Cardiol Young 2005; 15 (Suppl. 3): 57–60
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ISSN 1047-9511

Mathematical modelling of the impact of preoperative hypertrophy on the outcomes of completion of the Fontan circuit

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Keywords: Ventricular function; functionally univentricular heart; diastolic impairment

THE IDENTIFICATION OF THE IMPORTANT relationship between shape and function of ventricular chambers represents a milestone of modern cardiology. Application of the law of Laplace for an ideal sphere furnishes intuitive insights on the progression of heart failure. A dilated heart, by virtue of its large size, must generate greater stress in the myocardial wall to achieve sufficient pressure so as to eject the required amount of blood. The mural hypertrophy represents a compensatory mechanism, guaranteeing a lower stress. When the ratio between the radius of the chamber and the thickness of its wall increases abnormally, the heart fails.[1]

The availability of complex three-dimensional finite element mathematical models, based on modern techniques for clinical imaging, such as magnetic resonance or helical-computerized tomography,[2] has permitted us a deeper understanding of the regional mechanics of the heart. Knowledge of distribution of stresses in the intact myocardium is able to provide useful insights into normal and abnormal ventricular function. The accuracy of the finite element method, however, is dependent upon the accuracy of the initial assumptions, such as the material property law, for example, the stiffness of ventricular wall, the detailed three-dimensional geometry, and the boundary conditions of the problems in continuum mechanics, for example, the ventricular pressure or the transvalvar flow. Even if our knowledge of the material property law is not perfect, nonetheless, using the geometrical parameters of ventricles as the base has permitted the study of the evolution of heart failure, the effectiveness of pharmacological treatment, the development of new surgical procedures,[3,4] and the design of new mechanical devices.

Acute changes in ventricular geometry have been reported after completion of the Fontan circuit,[5] with significant impact on the postoperative function of the functionally univentricular heart, and then in the resulting Fontan circulation. The macroscopic effect of the Fontan procedure is to pass from a volume-overloaded ventricle to an unloaded one, with an instantaneous increase of mural thickness, and a corresponding decrease in ventricular size, producing a significant mismatch in their ratio.[5] This dramatic increase is supposed to be a major determinant of an abnormal diastolic function, as expressed by an increase in the isovolumic relaxation time, and a decrease of diastolic compliance.[6–8]

The active phases of relaxation during diastole have also been found to be altered after completion of the Fontan circuit. The acute abolition of the volume overload is associated with a significant increase in the isovolumic relaxation period. Active relaxation is then impaired, because it coincides with an increased mural thickness, and this drags away the diastolic compliance.[9,10] Moreover, the excessive myocardial mass, in relation to the volume of the chamber, may change the lusitropic properties of the ventricle by impairing passive filling, and then altering again the ventricular diastolic compliance. If there is no longer any doubt about the relationship between the acute mismatch between mass and volume, and the diastolic dysfunction noted after conversion to the Fontan circulation, it remains as fact that a means of assessing

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https://doi.org/10.1017/S1047951105001654 Published online by Cambridge University Press

quantitatively the impact of preoperative hypertrophy on the outcomes of the procedure would be of great help in selecting the appropriated patients for conversion to the Fontan circuit. We addressed this problem by creating a mathematical model.

Materials and methods

In this work, we adapted the paradigm of function as related to shape to the study of the functionally univentricular heart in the Fontan circulation, devoting our main attention at the interplay between ventricular function and the critical pulmonary circulation.

We developed a mathematical model of the global cardiovascular system. We used lumped components, such as the viscous resistances to represent the relations of pressure to flow in the vessels, to simulate the Fontan circulation. We then exploited the one-fibre model[11] to simulate the mechanical behaviour of the ventricle, using the function of the ratio of the volumes of its cavity to its wall. With the one-fibre model, the ventricular wall is considered as a single long thin fibre, wrapped around the cavity. Multiple wrappings are performed from endocardium to epicardium in order to provide a realistic distribution of the orientation of the myocardial fibres. We coupled the one-fibre model to the lumped components of circulation, studying the active phase of relaxation of the cardiac cycle by exploiting a myofibre mechanical model.[12]

The atrioventricular and neoaortic valves were represented by ideal diodes. The systemic circulation was divided in inferior and superior components, arterial and venous, each directed into the right atrium. We took note of the increased systemic vascular resistance, characteristic for patients after conversion to the Fontan circulation. The pulmonary circulation was divided into components for the right and left lungs, assigning equal properties to each lung. The right and left atriums were connected by the atrial septal defect, modelled as a simple viscous resistance. The right atrium, through the ideal atrioventricular valve, was then connected to the functionally single ventricle. In the theoretical framework based on the one-fibre model, we have expressed the instantaneous cavity pressure as a function of the instantaneous cavity volume, of the wall volume and of the myofibre mechanical model.

To simulate the myofibre mechanical behaviour, we used Voigt's model of the myocardium, simplified by neglecting the elastic series element, but complicated by considering a parallel viscous element. We introduced this element to account for the impact of the collagen matrix on the lusitropic properties of the ventricle. The tension of the fibre was then expressed as a function of length, velocity and time, while the tension developed by the contractile element was modelled using the hyperbolic Hill relation. The passive and viscous behaviour of the fibre was described by a single exponential equation relating stress and strain.[12–14] So as to have the isovolumic phase of relaxation explicitly expressed in the model of the fibre, in agreement with the approach of Beyar and Sideman,[15] we represented the activation function with a raised cosine function during activation, and an exponential decay curve during relaxation.

