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Abstract (for dissemination)	Research in VPH-CaSE is driven by 14 Early Stage Researchers (ESRs), all but one of which are employed as PhD students. The individual projects are clustered under three topic headings (Fig1), obtaining a natural dissemination focus through the activities of IRP11, and together are executed within a structure of 3 technical workpackages: WP2 – Simulation, WP3 – Experimental measurement and imaging, WP4 - Clinical translation and interpretation. This deliverable contains a report on the progress of the activities undertaken as part of WP3 (Experimental Measurement and Imaging), summarising, clustering, and placing into context activities associated with the individual research projects, the VPH-CaSE training events {held at Sheffield (UK), POLIMI (Italy), CNRS (France) and TU/e (Netherlands)} and events organised by local institutions and external organisations
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Contents

1 EXECUTIVE SUMMARY

Research in VPH-CaSE is driven by 14 Early Stage Researchers (ESRs), all but one of which are employed as PhD students. The individual projects are clustered under three topic headings (Fig1), with a natural dissemination focus through the activities of IRP11. Together these are executed within a structure of 3 technical workpackages:

- WP2 – Simulation
- WP3 – Experimental measurement and imaging
- WP4 - Clinical translation and interpretation

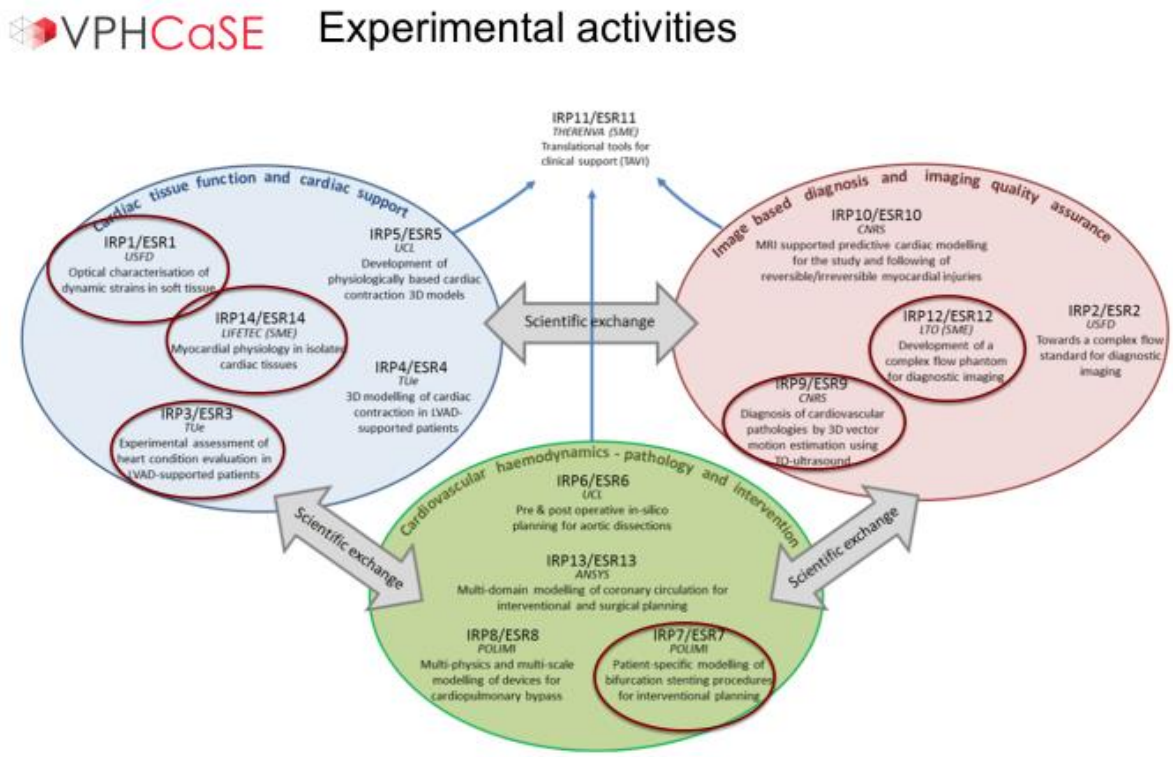

Figure 1 – the research projects are clustered according to 3 headings (i) Cardiac tissue function and cardiac support; (ii) Cardiovascular haemodynamics – pathology and intervention; (iii) Image based diagnosis and imaging quality assurance. The highlighted projects are those with a significant experimental component.

