Initial insight to effect of exercise on maximum pressure in the left ventricle using 2D fluid-structure interaction model

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Aims: Study of maximum pressure in the left ventricle (MPLV) has already been a challenging aspect of clinical diagnosis.
Study design and methodology: The aim of this study was to propose a model to estimate the MPLV for a healthy subject based on cardiac outputs measured by echo-Doppler (non-invasive) and catheterization (invasive) techniques at rest and during exercise**.** Blood flow through aortic valve was measured by Doppler flow echocardiography. Aortic valve geometry was calculated by echocardiographic imaging. A Fluid-Structure Interaction (FSI) simulation was performed, using an Arbitrary Lagrangian-Eulerian (ALE) mesh. Boundary conditions were defined as pressure loads on ventricular and aortic sides during ejection phase. The FSI modelling was applied to determine a numerical relationship between the cardiac output to left ventricular pressures and aortic diastolic. This relationship enables the prediction of pressure loads from cardiac outputs measured by invasive and non-invasive clinical methods.
Results: Ventricular systolic pressure peak that was calculated from cardiac output of Doppler method, Fick oximetric and Thermodilution methods led to a 82.1%, 95.6% and 147% increment throughout exercise, respectively. The mean slopes obtained from curves of ventricular systolic pressure based on Doppler, Fick oximetric and Thermodilution methods are 1.27, 1.85 and 2.65 mmHg*min, respectively. Our predicted Fick-MPLV values were lower 8% to 19%, Thermodilution-MPLV ones 17% to 25% ,and Doppler-MPLV ones 57% to 73% when compared to clinical reports.
Conclusion: Initial outcomes from the subject show that results are in good agreement of literature values. The method, however, requires to be validated by additional experiments, comprising independent quantifications of MPLV. Since flow depends on the pressure loads, measuring more accurate intraventricular pressures helps to understand the cardiac flow dynamics for better clinical diagnosis. Furthermore, the method is noninvasive, safe, cheap and more practical. As clinical Fick-measured values have been known to be more accurate, our Fick-based prediction could be the most applicable.

Keywords: Fluid-Solid interaction, Fick oximetric,maximum pressure in the left ventricle, Thermodilution.

1. INTRODUCTION

Cardiac disease is a major cause of death in industrialized countries, in spite of advances in prevention, diagnosis, and therapy [1]. Despite challenging aspects of clinical diagnosis, the investigation of maximum pressure in the left ventricle (MPLV) assessment is among the most clinically important [2]. Therefore, detecting MPLV during blood pumping is important for recognition of such diseases. This study has used a FSI model to predict MPLV and trans-aortic pressure. Common invasive techniques like Fick oximetric and Thermodilution have associated risks [4]. MPLV measurements were first examined using invasive catheters [5]. Brenner et al. studied the MPLV at peak which was estimated in five infants using echo-Doppler and catheterisation method [6]. Greenberg et al. introduced a method to evaluate the MPLV by analyzing intraventricular flow velocities [7]. Firstenberg et al [8] and Tonti et al [9] non-invasively determined correlations between the earlier invasive MPLV measurements. Few studies have estimated MPLV with respect to the heart rate variations during exercise. However, heart rate changes during exercise, simultaneous intraventricular pressure gradients and ejection flow patterns have been measured by a multisensor catheter at rest and exercise [10]. Redaelli and Montevecchi studied only intraventricular pressure gradients using fluid structure interaction at a heart rate of 72 bpm. Without using an exercise protocol [11] Clavin et al and Spinelli et al used an electrical model to assess cardiac function based on left intraventricular-impedance at rest condition [12, 13]. Experimentally, intraventricular pressure is a valuable measurement. Nonetheless, due to the fact that the heart is not perfused via the normal route, intraventricular pressure cannot be measured even with sophisticated medical instruments like an open-ended catheter [14]. These studies demonstrated the importance of pressure measurement to make certain efficient LV performances.

FSI simulations are overall well matched to cardiovascular modeling [15 , 16]. This method requires the use of an Arbitrary Lagrange-Euler (ALE) mesh to analyze both structural deformation and fluid flow; i.e. Computational Fluid Dynamics and Finite Element Analysis [17 , 18]. Recently, FSI has been used to investigate heart valves [19 ,20 , 21 , 22 , 23 , 24 ,25 , 26]. Previously we have measured the cardiac output and stroke volume for a healthy subject by coupling an echo-Doppler method with a FSI simulation at rest and during exercise and particular attention was given to validating the model versus measures of cardiac function that could be reliably calculated by applying clinical protocols, with varying exercise [27] and the effect of exercise on blood flow hemodynamics including the change of flow patterns across the aortic valve, vorticity, shear rate, stress and strain on the leaflets while exercise [28]. In our previous studies pressures across the aorta were measured and applied to models. However, accurate predictions of aortic pressures are only possible using invasive techniques. Numerical calculation method is a useful tool for prediction of the real pressure values and it can analyze how different parameters, like material properties, affect output . It also has a potential role in clinical diagnosis.

The purpose of this study is to predict MPLV (mmHg) by numerical derivation from the relationship of cardiac output to MPLV (mmHg) [27] from invasive clinical cardiac output measurement [29]. First, the relationship between cardiac output and systolic ventricular pressure and systolic aortic pressure is derived, based on our previous numerical study [27]. Additionally, Christie et al.[29] clinically obtained equations for Thermodilution cardiac output (COT (ml/min)) and Fick oximetric cardiac output (COF (ml/min)) to Doppler cardiac output (COD (ml/min)). Therefore, COT (ml/min) and COF (ml/min) were measured for the subject [27]. Then, MPLV (mmHg) was calculated noting to the numerical relationship among cardiac output, systolic ventricular pressure and systolic aortic pressure.

2. MATERIAL AND METHODS

2.1 Overview

We have presented our two-dimensional FSI aortic valve model previously [27 , 28]. The model, as well as clinical measurements, are briefly described in section 2.2. Section 2.3 presents the methods to calculate pressure predictions based on cardiac output. Figure 1 shows workflow diagram.

