European Commission
Directorate General for Communications Networks, Content and Technology
Sustainable and Secure Society - Health and Well-being

H2020 PHC-30-2015 689617
Research and Innovation Action

Work Package: WP6

Operation on Study Cohort and Evaluation of DSS

Deliverable: D6.1

Model-Based Data Augmentation Report

Version: 1v1

Date: 31-May-18

DOCUMENT INFORMATION

IST Project Num	H2020 PHC-30-2015 689617	**Acronym**	EurValve
Full title	Personalised Decision Support for Heart Valve Disease		
Project URL	http://www.eurvalve.eu		
EU Project officer	Carmen LAPLAZA SANTOS (CNECT/H/01)		

Work package	**Number**	6	**Title**	Operation on Study Cohort and Evaluation of DSS
Deliverable	**Number**	6.1	**Title**	Model-Based Data Augmentation Report

Date of delivery	**Contractual**	31-May-18	**Actual**	31-May-18
Status	Version 1v1		Final ☑	
Nature	Prototype ☐ Report ☑ Dissemination ☐ Other ☐			
Dissemination Level	Public (PU) ☐ Restricted to other Programme Participants (PP) ☐ Consortium (CO) ☑ Restricted to specified group (RE) ☐			

Authors (Partner)	Rod Hose (USFD), Krzysztof Czechowicz (USFD)			
Responsible Author	Rod Hose		**Email**	d.r.hose@sheffield.ac.uk
	Partner	USFD	**Phone**	+44 (0) 114 215 9533

Abstract (for dissemination)	This document defines the augmented data that is derived by parameter personalisation and by operation of a computational physiological model to characterise the effect of valve disease, and of the potential effects of intervention, on simple measures of cardiac energetics derived from the left ventricular pressure-volume loop.
Keywords	Heart Valve Disease, Computational Physiology, PV loop

Version Log

Issue Date	Version	Author	Change
30-Apr-18	0v1	Rod Hose	Template and structure
29-May-18	0v2	Rod Hose	Text draft
29-May-18	0v3	Rod Hose Krzysztof Czechowicz	Update to include case processing data, section 3
31-May-18	0v4	Rod Hose Krzysztof Czechowicz	Improvement of case results reporting
31-May-18	0v5	Krzysztof Czechowicz	Tables of case results added
31-May-18	0v6	Krzysztof Czechowicz	Tables of case results finalised and other minor amendments
31-May-18	0v7	Krzysztof Czechowicz	CFD illustrations added
31-May-18	1v0	Rod Hose	Update to reflect comments from internal review
31-May-18	1v1	KC & PMO	Final corrections, release version

CONTENTS

LIST OF FIGURES

LIST OF TABLES

EXECUTIVE SUMMARY

The EurValve project is predicated on the assumptions that:

- If we could characterise cardiac performance parameters, and the degree to which these are affected by the valve disease, this could be important diagnostic information. The hypothesis, rather similar to the familiar concept of coronary FFR (Fractional Flow Reserve), is that the important issue is the contribution of the valve disease to the physiology of the system, not just the local pressure gradients.
- If we could predict the immediate post-interventional changes in the PV (pressure-volume) loop following intervention, under rest and exercise conditions, significant reduction in the work and power measures would promote positive cardiac remodelling.

The EurValve analysis process seeks to personalise a few parameters in a zero dimensional model, including a representation of the pressure gradient v flow curve for the diseased valve, determined by computational analysis, to compute cardiac performance parameters (work, peak power, 'wasted' energy) under rest and exercise conditions. EurValve then performs a virtual intervention, replacing the characteristics of the diseased valve with those of a prosthetic valve, to compute the anticipated changes in these parameters under a candidate intervention. The most important output of the model is the Pressure-Volume curve, characterised by the above measures. The original intention of the project was to develop a single analysis protocol to apply to every case in the clinical cohort, utilising a minimal data set that might be available in normal clinical practice. Instead three analysis protocols have been developed: the first follows the original intention to use only non-invasive clinical data, with the valve characterised from a computational fluid dynamics analysis based on the segmentation of a medical image of the valve in the appropriate configuration.

The two additional protocols drive to opposite extremes. One uses no medical image data, so that it can be applied to cases for which no medical image data of the valve is available, or it is not of adequate quality to support CFD analysis. This potentially extends the applicability of the EurValve process to a much larger cohort in a routine clinical pathway. In contrast, to reflect the fact that richer data is available for many of the EurValve clinical cohort, the final protocol exploits these data where they are available. The three protocols use, respectively: i) minimal, non-invasive, physiological data; ii) as (i) plus left ventricular time-series volume data; iii) as (ii) plus invasive left-ventricular and systemic artery time-series pressure data.

Deliverable D4.1 summarised the clinical data, in a series of tables grouped by data type, and the data associated with the computational model, identified as input data or output data. The augmented data that is the subject of this current report is the data associated with the computational model that is additional to the measured clinical data. Strictly the augmented data is the union of the original clinical data plus the data provided by the computational model, but in the context of this deliverable augmented data refers to the computer generated additional data. It falls into two categories:

- Model input data that is derived by personalisation of the model parameters to fit clinical observations. These data might be valuable in their own right, in that they might already provide useful additional diagnostic characterisations of the patient (for example the maximal ventricular elastance, which is not measured directly but can be derived by model-fitting).
- Model output data, the primary output of the EurValve analysis protocols. These are the cardiac energetics measures, derivable from the computed pressure volume loops. EurValve will report these parameters in the pre-interventional rest state, based on the model parameters fitted to the measured data, and in the pre-interventional exercise and post-interventional rest and exercise states, based on simulated extrapolation to these conditions.

This report summarises the augmented data and reports the values for a subset of the EurValve clinical cohort.

1 INTRODUCTION

The overall goal of EurValve is to develop a model-based decision-support system. The aim of work package 6 is to operate the model on the study cohort and to evaluate the clinical usability and potential usefulness of the DSS in a small evaluation cohort. One of the aims of the DSS is to present additional, potentially diagnostic and prognostic, information that is extracted from a personalised computer model. This additional data is referred to in the project as 'augmented data', and it falls into two categories, model input data that is derived using an optimisation process to fit some model outputs to sparse clinical observations and model output data that provides measures of cardiac work and energy.

This deliverable provides:

- A summary of the augmented data fields.
- A very brief overview of the computational analysis protocols from which the augmented data is derived.
- A table of augmented data computed by the operation of one of the analysis protocols for a subset of the cohort.

2 DATA OVERVIEW

2.1 Clinical Data and Computational Model Concepts for the EurValve cohort

The EurValve study cohort comprises 120 patients, 60 with aortic valve disease and 60 with mitral valve disease, recruited at three clinical centres in Europe. The study protocol includes a pre-operative assessment and a post-operative follow-up. The monitoring of the clinical data collection process is carried out in work package 4. For many of the patients the comprehensive data collection protocol has been completed. The data fields are summarised in multiple tables in deliverable 4.1. In particular, an extensive list of the computational measures and concepts associated with the modelling process were presented in Table 10 of D4.1, reproduced in Table 1 below. The EurValve study is predicated on the assumptions that the cardiac energetics measures computed by the model, if they can be computed accurately for a given patient, should be of strong diagnostic value and that the computed changes of these parameters following an intervention should be of prognostic value. In particular, it was assumed that a reduction of cardiac work and/or of peak cardiac power for a given physiological demand would be beneficial, and that accurate prediction of the quantitative changes in these parameters if an intervention were to be performed would assist in the planning and timing of the intervention. There are several reasons, including procedural and post-procedural risk, why an intervention should not be performed unless there will be real clinical benefit, and indeed it is important not to intervene too soon, partly because there are greater risks of any follow-up intervention.

