .3 microns can bypass the lungs normal filtration mechanisms, the mucus secretions and cilia, and deposit in the alveoli, where the exchange of blood/gas takes place.

Furthermore, surgical smoke can cause burning, water eyes, nausea and respiratory problems (Ball 1996) as a physical reaction.

In addition to the health risks, plumes reduce the view in laparoscopic approach, by the nucleation of vapor as they cool, thus potentially increasing the risk for complications (Weld 2007).

The biological matter of the plume contains blood, and potentially infectious viruses and bacteria. Several investigations regarding infectivity, mutagenicity and cytotoxicity of elements generated by energy-based instruments have been performed. Indeed, viable cells (In 2015; Fletcher 2009), viral DNA and RNA, Mycobacterium tuberculosis (Chowdhury 2011), and group-I carcinogens (Pierce 2011) were isolated into surgical smokes.

Case reports mentioned HPV positive tonsillar cancer in two gynecologists that used laser ablation (Rioux 2013), as a cause-effect of professional exposition.
Former studies conducted in the '90s highlighted a connection between laparoscopy and viable cells (Hubens 1996; Cavina 1998; Taffinder 1996), and clarified the phenomenon of port-site metastases, also called “chimney effect”.

AIM OF THE STUDY

The aim of this project is to assess the health risks for medical OR personnel associated with surgical plumes derived from laparoscopic procedures.
The purpose of this model is to check the correlation between the concentration of toxic elements derived from electrosurgical procedures in the operating setting air and the concentration of the same substances in urine and plasma of patients and operating staff. Moreover, it will be considered also the correlation between toxic concentration and time of exposure.
The study design has been submitted to regional ethic committee and regularly approved.
The study received a research fund (FRA) from the University of Genova.

MATERIAL AND METHODS

1) Preoperative phase: sampling of urine and plasma for patient and operating staff.
2) Operative phase: during the laparoscopic intervention the surgical plume is sampled by means of desufflation of the peritoneal cavity and through port aspiration. The sampled smoke is analysed for the presence of chemical substances by spectrofhotometer.
To date, a widely used method for the quali-quantitative characterization of abdominal surgical smoke generated during laparoscopy by electro-cauterization exploits the use of a smokes concentration procedure using SPME (solid phase microextraction) and their analysis by gas chromatography coupled to mass spectrometry, GC-MS (Dobrogowski 2015). Furthermore, the method provides that the "trocar" sampling apparatus can be directly connected to the gas chromatograph enrichment and injection system (Dobrogowski 2014; Balog 2013).
Samples have to be examined also by electron microscopy (Minuto 2018) for the evaluation of viral or bacterial fragments.
3) Post operative phase: a) the urine and plasma sampling will be repeated at 15 minutes after the operation closure and at 30 minutes and 6 hours after the operation closure, for patient and operating staff.
The type of surgical procedures inclosed in the present study will be: appendectomy, colecistectomy, colo-rectal resection.
Operating staff inclosed in the study will be: surgeon and assistant, table nurse and anhestesist. The staff has to wear the normal individual protection devices employed in the opeating room activity.
All the people (patients and staff) gave informed consensus to the study.

RESULTS

Because the method that provides the by "trocar" sampling apparatus directly connected to the gas chromatograph enrichment and injection system was not available, several attempts were made to try to characterize, at least qualitatively, the compounds, more or less toxic, present in surgical smokes.
A first approach consisted in collecting the smokes by “trocar” and bubbling them in different solvents (dichloromethane, hexane) in the attempt to dissolve/concentrate the molecules of potential interest. In any case the GC-MS analysis carried out using gas chromatographic columns with different polarity degree did not allow the detection of any compound.
Assuming that this could be due to a reduced amount of smoke, a dedicated experiment was carried out.
A surgical piece was treated for a long time, under a extractor hood, with electrocautery and the considerable quantity of fumes obtained was bubbled, as previously described, in different solvents; subsequently the GC-MS analysis was carried out using different columns. Also in this case it was not possible to detect any molecule of interest. Considering that the problems could also derive from the use of a not appropriate stationary phase, a dedicated , widely used in the literature, chromatographic gas column was also employed for these purposes (INNOVAX 60m, 0.25mm, 0.5µm).
The lack of signals even after this last attempt, makes us believe that, as initially assumed, failures derive from a lack of sensitivity of the system as a whole, starting from the sampling phase and ending with the analytical one.
It is therefore clear that the analytical problem could be faced and solved only by having available a dedicated instrumentation useful for an adequate sampling and for the subsequent concentration and analysis phases. These different preparation and analysis phases of the sample in fact require an instrumental optimization that allows to carry out the whole procedure in-line in order to allow an adequate concentration of the molecules of interest and therefore their detection and characterization.
For the reason of the failure of the kind of analysis we decided to not evaluate any sample of the blood collection.
The Authors are now looking for a solution of this unexpected difficulty, cooperating with the chemical experts of our team.

DISCUSSION

Previous reviews (Barrett 2003; Mowbray 2013; Fan 2009) detailed the potential hazards of surgical smoke, without distinction between open and laparoscopic procedures.
Theoretically, exposition of operating room (OR) personnel to chemical compounds, viable cells and infective material is inferior during endoscopic surgery then using traditional approach, because gas is contained in a closed cavity.
However, since the gas is not appropriately evacuated, this assumption is not completed correct. In fact, during

laparoscopic procedures or at the real end of them, the peritoneal cavity is desufflated through ports, so gas and toxic and infective elements concentrated in the plumes are released in the operative theatre.

The majority of the papers identify the presence of toxic and infective materials in surgical smoke derived from laparoscopic surgery. However, none of the studies analyzed the concentration of particles in the blood or urine of the OR personnel, indicating that no risk evaluation for OR has been taken into account.

Three of the reviewed studies (Gianella 2015; Dobrogowski 2015; Fitzgerald 2012) did not retrieve toxic substances at relevant quantity and thus even exclude adverse health effects for the OR staff, at least in the short-term period. Only one article (Choi 2015) detects toxic concentrations of the isolated compounds and small particles, even if the Authors clarify that the surgical plumes concentrations decreased once the smoke is desufflated from the peritoneal cavity. Hence, neither this article investigates the real hazard of the surgical smokes during laparoscopy for the OR staff. In these studies, the particle size detected ranged from 0,1 to 25 μm (DesCoteaux 1996; Nezhat 1997). Since the standard surgical mask filters up to 5 μm size particles, this common respiratory protection device turns out to be ineffective for smaller sized particle.

It is clear that electrosurgery produces a quantity of toxic or viable elements in laparoscopic interventions too, even if the literature screened did not assess the actual risk for the OR staff.

Most of the analyzed papers conclude assessing that people working in the OR should be aware of potential long-term health risk related to professional exposure, although there are not strong evidences that surgical smoke could directly cause a malignant pathology. Therefore, a slight possibility of surgical plumes harmful effect does exists and simple measures to minimize this risk should be taken. One article (Fitzgerald 2012), for example, highlights the risk based on the cumulative exposure to these identified elements during a long-lasting professional life. Of note, in order to reduce the OR staff health risk, the Association of periOperative Registered Nurse (AORN) published a panel where simple instructions such as adopting a closed evacuation system and high filtration surgical masks were recommended (30).

For these reasons the authors based the project of the study on analysis of surgical smoke limited to laparoscopic procedures.

To obtain a complete evaluation of the risk exposure the authors planned to analyse the smoke contain and the blood and urine sample of patients and of operating room personnel: surgeon, anesthesist and nurse. However, due to the difficulties occurred during the sampling of the smoke, the amount of toxic concentration resulted inconsistent for the sensibility of the spectrophotometer analysis.

CONCLUSION

The authors as previously described encountered unexpected difficulties that have been described.

Despite a consistent body of literature support that electrosurgical devices release toxic chemical products free viable cells and viral components into surgical smokes, but their potential long-term toxic effects on the OR staff, the consistency of this presumption has not been demonstrated yet. As medical personnel is repeatedly exposed to surgical plumes of very diverse toxicity, even at very low concentrations of individual components, the risk to the health of the exposed persons may be significant and thus the problem cannot be ignored. We envisage that further focused research on risk assessment and development of safety guidelines will lead to a safer work environment for OR staff. Meanwhile, we recommend the use of simple-to-use advanced protection systems.

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TABLE 1: chemical by-products previously identified in surgical smoke classified according to IARC

Acrolein
Acetonitrile
Acetylene
Acrylonitrile
Benzaldheyde
Benzene
Butadiene
Butene
Carbon Monoxide
Creosols
Ethane
Ethylene
Formaldehyde
Free radicals
Hydrogen cyanide
Isobutene
Methane
Phenol
Propene
Propylene

SERIOUS GAME, LECTURES OR SIMULATION-BASED MASTERY LEARNING COURSE WHICH IS THE BEST METHOD FOR TRAINING STUDENTS ABOUT CARDIAC ARREST MANAGEMENT?

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ABSTRACT

Background and aim: This study aimed to compare a serious game and lectures for the pretraining of medical students before learning about simulation-based management of cardiac arrest.

Methods: Participants were 150 volunteer second-year medical students between April and June 2018 randomly assigned to CPR training using either lectures (n = 75) or a serious game (n = 75). Each participant was evaluated on a scenario of cardiac arrest before and after exposure to the learning methods. The primary outcome measures were the median total training time needed for the student to reach the minimum passing score. This same outcome was also assessed three months later.

Results: The median training time necessary for students to reach the minimum passing score was similar between the two groups (p=0,45). Achieving an appropriate degree of chest compression was the most difficult requirement to fulfill for students in both groups. Singing the refrain of the song "staying alive" significantly increased the number of compressions with the correct rate. Three months later, the median training time decreased significantly in both groups. However, students have remained interested in the serious game for a longer time showing a preference for using this method.

Conclusions: The serious game was not superior to lectures to pretraining medical students in the management of a cardiac arrest.

Keywords: serious game, Cardiac Arrest

1. INTRODUCTION

Simulation training is fundamental to good learning of cardiopulmonary resuscitation (CPR) (Greif 2015; Bhanji 2015), a life-saving technique in the event of cardiac arrest, one of the leading causes of death in the world (Writing Group 2016; Berdowski 2010; Grasner 2010). The Italian Resuscitation Council (ERC) and American Heart Association (AHA) guidelines recommend the use of high-fidelity dummies, simulators, feedback devices and online training courses as resources for teaching and learning CPR (Berdowski 2010; Thorne 2015; O'Leary 2010). Since 2015, several studies have shown that the practice on dummies under the supervision of an instructor is the most effective training mode (Ericsson 2004; Wayne 2006). The training of second-year students at our university includes CPR lectures. The addition of a relevant session before the mastery learning course has been shown to reduce learning times during subsequent laparoscopic simulation training sessions (Rosenthal 2009; Stefanidis 2010) and central venous catheterization training, (Cheung 2016) as well as increasing post-test performance in CPR training (Creutzfeldt 2012; Cook 2012; Boada 2015). Serious games were used for pre-trained medical students, but only one study compared the effectiveness of recorded lessons and serious games before simulation training (Drummond 2017). Serious games promote active learning, which is associated with better learning outcomes in scientific domains, (Freeman 2014) and experiential learning when they include a 3D realistic environment close to real life (Kolb 2005).

To our knowledge, although both lectures and serious games have been used to teach health professionals before simulation training, these have never been compared. The objective of this study was to compare the effectiveness of these two modalities for second-year medical students of preparation before a CPR simulation training session.

2. MATERIALS AND METHODS

A prospective, simulation-based, randomized controlled trial was conducted in the Department of Medicine in the University of Salerno, Campus of Baronissi (Italy).

Participants were second-year medical students from the University of Salerno who volunteered between April 2, 2018, and June 10, 2018. Eligible participants were all students aged 18 or over who had never participated in CPR training. Students were invited to participate directly while attending their regular courses. Informed consent was obtained from all the individual participants included in the study. The demographic data was collected by all the participants at the entrance to the study. The participants were divided into two groups: the "only lessons" and "serious games" groups.

The study design is presented in Fig. 1. Both were developed based on the 2018 ERC Guidelines for CPR and Cardiovascular Emergency (ECC). All participants received the guidelines and followed a theoretical lecture before the training session on manikins.

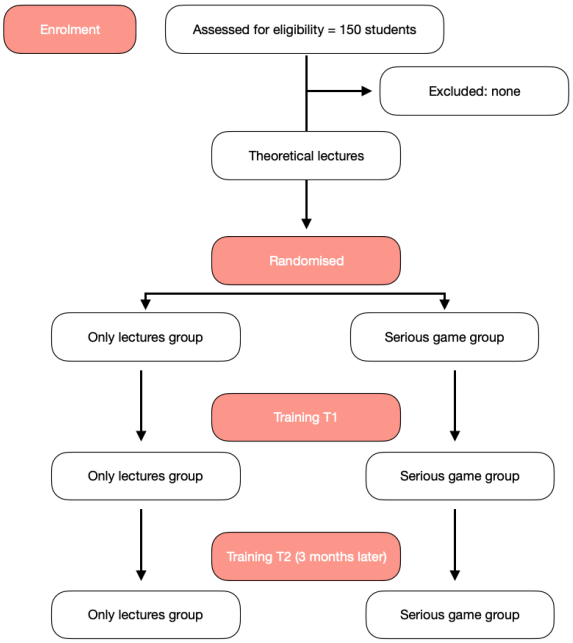

Figure 1: The study design

The serious game was designed to be a CPR self-learning tool for both healthcare professionals and lay people and simulates an urban public space where the player must identify a victim of cardiac arrest and perform CPR maneuvers to help the victim. During the game, the player must identify the victim, reach a correct cardiac arrest diagnosis, and begin CPR as soon as possible (https://youtu.be/wQsG8p3cOSI).
All the students followed a theoretical lesson given by a professor of anesthesia and resuscitation in which the ERC guidelines were illustrated with the support of a power point presentation.
After exposure to serious game and lectures, the participants were individually re-evaluated for their functional performance by five blind examiners in the group assignment who independently assessed the participants actions on a simulated 10-minute cardiac arrest scenario using a CPR training dummy (practical post-test Training T1).
During the three months of training, the participants were individually trained on cardiac arrest management using a low-fidelity dummy (ResusciAnne QCPR). The students were divided into small groups and were trained by instructors in simulation on the execution of: cardiac massage, mouth-to-mouth ventilation and with a face mask and correct use of the defibrillator. Following the principles of mastery learning, they repeated their command on the same scenario as a simulated cardiac arrest until they reached a minimum passing score (Table1)

Action	0 points	1 point	2 points
Recognizes ACC within 30 s	Incompletely or not done	Done	
Calls emergency services within 60s	Incompletely or not done	Done	
Calls for help and sends the facilitator to get AED within 60s	Incompletely or not done	Done	
Percentage of compressions with correct hands position	< 50%	50-75%	> 75%
Percentage of compressions with correct rate (100 to 120 min)	< 50%	50-75%	> 75%
Percentage of compressions with correct depth (5 to 6 cm)	< 50%	50-75%	> 75%
Flow fraction	< 50%	50-75%	> 75%
Automated external defibrillator	- not used - Incorrectly used	correctly used	

Table 1: Checklist used to determine a performance score for ACC management

A single simulated scenario of cardiac arrest was used: for the first assessment before the preliminary session, and all subsequent attempts needed to reach the minimum passing score. Medical students were asked to manage a 50-year-old patient with cardiac arrest. When the student entered the simulation room, the mannequin lay on the floor, unconscious, unresponsive to stimulation and without respiratory effort or pulse. Students had to recognize cardiac arrest, call medical emergency services, ask for help, ask for an external automated defibrillator (AED), provide chest compressions, and give a shock. A facilitator could call emergency medical services or carry an AED if requested and entered the room with the AED only when the participant performed 2 minutes of chest compressions. The scenario ended with the arrival of an emergency team immediately after the first shock or after 4 minutes if the shock was not delivered. The instructors provided a debriefing in the form of a feedback of the terminal directive after each attempt. The instructors examined with the participant all the actions performed in the light of their checklist, describing in detail the correct and incorrect responses. The participants alternated between the simulation and debriefing phases until reaching the minimum passing score. The main result was the average training time required by the students to achieve the minimum score during the practice session. The total training time for each participant, calculated using a stopwatch, corresponds to the full time dedicated to the various attempts and their debriefings. Secondary outcomes included the average student performance score that occurred immediately after pretreatment, and the median performance score assessed after three months of training. Five qualified instructors in simulation (G.S., F.O., D.B., V.M., R.S.) were involved in the evaluation of the participants' actions. Each instructor, blind to the allocation of the participants, independently assessed both the responses of the participants and the sequence of events in real time. The compression score was calculated based on the information provided by the Resusci Anne Skills software (flow fraction, hand

position, speed, and depth of the compressions performed).

3. RESULTS

A total of 150 participants were included in the study and randomly assigned to the group "only lessons" (n = 75) or the "serious game" group (n = 75). All participants completed the process and were included in the data analysis. Most of the participants were women. The primary demographic characteristics were similar in the two groups (Table 2).

Characteristics	Only lessons group	Serious game group
Age,years, mean ± SD	21.6 ± 2.63	21.9 ± 2.63
Female %	59.1	65.2

Table 2: Demographic characteristics of the study population

The training time needed to reach the minimum score was similar between the two groups: 20 min in the "serious game" group (average number of attempts 3) versus 23 min in the group "only lessons" (average number of attempts 4), P = 0.51 (Fig 2).

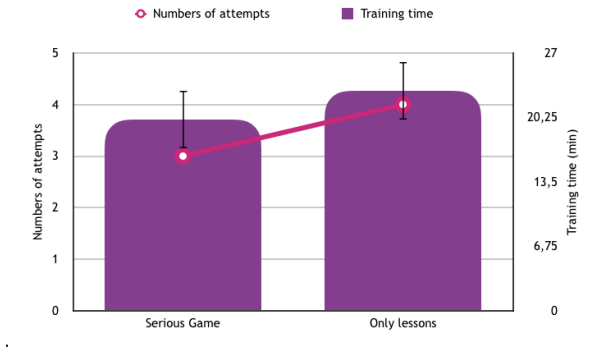

Figure 2: Median training time and median number of attempts necessary for students to reach the minimum passing score during training 1.

Figure 3: Median training time and the median number of attempts necessary for students to reach the minimum passing score during training 2 (Three months later).

Three students in each group failed to get the minimum passing score after six attempts. These six students were unable to provide more than 50% of the compressions with the appropriate depth. Three months later, the median training time decreased significantly in both groups at 12 min in the "serious game" group and 13 min in the group "only lessons" (P = 0.78 between the groups, P <0.001 for the comparison of training 1 and 2 for both groups, Fig. 3).
Two students in the group "only lessons" that failed to reach the minimum passing score due to inappropriate compression depth failed again three months later on the other training. Achieving an appropriate compression depth was the most difficult requirement to fulfill for students in both groups and during both pieces of training (Fig.4). Among all the participants, 28% of students required more than three attempts to reach a correct compression depth.

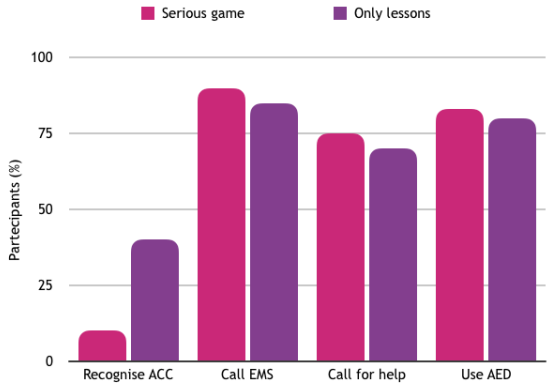

Figure 4: Percentage of participants who correctly performed each action recommended by the European Resuscitation Council guidelines after pretraining and 3 months after the training session. AED, automated external defibrillator; EMS, emergency medical services.

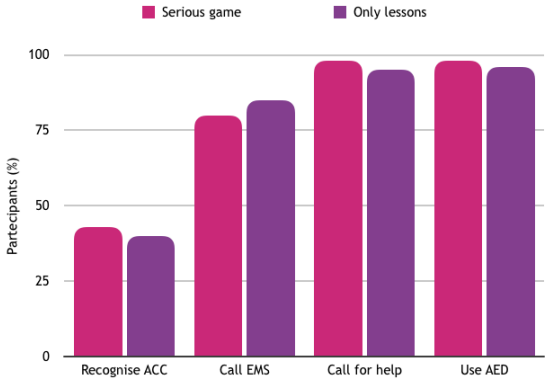

Figure 5: Percentage of participants who correctly performed each action recommended by the European Resuscitation Council guidelines three months after the training session. AED, automated external defibrillator; EMS, emergency medical services.

Finally, singing the refrain of the song "staying alive" significantly increased the number of compressions with the correct rate in both groups($p< 0.05$).

4. DISCUSSION

Although a growing number of theoretical considerations that claim that serious games are more effective than lectures, our study failed to demonstrate a difference in terms of training time between the serious game and a lecture when used as pre-training tools. Our study also revealed that most of our students had difficulty reaching an appropriate depth of chest compression. The most crucial action in CPR procedures to improve patient outcome is high-quality chest compression (Dris 2015; Vadeboncoeur 2014). However, it requires practical sessions for the appropriate acquisition of skills, preferably with the use of a feedback system (Perkins 2015; Kleinman 2015). Cortegiani et al. (Cortegiani 2017), evaluating the training of secondary students on chest compressions with an instructor and a real-time electronic feedback system (Laerdal QCPR), suggested that software feedback can improve the technical acquisition on the ability to perform chest compressions with an adequate recoil compared to training with instructor-based regular feedback. The other studies that used a serious game as a supplement to CPR training found that compliance with the guidelines was slightly better for students who had been trained with a serious game (Creutzfeldt 2012; Cook 2012; Boada 2015; Alam 2016).

However, these studies did not include a group control with another mode of pre-training, nor have they involved learning the mastery of simulation.

We expected students in the serious gaming group to learn faster during the next physical simulation session than their peers who only attended the lecture because it was suggested that serious games that actively involve students in learning activities are more effective than lessons (Garris 2002). Instead, we found that both groups similarly improved their performance. The limited gameplay can explain this: the player does not have to be very busy, as mostly all that was required of the player was a simple mouse click to proceed to the next step. The only real choices made by the player were the position of the hand and the rate of chest compression. These results correspond with those of a meta-analysis, which found that simulation games were more effective than passive instructions when most of the game's instructions were active (Sitzmann 2011). Therefore, student performance in the serious game group could have been better if they had been pretreated with a more interactive serious game.

The development of serious games is more expensive and time-consuming than using methods based on lectures. In the present study, the sequence of CPR maneuvers to be performed during the gestational cardiac arrest was best recognized by the students of the "only lessons" group, although the students in the "serious game" group were more interested in the method.

The two pre-treatment modalities tested in this study, a serious game and a lecture, led to similar learning times during the subsequent practical CPR simulation training. The same level of performance achieved among students at the end of the first learning session of simulation-based mastery was not reflected in training times three months later. This suggests that some elements in the management of cardiac arrests, such as compression depth can be learned only partially by learning simulation-based mastery and supporting the use of CPR feedback devices.

5. CONCLUSIONS

Although in both groups the students improved their CPR performance scores after exposure, we cannot guarantee that, in real life situations, this performance is as effective as that of students who have received direct training as an instructor or have had access to real-time CPR feedback devices. We believe these two ways of self-learning are useful in helping students and can be used as a primary method for CPR training since they are easily accessible from a smartphone and can be integrated into face-to-face training courses for professionals in the health and also for lay rescuers.

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DESIGN AND PRODUCTION OF CUSTOM-MADE PROSTHETIC IMPLANTS IN PECTORAL RECONSTRUCTION IN PATIENTS WITH POLAND SYNDROME USING INTEGRATED CAD / CAM SYSTEMS

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ABSTRACT

1.1. Background
Poland Syndrome is a rare congenital condition characterized by deformities affecting soft and skeletal tissues of thorax and ipsilateral upper limb. Psychophysical integrity, especially for young people, is influenced by early diagnosis and an effective therapeutic strategy. Reconstructive surgery is the gold standard treatment and developing custom-made implants could dramatically change the outcomes for those patients.

1.2. Methods
The study aims to develop an entire production process which starts from morphological data acquisition to definitive implant production through 3D-printing processes. Data were acquired from 10 male patients affected by Poland Syndrome.

1.3. Results
An MRI acquisition protocol was developed, leading to the creation of the first 3D-model and custom-made prototype then evaluated directly on the patient.

1.4. Conclusions
Nowadays, impressive personalized healthcare experiences can be achieved with software and 3D-printing techniques. The advantages of custom-made implants are unquestionable, though a cost-benefit analysis should be evaluated in detail.

2. INTRODUCTION
Poland Syndrome is a rare congenital condition characterized by unilateral deformities affecting soft and skeletal tissues of thorax and ipsilateral upper limb. The main diagnostic criterion is the unilateral, partial or complete, lack of the pectoralis major muscle. Rib cage deformities are often present and vary from mild forms of asymmetric pectus excavatum/carinatum up to the absence of multiple costal arcs and/or complex sternal deformities (Romanini et al., 2016).

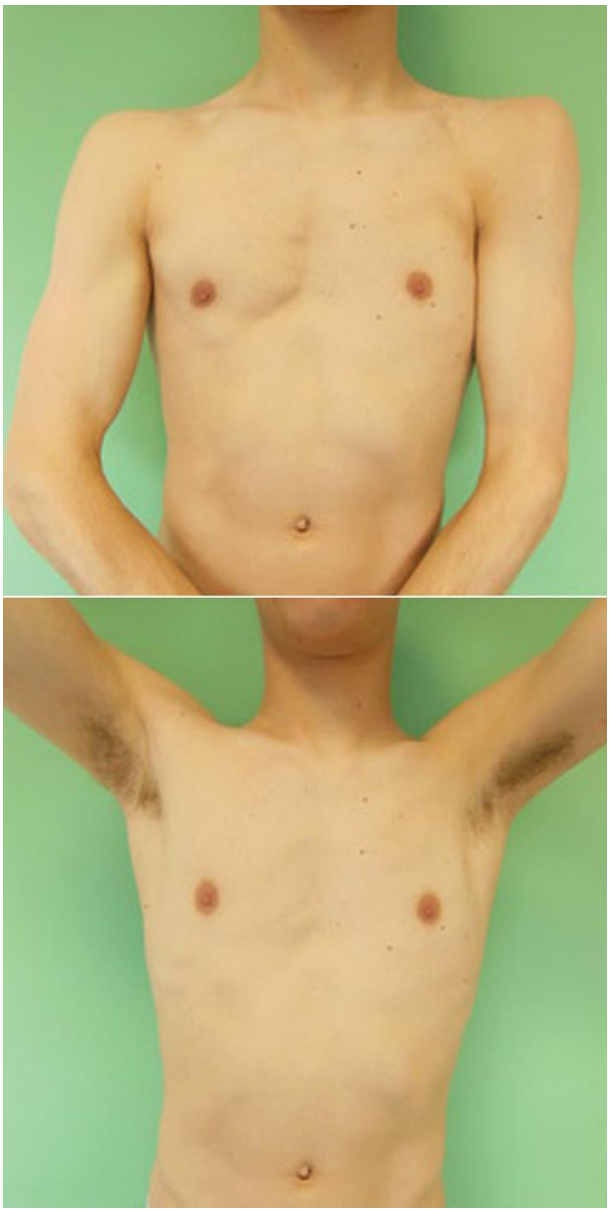

Figure 1: Example of mild Poland Syndrome chest deformity of a young male patient.

