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The physiology of the Fontan circulation

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Abstract

The Fontan circulation, no matter which of its various iterations, is abnormal in virtually every aspect of its performance. Some of these abnormalities are primarily the result of the procedure itself, and others are secondary to the fundamental disturbances of circulatory performance imposed by the 'single' ventricle circulation. The physiology of ventricular, systemic arterial and venopulmonary function will be described in this review.

Keywords: palliation; Fontan circulation; Cavopulmonary anastomosis; Antriopulmonary anastomosis

1. Introduction

In this personal overview, I will discuss the physiology of the Fontan circulation. Bob Freedom's contribution to our understanding of complex congenital heart disease has meant that many more of these patients are surviving with this physiology than could have been contemplated 30 years ago. Nonetheless, they represent a very difficult group of patients and we continue to learn more about this unique circulation. In this, necessarily superficial, overview, we will walk around the Fontan circulation discussing the relationships between the heart and vessels, both beneficial and disadvantageous.

2. Basic principles

The Fontan circulation provides definitive palliation for those with complex cardiac lesions that are not suitable for biventricular repair. Most patients will have undergone some form of palliation in early infancy (pulmonary artery banding, shunt, Norwood), leaving them with a parallel pulmonary and systemic circulation and a net increase in preload to their ventricle. Since the early 1990s, most patients undergo a staged transition to their completed Fontan circulation, via a bidirectional cavopulmonary anastomosis. It is at this stage that the most marked preload reduction of the ventricle occurs, which has the profound consequences for the systemic ventricle that will discussed below. At the same time as the bidirectional cavopulmonary anastomosis was becoming almost uniformly adopted, there was abandonment of the 'classical' atriopulmonary anastomosis, in favour of the total cavopulmonary connection (TCPC). The 'lateral wall' TCPC, popularised by Marc deLeval [1], was shown experimentally and clinically to be haemodynamically more efficient [1,2] and set the scene for the subsequent iterations. The inferior cavopulmonary anastomosis is now most frequently completed in the operating room, using an extracardiac tube, although the era of catheter-laboratory based completion [3], by which an intra-atrial baffle using a covered stent is created, is now with us.

Regardless of the exact nature of the connections, the completed circulation is often described as one having a single energy source, the systemic ventricle. This energy is dissipated through a series of resistors: in the ventricle itself (related to diastolic function), the systemic vascular bed, the systemic venous bed and the pulmonary vascular bed. As we 'walk through' the Fontan circulation, it will become apparent that additional sources of energy and potentially additional sources of energy dissipation exists, and that these are modified by time. Understanding these changes may be the key to understanding the issues of late failure of this circulation.

3. The ventricle

Before describing some of the ventricular events that are related to establishing a Fontan circulation, it may be

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worthwhile to discuss whether the systemic left ventricle differs significantly from the systemic right ventricle. This is increasingly pertinent given the improved survival of patients with hypoplastic left heart syndromes. There can be no doubt that there are inherent differences between the architecture, atrioventricular valve characteristics and functional responses when the LV and RV of these patients is compared. The same can be said, however, if one compares the systemic LV of patients with tricuspid atresia and double inlet left ventricle [4]. It is difficult to discern differences between the latter two groups, in terms of early geometric adaptation and outcomes of the Fontan operation and, similarly, little evidence exists to differentiate between those with a systemic RV or LV. Indeed, in one large study, a systemic right ventricle was shown not to influence early outcomes of the Fontan [5], and in another, those with systemic RV had superior survival to albeit more complex patients, with a systemic left ventricle [6]. Thus, for the purposes of this discussion, the physiologic characteristics of the systemic ventricle in the Fontan circulation will be discussed generically, although it has to be said that most of the data has been obtained from those with left ventricles.

At the time of the bidirectional Glenn procedure, or at the time of Fontan operation, if no bidirectional Glenn procedure has been performed previously, there is usually a marked decrease in the preload to the systemic ventricle. The degree of reduction primarily depends on the prior pulmonary to systemic flow ratio, which often exceeds 2:1. It is the reduction of preload and hence ventricular dilation and work, which, of course, provides much of the rationale for the operation. While few would disagree that reduction of systemic ventricular volume load is generally beneficial, it does come at a price in the Fontan circulation.

Abnormal systolic ventricular performance is rarely a major problem in the early years of palliation prior to the Fontan circulation and is sustained or improved in most, after completion of the Fontan circuit. In an elegant study from Boston's Children's Hospital, it was shown that restoration of normal systolic wall stress was achieved in most individuals undergoing a Fontan procedure prior to the age of 10 years [7]. This is important to bear in mind when we examine the potential effects of volume unloading of the systemic ventricle. The law of preservation of mass predicts that given a marked reduction in ventricular preload, preserved shortening and constant wall mass, a resulting increase in wall thickness must occur. This was shown experimentally [8] and demonstrated clinically in children undergoing the Fontan operation [9] some time ago. Fig. 1 shows an example of the changes seen in one of the patients undergoing a primary Fontan operation, as reported in our initial report of this phenomenon. There is a massive increase in wall thickness coincident with the acute reduction in end-diastolic volume.