This deliverable contains a report on the progress of the activities undertaken as part of WP3 (Experimental Measurement and Imaging), summarising, clustering, and placing into context activities associated with the individual research projects, the VPH-CaSE training events {held at Sheffield (UK), POLIMI (Italy), CNRS (France) and TU/e (Netherlands)} and events organised by local institutions and external organisations.

Maximising the impact of results and the sustainability of the methodologies obtained from the experimental and simulation techniques developed as part of WP3 and WP2 effort, requires close collaboration across the disciplines. Additionally, clinical aspects help to place the research in context, whilst the industrial contribution clarifies opportunities for exploitation as well as economic and regulatory constraints to translation. Of course within the biomedical arena, it is also important to be mindful of ethical responsibilities to individuals who provide data or tissue for use in research.

Looking forward to possible and eventual application of the research, it has been challenging to address the clinical and interpretation emphases of WP4 during the 1st year of the ESR projects, because the nature of the research has been developmental. This has focussed on understanding of fundamental techniques, which is necessary to equip the ESRs with the requisite tools to address their individual areas of research. However, the collaborative nature of this Marie Curie network has already allowed us to expose the ESRs to a range of clinical areas and research methodologies that would not have been possible with a purely local training approach. Secondments have also provided an effective mechanism for ESRs to engage across the network, not forgetting the role that dissemination/outreach plays as a mechanism for promoting network cohesion and communication of our science to the public.

This report begins by reviewing the tasks associated with this Workpackage, and this is followed by a summary of overall network progress to date. A specific focus relates to the responsibilities of this Workpackage and the activities that have taken place by the end of the review period.

2 CONTRIBUTORS

- TUe; Marcel Rutten
- USFD; Andrew Narracott, John Fenner
- Contributions from all partners for local reporting of WP3 activities

3 INTRODUCTION

The science within the VPH-CaSE European Training Network (ETN) revolves around basic and applied research in the field of Medical Devices and Cardiovascular Science, with a focus on cardiac tissue function/support, haemodynamics, imaging and QA (i.e. quality assurance). Our approach relies on two main paradigms identifiable as:

(i) in-vitro and in-vivo experimentation (experimental science), and
(ii) modelling and simulation (computational science).

Translation of this basic and applied research to the clinic is also a contributor to this research, helping to deliver tangible content to the Science and Technology agenda for VPH-CaSE.

The core of this network is formed by 14 Early Stage Researchers (ESRs) and their individual research projects (IRPs) operate under the auspices of 3 main work packages in VPH-CaSE:

- WP2 – Simulation
- WP3 – Experimental measurement and imaging
- WP4 - Clinical translation and interpretation.[1]

This deliverable D3.1 contains a report on the progress of the activities undertaken as part of WP3, summarising, clustering and placing into context all relevant ESR effort, during the first year of the research projects. The accompanying deliverables D2.1 and D4.1 contain comparable reports for WP2 and WP4. This deliverable does not attempt to provide detailed results from the work of the IRPs, since those can be found in the first year ESR report deliverable D1.4.

Activities in this WP are (quoting from the description of work):

- Task 3.1: Coordinate horizontal experimental/imaging effort through the Steering Committee and secondments
- Task 3.2: Coordinate reporting of experimental/imaging activity to contribute to D3.1 and D3.2

Relevant milestones associated with these tasks at this stage of the project have been achieved (MS2 – All ESRs recruited; MS3 – ESRs complete first year assessment (see D1.4)).

[1] The other work packages of the network relate to Management (WP1), Training (WP5) and Dissemination (WP6).

4 METHOD

The 14 individual research projects (IRPs) of the ESRs have been described at length in the VPH-CaSE deliverable D1.4 (ESR 1st year reports, due in M22 of the project) and will not be described here. Deliverable D1.4 also contains the results obtained by each ESR during the first year of their employment. However, the experimental focus of this workpackage (WP3) requires that experimentation aspects are clarified and their outcomes described. These are presented below, placed in the context of tasks 3.1/3.2 described above.