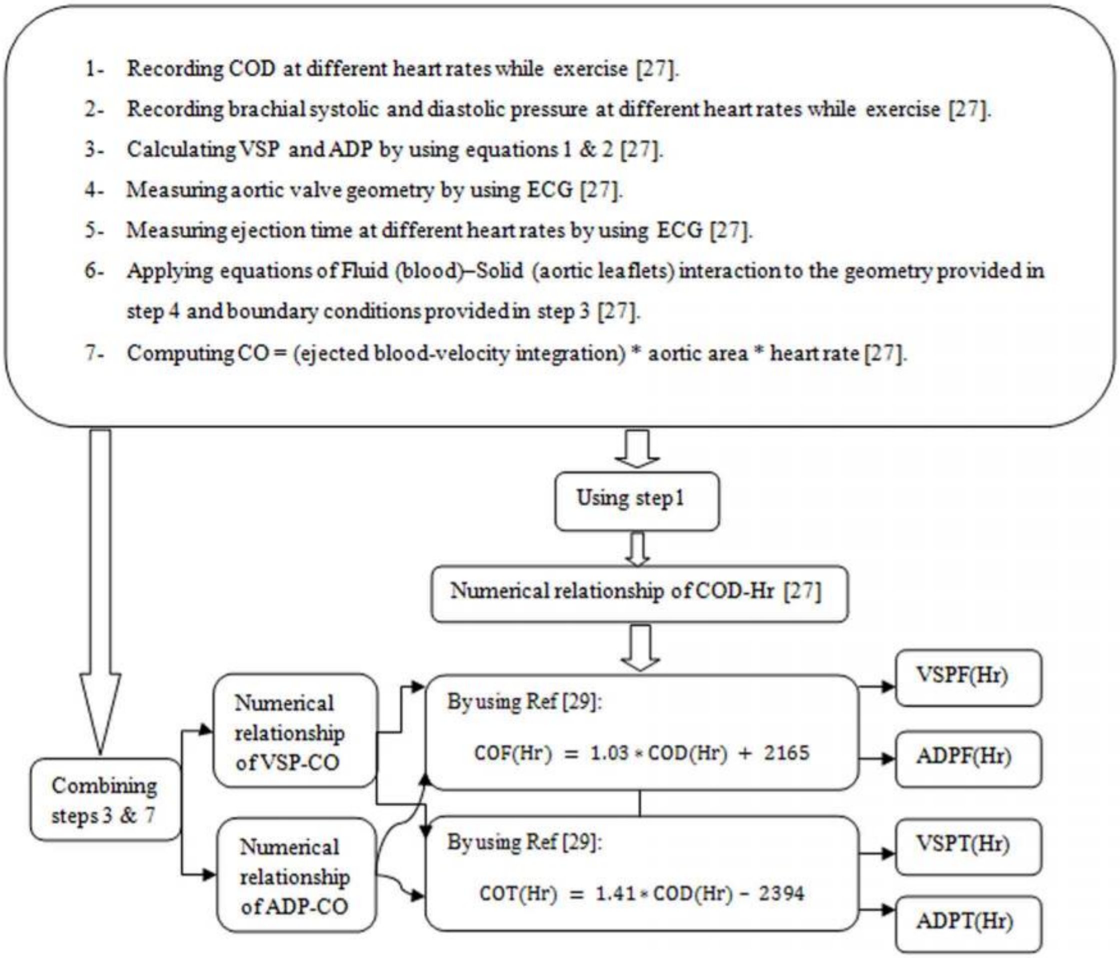

Figure 1. Workflow diagram

2.2 Combined clinical and numerical approach

A healthy male, aged 33, with normal cardiovascular function had his hemodynamic data recorded while rest and exercise. Informed consent was acquired for the participant in line with accepted procedures approved by the Department of Cardiovascular Imaging (Atherosclerosis research center, Tehran, Iran). Hemodynamic data was assessed from maximal bicycle exercise tests and Doppler echo. Systolic and diastolic pressures of the brachial artery were measured and related to heart rate changes at rest and exercise (Figure 2). Equations 1 and 2 were used to determine the central aortic pressure from brachial aortic pressure measurements. This relationship was previously determined by comparing brachial pressure (acquired by Oscillometry) to the central pressure acquired using an invasive method [30].

$$\textit{Central systolic pressure} \approx \textit{Brachial systolic pressure} + 2.25 \qquad (1)$$

$$\textit{Central diastolic pressure} \approx \textit{Brachial diastolic pressure} - 5.45 \qquad (2)$$

where all pressures were measured in *mmHg*.

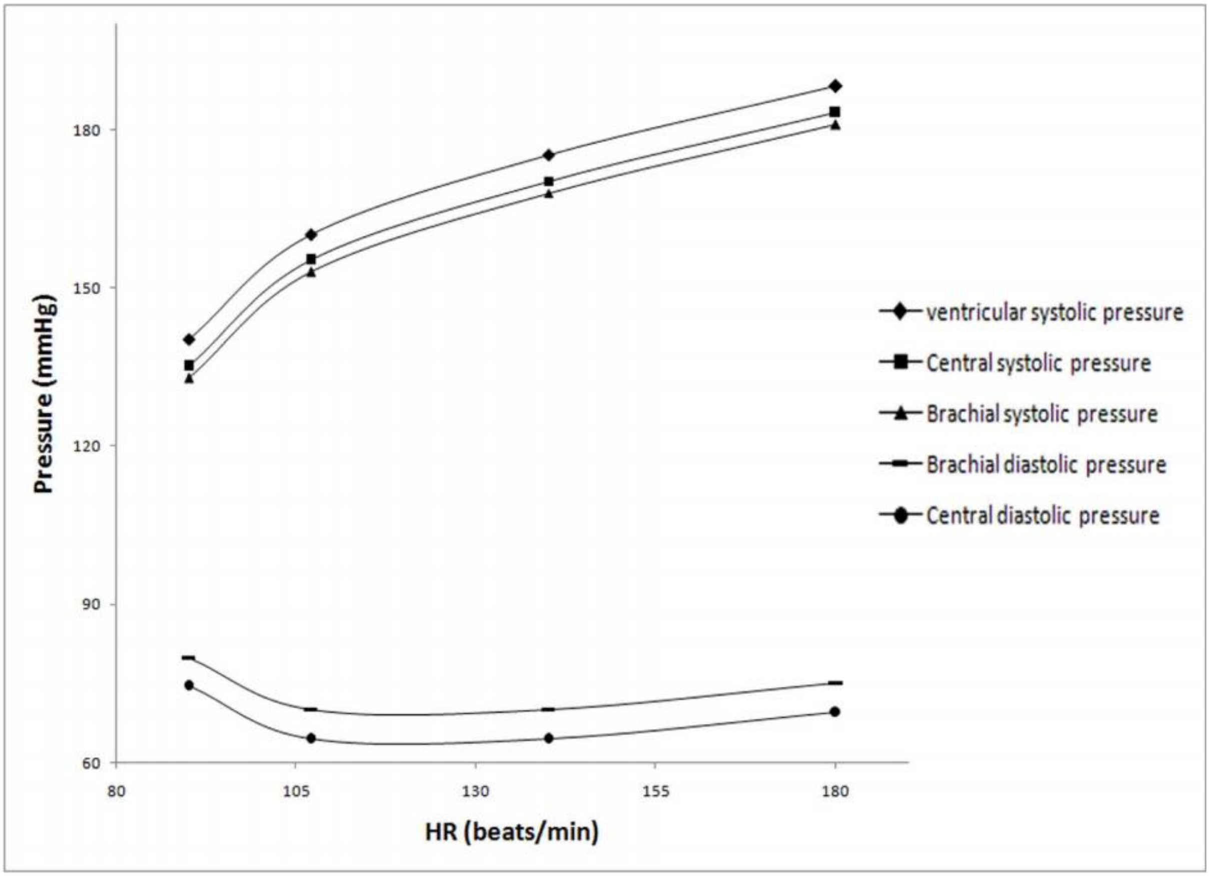

Figure 2. Interpolated curves for brachial, central and ventricular pressures.

Left ventricular systolic pressure was derived from the calculated central systolic pressure. Previously, a pressure difference of around 5 mmHg was found between peak left ventricular systolic pressure and central systolic pressure, using catheterization [31]. The ejection times were derived from Doppler-flow imaging under B-mode.

Table 1. Geometric parameters of the aortic valve as shown in figure 2.

(a)	(b)	(c)	(d)	(e)	(f)	(g)
Ascending aorta radius after sinotubular junction (mm)	Aortic side radius (mm)	Leaflet's thickness (mm)	Valve's height (mm)	Leaflet's length (mm)	Ventricular side radius (mm)	Maximum radius of normal aortic root (mm)
11.75	11.5	0.6	20.36	16.6	11.1	16.65

Table 2. Mechanical properties.