The implications of this increased wall thickness are, perhaps, not intuitive. It might be reasonable to think that this increased wall thickness would modify end-diastolic compliance (ventricular wall stiffness) properties. There is very little evidence for this. Rather, the evidence points to abnormalities of early relaxation as being the major result. We have shown that prolongation of the time constant of early relaxation (tau) and the isovolumic relaxation time are both inversely related to the characteristically reduced early rapid filling [9,10]. Consequently, much of diastolic filling is dependent on atrial systole (Fig. 2). Very recently, this early diastolic dysfunction, also demonstrable after bidirectional Glen procedures, was shown to negatively impact recovery after subsequent Fontan operation [11] and may be important also in the late follow-up of these patients (see below).

This incoordinate relaxation is a feature of hearts affected by hypertrophy, ischemia and abnormal wall motion, all of which may exist in the Fontan myocardium. However, it is the adverse effect of wall motion abnormalities that appears to predominate in this group. Using both direct angiographic analysis [12] and surrogate measurements by Doppler echocardiography [13], we

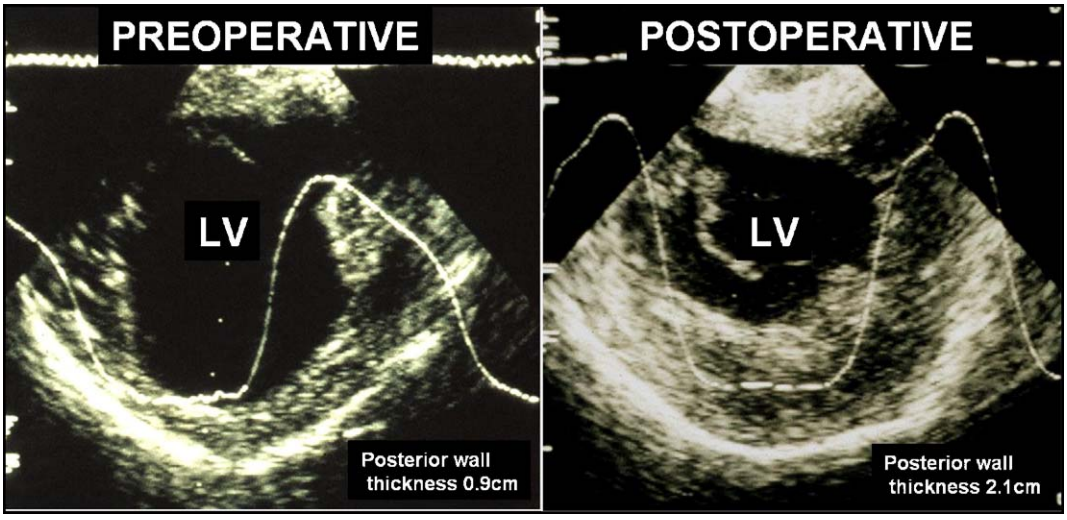

Fig. 1. Intraoperative echocardiograms taken before (left panel) and after (right) the Fontan operation, in a patient without prior staging with a bidirectional Glen anastomosis. The acute reduction in ventricular preload, maintained systolic shortening and preservation of wall mass leads acutely to a massive increase in wall thickening.