5 RESULTS

The purpose of this workpackage is to be alert to and exploit experimental techniques (in vitro, ex vivo and in vivo biological systems), as well as considering the application of imaging technologies (including the development of experimental phantoms), in order to address the challenges of each Individual Research Project. In particular, this experimental work is targeted at the clinical problems described in each Individual Research Project, which has implications for all Beneficiaries within the network. For example, high quality experimental data are essential for validation of simulations, and imaging technologies are central to the application of patient-specific simulations. As a result there must be close integration between WP2 and WP3. In addition to model validation, experimental developments also contribute to commercial prototypes of phantom and imaging technologies, and therefore interaction with WP4 is essential. This contribution recognises that translation to industry, and subsequent industry development is influenced by the needs of clinical end-users. The commitment to appreciating industrial needs ensures that ESRs become familiar with industrial priorities to complement their academic training.

This section reports the main results obtained within WP3, clustering results according to the tasks as mentioned in Section 3. Detailed accounts, including references to the scientific literature, can be found in the Deliverable D1.4.

5.1 Experiment and Imaging – a Network-wide Perspective

Purpose: VPH-CaSE aims to bring simulation methods, applied to the cardiovascular system, to such a level that they can be applied in diagnostic and therapeutic procedures as used in the clinic. To this end, besides all ethical and regulatory requirements, experimental and imaging methods need to be developed and applied to assess the validity and applicability of the simulation models. WP3 of VPH-CaSE supplies these methods, integrating them within the development process as shown in figure 2. Ultimately, after proper validation of the models and development of high fidelity corresponding simulations, the experiments are no longer necessary - WP3 will have made itself superfluous.

Tools: To perform physiological measurements, at least parts or models of physiological systems need to be available, as well as the (clinically relevant) measurement devices and imaging modalities. The ESRs have access to the tools needed, either through the laboratory where they have been recruited, or through secondments in academia and industry. Furthermore, training in the use of (new) tools is a major topic in the training activities for the ESRs.

Techniques: Much of the experimental work in VPH-CaSE involves physiological measurements and imaging of anatomical structures. In particular during TA3, many of these techniques were demonstrated and taught hands-on to the ESRs. For the heart-related IRPs, the techniques tended to rely on ultrasound imaging, 3D video registration, and pressure/flow measurements (time series). IRP14 typically uses assays to establish physiological parameters of the live beating hearts.

Support: The steering committee actively cooperates to bring together the IRPs of the ESRs, so as to enhance their experience in fields other than their own. By stimulating secondments and by the sharing of facilities and methods, ESRs are able to learn from each other and develop a broader view of their own IRP, contributing to and benefitting from a collaborative ethos that delivers added value in comparison with a 'standard' PhD.