Hand and upper limb anomalies generally include clinical presentations of increasing severity from an hypoplastic hand without morphologic and functional anomalies to symbrachydactyly with absent or non-functioning fingers (Catena et al., 2012). Reconstructive thoracic surgery is mandatory when functional impairment or severe chest wall deformities are present. Fortunately, in most cases chest wall deformities are mainly "cosmetic" and characterized by the lack of the anterior axillary pillar, subclavicular hollow and dislocation of the nipple-areola complex due to agenesis of the pectoralis major muscle. Cosmetic and social aspects of this pathology are not negligible. Early diagnosis and timing in therapeutic approach are essential for patient psychophysical integrity, especially for young people (Baldelli et al., 2016; Romanini et al., 2018). Reconstructive surgery with autologous adipose tissue associated or not with a pectoral implant is the least invasive and most suitable surgical choice, especially if performed in teenagers. However, male pectoral implants available on the market do not suit the particular anatomic conditions characterizing Poland Syndrome. This project aims to develop specific custom-made design implants for patients affected by this malformation by processing data acquired by Magnetic Resonance Imaging rather than three-dimensional volume-rendered computed tomographic scans (Chavoin et al., 2018).

3. METHODS

Ten male teenagers with Poland syndrome were selected from patients with no thoracic functional impairment and no functional specialist reconstructive surgery required; in particular, they were also not candidate for reconstruction with pectoral implants available on the market due to their anatomical characteristics. Data regarding patient age and physical characteristics are shown in Table 1.

Table 1: Descriptive data of the 10 patients in the study

	Min	Max	Mean	Std. Deviation
Age (years)	16	40	27	8,804
Height (cm)	170	182	176	3,335
Weight (Kg)	54,0	76,0	68,5	7,2971
BMI	18,7	24,2	21,7	1,8690

An overall view of the presentations of the selected patients, ranked according to their thorax, breast, nipple-areola complex (TBN) classification (Romanini et al., 2016), is shown in the following pie chart (Figure 2).

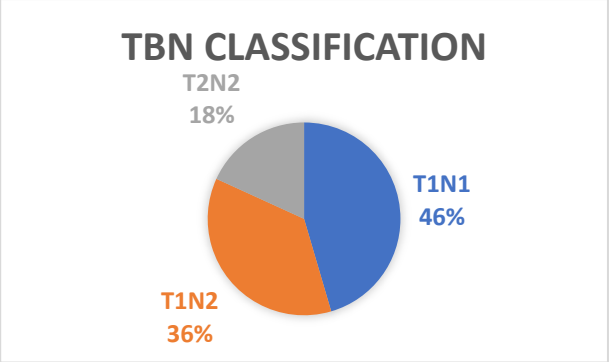

Figure 2: Percentages of TBN ranks of selected patients.

Utilization of CT imaging to acquire the necessary morphoanatomical data was strongly limited by the high amount of radiations to which the patients could be exposed. MRI was the most effective choice for the purpose thanks to high resolution and negligible impact on the patient. An MRI acquisition protocol for the chest was developed in cooperation with the production company and performed at different radiological centres, based on residency of the patients. Finding the best projection to gather most of the morphological data was the main difficulty.

Table 2: Descriptive data and comparison of measures in affected/not-affected chest sides; distances are expressed in cm.

	Min	Max	Mean	Std. Deviation
G-C Distance *Poland side*	14,0	19,5	16,4	1,6964
G-C Distance *not-affected side*	15,5	22,0	19,0	2,0261
S-C Distance *Poland side*	8,5	11,0	9,7	0,9443
S-C Distance *not-affected side*	9,5	12,5	11,0	1,0395
Areola Diameter *Poland side*	1,2	3,0	2,3	0,5190
Areola Diameter *not-affected side*	1,9	3,2	2,6	0,4315

High resolution and a large enough window were necessary to fully acquire data regarding muscle insertion and chest wall and soft tissue morphology, alongside the sequence to correctly discriminate the area of interest from negligible anatomical structures. Patient height and body-type limitations were an exclusion criterion, since MRI acquisition window was limited. 18 channels Siemens body coil excluded patients with a chest which exceeded frame edges. The technology adopted for the production process and data acquirement is the same utilized in several surgery contexts: neurosurgery with polyetheretherketone (PEEK) cranioplasties, mammoplasty with the development and production of silicone implants through dipping techniques. The possibility of thin film deposition with physical vapor deposition (PVD) sputtering technique could be considered as a next step.

4. RESULTS

The complete production process of a custom-made 3D-printed implant was developed, analysing possible benefits on 10 male patients affected by Poland Syndrome with no thoracic functional impairment and no functional specialist reconstructive surgery required. The process can be divided in several steps, from morphological data acquisition to device testing with the patient and subsequent surgical implantation. The first custom-made 3D-models, based on the selected patients, reached the prototype production phase.

4.1. Morphological Data Acquisition

Through a strict collaboration between Radiologists and Clinicians, an MRI acquisition protocol was designed. MRI imaging must include the whole area of the pectoralis major muscle with scans from the upper clavicular origin to the lower abdominal one (clavicle-to-diaphragm). T1 and T2 isotropic sequences are preferred with repetition times (TR) of 500-600ms and 4000ms respectively, and echo times (TE) of 10-15ms and 150ms respectively. Slices have a maximum width of 1mm, with voxel's dimensions of 1mm x 1mm x 1mm. Patient should be supine with arms resting alongside the body to limit respiratory artefacts while right-left axial scanning is performed with 1,5 Tesla magnet. An example is reported in Figure 3.

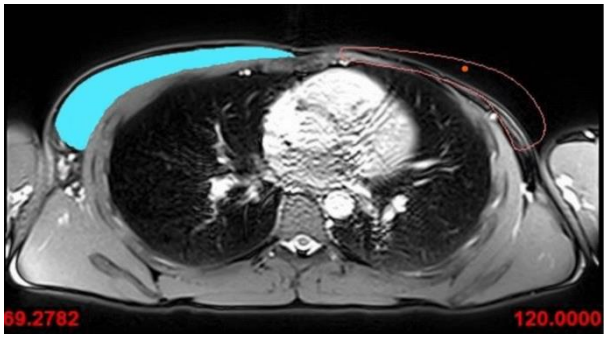

Figure 3: MRI slice with highlight of contralateral pectoralis muscle (blue) and mirror outlining

4.2. Data Elaboration

DICOM files were imported in Mimics Suite® software (Materialise NV, Leuven, Belgium). Segmentation and thresholds to identify tissues of interest were defined (Figure 4).

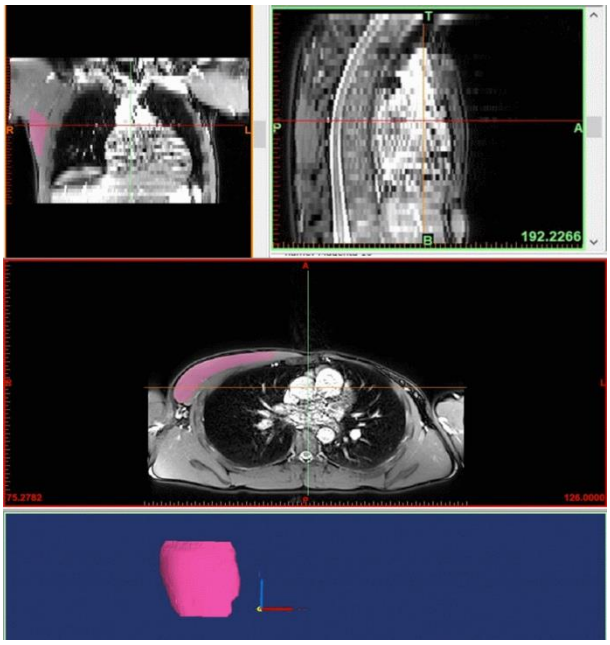

Figure 4: DICOM data elaboration from MRI imaging, identification of pectoralis area (pink highlight) and extrapolation of the pectoralis muscle area

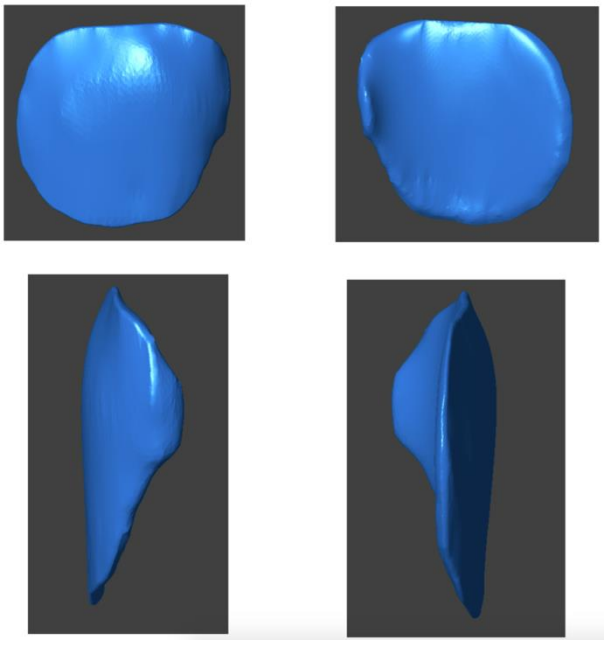

Figure 5: 3D model obtained through Mimics elaboration (standard sections: front, back, right and left)

The procedure must consider pectoralis major muscle asymmetry alongside possible thoracic plan deformations and characteristics of vascular district. Proceeding to 3D-printing requires a stereo lithography interface format file (STL file) adequately corrected to avoid missing edges and/or surfaces overlaps, etc. (Figure 5) A software with haptic functionalities (like Geomacic Freeform® or equivalent open source software) was adopted to transform STL files into CAD format, allowing finite element method (FEM) analysis of the model to test physical properties and performance. 3D modelling capabilities of such software can also be utilized in revision phase by the clinician to better fit the model to the specific patient.

4.3. Prototype Realization

An aluminium mould was designed with CAD software and a first prototype was obtained with technical silicone polymer (Figure 6). The mould consists in two pieces obtained through computer numerical control (CNC) process, specifically treated to achieve an adequate texturization of the implant.

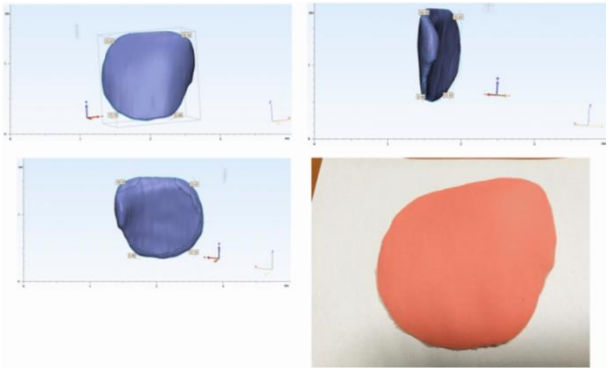

Figure 6: CAD design of mold and implant prototype in technical silicone polymer (pink element)

4.4. 3D Model Check

Technical and clinical checks were performed on the designed model. First step was to scan the prototype and virtually insert it in patients MRI images to check if all the project characteristics have been maintained over the printing process (Figure 7).

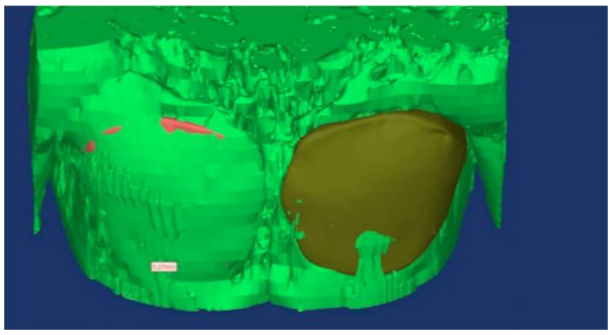

Figure 7: Reconstructed prototype inserted in patient chest MRI

FEM, a numerical method which allows to solve mathematical and physical problems with complex geometry, was performed with medical grade silicone parameters. Static constraints and standard loads can be applied to test physical interactions between implant, skeleton and surrounding tissues. Clinical observations, supported by computer mechanical analyses, are the focal point of model check-up which must be tested directly on the patient (stretchable t-shirt) with particular concern to necessary surgical techniques. An example of technical silicone prototype is reported in Figure 8.

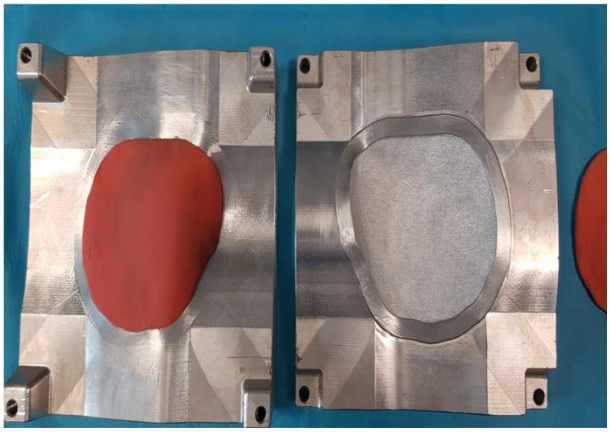

Figure 8: Prototype of the implant realized in technical silicone with aluminium mould

4.5. Implant Production

After revision and acceptation of the 3D-model, definitive long-term implant production initiates. Different techniques can be applied in production process: moulding and dipping were the two techniques considered by production company. Moulding technique is considered the most appropriate choice and medical grade silicone, due to its reliability, biocompatibility, stability over time and extensive utilization in breast implant surgery and production industry was selected. Silicone mechanical characteristics required consist in high flexibility and tear resistance: elastomeric silicone with hardness value of 6-12 Shore, tensile strength range of 3-5 MPa, elongation value of approximately 1075% and tear strength of at least 11 kN/m was selected to achieve high tensile strength and a realistic feel with an adequate density. The two sides of the mould (Figure 8) are then assembled, silicone is treated to remove air and introduced in the mould with a pump to avoid bubble formation (trapped air should escape through specific outlets). Mould can be adapted to offer different types of texturization (Figure 9) through an automatized engraving process operated by a software which considers peeks/indentations ratio and engraving uniformity. Filled mould undergoes a 5 minutes thermal curing process at 150° Celsius, which allows temperature-induced chemical changes in silicone, and

a stabilization phase of 3 hours. Mould is then opened and the silicone implant is removed, removing macroscopic residues.

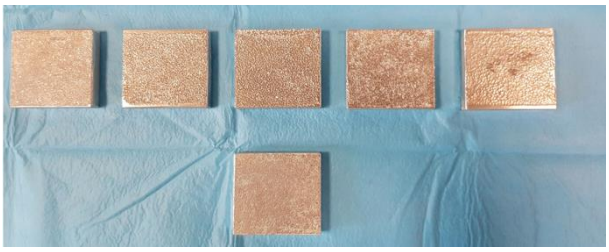

Figure 9: Selection of 6 texture types of mould surface

Newly created implant will be sanitized in specific clean-rooms and washed with pyrogen-free, double distilled water. The most appropriate sterilization process depends on medical silicone type. High performance liquid chromatography (HPLC) and Fourier transform infrared spectroscopy (FTIR) analyses will be performed to verify superficial contamination and eluates alongside tests to check sterilization and possible cyclodextrin residues. Alternatively, a Delrin model can be created from definitive 3D-model and a standard dipping production process can be applied obtaining an implant which is similar to those produced for mammoplasty purposes, with some shape limitations.

5. CONCLUSION

Alongside yearly changes in guide lines and evidence-based medicine, technology and bioengineering evolve to assist medical professionals in obtaining ever better outcomes for patients. 20 years ago, utilizing imaging techniques to obtain a custom-made silicone implant was inconceivable. Even if Poland Syndrome does not necessarily cause significant functional impairment, it has a huge impact on psychophysical integrity, especially for young people. The possibility to create an implant which perfectly fits patient anatomy could substantially improve cosmetic results leading to a better social acceptance, specifically for mild forms. Coating the silicone implants with thin films of several materials with high-biocompatibility is considered a possible next step for the study. A recent study by Chen K. et colleagues analysed the reliability of 3D surface imaging to evaluate breast shape and volume with results similar to MRI in terms of precision and accuracy, thus an application of this technology in data acquirement phase could be considered afterwards. Regarding highly debilitating presentations, different approaches are necessary for either cosmetic and functional purposes: presentations with severe thoracic defects, pectus carinatum and pectus excavatum can determine serious functional impairment and a multidisciplinary surgical equipe is necessary (plastic and reconstructive surgeons, thoracic surgeons) (Romanini et al., 2016).

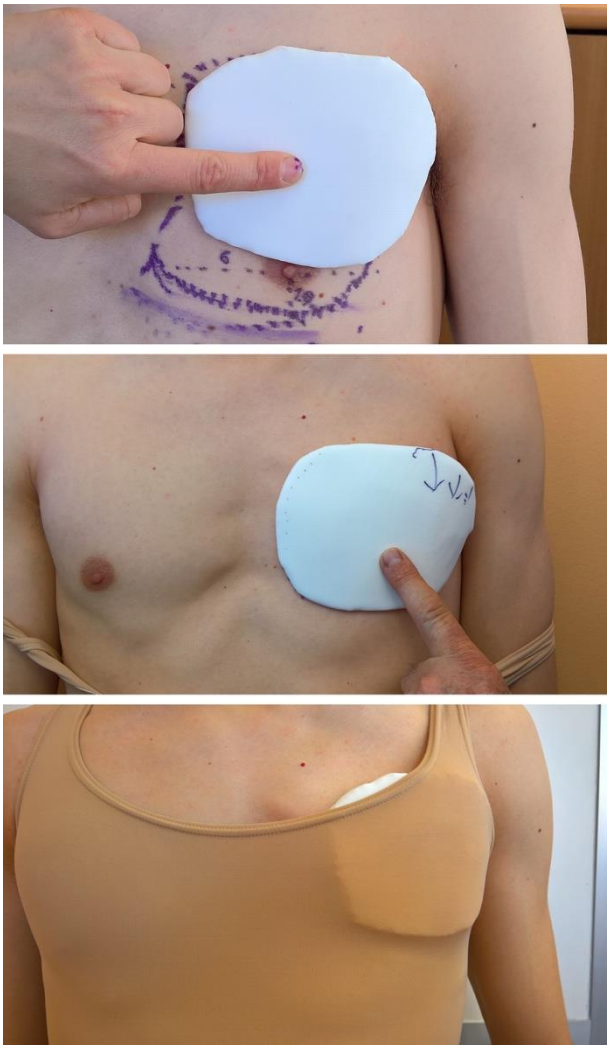

Figure 10: Prototype revision phase on the patient showing (from top to bottom picture) markings on the affected area and confrontation with prototype; clinician observations and device adaptation; implant testing with stretchable t-shirt

Even though 3D-printing of silicone devices is unquestionably promising in this area, a cost-benefit analysis must be considered. Clearly depending on the medical environment, is it public or private, the pursue of custom-made implants still relies on financial capabilities of the patient (in case of private healthcare) or structure (in case of public healthcare). Elaborating different 3D-models, aluminium moulds and/or Delrin models during the project obviously raised costs of the definitive implant. However, general costs and amortisation of the equipment/machines could be cut by the flexibility of the machines themselves, which could be utilized for elaboration, 3D-printing, moulding and dipping in several contexts (neurosurgery, plastic surgery, maxillofacial, etc.). Therefore, the cohort of

people who could benefit from this particular kind of implants is small (especially the mild presentations) and the higher cost could be afforded by a public healthcare system.

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MODEL OF A TRACHEOBRONCHIAL TREE FOR THE TRAINING OF BRONCHOSCOPY EXAMINATIONS

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ABSTRACT

Simulation in medicine has been extensively used for the training of medical students, as well as for learning new procedures or studying complex situations, which need a deep understanding of the clinical case. Specifically, in anesthesia and intensive care, bronchoscopy is a procedure entailing some risks, such as perforation, bleeding or other emergency situations. Therefore, it is necessary to train residents with the use of alternative methods before practicing on patients.

In this context, we combined a physical model of the tracheobronchial tree with a virtual reality-based system to create a low-cost simulator for bronchoscopy training. Specifically, we designed and implemented a system combining a physical and a virtual model of the tracheobronchial tree of a specific patient, starting from his/hers CT image. This system represents an innovative simulator combining visual and haptic feedbacks. Indeed, our prototype is intended to enhance clinicians' skills in a riskless environment.

Keywords: medical simulation, bronchoscopy, 3D modeling, virtual-reality, 3D printing

1. INTRODUCTION

Breathing is one of the main vital functions allowing the human body to bring in oxygen and flush out carbon dioxide. The respiratory tract can be divided into upper and lower airways. The former includes nose, pharynx, and larynx; the latter comprises trachea, bronchi, and lungs. Trachea and bronchi form the tracheobronchial tree which is a tube running from the larynx to the lungs, and diverging in two bronchial tubes that branch off 15-20 times into smaller sections inside the lungs (Castano and Garberi 1983). When diagnostic imaging reveals pathological signs in the tracheobronchial tree, a bronchoscopy is required to navigate the tract. Bronchoscopy is an invasive procedure performed by pneumologists, thoracic surgeons or anesthesiologists (Geraci et al. 2007). Every year, around five hundred thousand of bronchoscopies are required in the United States (Colt, Crawford, and Galbraith III 2001). Nonetheless, such procedure has a mortality rate of 0.1% and can cause medical complications in nearly five out of one hundred procedures (Hehn et al. 2003). In this context, it is important to properly train students during their residency. However, the minimum number of bronchoscopies required to be proficient is not well defined. A study from 1980 indicated one hundred as minimum threshold to confidently perform a bronchoscopy (Faber 1978); nowadays the threshold raised up to five hundred (Ost et al. 2001; Konge et al. 2011). Due to the complexity of the procedure, the high risks involved, and the number of exams required to be proficient, medical simulation is a suitable tool for bronchoscopy training. Historically, bronchoscopy has been trained using animals (Raz et al. 2003; Al-Ramahi et al. 2016) , as well as videos of real exams and simulations (Kastelik et al. 2013; Davoudi and Colt 2009); later on, some mannequins have been developed, even though with big limitations. Specifically, they did not fully resemble a realistic tracheobronchial tree, and moreover, they were too rigid to be safely used with commercial bronchoscopes which are fragile and expensive (Colt, Crawford, and Galbraith III 2001). Currently, three groups of simulators are used: virtual, low-fidelity and computer-based high fidelity simulators (Colt 2013). Virtual simulators lack of the haptic feedback and users cannot practice but merely observe a procedure; low fidelity simulators include animal model navigated with real instruments; computer-based high fidelity are expensive simulators combining visual and haptic feedback for a complete simulation experience (Colt 2013).

2. OBJECTIVE

Our work focuses on the implementation of a tool for the training of pneumologists and anesthesiologists who need to perform bronchoscopy examinations using realistic tools. Specifically, we aimed at combining two technologies commonly used in medical simulation: physical mannequins and virtual reality (VR) environments, to create a realistic simulation experience, which can boost the learning process (Peyre et al. 2006).

Indeed, we realized a 3D model of a tracheobronchial tree, starting from a Computed Tomography (CT) image. Such model was 3D printed and imported into a graphic engine to create a virtual environment. The result is a combination of physical and virtual models communicating together in real time. In other words, information from an endoscopic camera navigating the upper airways model is sent to the VR so as movements of the real camera correspond to movement of the virtual one. The combination of virtual and real let residents learn about the anatomy of the tracheobronchial tree while practicing how to navigate the upper airways in both physiological and pathological conditions. The combined used of VR visualization allows the simulation of pathological conditions in order to improve the training outcome.

3. SYSTEM DEVELOPMENT

3.1. CT image segmentation

Starting from a CT image (DICOM; 0.625 mm/slide; Pitch factor 1.375), we segmented the data to isolate the bronchial tree, using the Hounsfield Unit scale and ITK-Snap software (Yushkevich et al. 2006). Hounsfield Unit is a grayscale proportional to the degree of x-ray attenuation (White and Pharoah 2018; Razi, Niknami, and Ghazani 2014) and it is particularly useful to isolate the upper airways since its lower limit corresponds to the air (Kalender 2011). Segmentation consists in partitioning an image into groups of pixels, in order to locate a specific object (Tan and Ding 2016). In other words, each pixel of an image is labelled according to specific features such as color, gray intensity etc. ITK-Snap is an open source software for the segmentation of medical images through manual and semi-automatic methods. In our study we choose a semi-automatic segmentation, which has reported to reduce user-dependent errors (Yushkevich et al. 2006). In detail, we defined a macro region of interest containing the bronchial tree; subsequently, we selected the Region Competition algorithm of active contour to create probability maps for the segmentation (Zhu and Yuille 1996). Then, we defined the position of the starting points, i.e. spherical seeds which will be merged together during the segmentation. Finally, we set the parameters for algorithm evolution and we started the procedure that was manually stopped once the result was satisfying (Fig. 1).

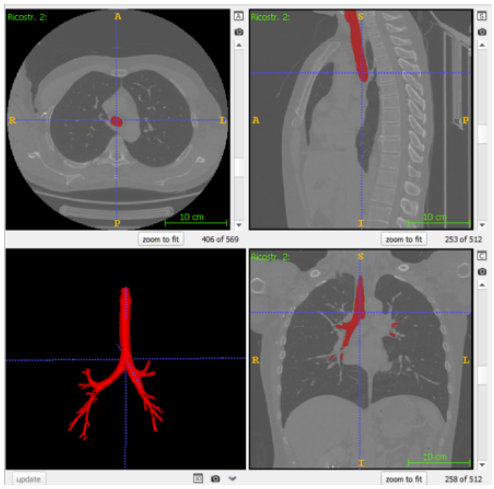

Figure 1. Digital model of the tracheobronchial tree obtained through the CT segmentation process.

3.2. Digital Model

At the end of the segmentation process, the tracheobronchial tree had 120 thousand vertices. Indeed, we reduced the number through a smoothing process, which makes the model both computationally lighter and geometrically more accurate. To do so, we imported the bronchial tree model into MeshLab, and we applied a three iteration Laplacian filter (Cignoni et al. 2008). After the smoothing, the model was imported into Rhinoceros 5© (https://www.rhino3d.com/, Robert McNeel & Associates, USA), a computer-aided design software (CAD) to be prepared for the 3D printing. Particularly, we added a 1-mm thickness and we divided the model into modules (Fig. 2), so that each module of the tracheobronchial tree had two opposite joints in the model reconstruction. This design choice was made for two reasons: firstly, the 3D printer we used had a build limit of 145x145x175ms; most importantly, such division of the model allows for modules substitution. In other words, it is possible to 3D print modules of different pathologies that can be added into the starting model, enhancing its usability. Briefly, each joint is oval-shaped and has either two holes or two nogs. In this way, the union of two intersections forms a linear joint connecting together different anatomical parts (Fig. 2).

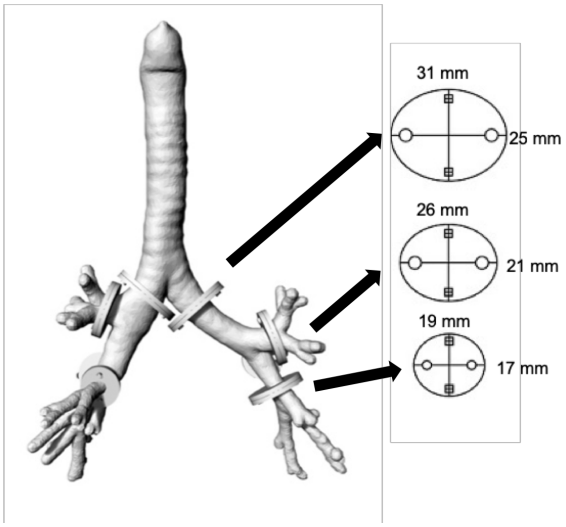

Figure 2. Left: digital model of the tracheobronchial tree divided into modules which are linked together with joints of different dimensions. Right: each circle represents a different measure of joint. Each module of the model has two opposite joints that can be linked to each other to create the tracheobronchial tree.