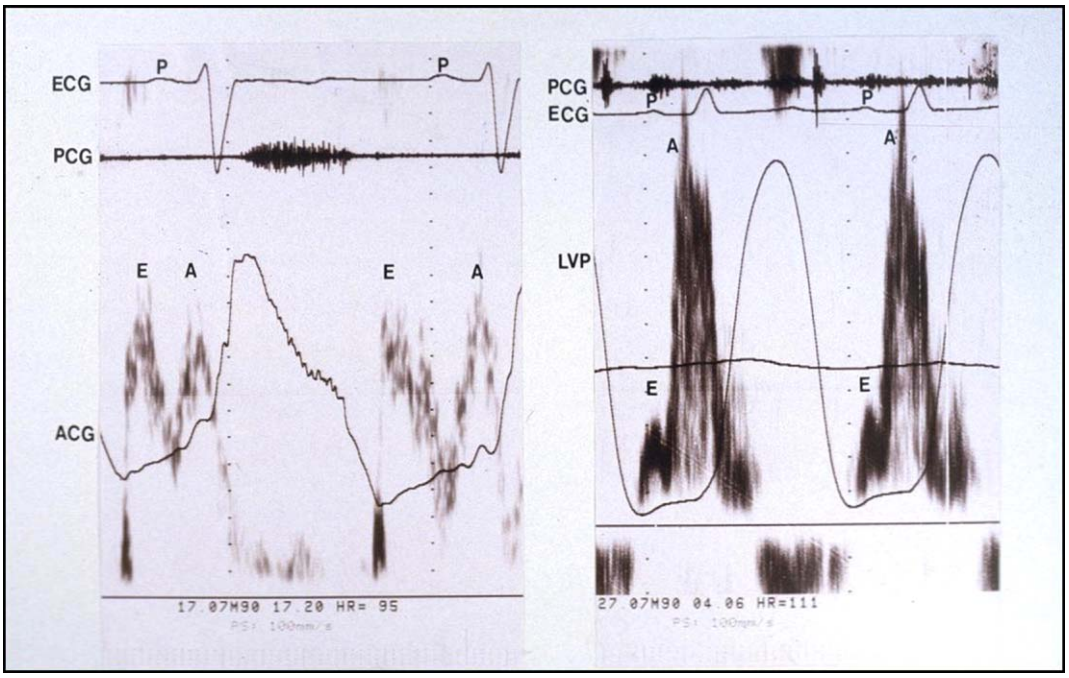

Fig. 2. Transmitral flow spectral from the same patient as in Fig. 1. Compared with preoperative recordings (left), there is a marked reduction in early rapid filling (E), with virtually all of ventricular filling occurring during atrial systole (A). Note that there is very little pressure increment during this period (micromanometer-derived LV pressure recording, LVP), suggesting that the ventricular compliance is not impaired. ACG=apexcardiogram, PCG=phonocardiogram.

have been able to show that abnormal base-to-apex wall motion abnormalities are mirrored by abnormal base-to-apex isovolumic relaxation flow in the cavity of these ventricles (Figs. 3 and 4). These relaxation abnormalities persist at mid-term follow-up, but interestingly, late diastolic abnormalities, characteristic of worsening ventricular compliance, start to become apparent at the same time [14]. The combination of persistently abnormal early relaxation with worsening ventricular compliance is particularly malignant combination, markedly reducing the ability of these ventricles to fill, potentially reducing pulmonary blood flow (or at least leading to elevated pulmonary artery pressure) and perhaps accounting for some of the late failure seen in these patients. There is little that can be done therapeutically to avoid the early diastolic abnormalities seen in these patients, and they may indeed worsen naturally with age as in the normal heart [15]. Nonetheless, avoidance of those factors known to lead to worsening compliance (e.g. persistent LV outflow tract obstruction, hypertension) is of fundamental importance.

While diastolic abnormalities predominate early-on, there is no doubt that systolic failure also becomes apparent in some patients late after the procedure. This may be a reflection of abnormal vascular properties, of ventricular vascular interactions (see below), or maybe intrinsic to the previously stressed or damaged myocardium itself. We, and others, have recently shown abnormal myocardial force frequency relationships in these patients [16,17], for example, probably reflecting abnormal calcium handling in the myocardium. Although abnormal, the changes seen are not at the level seen in adults with end-stage heart failure secondary to dilated cardiomyopathy, for example [18]. While a similar degree of physical incapacity may exist, with similar degrees of neurohormonal marker elevation [19], the response to pharmacologic interventions successful in dilated cardiomyopathy remains to be adequately addressed in these patients. As will be demonstrated below, sometimes the response of the Fontan circulation is counter-intuitive to the concepts established in heart failure of other causes.

While difficult to prove, it is likely that staged transition to the Fontan circulation will lead to overall improvements in outcome

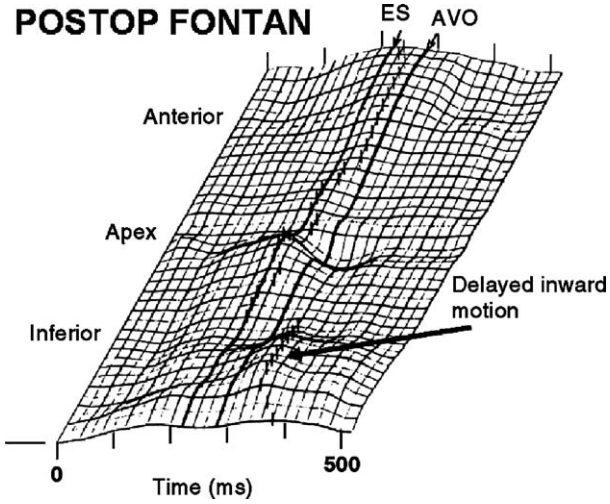

Fig. 3. Angiographic wall motion plot from a post Fontan patient. There is a characteristic pattern of delayed inward wall motion of the inferobasal segment, with compensatory outward motion, during isovolumic relaxation, of the apical segment. ES=end-systole, AVO=atrioventricular valve opening.

