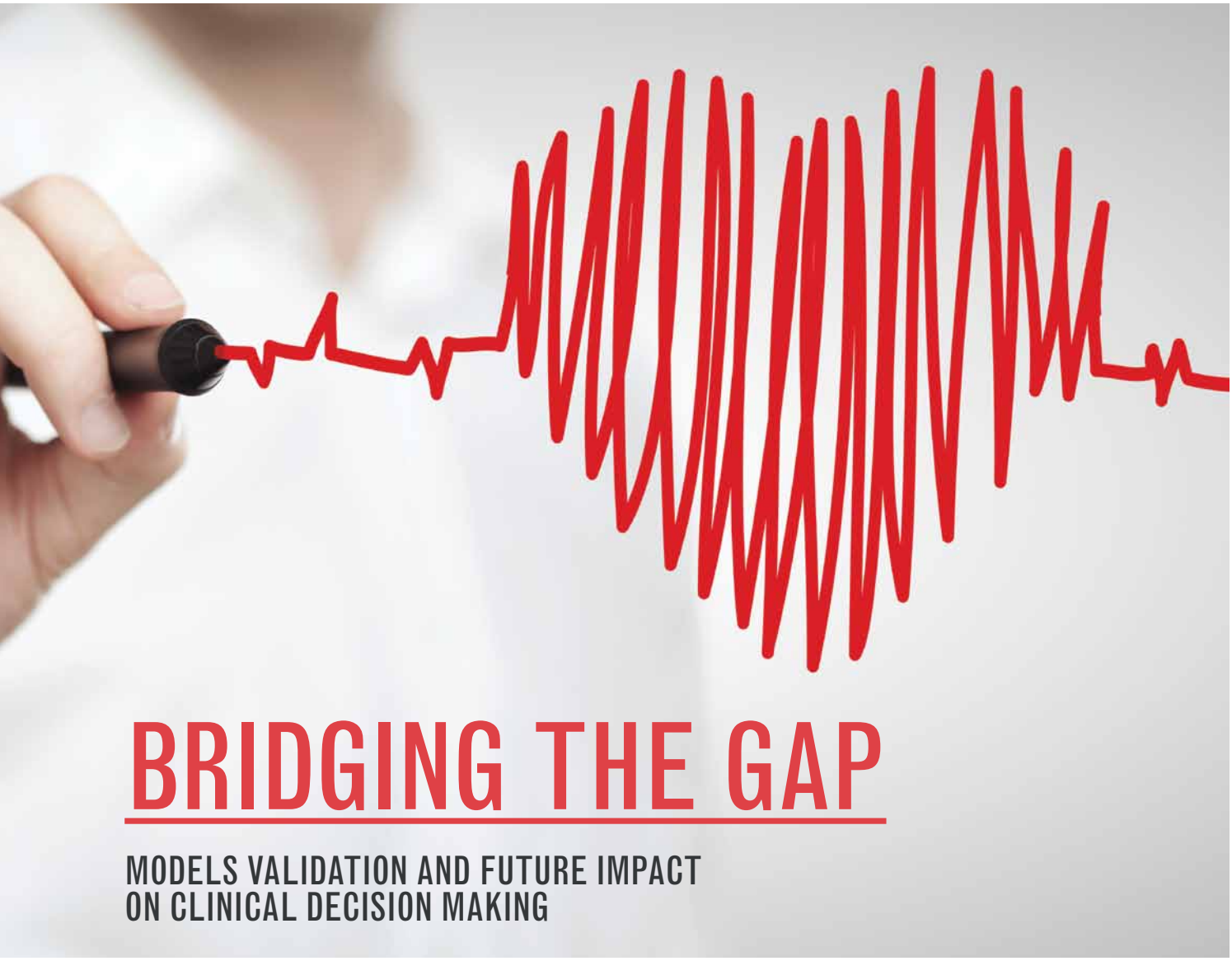
CARDIOPROOF PROJECT

NEWSLETTER | Issue #3 | December 2016



BRIDGING THE GAP

MODELS VALIDATION AND FUTURE IMPACT ON CLINICAL DECISION MAKING

NEWSLETTER INFORMATION

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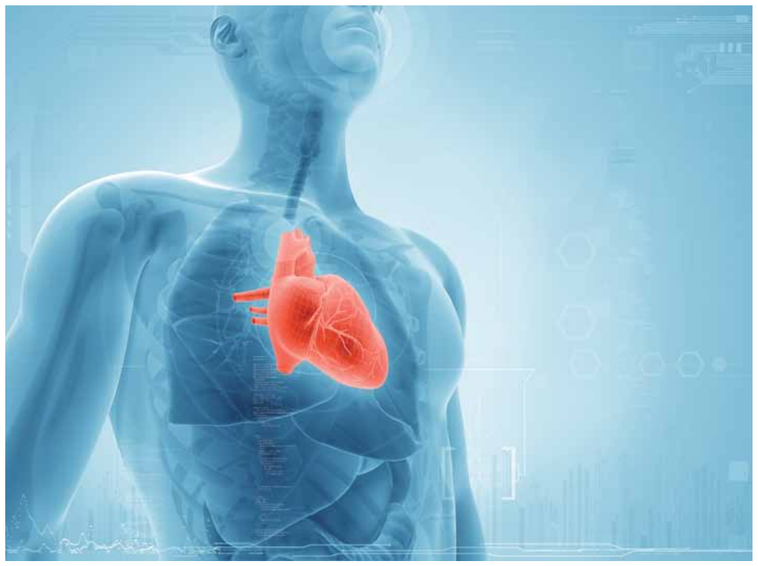
THIS ISSUE

Dear Readers,
Welcome to the third and last issue of the CARDIOPROOF annual newsletter. In this last year, the project entered its final stage, during which specific attention was devoted to finalising the development of clinical predictive models and relevant prototype tools across all lines of research, contextually **validating reliability and accuracy of simulation models in the clinical setting** by comparing physiological patients' parameters with model-based predictions **[page 13]**. Also, significant efforts have been put into the evaluation of their **future impact on clinical decision making and patient care [page 19]**, foreseeing possible applications integrating current medical practice workflow, supporting clinical research scopes, or either fostering **further innovation and business opportunities [page 17]**.

This final issue travels through major accomplishments attained throughout the project, their baseline principle, implementation workflow, validation and potential impact. Among the most advanced solutions we can emblazon the ***fluid-structure interaction*** (FSI) model by Siemens Healthcare GmbH, aimed at parallelly assessing **anatomy, haemodynamics and wall mechanics of the ascending aorta** in pathological and post-treatment scenarios, for the use of which a web-based visualisation tool with IMR-based enriched data is already available for cardiologists **[page 10]**. Also, the electromechanical model of the heart implemented by Medical University of Graz was demonstrated to be a solid base to describe **left ventricle pump function and blood flow patterns in aortic valve disease** by means of *computational fluid dynamics* (CFD) kinematic models **[page 4]**. Coupling this model with the *smoothed particle hydrodynamics* (SPH) method by ESI Group, it was possible to effectively **simulate valve replacement interventions** and predict hemodynamical flow after surgery **[page 7]**. These tools are flanked by the ***virtual stenting*** software, which has been perfected for allowing usage on a normal internet browser.

The issue also highlights some initiatives allied to the project scopes. Particularly, CARDIOPROOF successfully organised its final conference within the **Association for European Paediatric and Congenital Cardiology (AEPC) 2016 Annual Meeting**, with an exhibition booth showcasing project results, as well as organising a dissemination workshop. Also, during AEPC 2016 CARDIOPROOF managed to directly engage participants to the impact assessment of the ***virtual stenting*** tool on clinical decision making in cardiology **[page 23]**. Meanwhile, the project coordinator launched the **Health Data Interest Group** within the **Research Data Alliance**, to explore – together with relevant stakeholders from all around the world – the most suitable solutions enabling open data sharing and promoting the acceleration of data driven innovation in healthcare, particularly focusing on privacy and security of personal health data [**page 22**]. Finally, the Consortium managed to ensure the future sustainability of the project results, thanks to the involvement in a newly started Horizon 2020 project, **MyHealthMyData**, which will employ the existing project infrastructure and de-identified clinical datasets as base for the creation of an EU-based platform for consented health data sharing **[page 21]**.

Overall, the high level of commitment and cooperation between all partners has made it possible to achieve the vast majority of the project objectives and in important ways clearly exceed them. As a conclusive remark it can be said that, after three year of activity, CARDIOPROOF concretely contributed in laying the foundation of **the new era of model-based precision medicine**, where physicians will trustingly rely on itemised patient-tailored outcome predictions to make the most appropriate decisions for the good of their patients.