One of the major aims of EurValve is to attempt to quantify the likely physiological improvement. If this is minimal, most likely according to our hypothesis because the valve disease has lesser impact on the cardiac work and energy measures because of other, wider, system characteristics, then it might be that the procedure should be postponed until the valve disease does have significant impact on the system physiology. There are similarities in the more widespread use of fractional flow reserve (FFR) for assessing the need for coronary interventions. Generally, a prosthetic valve will restore the primary function of the valve but, in the case of the aortic valve, there might be a residual pressure gradient, and this can be included in the model to assist planning and valve selection. Furthermore, it was hypothesised that some of the model concepts, for example ventricular elastance, personalised to the individual, might also be of diagnostic value.

Field Label	Field Name	Data Type	Code/Unit/Comment
Maximum LV Elastance	com_elvmax	Double	[mmHg/ml]
Minimum LV Elastance	com_elvmin	Double	[mmHg/ml]
LV Elastance Offset parameters	com_elvoff	OrderedMap < Double>	[p0 mmHg, V0 ml]
LV Elastance timing parameters	com_elvtimepar	OrderedMap < Double>	[Dimensionless, fraction]
Maximum Left Atrium Elastance	com_elamax	Double	[mmHg/ml]
Minimum Left Atrium Elastance	com_elamin	Double	[mmHg/ml]
Left Atrium Elastance timing parameters	com_elatimepar	OrderedMap < Double>	[Dimensionless, fraction]
Aortic Flow/dP characterisation	com_aQdP	OrderedMap < Double>	[Q l/min, dP mmHg]
Aortic Flow/dP characterisation coefficients	Com_aQdPcoeff	OrderedMap < Double>	[mixed]
Mitral Flow/dP characterisation	com_mQdP	OrderedMap < Double>	[Q l/min, dP mmHg]
Mitral Flow/dP characterisation coefficients	Com_mQdPcoeff	OrderedMap < Double>	[mixed]
Total Blood Volume	com_tbv	Integer	[ml]
Heart Rate	com_hr	Integer	[beats/minute]
Systemic resistance proximal	com_sysresprox	Double	[mmHg/ml]
Systemic resistance distal	com_sysresdis	Double	[mmHg/ml]
Systemic compliance	com_sysresdis	Double	[ml/mmHg]
Systemic Oxygen Consumption	com_O2_rate	Double	[ml/min]
Left ventricle volume at ED	com_lvved	Integer	[mL]
Left ventricle volume at ES	com_lvves	Integer	[mL]

Field Label	Field Name	Data Type	Code/Unit/Comment
Volume curve left ventricle	com_vc_lv	OrderedMap <Integer,Double>	{*TimePoint*, *Measurement*}
Left ventricle Ejection fraction	com_lvef	Integer	[%]
Cardiac output	com_co	Integer	[mL/min]
Barocontrol afferent signal parameters	com_baro_cp	OrderedMap <Double>	*{fmin [s^{-1}], fmax [s^{-1}], Pn [mmHg], kn [mmHg]}*
Barocontrol efferent sympathetic signal parameters	com_baro_es	OrderedMap <Double>	*{fes0 [s^{-1}], fesinf [s^{-1}], kes [s]}*
Barocontrol efferent vagal signal parameters	com_baro_ev	OrderedMap <Double>	*{fes0 [s^{-1}], fesinf [s^{-1}], kev [s]}*
Barocontrol regulation effectors	com_baro_reg	OrderedMap <Double>	*{gain, time constant and time delay for each effector: effectors to be determined (WP3)}*
LV-EF	com_lvef	Integer	[%]
RV-EF	com_lvef	Integer	[%]
Left atrium volume at ED	com_laed	Integer	[mL]
Left atrium volume at ES	com_laes	Integer	[mL]
Volume curve left atrium	com _la	OrderedMap <Integer,Double>	{*TimePoint*, *Measurement*}
Aortic Valve dPmean	com_dpmean	Integer	[mmHg]
Aortic Valve dPmax	com_dpmax	Integer	[mmHg]
Aortic Valve Regurg.	com_ai	Integer	{0,1,2,3,4}
Aortic Valve dPcurve	com_dp_curve	OrderedMap <Integer,Double>	{*TimePoint*, *Measurement*}
Mitral Valve Regurg.	com_mi	Integer	{0,1,2,3,4}
Mitral Valve Vena contracta	com_mi_vc	Integer	[mm]
Mitral Valve Pressure Half Time	com_mi_pht	Integer	[msec]
Mitral Valve Effective Regurgitant Orifice Area	com_mi_eroa	Integer	[mm^2]
Mitral Valve Regurgitation Volume	com_mi_rvol	Integer	[mL/beat]
Right Ventricular Systolic Pressure	com_rvsp	Integer	[mmHg]
Doppler E-Wave	com_pw_e	Double	[cm/sec]
Doppler A-Wave	com_echo_pw_a	Double	[cm/sec]
Left Ventricular Work	com_lvwork	Double	[Joules]
Left Ventricular Peak Power	com_lvwork	Double	[Watts]
Pulmonary Vein Flow	com_pulmonary	Character	{systolic dominance, blunting, flow reversal}
Tricuspid Valve Regurg.	com_ti	Integer	{0,1,2,3,4}

Table 1: Reproduction of Table 10 of D4.1 - Computational measures and concepts

The purpose of careful definition of the clinical concepts, undertaken for and summarised in D4.1, was to capture all of the potentially relevant information that might influence the model parameters, so that associations could be sought, in machine learning operations, between the broader clinical data and the model parameters. The value would be that the model parameters might potentially be estimated even on patients for whom the complete data associated with the EurValve protocol has not been collected.

The most direct association will be where the predicted changes under intervention have actually been measured in the cohort, for example changes in ventricular stroke volume post-intervention. The computational modelling of longer term changes associated with ventricular remodelling is out-of-scope for EurValve, but the purpose of the follow-up studies, including activity monitoring as reported in WP3 as well as quality of life questionnaire data and six-minute walk tests in some of the cohort, is to seek outcome association.

2.2 Computational Analysis Protocols and Model Personalisation Process

2.2.1 Analysis Protocols

It was always intended that EurValve would deploy the simplest possible existing model of physiology ('existing' was an important predicate of the Call: the emphasis is on the DSS not on model development) that is able to capture the most basic physiological processes and measures associated with heart valve intervention. A candidate analysis protocol for the EurValve cohort was defined in D3.1.

The computational model comprised:

- A very simple 0D system model with a minimal number of parameters. The simple model is able to capture the fundamental concepts on which EurValve is based and its key input parameters can be personalised based on the minimal clinical measurements that might be available in a typical clinical work-up for valve patients. Despite its simplicity, the model contains 23 input parameters, only some of which can reasonably be personalised from the available data. Note that this model does not describe or compute all of the concepts in Table 1. In particular, in the trade-off between potential accuracy and constraints of minimal clinical data, the decision was taken not to include either an explicit representation of the pulmonary circulation or any representation of control mechanisms.
- A representation within the 0D model of the pressure-drop v flow characteristics of the diseased valve, computed using a 3D model based on the valve anatomy extracted by segmentation of the valve leaflets and surrounding region from medical image data. For aortic valve stenosis an image of the valve in the open configuration and for mitral regurgitation the closed configuration, with regurgitant orifice, was required.

The envisaged analysis protocol consisted of six steps.

- Segmentation of the medical image
- Characterisation of the pressure-drop v flow relationship for the diseased valve.
- Optimisation of a subset of input parameters in the model to reproduce measured data in the rest state for the patient, including for example the end systolic and end-diastolic volumes of the left ventricle and cuff blood pressures.
- Operation of the model to compute the cardiac work and power.
- Adjustment of model parameters to extrapolate to an exercise condition and computation of cardiac work and power in this state.
- Adjustment of model parameters to represent a candidate replacement of the valve and computation of associated changes of the cardiac work and power parameters in rest and exercise states.

Originally, it was intended that there would be a single standard analysis protocol applied to all patients. This 'non-invasive image-based protocol' was defined so that it was operable using minimal clinical data to increase the likelihood that it could be applied after the project in a less research-intensive environment, but it absolutely requires an appropriate 3D image of the diseased valve. The project has recognised two issues that make this approach restrictive.

