Cardiol Young 2005; 15 (Suppl. 3): 35–38
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ISSN 1047-9511

Contractility–afterload mismatch after the Fontan operation

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Keywords: Venous pressure; cardiac output; ventriculo-arterial mechanics

DURING THE PAST DECADES, DIFFERENT VARIANTS of the Fontan circulation have become the primary therapeutic option for physiological correction of congenital cardiac malformations in which restoration to biventricular circulations is impossible. Subsequent to creation of the Fontan circulation, the pulmonary and systemic circulations are in series, with only one pumping chamber. Thus, the functionally single ventricle must provide energy for flow of blood to the lungs, as well as to the body. Generally, patients who have undergone these procedures have a good prognosis, although they have subnormal cardiac output at rest,[1,2] while their central venous pressure is significantly elevated.[3] Despite an adequate haemodynamic situation at rest, exercise performance is usually reduced.[1,2,4] Thus far, this reduction has been attributed to cardiac factors, such as the absence of the morphologically right ventricle, or impaired function of the morphologically left ventricle. Due to the mechanical coupling between the heart and the peripheral circulation, however, the inadequate response to exercise in terms of cardiac output might also be dependant on insufficient peripheral vascular adjustments. In this review, we assess the existing experimental and clinical studies which provide detailed analysis of ventriculo-arterial mechanics in the setting of the Fontan circulation.

Theoretical studies

Better to understand the physiology of the Fontan circulation, Nogaki et al.[5] investigated the relationship between ventricular contractile properties and vascular afterloading properties on the plane of ventricular pressure related to volume (Fig. 1). Ventricular contractile properties were presented by end-systolic volume elastance (Ees, the slope of the end-systolic pressure–volume relationship), whereas the vascular afterload was presented by effective arterial elastance (Ea, the slope of the end-systolic pressure–stroke volume relationship). The ratio of ventriculo-arterial coupling ratio (Ea/Ees), and mechanical efficiency (the quotient of external stroke work and total pressure–volume area), were calculated to describe ventriculo-arterial mechanoenergetics (see Ref. 6 for review). The Fontan circulation was simulated in a simplified electrical circuit. They found that the theoretically estimated increase in arterial elastance, and the decrease in ventricular elastance, and thereby the mechanical efficiency, is reduced in the Fontan circuit. Simulations over a wide range of end-diastolic volumes and stroke works showed that, to maintain physiologic conditions, the dominant ventricle in the Fontan circuit has to provide almost maximal power with low efficiency. The adaptability of the Fontan circulation to conditions in which high energy is required appears to be limited. They postulated that the disadvantages stem primarily from increased ventricular afterload, due to the connection of the pulmonary and systemic vascular beds in series rather than parallel.

These findings were confirmed in the more detailed model of Magosso et al.,[4] which also included arterial and cardiopulmonary baroreflex mechanisms. The latter investigators concluded that relatively normal haemodynamics in patients with cavopulmonary connections at rest may be sustained by a combination of increased sympathetic activity, possibly caused by baroregulation, associated with permanent change

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https://doi.org/10.1017/S1047951105001617 Published online by Cambridge University Press

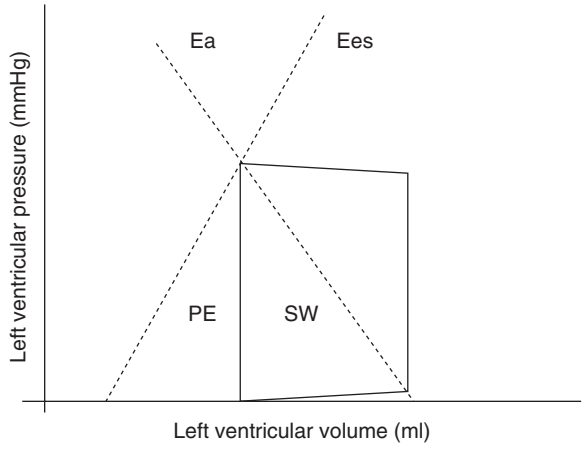


Figure 1.
Schematic representation of the pressure–volume plane. Ventricular contractile properties are presented by the end-systolic volume elastance (Ees, slope of the end-systolic pressure–volume relationship), whereas the vascular afterload was presented by effective arterial elastance (Ea, slope of the end-systolic pressure–stroke volume relationship). Ventriculo-arterial coupling ratio is calculated as Ea/Ees. Potential energy (PE) is generated during the isovolumic phase of contraction and represented by the triangle area between the end-systolic pressure–volume relationship and the pressure–volume trajectory of the isovolumic contraction phase. External work (SW) is equal to the area under the pressure–volume loop. Total pressure–volume area is defined as the sum of PE and SW. Mechanical efficiency is calculated as the quotient of external stroke work and total pressure–volume area to describe ventriculo-arterial mechanoenergetics.

in the parameters affecting the mean filling pressure, specifically a decrease in the unstressed venous volume, an increase in the total blood volume, and decreased compliance. Moreover, they showed that the response to moderate exercise is depressed compared with normal subjects, because patients with the functionally univentricular circulation may fail to raise the venous return.