AN ELECTRO-MECHANICAL MODEL OF THE HEART FOR PHYSIOLOGICAL PREDICTIONS

GERNOT PLANK
Medical University of Graz

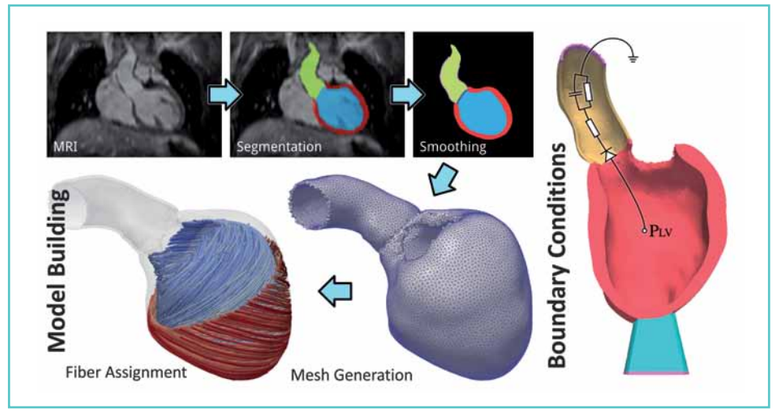
Aortic valve disease (AVD) is a disorder characterized by pressure and/or volume overload of the left ventricle (LV). Such overload conditions trigger a cascade of events referred to as remodelling, which entail **maladaptive structural and functional alterations of LV and aorta**. If left untreated, this condition may ultimately progress towards heart failure, a severe impairment of the heart pumping capacity. For most severe cases, AVD treatment appears essential, but the **optimal timing and type of treatment are often difficult to determine in the clinical setting**. Further, the guidelines are complex and largely rely on gross parameters characterizing only global pump function, which may provide an insufficient basis for diagnosing the state of disease and for planning an optimal therapy. For these reasons, the objective of our work was to augment current clinical decision-making support tools with the development of a **computational modelling workflow for building patient-specific in silico models of LV and aorta of AVD patients**. These are considered a comprehensive representation of all physiological mechanisms relevant to LV pump function and blood flow, and are custom-tailored to individual patients in a process referred to as "personalization" to ensure that the model replicates all clinical observations for a given patient. These mechanistic models can be reliably used to **probe the effect of different therapeutic options and identify which therapy yields the best post-treatment outcome**. Models of AVD must account for the **biophysics governing pumping capacity, i.e. the deformation of the LV** pushing the blood pool out of the LV into the aorta, and the **ensuing flow pattern**, influenced in turn by the opening dynamics and the geometric properties of the aortic valve in its open configuration.

Typically, modelling work resorts to image-based kinematic models using the observed endocardial motion as an input to blood flow simulations. While such models are suitable for analysing the hemodynamic pre-treatment status, they are limited in predicting the response to interventions that alter afterload conditions, such as aortic valve replacement or repair. To overcome this limitation, we implemented **mechano-fluidic models employing biophysically detailed electromechanical models to provide the kinematic input to blood flow**.

THE ELECTROPHYSIOLOGICAL MODEL IMPLEMENTATION WORKFLOW

Our team developed a three-stage automated workflow for the creation of *computational fluid dynamics* (CFD) kinematic models for combined cardiac and vascular blood flow simulations, including: **1) building of an anatomically accurate model of LV and aorta; 2) personalization of the electrophysiological model** to drive the LV electrical activation and trigger the build-up of active forces; and **3) tailoring of passive and active tissue properties** of the biomechanical model. The fully automated pipeline takes **segmented MRI images** to generate an accurate representation of a patient's LV and aorta in less than 10 minutes (Figure 1). Then, **clinical ECG data** are used as input to personalize the electrophysiology model. An electrophysiological forward model is developed to generate several activation sequences, among which the activation pattern best matching the clinical ECG data is adopted (Figure 2). **The biomechanical model** of the LV is based on three main components: **a constitutive model** describing the passive mechanical tissue properties; **an active myofilament model**, which drives mechanical contraction and relaxation; **a lumped haemodynamic model of the cardiovascular system**, to serve as a pressure-flow boundary condition during the ejection phase. All model components require personalization based on haemodynamic pressure-volume data, clinically measured prior to treatment (Figure 3).

Figure 1 | Left panel: workflow for building anatomical models. Right panel: Setup used for simulating LV electromechanics including boundary conditions and coupling with the circulatory system.



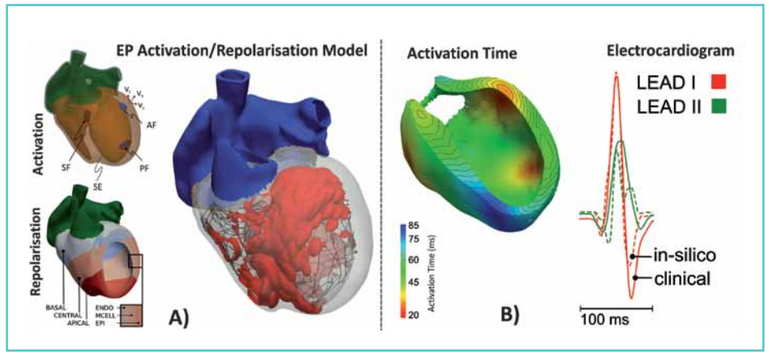


Figure 2| Modelling electrophysiological activation and repolarisation sequences driving mechanical contraction and relaxation.

A) Shown are factors governing activation and repolarisation of the LV as well as a visualization of activation wavefront traversing the myocardium (right panel).

B) Patient-specific activation sequence and comparison between clinically recorded and simulated ECG.

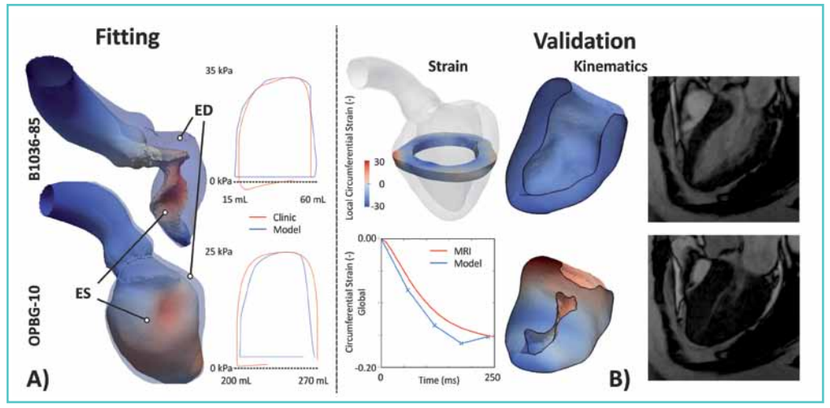


Figure 2| Fitting and validation of LV electromechanics simulations. A) Shown are end-diastolic (ED) and end-systolic (ES) configurations along with measured and fitted pressure-volume loops. B) Validation of simulated strains and kinematics. Shown are circumferential strain distribution (upper panel) and global circumferential strain (lower panel) over the LV slice indicated above. Comparison of kinematics at instants in time around ED (top panels) and ES (bottom panels) between model and clinical MRI.

MODEL VALIDATION, OPTIMISATION AND APPLICABILITY

The final phase of the project has been focused on **streamlining the entire workflow to facilitate the modelling of a larger cohort of AVD patients**, allowing to obtain the pre-treatment status of 20 patients so far. The goodness of fit (Figure 3A) was verified and a rigorous validation was performed with independent clinical data, not previously used for model fitting. Validation data include strain and kinematic metrics such as circumferential and radial strains as well as LV rotation and torsion (Figure 3B). The validated patient-specific heartbeat models were employed to set up a **CFD pre-and post-clinical intervention simulation framework**. As first step, the **patient's pre-treatment status** with the diseased aortic valve is reproduced to verify that blood flow and pressure traces match-up between biomechanical and CFD model. Then, **the diseased valve is replaced by a prosthetic valve to predict changes in pressure drop across the aortic valve** in a post-treatment scenario. The biomechanical model is also employed for simulating possible **alterations of the heartbeat pumping efficiency**, where additional metrics such as stresses and myocardial work can be computed and compared against pre-treatment data. Based on the assumption that strains and stresses beyond a critical threshold are driving remodelling and disease progression, we believe that differences in these metrics could indicate whether **reverse remodelling, i.e. recovery from heart failure symptoms**, is possible or not. At present, simulations and result analysis for the post-treatment scenarios is ongoing to identify the **critical factors providing the highest predictive power, particularly in regard to the patients' recovery ability after intervention**. Further analysis to compare outcomes across different valve models will also be performed to better understand their impact upon hemodynamic and heart pumping performance. The efficiency of the modelling workflow and execution, the efficacy of the biophysical representation and the excellent match between clinical data and model output render this in silico cohort and the relevant modelling workflows promising candidates for a future general purpose platform to derive computational models for a wider range of clinical use cases.