Firstly, in routine clinical practice many patients follow a clinical pathway that does not include imaging of the diseased valve in an appropriate state. The valve disease is inferred from other measures. The EurValve thought processes and hypotheses apply equally to this cohort. EurValve has developed a 'minimal clinical data protocol' that will support the analysis for these cases. In fact this serves also as a risk mitigation strategy for EurValve's own prospective study. Even in this research cohort, there is the risk that the quality of the images does not always support reliable segmentation of the three-dimensional valve structures. To mitigate this risk EurValve will apply the minimal clinical data protocol in these cases.

Secondly the standard protocol takes no advantage of extra information that has been collected on many of these patients that might potentially support a more accurate personalisation of the model and thus, potentially, a more accurate prediction of outcome. EurValve has therefore developed three analysis protocols.

Minimal Clinical Data Protocol

In this protocol it is assumed that image data that supports segmentation of the valve leaflets is not available, but that estimates of effective valve orifice areas (or measures from which they can be derived) are available, for example from Doppler ultrasound or other velocity or flow measurement devices. Although this protocol does not exploit the whole of the EurValve computational work flow it might nevertheless be of diagnostic benefit.

Non-invasive Image-based Data Protocol

This is the original protocol as defined in D3.1. The intention remains to perform this analysis for 120 patients and to report the results in project publications. For every case in which this protocol is operable any extra data that has been measured will be used either for model validation or for establishment of associations between personalised model inputs or model outputs and outcome.

Comprehensive Data Protocol

For many of the patients enrolled in the EurValve study more comprehensive data has been collected, the most useful of which is time series pressure, volume or flow data. Time series data is very rich in information, and supports a much stronger optimisation process for personalisation of the model inputs. Without time series data there are relatively few, generally maximum, minimum, or integral measures available for tuning, and of course it is not possible to personalise more parameters than there are observations. Furthermore, there may be many solutions for the parameters that produce the same or similar measures, but which vary extensively in detail. Where time series data is available this essentially yields many more points in the solution space to which the model must conform. Even if relatively few parameters are tuned, the faithfulness of the computed response over the whole cardiac cycle will be significantly improved. For these reasons, EurValve has developed an additional process to ingest time-series data into the optimisation. Examples of such time-series data include ventricular volume measurements from either magnetic resonance imaging (not part of the EurValve clinical protocol but available in many cases), 3D ultrasound or CT, or invasive catheter measurements of ventricular and systemic pressure sometimes taken during the interventional procedure. The optimisation cost function can be adjusted to recognise the data available for each specific case. This approach has already been followed on two test cases to develop and to prove the functionality, and in the final report it is anticipated that a significant subset of the patients will have been analysed using this protocol so that the results can be compared with those from the simpler protocols.

2.2.2 Pressure-drop v flow characterisation

When the project was planned, the standard protocol included a three-dimensional computational fluid dynamics analysis of the flow through the valve to establish the pressure-flow relationship. However, it was recognised that this process would always be computationally demanding, and so EurValve had a task dedicated to the exploration of Reduced Order Modelling technology to replace the full CFD model with a ROM. The project currently anticipates that this will be very successful for the aortic valve cases, as reported in D3.3, but less so for mitral valve cases for which CFD remains the option of choice. The primary reason is that there are stronger topological variations in the configuration of diseased mitral valves, and so this does not so readily lend itself to parametric representation. To support the operation of the ROM the geometrical configuration (anatomical shape) of the open aortic valve is

represented by eleven parameters, and these become part of the augmented data for these cases. The pressure drop at any particular flow can be extracted directly from the ROM, and this is done in the execution of the analysis protocol. Where the full CFD analysis is performed coefficients in a polynomial representation of pressure-drop v flow are computed and stored as augmented data. The same measures can be derived from the ROM but are not used in the analysis process.

2.2.3 Model Personalisation (Input Parameter Optimisation)

The methods for personalisation of the input parameters and for operation of the computational model have been developed in work package 3. The Beta release versions of the tools took place in April 2017. These tools have been the subject of continued development since the beta release, and the candidate release is due at project month 30 (end July 2018). The developments in the candidate release will reflect partly the experience gained by operation of the beta release on the data from the clinical cohort, summarised in this deliverable.

Whichever of the analysis protocols is to be followed, the first step in the computational process is to personalise the parameters in the model to represent the patient in the state in which the clinical data are measured. Generally, this is the rest state, although EurValve has access to a special data series from the Catharina hospital in which measurement were also taken under a pharmacologically-induced stress state. An optimisation process is used to derive the model input parameters. The optimum input parameters are those that minimise a cost-function that quantifies the relationship of model output parameters, such as end diastolic volume or cuff pressure, to the actual clinical measures. To maximise the likelihood of finding a true optimum, defined by a global minimum of the cost function, the process in EurValve is based on the operation of a genetic algorithm followed by a Nelder-Mead algorithm, both available in the Matlab optimisation toolbox. The former tends to find a point in the solution space in the vicinity of the global minimum, hopefully avoiding local minima, and the latter then seeks the optimum in that vicinity.

The output of the optimisation is a small number of model parameters that are personalised to the individual patient. These form part of the augmented data.

2.2.4 Model Outputs

The primary outputs of the model are cardiac work and power measures in four states: rest and exercise pre-intervention, and rest and exercise post intervention. The extrapolation from the rest to the exercise state is based on published methods recognising change in metabolic demand. This process has been implemented, but not yet fully tested, and is not featured in this deliverable. The representation of the post-intervention state is achieved by replacing the pressure-drop v flow characterisation of the diseased valve with one representative of the valve prosthesis, usually expressed simply as a valve coefficient.

3 AUGMENTED DATA

This section illustrates the process of model-based data augmentation, using the non-invasive image-based analysis protocol, for one mitral valve case, EURV_B_M_1254_18, and for one aortic valve case, EURV_S_A_0242_03. It goes onto to report in tabular form the augmented data computed by operation of the beta version of the workflow on 52 cases (15 mitral and 37 aortic). All cases will be re-processed using the candidate release of the software in the final period of the project, nevertheless it is anticipated that the reported data will be valuable in the establishment of confidence in the model and in the first efforts to discover associations in EurValve's own prospective case data.

3.1 Outline of operation for typical cases

3.1.1 Mitral Valve Case: EURV_B_M_1254_18

The medical images for case EURV_B_M_1254 were segmented and the resulting mesh was prepared for CFD analysis. A screenshot of velocity and pressure fields and selected cross-sections is presented in Figure 1 .

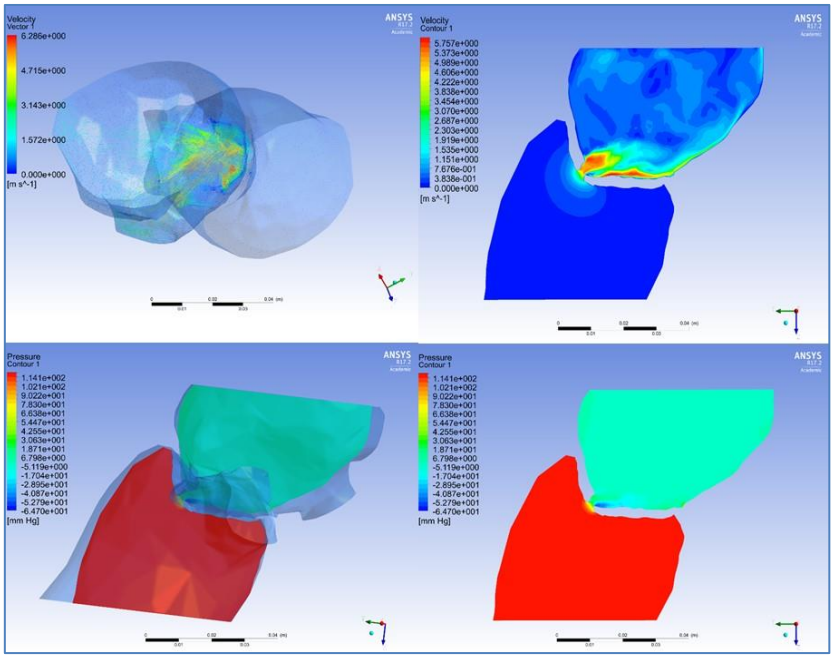


Figure 1: Screenshot from CFD analysis of regurgitant flow for case EURV_B_M_1254_18

Based on a quadratic fit to the pressure-drop as a function of flow rate yielded by the CFD analyses the relationship was characterised as:

$$\Delta p = a_1 Q + a_2 Q^2 \ .$$

For this valve the computed coefficients were:

$$a_1 = 0.00335 \quad \text{mmHg.s/ml} : \quad a_2 = 0.00484 \quad \text{mmHg.s}^2/\text{ml}^2 \ .$$

These parameters represent part of the augmented data for this patient. Both the values and the ratios of these coefficients provide immediate information on the nature of the flow and of potential severity of the regurgitant orifice. Alternative representations, such as effective orifice area, might also be derived from these coefficients.