Viscosity (Pa.s)	Density (kg/m^3)	Young's modulus (N/m^2)	Poisson ratio
3.5×10^{-3}	1056	6.885×10^{6}	0.4999

The aortic valve geometry simulated is presented in figure 3 and dimensions are provided in table 1. Briefly, dimensions were obtained with respect to T-wave of ECG (maximum opening area), with diameters of the aortic valve annulus and the sinus valsalva (Each aortic sinus can also be referred to as the sinus of Valsalva) measured at the peak T-wave time using a resting parasternal long-axis view. The two cusps were considered to be isotropic, homogenous and to have a linear stress-strain relationship. This assumption has been used in other heart valve models [20 , 23 , 24 , 32]. Blood was assumed to be an incompressible and Newtonian fluid [16]. All material properties are provided in table 2 and were obtained from the literature [33 , 34].

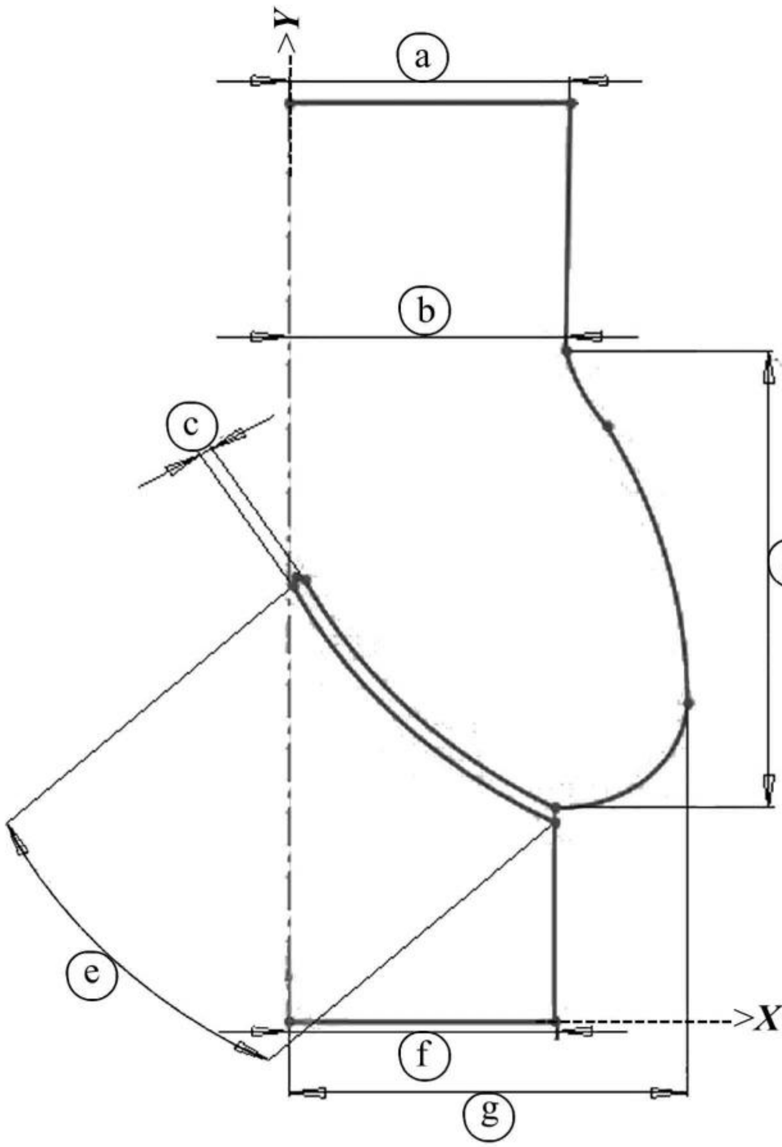

Figure 3. a) Ascending aorta radial after sinotubular site; b) Aortic side radial; c) Leaflet thickness; d) Valve height; e) Leaflet length; f) Ventricular side radial; g) Maximum radial of normal aortic root.

For fluid boundaries (figure 3), pressure was applied at the inflow boundary of the aortic root at the left ventricular side. A moving ALE mesh was used which enabled the deformation of the fluid mesh to be tracked without the need for re-meshing [35]. Second order Lagrangian elements were used to define the mesh. Two-dimensional triangular planar strain elements were applied to define the mesh. The mesh contained a total of 7001 elements (Figures 4a and 4b). The finite element analysis package Comsol Multi-physics (v4.2) [36] was used to solve the FSI model under time dependent conditions [23 , 24]. The fluid velocity is coupled to the structural deformation while the valve is loaded by the fluid, this ensures simultaneous coupling [37 , 38 , 39].

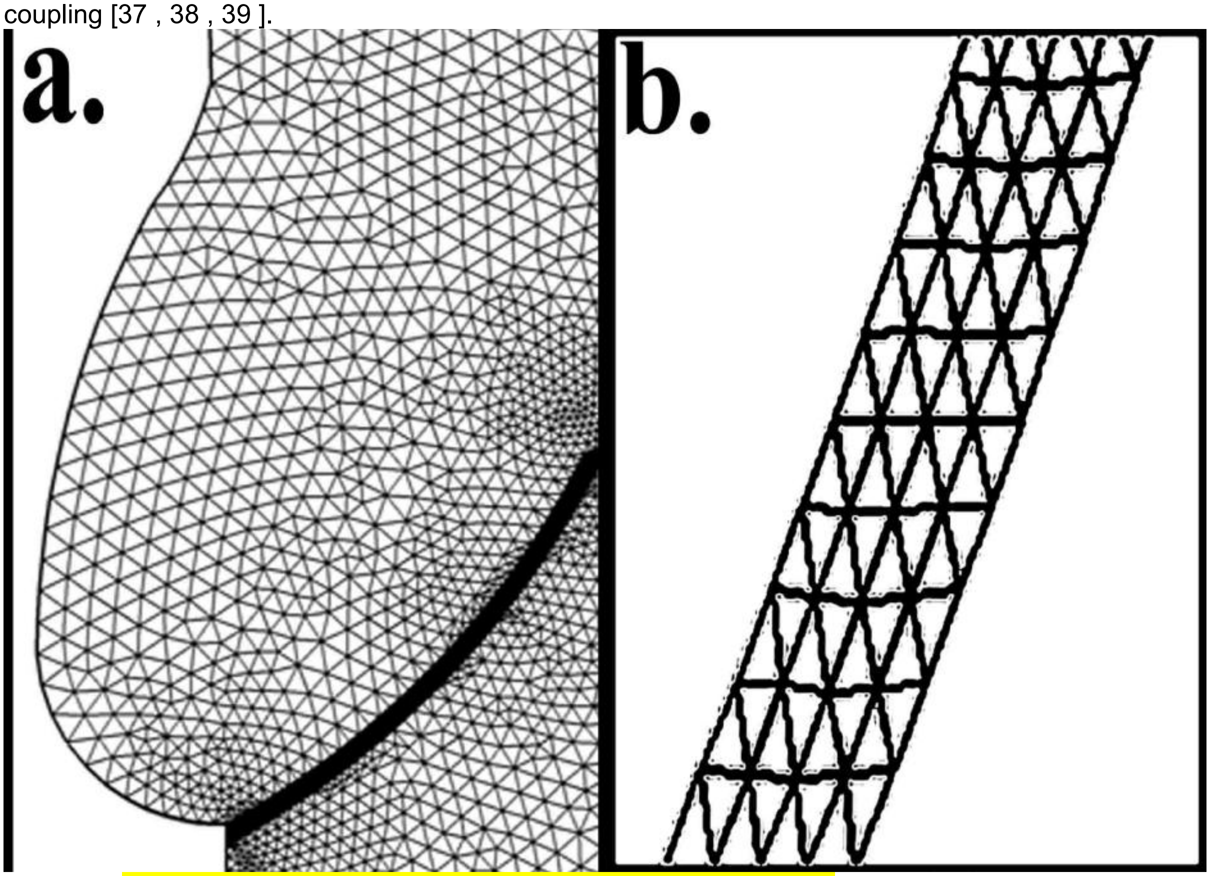

Figure 4. Meshes for the (a) the fluid domain and (b) the solid domain.