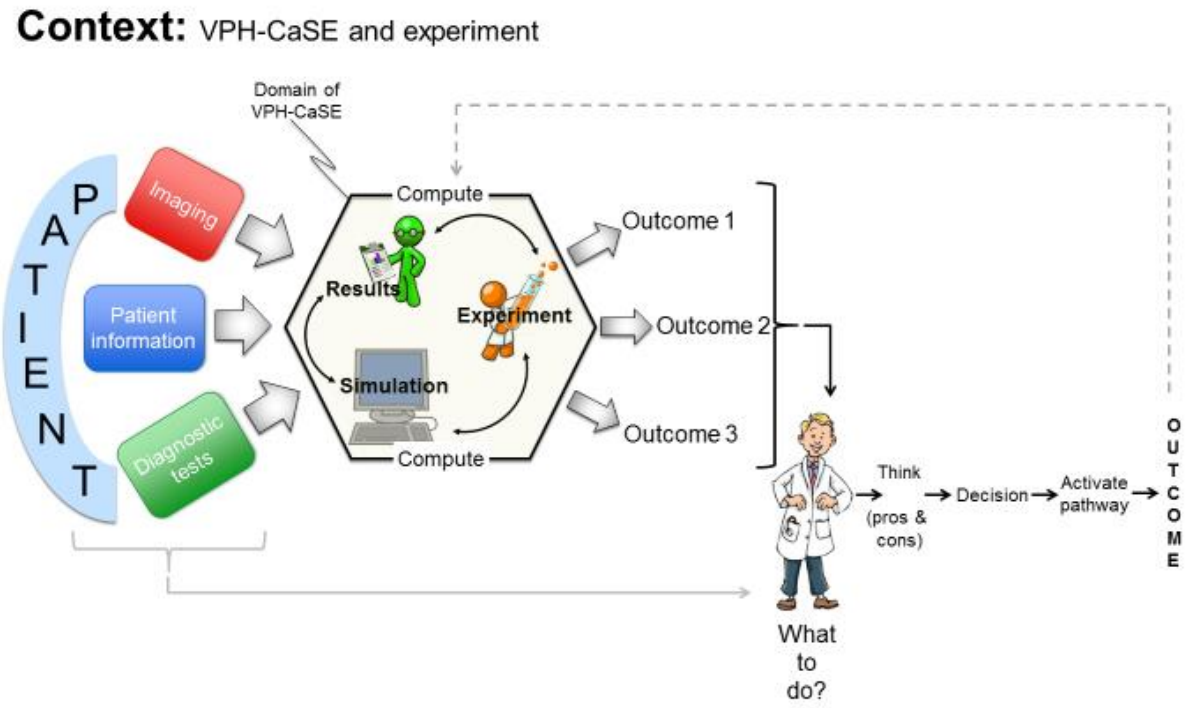

Figure 2 – Integration of experimental methods within the development of novel technologies can aid medical device design and clinical decision making

The paragraphs below summarise the different projects within the Network. In order to provide an overview of the whole network activity for VPH-CaSE in terms of experimental work, the effort of each researcher is described succinctly, highlighting the experimental components in each case.

IRP1: Paolo Ferraiuoli, USFD works on the characterisation of dynamic strain in cardiovascular soft tissues using optical methods. He has built an optical rig consisting of two cameras with lenses, and has performed tensile test on phantoms to show the capabilities of stereo-photogrammetry and digital image correlation (DIC) method to enable full-field surface strain measurements. So far, uniaxial tests have been done successfully.

IRP 3: Louis Fixsen, TU/e: The project concerns the dynamic strain measurement of a beating heart, with or without mechanical circulatory support. So far, he has learned how to work with ultrasound equipment, and has done a set of experiments together with other ESRs in VPH-

CaSE, on the physioheart platform at LifeTec. With one more experiment to go, he is ready to write his first paper on this subject.

IRP 7: Susanna Migliori, POLIMI: Susanna's project on the reconstruction of stented coronary artery from Optical Coherence Tomography (OCT) images has led to a validated method for the reconstruction of a 3D-printed coronary artery model with stent. The model is printed, and using OCT after stent deployment (alongside a commercially available reconstruction software - Mimics), the reconstructed geometry from medical images is compared with micro-CT data taken from the 3D printed model with the implanted stent. The coincidence of both data sets is better than 95%.

IRP 9: Emilia Badescu, CNRS: Emilia is working on tissue motion estimation using ultrasound, and more specifically, transverse oscillation ultrasound (TO-US). The aim is to find lateral motion in soft tissue with respect to the ultrasound beam. She has been working on filtering methods for the raw RF ultrasound data, to find improvement in the motion estimation algorithm. The application of Gabor filters has improved motion estimation by 70-80%.

IRP 11: Massimiliano Mercuri, Therenva: Massimiliano is working on deriving patient-specific boundary conditions from available clinical data in order to perform fluid dynamic simulations for planning surgical interventions. The aim is to find a strategy for incorporating clinical data in a simulation workflow that integrates Therenva's expertise in image processing and ANSYS expertise in numerical simulation. So far, he has been working on defining a strategy for segmenting and preparing CFD models from available CT scan data, as well as a strategy that could be used for tuning inflow and outflow boundary conditions for CFD models using a combination of MRI and CT scan data.