Experimental studies

To elucidate the changes of ventriculo-arterial mechanics in the Fontan circulation, we assessed the relationships of pressure and volume in an acute canine model of the total cavopulmonary connection.[7] As ventricles eject pulsatile flow into distensible arterial system, a complete description of ventricular afterload and hydraulic power driven by the ejecting ventricle must include both behaviours during conditions of both pulsatile and steady flow. We included, therefore, an analysis of the spectrum of arterial impedance. We observed rather marginal changes. We noted that cardiac output decreased, albeit without reaching the level of significance, while heart rate, the mean aortic pressure, end-systolic pressure, and volume remained almost identical to the values at baseline. End-diastolic and stroke volume, however, decreased significantly.

Although the changes noted in several of the basic haemodynamic parameters were rather small, these changes had a profound influence on mechanoenergetics. The parallel decrease of myocardial contractility, and the slight increase of arterial elastance, led to a highly significant worsening of the ratio of ventriculo-arterial coupling. Similarly, the decrease of stroke work, combined with an unchanged pressure–volume area, the latter representing total mechanical energy, resulted in significant reduction of mechanical efficiency (Fig. 2).

Our data suggest that multiple, and in certain cases small, changes of afterload, preload, and contractility additively result in unfavourable mechanoenergetics in the Fontan circulation. We determined ventricular afterload in terms of vascular resistances and arterial elastance, as well as input impedance and characteristic impedance. Systemic vascular resistance in itself did not change significantly, this finding being consistent with the study of Macé et al.[8] These workers used a nearly identical model of the Fontan circulation created in pigs. The presence of the systemic and pulmonary vascular resistances in series, however, create a significantly higher afterload for the functionally single ventricle in the Fontan circulation than does systemic vascular resistance alone for the left ventricle in the normal circulation.[4,5] The strong tendency towards elevated arterial elastance in the Fontan circulation confirms previous theoretical assumptions,[4] and also suggests a moderate elevation of afterload. Further to elucidate the changes in afterload, we analyzed the spectrums of impedance. While the increase of input impedance, so-called zeroth harmonics, an equivalent of vascular resistance, did not reach the level of significance, characteristic impedance Z_c, a measure of the reflections of pulse waves, was significantly elevated. This indicates an increased stiffness of the arterial tree.[9] The causes of the elevation in the so-called characteristic impedance remain unclear. Previous studies[3,4] suggest that sympathetic activation, as a compensatory mechanism to maintain arterial pressure in the face of reduced cardiac output, may play a central role. Indeed, Kelley et al.[3] found increased forearm vascular resistance, increased heart rate, and elevated levels at rest of norepinephrine in the plasma of patients with the Fontan circulation when in compared to healthy control subjects.

We also showed that the functionally single ventricle inadequately utilizes the heterometric, or Frank–Starling, mechanism, as well as homeometric autoregulation, the so-called Anrepp effect, in the face of the elevated afterload provided by the Fontan circulation.[7] Instead of a compensatory increase of

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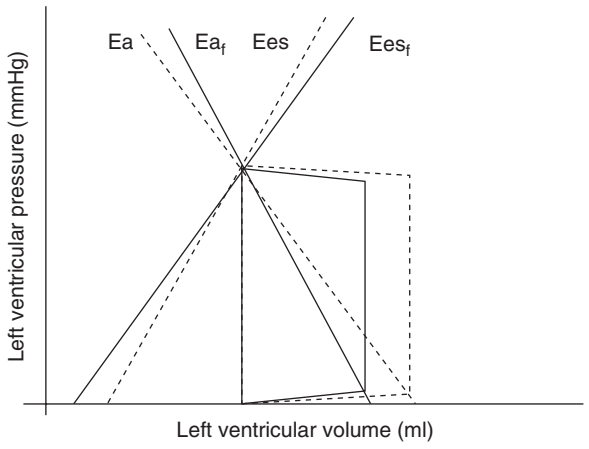


Figure 2.
Schematic pressure–volume loops in normal controls (dotted line) and after Fontan operation (solid line, "f" in index). The end-systolic pressure–volume (Ees$_f$ versus Ees) and arterial elastance (Ea$_f$ versus Ea) trajectories are indicated. In the Fontan circulation Ees decrease and Ea increases resulting in a worsened ventriculo-arterial coupling ratio which represents a mismatch between afterload and contractility. It should be also noted that the external work decreases and potential energy increases which leads to a marked decrease of mechanical efficiency.