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PREDICTIVE MODELLING OF HEMODYNAMICAL FLOW AFTER AORTIC VALVE REPLACEMENT

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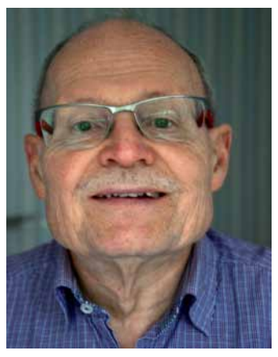


One of the CARDIOPROOF main goals is the development of computational models and tools for predicting effects of therapeutic intervention to support clinical decision making. In this context, the activity of ESI Group has been focused on the **simulation of hemodynamical effects of aortic valve replacement based on electro-mechanical models from the Medical University of Graz (MUG)**. These models are based on patient imaging data of left ventricle, aortic root and aorta geometry. In the last year, ESI succeeded in obtaining **complete flow simulations at various outflow conditions, in terms of pressure and flow rates including those corresponding to severe malfunctioning of the valve**, relying on a model of a segmented valve from 3D echocardiographic sequences. Moreover, flow simulations were conducted with **two artificial valves replacing the original one, opening**

Figure 1 | Morphology and opening of a numerical valve model for patient B2804-29.

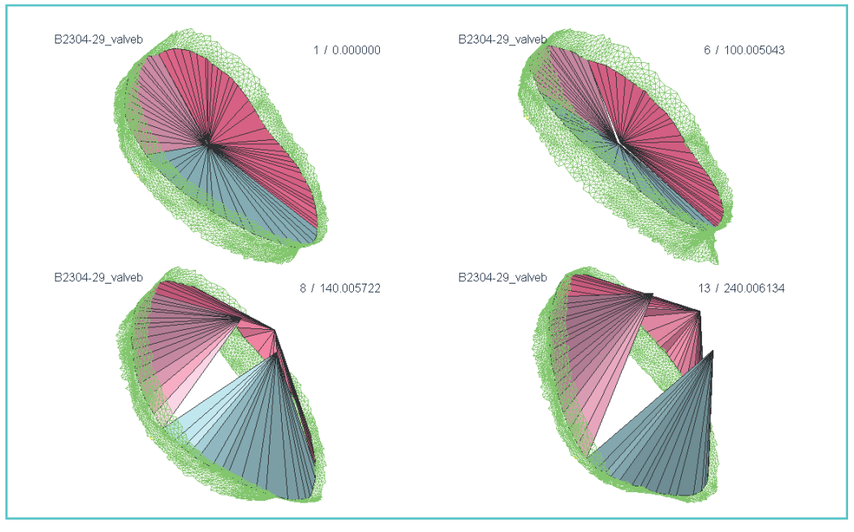
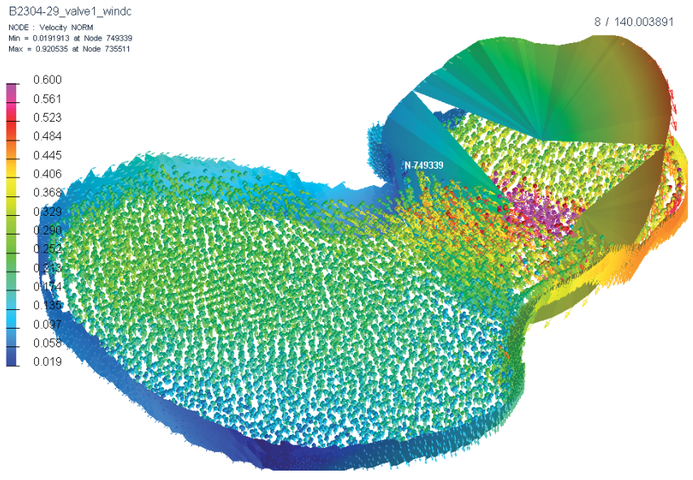


Figure 2 | Velocity vectors in a section of the B2804-29 model at 140 milliseconds after end-diastole showing the partial opening of the numerical valve.



the way for virtual valve replacement assessment.

MODEL IMPLEMENTATION

Simulation of hemodynamics across opening and closing valves is challenging, which motivated to use the ***smoothed particle hydrodynamics* (SPH) software developed and enhanced by ESI Group [1,2]**.
The wall displacements responsible for ejecting the blood during systole are taken from the **patient-specific electromechanical models of the heart from MUG**. Additional required information, such as the morphology
and opening characteristics of the aortic valve, and the outlet conditions at the cut section of the ascending aorta, were provided through **numerical valve models (Figure 1) with assumed flow areas during opening**. In one single case, though, it has been possible to use **echocardiographic images to create a valve model.**

AFTER-SURGERY FLOW SIMULATION

Predicting hemodynamical flow after valve surgery requires computer models where a replacement valve can be integrated in the morphology of the patient-specific model. To achieve this goal, algorithms have been developed to **position mechanical replacement valves and make them fit as a sort of "virtual surgeon"**.
The blood flow in the left ventricle and ascending aorta was simulated with **a numerical model of a healthy valve**, and the outflow into the upper part of the aorta using **parameters of the windkessel model [3].** Figure 2 shows the flow field through the valve at high ejection rate in a section of the left ventricle and the aorta. Then, the effects of the implantation of an artificial valve on the flow were assessed with **two types of artificial valves, the ONXA-29 (Figure 3) and the smaller SJM-27**. For both, a finite element model of the mechanical valve has been generated and inserted into the patient-specific aorta geometry (Figure 4), and **the fitting of the aorta wall near the valve was conducted through a tool simulating the real surgical procedure [4], allowing the valve to follow the deformation of the aortic root**.
For ONXA-29 the pressure difference between the two sides of the valve showed a significant decrease in pressure loss. Replacement with SJM-27,

Figure 3 | Computational model of the ONXA-29 valve, in open position.

Figure 4 | Part of the model after virtual surgery showing the fit to the valve.

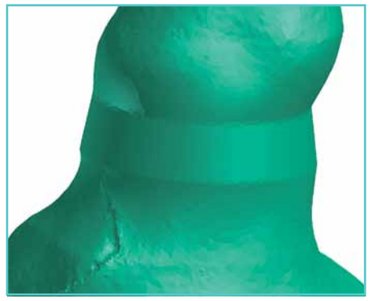
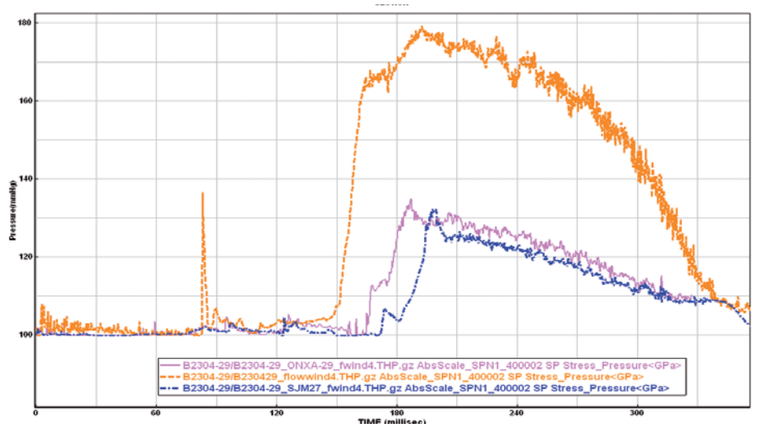


Figure 5 | Pressure in a specific location of the left ventricle for no valve replacement (orange), replacement with ONXA-29 (pink) and SJM27 (blue).

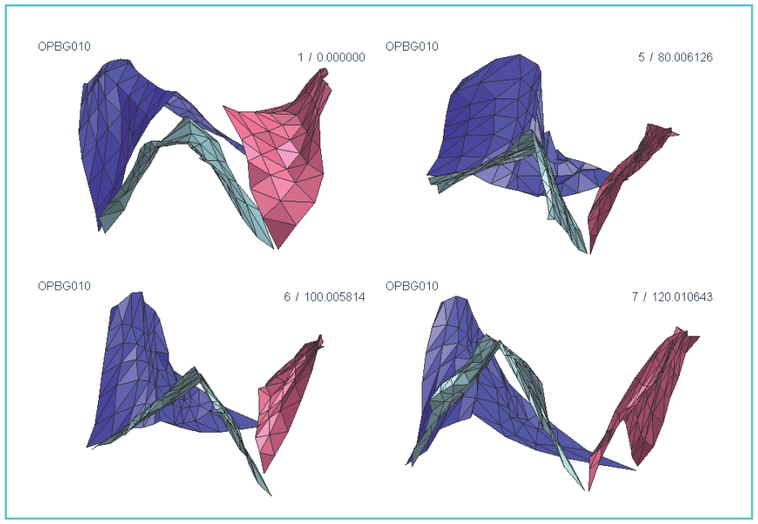


besides some differences in the velocity field near the valve, yielded similar results (Figure 5). Besides pressures in the left ventricle and aorta and the flow field, other clinically relevant results of numerical simulations were flow rate, flow velocity at the valve, forces on the wall and the valve, and the corresponding work, pre-and post-intervention.