3.3. Physical Model

Once the model was ready, we printed it using the 3D printer Form 2 (FormLabs, USA), which is a stereolithographic 3D printer with a wide variety of resins. We selected a translucent resin that could be easily navigable by a bronchoscope (Fig. 3).

3.4. Virtual Reality

Afterwards, we imported the 3D model into Unity 3D (Unity Technologies, USA) to create the virtual reality environment for the bronchoscopy examination. Specifically, we inserted a Unity virtual camera to navigate the model, and we set the physical characteristics including:

- texture of the model;
- collisions between the model and the camera;

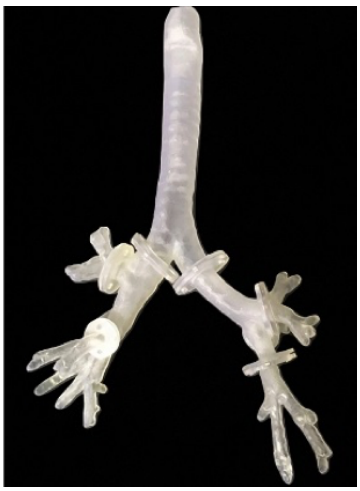

Figure 3. 3D printed model of the tracheobronchial tree

- view-blurring (redout) as a consequence of a collision;
- light settings to simulate the illumination effect of the broncoscope

The result is a realistic representation of the bronchial tree, as shown in Fig. 4.

3.5. Interaction between physical and virtual 3D model

Then, we connected the physical model with the virtual one through a client-server system, so as the virtual camera followed frame-by-frame the movements of the real endoscopic camera. In order to navigate the physical model and to replicate the movements in virtual reality, we solved the correspondence problem between real and virtual environments. In particular, we had to detect the exact position of the bronchoscope in the real model and to transfer this position to the virtual camera. To do so, we equipped the physical model with three Light Emitting Diodes (LEDs, Kingbright, USA; Fig. 5), each one with a different color (red λ=600 nm; orange λ=610 nm; yellow λ=588 nm). The three markers were positioned so as their location, from the point of view of the camera navigating the tree, corresponded to a triangle changing its dimension, according to the camera position. Moreover, the camera could capture different colors, depending on its rotation in the bronchial tree. Video frames from the endoscopic camera were analyzed in Matlab (Mathworks, USA). Specifically, each frame was decomposed into RGB (Red, Green, Blue) components, adding thresholds to separate the background from the light. The result was a binary image with light and background represented as 1 and 0, respectively. After an initial calibration phase, and assuming that the perimeter of the triangle composed of the three LEDs changes linearly with respect to the position of the camera, it was possible to reconstruct the camera location considering the lights position in the frame (Fig. 5).

4. CONCLUSIONS AND FUTURE DEVELOPMENT

This study aimed at the development of the first proof of concept of a bronchoscopy simulator. Starting from a CT image, we realized a low-cost and high-fidelity 3D model of the tracheobronchial tree. Additionally, we 3D printed it into modules which can

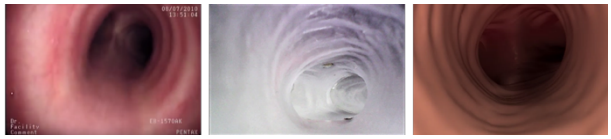

Figure 4. Left: image of a real bronchial tube, obtained with an endoscopic camera. Center: bronchoscope image of the physical model, realized through stereolithography. Right: frame from the virtual bronchoscopy examination.

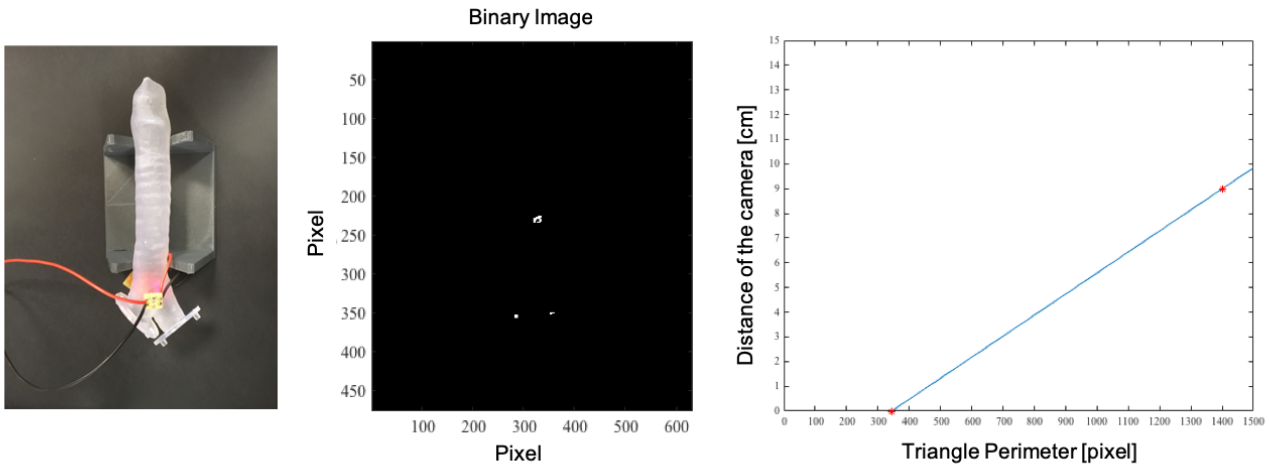

Figure 5: Left: physical Model equipped with LEDS to detect the position of the endoscopic camera. Center: Binary image used to determine the perimeter of the triangle formed by the LEDs, acquired by the camera in the physical model. Right: Relationship between LED-triangle perimeter and position of the endoscopic camera in the physical model.

be substituted to simulate different pathologies. This project may be used in different scenarios:

- to train residents who have to acquire basic skills;
- to simulate complex clinical cases before performing the bronchoscopy on the patient;
- to create a patient-specific tracheobronchial tree that guides the manufacturing of personalized stents.

Also, the way the simulator has been realized can be generalized to other medical procedures such as gastroscopy, colonoscopy, cystoscopy, etc.

The realization of the first prototype allowed us to define critical elements that need to be addressed to make the system more flexible. An important point is the development of new software for camera tracking, in lieu of physical sensors. Specifically, we equipped the physical model with LEDs, in order to solve the correspondence problem between real and virtual environments. Even though this is a robust solution, it has several practical issues such as the presence of hardware components (the LEDs) into the physical models which required calibration. Moreover, we assumed a linear relationship between the perimeters formed by the LEDs and the camera position in the physical model. This could not be valid in general. To overcome these issues, it would be possible to exploit computer vision techniques to extract visual features directly from the images captured by the bronchoscope. In detail, we will consider SURF (Speeded Up Robust Features) and SIFT (Scale Invariant Features Transform) approaches. Once detected the features on a sample of images captured in different physical positions, it is possible to apply a matching algorithm (e.g. the FLANN - Fast Approximate Nearest Neighbor) in order to detect the actual bronchoscope position. Such possibility would make the system completely plug-and-play. In other words, doctors can ask for a tracheobronchial tree, following the CT image, without any technical intervention other than the 3D printing. Also, our study should be replicated using CT images of different pathologies to evaluate the precision of the model in uncommon cases.

In conclusion, with our project we could evaluate the usability of patient-specific organs for endoscopy training. Results are promising and suggest that patient-based simulation should be pursued to make doctors more confident while performing clinical examinations. This would in turn reduce experience-dependent mistakes and error-related healthcare costs.

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IMPLEMENTATION OF A SENSORIZED NEONATAL HEAD MODEL FOR GYNECHOLOGICAL TRAINING

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ABSTRACT

During labor it is very important to know the exact position and orientation of the fetal head when descending the birth canal. Indeed, incorrect evaluations may lead to dangerous situations for both the infant and the mother. Usually, gynecologists and midwives rely on their experience to determine the head position and to evaluate the risk level of each delivery. In this context, it is essential to train new physicians and midwives to correctly manage different types of delivery.

Here, we present the design and implementation of a realistic sensorized neonatal head that could be used on low-cost birth simulators for training and evaluation of residents and midwifery students.

Keywords: medical simulation, delivery, 3D modeling, 3D printing

1. INTRODUCTION

Residents and students estimate the hazard of a labor by looking at the position of the fetus in the birth canal. Emergency cases are treated with instruments such as the forceps and ventouse or through cesarean section. In order to define the fetal position, physicians take advantage of anatomical landmarks in the maternal pelvis and fetal head. In this way, they can establish whether the head of the fetus can descend in the birth canal without any risk. Specifically, they consider the maternal ischial spines and the fontanels in the fetal head (Cunningham et al. 2010). The former determine the interspinous diameter that is the narrowest space of the birth canal; the latter are membranous spaces linking different bones in the head; the anterior fontanel has a lozenge shape, while the posterior is triangular and smaller, compared to the anterior one (Cunningham et al. 2010). Briefly, the labor can be divided in three phases: the first starts when regular contractions occur and ends once the cervix is 10 cm dilated; the second ends after the baby is born; the last phase includes the delivery of the placenta. During the second stage, the baby undergoes strong pressures, i.e. uterine contractions, to descend in the birth canal. In order to cross the interspinous diameter, the head needs to be in the correct position (Cunningham et al. 2010).

Physicians and midwives mainly rely on their previous knowledge and experience to determine the fetal head position. Therefore, it is critical to train student to build a solid background based on evidence (Rubin and Coopland 1970).

Currently, residents can practice only in routine deliveries; however, when they start their practice it is important for them to be able to identify and treat also unusual and risky situations.

In this context, simulation in medicine can be the right tool for the training of doctors and paramedics. Actually, different type of clinical cases can be simulated, and users can learn how to react in specific scenarios (Macedonia, Gherman, and Satin 2003). In order for the simulation to be useful, it is important that the right level of realism is reached (Christou 2010; Witmer and Singer 1998). This would enhance the emotional and psychological involvement, resulting in an optimization of the learning process (Christou 2010; Witmer and Singer 1998). Medical simulators can be divided into three categories (Bradley 2006):

- part-task trainers, i.e. simple body districts lacking any advanced technology, which are used to learn simple tasks such as: intramuscular injections;
- computer-based system used to train decision making through serious games, virtual reality, haptic systems
- integrated simulators: full-body mannequins equipped with sensors and used for multidisciplinary training, i.e. first aid procedures

Each class has positive aspects which can enhance the learning process of students (Stabilini et al. 2013); to this extent, a combination of technologies may be suitable to make medical simulation more efficient. Currently, several commercial products exist. Among the others, it is worth mentioning Noelle (Gaumard Scientific, USA), SimMom (Laerdal, Norway), and SIMone (3b Scientific, Germany). The first two tools are integrated simulators, while SIMone combines a part-task trainer model with hardware and software components. Additionally, some research groups

worked on prototypes of birth simulators aimed at training residents who need to perform pelvic examinations and forceps extractions (Pugh and Youngblood 2002; Dupuis et al. 2006). Despite the fact that they are all useful tools, their high cost and size make them not fully accessible by end users. In this context, we combined low-cost hardware and software to develop a new birth simulator. Specifically, we focused on the fetal head which is the core of our simulator.

2. OBJECTIVE

Recently, our group has developed eBSim, a birth simulator which combines features of part-task trainers, computer-based systems and integrated simulators (Ricci et al. 2015; Paci et al. 2016; Ricci et al. 2019). eBSim incorporates a physical model of the maternal pelvis and fetal head, with a corresponding virtual representation. Specifically, the simulator measures the position, i.e. the orientation of the head with respect to the ischial spines; the level of descent of the infant in the birth canal (station); the touch of the two main fontanels in the fetal head. Physical and virtual models communicate in real time thanks to sensors located in the fetal head and pelvis, so that a movement in the mannequin corresponds to the same movement in its virtual representation. eBSim was designed to be an educational tool for the training and evaluation of students in gynecology and obstetrics. The goal of the project was to realize the proof of concept of a low-cost simulator, which was also portable and plug and play. Moreover, we decided to assess the potentialities of low-cost open source hardware and software. After the realization of the first prototype, we were able to define the major criticisms of the project, defining corrective actions to improve usability of eBSim.

One of the most important features of birth simulators is the fetal head, which has to be realistic in its anatomical markers so that doctors can learn how to take advantage of them during labors. The first prototype we developed included a 3D model of the fetal head which was divided in two hemispheres and 3D printed in ABS material (Acrylonitrile butadiene styrene). This model was difficult to use for efficient training because the material was too rigid to resemble a fetal skin and the precision of the 3D model was far from being a high-fidelity fetal head. Additionally, the model contained slots for sensors which were not optimized. For all these reasons, this project focuses on the realization of a high-fidelity fetal head usable on eBSim. The result is a multi-layers 3D model of the fetal head containing the majority of eBSim's hardware and designed so that the main anatomical landmarks, i.e. sutures and fontanels are clearly detectable on the head's surface.

3. SOLUTION

The implementation of the head can be divided in three phases:

- Hardware advancement
- 3D modelling
- 3D printing

3.1. Hardware advancement

As described below, eBSim determines orientation and descent of the mannequin inside a simulated birth canal; additionally, it detects the user touch of the two fontanels. To do so we selected two types of sensors, preferring devices which were both low-cost and small. Specifically, we chose:

- Inertial Measurement Unit (IMU, InvenSense MPU-6050) to define the position of the head (orientation with respect to the maternal ischial spines);
- Two force sensors (Force Sensing Resistors 0.6") to distinguish the touch of the fontanels;

The IMU is an integrated chip embedding a 3-axis MEMS (Micro Electro-Mechanical Systems) accelerometer and gyroscope converting mechanical oscillations into numerical values through three 16-bit ADC (Analog-to-Digital Converter), one for each x, y, z, direction. Such values represent movements with respect to the reference system, which depends on the initial position of the sensor. A Digital Motion Processor (DMP) combines accelerations and rotations from the three directions into a quaternion. Quaternions were sent in real time via Bluetooth (BLE) to the software (described below) to replicate the head position in the virtual representation. IMU, two force sensors and the Bluetooth modules are located inside the fetal head and connected to an Arduino Uno® Board (Figure 1).

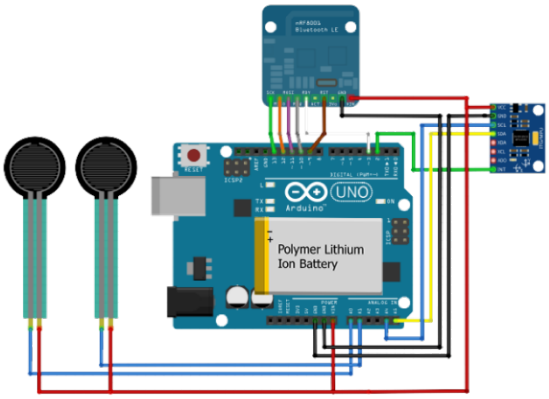

Figure 1. Schematic of the Arduino Uno board. Two force sensors (on the left), a Bluetooth module (top) and an IMU (right). The whole system is powered by a lithium battery.

3.2. 3D Modelling

The first version of the simulator provided a 3D model of the fetal head divided in two hemispheres, which also included slots for all the hardware (Figure 2). However, such model lacked in interlocks and needed an optimization of both the computational complexity and slot locations. Thus, we decided to print the head in two separated layers with different thicknesses and materials. The internal layer needed to be rigid in order to resemble the skull and to enclose and protect the hardware. The external one, instead had to be soft and detailed to mimic the fetal skin covering sutures and fontanels.

The design and the development of the 3D model followed a two stages workflow. In the first stage, we used a free model of a baby head in order to test the idea and the concept. After the first successful test, in which we tried the synchrony between the physical model and its virtual representation, we decided to improve our model and its features reproducing a more accurate and detailed 3D version of the fetal head. We thus acquired the geometry of a mannequin representing a realistic baby. Firstly, we imported the model into 3DS Max® (Autodesk, USA), to separate the head from the body and we applied retopology, a process useful for decreasing the level of the definition without losing quality or detail. Briefly, starting from the first version, we built an identical model with less polygons to make it easily usable in the game engine. Since we had to print two layers, we decided to create a 3D model with no thickness. In this way, it was possible to add thickness in one of the two sides of the interface and thus design the internal or external layer.

The internal layer also required a reorganization of the hardware slots and the addition of an interlock mechanism. Hence, we firstly added a 3 mm thickness to the model to make it rigid enough to contain all the hardware, and with a realistic weight. We decided to locate all the sensors in the left hemisphere and to use the right one as a cover. In detail, the Arduino Uno slot is vertical and merged together with the IMU and Bluetooth slots (Figure 3). Additionally, the internal layer has two openings on its surface, in correspondence of the two fontanels, containing the force sensors. Finally, we added four lock-blocks to the system to join the two hemispheres (Figure 4A).

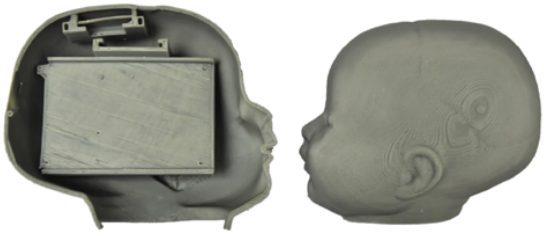

Figure 2. First model of the fetal head printed in ABS material. The right hemisphere contained slots for Arduino, IMU and Bluetooth modules.

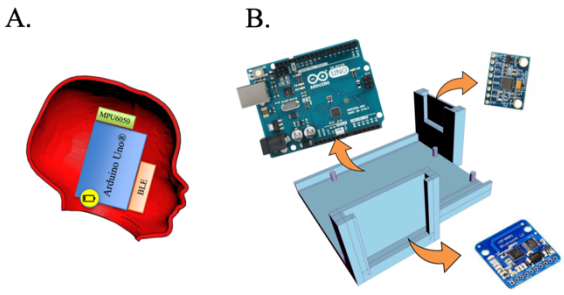

Figure 3. A. Schematic of the right hemisphere of the fetal head. B. 3D model of the hardware slots.

The external layer had been realized following the same steps of the internal one, with the exception of the hardware slots and lock-blocks. The differences of this model with respect to the internal one concern mainly the thickness and the precision of the head. Specifically, the thickness of this layer was lower than 3 mm and it was added from the external side of the interface; also, we increased the number of polygons of this level making it more precise and high-fidelity than the internal layer (Figure 4B). Finally, the two hemispheres were merged together, and this model was imported in Unity platform, to create the virtual scene of the delivery.

3.3. 3D printing

The internal layer was printed in ABS using Makerbot™ Replicator 2X (Makerbot, USA), a Fused Deposition Modeling printer. This material was selected because it is a low-cost polymer which is also resistant with a low weight. The external layer, instead, was printed using SLA (stereolithography) printer (Form2, Formlabs, USA). SLA allows for high resolution printing. Specifically, we used a Flexible Resin (Formlabs, USA), designed for the simulation of soft touch-materials and multi-materials models (http://www.formlabs.com/). After the printing, the two layers were assembled together. Particularly, the two internal hemispheres were joint through the four lock-blocks, while the external layer, having elastic characteristics, adhered to the internal one (Figure 5).

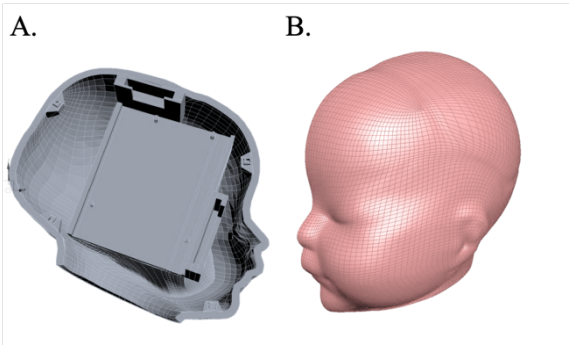

Figure4. A. 3D model of the internal layer of the fetal head. B. external layer, right hemisphere

Figure 5. 3D printing of the fetal head

3.4 Usage

The final version of the head was used for real-time data acquisition of the position and orientation data, as well as for the detection of fontanels touch. Information from the head was sent to a server which shared such data through two different protocols (BLE, websocket) with the clients connected (i.e. desktops, laptops, tablets). In this way, it was possible to replicate the physical behavior inside a virtual representation, in order to give visual feedback to the users.

With such system, the students can have a feedback on what they are doing and thus acquiring skills that they will reuse during their professional career. eBSim was developed with the aim to give students two possibilities: training mode and simulation mode. The former, allows them to learn skills through the virtual representation, the latter instead can be used as a self-evaluable tool which does not allow for the visual feedbak. Furthermore, we implemented an exam mode that instructor can use to objectively tests students (Ricci et al. 2019).

4. CONCLUSIONS AND FUTURE DEVELOPMENT

The goal of the project was to redesign a model of a fetal head, which is a part of eBSim, a low-cost birth simulator for the training and evaluation of gynecologists and obstetricians. Starting from the first prototype, we worked on the 3D head model, optimizing hardware and software. Even though the model has improved considerably compared to the first prototype, a few points still need to be addressed to make the head fully usable by learners and instructors. In detail, the IMU sensor presented some malfunctions in the initialization and determination of the rotation angles. This issue should be deeper investigated, and alternative sensors might be tested, and compared to the current device. Also, the 3D model could be further improved: currently, the head is divided in two symmetric hemispheres; however, such division might be perceived by the user who could take advantage of an improper marker. For this reason, different partitions of the model should be tested; an idea might be to divide each hemisphere in three parts, following the head's sutures or to print the top layer without the hemisphere division so that it wraps the internal layer. Likewise, the interlocks system could be advanced, designing a joint system covering the whole head instead of simple lock blocks. Another important development would be to create a full-body mannequin, rather than the single head. This would make eBSim usable also for the simulation of both natural and breech deliveries, drastically improving its value as an educational tool. Finally, the way we designed our tool gives us the opportunity to be modular and flexible; this means that it would be possible to integrate new components and eventually make the fetal head usable with existing simulators. In particular, the use of different protocols of communication and hardware components can address the interoperability issue with external systems or platforms.

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PHYSICIAN/PATIENT RELATIONSHIP FOLLOWING HOSPITAL DISCHARGE – NEW METHODS OF THERAPEUTIC AND CARE CONTINUITY

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ABSTRACT

Healthcare organization aims to shorten hospitalization times, both to facilitate patient turnover and to avoid the risks of the nosocomial environment. Between March and September 2018, patients that were discharged after hospitalization for scheduled reconstructive breast surgery were given a portable device with the Dr. Link app installed, created to allow real-time communication with physicians. Patients and physicians completed a satisfaction survey on their experience with the use of the device. Analysis shows overall patient satisfaction in terms of improvement in relationships and quality of life. Physicians reported more responsible patient behaviour, better compliance, and earlier treatment of complications. Continuous interactive assistance can improve the discharged patient's quality of life and therapeutic path. However, the device risks becoming a negative tool if the health care professional has not made the proper initial emotional investment in the relationship, delegating the totality of the therapeutic relationship to the tablet.

Keywords: online communication, medical costs, care continuity, humanization

1. INTRODUCTION

In recent years, a number of studies have focused on patient support, which has shifted from the principle of "cure" to that of "care" in an effort to concentrate not only on the disease, but also on the subjective needs of the individual patient.

This approach follows the concept of treating the patient/disease entity as a whole, in line with the new bio-psycho-social model that is currently considered the standard path in health care. Based on this model, the disease is no longer managed as a mere biological entity, but it requires interaction among various professional figures that "cure" every aspect of the patient, from the specific disease to how it affects the patient's quality of life and his/her biological and social environment (Borgna 2017).

This complex interaction involving the biology of the disease, its psychological impact on the patient, and his/her social environment highlights the need to assemble a multidisciplinary team to relieve the negative consequences of the illness as a whole.

Thus, it is within this context that the need for the "humanization" of medicine arises, requiring attention to be focused on the human being throughout each step of his/her treatment. A great deal of attention is therefore paid to the therapeutic strategies as well as to the social, psychological and emotional aspects.

Surgical therapeutic strategies often involve invasive surgical treatments that require a continuous adaptive effort to redefine the relationship between one's body and identity (Baldelli et al. 2016, Casabona et al. 2017).

Hospitalization itself represents, in fact, a further stressful event *per se*, and is often associated with personal discomfort and psychological trauma that might worsen the disease (Hashem et al. 2016). Moreover, separation from one's family and social environment, with its relative emotional and professional ramifications, might significantly burden the course of the scheduled treatments (Lopez et al. 2019, Lund et al. 2014, Rabow et al. 2004).

On the contrary, the current organization of the health system aims at reducing hospitalization as much as possible, promoting patients' turnover (thus allowing more patients to be treated), and decreasing both overall costs and iatrogenic risks resulting in a positive impact in terms of medico-legal controversies (Stabilini et al. 2013).

In this context, it is essential to identify and develop new and more targeted strategies that might improve the interaction between the physician and the patient's environment/family. The effects of these interactions are known to be beneficial during the most critical phases of the disease, and on-going interaction may help prevent and/or allow early identification of psychological complications or iatrogenic morbidity (Epner et al. 2011, Back et al 2009).

Constant interaction between the discharged patient and his/her doctor also leads to an improvement in the quality of their relationship, as per the Italian Medical Ethics Code (2014) and the new Italian law on informed consent and advance directives (law n. 219/17) which places great value on the trust in the medical team involved in the

therapeutic course (Ciliberti and Gorini et al. 2018, Ciliberti and Alfano et al. 2018).
The study presented herein aims at identifying initiatives that could:
- promote strategies focusing on the centrality of the person and therefore maintain his/her personal status, dignity and perception of quality of life;
- develop technical improvements that might encourage continuous monitoring of the patient, even in a domestic environment, allowing for a safe and pain-free course of treatment;
- improve the quality of the relationships among discharged patients, relatives and health professionals.
In particular, the aim of this pilot study is to evaluate whether continuous telematic interaction between health professionals and patients can significantly increase humanization and consequently the quality of the relationship between patients and health care professionals (MacCabe et al. 2018), thereby possibly reducing morbidity and/or medico-legal issues (Franchelli et al. 2018). The study relies on information provided by a single app (Dr. Link), which is given to the patient at the time of his/her discharge from hospital.

2. MATERIALS AND METHODS

Between March and September 2018, 98 consenting patients who were hospitalized for scheduled reconstructive breast surgery were given a portable device (tablet) upon discharge with the Dr. Link app installed. Patients were provided with thorough instructions regarding the use of the app. They were free to use this tool, if and when needed, to communicate with the health care staff in real time. Dr. Link is an app that was created to allow real-time communication between patients and health care professionals by means of a real-time voice call or a personal chat or message. Therapeutic schedules can be set up, and postoperative follow-ups can be scheduled thanks to the creation of reminders. Lastly, it allows the patients to watch training videos for postoperative physical therapy (Tates et al. 2017).
WebRTC secure connection technology provided two-way, physician/patient video communication thus allowing greater human contact as well as the possibility to visualise the patient's sutures.
The device was returned when the patients came for their last postoperative check-up following the removal of the sutures. At that time, patients were asked to fill in a structured, anonymous questionnaire based on 18 questions about the usefulness of the device. An analogous anonymous questionnaire was also given to the health care professionals involved in the Dr. Link project to help understand the impact of the device on the clinical follow-up and on the social relationships between patients and health care professionals.
The results were evaluated and compared to each other
The study was fully approved by the Ethics Committee of the Liguria Region.