IRP 12: Simone Ambrogio, LTO: Simone Ambrogio is working on a dynamic flow phantom for clinical imaging modalities. This focusses on physical development of the phantom, and so far he has built and tested an air-based vortex ring generator, evaluating its reproducibility for flows in the Re 2000 range. Both ring velocity and change in size were measured and compared with analytical solutions. Data is encouraging and provides confidence for development of a device suitable for multimodal imaging.

IRP 14: Benjamin Kappler, LifeTec: Benjamin's project focuses on the improvement of LifeTec's PhysioHeart platform. While this platform is quite stable, the longevity of the heart in use may be improved further by good assessment (and consequent follow up) of the physiological changes of the muscle and circulating blood over time. Benjamin has done measurements on damage markers as found in the circulating blood. It appears that decreasing albumin levels, (after as soon as 30 minutes), may lead to increased oedema and consequently to later failure of the isolated heart.

For reference, a summary table with a brief description of projects, ESRs and Institutions involved in WP2 is presented in Table 1.

Table 1: Projects and ESRs

Paolo Ferraiuoli	ESR 1: Optical characterization of dynamic strains in soft tissue	University of Sheffield
Louis Fixsen	ESR 3: Experimental assessment of Heart condition evaluation in LVAD-supported patients	Technische Universiteit Eindhoven
Susanna Migliori	ESR 7: Patient-specific modelling of bifurcation stenting procedures for interventional planning	Politecnico Di Milano
Emila Badescu	ESR 9: Diagnosis of cardiovascular pathologies by 3D vector motion estimation using Tranverse Oscillations - Ultrasound	Centre National de la Recherche Scientifique
Massimiliano Mercuri	ESR 11: Tuning of boundary conditions parameters for hemodynamics simulation using patient data	Therenva SAS
Simone Ambrogio	ESR 12: Development of a Complex Flow Phantom for Diagnostic Imaging	Leeds Test Objects
Benjamin Kappler	ESR 14: Myocardial Physiology in Isolated Cardiac Tissues	Lifetec Group

Experimental and Imaging Methods and Technologies

A list of currently used experimental and imaging methods and technologies is provided in the table below. It is important to note that, whilst some ESRs may use diverse methods in their IRP, there is often commonality in the underlying technology providing opportunities for exchange of knowledge and common training within the network.

Table 2: Summary of Methods and Technologies for each project involved in WP3

IRP	ESR	Methods	Technologies
1	P Ferraiuoli	3D Digital Image Correlation	Digital CCD cameras, MATLAB
		Images captured using a stereo-system made of two digital CCD cameras equipped with c-mount lenses. Acquisition and synchronisation of cameras is achieved with a custom made graphical user interface (GUI) developed in Matlab. Calibration and 3D reconstruction is performed using the Matlab Image Processing Toolbox. Digital image correlation and strain computation are performed using an open source software (Ncorr) and custome made Matlab routines, respectively	

3	L Fixsen	US characterization of live tissue	MATLAB; Ultrasound; isolated beating hearts
		Radiofrequency data of the short-axis view of the left ventricle is acquired using a modified US system. Displacements and strain around the wall are calculated using a strain imaging algorithm developed at TU/e, in MATLAB.	
7	S Migliori	OCT	3D printing
		A rigid phantom was created to resemble a typical left anterior descending (LAD) coronary artery with bifurcations. A stent (Multilink8 from Abbott Vascular) was deployed in the phantom and medical imaging techniques (OCT and angiography) were applied. In addition, the phantom underwent a micro-CT scan that was performed both before and after stent deployment. A commercially available reconstruction software was used to extract the phantom centerline and reference data to validate the developed reconstruction method. Particularly, this method comprises the segmentation of OCT images to identify lumen contour and stent struts that are respectively defined as set of points. Then, these components are aligned with the phantom centerline according to planes that are orthogonal to the curve. The lumen is reconstructed by fitting a surface on the oriented lumen contour. The actual configuration of the deployed stent is obtained by morphing the centerline of the undeformed stent on the corresponding set of points. Lastly, the resultant reconstructed components were used to define a geometry for CFD analysis and the feasibility of computational simulations was then investigated.	
9	E Badescu	US vector imaging	MATLAB , echo
		Transverse Oscillations (TOs) introduced for US images A phase-based motion estimator has been developed Acquisition sequences for 3D imaging are being developed on a Verasonics system	
12	S Ambrogio	Instrumentation design; Video capture & measurement	MATLAB; Audio; Video; 3D printing; V.I.E.W
		Consideration of a physical flow phantom for medical imaging has led to the ring voretx as a candidate for controlled complex flows. Important characteristics of such a phantom are reproducibility, stability, controllability, and predictability. These features have been explored with a simple experimental rig involving a combination of 3D printing, instrumentation, video capture and analysis. The results indicate suitability of the ring vortex for complex flow phantom design, which will be developed in the coming period.	
14	B Kappler	Physiological assessment of isolated beating hearts	Clinical chemistry assays, blood sampling
		Blood tests (panels) are based on clinical chemistry assays to determine physiological and pathological situations of the body and its organs. Blood panels specific for the PhysioHeart platform were identified and used on blood samples. Blood sampling was performed at different time points during the PhysioHeart procedure from heart harvest until the heart failed during working mode. The panels for instance include tests for cardiac damage, metabolic state, nutrient, waste products. electrolytes, hormones, blood gas and more.	