NEXT STEPS AND FUTURE CHALLENGES

As mentioned above, in one single case it was possible to apply the **information from echocardiographic images to model the actual flow of the untreated patient** without relying on numerical valve models, by converting a segmented valve model from Siemens Healthcare GmbH into a finite element mesh and fitting this valve to the aorta model (Figure 6). The resulting SPH flow simulations yielded blood pressure values in better agreement with the ones obtained from the MUG heart model, showing the potential feasibility of including natural patient valve information into the patient-specific left ventricle and aorta model.
Based on the knowhow generated in CARDIOPROOF, we could more easily create **a modelling chain which will convert information from MRI images** into segmented models, in turn to be translated into electro-mechanical simulation of left ventricle and aorta walls. These will allow for SPH simulations of hemodynamical flow providing relevant information to support clinical decision making.

Figure 6 | Model of the natural valve at various stages.



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A WEB-BASED VISUALIZATION TOOL FOR FLUID-STRUCTURE INTERACTION MODELLING OF THE DILATED AORTA

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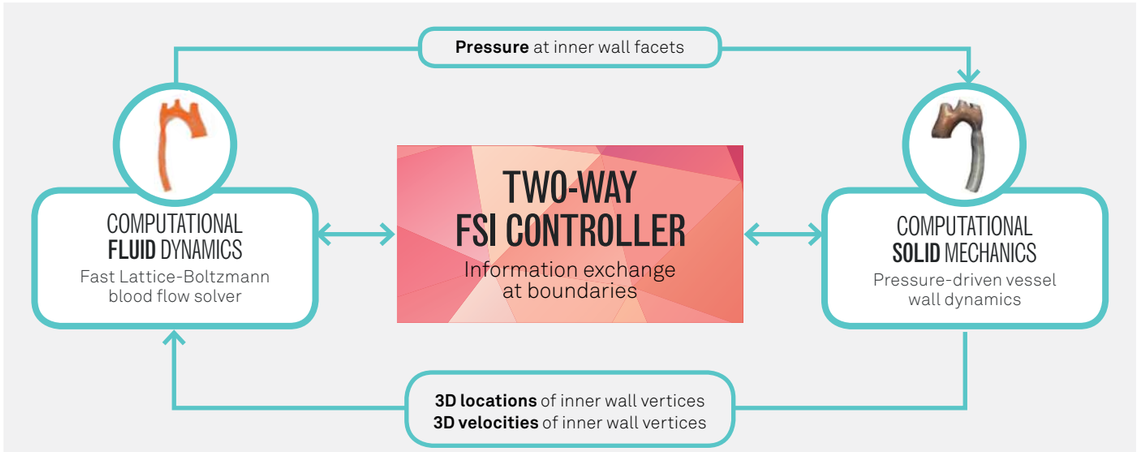
SIEMENS Healthineers

Comprehensive understanding of the state of a patient's cardiovascular system, i.e. blood pressure, flow pattern and velocity, as well as possible stresses interesting the vessel wall, can be decisive for clinical evaluation and procedure planning. For instance, the severity of aortic dysfunctions like aortic valve disease (AVD) or aortic coarctation (CoA) can be assessed from intraluminal pressure information, and arterial wall stresses in the ascending aorta and aortic arch can be important indicators of the development of cardiovascular diseases. However, to date, local aortic pressure measurements are only acquired invasively through catheterization, blood flow is measured at rather low resolution, and local arterial wall properties are not directly measurable, impeding effective clinical prediction.
Within CARDIOPROOF, Siemens Healthcare GmbH was interested in **the development and validation of fully-coupled computational models of blood flow and wall deformation, or in short *fluid-structure interaction* (FSI) models, aimed at assessing the role of haemodynamics, wall mechanics and anatomy in dilatation of ascending aorta.** Aortic arch dilatation, a malformation frequently occurring in patients suffering from aortic disease, constitutes a significant predictor of acute and potentially fatal cardiovascular events such as dissection and rupture, and an accurate knowledge of its evolution appears crucial for effective clinical decision making.

FULLY-COUPLED FSI MODELLING IN THE AORTA

Our FSI modelling approach followed **a standard paradigm for coupling fluid dynamics and solid mechanics models [1], where a two-way "FSI controller" (Figure 1) controls the exchange of information among them.** Fluid dynamics inside the aorta lumen are computed through a highly efficient Lattice-Boltzmann-based blood flow solver [2], and pressure generated by the fluid near the inner aorta surface is propagated towards a finite element solid model [3]. The fluid pressure, in turn, causes wall stresses at the fluid-solid interface, driving the aortic wall dynamics (e.g. dilatation of the ascending aorta during peak systole). Such changes in aorta geometry trigger adaptation of the computational fluid domain. To model this, the updated wall geometry and velocity at each time-step, computed by the solid solver, are propagated back to the fluid solver, which closes the two-way coupling cycle.
Within the final year of CARDIOPROOF, we investigated the feasibility of **combining non-invasive MRI with fully-coupled FSI models to predict post-procedural changes in pressure, blood flow and wall stresses, by virtually simulating the effect of actual therapies such as stenting or valve replacement.** To this end, patient-specific aorta geometry and blood flow information at baseline are used to compute high-resolution, time and space-based blood flow patterns, pressure fields and local wall stresses in the aorta, at pre- and post-procedural level. Then, baseline FSI simulations are compared to post-treatment virtual predictions.

Figure 1 | Fully-coupled, two-way FSI model: overview of the interactions between the two models.



MODEL VALIDATION AND INTEGRATION INTO A WEB-BASED TOOL

Together with clinical partners, we are now finalizing the **validation of this new approach by comparing simulation results with actual patient data.** For instance, in a set of experiments on CoA patient data, we compared the maximum pressure gradient at baseline and the one computed by FSI model after virtual stenting, observing a good consistency between actual post-operative data and FSI model predictions. In parallel, we are analysing flow patterns, wall stresses and other parameters of clinical interest, to acquire the widest understanding of applicability and limits of our FSI model in clinical setting.
As latest step, the integrated model has been translated into **a zero footprint, web-based visualisation tool meant to provide cardiologists with imaging-based enriched data to support clinical decision making (Figures 2-3)**, allowing straightforward and intuitive analysis of modelling predictions. Compared to the standalone application presented last year, the most recent version no longer requires installation, can be remotely accessed through any web-browser and run on either computers or handheld devices (e.g. tablets, smartphones). In addition, the prototype features were significantly extended (3D+t volume rendering, advanced plot tools, improved patient browser, etc.) to increase the overall usability.

STATE OF THE ART AND FUTURE DIRECTIONS

At present state, **fully-coupled computational FSI models have the potential to comprehensively represent realistic cardiovascular physiology** much more effectively than current standalone

fluid or solid models, as they **combine simulation of fluid dynamics, solid mechanics and their complex interactions in the human cardiovascular system.** Beyond the scope of CARDIOPROOF, FSI models could be possibly further extended to integrate other organs, such as the heart or even the whole cardiovascular system. However, besides the scientific-technical challenges inherent in the development of such models, their interpretation and validation would become increasingly complex, requiring advanced analysis tools.

The newly-implemented visualisation prototype constitutes the first step towards this goal, possibly paving the way for a seamless integration of these complex systems into a unique clinical workflow.

Figure 2| Patient-browser view in our new web-based prototype.