2.3 Cardiac measurements

Regression equations were used to calculate left ventricular systolic pressure (VSP (mmHg); equation 3) and aortic diastolic pressure (ADP (mmHg); equation 4) from the cardiac output predicted numerically (figure 5). :

$$\mathrm{VSP} = 1.266\mathrm{E}-06 * (\mathrm{CO})^2 - 0.017 * (\mathrm{CO}) + 152.3 \; ; (R^2=0.997) \qquad (3)$$

$$\mathrm{ADP} = 5.915\mathrm{E}-07 * (\mathrm{CO})^2 - 0.014 * (\mathrm{CO}) + 142.2 \; ; (R^2=0.965) \qquad (4)$$

Please note that E refers to exponent.

Previously we extracted the relationship between Doppler cardiac output and heart rate (beat/min) using equation 5 [27 , 40]:

$$\mathrm{COD} = -0.498 * (\mathrm{Hr})^2 + 213.550 * (\mathrm{Hr}) - 6164 \; ; (R^2 = 0.995) \qquad (5)$$

Christie et al. [29] obtained regression equations for the relationships between Thermodilution cardiac output (COT (ml/min)) and Fick oximetric cardiac output (COF (ml/min)) to Doppler cardiac output (COD (ml/min)), based on the data given from 15 subjects:

$$\mathrm{COT} = 1.41 * \mathrm{COD} - 2394 \qquad (6)$$

$$\mathrm{COF} = 1.03 * \mathrm{COD} + 2165 \qquad (7)$$

Combining equations (6) and (7) with equation (5) by applying Matlab [40], we have extracted the following relations and shown the curves of Fick oximetric (COF (ml/min)) and Thermodilution cardiac output (COF (ml/min)) relative to the heart rate in Figure 6.

$$COT = -0.705 * (Hr)^2 + 301.796 * (Hr) - 11131; \ (R^2 = 0.995) \qquad (8)$$

$$COF = -0.515 * (Hr)^2 + 220.461 * (Hr) - 4217; \ (R^2 = 0.995) \qquad (9)$$

Combining equations (3) and (4) with equation (8), enables VSP and ADP to be plotted with respect to heart rate respectively, based on Thermodilution method. These plots are shown in figures 7 and 8. Also, Combining equations (3) and (4) with equation (9) enables us to plot VSP and ADP with heart rate, respectively. The plots derived from a Fick oximetric method are shown in figures 7 and 8. Combining equations (3) and (4) with equation (5), enables the plotting of VSP and ADP with respect to heart rate, respectively. The plots derived from the use of a Doppler method for our subject are shown in figures 7 and 8.

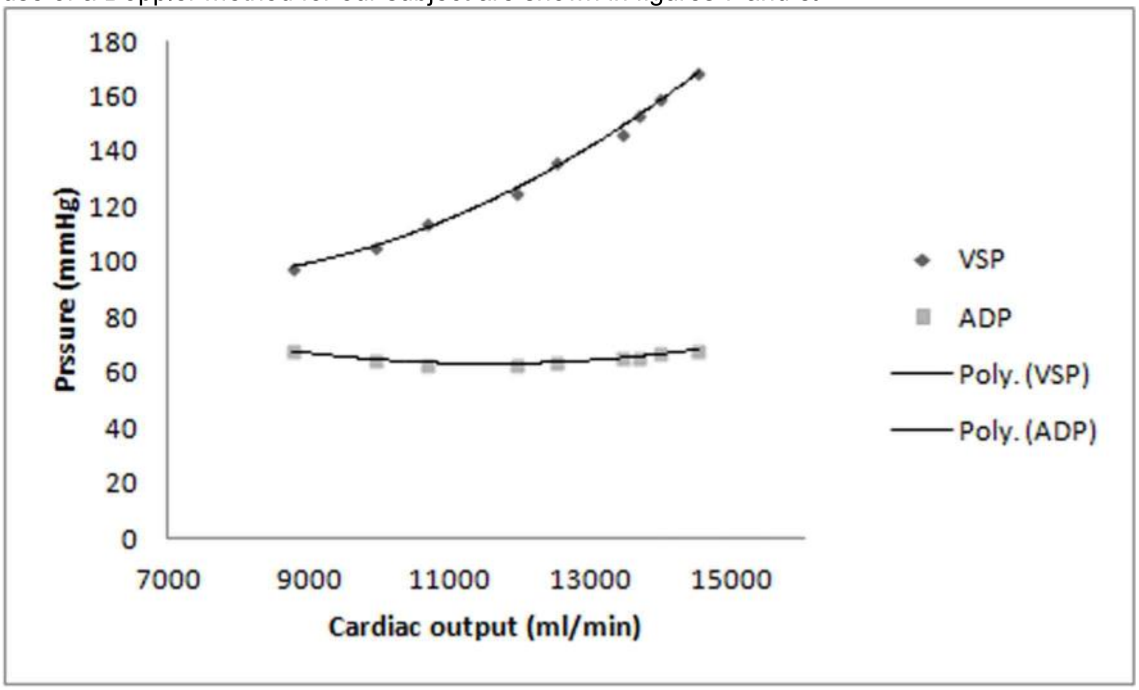

Figure 5. Ventricular systolic pressure (VSP) and Aortic diastolic pressure (ADP) to cardiac output that were plotted for numerical method.