5.2 Experiment and Imaging – a Perspective from Within the VPH-CaSE Clustered Topics (Figure 1)

5.2.1 Cardiac tissue function and cardiac support.

This topic involves a significant amount of experimental work, mostly focussed on isolated beating hearts, as provided by LTG. ESRs from TU/e, LTG, UCL and CNRS work together on assessment of mechanical behaviour, electrophysiology and clinical assays to provide a complete characterisation of the platform. Moreover, electrophysiological measurements are done by guest researchers from Amsterdam University, who specialise in high-resolution electro cardiogram measurements. The experimental approach involves complete assessment of the cardiac function of the isolated beating heart platform. As such, it delivers information for development of new diagnostic methods, to be used in clinical applications related to heart disease. Examples include the remaining functional capabilities of the heart in heart failure patients, with or without mechanical circulatory support, and local ischaemia patients. Benefits are to be expected for both industrial beneficiaries (LTG; improvement of the platform) as well as academic beneficiaries (TU/e, UCL, CNRS; development of research methods, measurement methods and image processing) and clinical partners (UMCU, CHE; new diagnostic opportunities for patient studies).

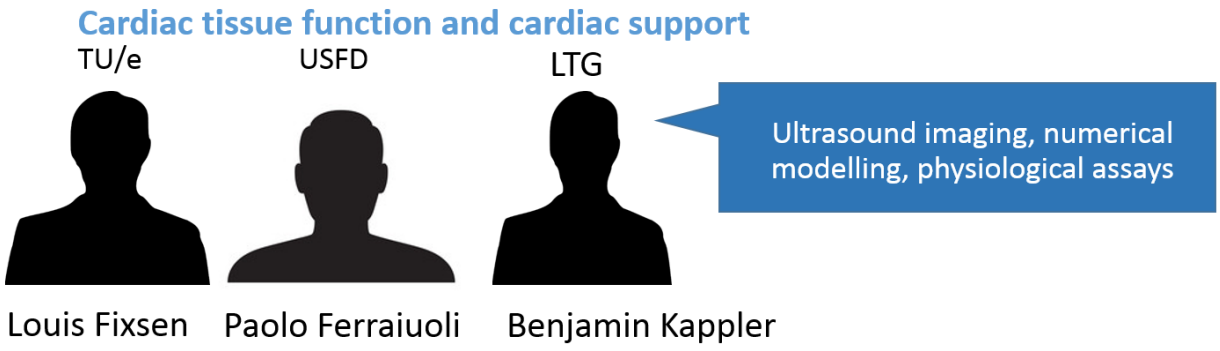

Figure 3: ESRs working on Cardiac tissue function and cardiac support

5.2.2 Cardiovascular haemodynamics – pathology and intervention

Experimental work within this topic focuses on validation methods being developed by Susanna Migliori, POLIMI as a complement to her simulation work within WP2. This includes use of Optical Coherence Tomography (OCT) methods and 3D-printing to produce coronary artery models. In addition, 3D printing has been explored by other ESRs as a tool to promote public understanding of simulation techniques as part of the Outreach activities undertaken by VPH-CaSE.