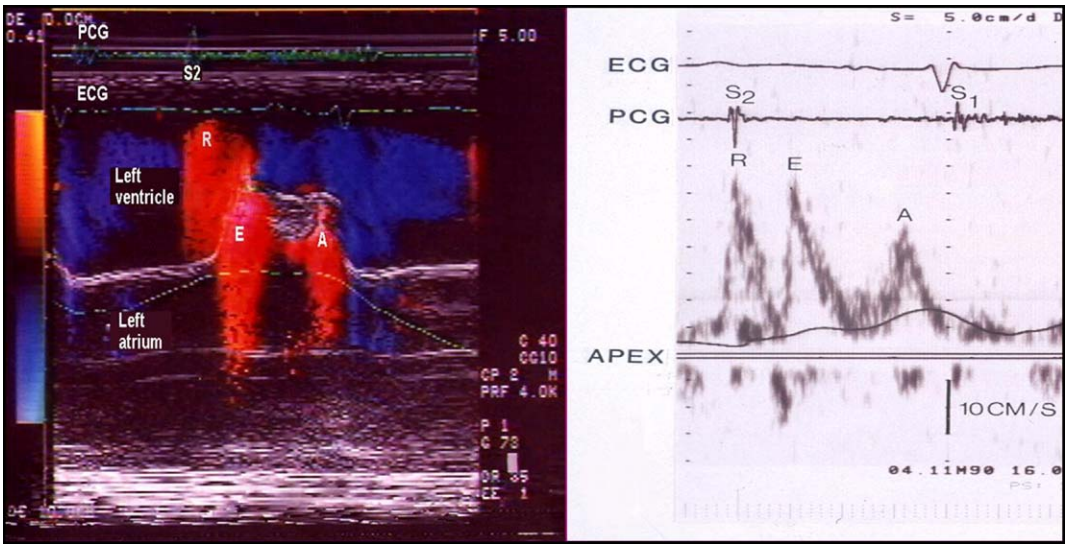

Fig. 4. Pulsed and colour flow Doppler recordings from a patient several years after Fontan operation. The colour Doppler m-mode shows intraventricular base to apex flow during isovolumic relaxation (R). Similarly, the spectral Doppler shows the presence of an 'additional' wave of flow preceding the early rapid filling wave (E), occurring during isovolumic relaxation. PCG=phonocardiogram.

for these patients. Avoidance of excessive early volume loading, avoidance of excessive myocardial hypertrophy and therefore avoidance of the major geometric changes discussed above would all seem conceptually beneficial. For the long-term outcome of these patients, avoidance of the age related naturally occurring changes in late diastolic performance, particularly in relation to the changes in chamber compliance seen with aging, hypertension, etc., may be the next frontier for maintenance of myocardial performance in these patients.

4. Systemic vascular bed and ventricular–vascular coupling

Many studies have reported uniformly elevated systemic vascular resistance after the Fontan operation [20,21]. How much of this is primarily related to the intrinsically low resting cardiac output, also uniformly reported, and how much is secondary to circulating vasoconstrictors, etc., has not been fully elucidated. The impact of this elevation of systemic vascular resistance on ventricular–vascular coupling also remains fully to be elucidated. However, there is no doubt that ventricular–vascular coupling is abnormal in this circulation [22]. Our own data derived from conductance catheter analysis of ventricular and arterial elastance (see Fig. 5) shows that, compared with expected normal values, patients after the Fontan operation have highly abnormal arterial elastance. This is somewhat compensated for by increased end-systolic ventricular elastance (going along with maintained systolic performance) but nonetheless overall there is abnormal ventricular–vascular coupling. Interestingly, patients with the Mustard operation have similarly abnormal ventricular–vascular coupling, but for different

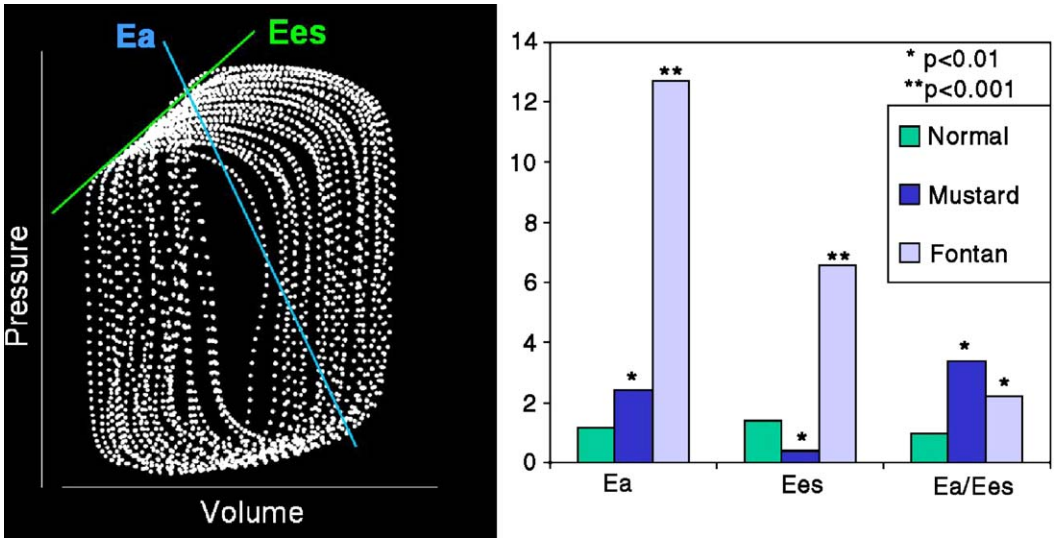

Fig. 5. Graphs showing ventricular (Ees) and arterial elastance (Ea) in normal, post-mustard and post-Fontan patients. Both patient groups show evidence of abnormal ventricular–vascular coupling (see text for details).