A subset of the most important parameters in the 0D model, identified by WP3 in a sensitivity study, were personalised by the optimisation process outlined in section 2.2.3.

Short Case Name	Heart Period [s]	Maximum LV elastance [mmHg/ml]	Distal systemic resistance [mmHg*s/ml]	Systemic capacitance [ml/mmHg]	Stressed blood volume [ml]
BM_18	1.00	0.99	1.00	3.33	655.37

Table 2: Personalised 0D model input parameters for case EURV_B_M_1254_18

The results of the operation of the model are illustrated in Figure 2 and Figure 3. Figure 2 shows the computed left ventricular pressure-volume loop prior to intervention, and indicates the timing of key events in the cardiac cycle. It also summarises the work and power parameters that form part of the augmented data produced by the model.

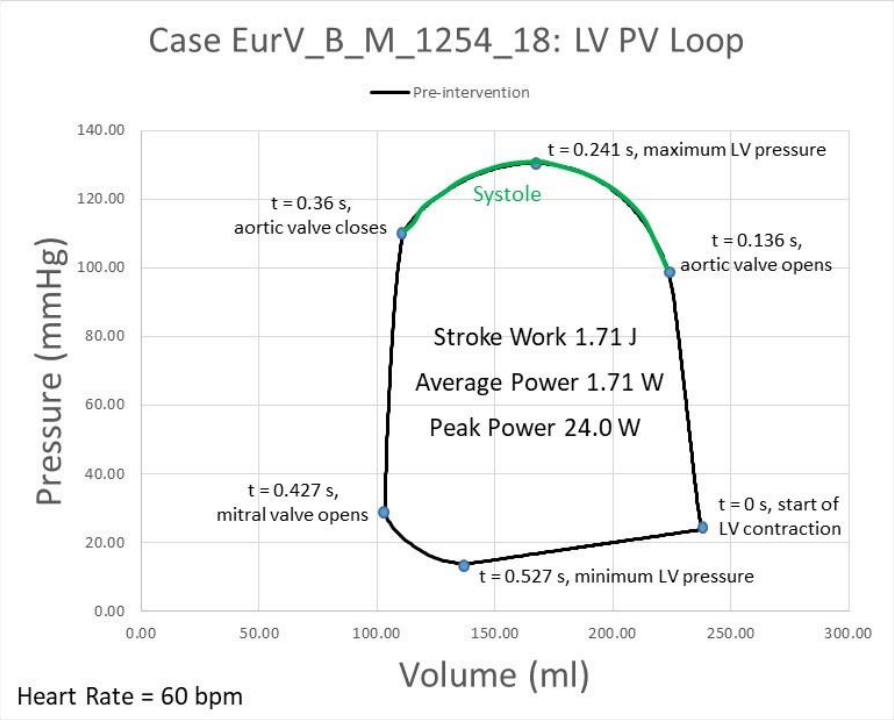


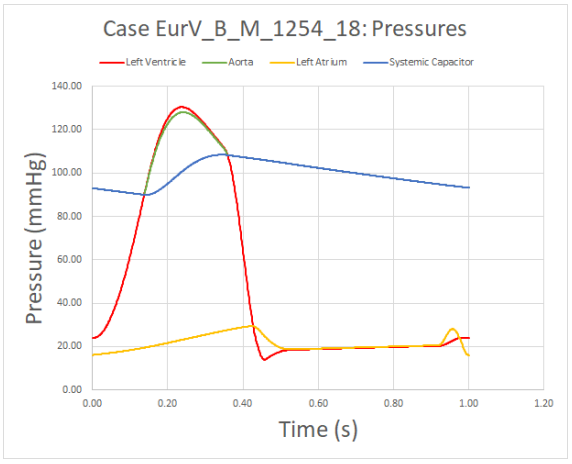
Figure 2: Computed left ventricular PB loop, pre-intervention, for case EURV_B_M_1254_18

Figure 3a and Figure 3b show the computed pressure and volume respectively at locations in the left side of the heart and in the systemic circulation for the pre-intervention rest state. Figure 3c shows the computed left ventricular pressure-volume loop for this case (the primary model output), from which the cardiac work and power can be quantified. For this case the power expended by the left ventricle at rest is 1.71 W, of which the power that is used positively to drive the systemic flow is 1.28 W. The remainder is wasted in driving the regurgitant flow across the diseased valve back into the atrium. Note that this takes into account only the power associated with the flow, and does not include the wasted energy of contraction[1]. The peak power that the ventricle generates at any point in the cardiac cycle is 24.01 W. The computed cardiac output supplied to the systemic circulation is 4.68 l/min. Following

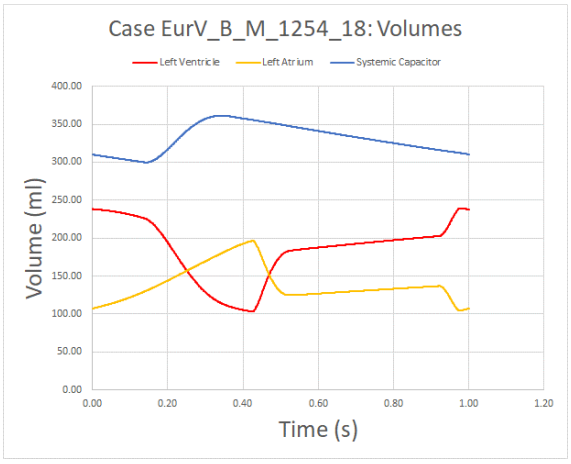
[1] K. R. Walley, "Left ventricular function: time-varying elastance and left ventricular aortic coupling," *Crit. Care*,

simulated intervention the left ventricular end diastolic volume decreases and the end systolic volume decreases, reducing the stroke volume of the left ventricle but now all of the volume is propelled forwards into the systemic circulation. The power expended by the left ventricle reduces to 1.41 W (a reduction of 21%) and the peak power at any point in the cycle increase slightly to 24.79 W. The cardiac output increases to 5.41 l/min (an increase of 16%). One of the aims of the prospective study is to evaluate whether these computed changes might correlate to clinical outcomes.