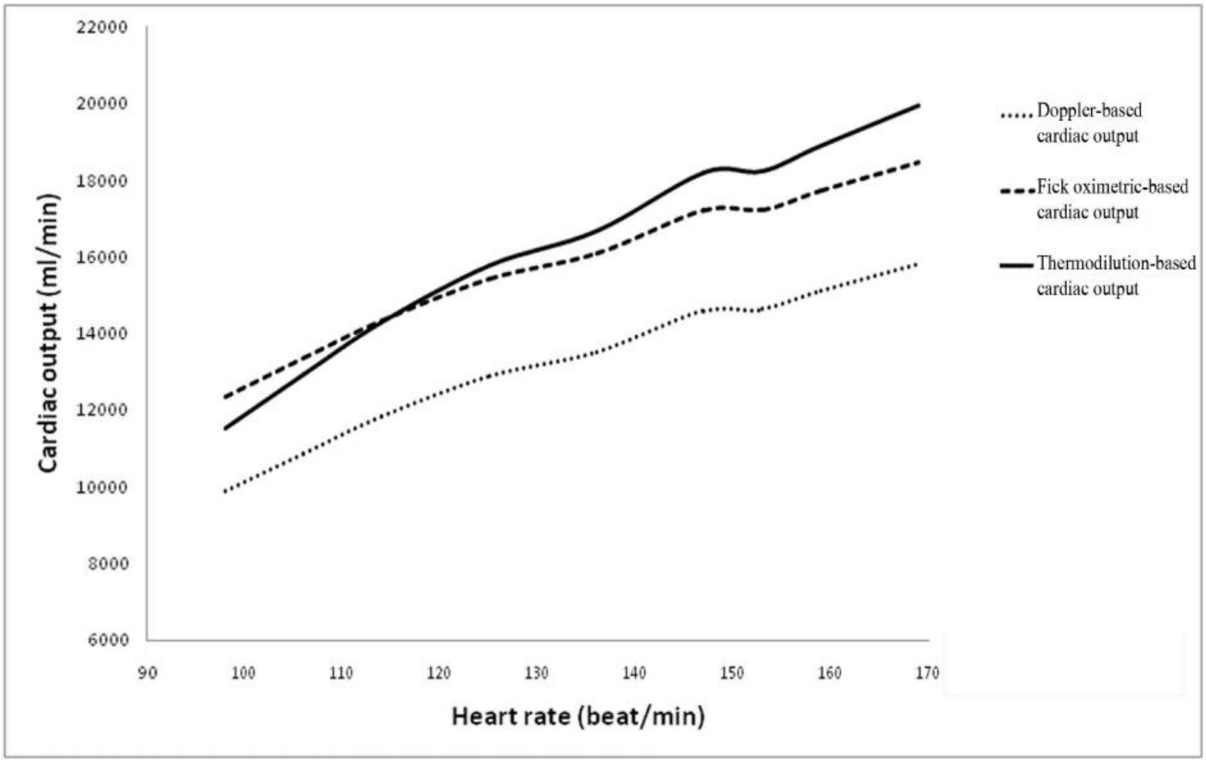

Figure 6. FSI prediction of cardiac output's change relative to heart rate based on Doppler method (round dot line), Fick oximetric method (square dot line), Thermodilution method (solid line).

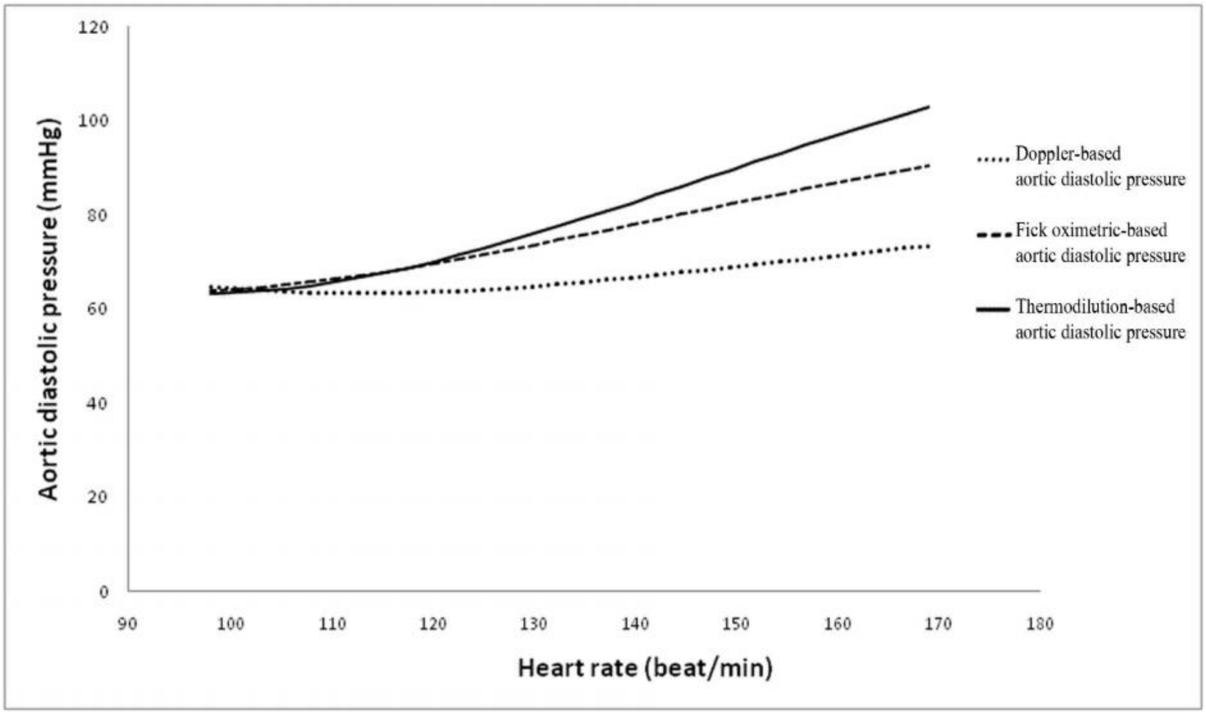

Figure 7. FSI prediction of aortic diastolic pressure's change relative to heart rate based on Doppler method (round dot line), Fick oximetric method (square dot line), Thermodilution method (solid line).

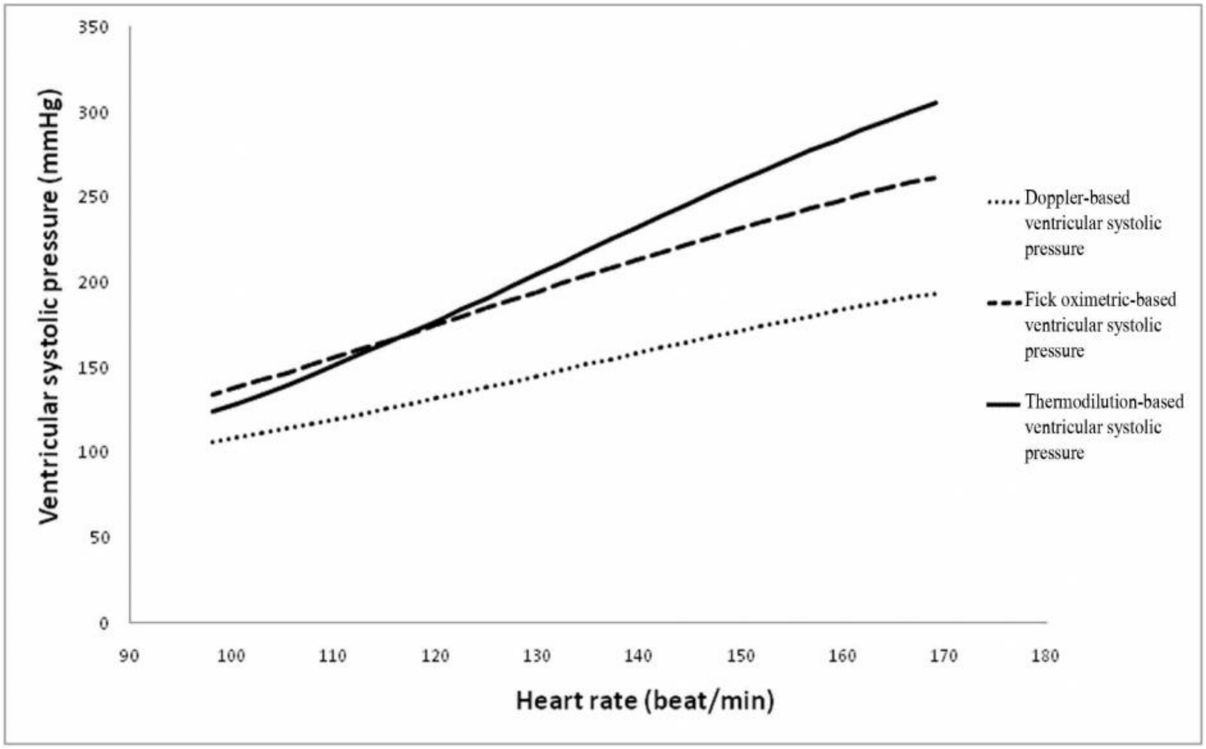

Figure 8. FSI prediction of ventricular systolic pressure's change relative to heart rate based on Doppler method (round dot line), Fick oximetric method (square dot line), Thermodilution method (solid line).