reasons. While the systemic vascular elastance is not so elevated, there is reduced ventricular systemic performance, emphasising the need to take both elements of the equation into account. Senzaki et al. [21] have taken a different approach to the analysis of ventricular vascular coupling. Using fast Fourier transform of the arterial pressure and flow, they have shown abnormal pulse wave characteristics and highly abnormal vascular impedance in these patients. Compared with controls and patients after Blalock-Taussig shunt for example, the relationship between cardiac index and vascular impedance, at baseline and with dobutamine, was highly abnormal in the Fontan group. A careful analysis of their data (the relationship between cardiac index and impedance being almost flat in the Fontan patients) however suggests that simply changing impedance may not necessarily lead to an improved cardiac index. This is crucial when considering the potential role for vasodilation in these patients.

It would appear intuitive, that in these patients with markedly elevated systemic vascular resistance and abnormal ventricular–vascular coupling, that vasodilation would improve their circulatory performance. However, this would only be the case if the abnormal vascular characteristics were of primary importance, rather than a secondary phenomenon. Randomized double-blind, placebo-controlled studies of therapeutic intervention in congenital heart disease are a rarity, but Kouatli et al. [23] provide us with such data for the use of angiotensin converting enzyme (ACE) inhibition in Fontan patients. Enalapril or placebo was given in cross-over fashion for 10 weeks in 18 patients approximately 14 years after the Fontan operation. Overall, there was no change in Doppler echo characteristics and a tendency to worse exercise performance. Indeed, there was reduced incremental cardiac index during exercise in the patients receiving enalapril. Despite these data, many patients continue to receive ACE inhibition, presumably in the hope of a beneficial effect when given chronically. It is possible, but unproven, that there are subgroups (e.g. those with severe systolic dysfunction, atrioventricular valve regurgitation) that may benefit. One might also be able to construct a theoretical argument for the use of ACE inhibitors with tissue-ACE inhibitory properties (e.g. quinapril, ramapril) in order to avoid the adverse remodelling described above. Nonetheless, however attractive the theory, there is presently no evidence for this therapy being beneficial in these patients.

5. The veno-pulmonary circuit

There has been a major evolution in the hemodynamic design of the Fontan operation since its inception. The initial right atrial to pulmonary connection has been abandoned in favor of more streamlined versions (see above). The benefits of this approach have been confirmed experimentally and in patients. We showed this in an early comparison of a contemporaneously treated group of patients undergoing either atrio-pulmonary Fontan or lateral tunnel Fontan procedures [2]. Using respiratory mass spectrometry and an acetylene re-breathing method to measure cardiac output, there was no difference between the patient group at rest, although their cardiac output was significantly lower than the normal comparison group. However, not only was cardiac output higher in the lateral tunnel group than the atriopulmonary group at low and moderate workloads, but so was respiratory rate. Despite a similar carbon dioxide production, and similar minute ventilation, these patients were taking more frequent, smaller, breaths during exercise, compared both with controls and the atrio-pulmonary Fontan patients. While speculative, we concluded that these patients were harnessing the beneficial effects of the work of breathing on the pulmonary circulation that is a particularly prominent feature in patients with veno-pulmonary connections.

The work of breathing is a significant additional energy source to the circulation in these patients. Normal negative pressure inspiration has been shown to increase pulmonary blood flow in patients with after the Kawashima operation [24], the atrial pulmonary connection [25] and in patients after TCPC [24]. Fig. 6A shows the direct temporal relationship between pulmonary blood flow and the respiratory cycle in these patients. A marked attenuation of pulmonary blood flow occurs with the Valsalva procedure for example (Fig. 6B) and a marked augmentation will occur during a Mueller maneuver [24]. The Philadelphia group, using magnetic resonance flow measurements, have estimated that approximately 30% of the cardiac output can be directly attributed to the work of breathing in patients after the TCPC [26]. It is very interesting to look at the regional subdiaphragmatic venous flow properties in these patients, in this regard [27]. While portal venous blood flow characteristics are markedly abnormal in patients after the Fontan operation, the respiratory influence is relatively limited. Inferior caval flow does vary with respiration, but in a relatively normal fashion. It is the hepatic venous flow that differentiates these patients from their normal counterparts. There is a very marked influence of respiration on total hepatic venous flow. Inspiration, presumably by a dual effect on venous pressure and compression of the liver by diaphragmatic decent, markedly augments hepatic venous contribution to the total venous return. The liver appears to act as a sump of blood which can be drawn upon during inspiration.