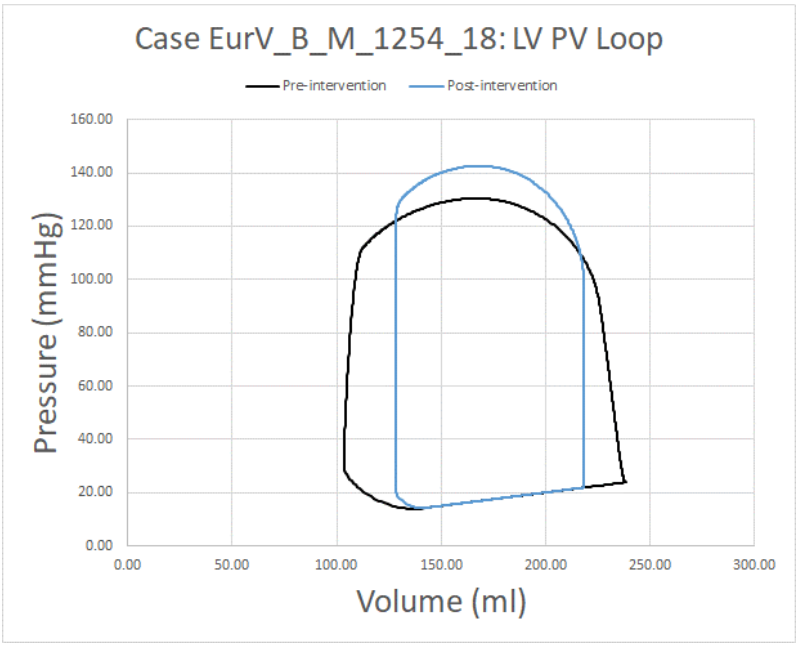
In this deliverable, the focus is on the rest condition, but in the final analysis both rest and exercise computations will be reported.



a) Pressures



b) Volumes



c) PV Loops

Figure 3: Results of operation of 0D model for case EURV_B_M_1254_18

3.1.2 Aortic Valve Case: EURV_S_A_0242_03

The process for an aortic valve case is similar to that outlined in the previous section for a mitral valve case. The medical images for case EURV_S_A_0242_03 were segmented and the resulting mesh was prepared for CFD analysis. A screenshot illustrating velocity and pressure fields from one of the CFD analyses used to characterise the diseased aortic valve is presented in Figure 4.

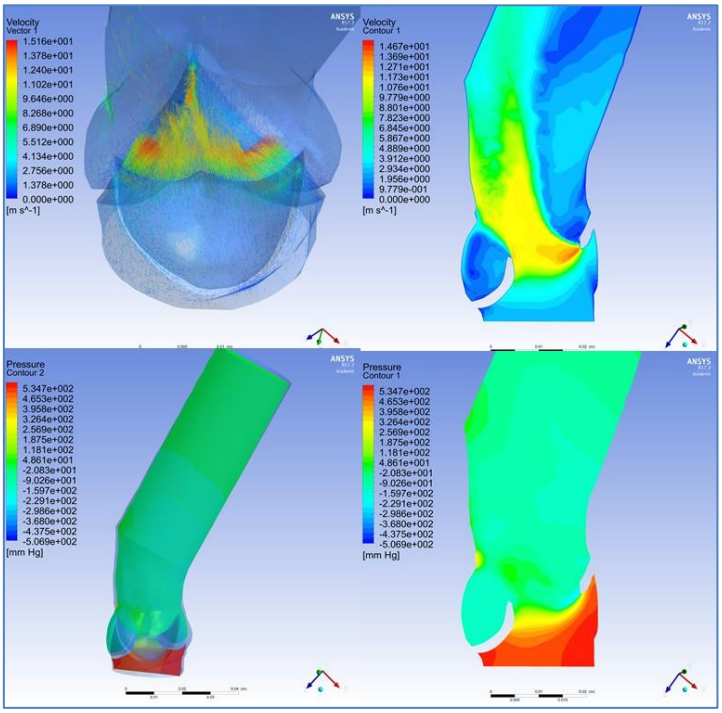


Figure 4: Screenshot from CFD analysis of aortic valve flow for case EURV_S_A_0242_03

Once again a quadratic fit to the pressure-drop as a function of flow rate yielded by the CFD analyses the relationship was computed, and the resulting coefficients were:

$$a_1 = 0.00074 \quad \text{mmHg.s/ml} : \quad a_2 = 0.02101 \quad \text{mmHg.s}^2/\text{ml}^2 \ .$$

Similarly, the 0D model parameters were personalised by the optimisation process outlined in section 2.2.3 this time with the results reported in Table 3.

Short Case Name	Heart Period [s]	Maximum LV elastance [mmHg/ml]	Distal systemic resistance [mmHg*s/ml]	Systemic capacitance [ml/mmHg]	Stressed blood volume [ml]
SA_03	0.73	3.74	1.50	1.26	215.90

Table 3: Personalised 0D model input parameters for case EURV_S_A_0242_03

The results of the operation of the model are illustrated in Figure 5 and Figure 6: Results of operation of 0D model for case EURV_S_A_0242_03

. As for the mitral case the first, Figure 5, shows the computed left ventricular pressure-volume loop prior to intervention, and indicates the timing of key events in the cardiac cycle. It also summarises the work and power parameters that form part of the augmented data produced by the model. Note that the main difference between the aortic valve case and the previous mitral valve case is that there are periods of true isovolumetric contraction and relaxation, which are not possible when the mitral valve is leaking in the closed position.

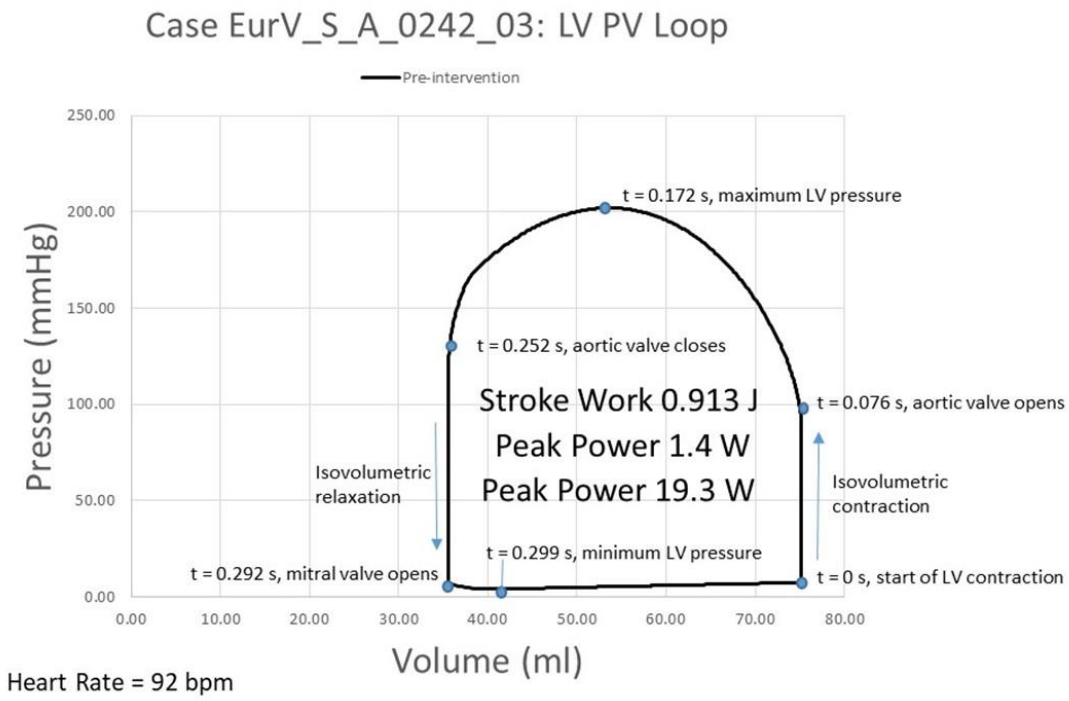


Figure 5: Computed left ventricular PB loop, pre-intervention, for case EURV_S_A_0242_03