3. RESULTS

Aortic diastolic pressure, derived from Doppler based measurements, increased by 13.4%, corresponding to 8.7 mmHg, with increasing heart rate from 98 bpm to 169 bpm. Instead, using the Fick oximetric method a 42%, corresponding to 26.7 mmHg, increase was calculated. Whereas thermodilution led to a prediction of a 62.6% increase, corresponding to 39.6 mmHg. The mean slopes obtained from curves of aortic diastolic pressure based on Doppler, Fick oximetric and thermodilution methods were 0.14, 0.40 and 0.60 (mmHg*min), respectively.

The ventricular systolic pressure, predicted from the Doppler method, increased 82.1%, corresponding to 87.2 mmHg, with increasing heart rate from 98 bpm to 169 bpm (figure 8). This increase was calculated to be 95.6%, corresponding to 127.9 mmHg, using the Fick oximetric method and 147% (or 181.6 mmHg) for the Thermodilution method. The mean slopes obtained from curves of ventricular systolic pressure based on Doppler, Fick oximetric and Thermodilution methods are 1.27, 1.85 and 2.65 (mmHg/heart rate) respectively.

4. DISCUSSION

4.1 Study findings

The study has combined FSI hemodynamic measurements of the cardiac output, from a healthy subject [27] with invasive clinical measurements [29] in order to estimate the maximum pressure in the left ventricles during exercise. Based on current authors' knowledge, FSI discipline has been integrated with exercise measurements to numerically predict of cardiovascular performance for the first time. Despite using a simplified two-dimensional model, the method developed has potential for clinical application (section 4.2) and the obtained values show good agreement with the literature (see section 4.3). Moreover, the FSI model reliably predicted MPLV over a range of heart rates based on clinical measurement of cardiac outputs. MPLV was calculated by cardiac output of Doppler method, Fick oximetric and thermodilution method which shows 82.1%, 95.6% and 147% increment during exercise. Our predicted Fick-MPLV values were lower 8% to 19%, Thermodilution-MPLV ones 17% to 25% ,and Doppler-MPLV ones 57% to 73% when compared to clinical reports. So, Our predicted Fick-MPLV values are probably be corrected by 81% to 92%, Thermodilution-MPLV ones 75% to 83% ,and Doppler-MPLV ones 27% to 43% when compared to clinical reports.

Since cardiac output calculated with Fick method eliminates the plights associated with measuring VO2 precisely and do not require either an assumption of or measurement of the respiratory exchange ratio, that may prove to be more clinically useful for continuous cardiac output monitoring than Thermodilution cardiac [41, 42]. In this regard we can say that our Fick-based results could be more precise than the other two methods. Christie et al, furthermore, reported the advantage of Doppler measurement is its operational feasibility, although its outputs can be modified by the correlation equations between that and invasive techniques [29].

The mean slopes derived from curves, shown in fig 8, of VSP, are 1.27 (Doppler-based), 1.85 (Fick-based) and 2.65 (Thermodilution-based) (mmHg*min).

4.2 Clinical application & reliability

Predicting reliable intraventricular pressures is important in clinical diagnosis and treatment [2]. For instance, one of the recent commercially available medical investigating devices to assess intraventricular pressure has a fluid-filled, balloon-tipped catheter that is intended for insertion into the ventricle [14]. The balloon provides a closed system from which intraventricular pressure is determined. The balloon is attached to a fluid-filled catheter and connected to a pressure transducer and bridge amplifier [14]. This highly advanced method clearly demonstrates its involved risk and because of that they are mostly applicable for animal studies due to their invasive method.

The presented non invasive method lets us predict more accurate MPLV by measuring brachial pressures of subjects. Our numerical estimations based on Fick oximetric have potential for clinical application (8% to 19% underestimation when compared to clinical approaches; see discussion, Comparison to literature), this is important because Fick methods' evaluations have been reported to be more accurate than other clinical approaches [41, 42, 43, 44]. Catheterization-thermodilution , the current gold-standard for measuring intraventricular pressure [4], is an invasive procedure with potential risks such as heart failure, cardiac arrhythmia, and even death [4]. Moreover, thermodilution exposes the patient and doctor to radiation. Exercising while catheterized results in a range of practical problems too, therefore, is not common customary action. However, the use of a numerical method permits the estimation of cardiac function by non-invasive measurements during an exercise protocol. Therefore, the key-concern is the dependability of numerical methods when predicting MPLV while exercise. Yet, computational methods have not been combined with non-invasive clinical measurements to predict a patient's MPLV. Our model enables assessment of cardiac function and hemodynamic changes from rest to exercise [27 , 28]. It was feasible to derive the relationship for cardiac output to MPLV. Concerning invasive clinical cardiac output measurement as more accurate [29], we are able to estimate more precise MPLV. It should be mentioned that most of clinical measurement of MPLV have done for animals like dog such as Monroe study [45] due to the risk associated with them. It is generally accepted that cardiovascular modelling is mechanical-based system, in particular when the mechanical characteristic (e.g. MPLV) is intended to investigate. In this point of view, development of such mechanical simulations can be resulted in more accurate prediction of cardiovascular performance. By this it is thought that electrical-based simulations are more limited and less useful as compared to mechanical-based modelling. Based on our current knowledge, Max pressure of left ventricle, for example, has not been studied yet by electrical-based modelling.

4.3 Comparison to literature

Following a literature search we have not found a previous comparable study that combined a clinical and numerical approach to predict MPLV during exercise. In our study, the patient specific MPLV were predicted at a range of heart rates induced by exercise for echo-Doppler, thermodilution , and Fick oximetric methods. While the variation for MPLV from rest to peak of external work is established [3] this is the first study to use numerical methods to predict these values for an individual. Textbook MPLV range from 80 (mmHg) at 70 bpm to 270 mmHg at 180 bpm. It could also be approximated that the slope of MPLV is about 2.2 mmHg*min for non athletes during exercise [3]. Our subject is also a nonathlete. Our thermodilution-based prediction is overestimated by 17%, our Fick oximetric-based prediction is underestimated by 19% and our Doppler prediction is underestimated by 73% when compared to textbook values.

Loeppky et al. clinically investigated the systolic blood pressure changes while exercise for ten subjects. The mean slope of MPLV over the exercise protocol roughly was 2 mmHg*min [46]. Our thermodilution-based estimation is overestimated by 25%, our Fick oximetric-based estimations is underestimated by 8% and our Doppler-based estimation is underestimated by 57% when compared to the results from Loeppky et al.

Compared to published values [3, 46], our results based on thermodilution method are overestimated by 17% to 25%, the Fick oximetric method underestimates values by 8% to 19% and the Doppler method leads to underestimates of 57% to 73% when compared to clinical data.