3. RESULTS

All 98 (100%) patients (females, mean age: 58 years) completed the structured survey. Education of the population: 35 patients held a degree of any kind, 41 a high-school diploma, 22 a junior high school certificate.
An analysis of the survey answers showed the following:

3.1 Patients' survey results

The instructions and explanations regarding the use of the device and the Dr. Link app were evaluated with regard to the degree of satisfaction and the results were as follows: very satisfied in 48 cases, quite satisfied in 30 cases, satisfied enough in 15 cases and not very satisfied.
The technology itself (confidence with the tablet + use of the app) was considered easy to use by 65 subjects, while 28 patients reported some difficulty only at the beginning, and 5 patients described the technology as "difficult to use".
With respect to the information they received via the Dr. Link system, 24 patients described the instructions as very clear, 28 as clear, 37 as clear enough, 9 as not very clear.
The procedure to be followed for contacting the health care staff was considered very easy in 16 cases, quite easy in 38 cases, easy enough in 42 cases and not very easy in 2.
Thirty-six patients reported a significant improvement in communication between the health care professional and the patient with the use of the device, 21 patients reported sufficient improvement, and 41 patients reported fair improvement.
Significant enhancement in the quality of communication between the health care professional and the patient was reported by 25 patients, good enhancement was reported by 35 patients, adequate enhancement by 28 patients, whereas 10 patients reported only little enhancement.
With regard to the question about whether the patient believes that monitoring constitutes a simple "facilitation" of the physician's professional obligations, 12 respondents answered "very much", 21 "much", 18 "enough" and 47 "a little".
When dealing with the perception of "safety", the device was described as offering a very strong "sense of safety" by 47 patients, a strong "sense of safety" by 49, and a sufficient "sense of safety" by 2.
Overall, 29 patients think that involving other professionals might significantly improve the efficacy of the technology (device + Dr. Link app), 28 thought it might have an impact on the system, and 41 felt it might be of some help in improving the system**.**
Thirty-four patients perceived the whole system as a tool that should "very much" be encouraged, 61 subjects replied it should "definitely" be promoted, and 3 said it should "somewhat" be promoted.
With regard to their postoperative course, 77 patients reported that the system had a positive impact, 1 reported a significant impact, 42 a good impact, 34 a fair impact, whereas 21 patients reported a poor impact.
When asked if they think that the whole system could have an impact on their self-responsibility after surgery, 38

patients answered “yes, very much”, 15 said “much”, 32 replied “enough”, and 13 answered “a little”.
Ninety-three patients ruled out the possibility of any negative effect on the postoperative course with the use of the device, whereas 5 patients answered that the possibility of negative effects was unlikely.
The degree of satisfaction regarding adhesion to the project was considered very high (18 patients), high (15), sufficient (62), little (3).
A large majority of respondents believe that the tablet is useful to ensure continuation of hospital care at home: 42 replied that it was useful and 36 said it was very useful, while 18 patients responded useful enough and 2 responded not very useful.
When asked if they would like to continue using the system in their future treatments, 7 patients answered very much, 28 said much, 51 replied enough, and 12 said a little. When asked if they think that the system might be of some help even in other medical settings, the patients answered: very much in 36 cases, much in 24 cases, while 31 answered enough and 7 patient a little (Tables 1, 2 and 3).

	Increased dialogue		Quality of communication		Support for self-empowerment	
Level of agreement	**Pt (%)**	**MD (%)**	**Pt (%)**	**MD (%)**	**Pt (%)**	**MD (%)**
A little	---	--	10 (10%)	--	13 (13%)	1 (8%)
enough	41 (41%)	--	28 (28%)	--	32 (32%)	2 (17.8%)
much	21 (21%)	12 (100%)	35 (35%)	8 (67%)	15 (15%)	9 (75%)
very much	36 (36%)	--	25 (25%)	4 (33%)	38 (38%	--

	Tool to be promoted		Positive health effects		Contribution to the continuity of care	
Level of agreement	**Pt (%)**	**MD (%)**	**Pt (%)**	**MD (%)**	**Pt (%)**	**MD (%)**
A little	3 (3%)	--	21 (21%)	--	2 (2%)	--
enough	--	--	34 (34%)	2 (17%)	18 (18%)	--
much	61 (61%)	12 (100%)	42 (42%)	9 (75%)	42 (42%)	11 (92%)
very much	34 (34%)	--	1 (1%)	1 (8%)	36 (36%)	1 (8%)

	Satisfaction with tablet use		Will to continue tablet use		Extended use to other areas	
Level of agreement	**Pt (%)**	**MD (%)**	**Pt (%)**	**MD (%)**	**Pt(%)**	**MD (%)**
A little	3 (3%)	--	12 (12%)	1 (8%)	7 (7%)	--
enough	62 (62%)	2 (17%)	51 (51%)	8 (67%)	31 (31%)	2 (17%)
much	15 (15%)	8 (67%)	28 (28%)	2 (17%)	24 (24%)	9 (75%)
very much	18 (18%)	2 (7%)	7 (7%)	1 (8%)	36 (36%)	1 (8%)

3.2 Health care professionals

Twelve health care professionals (4 males, 8 females, all with medical degrees) answered the survey on the clinical impact of the system on the postoperative course of the patients.
All of them declared a significant increase in communication with the patient and an improvement (very much for 4 doctors, much for 8 doctors) in the quality of the communication.
The instructions and explanations regarding the use of the device and the Dr. Link app were considered—very understandable in 1 case, quite understandable in 7, understandable enough in 4.
The technology (confidence with the tablet + use of the app) was considered easily accessible by 11 doctors, while one described it as accessible enough.

All the physicians agreed on the need to extend the use of this technology to other health care professionals (nurses, psychologists, physical therapists, etc.), in order to improve the overall system.
Moreover, when asked for their opinion about the impact of the system on the patients’ postoperative course, 9 physicians reported a strong impact, 1 reported a very strong impact, and 2 reported a good enough impact. All doctors also reported a good impact of the technology on the patient-doctor relationship, and all agreed on the usefulness of the technology and the need to promote and spread it: 9 much; 1 very much; 2 enough.
Concerning the question of whether the new system might have a positive impact on the patient's personal self-responsibility following hospital-discharge, 9 of the physicians answered a great deal, 2 enough and 1 a little.
Almost all of the physicians considered the monitoring system to be very useful in guaranteeing the continuation of hospital care at the patient's home (only 1 answered “quite useful”).
When asked if they would like to continue using the system, 1 physician answered very much, 2 much, 8 enough, 1 a little.
When asked if they think that the system might be of some help even in other medical settings, they answered: 1 very much, 9 much, and 2 enough.
The physicians believe that including other professionals might improve the usefulness of technology (device + Dr. Link app) very much in 2 cases and much in 10 cases. (Tables 4 and 5)

	Exhaustiveness of Information on the system		Initial difficulties		Involving other professionals	
Level of agreement	Pt (%)	MD (%)	Pt (%)	MD (%)	Pt (%)	MD (%)
A little	5 (5%)	--	65 (65%)	11 (92%)	41 (41%)	--
Enough	15 (15%)	4 (33%)	28 (28%)	1 (8%)	28 (28%)	--
much	30 (30%)	7 (58%)	5 (5%)	--	29 (29%)	10 (83%)
Very much	48 (48%)	1 (8%)	--	--	--	2 (17%)

Satisfaction with tablet use			Will to continue tablet use		Extended use to other areas	
Level of agreement	Pt (%)	MD (%)	Pt (%)	MD (%)	Pt (%)	MD (%)
A little	3 (3%)	--	12 (12%)	1 (8%)	--	--
enough	62 (62%)	2 (17%)	51 (51%)	8 (67%)	--	2 (17%)
much	15 (15%)	8 (67%)	28 (28%)	2 (17%)	--	9 (75%)
very much	18 (18%)	2 (17%)	7 (7%)	1 (8%)	--	1 (8%)

4. DISCUSSION

Studies have shown that good communication between health care professionals and patients might result in better clinical outcomes, reduced costs, an overall increase in patient satisfaction, and lower rates of physician burnout (Weng et al. 2011, Boissy et al. 2016). Improving communication is an ethical imperative and requires a multidisciplinary effort, adequate expertise, appropriate training, and the continuous development of new strategies and methods, even from a technological point of view.

An analysis of our results shows that there is overall satisfaction with the Dr. Link system, both by patients and by physicians. The satisfaction would appear to be in terms of an improvement in the doctor/patient relationship and in supporting the clinical course of the postoperative period.

The general view that such a system can improve communication is an important factor in the relationship, particularly in critical situations (Fughelli et al. 2019). In fact, dialogue is key in the care of the patient and implies a form of respect for him/her. Furthermore, dialogue can also prevent, or at least reduce, some types of behaviour that may be harmful to the patient's health.

Undoubtedly, the procedure that in some respects reminds us of online psychotherapy (the possibility to communicate through systems and applications) has some indisputable advantages (American College of Physicians and the Federation of State Medical Boards, 2013).

First of all, it makes access to one's "contact" simpler, even for individuals who would not normally have access (because they live too far away or are often away on business trips).

It also has an emotional advantage, in that it can be used by people who, on account of their personality structure and/or transitory psychopathological conditions, are not very prone to dealing with direct contact. It allows patients to gradually establish a "therapeutic" relationship based on their own needs and at their own pace, all the while respecting their privacy and their own personal characteristics. Furthermore, it also fulfils the need some patients have to stay in touch with the treatment centre because it makes them feel safer and better protected.

Undergoing a mastectomy is a traumatic event in a woman's life and the need for reassurance is a constant that is seen in those who suffer a traumatic event (Rubino et al. 2007). Using the tablet can play a role in the dynamics of de-escalating difficult relationships which may become even more complicated due to the outpouring of anger and irritability into the relationship (Nivoli et al. 2008; Nivoli et al. 2017). The tablet may act as an "emotional buffer" since establishing a space-time distance also creates an emotional distance which allows emotions to be vented without increasing the tension in the relationship. Moreover, the use of the tablet contributes to building and maintaining a relationship of trust with the treatment centre since it provides answers without delays and/or uncertainties about timing. Particularly, the "perception of the availability" of the physician towards the patient constitutes a powerful therapeutic intervention in itself, generating positive effects (Gerretsen and Myers 2008, Dale et al. 2008).

This concept, which aligns with the fundamental ethical principles of care, should be key in the students' training and highlighted in everyday professional practice (Gulino et al. 2018).

In situations that can cause concern, the availability of a tool that allows the patient to interact with the physician promotes the immediate sense of control over the patient's health (Lorettu et al. 2017). Furthermore, this system facilitates timely access by the patient to information provided directly by qualified staff rather than from potentially misleading sources (Ryan et al. 2016).

However, the high number of positive responses, both from patients and doctors, regarding the possibility that telemonitoring promotes self-empowerment suggests that the conscious involvement of the patient not only improves the relationship and the sense of trust towards the healthcare facility and the operators, but also the clinical outcome.

Moreover, the perception of safety related to the use of intelligent devices suggests that these tools are perceived as a way to provide more dedicated and qualified attention to the patient.

The possibility of supporting active involvement by the patient in their home-care can also prevent adverse events after discharge, with an important deflationary role in possible medico-legal disputes.

This consideration is in agreement with data indicating that the majority of patients declare they are satisfied with having participated in the home telemonitoring project. Both patients and physicians express a high degree of agreement with the need for this system as a tool to be promoted in other health sectors as well. This methodology could, in fact, be implemented by adding additional health control parameters that the device would be able to provide doctors.

The benefits that may be had from this type of "connection" between health professionals and patients therefore suggest the opportunity to implement these new information technology (IT) tools in clinical practice (Alkureishi et al. 2016), e.g. in chronic disease (Fornaro et al. 2008, Fornaro et al. 2009).

At the same time, it is essential that the use of these new technologies be supported by clear rules aimed at ensuring

confidentiality of the data, as well as the application of principles of professionalism by the operators in the new setting (American College of Physicians and the Federation of State Medical Boards, 2013).
In particular, increasing use of these tools in clinical practice suggests the need for proper training with regard to the fundamental ethical and deontological principles that have to govern their use, and which must already be provided at medical school (Gulino et al. 2018; Ciliberti et al. 2019).
The higher degree of difficulty the patients reported regarding the use of the device as compared to what was reported by the physicians may be explained by the greater experience and practice the medical staff has with IT tools**.** The risk is that of placing a communicative and empathetic distance between the physician and the patient.
A great deal depends on the initial communication regarding the meaning and functioning of the tablet. Communication must be explicit in stating that the role of the tablet is to add and not to replace. What is said in the initial communication will be decisive in how the patient eventually perceives the tablet.
Moreover, the tablet cannot replace the physician should the patient feel the need to speak to him/her directly, regardless of the option of using the tablet, otherwise there is the risk of feeling abandoned and/or neglected.
It must also be mentioned that there does exist the possibility of developing an addiction because this system has two characteristics that could lead to this occurrence. The first characteristic is reassurance (which can work as a reward circuit in addictions, especially in behavioural addictions). The other is the freedom one has in managing the system which itself has no particular limits except for subjective control that could be conditioned by the continuous (but not useful) need to stay in touch.

5. CONCLUSIONS

An analysis of the data highlights how continuous, interactive assistance by constant monitoring of the post-operative period can improve the patient's therapeutic course, promote the centrality of his/her role, improve the quality of his/her life and develop his/her sense of responsibility in the therapeutic process. Patients feel more looked after and therefore have a higher feeling of safety than in the standard post-discharge period.
In addition to these advantages, such assistance can reduce costs for the person being cared for and for his or her family in terms of unnecessary trips to the hospital.
Finally, as far as the healthcare system is concerned, this interaction and control method leads to results in optimization of the activity and a possible cost-savings, even thanks to the decrease in medico-legal litigation.
The benefits derived from the use of IT tools can be divided into three categories:
- Therapeutic results of the intervention
-Saving of health system resources due to the intervention (direct benefits)
- Changes in the use of resources by patients and family members (indirect benefits)

In conclusion, the tablet can be beneficial if the correct therapeutic value is assigned to it in advance through proper communication, and if its use is subject to monitoring. By linking patient care with organizing visits and check-ups, it responds to the principle of taking care of the patient.
However, it risks becoming a negative tool if the health care professional has not made the proper initial emotional investment in the relationship and has delegated the totality of the therapeutic relationship to the tablet.

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SMART PLATFORM-BASED IOT-MODULES FOR APPLICATIONS IN HEALTH CARE AND REHABILITATION

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ABSTRACT

Embedded systems and the Internet of Things (IoT) enable new procedures, measurement and analysis methods in the field of biomedical systems. The measurement of data, based on electrocardiogram (ECG)-, electromyogram (EMG)- or electroneurogram (ENG)-signals, allows a multitude of new approaches in diagnosis, prevention or rehabilitation. As part of a project for ENG-based control of prostheses, a platform has been designed, called smart modular biosignal acquisition, identification and control system (SMoBAICS), that also uses IoT-devices.

In this paper, different IoT-devices are presented and described. In the context of an analysis of use cases, it becomes clear that the platform represents a toolbox, which provides appropriate modules and module configurations for different requirements. The designed IoT-devices use standard interfaces in order to integrate a specific additional function into the system. In the focus are two microcontroller (mC)-devices with different characteristics and a front-end system that enables the connection of a variety of Force Sensing Resistor (FSR)-sensors. Based on this platform architecture, many applications were presented, and examples were given of how the required functionality for the corresponding application can be achieved with the help of these IoT-systems.

This platform enables a fusion of the various sensor data with the objective of motion identification and prosthesis control based on this by reading out various data (forces, acceleration, ENG-data, etc.) and integrating identification algorithms.

Keywords: Hardware-/Software-Platform, Data-Driven Methods, Modelling, Simulation, Sensor Fusion

1. INTRODUCTION

Embedded systems open new approaches in biotechnology and medical therapy. Based on modelling and simulation methods, biological, physical and technical relationships can be described and verified (Kandel et al., 2000), (Law and Kelton, 2000), (Zeigler et al., 2000), (Klinger, 2014). The integration of hardware and software components offers an smart and application-specific system. The integration of sensors and actuators into an adaptive hardware/software system platform extends the functionality to include the recording of states, events or the execution of actions. In diagnosis, therapy and rehabilitation there are many applications that can support conservative forms of treatment. Continuous data acquisition as well as online- and offline-data processing and, in particular, identification on the basis of correlated sensor information are at the center of interest and represent the essential challenge.

The platform paradigm describes the project-specific adaptation possibilities of a system through a modular and layer-oriented architecture. Changes and adaptations of an existing system are always necessary, for example by changing the interfaces, modifications of the graphical user interface, the number of channels, changes of sensor and actuator types, scaling of sensor and actuator systems and the project-specific processing of data in the broadest sense, which can also manifest itself in a corresponding scaling of the processing power and memory resources. If a system does not satisfy the platform paradigm, the system can in most cases only be used in another application area or the required system parameters can only be adapted by developing a new system. Here, the platform paradigm is to be used both, in the area of hardware domain and in the area of software domain, if the entire system is to satisfy the requirements of a platform. A hardware-focused view of a typical data acquisition platform is shown in Figure 1 in principle.

The SMoBAICS-platform is such a hardware and software platform based on this paradigm, which contains the following functional blocks:

- Identification,
- Data acquisition and stimulation,
- Data processing,
- Data Conditioning,
- Data archiving,
- Data exchange/Connectivity,
- User interface,
- Configuration,

as described in (Klinger, 2016). Using the platform paradigm, the partitioning between hardware- and soft-

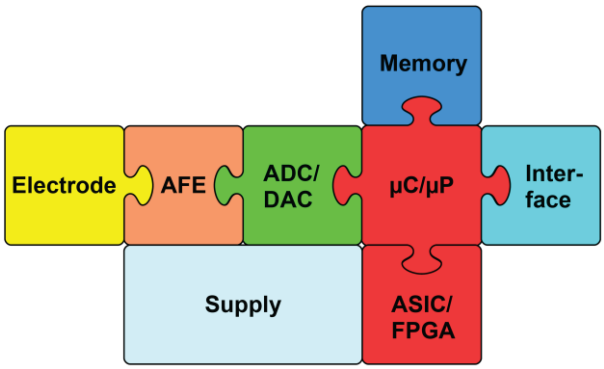


Figure 1: Illustration of the modular strucutre of a platform system

ware-components is adaptable concerning project-specific requirements. Furthermore, the platform characteristic enables a modular architecture with high-level flexibility. The integration of sensors and actors in this adaptive hardware/software-platform increases flexibility and provides a measurement and identification platform for lots of applications. Furthermore, the integration of IoT-devices, based on standard interfaces creates a toolbox that can be used in various projects. In (Klinger and Klauke, 2013), (Klinger, 2014) and (Klinger, 2015) we have presented a first modular platform focused on the acquisition of electromyogram (EMG) and electroneurogram (ENG)-signals and a data-based identification approach. The identification, basis for prosthesis control, requires specific motion data acquired by micro-electro-mechanical systems (MEMS) and mobile control skills which require mobile, smart and intelligent devices. The entire platform is presented schematically in Figure 2. This architecture covers the whole SMoBAICS-platform, including the IoT-module, providing the signal acquisition and the first-level signal processing. The current IoT-extension, designed for SMoBAICS (SMoBAICS-IoT- Device.1 (SID1)) integrates additional sensors, like pedobarographic and MEMS for specific applications. The recording and evaluation of EMG-data, for example, are also currently used in other projects (Ryser et al., 2017), (Wu et al., 2018), (Yang et al., 2018). Here, too, IoT systems represent a central architectural component or could replace parts of the existing architecture. A corresponding platform architecture, which enables better integration of components and reusability of systems, creates a modular character that allows for much more efficient prototyping. We will introduce different types of applications in section 3.

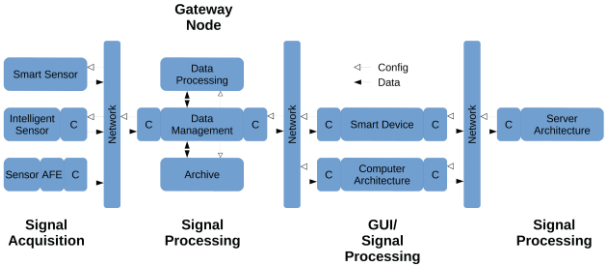


Figure 2: Hardware platform, presenting the modular und service-oriented Architecture (AFE: Analog Front-End, C: Connectivity)

2. IOT-PLATFORM

As described in (Klinger and Klauke, 2013) and (Klinger, 2014), SMoBAICS is a modular system with the objective of ENG-based motion identification and prosthesis control. Based on the acquisition of action potentials via ENG, the information of the peripheral nervous system is used to identify movement patterns. A MEMS used during the mobile operation of the prosthesis control (mobile phase (Klinger and Klauke, 2013)) and/or camera system (learning phase (Klinger and Klauke, 2013)) is necessary to get information about the movement trajectories and about plausibility. To integrate the MEMS, an IoT-module was designed to improve flexibility and to simplify the integration of different sensors using wireless connection. In this paragraph, a general concept of the SID1 is presented. The hardware platform is a system which can be used for multiple applications, is modular and can be used with different types of software. As hardware is less flexible than software and the effort and costs are much higher in terms of redesigning the hardware, the priority of the project was set on the design of a universal hardware platform, which can be used for multiple applications. Each specific application field of the device will require a dedicated software, while the hardware part will stay the same. Moreover, designing, manufacturing and storing only one type of hardware system is much more time, place and cost efficient than preparing and executing the whole process for application specific systems. In order to increase the field of applications, it was decided to split the platform (SID1) into data processing (SID1_UC) and signal acquisition (SID1_FE) parts and to develop an embedded platform with an interchangeable application specific front-end. The platform itself is an autonomous device, equipped with a microcontroller for data processing.

2.1. Machine Learning: Operation Modes

The hardware part of the project includes the partitioning between the different printed circuit board (PCB)s. The architecture of the IoT-device is realized according the platform paradigm, too. The mC-board is designed as a standalone board that can be run independently from the presence of an application specific front-end. Such an assumption forced the designer to include several components on the board. The key constraints for the design are defined by the four basic characteristics of an IoT-system (Klinger, 2016): Connectivity, processing, memory, sensor/actor integration.

1) Microcontroller-Board (SID UC CC2650): The main tasks of this component are data processing, archiving and connectivity, based on Bluetooth Low Energy (BLE). As the system's main task is data acquisition, one of the main requirements was sufficient number of analog inputs and integrated analog-digital converter. Another required feature were an integrated Bluetooth 4.1 transceiver and SPI interface. The microcontroller CC2650 (CC2650F128RGZ) of (Instruments, 2015) was chosen. On this PCB several sensors are integrated,

like a motion sensor with “wake-on-motion”-capability, MPU-9250 (InvenSense, 2014), a microphone, temperature sensor, light sensor and buzzer. Additionally, a SD-card slot is integrated for logging and archiving, and the whole infrastructure for communication (e.g. antenna) is integrated.

2) Microcontroller-board (SID_UC_ESP32): The CC2650 component, selected for the first microprocessor board offers a high level of functionality for the IoT-area and also provides a good combination of sensors in the environment used here. This module is ideal for additional scenarios (see section III) and offers both, the required connectivity and sufficient processor power for processing events and linking multiple sensor values. If the identification functionality, already described in (Klinger, 2015) is to be used in operation mode, greater processor power is required. In order to perform the necessary tests, a second mC-module with a more powerful architecture was designed, the ESP32. This offers additional interfaces for the sensor/actuator connection, e.g. a DAC is integrated. The processor performance is considerably higher, and 2 cores are available for for algorithms that require higher computational power. In addition, this module also provides WLAN functionality, extending the range of applications. Depending on the application, the uC-module SID_UC_CC2650 or the new microprocessor module SID_UC_ESP32 can be used. Figure 3 shows a qualitative comparison of the two microprocessors, related to the key parameters of IoT-systems, introduced in (Klinger, 2016).

3) FrontEnd-Board (SID FE P): The Front End (FE)-board provides the application specific sensor/actor interface, integrating filtering and signal conditioning. It delivers the measurement signal to the mC-board. Due to the platform paradigm, the IoT-system is partitioned into different boards, providing flexibility according the functional characteristics. In the current application, the front-end is used to measure the changes in resistance of the FSR sensors, described in the next paragraph. In Figures 8(a) to 8(d) (see last page), the two PCB designs, the mC-board (SID1_UC_CC2650) and the FrontEnd-board (SID1_FE_P), are shown.

4) Force Sensors: The FSR-sensors are the interface between mechanical pressure and electrical representation. They convert the change of the pressure of the foot into the change of electrical quantities.

FSR show the following advantages: Higher sensitivity than tensometric sensors, possibility of static measurements in contrary to piezoelectric sensors and finally, higher operation frequency than capacitive sensors. Moreover, a relatively low price and the small construction space are additional advantages of resistive sensors. One of the disadvantages of this type of sensors is time drift of resistance, therefore calibration functionality should be available. Using the mC-board, a zero-point calibration can be performed automatically before each use.

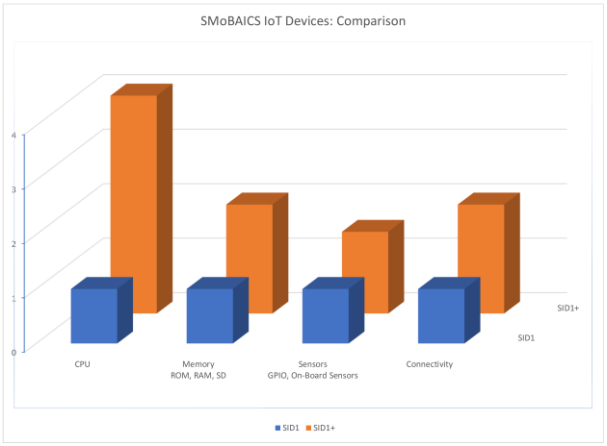


Figure 3: Qualitative comparison of SID_UC

In Figure 4 a typical FSR-sensor is shown, Figure 5 presents the positioning of the three FSR-sensors and of the SID1 sensor inside the sole.

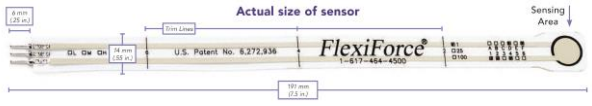


Figure 4: FSR-sensor

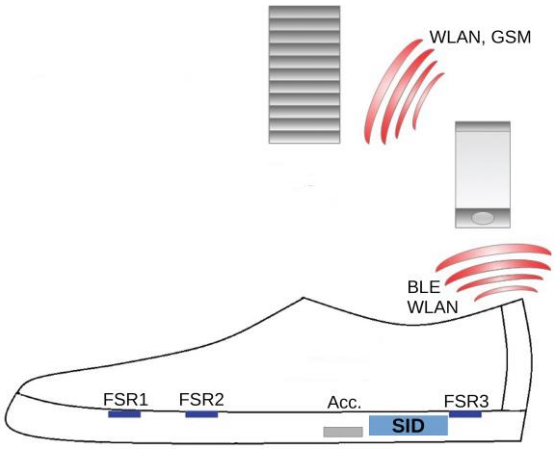


Figure 5: Learning and Operating Mode

2.2. Software

The software platform provides an operating environment, or an operating system under which other smaller applications can be executed. Regarding the platform paradigm, different types of software have to be implemented, embedded software for the mC and software for an Android smartphone to control the device.

Microcontroller-based: Embedded software is necessary for microcontroller operation, e.g. read-out from the sensors, setting the gain, DAC levels and BLE stack. Microcontroller software can be subdivided in three groups: Application software, stack software, both composed with help of an integrated development environment (IDE). CC2650 consists of two different processor cores, an Advanced RISC Machines (ARM)-

M3 (Application) and an ARM-M0, responsible for low level communication. Texas Instruments provides a framework for a double-image architecture software, to be able to update application software independently from the stack software development. The stack software provides basic host roles, like

- Broadcaster: Only advertising, no connection possible
- Observer: Cannot initiate connections
- Peripheral: Connectable advertiser, slave single-link operation
- Central: Master operation, multiple connections

In current project, peripheral role was selected. In order to assure appropriate communication between stack and application, a special ICall framework is provided by the vendor and is a part of the application project. This framework handles the communication between both, the M3 and the M0.