All the parameters inserted in this model have previously been used,[16] albeit with some concern about the major uncertainty regarding the values of the parameters of the constitutive equation of the fibre, specifically the mathematical expression relating tension and strain in the fibre, along with the maximal stress, the maximal shortening velocity, the scaling factor of the Hill's equation, and the two parameters describing the passive and viscous behaviour of the fibre.[14]

Statistical methods

We used the method of the Monte Carlo Metropolis[17] to combat the uncertainty regarding the values of the parameters in the fibre constitutive equation. Thus, we defined a normal distribution, and then a mean value and a standard deviation, for each of the five parameters of this equation. We then randomly and successively extracted 1000 values from each distribution, and used them in 1000 consecutive simulations. The solutions were found studying the distribution of numerical results obtained from the 1000 simulations, which we reported as means and standard deviations. The normality of the distributions was checked by the Kolmogorov–Smirnov test, and statistically significant differences were assessed by the independent samples t-test; taking a p value of less than 0.05 as statistically significant.

Results

We simulated two different scenes. In the first, we supposed completion of the Fontan circuit in a patient with a mildly hypertrophied heart, with a great isovolumic relaxation time. In the second case, we posited completion of the circuit in the setting of a grossly hypertrophied heart, with a major isovolumic relaxation time. The two scenes correspond to early and late interventions on a volume-overloaded heart. We took values for the isovolumic relaxation times from previously reported clinical experience,[9,10] these being 70 milliseconds and 100 milliseconds, respectively. The two scenes were also characterized by different volumes for the functionally univentricular heart, taking an indexed value of 110 millilitres per square metre for the mildly hypertrophic heart, and

https://doi.org/10.1017/S1047951105001654 Published online by Cambridge University Press

Table 1. Results of the Monte Carlo Metropolis simulations in the two scenes. Scene 1 corresponds to a mildly hypertrophied preoperative heart; while Scene 2 corresponds to a grossly hypertrophied preoperative heart. End-diastolic volume is measured in millilitres, pressures are measured in millimetres of mercury, and flows in millilitres per second.

	Scene 1	Scene 2	p value
End-diastolic ventricular volume	50 ± 7	42 ± 6	<0.001
End-diastolic ventricular pressure	10 ± 2	16 ± 5	<0.001
Mean pulmonary pressure	10 ± 3	15 ± 5	<0.001
Mean pulmonary flow	9.2 ± 3.5	12.1 ± 4.2	<0.001
Mean aortic flow	74.5 ± 12.2	95.6 ± 13.8	<0.001

160 millilitres per square metre for the severely hypertrophic heart.

The results for mean pressure and flow in the pulmonary arteries, for the end-diastolic pressure and volume in the functionally univentricular heart, and for aortic flow, shown as mean values and standard deviations, are listed in Table 1. When increasing the isovolumic period of relaxation, and then going from a mildly to a highly hypertrophied heart, a marked decrease in the end-diastolic volume of the functionally single ventricle was found to be accompanied by a marked increase in its end-diastolic pressure. At the same time, the simulations showed concomitant increases in the mean flow of blood to the lungs, the mean pulmonary arterial pressure, and the mean aortic flow.

Discussion

The results of our simulations, therefore, were largely in agreement with the fundamental theoretical hypothesis of a relationship between the outcomes of conversion to the Fontan circuit and the preoperative ratio of wall mass to the volume of the functionally single ventricle. In this work, we have simulated mathematically preoperative hypertrophy, considering a major wall volume and its impact on the active phase of the relaxation, as expressed by a greater period of isovolumic relaxation. We chose the period of isovolumic relaxation as a meaningful parameter of preoperative diastolic function because of the known early manifestation of ventricular dysfunction during the active phase of diastole.[18] Should intervention be delayed, so that the Fontan circuit is completed in the setting of a more hypertrophied heart, with hypertrophy being the main compensatory mechanism for a prolonged volume overload of the functionally single ventricle, then our simulations predicted worse postoperative diastolic dysfunction. This is in agreement with the general observation of worse clinical outcomes in aged patients.

This general fitting of our mathematical model to known clinical observations encourages us to use its results for a more careful selection of the patients to be treated by Fontan procedure. Extending from this basis, further investigations may permit us to create patient-specific cut-off values for the preoperative ratio of wall mass to the volume of the functionally univentricular heart. Indeed, the modularity of our model gives us the potential to account for specific characteristics of given patients, such as vascular resistances and septal defects. Furthermore, our use of the approach of the Monte Carlo Metropolis seems effective in combating the uncertainties about the values of the parameters used in the model. The limitation of this approach is in the extensive time required to achieve the solutions, a limitation surely reducible in the near future when we are able to exploit the low cost of grid computing technology. When the necessary computing power is available in the clinical environment, mathematical modelling will offer a substantial aid in the selection of patients, the individualizing of the significant parameters, the provision of cut-off values for the decision-making process.

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