Fick methods' evaluations has been reported to be more accurate [41, 42]. Hence, our numerical estimations based on Fick oximetric are more reliable when it is considered that an 8% to 19% underestimation could be due to our considered limitations for the numerical model or that only single subject was investigated. Textbook maximum systolic pressure for the normal left ventricle range from 250 to 300 mmHg, but varies widely among different subjects with heart strength and degree of heart stimulation by cardiac nerves. [10] MPLV has been studied by catheterization. MPLV ranged between 121 (mmHg) at the heart rate of 75 bpm to 210 (mmHg) at 180 bpm. They reported the average of MPLV of 6 patients with normal left ventricular function and no valve abnormalities, was 121 (mmHg) at 75 bpm at rest to 149 (mmHg) at 108 bpm during exercise. Although our study is numerical and based on one subject, our model predicted MPLV would be useful to quantify how closely the values match the literature.

4.4 Limitations & future trends

A fully developed discussion of the limitations of the FSI model has been explained previously [27]. In short, the main limitations are that:

- simplifications of the mechanical properties, plus using a constant orifice area and a single diameter for the ascending aorta in the model;
- statistical and generalized data was applied for clinical determination of hemodynamic;
- Instead of three-dimensional structure a two-dimensional model was used to investigate;

- The model was performed for a healthy subject. However, it should be noted that patients with cardiopathies may present different hemodynamic and structural alterations.

Despite model limitations we previously presented excellent agreement with clinical measurements and the general literature [27]. A real model as three-dimensional could results more precise predictions, while, it would also increase the solution time (currently less than 15 minutes). This would hold disadvantages for clinical applications, yet, it is required to be balanced against the short solution time for a 2D FSI model. Our model solution time is potentially able to be translated into clinical practice; moreover, ameliorating of solution time can be possible with more robust computer power. Furthermore, a range of values for statistical comparison are not predictable without the including variability in models [24]. At this time, there is a tendency towards patient specific models, like [47], due to potential profits in aiding treatment/diagnosis for an individual. Prediction of intraventricular pressure could be useful to construct more reliable heart valve prototypes [48].

Although pattern pressure of left ventricle is imposed by its walls contraction, we predicted this with comparing the underestimated numerical values of cardiac output [27] with that of invasive clinical reports [29]. Needless to say, this underestimation resulted from pressures of boundary conditions. Consequently, they were studied to be modified to correspond with clinical approaches.

4. CONCLUSION

We introduced a two-dimensional model of aortic valve which is able to predict maximum pressure in the left ventricles during exercise using FSI. The model was analyzed against results from echo-Doppler, thermodilution and Fick oximetric methods as invasive and non-invasive clinical methods. The model has potential applications in the prediction of ventricular pressures. As clinical Fick-measured values have been suggested as most accurate, our Fick-based predictions are likely the most applicable. The credibility and preciseness of this numerical technique for clinical application with human subjects would require further appropriate clinical studies.

5. Abbreviations

Term	Description
MPLV	Maximum pressure in the left ventricle
ALE	Arbitrary Lagrangian-Eulerian
FSI	Fluid-structure interaction
COT	Thermodilution cardiac output
COF	Fick oximetric cardiac output
COD	Doppler cardiac output
VSP	ventricular systolic pressure
ADP	Aortic diastolic pressure
ADPD	FSI prediction of aortic diastolic pressure’s change relative to heart rate based on Doppler method
ADPF	FSI prediction of aortic diastolic pressure’s change relative to heart rate based on

	Fick oximetric method
ADPT	FSI prediction of aortic diastolic pressure’s change relative to heart rate based on Thermodilution method
VSPD	FSI prediction of ventricular systolic pressure’s change relative to heart rate based on Doppler method
VSPF	FSI prediction of ventricular systolic pressure’s change relative to heart rate based on Fick oximetric method
VSPT	FSI prediction of ventricular systolic pressure’s change relative to heart rate based on Thermodilution method

COMPETING INTERESTS

The authors of the manuscript declare that they have no conflict of interest.

REFERENCES

1. Murphy SL, Xu J: Deaths: Preliminary Data for 2010, National Vital Statistics Reports 2012 4(60):31, 2010.
2. Bonow RO, Mann DL, Zipes DP, Libby P, Book Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine 9th ed, Philadelphia, Pa: Saunders Elsevier 2011.
3. Guyton. AC, Hall JE, Textbook of Medical Physiology, Philadelphia PA, WB Saunders P:27, 1996.
4. Lavdaniti M, , *Int J Caring Sci* 1(3):112–117, 2008.
5. Courtois MA, Kovacs SJ, Ludbrook PA, Physiologic early diastolic intraventricular pressure gradient is lost during acute myocardial ischemia, *Circulation* 82:1413–23, 1990.
6. Brenner JI, Baker KR, Berman MA: Prediction of left ventricular pressure in infants with aortic stenosis. *Br Heart J* 44(4):406-10, 1980.
7. Greenberg NL, Vandervoort PM, Thomas JD, Instantaneous diastolic transmitral pressure differences from color Doppler M mode echocardiography, *Am J Physiol* 271:H1267–76, 1996.
8. Firstenberg MS, Vandervoort PM, Greenberg NL, et al, Noninvasive estimation of transmitral pressure drop across the normal mitral valve in humans: importance of convective and inertial forces during left ventricular filling, *J Am Coll Cardiol* 36:1942–9, 2000.
9. Tonti G, Pedrizzetti G, Trambaiolo P, Salustri A, Space and time dependency of inertial and convective contribution to the transmitral pressure drop during ventricular fi lling, *J Am Coll Cardiol* 38:290–1, 2001.
10. Pasipoularides A, Murgo JP, Miller JW, Craig WE, Nonobstructive left ventricular ejection pressure gradients in man, *Circ Res* 61(2):220-7, 1987.
11 Redaelli A, and Montevecchi FM, Computational evaluation of intraventricular pressure gradients based on a fluid-structure approach, Journal of Biomechanical Engineering, transactions of the ASME 118 (4): 529–537, 1996.
12. Clavin OE, Spinelli JC, Alonso H, Solarz P, Valentinuzzi ME, Pichel RH, Left intraventricular pressure–impedance diagrams (DPZ) to assess cardiac function. Part 1: morphology and potential sources of artifacts, Med Progn Technol 11: 17–24, 1986.