The converse is true when one considers positive pressure ventilation. It has long been known that increasing levels of positive end-expiratory pressure, during positive pressure ventilation, are adverse to the Fontan circulation [28]. We have learnt over the years that early postoperative restoration of normal negative pressure ventilation can be beneficial in these patients. We investigated this experimentally in children after the Fontan operation, comparing the effects of a negative pressure cuirass device with standard positive pressure ventilation [29]. By mimicking the normal action of breathing, negative pressure ventilation led to an increase in cardiac index of approximately 40% on average, compared with positive pressure ventilation. While not advocated as a routine clinical tool (although sometimes very useful therapeutically), these data heighten our awareness of the relationship between mean airway pressure and cardiac index in these patients. The available data suggests an approximately linear relationship between the two; the higher the mean airway pressure, the lower cardiac index. The management of these patients should therefore be directed towards minimizing mean airway pressure when these patients are being

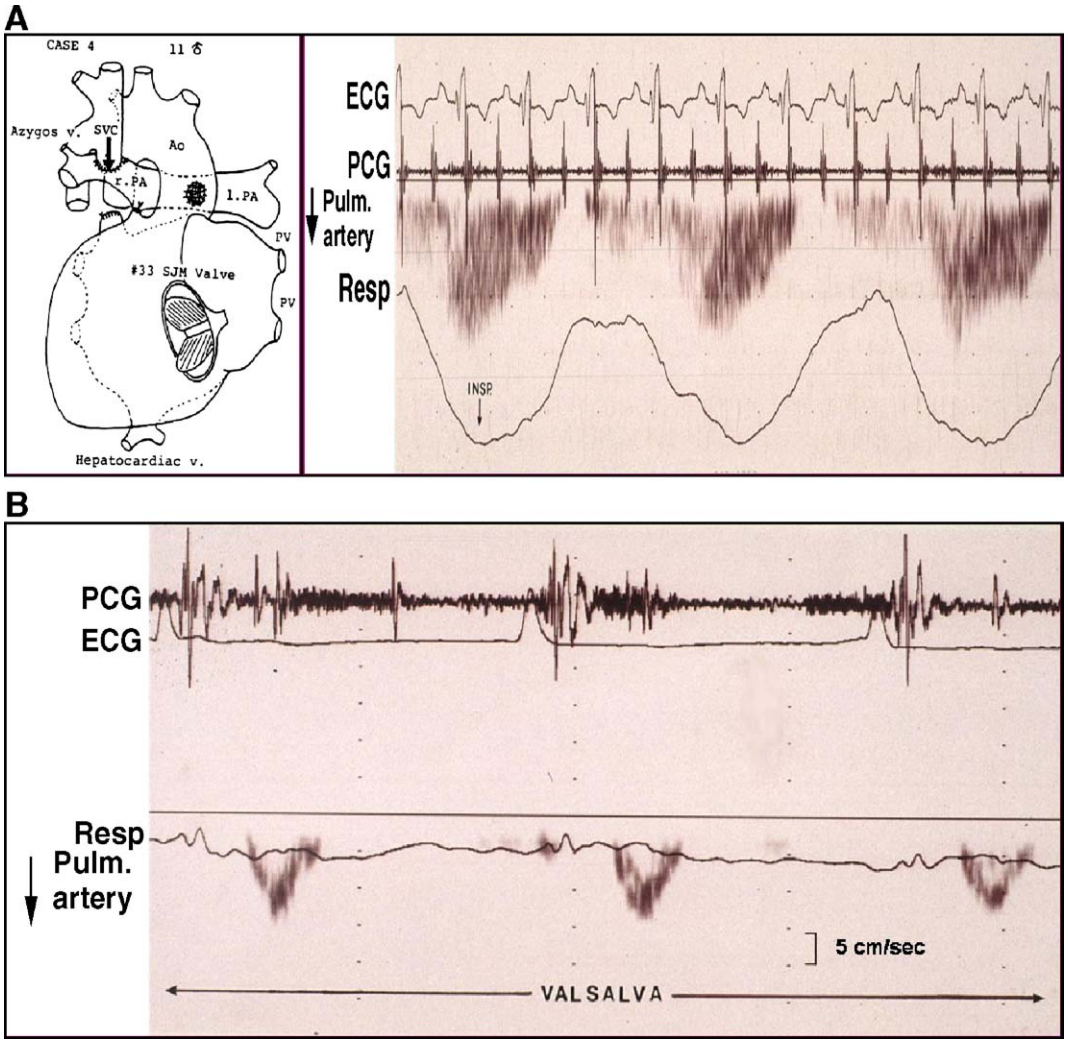

Fig. 6. (A) Pulsed Doppler recording just distal to the superior caval–pulmonary artery junction in a patient after total cavopulmonary anastomosis. Note the close temporal relationship between pulmonary artery flow and respiration. There is little apparent cardiac influence. (B) The same patient during a Valsalva manouvre. There is absence of spontaneous pulmonary blood flow, with only low velocity flow coincident with the x-descent of left atrial pressure (ventricular suction). Resp = respirometer, PCG = phonocardiogram.

ventilated for cardiac and non-cardiac procedures. This can be achieved by e.g. minimizing plateau pressures, end-expiratory pressures and rate of rise of pressure. The bottom line is that one should maintain these patients with the minimum mean airway pressure compatible with normal oxygenation (avoidance of airway collapse, etc.) and adequate alveolar ventilation (normal pCO_2).