preload and/or contractility, both these determinants of ventricular function are reduced. We were able to characterize the reduction in preload according to the significant decrease of end-diastolic volume. The main reason might be the reduced venous return in the functionally univentricular circulation associated with the elevated central venous and pulmonary arterial pressures, both of which are essential to maintain the pulmonary circulation. Macé et al.[8] investigated the changes in these parameters of venous return parameters by means of Guytonian relationships, which examine mean filling pressure related to the systemic flow of blood. They found that, in the functionally univentricular circulation, the slope of the Guytonian relationship significantly decreases, and the pressure intercept at zero venous return significantly increases. They concluded that placing the systemic and pulmonary vascular resistances in series induces a decrease of the slope of the Guytonian relationship. The greater the decrease in the slope, the more increase in the driving force, or the pressure gradient for venous return, is necessary to keep cardiac output constant.

Besides a reduced venous return, the alterations of characteristic impedance described above may themselves influence ventricular preload. Yano et al.[9] reported that an isolated increase of characteristic impedance, achieved by stiffening the aorta with a perivascular rigid tube, leads to a decrease in preload and stroke volume, and thereby to a mismatch in preload and afterload in the intact heart. Berger et al.[10] systematically investigated the determinants of propagation of waves in a system coupling the left ventricle to the systemic arterial tree. They described a linear inverse relationship between characteristic impedance and stroke volume. An isolated increase in characteristic impedance was noted to lead to a subsequent fall of stroke volume. This indicates that the isolated increase of characteristic impedance may also contribute to decreased preload and stroke volume in the Fontan circulation.

As a third determinant of ventricular function, myocardial contractility decreased. The observed changes of afterload and preload may have opposite effects on contractility. It has been described[11] that increased afterload leads to an increased contractility, even in the absence of neural control. In contrast, the decrease of preload leads to a decrease of myocardial contractility, via reduced affinity of contractile proteins for calcium, altered intracellular release of calcium, changes in the action potential, and changes in the stretch-activated ion channels.[12] As the increase of systemic afterload was rather small, and the reduction in preload seemed to be more prominent, the reduced contractility probably reflects the net effect of changes in both preload and afterload. The intracellular mechanisms leading to reduced contractility need further investigations.

Clinical studies

Recent clinical studies[13,14] confirm the findings of the theoretical and experimental studies discussed above. Tanoue et al.[13] approximated the ratio of ventriculo-arterial coupling from routine data obtained at cardiac catheterization in patients with the Fontan circulation. They found a worsened coupling, and thereby a mismatch between contractility and afterload in the setting of the primary total cavopulmonary connection. They compared their findings in this group of patients with another group who had previously undergone creation of the bidirectional Glenn anastomosis. In the latter group, ventriculo-arterial coupling decreased, thereby providing an improved energetic profile. The exact mechanism for the superiority of the staged creation of the Fontan circulation, however, remains unclear.

It has also proved possible to document altered impedance spectrums in the setting of the Fontan circulation. Senzaki et al.[14] showed that both vascular resistance, or the non-pulsatile load on the ventricle, and characteristic impedance, represented by the pulsatile components of the ventricular load, were significantly higher in patients with the Fontan circulation than in normal controls. In addition, the cost of hydraulic power for each unit of forward flow was

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lower by two-fifths in the normal circulation, suggesting lower ventricular efficiency in the setting of the Fontam circuit. They also demonstrated an inverse relationship between cardiac index and the first harmonic of the impedance spectrum. Furthermore, in the patients with a Fontan circulation, β-adrenetgic reserve was markedly decreased because of a limited preload reserve.

Conclusions and therapeutic implications

Patients converted to the Fontan circulation exhibit quite normal systemic arterial pressures, a moderate reduction in cardiac output and stroke volume, but an elevated venous pressure. This indicates that, after conversion to the Fontan circulation, the functionally single ventricle is able to maintain a sufficient circulation at rest which, however, becomes critical in response to exercise when compared to the normal circulation. This impairment is mainly evident in the insufficient capacity to increase stroke volume, and hence cardiac output, during exercise. Although these aspects are well-documented, a clear understanding of the phenomenons involved, and the key role of individual haemodynamic factors, is still lacking.

Recent data show that even small but complex changes of preload, afterload, and myocardial contractility in patients with the Fontan circulation have profound effects on ventriculo-arterial mechanoenergetics. This becomes manifest in terms of a mismatch between contractility and afterload, and reduced mechanical efficiency. These alterations may also limit the potential of the functionally single ventricle to adapt in response to exercise. Based on the inherent pathophysiology of the Fontan circulation, optimization of the operative strategies to create the circuit in terms of staged versus primary procedures, and treatment designed post-operatively to reduce afterload, might be key factors in improving the functional results of surgery. Further clinical studies are certainly warranted.

Acknowledgements

The present study was supported by the grants "Forschungsschwerpunkt Transplantation", University of Heidelberg and SFB414/H2 of the German Research Foundation.

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