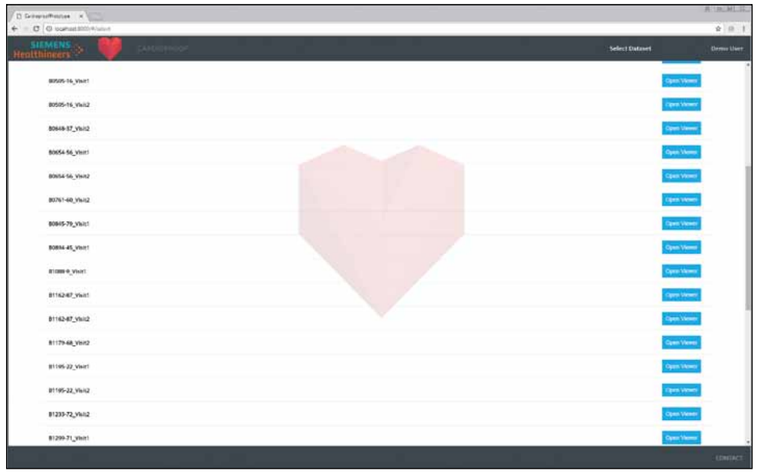


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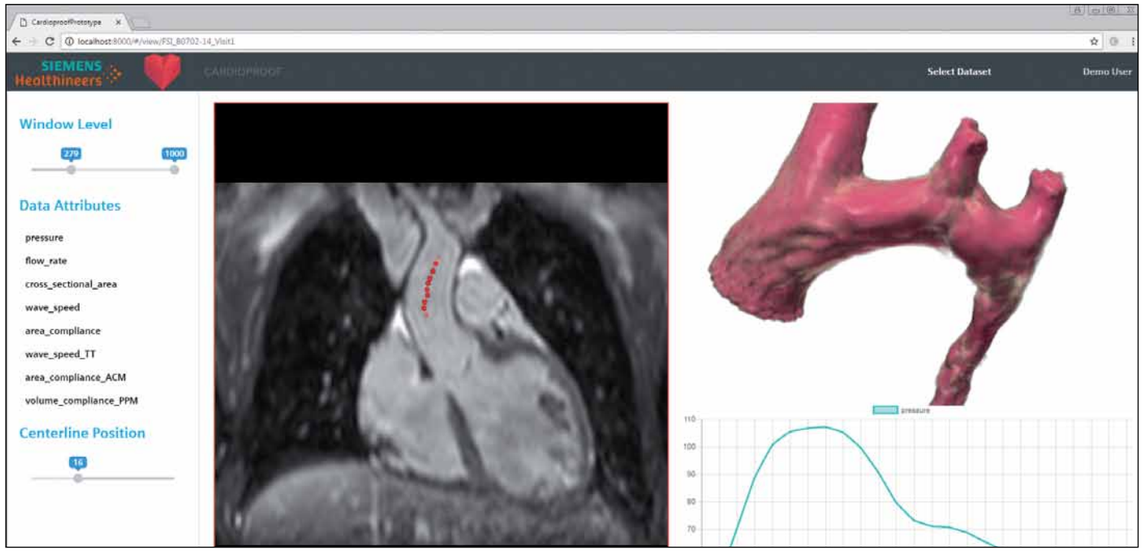
Figure 3| Web-based prototype: analysis and visualization of modelling results with in-browser clinical data rendering (MRI on the left) and 3D+t volumetric rendering of FSI simulations (right). No installation required. It runs in any modern browser.



THE VALIDATION CHALLENGE: TRANSLATING MODELS INTO CLINICAL PRACTICE

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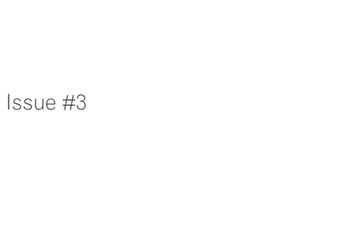

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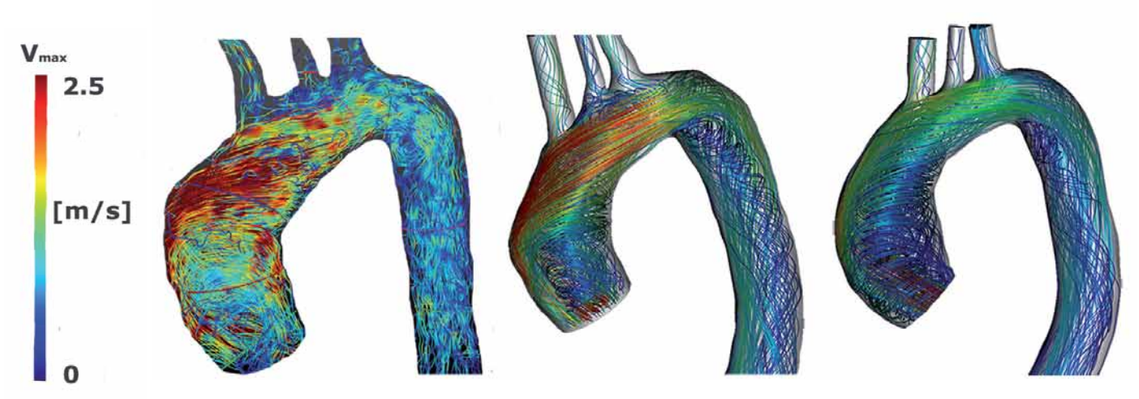
CARDIOPROOF was launched at a key juncture in the evolution of mechanistic models in cardiology, as simulation systems were approaching sufficient stability and breadth to simulate actual clinical case. On this background, the project established as its main focus the task to **bridge the gap between rapidly maturing technology and patient care, by defining applicability and quantifying clinical advantages of different models of pediatric cardiovascular diseases and intervention**.

To this end, the project planned a series of **prospective clinical studies to compare actual clinical cases with treatment outcomes simulated by the models**. An overall of **180 patients** were recruited and followed up in the two clinical areas of interest, **aortic coarctation and artificial valve replacements**, and during the last reporting period, encouraged by promising results gathered in the initial phases, new areas were added further expanding the scope into **cardiovascular responses to exercise and correlations between aortic arch shape and functional heart dynamics.** In all these areas, models have shown to be able to accurately predict target metrics in a statistically significant way. While models were developed using a variety of retrospective data sources, validation was carried out prospectively, following formal protocols of pre-and post-operative diagnostic follow-up, on data collected at **Deutsches Herzzentrum Berlin (DHBZ), Ospedale Pediatrico Bambino Gesù (OPBG) and Great Ormond Street Hospital (GOSH).**

CLINICAL VALIDATION OF MODEL BASED PREDICTION IN AORTIC VALVE DISEASE

In **aortic valve disease (AVD)**, hemodynamics after aortic valve surgery are far from perfect in most cases, resulting in potential risks for the patient, need of subsequent interventions, increased morbidity, mortality and medical costs. In a multidisciplinary team of

Figure 1 | Left: Aortic hemodynamics acquired by 4D flow MRI after an aortic valve replacement with a biological valve prosthesis. Middle: CFD simulation predicting aortic hemodynamics after the treatment based on MRI data acquired before treatment. Right: CFD simulation of the aortic hemodynamics using post-treatment MRI acquisition.



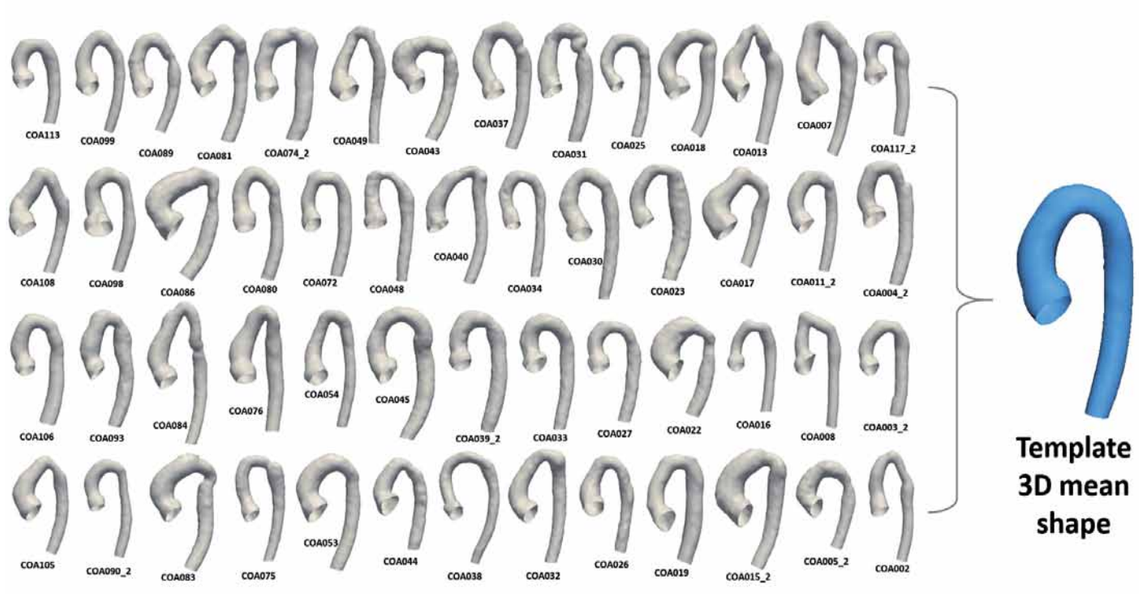
clinicians and engineers, DHZB developed a **workflow for a 4D flow MRI-based virtual aortic valve treatment procedure, personalizing general models on actual patient parameters**. After a clinical validation process involving patients from the three clinical centers, the team successfully demonstrated that modeling results were comparable to the actual hemodynamic outcomes after surgical aortic valve substitution procedures (Figure 1).
As model-based therapy planning has shown able to accurately predict postoperative haemodynamic patterns [1-2], virtual treatment procedures open up new opportunities for **individually tailored interventions**, providing actionable insights for planning of artificial valve replacements in regard to **geometry, size, position and orientation of the valvular planes**, to achieve an optimal physiological hemodynamic restoration on an individual basis.
Besides personalised interventions, virtual patient models also carry some promising potential for future in silico studies not limited to aortic valve disease. Without any risk for the patient, these models could help overcome issues like **inhomogeneity between treatment groups or carryover bias**, currently representing major challenges for interventional studies as well as conventional single case design trials.