Figure 6: Results of operation of 0D model for case EURV_S_A_0242_03

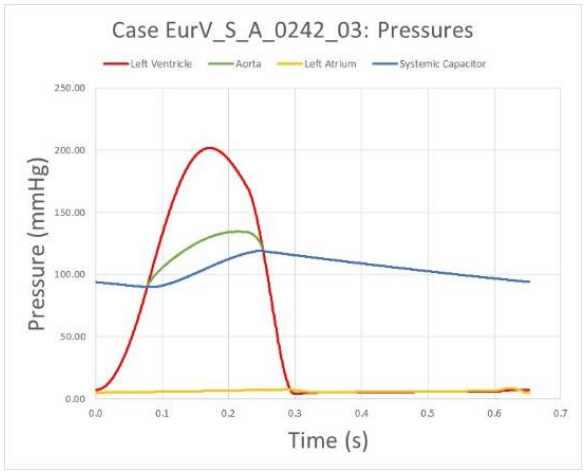
a and Figure 6: Results of operation of 0D model for case EURV_S_A_0242_03

b show the computed pressure and volume respectively at locations in the left side of the heart and in the systemic circulation for the pre-intervention rest state. Note that for the aortic stenosis case there is a large computed pressure drop, of the order of 70 mmHg, across the aortic valve. Figure 6: Results of operation of 0D model for case EURV_S_A_0242_03

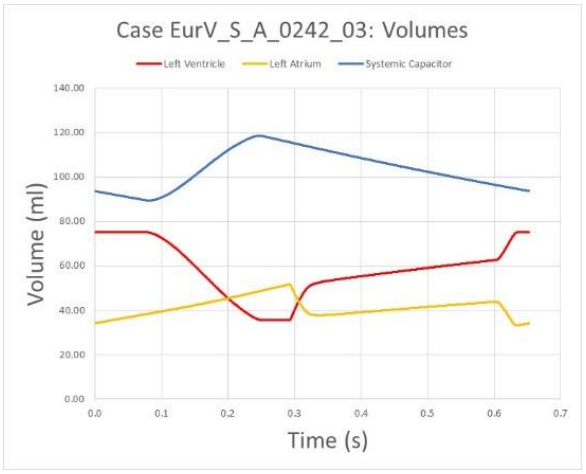
c shows the computed left ventricular pressure-volume loop. For this case the power expended by the left ventricle at rest is 1.4 W. Once again, this takes into account only the power associated with the flow, and does not include the wasted energy of contraction. The peak power that the ventricle generates at any point in the cardiac cycle is 19.34 W. The computed cardiac output supplied to the systemic circulation is 3.65 l/min.

Following simulated intervention the left ventricular end diastolic volume and end systolic volume both decrease. The power expended by the left ventricle reduces to 1.18 W (a reduction of 16%) and the peak power at any point in the cycle shows a small (3%) decrease. The cardiac output increases to 3.9 l/min

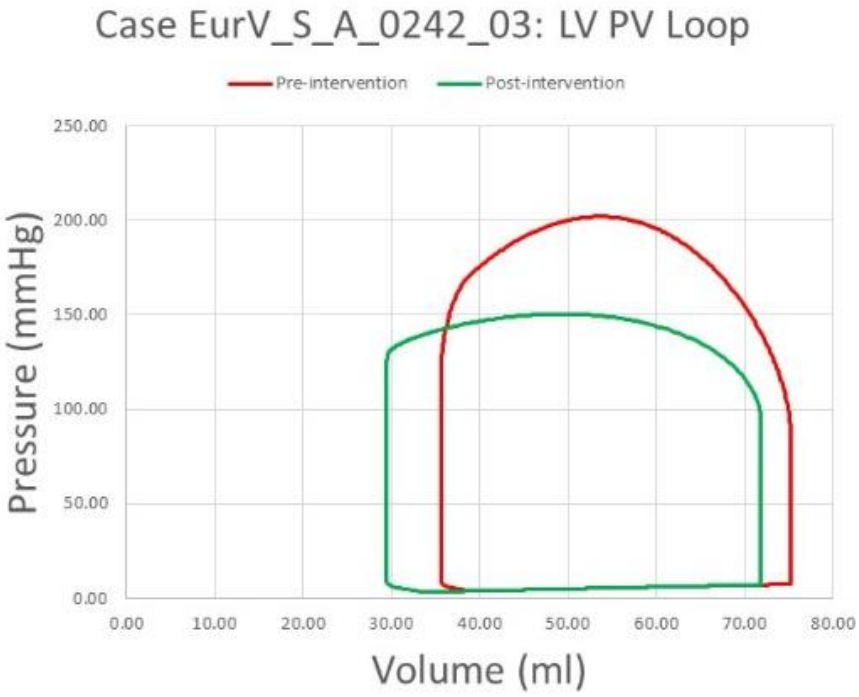
(an increase of 8%). Again, as for the mitral case, one of the aims of the prospective study is to evaluate whether these computed changes might correlate to clinical outcomes.



a) Pressures



b) Volumes



c) PV Loops

Figure 6: Results of operation of 0D model for case EURV_S_A_0242_03

3.2 Summary data: EurValve cohort

The tables in this section show preliminary results of the model. Table 4 shows the results of the aforementioned parameter optimisation. The data used to obtain these values were the diastolic and mean pressure from cuff measurements, end systolic and end diastolic LV volumes and an ultrasound pressure drop across the aortic valve measured with ultrasound.

Case ID		Patient specific model input parameters					
No	Case Name	Heart Period [s]	Left ventricular maximal elastance [mmHg/ml]	Aortic valve coefficient [ml/s* mmHg^(-0.5)]	Distal systemic resistance [mmHg*s/ml]	Systemic capacitance [ml/mmHg]	Stressed blood volume [ml]
1	BA_18	1.05	1.68	76.20	0.67	2.18	433.32
2	BA_28	0.81	1.50	61.75	0.42	2.99	510.11
3	BA_29	0.60	1.38	103.29	0.22	2.48	499.86
4	BA_30	1.00	3.74	37.15	1.28	0.95	257.50
5	BA_31	1.11	1.83	50.02	0.97	0.90	326.40
6	BA_32	0.88	2.88	45.59	0.78	1.48	285.57
7	BA_33	0.94	2.97	62.46	1.36	0.84	266.71
8	BA_34	0.95	3.68	26.83	1.42	1.23	249.22
9	BA_35	0.95	2.64	49.22	1.15	1.54	291.96
10	BA_36	1.07	1.02	31.70	0.84	1.58	517.26
11	BA_37	0.94	3.22	26.77	0.96	1.46	287.10
12	BA_38	1.03	1.60	65.55	0.71	1.35	397.58
13	BA_39	1.11	1.16	63.45	0.39	1.80	576.19
14	BA_40	0.94	2.06	48.56	0.99	2.44	447.30
15	BA_41	0.90	1.69	52.04	0.66	2.22	465.99
16	BA_42	0.82	1.86	57.32	0.68	1.71	416.30
17	BA_43	0.73	2.21	70.98	0.89	1.61	331.32
18	BA_44	0.98	1.49	55.40	0.62	3.90	606.54
19	BA_45	0.94	1.38	53.77	0.52	2.63	447.30
20	BA_46	0.91	2.32	51.98	1.07	1.30	313.95
21	BA_47	0.79	1.88	53.02	0.79	1.28	348.62
22	BA_48	0.91	1.27	89.28	0.47	4.72	628.14
23	BA_49	0.74	2.66	53.14	0.66	1.16	320.39
24	BA_50	0.90	1.31	74.14	0.45	2.66	607.04
25	BA_51	0.68	1.56	61.66	0.64	2.80	546.06
26	BA_52	1.05	2.66	46.51	0.92	1.30	293.00
27	BA_53	1.20	3.06	39.01	1.04	1.49	281.81
28	BA_54	1.02	1.77	31.25	0.91	1.11	263.18
29	BA_55	0.88	4.30	30.25	1.29	1.11	229.44
30	BA_56	1.11	3.16	42.37	1.23	1.54	322.87
31	BA_57	1.02	2.67	38.21	1.36	0.75	232.59
32	CA_02	0.67	1.22	59.11	1.03	1.16	309.48
33	SA_04	0.83	5.31	33.78	1.70	0.65	156.30
34	SA_08	0.80	4.12	18.75	1.94	0.45	145.66
35	SA_10	0.73	3.43	66.90	1.51	1.30	217.45

Table 4: Augmented input parameters for each patient analysed with minimal non-invasive data only

A snapshot of the results of the tuning is shown in Table 5. The intervention has been simulated by replacing the aortic valve coefficient from the patient specific one, to a representation of a healthy valve. The simulated results for the post intervention state are shown in Table 6. In all cases, the aortic systolic and diastolic pressure increased, and both the LV end systolic and LV end diastolic volumes dropped. In most cases, the power the left ventricle needs to produce has decreased. These results are qualitatively consistent with clinical expectation, but the real value of the analysis process is in the quantitative prediction and evaluation of these parameters and their association with clinical outcome.

