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Original Article

Assessment of the pulmonary circulation in patients with functionally univentricular physiology

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The modified Fontan operation has become the procedure of choice to provide definitive palliation for patients born with one anatomical or functional ventricular chamber. At birth, the systemic and pulmonary circulations are in parallel and consequently, the dominant ventricle is volume overloaded. After the Fontan operation, the two circulations are separated and placed in series, without the interposition of a subpulmonary pumping chamber. The state of the pulmonary vascular bed is therefore of crucial importance to the outcome of such surgery. To that end, the trend is towards aggressive neonatal palliation, albeit with parallel but hopefully 'balanced' pulmonary and systemic circulations, with most institutions favoring ever earlier conversion to a superior cavopulmonary connection, usually between 3 to 6 months of age. This not only provides early volume 'unloading' of the systemic ventricle, but also facilitates early correction of associated anomalies, such as pulmonary arterial stenosis, atrioventricular valvar regurgitation, subaortic obstruction and abnormalities of pulmonary venous return. This approach has led to markedly improved morbidity and mortality throughout the process of 'staged palliation' with improved early results of the Fontan procedure itself. Despite this trend towards early caval anastomosis, there is limited long-term data comparing this approach to later caval procedures as well as the complete Fontan operation.

Careful selection of patients and optimal timing of intervention remain cornerstones of successful outcomes. While criteria continue to evolve, the optimal requirements can be summarized as: normal ventricular systolic and diastolic function, unobstructed ventricular inflow (no atrioventricular valvar stenosis, no severe regurgitation), unobstructed outflow (no subaortic stenosis, no coarctation), low transpulmonary gradient and vascular resistance, good sized pulmonary arteries without distortion, a well developed distal pulmonary vascular bed, and unobstructed pulmonary venous return.[1] While these are optimal, relatively few patients will fulfill all of these criteria. While, however, the 'limits' of Fontan inclusion criteria continue to be challenged, it remains the case that preoperatively impaired ventricular function and elevated mean pulmonary arterial pressure (greater than 15 to 20 mmHg) still have an adverse impact on surgical outcomes in contemporary series.[2–5]

Assessment of the pulmonary circulation in cavopulmonary connections

The pulmonary vascular bed

A low pulmonary arterial pressure and vascular resistance is a requirement for good outcome after completion of the Fontan procedure. Total pulmonary resistance reflects the effect of proximal pulmonary arterial size and the presence of stenoses, pulmonary arteriolar resistance, pulmonary venous resistance and left atrial pressure. The latter may be

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affected by abnormalities of the atrioventricular valves, or abnormalities of diastolic systemic ventricular performance,[6] both of which are common in these patients. Abnormalities of pulmonary venous pathways may be part of the disease itself, or secondary to anatomic changes consequent upon its surgery (e.g. compression of right pulmonary veins by an enlarged right atrium, or extracardiac conduit). Similarly, pulmonary artery size and the presence of stenosis may be intrinsic to the underlying abnormality, or secondary to the effect of interventions, but are usually remediable by transcatheter balloon dilation with or without endovascular stenting. Abnormalities of pulmonary arteriolar resistance are more difficult to assess, but not less important when assessing a patient prior to or after the Fontan procedure. Adequate assessment requires careful, usually invasive evaluation. Uptake of oxygen is an essential part of the calculation of pulmonary vascular resistance using the Fick method. It is widespread practice to use an estimate of oxygen update from predictive formulas based on body surface area or weight instead of measurements. Studies designed to determine the validity of those equations in calculating uptake of oxygen have proven to be unreliable, tending to overestimate its value and underestimate the pulmonary vascular resistance.[7–9]

Patients undergoing cardiac catheterization for quantitative assessment of the pulmonary vascular resistance, in order to base clinical decision-making, should preferably have measurement of oxygen consumption instead of using estimated values from predictive formulas.

Class: IIa. Level of evidence: B.

The role of cardiac magnetic resonance

Cardiac magnetic resonance imaging has been used to evaluate patients with univentricular physiology at each stage through the Fontan protocol. While it clearly can provide accurate anatomical and functional information, as with other techniques, it relies on availability of appropriate equipment and skilled personnel.