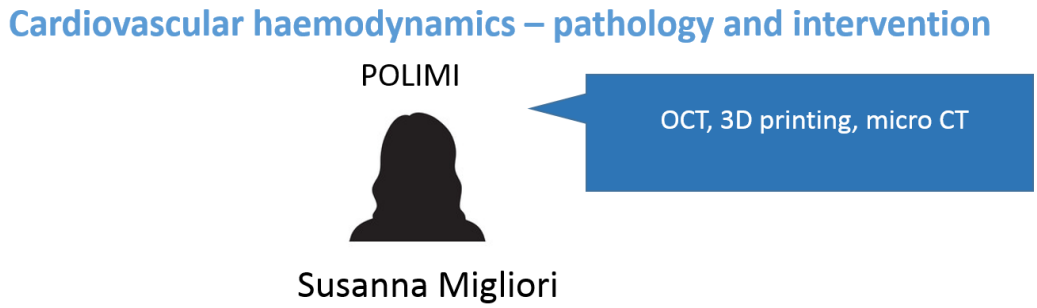

Figure 4: ESR 7 contributes work related to Cardiovascular haemodynamics – pathology and intervention

5.2.3 Image based diagnosis and imaging quality assurance

Emilia Badescu (CNRS) is focussed on development of improved image-processing techniques to derive motion information from ultrasound images. Experimental work within this project relates to the acquisition of appropriate ultrasound images with which to evaluate the effectiveness of these novel techniques. Simone Ambrogio (LTO) works closely with Simone Ferrari (USFD) with focus on the experimental characterisation of the performance of a dynamic flow phantom for clinical imaging modalities. The design and experimental assessment of the phantom involves a number of experimental techniques including instrumentation design, flow visualisation and 3D printing for rapid prototyping.

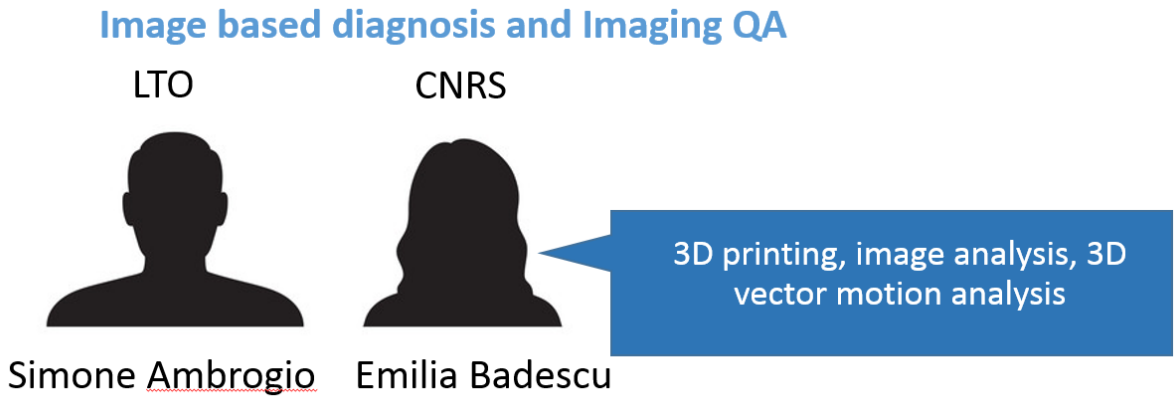

Figure 5: ESRs and work related to image-based diagnosis and imaging quality assurance

5.3 Experiment and Imaging – Training and Secondments

Experimental methods and ultrasound imaging were dominant topics of training activity 3 (TA3), held in Eindhoven from October 3-7, 2016. A detailed description of this training activity is given in deliverable 5.4. In short, ESRs were introduced to experimental methods pertaining to heart function assessment, as well as vascular properties measurement, both including imaging methods, so as to cover most topics relevant to VPH-CaSE. One day of TA3 was dedicated to introductory lectures on methods used in the remainder of TA3, and ethical considerations regarding measurements on humans. Each of the ESRs subjected to personal cardiac output (CO) measurement was required to give his informed consent, in relation to the ethical regulations regarding these measurements. During three days, besides personal CO measurement, ESRs performed experiments on mock circulatory systems involving coronary disease assessment, mechanical circulatory support and vascular tissue properties. Furthermore, LTG demonstrated their isolated beating heart platform.