The application software is running on a real time operating system (RTOS) providing services and handling of the different tasks, like BLE communication, sensor data acquisition, data processing and other ser-vices. According to the Bluetooth specification, the de-vice acts as a GATT (Generic Attribute Profile) server.

2) Android-based: A basic Android application for monitoring and configuration of SID1s was developed. The main task is to read-out the motion values from the motion sensor and the force data, provided by the FSR-sensors. Additionally, the mobile phone takes the role of a global system for mobile communications (GSM)-based emergency call device (e.g. fall detection, see Table 1). Currently the application consists of different pages, e.g. for configuration, event display and raw data terminal for debugging. The debugging page shows after initiating the connection, the current FSR values to the user. The user should enter calibration values and confirm by pressing a button. Pressing of the button results in sending updated values to the DAC and amplifiers. When the circuit is calibrated, the measurement can be switched on by enabling notifications and measurement indicator. To stop measurements, measurement indicator, as well as notification handle, switches to zero. In Figure 6 the debugging page is presented.

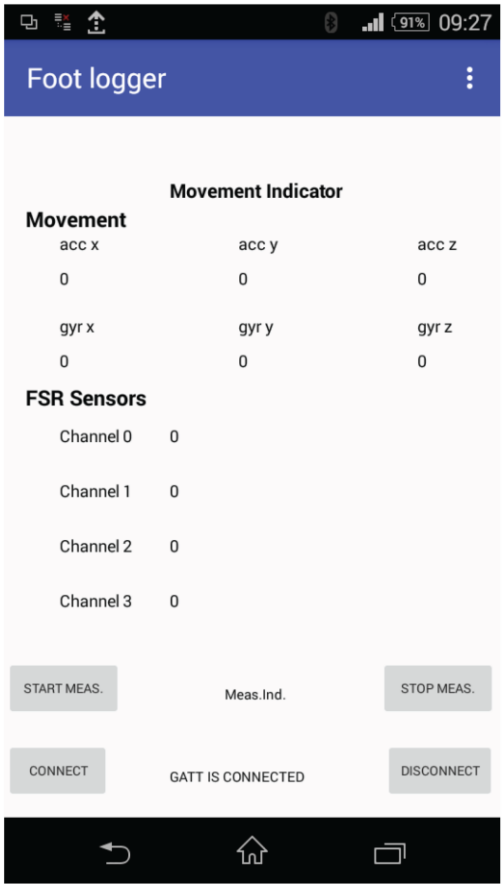


Figure 6: Debuggung page of the Android application

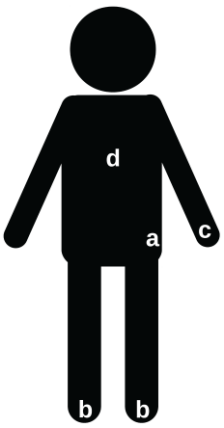


Figure 7: Learning and Operating Mode

3. APPLICATION SCENARIOS

There are a variety of possible scenarios, based on standalone SID-IoT-modules and based on a network of these modules. Therefore, to somehow visualize the range of application, some use cases are presented in Table 1 (see last page) and in Figure 7 the positions of the IoT-modules with regard to the scenarios are shown (see column “position”).

Fall detection, (FD): According to (CDC, 2016), in USA more than 700 000 people a year are hospitalized as a result of fall injury. The motion sensor, integrated on the SID1_UC_CC2650-board, is able to detect abnormal acceleration values in the ground direction and inform emergency department using Bluetooth and mobile phone connectivity. In addition, GPS coordinates from the smartphone can be included in the emergency message. The time of the event can be saved on the SD Card. The system operates in a low power mode until an interrupt from the motion (MPU-9250, see subsection 2.1) is triggered. When no user reaction

is detected, a smartphone notification and alarm are generated.

Pedobarographic front-end (P1): After the smartphone application and platform are initialized, an automatic BLE connection is established. After it is formed, it is possible to manually input configuration data for the platform, e.g. the measurement period for foot sensors and accelerometer. Moreover, it is possible to calibrate the signal path of the force sensors: Offset, gain, filter parameters and filename. When “Initialize”-button in configuration screen is pressed, the calibration values are sent to the platform. Pressing of “Start”-button in the main screen starts acquisition of the data. Pressing “Pause” suspends the acquisition, however, does not close the file. Being in the suspend state and pressing “Pause” again leads to the data acquisition. “Stop”-button pressed any time ends the measurement procedure. Another application scenario might be a stand-alone use of the platform. The measurement results can be saved on the SD Card. The motion sensor is used to switch the system into a low power mode in case of not being used for a certain period of time. The sensor can also switch the system on in case of any movement is detected, it generates a wake-on-motion interrupt. If the values are out of range, in case of need for new calibration values, the buzzer is switched on for 5 seconds. Then, the system needs to be calibrated via Bluetooth, or one of the buttons has to be pressed for 15 seconds to download default calibration coefficients. If the calibration is successful, both LEDs are blinking. Emergency notification functionality seems to be the most promising and could be useful among all use cases. Appropriate frontends and Android software would help to improve the overall functionality.

Gait Evaluation (GE): This scenario focuses on the measurement, archiving and evaluation of pressure, shear and torsion loads on the foot. The gait evaluation helps for precaution and rehabilitation after a fracture, luxation, etc. of the lower extremities. Using this system, a static therapy plan is not necessary. It is rather possible, based on the individual circumstances of the patient, to determine the type and intensity of the phases of stress and the frequency of the resting phases at the progress of the healing process. This also makes it possible, for example, to make a detailed assessment of the rehabilitation progress in relation to the static and dynamic loads and the corresponding accumulated load. This local system enables, in contrast to the fixed system base plate or to alternative camera-supported measuring systems, a mobile application of the system.

The sensors can be used to measure the load data and the local intelligence can also be used for online evaluation and archiving. The feedback about the load case or an achieved limit load can be displayed in the Android App. The simplest case can be an acoustic or optical alarm. In addition, the connection of the embedded system via BLE with a so-called Smart Device, is possible. This connection can be used for data exchange, system configuration and display of current or historical data. Since this is a standard interface, almost any systems can be used as Smart Devices. This also means that the communication path to the attending physician, who can adapt the therapy in knowledge of the data or specific events.

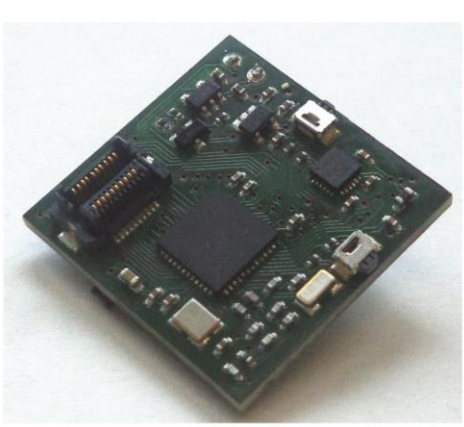
4. SUMMARY AND FURTHER WORK

The implementation of prosthesis control based on ENG-signals, requires the integration of sensors into the overall system. It is helpful to define a hardware-/software-platform that is not only flexible, but also has great expansion potential and good integration capabilities for additional systems and devices, such as sensors and actuators.

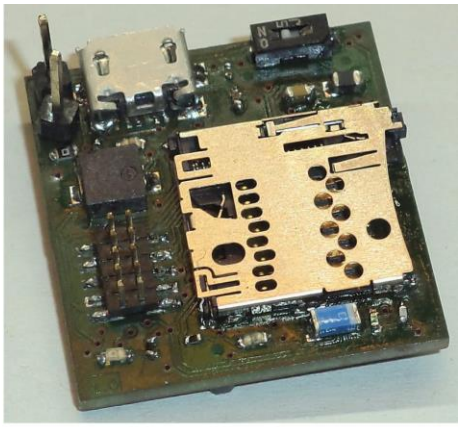
In this paper, such additional devices were presented that use standard interfaces based on the IoT-concept in order to integrate a specific additional function into the system. These are already two mC-modules with different characteristics and a front-end system that enables the connection a variety of FSR sensors. On the basis of this IoT-platform architecture, a large number of applications were presented, and examples were given of how the required functionality for the corresponding application can be achieved with the help of these IoT-devices. The paradigm of platform-based architecture that underlies the approach presented here, provides great flexibility in the acquisition and data-based identification of measured values. The focus on biotechnological applications, especially the focus on EMG- and ENG-signals, enables a multitude of applications in research, therapy and rehabilitation. The design of a second microprocessor module was necessary in order to implement new experiments that will enable identification during mobile operation of the prosthesis control. The new mC-IoT-device can be used to replace the CC2650-based variant.

The further work has the following key aspects:

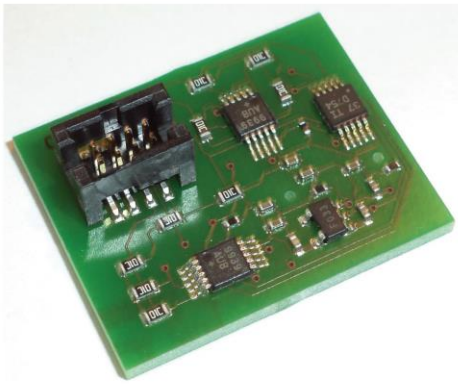
- The peer-to-peer Bluetooth communication has to be replaced by the new mesh functionality of BLE. It allows an even better integration of additional IoT-systems into a so-called body area network (BAN), corresponding to wireless personal area network (WPAN), a wireless LAN protocol.
- Ongoing tests to improve the sensor fusion and to verify additional use cases based on the platform architecture.
- Comparison of different implementations of a local identification method, running on the SMoBAICS-IoTDevice.1 with enhanced performance (SID1+). Analyzation of the power consumption and optimization characteristics, compared to a hardware-based optimization algorithm (Klinger, 2018), should help to pro-vide a better analyzation in the ENG-based motion detection using mobile identification.



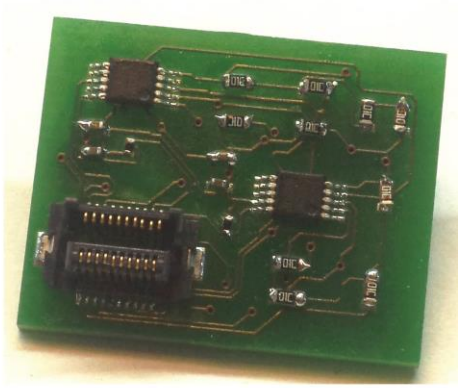
(a) SID1_UC_CC2650 (Front)



(b) μC-modul (SID1_UC_CC2650, Back)



(c) FronEnd-modul (SID1_FE_P, Front)



(d) FrontEnd-modul (SID1_FE_P, Back)

Figure 8: SMoBAICS-IoT-Device.1

Table 1: APPLICATION SCENARIOS

Use Case	ID	Sensor	#Systems	Position in Fig. 7	Android Support	#IO Analog (A) Digital (D)	Description
Fall detection	FD	Motion	1	a	+	-	System detects fall (motion sensor) and sends a notification to a smartphone to trigger an emergency call.
Pedobarography	P1	Pedobarographic	2	b	+	A: 4, D: 8	Acquisition of values of pressures in 3 or 4 points on the feet. Controlled by an Android application.
Pedobarography	P2	Pedobarographic	2	b	-	A: 4, D: 8	As above, but no Android control – results saved on SD Card
Gait Evaluation	GE	Pedobarographic	3	b, a	+	A: 4, D: 8	Acquisition of values of pressures in 3 or 4 points on the feet. Additional motion sensor attached to the belt, providing sensor fusion and gait evaluation. Controlled by an Android application
Interval running	IR	Heart-rate (HR), Pedobarography	3	b, c	+	A: 5, D: 10	System monitors heart-rate of the runner and the time of intervals
Sleep monitoring	SM	Microphone	1	c	+	A: 2, D: 1	For patients with sleep disorders – snoring, bruxism monitoring
Life activity monitoring	LAM	HR + ECG + Blood Pressure + Glucose + Breath	4	a, b, c, d	+	A: 8, D: 10	Live monitoring of life activities and emergency notifications
Prosthesis Control System	PCS	MEMS + Pedobarographic	4	b, c, d	+	A: NN, D: NN	Movement identification and prosthesis control

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ELECTROCHEMOTHERAPY: A novel treatment option for unresectable tumors.

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ABSTRACT

Electrochemotherapy (ECT) is a combined treatment that exploits the administration of chemotherapeutic drugs and cell membrane reversible electroporation. ECT increases elective drug penetration into cytoplasma of treated tissues and allows a tissue sparing treatment. This article describes a single center experience of ECT for the treatment of unresectable cutaneous and subcutaneous tumors. Safety, tolerability and correlation between tumor's characteristics and clinical response were the question of research. On the basis of the study, other important application should start.

Keywords: electrochemotherapy, surgical oncology, melanoma, skin tumor

BACKGROUND

Technology has powerfully entered in all surgical field, in the treatment of functional diseases (Stabilini 2013), of inflammatory diseases (Fornaro 2008, 2009), and in cancer treatment. The present study is related to an application of technology in oncological surgery.

Electrochemotherapy (ECT) is a combined treatment that exploits the administration of chemotherapeutic drugs and cell membrane reversible electroporation. Electroporation, induced by specific electrodes, increases elective drug penetration into cytoplasma of treated tissues, up to 1000 folds than the traditional way of administration. This allows the administration of low dose of chemotherapeutic drug, with consequent less rate of collateral effects. Treatment is "tissue sparing" because just pathological cells in rapid turn-over die for apoptosis due to DNA damage. Instead, surrounding stroma and healthy cells are not affected by the treatment (selective cytotoxicity) (Cadossi 2014).

First phase II clinical trials belong to the nineties (Belehradek 1993), but the entrance of this treatment in clinical practice is quite new. Major evidences for ECT are on plurirecidive or extensive epitheliomas and other Non-Melanoma Skin Cancer (NMSC) (Rotunno 2016); in transit (Quaglino 2008) or at distance (Kunte 2017) cutaneous and subcutaneous metastasis from melanoma; cutaneous metastasis from breast cancer (Campana 2012); cutaneous Kaposi sarcoma (Di Monta 2014). More recent studies are examining the effect of ECT in head and neck neoplasias, both cutaneous one, and mucosal one (Bertino 2016), vulvar relapses of disease (Perrone 2019), bone metastasis (Bianchi 2016), metastatic (Edhemovic 2014) and primitive (Tarantino 2017, 2018) hepatic tumors, locally advanced pancreatic cancer (Granata 2015).

In 2006 European Standard Operating Procedures of Electrochemotherapy (ESOPE) were published, giving the "rules" of correct treatment plan and clinical results. Objective clinical response (defined as the sum of complete and partial response) observed in that study was 80% (Mir 2006, Marty 2006).

Based on the rise of ECT treatment in Europe, from 2016 our Institute have started to use it in clinical practice. Key points of study were safety and tolerability, taking in great account the pain linked to the treatment, and clinical response related to tumor characteristics.

MATHERIALS AND METHODS

From November 2016 to April 2019, 35 electrochemotherapy treatments with intravenous injection of bleomycin for unresectable primary or metastatic cutaneous neoplasias were performed. Inclusion criteria were pluricecidive or extensive epytelioma; in transit or at distance metastasis from melanoma; cutaneous metastasis from breast carcinoma; vulvar relapses of disease; cutaneous and subcutaneous metastasis from visceral neoplasms; painful bone metastasis. Exclusion criteria were a previous prolonged treatment with bleomycin; life expectancy lower than 3 months; patient refusal of proposed treatment. Indications and timing of treatment were multidisciplinary decided.

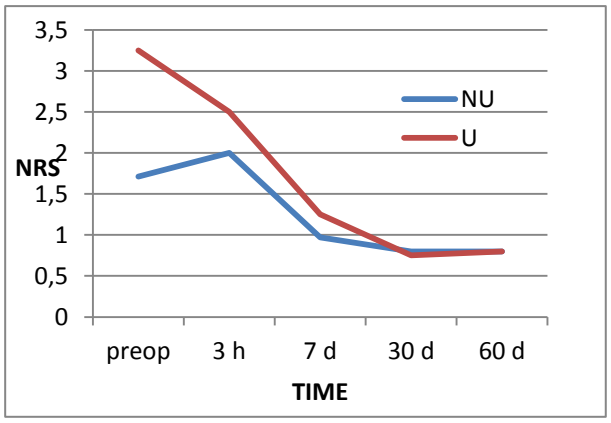
Every treatment was administered by one of 3 surgeons of a single center. In particular, one of the surgeons and Author of this article (M. M.) was in the operative room in every treatment and performed 33 treatments as first operator. Every patient was adequately informed about technical and clinical aspects of ECT. Informed consent for treatment and scientific research was achieved.

Bleomycin was administered intravenously at the dosage of 15.000 IU/m2. Dosage was adjusted according to glomerular filtration rate (GFR). We used Cliniporator VITAE^{TM}, that is CE certified for use on patients (Mir 2006), as the technological platform to deliver the pulses. Pulses were delivered through the use of multiple needle electrodes joined in a pre-set

geometry for skin or subcutaneous tissue lesions; or through individual needle electrodes in a custom modality for deep-seated tumors and bone. Pre-set geometry electrodes were needle row or hexagonal shape.
A prospectively maintained database was created in November 2016. Clinical features, treatment response and adverse effects were collected and evaluated for a minimum of one month follow-up. Every treatment was performed according to the European Standard Operating Procedures of Electrochemotherapy. Clinical results were evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria (Therasse 2000).

RESULTS

Thirtyfive ECT treatments were performed in 26 patients. For practicality we chose to list the individual treatment instead of individual patient, because clinical presentation and personal features could vary through time.
Median age was 74.2 years, ranging from 34 to 103 years. In 25 cases ECOG (Eastern Cooperative Oncology Group) Performance Status (Oken 1982) was 0-1; in the remaining 10 cases ECOG was 2-3. ASA (American Society of Anesthesiology) score was greater than 2 in 19 cases. Primitive histotype was melanoma in 18 cases, breast in 7 cases, non-melanoma skin cancer (NMSC) in 6 cases. Remaining 4 treated were metastasis from rectal carcinoma or kidney and vulvar local relapse carcinoma. Tumors were classified according to histotype, maximum size and setting of tumor growth: nodular, flat, and ulcerated for cutaneous or subcutaneous lesions; deep for visceral or intra-abdominal lesions.
ECT was administered under general anesthesia in 21 treatments, under loco-regional anesthesia in 5 cases; in 10 cases just local anesthesia, with or without sedation, was adequate to perform the treatment. In two cases, electrodes were positioned under CT scan. Mean operative time was less than 5 minutes, from the first to the last pulse. In the greater part of cases, patient was discharged the day of treatment or in post-operative day (POD 1). Cardiac arrhythmia was registered as the only intraoperative complications, requiring electric cardioversion, without further sequelae.
All the patients completed the minimum one month follow-up. Minor later complications, such as fever and local ulceration, affected few patients and the introduction of steroid premedication drastically reduced the incidence. Arising pain compared to basal pain was observed in 2 cases. In 30 cases, patients did not take any pain medication at the POD 7 ambulatory control. Complete clinical response was achieved in 15 cases (43%), while partial clinical response in 16 cases (46%). Thus, objective response rate is up to 89%. Correlation between demographic and pathological data and clinical response are listed in appendix A. A visual representation of pain is reproduced in picture 1.



Picture 1: Trend of pain before and after ECT, evaluated according to NRS (Numerical Rating Scale)

Preop: preoperative NRS
3 h: NRS after 3 hours
7 d: NRS after 7 days
30 d: NRS after 30 days
60 d: NRS after 60 days
NU: not ulcerated tumor

DISCUSSION

ECT is a relatively new kind of treatment; it is not so diffused in Europe, but its knowledge and application fields are rapidly increasing.
ECT let patients be eligible for a treatment, regardless of comorbidities and ASA score, thanks to its short operative time and lack of major collateral effects. Biological age and life expectancy and, most of all what we expect from treatment (bridge to radical surgery; combination with systemic treatment; palliation for ulceration or pain), are the key features to look for during the first visit.
ECT is an alternative to surgery for unresectable tumors. The criteria of unresectability are very subjective and diversified. Extension of disease is the main contraindication to a radical resection, both for dimension, both for number of lesions, as we classically observe in patients affected by in transit melanoma. Otherwise, severe comorbidities with high operative risk could be the reason why some patients are not candidate to an elective radical surgical procedure. Most of patients are affected by great lesions that require an extensive and demolitive intervention: the length of necessary general anesthesia and the long post-operative course often worry the patient and the surgeons, too. On the contrary, ECT could be delivered under loco-regional anesthesia or under local anesthesia, with a mild sedation. Operative time is really short. According to ESOPE, 8 minutes after the drug is administered, the operator can deliver pulses for 20 minutes. Therefore, maximum operative time is less than 30 minutes. Short operative time and the possibility of non-general anesthesia are perhaps the reason why 13 patients over 80 years age old are included in our study. Old age must

not discourage, on the contrary ECT should be taken into account when lesion are not so big and devastating.
Aims of ECT treatment could be several. The first one could be palliation in case of painful or bleeding tumors, that is frequent in the case of in transit metastases from melanoma or bone metastases. In certain cases, ECT is a neoadjuvant treatment to a radical surgical, with the purpose to reduce tumor size and let a less invasive operation. In few and selected cases, treatment is administered with curative purpose, as an alternative to surgery. Treatment could be replicated in selected cases, such as a partial but convincing response or a relapse of disease in untreated area when first treatment produced a complete response.
When we analyzed database, it was evident that in the first 10 ECT treatments, number of pulses were bigger and total operative time longer than from the 11th case. On the contrary, after 10 treatments, operative time was shorter and local complications (such as local edema or ulceration) less frequent, with the same clinical results. For example, we observed that needle row electrodes are more adequate for the treatment of head and neck lesions, because they created less local inflammation, which is at the basis of local edema; clinical result were the equivalent to using the hexagonal electrode. This let us to say that learning curve is quite fast and the choice of the electrode is the key for a good outcome.
Rising experience of ECT, a premedication with one shot steroid, intravenously administered just before bleomycin, has proven to reduce the rate of predictable collateral effect drug-related, such as asthenia, fever and local edema. One shot steroid administration does not affect clinical response after ECT.
To answer our previous question about ECT, this treatment seems to be well tolerated by patients. No severe adverse event was observed in our series. Cardiac arrhythmia was registered in a patients with chemotherapy-induced cardiopathy, at the end of 20 minutes of pulses on chest cute; probably a mechanical stress due to muscle contraction contributed to its genesis.
Pain is universally considered the most important trouble by the side of patients. Picture 1 visually describes the trend of pain, measured using Numerical Rating Scale (NRS), stratified in ulcerated and not ulcerated tumors. Patients with ulcerated tumors are affected by a higher value of pain, at the baseline. After treatment a gradually descending trend is observed in both class of patients. In particular, patients with a painful tumor reported a significant benefit in less than 3 hours. After 30 days there is a long-lasting plateau of NRS value, likely the clinical response.
Patients were always discharged with an analgesic drug, if necessary. Drug was paracetamol if NRS at discharge was lower than 2; if NRS was higher than 2, patient was discharged with a combination of paracetamol and codeine. At the control visit after one week, 28 of 35 patients reported that they did not take any medication for pain. Further, most of patients, when they were questioned, said they would repeat the treatment if necessary.
Discussing the correlation between tumor characteristics and clinical response, principal independent factors are tumor histotype, size (evaluated as maximum diameter), and setting of tumor. Regarding setting tumor, we define it nodular when tumor elevates from skin or it growths in the subcuticular layer without ulceration of skin; we define flat the tumor that is like a "macula". Ulceration is defined as the complete loss of epidermis above the tumor, with or without any secretion. Deep tumor is used when neoplasia is located under muscle fascia. As reported in table 1, there is no substantial differences in term of clinical response between NMSK, melanoma and breast. The fourth category, listed as "other", includes 3 kind of tumor, with a great difference in term of size and deepness; for this reason, the analysis is not valuable. Nodular and flat tumor are the main responders, while ulcerated and deep tumors register a lower regression. Size is also a great predictive indicator of clinical response. As previously seen in literature, tumors sizing less than 2.0 cm have a high rate of objective response. On the contrary, while tumor size increases, objective response rate dramatically decreases. Lection learnt is double. Treatment should be administered when lesions are smaller, eventually numerous. Secondly, ECT could be used for great tumors as a pure palliative treatment (e.g. bloody mass), or as a neoadjuvant treatment, to reduce the neoplasia and to make it resectable.
Finally, ECT is an unconventional surgical treatment. The first key adjective is "translational". General and plastic surgeons, dermatologists, medical oncologists, and other medical professional figures could have this kind of weapon in their own portfolio. Melanoma and NMSC are the best studied pathologies treated with ECT, but in the future clinical application should be extended to other tumors. The rational of the electroporation can be translate to non-cutaneous solid tumor, inside clinical trials. This is a mirror of modern medicine, in which patient's health is evaluated in a multidisciplinary way, and a promising medical treatment (e.g. antiPD1 drugs) could be applied successfully to a spectrum of malignancies. The second key adjective linked to ECT is "simplicity". Skills required are simple and, after few treatment, the methodology is often acquired. The only concept not to be forgotten is that every clinical case should discussed with all the specialists involved in the treatment, to verify if ECT is really the best treatment, for that patient and in that moment. According to this sentence, ECT should be performed in centers with a proven experience in oncological treatment.

CONCLUSION

On the basis of this study, ECT is a safe and feasible treatment. Learning curve is fast and clinical results are encouraging. Tumor histotype is not related to response; on the contrary, tumors measuring less than 2 cm have a better outcome; on the contrary size tumor bigger than 3

cm is a negative indicator for clinical response. Preliminary multidisciplinary discussion is mandatory to have a significant good outcome. On the basis of the experience with cutaneous treatment, other trial about the use of ECT for other kind of solid tumors should start.

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APPENDIX A
Correlation between demographic and pathological data and clinical response according to RECIST

Demographic and pathological data		30 days clinical response								
	N	CR	%	PR	%	OR (%)	SD	%	PD	%
Sex										
Male	13	4	31	8	61	92	1	8	0	0
Female	22	11	50	8	36	86	1	5	2	9
Age (years)										
< 40	1	1	100	0	0	100	0	0	0	0
40 - 59	4	2	50	1	25	75	1	25	0	0
60 - 79	17	7	41	9	53	94	1	6	0	0
≥ 80	13	5	39	6	46	85	0	0	2	15
ASA score										
1 - 2	16	9	57	5	31	88	1	6	1	6
3 - 4	19	6	32	11	58	90	1	5	1	5
Histotype										
Melanoma	18	7	39	10	56	95	0	0	1	5
NMSK	6	3	50	2	34	84	1	16	0	0
Breast	7	4	57	3	43	100	0	0	0	0
Other	4	1	25	1	25	50	1	25	1	25
Setting of tumor										
Nodular	19	6	32	12	63	95	0	0	1	5
Flat	10	7	70	3	30	100	0	0	0	0
Ulcerated	4	1	25	1	25	50	1	25	1	25
Deep	2	1	50	0	0	50	1	50	0	0
Max diam of tumor										
0 - 1.0 cm	6	6	100	0	0	100	0	0	0	0
1.1 - 2.0 cm	6	4	67	2	33	100	0	0	0	0
2.1 - 3.0 cm	10	3	30	6	60	90	0	0	1	10
> 3.0 cm	13	2	15	8	62	77	2	15	1	8
Mean rate of response (%)			48		37	85		9		6

NMSC: Non-Melanoma Skin Cancer
CR: Complete Response
PR: Partial Response
OR: Objective Response
SD: Stable Disease
PD: Progression Disease

CONTINUOUS GLUCOSE MONITORING IN ACUTE STROKE

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ABSTRACT
Hyperglycaemia upon admission is a pathophysiological response to acute brain ischemia that has been independently associated with high mortality rate and poor prognosis. Glycaemic variability (GV) has also shown association with poor clinical outcomes among stroke patients. GV is best assessed by continuous glucose monitoring (CGM), which enables consecutives glucose measurements every 5 minutes. This pilot study aimed: 1) To describe safety, feasibility and tolerability of CGM in the acute stroke setting; and 2) To compare CGM and conventional FS glucose-based monitoring regimen in terms of their relationship with GUA and the accuracy of hypoglycaemic episodes detection. Safety, feasibility and tolerability of CGM was excellent in our cohort of 23 patients with acute stroke (61% ischemic and 39% intracerebral haemorrhage) and there were no adverse events. CGM recorded ten hypoglycaemic episodes that were not detected by conventional FS monitoring. GUA was associated with coefficient of variation (CV) of CGM (p=0.03), CV of FS (p=0.01), standard deviation (SD) of CGM (p-value=0.01) and mean amplitude of glucose excursions (MAGE) (p-value=0.001).