Cardiac magnetic resonance is excellent in assessing the anatomy and flow physiology of the pulmonary circulation, and in this regard is superior to echocardiography.[10–14] It also avoids the need for cardiac catheterization in some patients who have undergone bidirectional cavopulmonary anastomosis.[15] It remains, however, to be demonstrated unequivocally whether it can safely replace cardiac catheterization in all patients prior to staged surgery. For that reason, many centers continue to perform catheterization to measure pulmonary arterial pressure and resistance prior to cavopulmonary anastomoses.

Indications for cardiac catheterization throughout the staged Fontan protocol

Prior to superior cavopulmonary anastomosis. Routine preoperative cardiac catheterization prior to superior cavopulmonary anastomosis is still part of preoperative evaluation in most institutions. It is usually performed to assess the pulmonary arterial and venous pressure, the pulmonary vascular resistance, and dynamic assessment of systemic outflow tract and aortic arch anatomy. Moreover, it is possible to perform therapeutic interventions, such as occlusion of significant aortopulmonary or venovenous collaterals, balloon dilation of aortic arch, pulmonary artery or pulmonary veins, and also, creation or dilation of atrial septal defect. Echocardiography and cardiac magnetic resonance provide superior information regarding ventricular function, atrioventricular and semilunar valvar regurgitation, resting gradients across outflow tracts, the anatomy of branch and distal pulmonary arteries and pulmonary veins, as well as the anatomy of proximal and distal aortic arch. Nonetheless, it is not possible to measure pulmonary arterial pressure and resistance with the accuracy required for decision-making using noninvasive imaging. Two recent retrospective studies, however, have pointed out that is possible to identify a low-risk subgroup of patients in whom cardiac catheterization would not add new information on patient management.[16,17] In addition, a prospective, randomized, single-center clinical trial comparing cardiac catheterization with magnetic resonance in the preoperative evaluation of a low-risk group of patients with single ventricle physiology considered for superior cavopulmonary conection was recently published.[15] The study showed that catheterization is associated with greater frequency of minor adverse events, longer hospital stay and higher hospital charges than cardiac magnetic resonance imaging. The postoperative outcome was similar between the groups, both in-hospital and at the three-month follow up visit. The results indicate that routine cardiac catheterization may not be necessary in selected patients before surgery.

Cardiac catheterization prior to superior cavopulomonary anatomosis may not be necessary in patients in whom no issues indicating need for catheterization are identified by expert goal-directed echocardiography and/or cardiac magnetic resonance. Patients with uncertain pulmonary vascular physiology or lesions requiring catheter-based intervention or those with inadequate imaging of the aortic arch, pulmonary arteries, and pulmonary veins may benefit from cardiac catheterization prior to surgery.

Class: IIa. Level of evidence: B.

Prior to Fontan procedure. Diagnostic assessment before the Fontan procedure in patients with functionally univentricular physiology has usually

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included noninvasive evaluation with echocardiography and cardiac magnetic resonance, and invasive hemodynamic and angiographic evaluation by cardiac catheterization. The objectives of this approach is to recognize patients in whom the Fontan operation should not be performed because of excessive risk and also to identify patients in whom additional interventions are necessary, either by cardiac catheterization or at surgery. The role of non-invasive evaluation and the possibility of avoiding cardiac catheterization before conversion to the Fontan circulation has been addressed recently.[18]