Case ID		Pre intervention						
No	Case Name	Systolic Blood Pressure [mmHg]	Diastolic Blood Pressure [mmHg]	Max pressure drop across the aortic valve [mmHg]	LV end diastolic volume [ml]	LV end systolic volume [ml]	Stroke Work [J]	Heart Power [W]
1	BA_18	118	71	52	187	71	1.98	1.88
2	BA_28	100	65	95	209	94	2.22	2.73
3	BA_29	100	55	92	238	94	2.58	4.29
4	BA_30	151	82	97	122	44	1.99	1.99
5	BA_31	149	65	63	184	88	1.94	1.75
6	BA_32	113	65	87	128	45	1.68	1.91
7	BA_33	167	88	48	130	55	1.69	1.80
8	BA_34	125	79	103	102	44	1.40	1.47
9	BA_35	121	77	55	117	48	1.30	1.37
10	BA_36	117	71	107	276	192	1.77	1.65
11	BA_37	112	68	140	127	55	1.85	1.97
12	BA_38	137	68	63	207	92	2.21	2.13
13	BA_39	131	60	100	318	144	3.56	3.21
14	BA_40	126	88	75	156	73	1.78	1.90
15	BA_41	121	77	94	198	95	2.23	2.49
16	BA_42	132	79	90	188	88	2.24	2.72
17	BA_43	128	82	50	133	61	1.37	1.88
18	BA_44	108	77	83	205	94	2.17	2.20
19	BA_45	95	60	77	195	92	1.74	1.85
20	BA_46	136	81	63	141	64	1.60	1.76
21	BA_47	132	75	80	170	87	1.78	2.25
22	BA_48	96	69	50	200	82	1.76	1.93
23	BA_49	139	72	110	159	64	2.35	3.17
24	BA_50	126	78	91	266	121	3.05	3.41
25	BA_51	124	88	90	198	110	1.96	2.88
26	BA_52	125	67	75	140	50	1.81	1.72
27	BA_53	115	65	77	125	39	1.67	1.39
28	BA_54	99	51	75	142	77	1.10	1.09
29	BA_55	128	78	106	97	36	1.50	1.70
30	BA_56	137	85	79	130	45	1.93	1.74
31	BA_57	142	69	64	124	58	1.37	1.35
32	CA_02	112	70	36	154	107	0.71	1.06
33	SA_04	139	76	68	73	27	1.02	1.22
34	SA_08	132	66	102	80	45	0.84	1.05
35	SA_10	122	81	26	76	33	0.71	0.98

Table 5: Augmented outputs for each analysed patient using minimal non-invasive data only pre intervention

Case ID		Post intervention						
No	Case Name	Systolic Blood Pressure [mmHg]	Diastolic Blood Pressure [mmHg]	Max pressure drop across the aortic valve [mmHg]	LV end diastolic volume [ml]	LV end systolic volume [ml]	Stroke Work [J]	Heart Power [W]
1	BA_18	122	72	5.28	186	67	1.63	1.55
2	BA_28	112	69	10.27	200	68	1.69	2.08
3	BA_29	109	57	21.21	234	74	1.98	3.30
4	BA_30	159	83	3.07	121	39	1.52	1.52
5	BA_31	155	66	2.73	183	81	1.64	1.47
6	BA_32	121	66	4.62	126	38	1.24	1.41
7	BA_33	169	88	2.66	130	53	1.49	1.59
8	BA_34	140	84	2.15	97	33	1.07	1.12
9	BA_35	129	78	2.54	115	43	1.09	1.14
10	BA_36	150	85	3.87	257	142	1.83	1.70
11	BA_37	130	74	3.87	120	36	1.28	1.37
12	BA_38	142	69	4.79	206	84	1.83	1.77
13	BA_39	143	62	9.20	315	117	2.71	2.44
14	BA_40	140	92	4.00	149	59	1.48	1.57
15	BA_41	135	82	6.76	189	73	1.79	2.00
16	BA_42	144	83	7.08	182	71	1.83	2.23
17	BA_43	135	84	4.33	131	55	1.20	1.64
18	BA_44	121	81	6.60	193	71	1.70	1.72
19	BA_45	106	64	6.06	187	70	1.37	1.46
20	BA_46	144	83	3.29	139	57	1.36	1.50
21	BA_47	145	80	5.10	165	72	1.52	1.92
22	BA_48	103	70	7.47	195	72	1.45	1.59
23	BA_49	150	75	7.83	157	52	1.78	2.40
24	BA_50	137	82	11.66	258	97	2.46	2.75
25	BA_51	142	96	8.31	182	81	1.69	2.48
26	BA_52	130	68	3.49	139	45	1.39	1.32
27	BA_53	120	65	2.72	125	35	1.23	1.03
28	BA_54	113	56	2.03	137	60	0.93	0.92
29	BA_55	141	81	2.75	95	29	1.10	1.25
30	BA_56	146	86	3.08	129	41	1.51	1.36
31	BA_57	148	71	1.76	123	53	1.16	1.14
32	CA_02	123	76	2.13	149	97	0.71	1.07
33	SA_04	144	77	1.52	73	25	0.82	0.99
34	SA_08	153	74	1.02	77	35	0.73	0.91
35	SA_10	127	82	1.53	75	32	0.66	0.90

Table 6: Augmented outputs for each analysed patient using minimal non-invasive data only post intervention

The same analysis has been carried out using the imaging based protocol. The input personalised model input data for this protocol are shown in Table 7. In this protocol, the valves are characterised using CFD analysis of the flow through the geometry based on imaging of the valve instead of being a result of parameter optimisation. This process results in two values for each valve that represent the parabolic relationship between the pressure drop across the valve and flow. For aortic valve cases, the coefficients represent the characterisation of the flow through the stenosed valves and, for the mitral valve, the coefficients characterise the regurgitant mitral valve.

Case ID		Patient specific model input parameters					Valve Parameters			
No	Case Name	Heart Period [s]	LV max.el. [mmHg/ml]	Distal sys. Res. [mmHg*s/ml]	Sys. cap. [ml/mmHg]	Stressed blood volume [ml]	AV Z1	AV Z2	MV regurgitation char. Z1	MV regurgitation char. Z2
1	BM_01	0.90	2.21	2.06	0.73	241.42	0	0	0.006277	0.009716
2	BM_05	1.00	1.50	0.71	1.65	347.74	0	0	7.052358	3.594125
3	BM_06	0.80	1.07	0.79	3.93	766.25	0	0	0.000692	0.003099
4	BM_07	0.98	1.03	1.55	1.36	412.72	0	0	0.004978	-0.00322
5	BM_08	1.22	0.91	0.80	3.00	588.09	0	0	0.013795	0.000589
6	BM_11	0.83	1.01	0.69	2.19	407.67	0	0	0.001592	0.0082
7	BM_12	0.92	1.15	1.23	1.81	483.60	0	0	0.003795	0.010966
8	BM_12	0.92	0.90	1.22	1.74	523.38	0	0	0.003845	0.009012
9	BM_14	0.98	0.76	0.72	2.83	549.75	0	0	0.001383	-0.00329
10	BM_15	0.76	0.66	0.52	3.24	702.27	0	0	0.007895	0.004751
11	BM_18	1.00	0.99	1.00	3.33	655.37	0	0	0.00335	0.004839
12	BM_19	0.94	0.61	0.73	2.64	787.63	0	0	0.000913	0.005309
13	BM_22	0.91	1.26	0.67	2.80	446.89	0	0	0.150334	0.386554
14	BM_28	0.80	0.75	0.72	4.00	837.36	0	0	0.000511	0.00109
15	BM_30	0.73	1.34	0.77	1.71	469.01	0	0	0.003418	0.008463
16	SA_03	0.65	4.40	1.61	1.00	203.00	0.00074	0.021008	0	0
17	SA_10	0.73	3.74	1.50	1.26	215.90	0.000464	0.012102	0	0

Table 7: Augmented input parameters for each patient analysed with imaging based protocol

The results of the simulations before intervention are shown in Table 8, and post intervention in Table 9. For the aortic valve cases, the same observations can be made for this set of data as for the minimal non-invasive protocol. Surgery results in an increase in the systolic and diastolic pressures in the aorta, and a decrease in the left ventricular volumes. The mitral valve replacement leads to an increase in the aortic systolic and diastolic pressures, a reduction of the LV end diastolic LV volume, and an increase in the LV end systolic volume.