The Description of Work, highlights a range of secondments relevant to the IRPs. Following TA3, many ESRs expressed their interest and enthusiasm for secondments at TU/e and LTG. Since these beneficiaries can host only a limited number of ESRs at any one given time, careful secondment planning is required. Within VPH-CaSE, secondments are designed to be beneficial for both ESR and beneficiary (which requires due consideration) so that without inconvenience, both parties can benefit.

Numerous secondments have been undertaken or are ongoing between UCL and LTG/TUE (isolated beating hearts in combination with numerical modelling), LTG and TUE (mock circulatory systems, cardiac physiology, ultrasound measurements of cardiac function for mechanical circulatory support), and vice versa. In the latter case, there is not a confined time slot for the secondments, since these facilities are geographically close to each other, enabling mutual visits when they are particularly useful (e.g., when an IPH experiment is performed).

Other secondments (undertaken and planned) in the experimental area include a visit from USFD to TU/e, on vascular stenting and repeated visits from UCL to TUe/LTG, for isolated beating heart experiments. Interactions are also being forged between LTO and USFD (in respect of phantom design), and between CNRS, LTO and USFD to further support the phantom work.

5.4 Experiment and Imaging - Dissemination/Outreach

Effort directed at both dissemination and outreach has been undertaken within 1 year of the ESRs recruitment. This is positive, both for the Network and the ESRs themselves. Table 5 summarises the scientific dissemination activities within VPH-CaSE pertinent to this WP while Table 6 shows the outreach activities:

Table 5: Scientific Dissemination. Type: C = Conference; P = Paper. Modality: O = oral presentation; Po = poster

Date	Target	TYPE	Modality	Title	Partner	Name	Place
26/01/2017		C	Imaging/ Experimental	Ultrasound Strain Imaging of Mechanically supported ex vivo beating porcine hearts	LifeTec	Louis Fixsen	NL
Jul-17	Journal of Medical Devices	P	submitted	The ring vortex: a novel concept for a complex flow Phantom	LTO	Simone Ambrogio	--

Table 6: Outreach Activities

ESR 1	Paolo Ferraiuoli, USFD
	• Festival of Life, USFD, April 2016: How stereoscopic system works and how camera parameters affect image quality • Researchers' Night, September 2016, USFD: 3D object reconstruction using two Raspberry Pi cameras
ESR 3	Louis Fixsen, TU/e
	Biomedical Engineering Research Day April 2016, TU/e
ESR 7	Susanna Migliori, POLIMI
	Researchers' Night, September 2016, USFD
ESR 9	Emilia Badescu, CNRS
	Festival of Life, USFD, April 2016
ESR 12	Simone Ambrogio, Leeds Test Objects
	Festival of Life, USFD, April 2016 Researchers' Night, September 2016, USFD
ESR 14	Benjamin Kappler, Lifetec Group
	Festival of Life, USFD, April 2016

6 SUMMARY AND DISCUSSION

Good experimentation is an underlying principle that underpins VPH-CaSE effort, and it is a feature of each of the three clusters that span the Network. The experimental work of TUe and LTG in respect of heart physiology and measurement is particularly valued for the insights it provides on physiology and its capacity to inform and validate the simulation models. Expertise elsewhere across the Network includes various forms of imaging, analysis and 3D printing. Opportunities for instrumentation design, development, data acquisition etc. abound, which collectively offers sophisticated tools for improved understanding and model validation. The latter is a recurring them in VPH-CaSE, because only through rigorous validation can evidence be provided that instils confidence for use of computational tools by the industrial and clinical end users.

7 CONCLUSION

The work reported shows significant progress of experimental efforts in VPH-CaSE over the first year of the ESR projects. Key experimental skills have been delivered to the full ESR cohort during TA3 (Eindhoven, October 2016). During the next year further results are expected for the individual projects, with increasing collaboration and synergy between them. This will happen as a result of continued training and secondments as agreed by the VPH-CaSE steering group.

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