6. The pulmonary vascular bed

A low pulmonary vascular resistance is a prerequisite for early success after the Fontan operation. The lower the total pulmonary resistance (which incorporates the pulmonary vascular resistance, pulmonary venous resistance and left atrial resistance) the better. We have already discussed the influence of abnormal ventricular responses to potentially raise left atrial pressure and therefore left atrial resistance. Structural pulmonary venous abnormalities are also important. Naturally occurring pulmonary venous stenosis may occur in many of the disease substrates that necessitate the Fontan circulation (right atrial isomerism), for example, or may evolve as a result of abnormal hemodynamics after, for example, atriopulmonary anastomosis. In the latter case, gross enlargement of the right atrium may compress the adjacent pulmonary veins as they return to the left atrium [30], and should always be excluded in patients with worsening functional performance late after these operations. Less well characterized is the chronic effect of the Fontan circulation on pulmonary arterial resistance. Pulmonary thromboembolism is not infrequent [31], may be covert [32] and clearly will lead to adverse changes in vascular resistance. Abnormalities of arteriolar resistance adversely influence early outcome, in terms of morbidity and mortality [33,34], but there are few data available regarding the long-term effects of the Fontan circulation on the pulmonary vascular bed. Clearly, the relatively low velocity, laminar flow in the pulmonary artery, is very different to the normal pulsatile flow experienced by the pulmonary vascular bed in the normal circulation. Release of nitric oxide from the endothelium is dependent on the waxing

and waning of sheer stress in response to pulsatile flow in the normal circulation. Experimentally, reducing pulsatility leads to reduced nitric oxide production by the endothelium and an increase in vascular resistance [35]. Recently, we examined a group of teenagers and young adults after the Fontan operation undergoing cardiac catheterization [36]. Using respiratory mass spectrometry, we measured pulmonary vascular resistance using the direct Fick principle. It has long been established that inhaled nitric oxide (NO) does not lead to significant pulmonary vasodilatation in the normal pulmonary vascular bed. However, in a significant proportion of patients after the Fontan operation, there was a marked reduction in the pulmonary vascular resistance, in response to 40 ppm of inhaled NO. These data suggest that, at least under the circumstances of cardiac catheterization under general anesthesia, that there is abnormal pulmonary endothelial function late after the Fontan operation. We are a long way from proving that modification of the pulmonary vascular bed, with e.g. NO donors or sildenafil, would lead to a functionally relevant improvement, but this is an area of current investigation.

7. Summary

The Fontan circulation is inherently abnormal in every aspect. Many of the adaptive changes, and the responses to interventions, are counterintuitive. So far, we have only scratched the surface of potential therapeutic interventions. With increasing understanding of those factors related to late failure, the next challenge will be to develop therapeutic algorithms that might delay the, perhaps, inevitable ultimate decline of this functionally abnormal circulation.

References

[1] de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg Nov 1988;96(5):682–95.

[2] Rosenthal M, Bush A, Deanfield J, Redington A. Comparison of cardiopulmonary adaptation during exercise in children after the atriopulmonary and total cavopulmonary connection Fontan procedures. Circulation Jan 15 1995;91(2):372–8.

[3] Hausdorf G, Schneider M, Konertz W. Surgical preconditioning and completion of total cavopulmonary connection by interventional cardiac catheterisation: a new concept. Heart 1996;75(4):403–9.

[4] Redington AN, Knight B, Oldershaw PJ, Shinebourne EA, Rigby ML. Left ventricular function in double inlet left ventricle before the Fontan operation: comparison with tricuspid atresia. Br Heart J Oct 1988;60(4):324–31.

[5] Gaynor JW, Bridges ND, Cohen MI, et al. Predictors of outcome after the Fontan operation: is hypoplastic left heart syndrome still a risk factor? J Thorac Cardiovasc Surg Feb 2002;123(2):237–45.

[6] Gentles TL, Mayer Jr JE, Gauvreau K, et al. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. J Thorac Cardiovasc Surg Sep 1997;114(3):376–91.

[7] Sluysmans T, Sanders SP, van der Velde M, et al. Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. Circulation Dec 1992;86(6):1753–61.

[8] Gewillig M, Daenen W, Aubert A, Van der Hauwaert L. Abolishment of chronic volume overload. Implications for diastolic function of the systemic ventricle immediately after Fontan repair. Circulation Nov 1992;86(5 Suppl):II93–9.

[9] Penny DJ, Lincoln C, Shore DF, Xiao HB, Rigby ML, Redington AN. The early response of the systemic ventricle during transition to the Fontan circulation: an acute hypertrophic cardiomyopathy? Cardiol Young 1992;2:78–84.

[10] Penny D, Redington AN. Diastolic ventricular function after the Fontan operation. Am J Cardiol 1992;69:974–5.

[11] Border WL, Syed AU, Michelfelder EC, et al. Impaired systemic ventricular relaxation affects postoperative short-term outcome in Fontan patients. J Thorac Cardiovasc Surg Dec 2003;126(6):1760–4.

[12] Penny DJ, Redington AN. Angiographic demonstration of incoordinate motion of the ventricular wall after the Fontan operation. Br Heart J Dec 1991;66(6):456–9.