MODEL-DRIVEN AORTIC COARCTATION REPAIR ASSESSMENT

Despite a successful **aortic coarctation** repair, patients continue to have long-term morbidities affecting cardiac function and blood pressure. For this reason, being able to foresee intervention outcomes and individually target them on the patients' anatomy is of key importance for improving patient care.
In this regard, OPBG has been involved in verifying validity of the ***fluid-structure interaction*** (FSI) modelling approach developed by Siemens Healthcare GmbH [page 10], providing a bi-directional coupling between a fluid dynamics model describing blood flow and a solid mechanics model of wall deformation, with the ultimate goal of **defining changes in fluid structure interaction in patients with aortic disease**.
The validation approach consisted on **comparing model-predicted physiological variables with the actual state of the ascending aorta at follow-up**, after surgical or catheter intervention.
To accomplish this, post interventional data, including echocardiographic flows, cardiac MRI and catheterization-derived pressure were merged to derive parameters of aortic flow and stiffness, and compared to model-predicted values.
According to results, model showed able to **correctly predict direction of change in pressure drop and aortic wall stress after intervention**, despite minor differences in the magnitude of change, proving able to accurately determine structural and hemodynamical changes in aortic flow, encouraging the use of FSI models as a valuable support to clinical decision making.
In this same strand of research, University College of London (UCL) developed a novel **statistical shape model (SSM) able to extract the entire 3D arch morphology from MRI data (Figures 2-3) and to detect arch shape patterns associated with left ventricular (LV) mass and functional outcomes**, i.e. LV ejection fraction, LV end-diastolic volume, LV mass and blood pressure [3].
Overall larger aortic arches with high arch height-to-width ratio resulted functionally inferior - poor LV function, increased LV end-diastolic volume and mass - to more compact and rounded aortic arches. Using the SSM template, UCL demonstrated as **arch shape can be employed to determine long-term informed follow-up, risk stratification and suitable timing of re-interventions**. The ensuing objective will be to validate this model in a variety of complex

Figure 2 | SSM template yielding deformation vectors to create a 3D clinical aortic arch shape clusters

Figure 3 | Anatomical 3D modelling of complex arch morphology used to statistically identify associated correlation with functional parameters.



heart diseases like aortic valve disease and tetralogy of Fallot, as a predictive tool providing functional parameters for risk-assessment patient stratification and valuable insights for clinical intervention.
In the last year of the project, UCL further expanded its scopes implementing a new methodology to **acquire 4D flow sequence and measure myocardial motion in a breath hold**, allowing to assess complex information about cardiovascular dynamics in a short-period, as during physical exercise [4]. This method is going to be validated in a clinical study with patients with previous repaired coarctation of the aorta, who will undergo **a cardiac MRI while performing an isometric exercise**, to look for haemodynamic changes in terms of heart rate, blood pressure, stroke volume, cardiac output, ventricular mass and function.
Final study goal will be the development of a clinical tool for patient stratification, based on 4D flow and a tissue phase mapping (TPM), comparing physiological response at rest and during exercise. The sequence is acquired using novel rapid breath-hold spiral unfold-ed SENSE TPM for assessment of myocardial velocities in the left ventricle. The tool will be able to **demonstrate changes in the arch physiology, haemodynamics and function during peak exercise**, supporting prediction of timely intervention and appropriate treatment (Figure 4).

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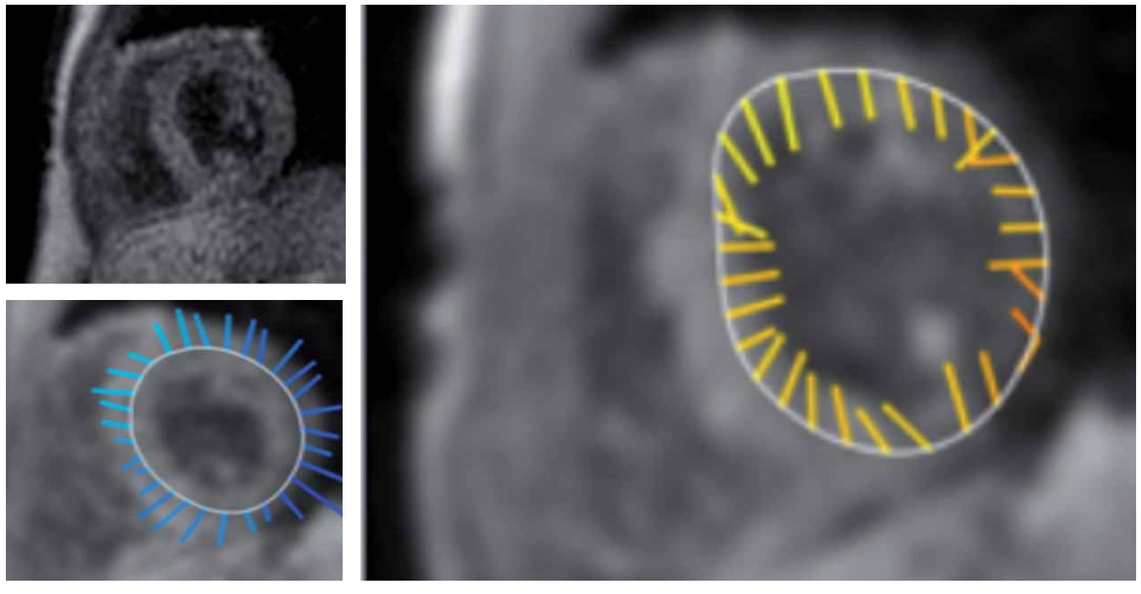
Figure 4 | Rapid breath-hold assessment of myocardial velocities using spiral UNFOLD-ed SENSE tissue phase mapping. The blue and yellow color depicts velocity vector plots.



THE FUTURE OF CARDIOPROOF: AT THE EDGE OF MEDICAL INNOVATION

While approaching the end of the project, the CARDIOPROOF Consortium intensified the exploration of possible exploitation routes, with the aim of **ensuring the future sustainability, re-use and further developments of the project results**. In fact, these are vital aspects of every EU-funded project, which shall make sure that the public resources invested by the European Commission don't get consumed in activities without concrete follow-ups, and not capable of providing an added value to EU citizens, society at large and economy.

CARDIOPROOF focused on two exploitation routes: **on the short-term, the involvement of the project in new research activities, to guarantee the essential objective of the project results sustainability; on the long-term, the creation of a new entrepreneurial initiative,** aimed at commercially exploiting the project results and at the same time creating a new marketplace and business environment for the flourishment of similar VPH tools.

THE SHORT-TERM PERSPECTIVE: CARDIOPROOF RESULTS SUSTAINABILITY

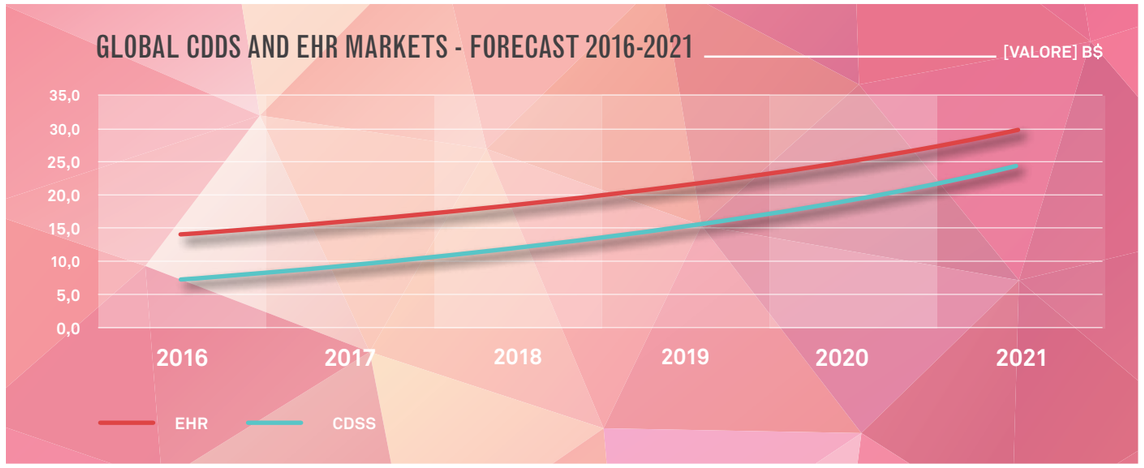
To guarantee the sustainability of its core results in the medium term, a specific effort has been put in place **to make some of the CARDIOPROOF results available for future research initiatives**. This effort led to the submission of a new Horizon 2020 project proposal, eventually funded by the EC: the **MyHealthMyData (MHMD)** project, which will leverage on the **CARDIOPROOF Infostructure** as a basis to create an **advanced and secure repository for personal health data**. Furthermore, the project will make use, for testing and validation purposes, of the **datasets collected within CARDIOPROOF** [see more at page 21].