Keywords: acute stroke, glycaemic variability, continuous glucose monitoring, hypoglycaemia.

1. INTRODUCTION

Hyperglycaemia is a common phenomenon in critically ill patients (Kruyt et al. 2010). Both diabetic and non-diabetic acute ischemic stroke (IS) and intracerebral haemorrhage (ICH) patients commonly manifest high glucose levels upon admission (Siegelaar et al. 2011). Admission hyperglycaemia is independently associated with worse clinical outcomes, such as early neurological deterioration, IS haemorrhagic transformation, a more than threefold increase in the 30-day mortality rate, and poor 90-day functional status (Capes et al. 2001, Seners et al. 2015, Paciaroni et al. 2009). These associations remain true regardless of stroke subtype, stroke severity, or diagnosis of diabetes (Poppe et al. 2009). Peaks in glycaemia lead to an overproduction of superoxide radicals and activation of oxidative stress that result in neurodegeneration and endothelial dysfunction. Current glucose monitoring protocols used in acute stroke clinical practice and clinical trials consist of serum glucose upon admission (GUA) followed by finger-stick (FS) glucose every 6 hours (4 glucose measurements per day) during the first 1-2 days (Yoo et al. 2014, Fuentes et al. 2009) with reactive adjustment of glucose levels by insulin administration. Intensive glycaemic monitoring and corrective protocols with more frequent glucose measurements have also been tested in clinical trials, which have failed to achieve better clinical outcomes despite achieving their primary target of significantly lowering mean serum glucose (Godoy 2010, Gray et al. 2007, Staszewski et al. 2011, Kreisel et al. 2009,, Johnston et al. 2019). Additionally, all glucose-lowering trials in acute stroke resulted in substantial increase in hypoglycaemic episodes (Gray et al. 2007, Staszewski et al. 2011, Kreisel et al. 2009). Similarly to hyperglycaemia, hypoglycaemia adversely affects the acutely injured brain tissue (Rabinstein 2009). Glycaemic nadirs cause the release of counter-regulatory hormones such as norepinephrine and epinephrine inducing vasoconstriction and platelet aggregation (Eslami et al. 2011).

In addition to hyperglycaemia and hypoglycaemia, glycaemic variability (GV) has emerged as a third component of dysglycaemia (Monnier 2008). Glycaemic oscillations measured by blood glucose coefficient of variation (CV) are associated with high mortality rate in ICU patients. Detrimental effects are more profound in non-diabetics and are independent of age, illness severity, comorbidities, and hypoglycaemia (Lanspa et al. 2014). The mechanism of this association is unclear, but it is possible that diabetic patients receive insulin more frequently, which might confer benefits independent of glycaemic control (Falciglia et al. 2009).

Another hypothesis is that chronic diabetic patients may be conditioned to glucose fluctuations with periods of extreme hyperglycaemia (Graham et al. 2010). GV is best assessed by continuous glucose monitoring (CGM). For instance, area under the curve more than 144mg/dL of CGM glucose during the first 72 hours post-stroke was associated with death or dependency at 3 months (Wada Shinichi et al. 2018). CGM enables repeated measurements of interstitial glucose in 5-minute intervals. CGM offers more accurate and timely glycaemic monitoring as compared to even hourly glucose FS monitoring regimens that come with significant patient discomfort from repeated FS punctures and mobilization of resources and personnel (Egi et al. 2009).

Thus, CGM is an attractive glucose monitoring method that is already in use by community-dwelling diabetics.

However, CGM presents some technical limitations. Regarding the calibration of the device with 4 FS measurements per day, it is possible to introduce an error if the capillary glucose level is recorded after exercise or meals, where rapid changes in glucose levels (>2mg/dL/min) may occur. In addition, the accuracy of the CGM decreases during the first 24 hours after its insertion, due to reactive local inflammation (Zijlstra et al. 2013). Its safety, feasibility, tolerability in the acute stroke setting has not been thoroughly tested and it is not known whether its theoretical advantage over conventional glucose monitoring methods translates into a practical benefit.

This pilot study aimed to assess safety, feasibility and tolerability of CGM in the acute stroke setting and compared CGM and conventional FS glucose-based monitoring regimen in terms of their relationship with GUA and the accuracy of detecting hypoglycaemic events.

2. METHODS

This was a prospective, single centre observational study. Consecutive adults with acute IS or ICH presenting within 48 hours of symptom onset and admitted to the stroke service or NeuroICU at Beth Israel Deaconess Medical Centre (BIDMC) were included. Eligible participants signed an informed consent approved by the BIDMC Committee on Clinical Investigations and were enrolled. Informed consent was obtained by subject's surrogate if the subject was unable to consent. Diagnosis of IS or ICH was confirmed by appropriate clinical and imaging criteria. All consenting participants underwent CGM for 72 hours or until discharge (whichever occurred first). Demographic characteristics, past medical history, National Institute of Health Stroke Score (NIHSS) and laboratory tests including Haemoglobin A1c, lipid panel, white blood cells count (WBC), and blood glucose on admission were collected from medical records. For ICH patients, the haemorrhage volume (cm^3) was computed. All patients received the standard of care glucose FS monitoring every six hours with appropriate correction with sliding scale insulin according to hospital protocol. Feeding was started according to hospital guidelines and the judgement of treating physician and swallow therapist. Adverse events and CGM discontinuation were recorded.

2.1 Continuous glucose monitoring (CGM)

This study used CGM - Medtronic MiniMed, Northridge, CA, which is a portable and minimal invasive subcutaneous device that measures interstitial blood glucose every five minutes(Signal et al. 2010). CGM device requires to be calibrated with four glucose FS measurements per day. It utilizes an enzymatic technology using oxygen as a cofactor with subsequent release of an electron per glucose molecule. Electrons are transferred to an electrode generating an electric current, which is translated into a glucose value(Vaddiraju et al. 2010). Intra-day GV was assessed by the mean amplitude of glucose excursions (MAGE) and the standard deviation (SD) around the mean CGM glucose values. SD is considered the "gold standard" CGM metric and takes into account all fluctuations during CGM recording equally, whereas MAGE accounts only for major intra-day oscillations (Weber 2009). CGM indices were calculated using the EasyGV calculator version 9.0 (Hill 2010).

2.2 Glucose parameters

- **Mean FS**: is the mean of all glucose recordings by conventional FS glucose monitoring per subject.
- **Mean CGM**: is the mean of all glucose readings from the CGM per subject.
- **SD**: is a measure of the variability around the mean of all glucose values from the CGM per subject.
- **CV**: is the SD over the mean glucose value from CGM and FS, expressed as a percentage. A CV of less than 36% has been shown to distinguish stable from unstable glucose homeostasis(Monnier et al. 2017).
- **MAGE**: is the sum of the differences from peaks to nadirs divided by the total number of glucose values. The difference is only considered when greater than 1 SD of the mean in a 24-hour period (Weber and Schnell 2009).
- **Hypoglycaemic episode**: at least 4 consecutive measurements (15 minutes) (Danne et al. 2017) of glucose readings below 70 mg/dL using CGM (American Diabetes Association 2019).
- **Hyperglycaemia duration**: time period of glucose readings above 180 mg/dL over total recording time using CGM, expressed as a percentage.

2.3 Statistical analysis

Baseline contingency table was generated to describe demographic, clinical characteristics (past medical history, lipid panel, WBC, and severity of stroke upon admission) and glucose parameters (serum GUA, CGM indices and glucose FS). Continuous variables are expressed as mean ± SD and range, whereas categorical variables are expressed as total number (N) and percentages (%). Hypoglycaemic episodes and hyperglycaemia duration were calculated. Univariable

analysis using simple linear models was used to determine the unadjusted association between serum GUA as predictor and GV metrics such as CV of FS, CV of CGM, SD and MAGE as outcomes. Statistical significance was set at p-value <0.05 and all statistical analyses were performed using SAS 9.4 software.

3. RESULTS

Table 1 presents the baseline characteristics of our cohort. 23 acute strokes (14 IS, 9 ICH), 12 (52%) men, mean age 68±11.8 years. Most common comorbidities were hypertension (65%) and dyslipidaemia (65%). The majority of the cohort was classified as moderate stroke severity on admission (NIHSS median=10 and IQR=15). Mean GUA was 132mg/dL. CGM detected 10 hypoglycaemic episodes whereas none were detected with FS. Lowest glucose level detected by FS was 78mg/dL and lowest mean FS was 89.5mg/dL.

Table 1. Baseline characteristics

Demographics	**N=23**
Male	12 (52%)
Age, years	68.0 ± 11.8
	46.0 – 87.0
Past medical history	
Diabetes	4 (17%)
Hypertension	15 (65%)
Dyslipidaemia	15 (65%)
Laboratory	
Haemoglobin A1c, %	6.10 ± 1.42
	4.90 - 10.80
LDL cholesterol, mg/dL	99.70 ± 38.57
	29.00 – 164.00
HDL cholesterol, mg/dL	54.45 ± 17.94
	37.00 - 103.00
WBC, K/uL	9.23 ± 2.77
	5.60 – 14.70
Stroke Severity	
NIHSS, median (IQR)	10 (15)
	1.00 - 30.00
Glucose parameters	
GUA, mg/dL	132.09 ± 46.24
	94.00 – 325.00
Mean FS, mg/dL	128.91 ± 37.10
	89.50 - 246.50
Mean CGM, mg/dL	128.10 ± 33.78
	75.78 - 233.42
CV of CGM, %	15.60 ± 5.95
	8.12 - 30.25
CV of FS, %	14.89 ± 8.27
	3.73 - 33.52
SD of CGM	20.61 ± 12.99
	9.62 - 66.36
MAGE	45.62 ± 20.31
	16.04 - 104.22
Hypoglycaemic episodes	10
Hyperglycaemia duration, %	9.23 ± 23.03
	0.00 - 80.67

WBC, white blood cells; NIHSS, National Institutes of Health stroke scale, GUA, glucose upon admission, FS, finger-stick; CGM, continuous glucose monitoring; CV, coefficient of variation; SD, standard deviation; MAGE, mean absolute glucose excursions.

Linear models (Figure 1.) showed a significant association between GUA and CV of CGM (p-value=0.03, R^2=0.19), CV of FS (p-value=0.01, R^2=0.28), SD (p-value=0.01 and R^2=0.23) and MAGE (p-value=0.001 and R^2=0.38). Conversely, mean FS and mean CGM did not show a significant association with GUA. There were no significant associations of GUA with GV metrics when outliers where excluded from the sample.

3.1 Feasibility and safety of CGM

92 patients met eligibility criteria. Signed ICF was obtained for only 25 patients who underwent CGM. Limitations for CGM among the 67 patients that were eligible but not enrolled were patient or family decline participation (43%), missing 48-hour from symptom onset window period due to expected need of magnetic resonance imaging (MRI) scans or any other therapeutic procedure (23%), subject unable to consent and surrogate not reachable within enrolment period (16%), discharged the same day of admission (9%), treatment plan consisting of comfort measures only (7%) and seizures (2%). Of 25 enrolled subjects, 23 were able to complete the monitoring. One patient was discharged prematurely prior to inserting CGM; CGM malfunction led to loss of data on another patient. Mean of CGM recording period was 46.54±23.14 hours (range=12.25 – 84) among the 23 patients. There were no adverse events reported throughout the duration of the study. None of the enrolled patients dropped out of the study. CGM was well tolerated and did not lead to any disruption to patient care

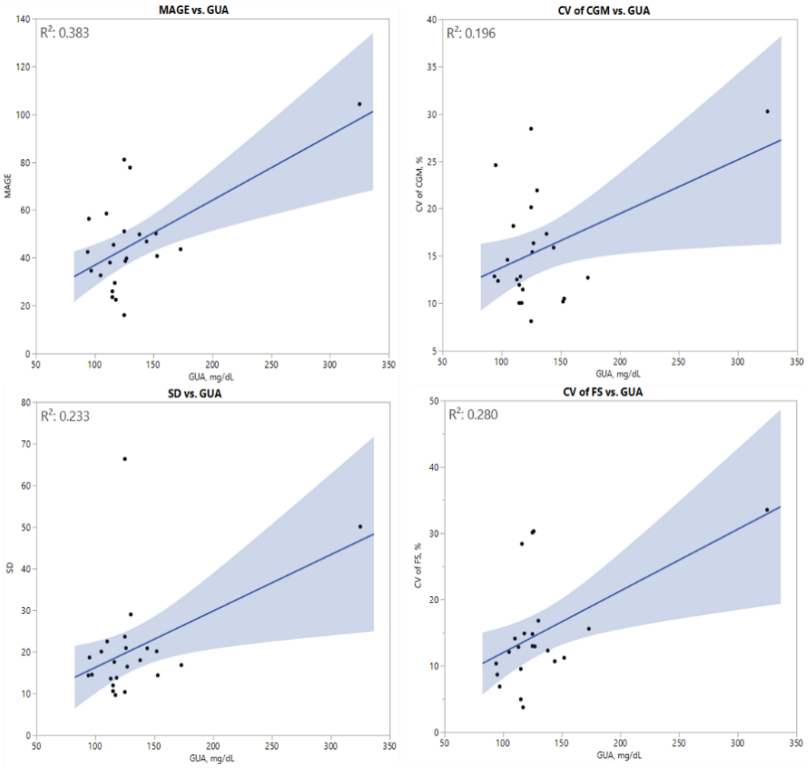

Figure 1. Linear regression models: GUA as predictor and MAGE, SD, CV of CGM and CV of FS as outcomes.
GUA, glucose upon admission, CV of FS, coefficient of variation of finger-stick; CV of CGM, coefficient of variation of continuous glucose monitoring; SD, standard deviation; MAGE, mean absolute glucose excursions.

4. DISCUSSION

In this prospective pilot study of CGM in acute stroke patients, we found excellent tolerability and safety. There were no reported side effects and none of the patients terminated the participation in the study prematurely. With regards to feasibility, in the pilot phase of the study only the principal investigator was involved in CGM insertion and monitoring. Due to the unpredictable nature of acute stroke and the time-sensitive of stroke physiology and outcomes, house staff and/or nursing would have to undergo training in CGM insertion and maintenance for this study to be performed at a larger scale. One additional potential layer of complexity is the need for brain MRI in this patient population which might occur in unpredictable hours, depending on scanner availability. Given incompatibility of CGM and MRI magnet, the monitor will need to be temporarily discontinued, re-inserted and recalibrated after the MRI scan.

Given the ease of use and the incorporation of alarm systems for hypoglycaemia of newer generation CGM, we anticipate that house staff and nursing training in these procedures will be feasible and the risk of inaccuracy due to repetitive calibrations will be optimized.

As reported above, hypoglycaemia can be particularly detrimental in the acute stroke phase and it is considered a potential reason for lack of clinical benefit in glucose-lowering trials in acute stroke. Despite best efforts and use of decision algorithms, these hypoglycaemic events could not be prevented. Blood glucose of 70mg/dL has been recognized as a threshold for neuroendocrine responses in non-diabetics and for impaired contra regulatory responses to hypoglycaemia in diabetics (American Diabetes Association 2019, Danne et al. 2017). In our study, CGM conferred a marked advantage over conventional, FS-based monitoring regimens: 10 hypoglycaemic episodes were detected with CGM, compared to none by FS. Hypoglycaemia was considered when glucose value was below 70mg/dL, also referred to as “level 1 hypoglycaemia” in medical literature (American Diabetes Association 2019).

This finding suggests that CGM confers a significantly more granular view of the glycaemic curve in acute stroke and allows capturing and potentially preventing clinically meaningful phenomena, such as hypoglycaemia.

This study did not find a statistically significant association between GUA and mean FS or mean CGM glucose, but found a statistically significant effect of GUA on GV in terms of CV of FS and CV of CGM. This might suggest that the pathophysiology involved in poor clinical outcomes of patients with hyperglycaemia on admission may be linked to the deleterious effect of GV.

Limitations of this study include a small sample size that does not allow safe assumptions regarding the association between GV and GUA neither control of the effect of outliers in the model. Also, there was lack of CGM recording in the very early stages of acute stroke due to limited resources in the pilot phase and MRI incompatibility device.

In summary, this pilot study demonstrated excellent safety and tolerability of CGM in the acute phase of stroke and suggests that CGM can provide clinically meaningful data, especially regarding hypoglycaemic episodes, which are not captured by conventional glucose monitoring methods. Future trials evaluating the feasibility and reliability of CGM in larger patient samples are needed in order to further implement measures of GV in acute stroke management.

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STRATEGIES FOR NOSE-TO-BRAIN DRUG DELIVERY

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ABSTRACT
Intranasal drug administration is an effective method that has shown promise for delivering drugs directly to the brain. This approach is associated with many challenges, and efficacy in bypassing blood-brain barrier (BBB) is debated. This review describes the pathways of nose-to-brain drug delivery, physicochemical drug properties that influence drug uptake through the nasal epithelium, physiological barriers, methods to enhance nose-to-brain absorption, drug bioavailability and biodistribution, and intranasal devices for nose-to-brain drug delivery. The mechanism of each device is described and supporting evidence from clinical trials is presented. This paper summarizes strategies involved in nose-to-brain drug delivery and provides evidence of potential efficacy of nose-brain-delivery from clinical trials.

Keywords: Intranasal, nose-to-brain, bioavailability, biodistribution, devices, nebulizers

1. INTRODUCTION

Nose-to-brain drug delivery has emerged as a novel non-invasive route that has advantages over systemic drug administration including evasion of systemic toxicity, a better side effects profile, non-invasiveness, short time to effect onset, and increased central nervous system (CNS) bioavailability (Erdő et al. 2018; Craft et al. 2012). Intranasal insulin (INI) is the most widely used drug for nose-to-brain delivery in randomized controlled trials (RCT) due to its potential for improvement of memory, cognition, and appetite control. A review of short- and long-term clinical trials assessed INI safety in 1092 participants and showed that INI is safe and does not cause hypoglycemic episodes (Schmid et al. 2018).

The olfactory epithelium, located on the upper part of the nasal cavity, is the main absorption site for direct nose-to brain delivery (Bitter, Suter-Zimmermann, and Surber 2011). This route bypasses the blood-brain barrier (BBB) by providing direct neural connections between the olfactory epithelium and the brain (Dhuria, Hanson, and Frey 2010; Lioutas et al. 2015). Once a drug is intranasally administered, it can follow multiple pathways. The olfactory and trigeminal nerve pathways allow for most efficient nose-to-brain delivery. From the upper nasal cavity, the drug can travel through the perineural space into the subarachnoid space where the drug would be further transported into the brain tissue through the perivascular pump. In the nose, the drug may undergo mucociliary clearance allowing penetrance into the respiratory mucosa in order to be absorbed systemically. Negligible amounts of the intranasally administered drug enter the systemic circulation. The BBB acts as a deterrent for the drug present in the systemic circulation to enter the brain. An alternative route the drug may take from the respiratory mucosa is to the nasopharynx into the gastrointestinal tract (Pardeshi et al. 2013; Ruigrok and de Lange 2015). RCTs have demonstrated successful nose-to-brain insulin delivery through the use of fMRI (Kullmann et al. 2018, 2017; Brünner et al. 2016; Guthoff et al. 2010), cerebral blood flow measurements (Akintola et al. 2017; Kullmann et al. 2015; Schilling et al. 2014), cerebrospinal fluid (CSF) drug concentration levels (Born et al. 2002), and cognitive tests (Reger et al. 2008; Hallschmid et al. 2008).

The intranasal route for nose-to-brain drug delivery remains a novel, promising therapeutic alternative. This article aims to describe the pathways for nose-to-brain drug delivery, review the available information regarding bioavailability and biodistribution following intranasal administration, physicochemical properties of intranasal drugs, physiological barriers, and the evidence behind currently available non-invasive strategies that promote nose-to-brain drug delivery.

2. NOSE-TO-BRAIN DELIVERY BIOAVAILABILITY AND BIODISTRIBUTION

Quantitative pharmacokinetic evidence of direct nose-to-brain drug delivery was obtained in one clinical study, which measured concentrations of melanocortin, vasopressin, and insulin in CSF and systemic circulation after intranasal administration (Born et al. 2002). Post INI administration, CSF insulin increased within 10 minutes, peaked between 30 and 45 minutes, and remained elevated at 80 minutes (Born et al. 2002). INI did not significantly affect systemic glucose levels (Ruigrok and de Lange 2015). In terms of bioavailability and biodistribution, as human brain sampling is highly restricted, preclinical animal studies using small molecule drugs, biologics, and specialized drug delivery systems have been conducted

(Kozlovskaya, Abou-Kaoud, and Stepensky 2014; Chou and Donovan 1998; Stevens et al. 2011). In the animal studies, the area under the concentration-time curve (AUC) in the brain tissue and CSF has been used to calculate measures of extent and results have shown higher drug bioavailability when targeting the brain. This was attributed to direct nose-to-brain delivery after intranasal administration, as opposed to nose-to-systemic delivery (Ruigrok and de Lange 2015). One animal study measuring procaine, tetracaine, bupivacaine, and lidocaine concentrations in the CSF in rats after intranasal administration resulted in a relative bioavailability (AUC intranasal over AUC intra-arterial) of 43% for procaine and 100% for tetracaine, bupivacaine, and lidocaine (Chou and Donovan 1998). Intranasal administration of remoxipride showed a total bioavailability of 89% (Stevens et al. 2011). Drug targeting efficiencies (%DTE) represents the relative exposure of the brain to a drug following intranasal administrations vs systemic administration (Ruigrok and de Lange 2015). To date, the most extensive descriptive and quantitative study of brain targeting efficiency via nasal route analyzed 73 publications that reported data of 82 compounds. This study showed that the majority of drugs were characterized by a %DTE higher than 100%, which indicated a more efficient delivery to the brain after nasal administration, as compared to the systemic administration (Kozlovskaya, Abou-Kaoud, and Stepensky 2014).

These studies have confirmed the feasibility of nose-to-brain drug delivery. However, CSF and whole brain measurements do not necessarily provide accurate information of drug concentrations at the target site (Ruigrok and de Lange 2015). Qualitative and quantitative differences of factors involved in nose-to-brain transport between animals and humans may be another limitation for successful translation of preclinical evidence (de Lange 2013). Bioavailability, biodistribution, and the resulting efficacy of nose-to-brain delivery are determined by many dynamic and concurrent biological factors and processes. Therefore, advanced experimental animal studies using an integrated approach considering these components in the mathematical model should be performed to obtain more accurate and reliable results (Ruigrok and de Lange 2015).

3. PATHWAYS FOR NOSE-TO-BRAIN DRUG DELIVERY

The main target region for achieving effective nose-to-brain drug delivery is the olfactory epithelium in the upper nasal cavity. This region contains olfactory nerve cells which provide direct access to the brain and CSF (Figure 1).

3.1. Olfactory nerve transport

The olfactory epithelium is the predominant site of drug absorption for nose-to-brain delivery. Once absorbed through the olfactory epithelium, drug transport occurs along the olfactory neural cells which terminate at the olfactory bulb. From there, the drug enters the brain directly or via the CSF (Pardeshi et al. 2013). A study demonstrated successful delivery of intranasal Insulin Growth Factor-1 (IGF-1) along the olfactory nerve pathway to the brain. The study mapped the pathway along the olfactory nerve and showed activation of signaling pathways of the IGF-1 receptor in the brain (Thorne et al. 2004).

3.2. Trigeminal nerve transport

The trigeminal nerve innervates the respiratory and olfactory epithelium of nasal mucosa. After penetrating the olfactory epithelium, the drug is transported along the trigeminal nerve into the brain via the pons (Pardeshi et al. 2013). An animal study administered intranasal Interferon-Beta (IFN-β) and showed significant targeting of the drug along the trigeminal nerve pathway and brain (Thorne et al. 2008).

3.3. Perivascular pump and lymphatic transport

Drugs delivered into the olfactory epithelium are transported through the perineural space into the subarachnoid space by paracellular and lymphatic mechanisms, mainly through perivascular pumping and bulk flow. The perivascular pump mechanism depends on systolic arterial pressure. The pressure waves create a compression in the perivascular space and help move its contents forward (Crowe et al. 2018). A study showed presence of intranasally administered TR-Dex3 in the perivascular system within 20 minutes of administration (Lochhead et al. 2015).

4. PHYSICOCHEMICAL DRUG PROPERTIES

4.1. Dose & Concentration

When targeting the brain, intranasal drug administration has a significantly faster absorption rate and onset of action when compared to systemic administration. The nose-to-brain pathway achieves therapeutic effects at lower doses, reaches higher brain concentrations, and maintains the drug's efficacy while minimizing systemic side effects (Erdő et al. 2018). Most RCTs using INI have administered a dose of 40 IU and have achieved efficacy without any major adverse events (Novak et al. 2014; Akintola et al. 2017; Schilling et al. 2014; Zhang et al. 2015; Jauch-Chara et al. 2012; Xiao et al. 2017).

4.2. Molecular weight

Drugs with high molecular weight have low absorption rates due to low permeability and narrow absorption area through the endothelial basement membrane of the olfactory epithelium (Warnken et al. 2016). Drugs with molecular weights above 1000 Da show poor absorption through olfactory epithelium (Wu, Hu, and Jiang 2008). Even though insulin has a high molecular weight (5808 Da), studies have shown peptide molecules can also be absorbed through specialized pathways as previously described (Born et al. 2002; Fehm et al. 2000).