[13] Penny DJ, Rigby ML, Redington AN. Abnormal patterns of intraventricular flow and diastolic filling after the Fontan operation: evidence for incoordinate ventricular wall motion. Br Heart J Nov 1991;66 (5):375–8.

[14] Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. Heart Apr 2000;83(4):420–4.

[15] Cheitlin MD. Cardiovascular physiology-changes with aging. Am J Geriatr Cardiol Jan–Feb 2003;12(1):9–13.

[16] Erenberg FG, Banerjee A. Systolic and diastolic properties of univentricular hearts in children: insights from physiologic indices that reflect calcium cycling. Pediatr Res Dec 2003;54(6):885–91.

[17] Cheung M, Smallhorn JF, Van Arsdell GS, Redington AN. Systemic right ventricular force–frequency relationships are superior to those of the left ventricle in the univentricular circulation. Circulation 2003;108(suppl III):1286.

[18] Alpert NR, Leavitt BJ, Ittleman FP, Hasenfuss G, Pieske B, Mulieri LA. A mechanistic analysis of the force–frequency relation in non-failing and progressively failing human myocardium. Basic Res Cardiol 1998;93 (Suppl 1):23–32.

[19] Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation Jul 2 2002;106(1):92–9.

[20] Sanders SP, Wright GB, Keane JF, Norwood WI, Castaneda AR. Clinical and hemodynamic results of the Fontan operation for tricuspid atresia. Am J Cardiol May 1982;49(7):1733–40.

[21] Senzaki H, Masutani S, Kobayashi J, et al. Ventricular afterload and ventricular work in Fontan circulation: comparison with normal two-ventricle circulation and single-ventricle circulation with Blalock-Taussig shunts. Circulation Jun 18 2002;105(24):2885–92.

[22] Tanoue Y, Sese A, Imoto Y, Joh K. Ventricular mechanics in the bidirectional Glenn procedure and total cavopulmonary connection. Ann Thorac Surg Aug 2003;76(2):562–6.

[23] Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation Sep 2 1997;96(5):1507–12.

[24] Redington AN, Penny D, Shinebourne EA. Pulmonary blood flow after total cavopulmonary shunt. Br Heart J Apr 1991;65(4):213–7.

[25] Penny DJ, Redington AN. Doppler echocardiographic evaluation of pulmonary blood flow after the Fontan operation: the role of the lungs. Br Heart J Nov 1991;66(5):372–4.

[26] Fogel MA, Weinberg PM, Rychik J, et al. Caval contribution to flow in the branch pulmonary arteries of Fontan patients with a novel application of magnetic resonance presaturation pulse. Circulation Mar 9 1999;99 (9):1215–21.

[27] Hsia TY, Khambadkone S, Redington AN, Migliavacca F, Deanfield JE, de Leval MR. Effects of respiration and gravity on infradiaphragmatic venous flow in normal and Fontan patients. Circulation Nov 7 2000;102 (19 Suppl 3):III148–53.

[28] Williams DB, Kiernan PD, Metke MP, Marsh HM, Danielson GK. Hemodynamic response to positive end-expiratory pressure following right atrium-pulmonary artery bypass (Fontan procedure). J Thorac Cardiovasc Surg Jun 1984;87(6):856–61.

[29] Shekerdemian LS, Bush A, Shore DF, Lincoln C, Redington AN. Cardiopulmonary interactions after Fontan operations: augmentation of cardiac output using negative pressure ventilation. Circulation Dec 2 1997;96(11):3934–42.

[30] Kreutzer J, Keane JF, Lock JE, et al. Conversion of modified Fontan procedure to lateral atrial tunnel cavopulmonary anastomosis. J Thorac Cardiovasc Surg Jun 1996;111(6):1169–76.
[31] Jahangiri M, Ross DB, Redington AN, Lincoln C, Shinebourne EA. Thromboembolism after the Fontan procedure and its modifications. Ann Thorac Surg Nov 1994;58(5):1409–13.
[32] Varma C, Warr MR, Hendler AL, Paul NS, Webb GD, Therrien J. Prevalence of "silent" pulmonary emboli in adults after the Fontan operation. J Am Coll Cardiol Jun 18 2003;41(12):2252–8.
[33] Bartmus DA, Driscoll DJ, Offord KP, et al. The modified Fontan operation for children less than 4 years old. J Am Coll Cardiol Feb 1990;15 (2):429–35.
[34] Mair DD, Hagler DJ, Puga FJ, Schaff HV, Danielson GK. Fontan operation in 176 patients with tricuspid atresia. Results and a proposed new index for patient selection. Circulation Nov 1990;82(5 Suppl):IV164–9.
[35] Nakano T, Tominaga R, Nagano I, Okabe H, Yasui H. Pulsatile flow enhances endothelium-derived nitric oxide release in the peripheral vasculature. Am J Physiol Heart Circ Physiol Apr 2000;278(4): H1098–104.
[36] Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation Jul 1 2003;107(25):3204–8.