MY HEALTH MY DATA

THE LONG-TERM PERSPECTIVE: NEW BUSINESS MODELS AND MARKETS

The demand for automation in clinical decision making is rapidly growing as the medical IT environment becomes more and more mature. Triggered by the increasingly mainstream adoption of electronic health records (EHR), **a new era of advanced clinical decision support systems (CDSSs) will be soon become a more concrete perspective**, and – as shown by a recent forecast – CDSSs will be globally the fastest growing market segment in eHealth. From a 2016 capitalization estimated in $7.39 billion, **this segment is expected to grow at a compound annual grown rate (CAGR) of 27.1% from 2016 to 2021 (figure 1), reaching**

Figure 1| Global CDDS and EHR Markets - Forecast 2016-2021 - CAGR CDSS: 27.1% [1].



a total value of $24.55 billion [1]. Still, the growing amount of CDSSs currently in production or available will need dedicated validation methodologies to enter the market.

Considering these elements, the Consortium envisioned a business model in the form of a **multisided technology and services platform, to be then extended over the medium term into a marketplace to connect clinical centres and producers of computerized CDSSs**. The core aim of the system is to drastically **lower barriers to adoption of these advanced, model-based decision support technologies in healthcare and foster mainstream use in clinical care**. This initiative would be the dawn of a completely new market of eHealth tools ready to be adopted in clinical practices as advanced CDSSs, capable of triggering subsequent interactions and interoperability with different products, as well as among a variety of specialised suppliers.
This choice was also corroborated by the recent findings of **Gartner's 2016 Hype Cycle for Emerging Technologies [2]**, which explicitly talked about a "platform revolution". According to Gartner, *«Emerging technologies are revolutionizing the concepts of how platforms are defined and used. The shift from technical infrastructure to ecosystem-enabling platforms is laying the foundations for entirely new business models»*, concluding that *«within these dynamic ecosystems, organizations must proactively understand and redefine their strategy to create platform-based business models, and to exploit internal and external algorithms in order to generate value»*.
Finally, the associated value propositions reveal a potential huge impact for the relevant stakeholders: on one hand, **physicians' needs** will be addressed by CDSS at multiple levels, from **reducing medical errors**, thus increasing patient satisfaction, to **increase in efficiency of the decision-making process**, thus optimising the time available to see more patients or for other activities. On the other hand, the **medical device industry** could benefit of advanced CDSSs and models to **simulate device's behaviour in virtual environments**, thus accelerating the speed of the design process, at the same time **reducing the costs of clinical trials**, optimising the protocols using CDSSs.

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ASSESSING THE ROLE OF PREDICTIVE MODELS IN CLINICAL DECISION MAKING

As CARDIOPROOF was being designed, it soon appeared that the introduction of innovative technology in clinical care was not simply a matter of adding it to existing workflows, and was not going to succeed without **the engagement of physicians, the clear demonstration of their potential and the gathering of strategic feedback**. In this view, the leading role of clinical centers was established as a key driver of the project, for instance by setting up technical requirements driven by clinical expertise, to steer model development toward clinically relevant use cases.
More importantly, cardiologists were directly involved in evaluating **the impact of image-based simulation modeling on clinical decision making** as compared to current standard practice, by means of **a randomized controlled trial** conducted by **London School of Economics and Political Science (LSE)** in collaboration with clinical partners.

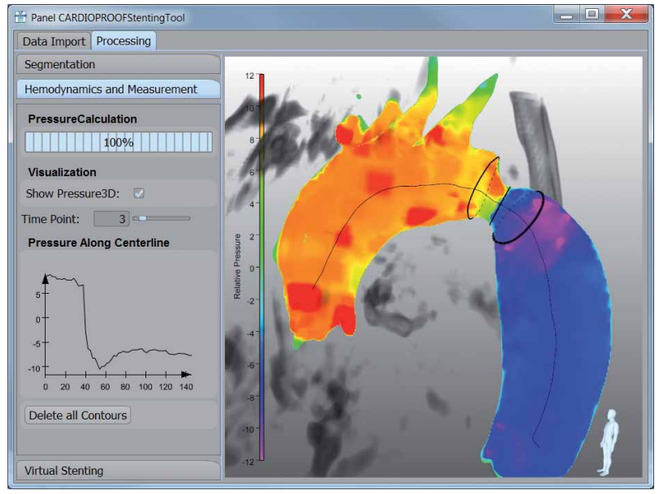


Figure 1| Pre-interventional pressure exploration with *virtual stenting* tool. The system calculates the hemodynamic parameters along the aortic arch, creating a pressure map which highlights the pressure differences before and after the point of coarctation. On this basis, the *virtual stenting* tool computes parameters of aortic arch haemodynamics after aortic stenting procedure.

The study, designed as a **web-based experiment** with a planned sample of 124 pediatric cardiologists practicing in Europe and US, was intended to assess **the clinical value and applicability of the *virtual stenting* system**, the predictive model for aortic stenting implemented by Fraunhofer MEVIS Institute (Figure 1). The trial was specifically directed to investigate **the extent to which treatment decisions in coarctation of the aorta (CoA) can be altered as a result of image-based simulation modeling**. According to the study design (Figure 2), professionals were randomly allocated to see either traditional diagnostic reports adopted by current clinical practice guidelines (group A), or an expanded dataset supplemented by additional parameters obtained from image-based simulation modeling of post-operative outcomes (group B). Participants were then asked to make hypothetical treatment

decisions for three carefully selected 'borderline' CoA cases. The null hypothesis of the experiment was that there would have been no difference between the two groups in the proportion of trial participants making a given clinical decision.

In addition to the online recruitment, LSE researchers took advantage of CARDIOPROOF participation to the latest **Annual Meeting of the Association for European Pediatric and Congenital Cardiology (Rome, June 2016)** to engage further participants in a live test session in situ [see more at page 23]. In this occasion, the study team deemed useful to interview participants to gather preliminary feedback with a quick exit poll, asking: *«Did the additional information provided by the simulation change your initial clinical thinking? Did it affect your initial decision in any way?»*. **Most physicians (76,4%) found these extended cases descriptions of immediate and clear clinical value**, especially in borderline and complex cases where indications between alternative types of treatment or simple medical therapy were significantly overlapping.

Official results are currently being finalized into a relevant publication in a high-impact peer-reviewed journal. Far exceeding the target sample size, eventually **an overall sample of 193 pediatric cardiologists** took part in the experiment, the majority of whom (~80%) were experienced practitioners having treated more than five CoA cases in the previous year. Across experience levels, seniority and other normalized factors, the experiment indicated a possible **influence on treatment decisions for the most complex cases**, in which the simulated, post-operative pressure gradient lead to changes in treatment/no treatment and stenting/simple ballooning decisions. The study suggests **a concrete applicability of the *virtual stenting* tool in clinical practice in selected populations**, hopefully leading to substantial improvement in clinical outcomes, reduction of medical errors, complication and sub-optimal treatment, as well as associated clinical costs.

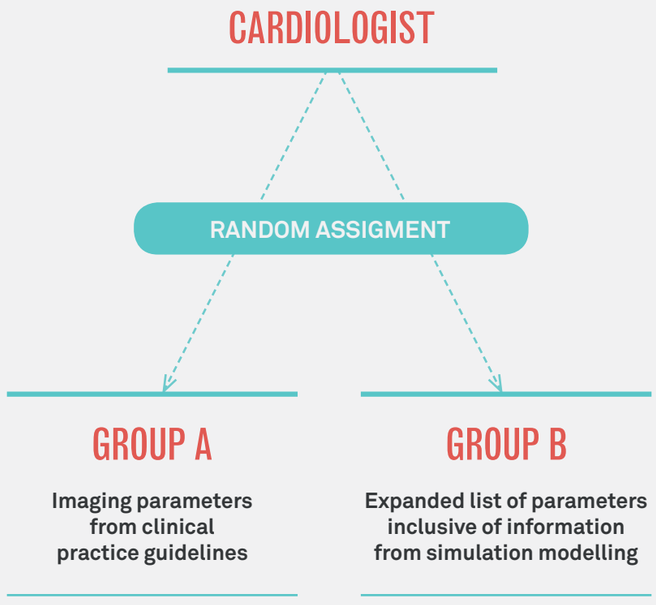


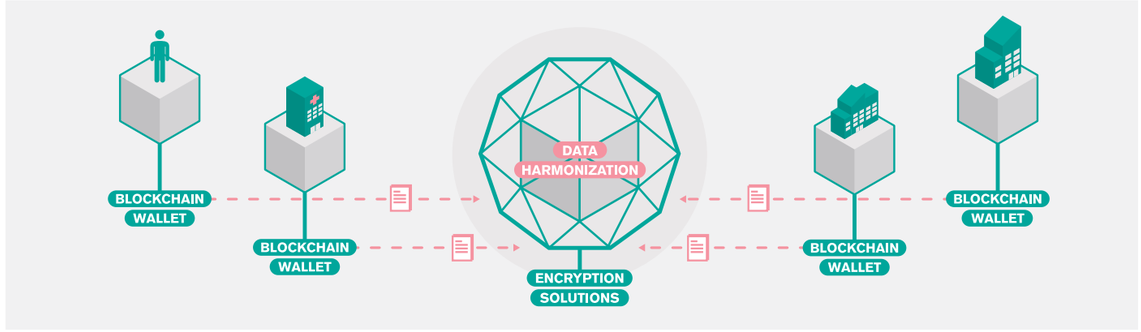
Figure 2| Randomized controlled experiment design scheme. Interventional cardiologists were randomly allocated to one of the two groups, respectively presented with a dataset with imaging parameters recommended by clinical practice guidelines (group A), or an expanded dataset inclusive of both traditional imaging parameters and information available from simulation modelling (group B). The trial addressed the question *«Does image-based modelling result in different clinical decisions as compared to clinical practice guidelines?»* by comparing the proportions of cardiologists making different types of intervention decisions in the two groups.