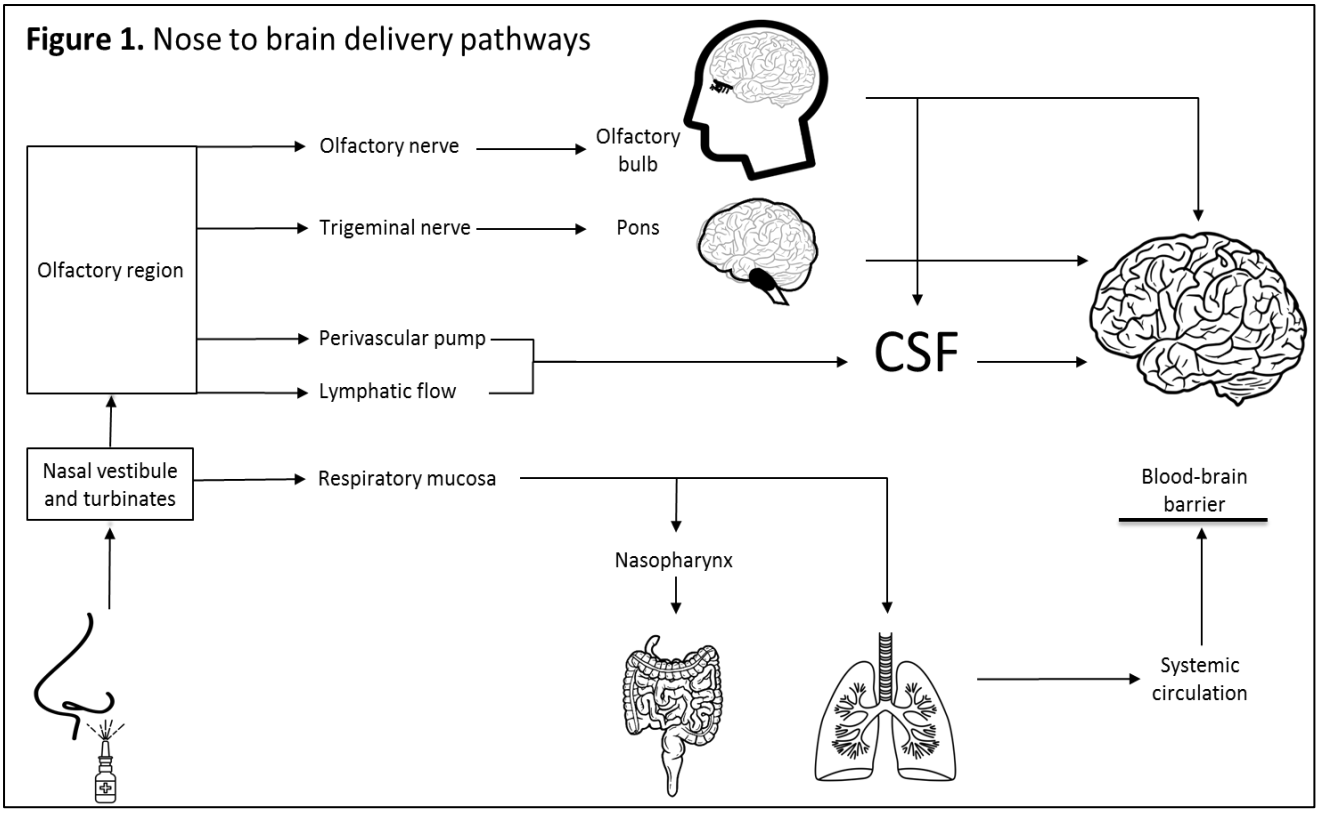

Figure 1: Once in the olfactory region, drugs can be transported into the brain bypassing the blood-brain barrier. Devices that target the nose-to-brain pathway deliver up to 47% of the administered dosage to the olfactory region. The portion that does not reach the olfactory region remains in the nasal vestibule and turbinates and undergoes local enzymatic degradation and transport via mucociliary clearance into the respiratory mucosa, nasopharynx and systemic circulation.

4.3. Lipophilicity & Hydrophilicity

Intranasal administration has led to improved brain uptake levels of lipophilic and hydrophilic drugs when compared to other routes (Warnken et al. 2016). Aqueous formulations have been shown to be more effective for intranasal drug delivery as opposed to lipophilic drugs, which are better suited for systemic administration (Warnken et al. 2016). An animal study using Raltitrexed, a hydrophilic chemotherapy drug, showed a 54-121-fold increase in AUC following intranasal administration when compared to intravenous administration (Wang, Gao, and Yun 2006).

5. PHYSIOLOGICAL BARRIERS

Nose-to-brain delivery bypasses the BBB, which contains intercellular tight junctions, endothelium-lined choroid plexus, and P-glycoprotein efflux transporters (Ruigrok and de Lange 2015). However, physiological barriers for nose-to-brain delivery include nasal epithelial tight junctions, nasal epithelial efflux transporters, mucociliary clearance, and nasal enzymatic activity (Bhise et al. 2008).

5.1. Nasal vestibule and turbinates

The nasal vestibule and lower turbinates are the first barriers that need to be overcome to reach the olfactory region and accomplish nose-to-brain delivery**.** Drugs delivered with conventional nasal delivery systems largely deposit in this regions and do not reach the upper nasal cavity where the olfactory epithelium is located (Warnken et al. 2016). Novel devices have been shown to deliver up to 45% of the administered dose past this barrier and into the olfactory epithelium (Warnken et al. 2016).

5.2. Nasal epithelium

Within the nasal cavity, the tight junctions of the nasal epithelium and its protective mucus lining act as selective filters that decrease drug permeability and their diffusion rates (Ruigrok and de Lange 2015). Mucus glycoprotein, also known as mucin, is the main component of nasal mucus. The viscoelastic properties of nasal mucus depend on mucin and water content, pH, concentrations of monovalent and divalent ions, and their physical interactions. Higher viscoelasticity leads to higher drug bioavailability due to increased nasal residence time (Erdő et al. 2018).

5.3. Mucociliary clearance

Nasal clearance transports different drugs from the olfactory epithelium to the nasopharynx through ciliary activity, increasing the risk of entering the gastrointestinal tract. This mechanism protects against inhalation of the drug (Gänger and Schindowski 2018). Risks of inhalation of INI were shown in the Exubera trial, which was terminated due to hypoglycemia and respiratory adverse events (Oleck, Kassam, and Goldman 2016). Mucociliary clearance reduces drug residence time in the nasal epithelium, which leads to decreased absorption rates (Gänger and Schindowski

2018). The mucociliary transit time in healthy subjects ranges from 2.5 to 25 minutes (Bhise et al. 2008).

5.4. Nasal metabolism

Drugs containing proteins and peptides undergo metabolism by cytochrome P450 enzymes, exopeptidases, and endopeptidases present in the nasal mucosa. This leads to local degradation of drugs, decreasing nose-to-brain delivery (Ruigrok and de Lange 2015).

5.5. P-glycoprotein efflux transport

P-glycoprotein acts as a multidrug resistance pump across the nasal mucosa and BBB. Drugs are detoxified by these efflux transporters, reducing the permeability potential of both barriers (Bhise et al. 2008).

6. STRATEGIES TO ENHANCE NOSE-TO-BRAIN DELIVERY

Nose-to-brain drug transport is highly dependent on the physicochemical characteristics of the delivered drug, the surface area of the olfactory region, and the presence of drug-specific target receptors/transporters (Illum 2000). New delivery devices, formulations, and excipients to transcend these barriers and improve CNS delivery are currently being developed and tested (Mittal et al. 2014; Crowe et al. 2018).

6.1. Auxiliary Agents

6.1.1. Enzyme inhibitors

The main purpose of these agents is to inhibit nasal metabolism. Peptides are the main target of cytochrome p450 enzymatic activity within the nasal cavity. Thus, peptidase inhibitors are the most commonly used components to improve molecule bioavailability (Hinchcliffe and Illum 1999).

6.1.2. Permeation enhancers

These excipients aim to improve the absorption of large molecular weight drugs. The mechanism of action is not completely known. Proposed mechanisms include: increasing membrane fluidity, increasing tight junction permeability, generating hydrophilic pores, diminishing viscosity, and reducing enzymatic activity (Bhise et al. 2008). Penetratin, a cell-penetrating peptide, was used in rats to successfully enhance insulin delivery into the brain (Kamei et al. 2018).

6.1.3. Mucoadhesive agents

Mucoadhesive properties alter nasal physiological mechanisms by reducing the number of open tight junctions (Hinchcliffe and Illum 1999) and enhancing the nasal residence time of the drug, resulting in an increased absorption rate (Erdő et al. 2018). Trymethyl chitosan complexes successfully enhanced insulin nose-to-brain delivery in rats (Jintapattanakit et al. 2010).

6.2. Formulations

6.2.1. Liquid formulations

Liquid formulations have been shown to have better absorption rates than lipophilic formulations (Gänger and Schindowski 2018). Insulin has been one of the most widely used drug in RCTs. Meta cresol is a colorless liquid with a sweet, tarry odor that mixes well with water (Wheeler and Taylor 2012) and is commonly used in insulin formulations such as Novolin R insulin (Novo Nordisk, Inc, Denmark), insulin lispro, insulin aspart, and insulin glulisine (Teska et al. 2014). Depending on the temperature, it can behave as a solid or liquid. Meta cresol is safe at low doses used in insulin formulations. High doses may irritate the nasopharyngeal epithelium (Wheeler and Taylor 2012).

6.2.2. Semisolid formulations

These gel-like formulations consist of both solids and liquids. Chitosan-containing formulations have been shown to improve bioadhesive properties and prolong residence time in the nasal mucosa. Semisolid gels with increased viscosity further enhance nasal residence time and drug uptake (Gänger and Schindowski 2018).

6.2.3. Particulate formulations

Nanoparticles encapsulate the drug and protect it from biological and chemical breakdown (Kulkarni et al. 2015). The P-glycoprotein efflux transporter present in the nasal epithelium and BBB can be bypassed with the use of nanocarriers (Kulkarni et al. 2015). Advantages of nanoparticle use include minimum toxicity, biocompatibility, biodegradability, physical stability, and compatibility with small molecules, peptides, and nucleic acids (Pardeshi et al. 2013).

6.2.4. Lipid-based formulations

Nanostructured lipid carriers have a wide range of uses and have less toxicity, allow for controlled or sustained release of the drug, and are able to encapsulate hydrophilic and lipophilic drugs (Selvaraj, Gowthamarajan, and Karri 2018). They achieve high efficacy by increasing absorption rates through the nasal mucosa and avoiding enzymatic breakdown (Selvaraj, Gowthamarajan, and Karri 2018).

6.3. Devices

Intranasal devices designed to enhance drug delivery to the olfactory epithelium and aid nose-to-brain delivery have been developed and tested in RCTs (Table 1). Nasal sprays that have not been specifically engineered for nose to brain drug delivery and conventional intranasal delivery devices largely deposit the administered drugs into the nasal vestibule and middle and lower turbinates (Warnken et al. 2016).

Table 1: Currently available nose-to-brain intranasal devices used in randomized controlled trials

Author	Year	N	Participants characteristics	Drug (dose)	Measurement	Conclusions
ViaNase™ (Kurve Technology, Inc. Lynwood, WA, USA) creates a vortex of nebulized particles to target the olfactory region, maximize intranasal distribution, and minimize pharyngeal deposition						
Akintola et al	2017	19 adults	20-69 years old, BMI 21-27 kg/m^2, Fasting glucose 4.5-6.0 mmol/L, Fasting insulin 2.9-8.2 pmol/L	INI Actrapid (40 IU) Placebo	MRA, Regional cortical tissue perfusion	INI improved perfusion of occipital cortical brain region and thalamus in older adults
Zhang et al	2015	28 adults	50-70 years old, HbA1c 5.4-8.0%	INI Novolin R (40 IU) Placebo	fMRI, Cognitive tests	A single dose of INI increases resting state functional connectivity in hippocampal regions in T2DM and may modify functional connectivity among brain regions regulating memory and complex cognitive behaviors
Novak et al	2014	29 adults	50-70 years old, HbA1c 5.4-8.8%	INI Novolin R (40 IU) Placebo	Regional perfusion, Vasodilation to hypercapnia, Neuropsychological evaluation	INI may improve cognitive function in T2DM patients, potentially through vasoreactivity mechanism INI appears to be safe and does not affect systemic glucose levels
AeroPump (Aero Pump, Hochheim, Germany) uses a mechanical spring mechanism with an integrated backflow block to deliver drugs and prevent contamination						
Scherer et al	2017	20 males	27-40 years old, BMI 24-26 kg/m^2	INI Actrapid (160 IU) Placebo	MRS, Gas chromatography	INI does not reduce hepatic lipid content, INI lowers BCAA levels, INI has low nose-brain uptake compared to vasopressin or melanocortin
Brunner et al	2016	16 males	Mean age 24.69 years old, Mean BMI 23.11 kg/m^2	INI Actrapid (40 IU) Placebo	fMRI, Recall mazes, Olfactometer	No enhancement of declarative memory performance
Jauch-Chara et al	2012	15 males	22-28 years old, BMI 22-23 kg/m^2	Insulin Actrapid (40 IU) Placebo	Brain ATP and PCr levels by MRS	Intranasal insulin administration considerably increases the cerebral high-energy phosphate content compared with placebo in humans

Schilling et al	2014	48 males	Mean age 23.98 years old, Right-handed	INI Actrapid (40 IU) + cortisol (30 mg) INI Actrapid (40 IU) + oral placebo Intranasal placebo + oral cortisol (30 mg) Intranasal placebo + oral placebo	CBF, Mood and hunger scales, Salivary cortisol	Insulin effects on regional CBF were present regardless of whether participants had received cortisol or not
Metered Nasal Dispenser (Pharmasystem, Markham ON, Canada) delivers 25–200 µl (median: 100 µl) per spray. It is well-suited for drugs administered daily over an extended duration						
Xiao et al	2017	9 males	45-51 years old, BMI 25-27 kg/m^2, Plasma glucose 4.8-5.0 mmol/L, Normal glucose tolerance, Plasma insulin 40-52 pmol/L	Insulin Humalog (40 IU) Placebo	Apo B100, Apo B48, Plasma lispro levels every 5 minutes for first 20 minutes after INI/placebo	INI did not affect triglyceride-rich lipoprotein secretion by liver or intestine in healthy men
Dash et al	2015	8 males	47-51 years old, BMI 23-25 kg/m^2, Fasting plasma glucose 4.8-5.0 mmol/L, Fasting plasma insulin 34-47 pmol/L	Insulin Humalog (40 IU) Placebo	Plasma glucose	INI lowers endogenous glucose production
Mistette MK Pump II, GL18 (MeadWestvaco Calmar, Hemer, Germany) uses a mechanical spring mechanism to produce a fine mist to deliver the drug into the olfactory region						
Stockhorst et al	2011	32 males	23-25 years old, BMI 22-23 kg/m^2	Insulin Insuman (120 IU) Placebo	Blood glucose, Insulin, Leptin, Epinephrine, Norepinephrine, Cortisol	Blood glucose decrease and insulin increase, while using INI, are caused by neurally-mediated signals from the brain to the pancreas
SP270+ (Nemera, La Verpillière, France) uses an actuator that produces droplets with a median size of 40 micrometers and an elliptical plume to deliver the compound into the olfactory region						
Wingrove et al	2019	16 males	20-28 years old, BMI 25-31.4 kg/m^2	Insulin Humulin (160 IU) Placebo	fMRI, Plasma glucose, Serum insulin, Serum C-peptide	fMRI showed statistically significant decreases in regional CBF within amygdala (bilateral) in response to INI compared to placebo No significant changes in plasma glucose, serum insulin, or serum C-peptide

Optimist™ (Optinose AS, Oslo, Norway) is activated by blowing into a mouthpiece in order to close the soft palate and isolate the nasal cavity while providing positive pressure						
Dale et al	2006	12 healthy adults	18-45 years old	IV midazolam (3.4 mg)	Functional disability questionnaire	Sumatriptan dose was highly effective in treating single migraine attack Optimist™ delivery device was effective, safe, and well-tolerated
				Intranasal midazolam traditional spray (6.8 mg)		
				Intranasal midazolam Optimist™ (6.8 mg)		
Djupes-land et al	2010	117 adults	18-65 years old, Moderate to severe migraine attack diagnosis	Intranasal sumatriptan (10 mg)	Pain severity score, Level of functional disability, Sustained pain-free status	Sumatriptan nasal powder administered during a migraine attack was effective and well tolerated
				Intranasal sumatriptan (20 mg)		
				Placebo		

Table 1 describes the randomized controlled trials which involved human subjects and provided evidence of nose-to-brain drug delivery such as fMRI and cerebral blood flow.

N, number of subjects; BMI, body mass index; INI, intranasal insulin; IU, international units; MRA, magnetic resonance angiography; HbA1c, hemoglobin A1c; fMRI, functional magnetic resonance imaging; T2DM, type 2 diabetes mellitus; MRS, magnetic resonance spectroscopy; BCAA, branched-chain amino acids; CBF, cerebral blood flow; ATP, adenosine triphosphate; PCr, phosphocreatine; ApoB, apolipoprotein B; IV, intravenous

6.3.1. ViaNase™ device

ViaNase™ (Kurve Technology, Inc. Lynnwood, WA, USA) electronic atomizers create a vortex of nebulized particles to maximize intranasal distribution to the upper nasal cavity and minimize pharyngeal deposition. They allow for precise electronic dosing and targeted delivery into the olfactory epithelium (Djupesland 2013). Intranasal insulin delivery using ViaNase™ devices have been shown to modify brain functional connectivity within memory networks (Zhang et al. 2015), enhance vasoreactivity and cognition (Novak et al. 2014), and improve functionality (Craft et al. 2012) without altering fasting plasma glucose and insulin measurements (Reger et al. 2008).

6.3.2. Precision Olfactory Delivery®

The Precision Olfactory Delivery® (Impel Neuropharma, Seattle, WA, USA) device features a semi disposable unit-dose format, promising consistent dose delivery and higher CNS bioavailability when compared to systemic administration. This device uses an inert liquid (hydrofluroalkane) that forms a gas propellant to deliver liquids and powders to the olfactory epithelium (Hoekman et al. 2017). This device has been shown to deliver up to 45% of the administered dose to the upper nasal cavity (Warnken et al. 2018). The device recently showed promising results in phase 1 studies in the setting of acute episodic migraine treatment using intranasal dihydroergotamine mesylate and is set to undergo phase 2 trials (Shrewsbury et al. 2019).

6.3.3. Unit Dose Systems

Unit Dose Systems (Aptar Pharma, Crystal Lake, IL, USA) are specifically designed to address the nose-to-brain pathway. This device uses a movable piston with a ball valve at the tip to deliver drugs. They feature one handed actuation and are suitable for both liquid and powder drug delivery (Djupesland 2013). This device is currently being used in an ongoing RCT, which will evaluate the safety and efficacy of three different dose levels of a third generation calcitonin gene related peptide receptor antagonist known as BHV-3500 in the acute treatment of moderate to severe migraine ("Acute Treatment Trial in Adult Subjects With Migraines - Full Text View - ClinicalTrials.Gov" NCT03872453).

6.3.4. SP270+

This device has an actuator that produces droplets with a median size of 40 micrometers and an elliptical plume. The SP270+ (Nemera, La Verpillière, France) was recently used in a double blind randomized crossover fMRI study to investigate the effect of intranasal insulin on cerebral blood flow. This study demonstrated changes in cerebral blood flow with intranasal insulin delivery when compared to placebo (Wingrove et al. 2019).

6.3.5. OptiMist™

The Optimist™ (Optinose AS, Oslo, Norway) device is activated by blowing into a mouthpiece in order to close the soft palate and isolate the nasal cavity while providing positive pressure. This delivery mechanism minimizes the risks of lung deposition during nasal administration (Djupesland et al. 2004) and optimizes delivery into the olfactory epithelium (Djupesland et al. 2006). This device has been reported to deliver up to 18% of the dosage to the upper region of the nasal cavity (Warnken et al. 2018). Recent double blind RCT using midazolam and sumatriptan nasal formulations in adults showed no serious adverse events and suggested drugs could be delivered directly into the brain through transport routes that bypass the BBB (Dale et al. 2006; Djupesland, Docekal, and Czech Migraine Investigators Group 2010).

6.3.6. Aero Pump Systems

The Aero Pump System for nasal application (Aero Pump, Hochheim, Germany) has only been used for the administration of intranasal insulin targeting the nose-to-brain delivery pathway. This device uses a mechanical spring mechanism with an integrated backflow block to deliver drugs and prevent contamination. Systematic reviews (Hallschmid et al. 2008; Benedict et al. 2007) have reviewed this device in assessing effects on memory and weight. Several double blind RCT (Schilling et al. 2014; Jauch-Chara et al. 2012; Scherer et al. 2017) have administered intranasal insulin using this device to assess the indirect effect on weight via parameters of cerebral energy metabolism (Jauch-Chara et al. 2012), Branched Chain Amino Acid levels (Scherer et al. 2017) and regional cerebral blood flow to the insular cortex (Schilling et al. 2014).

6.3.7. Mistette MK Pump II, GL18

The Mistette MK Pump II, GL18 (MeadWestvaco Calmar, Hemer, Germany) uses a mechanical spring mechanism to produce a fine mist. One RCT used this device to administer INI to the brain and assess the effect on glucose production by the pancreas. This trial reported no adverse side effects and results were indicative of brain-pancreas crosstalk (Stockhorst et al. 2011).

6.3.8 Metered Nasal Dispenser

The metered nasal dispenser (Pharmasystem, Markham ON, Canada) is a finger actuated device that can deliver 25–200 µl (median: 100 µl) per spray. It can be used in any position and is well suited for drugs administered daily over an extended duration. Drugs with a narrow therapeutic window demonstrate lower efficacy. Recent studies used the device to administer INI at a dose known to increase CSF insulin concentration and reduce hepatic glucose production (Xiao et al. 2017; Dash et al. 2015).

7. CONCLUSION

There is evidence supporting the safety and feasibility of nose-to-brain drug delivery. Nose-to-brain delivery has been confirmed by direct measurements in a clinical study and several preclinical studies. However, the current evidence for drugs targeting the brain following intranasal administration is not enough to determine the bioavailability and biodistribution parameters of the drug. Four pathways for nose-to-brain delivery have been proposed and supported by variable evidence. Currently available devices that target nose-to-brain drug delivery are moderately effective in bypassing the main physiological barriers for direct drug delivery to the brain. The advent of new nose-to-brain delivery technologies (devices and drug formulations) and the improvement of the currently available ones may increase drug delivery to the olfactory epithelium and enhance direct nose-to-brain drug delivery. These technologies will help broaden and exploit the therapeutic potential of this pathway and may shift the current paradigm of neurodegenerative diseases.

Future clinical studies are needed to determine optimal strategies based on drug formulation, device, and timing for nose-to-brain delivery. Additionally, advanced experimental, mathematical, and translational pharmacokinetic-pharmacodynamic modeling using preclinical studies with high predictive value should be performed to achieve reliable and accurate quantification of rates, extent, timing, and cerebral regions reached by drugs targeting the brain following intranasal administration.

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MODIFIERS OF CARDIOVASCULAR RISK SCORE ON DISABILITY IN THE ELDERLY

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ABSTRACT

Cardiovascular disease (CVD) affects daily living functionality, cognitive ability, and mood. We evaluated the effects of a CVD risk score on disability and assessed the characteristics that may modify this relationship in 192 older adults (mean age: 65.6 years, 96 women). WHODAS 2.0 was used to measure global disability and mobility difficulty. Framingham Risk Score (FRS) was used to predict 10-year cardiovascular mortality risk. Sociodemographic characteristics, mental status, overall mood, and gait speed were evaluated for their potential modification of the effect of FRS on WHODAS. We used general linear models to estimate the main effect and interaction effects for the modifiers. A higher effect of FRS was significantly associated with worse WHODAS total score and mobility sub-score. We found female gender, younger age, higher IQ, more years of education, higher MMSE, faster gait speed, and higher GDS to be potential effect modifiers.

Key words: Cardiovascular disease, functionality, mobility, gait speed, depression, disability, WHODAS

1. INTRODUCTION

The global population of older adults is expected to outnumber children under 5 by 2020 (World Health Organization 2018). Functionality progressively declines with advancing age (Lopes et al. 2013). Over 15 million people in the United States report having at least one limitation performing tasks that are essential for independent living (Manini 2011). Health care spending for adults over the age of 65 has been rapidly increasing, consuming over 30% of the national health care budget (De Nardi et al. 2015, Rice and Fineman 2004). However, disease and disability are not an inevitable part of just aging (National Institutes of Health 2010). Disability and functionality results from interactions between an individual's health conditions and their environment (Weltgesundheitsorganisation 2001). The World Health Organization Disability Assessment Schedule 2.0 (WHODAS) was developed and tested within a wide variety of cultural settings and provides a common measure of the impact that health conditions have over an individual's functionality (Üstün 2010).

Cardiovascular disease risk (CVD risk) is a strong predictor of physical disability (Wong et al. 2015). Maintaining low CVD risk has been suggested as a logical strategy for achieving long-term wellbeing (Keil et al. 1989; Pinsky et al. 1987). However, it is not well known which individual characteristics influence the relationship between CVD risk and disability in older adults.

The aim of this study is to measure the effects of CVD risk factors on disability and to determine which physical and demographic characteristics modify this relationship. We examined cross sectional data from 192 older adults from our on-going MemAID study.

2. METHODS

We used data from the Memory Advancement by Intranasal Insulin in Type 2 Diabetes (MemAID) study. MemAID is a five year, randomized, double-blinded, placebo-controlled clinical trial (ClinicalTrials.gov NCT02415556, FDA IND 107690) conducted at the Syncope and Falls in the Elderly (SAFE) Laboratory at

the Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH). Eligible participants that signed an informed consent approved by the BIDMC Committee on Clinical Investigations were enrolled and randomized. Eligible participants were between 50 and 85 years old, with or without type 2 diabetes, able to walk for six minutes, had a Mini Mental Status Examination (MMSE) >20, and had no major medical conditions or surgeries within the last six months. At baseline, participants underwent functionality, cognitive, and mobility testing which include the following:

- **WHODAS**: provides a global disability score that describes the degree of functional limitation by evaluating the difficulty functioning during the prior 30 days in six domains of life: cognition (understanding and communicating), mobility (getting around), self-care, getting along with people, life activities, and participation in society. Scores assigned to each item were summed (Üstün 2010). Maximum score is 128; higher scores indicate more disability. Adjusted mean for general population is 32 (Üstün et al. 2010).
- **MMSE**: test of cognitive functioning by assessing orientation, attention, memory, language, and visuo-spatial skills. Maximum best score is 30 and a score of less than 25 indicates cognitive impairment.
- **Geriatric Depression Scale (GDS):** assessment of self-reported overall mood in the elderly. Maximum score is 30, higher scores are worse, more than 20 is considered severe depression.
- **Wechsler Test of Adult Reading (WTAR™):** provides an estimate of premorbid intellectual functioning (Bright 2018). Participants read a list of 50 words and each correct pronunciation is given a score of 1, with 50 as the maximum raw score. The raw score is then standardized by age and reference group. Higher scores correspond with higher IQ.
- **Gait speed:** assessed by the Mobility Lab System (APDM, Inc., Portland, OR.) during 6 minutes of natural and regular pace walking (normal walk, NW) and during 6 minutes of walking while counting backwards in multiples of 7 (dual-task, DT). Gait speed is measured in centimeters per second (cm/sec). Speeds of more than 10 cm/sec are associated with longer survival than expected by age and sex alone (Studenski 2011).

CVD risk was assessed by the Framingham risk score (FRS) using the FRS worksheet developed by the Canadian Cardiovascular Society (Canadian Cardiovascular Society 2019). FRS total points were calculated according to age, gender, history of type 2 diabetes mellitus, smoking status, systolic blood pressure, current use of antihypertensive treatment, HDL, and total cholesterol levels. All parameters were measured and assessed during the first in-person visit. Risk of developing CVD to 10 years was calculated based on total points and categorized as low if less than 10%, moderate if between 10% and 19% and high if 20% or higher.

2. 1. Data analysis

Our primary outcome was the WHODAS 2.0 total score. Mobility score was used in the sub-analysis. Linear regression models were performed assessing the effect of CVD risk (FRS total points) on WHODAS total score and on mobility sub-score when each modifiable (MMSE, years of education, gait speed and GDS) and non-modifiable (gender, age, IQ-WTAR) predictors, and their interaction with FRS were included in the model. Type-I error was set at 0.05. We used STATA version 12 for all statistical analysis.

3. RESULTS

Demographic characteristics, medical history, and current medications of 192 participants were analyzed (Table 1). The sample was equally distributed between women and men (N=96) and the majority of them had high CVD risk (N=79) and a broad range of disability (mean ± SD of 14.9 ± 15.6).