Case ID		Pre intervention						
No	Case Name	Systolic Blood Pressure [mmHg]	Diastolic Blood Pressure [mmHg]	Max pressure drop across the aortic valve [mmHg]	LV end diastolic volume [ml]	LV end systolic volume [ml]	Mitral valve leakage [ml]	Stroke Power [W]
1	BM_01	135.72	79.00	0.87	125.52	46.84	40.73	1.23
2	BM_05	111.32	61.00	3.42	166.41	69.94	1.17	1.17
3	BM_06	131.51	94.00	4.60	263.73	87.92	98.17	2.77
4	BM_07	127.75	83.00	1.08	204.12	105.96	47.69	1.24
5	BM_08	113.66	75.00	2.92	245.47	108.29	33.80	1.28
6	BM_11	90.11	58.00	2.49	189.20	70.30	57.11	1.23
7	BM_12	137.37	91.00	2.09	214.90	97.93	52.41	1.74
8	BM_12	136.44	91.00	1.88	246.15	131.37	51.46	1.64
9	BM_14	95.56	65.00	2.33	247.50	101.83	73.97	1.27
10	BM_15	116.77	81.00	5.81	289.18	163.27	27.23	1.92
11	BM_18	128.04	90.00	2.66	238.79	103.41	57.68	1.71
12	BM_19	129.64	90.00	3.51	368.48	182.46	97.45	2.23
13	BM_22	104.49	68.00	3.97	170.95	73.85	7.05	1.24
14	BM_28	124.22	91.00	4.00	313.99	129.66	108.35	2.58
15	BM_30	139.27	87.00	5.15	212.51	86.21	44.81	2.52
16	SA_03	134.68	90.00	72.69	75.17	35.59	0	1.40
17	SA_10	120.37	81.00	47.29	75.69	33.31	0	1.09

Table 8: Augmented outputs for each analysed patient analysed with imaging based protocol pre intervention

Case ID		Post intervention						
No	Short Case Name	Systolic Blood Pressure [mmHg]	Diastolic Blood Pressure [mmHg]	Max pressure drop across the aortic valve [mmHg]	LV end diastolic volume [ml]	LV end systolic volume [ml]	Mitral valve leakage [ml]	Stroke Power [W]
1	BM_01	161.2	94.6	1.0	116	69	0.00	0.99
2	BM_05	111.6	61.3	3.4	166	70	0.00	1.16
3	BM_06	150.1	107.1	5.8	226	126	0.00	2.14
4	BM_07	144.6	92.8	1.3	193	134	0.00	0.97
5	BM_08	120.0	78.9	3.2	236	122	0.00	1.19
6	BM_11	104.0	66.4	3.1	175	96	0.00	1.07
7	BM_12	153.6	101.2	2.5	200	124	0.00	1.43
8	BM_12	151.6	99.9	2.3	234	160	0.00	1.32
9	BM_14	110.1	73.6	3.1	228	136	0.00	1.09
10	BM_15	121.5	83.7	6.3	282	177	0.00	1.77
11	BM_18	139.9	98.1	3.1	218	128	0.00	1.41
12	BM_19	148.7	100.5	4.8	347	235	0.00	1.81
13	BM_22	105.9	69.1	4.0	169	76	0.00	1.21
14	BM_28	143.4	103.4	5.5	278	179	0.00	1.94
15	BM_30	153.1	95.5	5.9	201	107	0.00	2.24
16	SA_03	149.0	94.3	1.9	72	29	0.00	1.18
17	SA_10	129.4	82.9	1.6	74	30	0.00	0.94

Table 9: Augmented outputs for each analysed patient analysed with imaging based protocol post intervention

The next step in the process is to complete these fields for all EurValve cases and to examine the results for consistency and for association with the wider clinical data from the EurValve cohort. Ultimately, the aim is to prove the underpinning EurValve hypotheses concerning the value of the cardiac work and energy parameters, by associating them with patient outcomes.

4 CONCLUSIONS

This deliverable provides an overview of the analysis protocols that are operated to derive the augmented data from the modelling process, illustrated by a more detailed examination of the results of two cases (one mitral and one aortic). It also presents, in tabular form, the augmented data computed by operation of one of EurValve's analysis protocols for a total of 52 cases. The project plan delivered in December 2017 indicated a target of processing of one half of the 120 cases in the prospective study cohort time for this deliverable. Several more cases, including more than 10 aortic cases are due for completion with the image-based protocol within the next two weeks. We continue to anticipate that the majority of the cases will have been processed before the candidate software release at the end of July.

The non-invasive image-based analysis protocol is fully operational for both mitral and aortic valves, but it remains the case that the first two steps in the process, the segmentation and the CFD-based valve characterisation, can be quite labour-intensive. The optimisation process for the parameters in the 0D model has been automated, and the cases are now run in batch mode. It is generally robust in operation, and converges to small minima of the cost function (typically of the order of 1×10^{-4} or lower). This means that the final operation with the candidate workflow will be completed quickly when the candidate release is made (scheduled for the end of July). The process produces the cardiac work and power measures that are the primary outputs of the modelling process.

For the aortic valve cases, the segmentation process is robust, and geometrical representations of the leaflets are rapidly extracted from the medical image data. This is especially true for cases for which CT images of the open aortic valve are available. When the image data is 3D TEE (trans-oesophageal echo), the process is also robust but, depending on image quality, some manual correction might be required. From the CT analyses, a parameterised representation is routinely produced, describing the valve configuration in terms of eleven geometric parameters. This will soon be extended also for the TEE-derived geometries. The importance of this parameterised representation is that it supports the operation of a reduced-order model, as described in D3.3. This is a major step forwards for implementation of a model-based DSS that can operate in time scales of the order of minutes rather than hours, and that are consequently more readily integrated into a clinical work flow. It is anticipated that the ground-breaking nature of this process will result in a transformation of model-based analysis across a range of clinical haemodynamic applications.

For the mitral valve cases, the segmentation process is also robust in that it does produce, quickly and effectively, a geometric representation of the valve, but there are significant challenges in the accurate identification of sometimes-small regurgitant orifices in the closed configuration. Extensive manual intervention is required to check and to correct the segmentation result, by adjustment of the surface contours, in most cases. Furthermore, the parameterisation has not yet been possible, and the characterisation workflow is based on a series of steady-state CFD analyses. Despite these limitations, EurValve aims to process the full sixty mitral cases from the study cohort using the non-invasive image-based analysis protocol. The computed cardiac work parameters, already illustrated for 52 cases in this deliverable, are of significant interest and the partners are keen to examine the correlation of these parameters with clinical outcome as the collection of follow-up data is completed in the next few months. If the expected correlations can be confirmed and reported in peer-reviewed publications this will provide additional impetus for the further refinement of the mitral valve process. It is recognised, however, that the full automation of this process will probably require improvement in the imaging process for 3D analysis of the geometries of the leaflets in regurgitant mitral valve disease.

A reporting sheet to present the results to clinical staff has been produced and is currently being discussed with the clinical centres; it will soon be presented to Therenva for proposed implementation in the DSS.

This page was intentionally left blank