13. Spinelli JC, Clavin OE, Cabrera EI, Chatruc MR, Pichel RH, Valentinuzzi ME, Left intraventricular pressure–impedance diagrams (DPZ) to assess cardiac function. Part II: determination of end-systolic loci. Med Progn Technol 11: 25–32, 1986.
14. Sutherland, Fiona J, et al. Mouse isolated perfused heart: characteristics and cautions. Clinical and experimental pharmacology and physiology 30.11 (2003): 867-878.
15 . Bellhouse BJ, The fluid mechanics of heart valves. In: Book Cardiovascular fluid mechanics, Volume 1, Bergel DH (ed), London Academic Press, 1972.
16 . Caro CG, Pedley TJ, Schroter RC, Seed WA, Book The mechanics of the circulation, Oxford: Oxford University Press, 1978.
17 . Donea J, Giuliani S, Halleux JP, An arbitrary Lagrangian–Eulerian finite element method for transient dynamic fluid–structure interactions, *Comput Methods Appl Mech Engrg* 33(1-3):689 –723, 1982.
18 . Formaggia L, Nobile F, A stability analysis for the arbitrary Lagrangian Eulerian formulation with finite elements, *East–West J Numer Math*7(2):105–132, 1999.
19 . Al-Atabi M, Espino DM, Hukins DWL, Computer and experimental modelling of blood flow through the mitral valve of the heart, *J Biomech Sci Eng* 5(1):78-84, 2010.
20 . De Hart J, Peters GW, Schruers PJ, Baaijens FP, A two-dimensional fluid-structure interaction model of the aortic valve, *J Biomech* 33(9):1079-1088, 2000.
21 . De Hart J, Peters GW, Schreurs PJ, Baaijens FP, A three-dimensional computational analysis of fluid–structure interaction in the aortic valve, *J Biomech* 36(1):103-112, 2003a.
22 . De Hart J, Baaijens FP, Peters GW, Schreurs PJ, A computational fluid-structure interaction analysis of a fiber-reinforced stentless aortic valve, *J Biomech* 36(5):699-712, 2003b.
23 . Espino DM, Shepherd DET, Hukins DWL, Evaluation of a transient, simultaneous, Arbitrary Lagrange Euler based multi-physics method for simulating the mitral heart valve, *Comput Methods Biomech Biomed Engin* In Press. DOI: 10.1080/10255842.2012.688818, 2012a.
24 . Espino DM, Shepherd DET, Hukins DWL, A simple method for contact modelling in an arbitrary frame of reference within multiphysics software, *J Mech*, In Press DOI: 10.1017/jmech.2012.128 , 2012b.
25 . Stijnen JMA, De Hart J, Bovendeerd PHM, Van de Vosse FN, Evaluation of a fictitious domain method for predicting dynamic response of mechanical heart valves, *J Fluids Struct* 19(6):835-850, 2004.
26 . Xia .G.H, Zhao .Y and Yeo .J.H , Numerical Simulation of 3D Fluid-Structure Interaction Using AN Immersed Membrane Method, *Modern Physics Letters B* 19(28-29):1447-1450. 2005
27 . Bahraseman HG, Hassani K, Navidbakhsh M, Espino DM, Sani ZA, Fatouraee N, Effect of exercise on blood flow through the aortic valve: a combined clinical and numerical study. Comput Methods Biomech Biomed Engin, In Press. DOI: 10.1080/10255842.2013.771179, 2013.
28 . Bahraseman HG, Hassani K, Navidbakhsh M, Espino DM, Fatouraee N, Combining numerical and clinical methods to assess aortic valve hemodynamics during exercise, Journal of perfusion, Accepted in 1/3/2014 & is in press.
29 . Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S, Determination of stroke volume and cardiac output during exercise: comparison of two-dimensional and Doppler echocardiography, Fick oximetry, and Thermodilution , *Circulation* 76(3):539-547, 1987.
30 . Park SH, Lee SJ, Kim JY, Kim MJ, Lee JY, Cho AR, Lee HG, Lee SW, Shin WY, Jin DK, Direct Comparison between Brachial Pressure Obtained by Oscillometric Method and Central Pressure Using Invasive Method, *Soonchunhyang Medical Science* 17(2):65-71, 2011.

31 . Laske A, Jenni R, Maloigne M, Vassalli G, Bertel O, Turina MI, Pressure gradients across bileaflet aortic valves by direct measurement and echocardiography, *Ann Thorac Surg* 61(1):48-57, 1996.

32 . Weinberg EJ, Kaazempur-Mofrad MR, A multiscale computational comparison of the bicuspid and tricuspid aortic valves in relation to calcific aortic stenosis, *J Biomech* 41(16):3482–3487, 2008.

33 . Govindarajan V, Udaykumar H.S, Herbertson L.H, Deutsch S, Manning K.B, and Chandran K.B, Two-Dimensional FSI Simulation of Closing Dynamics of a Tilting Disk Mechanical Heart Valve, *J. Med. Devices* 4(1): 011001(1-11), 2010.

34 . Koch TM, Reddy BD, Zilla P, Franz T, Aortic valve leaflet mechanical properties facilitate diastolic valve function, *Comput Methods Biomech Biomed Engin* 13(2):225-34, 2010.

35 . Winslow AM, Numerical solution of the quasilinear poisson equation in a nonuniform triangle mesh, *J Comput Phys* 1(2):149-172, 1966.

36 . Comsol Users Manual. 2011. Comsol Multiphysics Users Guide. Londen: Comsol Ltd.

37 . Dowell EH, Hall KC, Modelling of fluid-structure interaction, *Annu Rev Fluid Mech* 33(1):445-490, 2001.

38 . Wall W, Gerstenberger A, Gamnitzer P, Forster C, Ramm E, Large deformation fluid-structure interaction – advances in ALE methods and new fixed grid approaches *In: Fluid-structure interaction*, Bungartz HJ, Shafer M (Eds.) Berlin: Springer, 2006.

39 . Van de Vosse FN, De Hart J, Van Oijen CHGA, Bessems D, Gunther TWM, Segal A, Wolters BJBM, Stijnen JMA, Baaijens FPT, Finite-element-based computational methods for cardiovascular fluid-structure interaction, *J Eng Math* 47(3-4):335–368, 2003.

40 . MATLAB version 7.10.0, Natick, Massachusetts, The MathWorks Inc, 2010.

41. Mahutte CK, Jaffe MB, Chen PA, Sasse SA, Wong DH, Sassoon CS, Oxygen Fick and modified carbon dioxide Fick cardiac outputs, Crit Care Med 22(1):86-95, 1994.

42. Jarvis SS, Levine BD, Prisk GK, Shykoff BE, Elliott AR, Rosow E, Blomqvist CG, Pawelczyk JA, Simultaneous determination of the accuracy and precision of closed-circuit cardiac output rebreathing techniques, J Appl Physiol 103(3):867-74. Epub 2007 Jun 7, 2007.

43 . Maroni JM, Oelberg DA, Pappagianopoulos P, Boucher CA, Systrom DM, Maximum Cardiac Output During Incremental Exercise by First-pass Radionuclide Ventriculography, *Chest* 114(2):457-461, 1998.

44 .Sugawara J, Tanabe T, Miyachi M, Yamamoto K, Takahashi K, Iemitsu M, Otsuki T, Homma S, Maeda S, Ajisaka R, Matsuda M, Non-invasive assessment of cardiac output during exercise in healthy young humans: comparison between Modelflow method and Doppler echocardiography method, *Acta Physiol Scand* 179(4):361–366, 2003.

45 . Monroe RG, La Farge CG, Gamble WJ, Hammond RP, Gamboa R, Left ventricular performance and blood catecholamine levels in the isolated heart, *Am J Physiol* 211(5):124854, 1966.

46. Loeppky JA, Gurney B, Kobayashi Y, Icenogle MV. Effects of ischemic training on leg exercise endurance, J Rehabil Res Dev 42(4):511-22, 2005.

47 . Öhman C, Espino DM, Heinmann T, Baleani M, Delingette H, Viceconti M, Subject-specific knee joint model: Design of an experiment to validate a multi-body finite element model, *Visual Comp* 27(2):153-159, 2011.

48. Janko F Verhey,corresponding author, Nadia S Nathan, Otto Rienhoff, Ron Kikinis, Fabian Rakebrandt, and Michael N D'Ambra, Finite-element-method (FEM) model generation of time-resolved 3D echocardiographic geometry data for mitral-valve

volumetry, Biomed Eng Online 5: 17. Published online 2006 March 3. doi: 10.1186/1475-925X-5-17, 2006.