Table 1: Cohort Characteristics

Characteristic	N=192
Gender: men,women	50(96), 50(96)
Race: white, AA, asian, other	77(149), 16(30), 3(6), 4(7)
Age (years)	65.6 ± 9 (50 – 84)
Diabetes: yes, no	42(80), 58(112)
Hypertension: yes, no	47(90), 53(102)
Dyslipidemia: yes, no	51(98), 49(94)
Years of education	16.2 ± 3.3 (8 – 28)
MMSE score	28.3 ± 1.8 (21 – 30)
FRS category: low, moderate, high	29(56), 30(57), 41(79)
FRS total points	14.6 ± 4.8 (3 – 25)
WHODAS total score	14.9 ± 15.6 (0 – 72)
WHODAS mobility sub-score	2.5 ± 3.4 (0 – 13)
GDS Total Score	5.5 ± 5.4 (0 – 26)
WTAR score	113 ± 13.7 (71 – 131)
NW gait speed (cm/s)	115.8 ± 21.4 (36.8 – 189.2)

Continuous variables are expressed as mean ± SD (min – max) and categorical variables are expressed as percentages, % (N). MMSE: Mini Mental Status Examination; FRS: Framingham Risk Score WHODAS: World Health Organization Disability Assessment Schedule 2.0; GDS: Geriatric Depression Scale; WTAR™: Wechsler Test of Adult Reading; NW: Normal Walk

3.1 Linear regression of the effect of CVD risk on disability

FRS Total Points showed a significant linear relationship with both WHODAS total score (p=0.0025, Figure 1a) and WHODAS mobility sub-score (p=0.0002, Figure 1b). Diabetic participants had more disability in both WHODAS total score and WHODAS mobility sub-score.

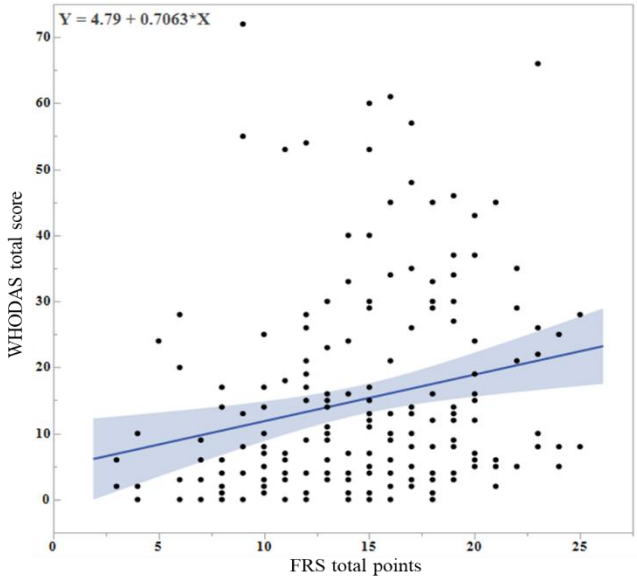

Figure 1a: Linear relation of WHODAS total score and FRS total points.

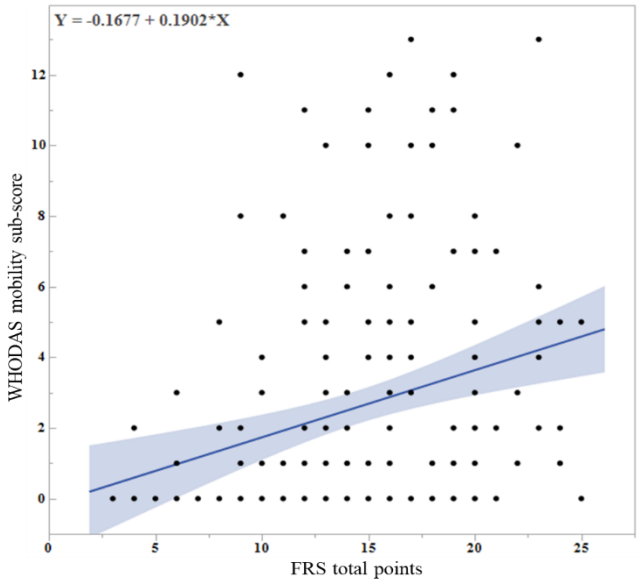

Figure 1b: Linear relation of WHODAS mobility sub-score and FRS total points.

3.2 Modifiers of the effect of CVD risk on global disability

The regression model showed that all covariates except for gender were significant predictors of WHODAS total score, when controlling for FRS Total Points (Table 2a).

Age, male gender, years of education, IQ, NW gait speed, DT gait speed, and MMSE were negatively associated with WHODAS total score. Advanced age and male gender increased the effect of FRS Total Points on WHODAS total score by 28% and 11%, respectively. The effect of FRS total points on WHODAS total score was decreased by 29% with higher IQ, by 11% with higher MMSE, and by 10% with more years of education. Faster gait-speed decreased the impact of CVD risk on WHODAS total score by 35% on normal walk and 18% on dual-task walking.

Table 2a: Regression model: Association between CVD risk and Disability (CVD risk in terms of FRS total points as predictor of WHODAS total score)

Covariate in a linear model	% Change in β FRS Total Points	Change in R^2	β covariate	Uncorrected p-value covariate
Age	**28.18**	0.019	-0.26	**0.046**
Gender	11.05	0.009	-3.15	0.165
Years of Education	-10.25	0.023	-0.73	**0.032**
IQ - WTAR	**-29.17**	0.058	-0.28	**0.001**
GDS	**-41.00**	**0.398**	1.84	**<0.001**
NW Gait Speed	**-35.00**	0.046	-0.16	**0.002**
DT Gait Speed	-18.22	0.025	-0.11	**0.024**
MMSE	-11.44	0.046	-1.89	**0.002**

Highlighted values correspond to change in β more than 20%, change in R^2 more than 0.1, and uncorrected p-value less than 0.05, respectively.

GDS was the only covariate with a positive relationship with WHODAS total score. A higher depression score was related to greater disability when controlling for CVD risk. However, when GDS was added to the model, the effect of FRS total points on WHODAS total score was decreased by 41%. Depression accounted for the largest change in variance for WHODAS total score (change in R^2=0.39) and WHODAS mobility sub-score (change in R^2=0.14).

3.3 Modifiers of the effect of CVD risk on mobility

Further, a subsequent regression analysis showed that all covariates except for age were significant predictors of WHODAS mobility sub-score, when controlling for FRS Total Points (Table 2b).

Age, male gender, years of education, IQ, NW gait speed, DT gait speed, and MMSE were negatively associated with WHODAS mobility sub-score.

The effect that FRS total points had over WHODAS mobility sub-score increased by 20% with older age and by 18% with male gender. The following factors decreased the impact of CVD risk on mobility: a higher IQ (by 20%), higher MMSE (by 7%), and more years of education (by 9%). Faster gait-speed decreased the relationship of CVD risk and WHODAS mobility sub-

score by 43% on normal walk and 27% on dual-task walking.

Table 2b: Regression model: Association between CVD risk and Mobility (CVD risk in terms of FRS total points as predictor of WHODAS mobility sub-score)

Covariate in a linear model	% Change in β FRS Total Points	Change in R^2	β covariate	Uncorrected p-value covariate
Age	**20.15**	0.016	-0.05	0.069
Gender	17.77	0.039	-1.38	**0.004**
Years of Education	-9.33	0.029	-0.18	**0.013**
IQ - WTAR	**-20.38**	0.043	-0.05	**0.003**
GDS	-19.58	**0.140**	0.24	**0.001**
NW Gait Speed	**-43.46**	**0.109**	-0.05	**<0.001**
DT Gait Speed	**-27.98**	0.083	-0.04	**<0.001**
MMSE	-7.49	0.032	-0.33	**0.01**

Highlighted values correspond to change in β more than 20%, change in R^2 more than 0.1, and uncorrected p-value less than 0.05, respectively.

GDS was the only covariate with a positive relationship with WHODAS mobility sub-score; with a higher depression score related to greater difficulty getting around when controlling for CVD risk. When GDS was added to the model, the effect of FRS total points on WHODAS mobility sub-score decreased by 20%.

4. DISCUSSION

The ability to maintain daily functionality with advancing age determines quality of life and survival. Daily functionality is a continuum of health states and depends on the interaction between an individual's health condition and their socio-demographic context across different domains (Weltgesundheitsorganisation 2001). The effect of these interactions on the different domains of functionality is not fully understood.

We examined the effect of CVD risk on disability, and measured the influence of gait speed upon this relationship. We saw CVD risk had a greater effect on the WHODAS total score than on the WHODAS mobility sub-score and found gait speed is a strong indicator of daily living difficulties. People with higher CVD risk scores had worse subjective (higher WHODAS mobility sub-scores) and objective (slower gait speeds) mobility measures.

Analysis of the impact of depression on daily functionality showed that higher levels of depression reduced the effect that CVD risk had on WHODAS total score and WHODAS mobility sub-score. These findings suggest that depression might have a direct independent effect on disability. Loss of primary motivation is a common symptom of depression in the elderly and has been shown to affect functionality and cognition (Sözeri-Varma et al.2019), therefore greater depressive symptoms may partially mediate the relationship between CVD risk and WHODAS score.

In people with higher IQ, more years of education, and higher MMSE score, CVD risk had a lesser impact on overall disability. This is consistent with prior studies which have suggested that higher educational levels promote better coping mechanisms, life satisfaction, subjective well-being, and overall functionality (Algilani et al. 2014). Furthermore, lifestyle modifications such as exercise and the Mediterranean diet that have been linked to reducing CVD risk (Martínez-González et al. 2019, Myers 2003) also have shown to decrease cognitive decline related to aging (Dumas 2017).

This study ratifies prior findings that cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, and tobacco use have significant deleterious effects on daily living functionality. Further, our results show that protective factors including higher IQ, higher MMSE, greater years of education, and faster gait speed may mitigate the relationship between CVD risk factors and functional impairment, suggesting possible future targets for improving functional outcomes in older adults.

Overall, our results suggest that providing better medical care for vulnerable older patients, such as people with slow gait speed, fewer years of education, and lower IQ might help prevent loss of functionality in the presence of strong CVD risk factors.

One of the biggest challenges for the health care system is to educate and train a workforce that can meet the complex health care needs of the elderly (Rice and Fineman 2004). Public health interventions aimed at influencing modifiable and non-modifiable characteristics might decrease disability and improve functionality amongst the unhealthy elderly population. Prevention of health problems by promoting lifestyle changes is one of the few known ways to reduce rising health care costs (Kojima et al. 2019, Rice and Fineman 2004). Accurate disability measurement tools may help monitor the impact of health care policy decisions (Üstün 2010) and may contribute to predict the most efficient measures to improve quality of life of vulnerable elderly populations.

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3D SOFTWARE SIMULATOR FOR PRIMARY CARE TRAINING

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ABSTRACT
Medical software simulators are used to teach specific procedures that allow the user to follow only a strict sequence of steps without the possibility of alternative, avoiding considering the consequence of an error and then potentially admitting its tolerance. Usually these applications are a state machine implementation where learners must make a specific action to obtain a specific result.
In our work we propose a brand-new approach with a "open world" serious game medical simulator, based on Agent Based Model Paradigm.
Starting by these concepts, a user can learn and test his skills in a dynamic environment that changes in real time based on his actions.
We provide a configurable starting set of conditions (patient heath state, available medical instruments and drugs) to create, potentially, infinite scenarios; alongside these boundary values the game permits to configure real time events that influence patient in an unpredictable way by the user side.

Keywords
Open word, serious game, Agent Based Model Paradigm, dynamic environment

1. INTRODUCTION

Training software for primary care behavior is one of the best tool to teach the best way to resolve real-life simulation emergencies (e.g. safe life after a hearth stroke).
Applications like MicroSim Inhospital[1] or DrSim[2] offer some clinical cases that must be resolved in a specific way and in a specific time lapse.
Obviously, this approach allows a deep clinical case analysis, but the simulation solution is only one, and in every interaction the user has to make always the same decisions (and obtain the same results) to end the simulation in the right way.

Starting by this observation we propose a new approach to this training scenario: a dynamic environment with his own rules that can change by user interactions or by real time events.
The user can interact with this environment in multiple ways and obtain multiple results.

The software implementation is based on the Agent Based Model Simulation (ABMS).
An Agent is shortly defined as an Entity with a set of actions that can change its own state or other agents state; an Agent can react to external stimuli only, be *cognitive* making its own decision, or a mix of these characteristics [3].
ABMS is used in various disciplines like biology, finance, engineering to study complex scenario too expansive or difficult to replicate [4].

Based on ABMS we defined three Agents (called Game Agents):

- Patient Agent
- Tool Agent
- Director Agent

The simulation was implemented as a 3D serious game where the user plays the doctor role.
We decide to develop this kind of simulation because it has been proved that Gamification [5] produces a better learning curve with respect the classic learning methods [6].

The ABMS paradigm offers the opportunity to approach the game in a "open world" way: to proceed in the simulation it's no need to do specific actions, but user can make his own decisions and see what happen in the game world: success or failure is not written in a decision tree.

Finally, with the simulator we implemented a powerful and simple editor to create the starting configuration (e.g. patient heath state, events, available drugs etc.); this set is called Plot.

2. PLOT AND GAME AGENTS

To create our training simulator, we focused on two key goals:

- Abstract the simulation concept to create a, potentially, infinite simulations cases
- Create a dynamic simulation environment where simulation can evolve runtime and not only after a user action.

For the first goal we create the Plot concept: a set of configurable variables that represent the starting simulation point.
For the second one we create the Game Agent concept: an Entity based on ABMS paradigm that can change runtime both his own and the environment state.

Our training simulation starts from a certain point and evolves by its own.
Every simulation is different from an another and the same simulation can evolve differently in any interaction.

2.1. Games Agents Interaction

We define three Game Agents; every agent can change his state and, in some case, the state of one or more other agents.
User can interact with simulation using the Tool Agent.
Figure 1 explains how this works.

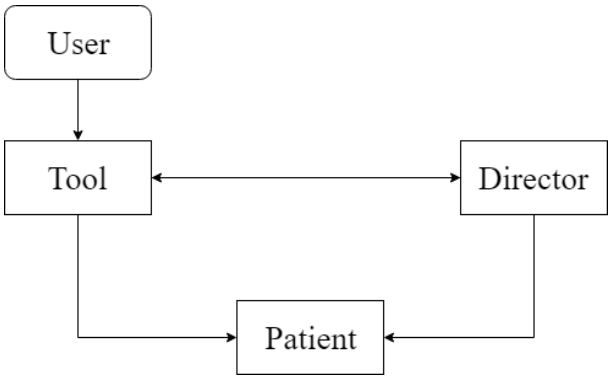

Figure 1: User and Game Agents interactions

2.2. Patient Agent

The Patient is a *hybrid* Agent: his state can be modified by other Agents (external stimuli) and his actions (Rules).

In our simulation environment, Patient is a human being abstraction, characterized by life parameters and physiological rules divided in three macro areas:

- Primary Parameters: a set of vital parameters like blood pressure and breath status.
- Secondary Parameters: another set of vital parameters, (e.g. ECG sinusoidal, CVP) that depend on Primary ones.
- Rules: a set of actions based on physiological functions that modify Primary and Secondary Parameters values.

Primary Parameters can be modified by other Agents and Patient Rules.
From the other hand Secondary Parameters can be modified only by Rules and only when Primary Parameters change occurs.
Patient checks Parameters and apply Rules in real-time.
Figure 2 explains this interaction.

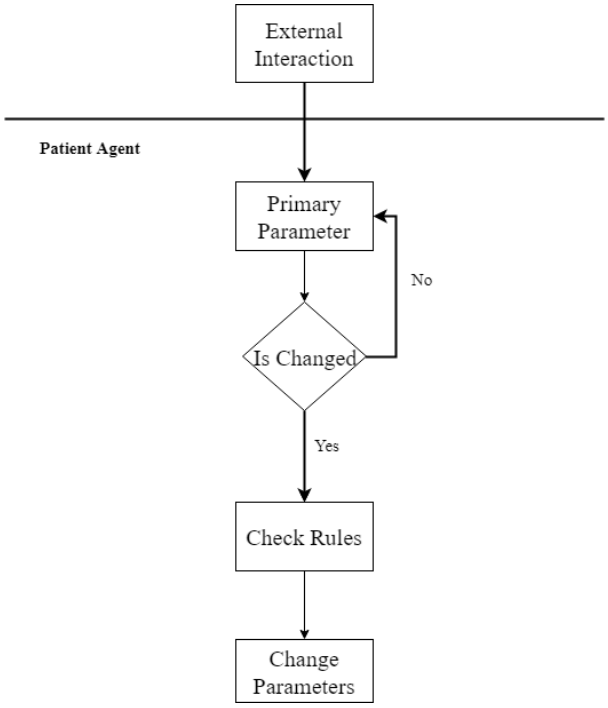

Figure 2: Patient Agent Logics

Here an example how Patient works.
We define a set of Primary Parameters: Systolic Pressure, Diastolic Pressure and Heart Frequency.
These values are related to a set of Secondary Parameters that includes ECG, Radial Pulse and Carotid Pulse.
The relation between these two sets is managed by following Rules:

- ECG rule sets ECG based on Heartbeat and both Pressures.
- Pulse rule set radial and carotid pulse based on systolic pressure threshold.

When, Heart Frequency change, ECG Rule checks the new value and consequently modifies (if needed) the ECG value.

In our implementation Patient Parameters and Rules are not fixed and can be added or modified in a simple way. We can focus, for example, on neurological or cardiopulmonary simulation or maybe a mix of them.

Obviously, an approach like this need a good knowledge of human physiology but, from the other hand, can offer a detailed and realistic simulation.

2.3. Tool Agent

Tool is a *cognitive* Agent that, with its actions, changes his own state and the Patient Agent one.

In our environment a Tool is a 3D object modeled on a real-life medical instrument, procedure or drug and represents the only way a user can interact with Patient**.**

2.3.1. Tool interaction and synchronization with simulation environment

Although is cognitive (it does no need stimuli from external source to work), Tool starts simulation in a Sleep State. It turns awake only when user actively uses it (as shown in Figure 1, Tools are the only way for user to interact with Patient) and only after it is synchronized with the simulation environment.

In real-life, a doctor usually can make only one action at the same time, for example it is impossible to administrate a drug and at the same time make a CPR (Cardiopulmonary Resuscitation)

To simulate this real-life situation, before starting his actions, a Tool must be synchronized with simulation environment and this process is managed by Director that detains simulation status and simulation time.

Finally, when user stops using a Tool, it returns in Sleep State.

2.3.2. Active and Passive Tools

We divide Tools in two macro types: Passive Tools that offer a real time Patient conditions snapshot, visualizing Parameters in a particular way (for example ECG monitor shows a sinusoidal curve based on Heartbeat) or simply showing them as they are (Breath per minutes or radial/carotid pulse are an examples). Figure 3 shows how they work.

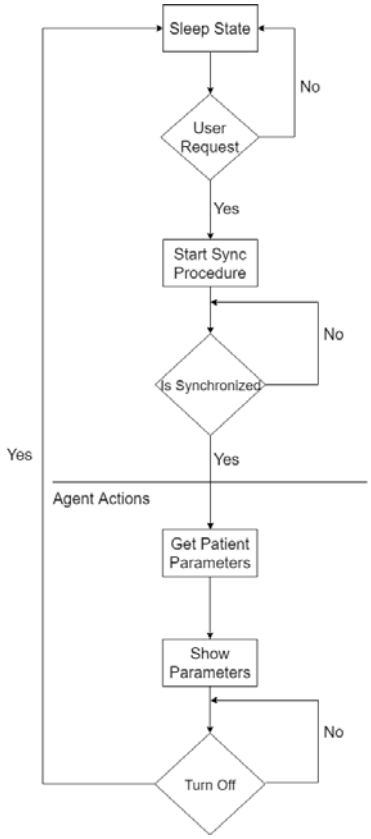

Figure 3: Passive Tool

The other type is Active Tools: the set of instruments, drugs and procedure used during simulation (CRP procedure, drugs and defibrillator are an example). These Tools modify Patient Primary Parameters in many ways: permanently, only when not in Sleep State or for a time lapse.

In real-life, using some of these Tools need a decision making, for example how much drug to administrate or where to apply defibrillator plates: a wrong decision could lead to a failure.

To simulate this aspect, Active Tools actions are parameterized, so, before using them, the user must set these variables. Figure 4 shows how Active Tools work.

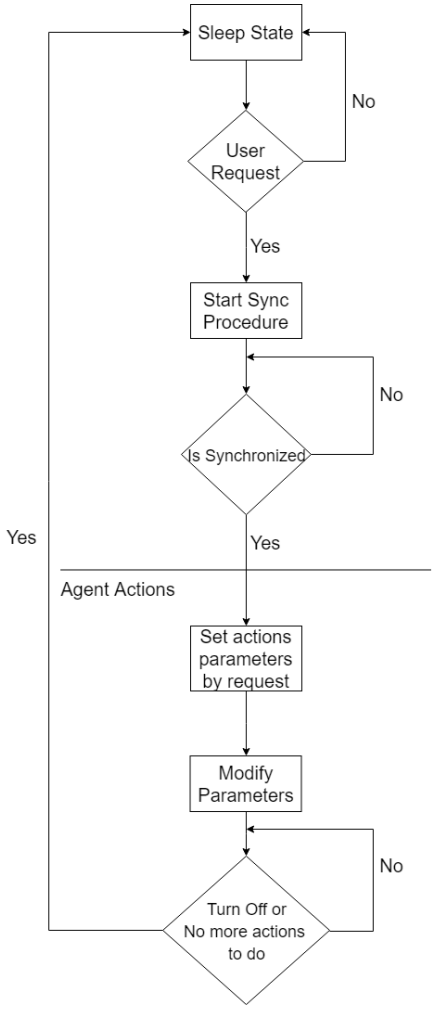

Figure 4: Active Tool

2.3.3. RNG Factor

In real-life a good decision couldn't always lead to success. Something unexpected can occur; let's make an example: during a heart stroke with a ventricular fibrillation doctor can use adrenalin to stabilize the patient. Let's suppose this doctor makes all the right decisions (right drug quantity, right administration way, etc.) but something goes wrong and patient conditions gets worse. At this time doctor must take some new decisions in a really stress situation.

To simulate these unexpected results, we introduce a configurable RNG factor to every Tool that affect actions success percentage.

2.4. Plot

Plot is related to Patient and Tool Game Agents and must be explained to understand Director Game Agent.

We defined Plot as a set of configurable variables that represent the starting simulation point.
These variables include:

- Patient Primary Parameters starting values
- Which Tools can be used
- Realtime Events list

Every training simulation has its own Plot and every Plot differs by little or big aspects.

Another concept we introduced is Realtime Event: A Realtime Event (RTE) is a configurable action that modifies Patient state in a default time/values condition.

In every RTE we can find:

- What Parameter must be modified
- When this change must occur
- In which conditions this change must be made

For example, if we want set Systolic Pressure to 150 after 10 seconds; we create a RTE like this:

- What: Systolic pressure
- When: after 10 secs
- Conditions: no conditions

In another case of we want set the heart frequency to 200 but only if systolic pressure is more than 150:

- What: heart frequency
- When: always
- Conditions: Systolic pressure more then 150

We create also an RTE that occurs after 10 second but only if a specific condition is verified.

2.5. Director Agent

Director is a *cognitive* Agent that manage simulation evolution and can interact with Tools and Patient Agents.

Director duties are:

- Read Plot
- Set starting Patient Parameters.
- Enable Tools availability
- Manage simulation time
- Synchronize Tools
- Register user actions
- Manage the Real Time Events

Director has a set of asynchronous actions, triggered by Tools requests, and a synchronous set made runtime. Figure 5 shows the synchronous behavior.

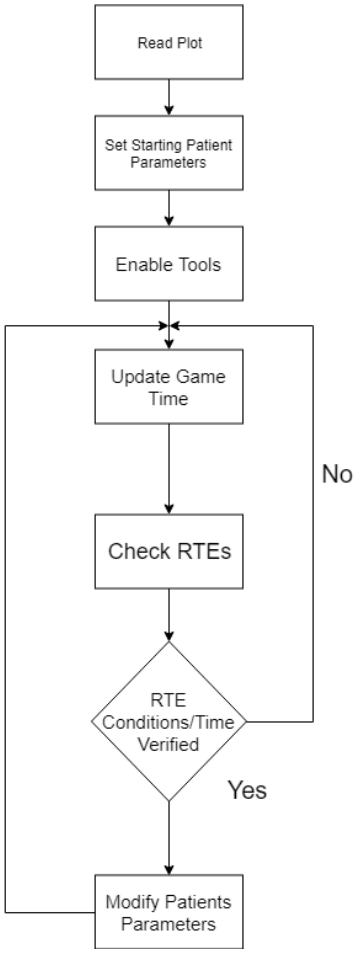

Figure 5: Director synchronous behavior

2.5.1. Asynchronous Actions and Simulation History

As we told, every Tool must be synchronized with simulation environment by making a request to Director that registers every Tool used during simulation, their values (for Active Tools) and the using time.

All these information can be used after the simulation is concluded to evaluate user decisions.

3. GAME WORLD IMPLEMENTATION

Usually simulation software offers detailed clinical cases, but they are limited in number and iterations: a user learns fast how simulation works and therefore can make always the right decisions.

An important aspect, especially in primary care training, is to put some pressure to the learner: in real life a doctor must take difficult decisions in short time and their consequences make difference between life and death: posology comes first then diagnosis.

To satisfy these requirements we create Plot that offer a flexible customization template to create a great number of clinical cases, and Game Agents that, with their own logic and RNG factor, creates a dynamic simulation with unpredictable evolutions.

Next step is to create a game environment where put our Game Agents.

3.1. A Serious Game as Immersive Simulation

In a medical training simulation learner improve his skills and understand how resolve emergency, but he knows that a wrong decision doesn't cost a life.

Many simulators offer all these features but lacks in realism. Emotional aspect, pressure and hurry are difficult to replicate sitting in front of a computer.

To overcome this problem, we propose a video game approach (obviously as serious game).

We told about Gamification and its learn curve, but serious game with its realistic graphic, VR helmet and wearable controller can offer a really immersive experience.

3.2. 3D Environment

Our simulation evolves in a 3d emergency room scenario. User avatar (the doctor) can use all 3d objects in the room (every object is a Tool Agent) and with them interact with the patient (Patient Agent).

Other than doctor and patient, we model a nurse avatar that helps doctor in particular procedure like CRP.

Thanks to the support of SimAv doctors we created a scenario and 3d models very similar to real ones; this is the first step to overcome the wall between a real experience and a simulated one.

3.3. Open World and Game Constrains

In an open world videogame player has the illusion to make what he wants when he wants.

We use this concept in our game and thank to Game Agents, learner has not to follow a script or do his actions in a specific order to proceed in the simulation.

Our Game Agents offers a dynamic world and the learner, as in real life, seed events happen independently of his actions.

3.4. Game Mechanics and Real-life Knowledge

A serious game user could not be a video game player, we focus our game design on this truth.

For this reason, we model Tool Agents as real-life instruments, so the learner used his medical knowledge to understand how an object works and how use it.

4. CONCLUSIONS

Medical training simulators represent an important way to teach how safe a life, especially in emergency.

The challenges are: give a realistic experience, offer multiple clinical case and be easy to use.

With our software we propose a brand-new approach that offer a high customizable scenario, an immersive simulation that evolve in time with real-time events and the opportunity to be different in every iteration.
User has a high freedom degree in his actions.
Finally, our game design permit to any user to play without know particular mechanics or understand difficult GUI. His medical knowledge is the best way to lead to success.

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