MHMD: A PLATFORM FOR PRIVACY-PRESERVING CONSENTED HEALTH DATA SHARING

As CARDIOPROOF project has come to an end, its infrastructure won't be an end in itself. **MyHealthMyData (MHMD)**, a newly started EU-funded project under the Horizon 2020 Research and Innovation Program, will include and extend the joint **MD-Paedigree-CARDIOPROOF Infostructure** into a new comprehensive **blockchain-based infrastructure** to serve as a **European health data platform for healthcare, research and business purposes**. The project, started on **November 1st 2016**, also involves a big part of the actual Consortium, including Lynkeus as Coordinator, Deutsches Herzzentrum Berlin (DHZB), University College of London (UCL), Ospedale Pediatrico Bambino Gesù (OPBG), Siemens Healthcare GmbH and Gnùbila, that will oversee the project architecture implementation.

The project aims to address two challenging issues at the same time.
On one side, **securely store patients' data**, constantly subjected to identity thefts and privacy breaches in local hospital repositories; on the other, to **grant patients for the very first time full control over their data**, with the possibility to unify their entire health data into cloud-based personal data accounts and manage consent to different type of data usage through a so-called dynamic consent interface, by lawful data transactions implemented with smart contracts. At the same time, the system will be designed to allow the application of advanced analytics to leverage the value of large datasets of biomedical de-identified data, fostering scientific research discoveries and technological innovation. As ultimate goal, MHMD aims to create a wide **EU-based information marketplace**, laying the foundation of **new mechanisms of trust and direct, value-based relationships between citizens, hospitals, research centres and businesses**.

Through MHMD CARDIOPROOF, and its cognate project MD-Paedigree, have thus ensured **the future sustainability of their common infostructure, also allowing the access to (and re-use of) the datasets collected during the two projects.**



RDA AND HDIG: DATA TO BE SHARED ACROSS BARRIERS

The **Research Data Alliance (RDA)** is a community-driven organization launched in 2013 and supported by the European Commission, the National Science Foundation and other US agencies, as well as the Australian Government, with the goal of **building the social and technical infrastructure to enable open sharing of data and promote the acceleration of data driven innovation worldwide.** The **Health Data Interest Group (HDIG)** was officially instituted in 2016 following a couple of successful sessions during the 6th and 7th RDA Plenary Meetings in Paris (September 2015) and Tokyo (February 2016). Before the creation of the HDIG, none of the RDA working and interest groups dealt directly with the intricacies of health data. HDIG aims specifically at filling this gap, by **providing a public place to discuss the specific issues concerning health data, with a particular focus on privacy and security.** Since the very beginning, Lynkeus has been joining RDA to actively contribute to the development of the HDIG, thanks to the experience gained in EU-funded projects such as CARDIOPROOF and MD-Paedigree.

The HDIG is co-chaired by **Yannis Ioannidis** (President and General Director of the ATHENA Research and Innovation Center), **Edwin Morley-Fletcher** (Lynkeus President) and **Anthony Chang** (Chief Intelligence and Innovation Officer at Children's Hospital of Orange County).

We invite anyone interested to subscribe to the HDIG to share initiatives and be updated on news and follow-ups, or to participate to the next session, taking place during the **9th Plenary Assembly planned for April 5-7, 2017 in Barcelona.**

NETWORKING INITIATIVES: CARDIOPROOF AT AEPC 2016

Among dissemination activities, CARDIOPROOF had foreseen one final event held within **the Association for European Paediatric and Congenital Cardiology (AEPC) 2016 Annual Meeting**, the main congress devoted to paediatric and congenital cardiology, occurring in Rome on June 1-4, 2016.

The event rounded up specialists – paediatric cardiologists, surgeons, intensivists, nurses - from all over the world, thus an excellent opportunity to **disseminate CARDIOPROOF concept and achievements** to the widest highly qualified audience, as well as to involve several interventional cardiologists into the **London School of Economics-driven randomised experiment for assessing the potential impact of the *virtual stenting tool-decision support system* on the clinical decision making process**.

Throughout the meeting, CARDIOPROOF maintained an **exhibition booth showcasing the final project outcomes** through videos and demos describing implemented tools, flyers and the issue #2 newsletter. AEPC 2016 also hosted a **CARDIOPROOF-dedicated workshop** where the project concepts, goals and outcomes have been presented together with the planned future clinical translation activities.

Most importantly, the event **contributed in the enrolment of eventually more than 193 specialists – including meeting attendants and online participants – into the randomised trial**, reserving a full room to the participants to perform the survey. To incentivize participation, CARDIOPROOF contextually organised a lottery raffling an iPad Pro, and offered a 10 € donation to Save the Children for each survey. Study results, illustrated in the dedicated focus [page 19], encouraged a **constantly increasing role of clinical decision support systems into the clinical practice**.

Indeed, the initial outcomes were already remarkably promising: **most of the participating paediatric cardiologists expressed their interest in the proposed technology, and declared that the model influenced their decision-making process** by providing additional information useful to either confirm their initial hypothesis or to change their preliminary evaluation and subsequent treatment decision.

PUBLICATION FOCUS

AUTHORS	AFFILIATION*	TITLE	JOURNAL	YEAR
Fernandes, J. F. *et al.*	DHZB	Beyond pressure gradients: the effects of intervention on heart power in aortic coarctation.	*PLoS One*	2017
Augustin, C. M. *et al.*	DHZB, MUG	Patient-specific modeling of left ventricular electromechanics as a driver for haemodynamic analysis	*Europace*	2016
Salcher, M. *et al.*	DHZB, LSE	Balloon dilatation and stenting for aortic coarctation: a systematic review and meta-analysis	*Circulation: Cardiovascular Interventions*	2016
Mirzaee, H. *et al.*	FME	MRI-based computational hemodynamics in patients with aortic coarctation using the Lattice Boltzmann methods: clinical validation study	*Journal of Magnetic Resonance Imaging*	2016
Bishop, M. *et al.*	MUG	Three-dimensional atrial wall thickness maps to inform catheter ablation procedures for atrial fibrillation	*Europace*	2016
Crozier, A. *et al.*	MUG	Image-based personalization of cardiac anatomy for coupled electromechanical modeling	*Annals of Biomedical Engineering*	2016
Salcher, M. *et al.*	DHZB, LSE	Bicuspid aortic valve disease: systematic review and meta-analysis of surgical aortic valve repair	*Open Heart*	2016
Augustin, C. M. *et al.*	MUG	Anatomically accurate high resolution modeling of human whole heart electromechanics: a strongly scalable algebraic multigrid solver method for nonlinear deformation	*Journal of Computational Physics*	2016
Kelm, M. *et al.*	DHZB	MRI as a tool for non-invasive vascular profiling: a pilot study in patients with aortic coarctation	*Expert Review of Medical Devices*	2016
Neugebauer, M. *et al.*	FME	Interactive virtual stent planning for the treatment of coarctation of the aorta	*International Journal of Computer Assisted Radiology and Surgery*	2016
Crozier, A. *et al.*	MUG	The relative role of patient physiology and device optimisation in cardiac resynchronisation therapy: a computational modelling study	*Journal of Molecular and Cellular Cardiology*	2016
Brose, J. L. *et al.*	UCL	How successful is successful? Aortic arch shape after successful aortic coarctation repair correlates with left ventricular function.	*Journal of Thoracic and Cardiovascular Surgery*	2016
Kowalik, G. T., Muthurangu, V., Khushnood, A. & Steeden, J. A.	UCL	Rapid breath-hold assessment of myocardial velocities using spiral UNFOLD-ed SENSE tissue phase mapping.	*Journal of Magnetic Resonance Imaging*	2016

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