A recent retrospective study has suggested that information obtained by hemodynamic and angiographic assessment before Fontan completion adds little to clinical decision compared to noninvasive evaluation for a subset of patients selected by clinical and echocardiographic criteria. Cardiac catheterization was considered necessary in the presence of the following findings: pulse oxymetry less than 76%, hemoglobin concentration more than 18 g/dL, stenosis of the left pulmonary artery, significant atrioventricular valvar insufficiency, decreased systolic ventricular function, presence of aortic coarctation, restrictive atrial septal defect and evidence of a decompressing vessel arising from the upper body venous system. These criteria correctly stratified all patients who died or did not proceed to Fontan and the majority who required additional interventions, with a negative predictive value of 93% and with a sensitivity of 81%.[19] While these results indicate that cardiac catheterization could be avoided in a large percentage of patients, without unfavorably influencing the postoperative outcome they reflect the dilemma of group versus individual risk. Given that neither the predictive values nor the sensitivity of the test were 100%, some patients may be compromised by a global decision to obviate cardiac catheterization altogether. It must also be said that cardiac catheterization has not been tested in the same way, and by no means is entirely predictive of outcomes. Nonetheless, elevated pulmonary arterial pressure is still described as a risk factor for poor outcomes after Fontan completion, even in more contemporary series.[2–5] Although noninvasive imaging can provide nearly all anatomic and functional information needed for clinical decision, it is not possible to measure pulmonary arterial pressures, allowing for calculation of pulmonary vascular resistance. Prospective, randomized studies assessing the results of conversion to the Fontan circulation following exclusively noninvasive evaluation are needed. Because these data are not available yet, some physicians who are considered experts in this field remain recommending cardiac catheterization for all patients who are potential candidates for completion of the Fontan procedure.

Most patients continue to require evaluation of pulmonary artery pressure and vascular resistance by cardiac catheterization prior to Fontan completion in order to optimize risk stratification.

Class: IIa. Level of evidence: C.

Possible therapeutic strategies in the postoperative management

Following the superior cavopulmonary conection

Successful adaptation after superior cavopulmonary connection is highly dependent on a low total pulmonary resistance. However, despite apparently good preoperative hemodynamics, early postoperative hypoxemia, sometimes severe, may occur, presumably secondary to the transitory elevation of the pulmonary vascular resistance (with extrapulmonary shunting) or lung parenchymal disease (with intrapulmonary shunting) consequent upon cardiopulmonary bypass. Paradoxically, under the circumstances, therapies expected to reduce pulmonary vascular resistance, such as hyperventilation induced alkalosis and inhaled nitric oxide have been shown to be relatively ineffective.[20,21] Indeed recent work has demonstrated that mild to moderate hypercapnia with respiratory acidosis may improve arterial oxygenation, by its effects to induce cerebral vasodilation thereby increasing effective pulmonary blood flow. Consequently, there is also an overall reduction in systemic vascular resistance, oxygen consumption and arterial lactate levels, suggesting that this ventilation strategy may improve overall transport of oxygen in children after superior cavopulmonary connection.[22,23] The role of pH and PCO_2, however, and their combination in the maintenance of pulmonary flow, and the benefits (if any) of respiratory acidosis are unclear and require further investigation.

Following the total cavopulmonary connection

Although there is no consensus for indicating a fenestration to all patients undergoing the Fontan completion, there is general agreement that it is beneficial postoperatively in selected patients. Early after the Fontan procedure, supplemental nitric oxide therapy has been shown to improve saturations and lower central venous pressure in patients with severe right-to-left shunting across a fenestration,[24] although whether such treatment leads to clinical benefit is unproven. A recent randomized controlled trial of oral supplementation of citrulline, a precursor to nitric oxide synthesis, has further highlighted the importance of endothelial dysfunction under these circumstances. This study

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suggested that adequate levels of citrulline (either endogenous, or supplemented) are required to avoid postoperative pulmonary hypertension early after the Fontan procedure, although again, direct clinical benefit was not demonstrated.[25]

There is evidence for abnormalities of pulmonary endothelial function late after Fontan completion. In one study, a significant proportion of patients demonstrated lowering of their pulmonary vascular resistance in response to inhaled nitric oxide during cardiac catheterization.[26] Such a response implies resting endothelial dysfunction and was more likely in those with increased pulmonary blood flow preoperatively (even though studied many years later) and was associated with worse functional class. There are no randomised studies of the effectiveness of other pulmonary vasodilators/antiproliferative agents (eg sildenafil, bosentan, beraprost, epoprostenol) either before or after the Fontan procedure, although there are case reports of their effectiveness in treating protein-losing enteropathy, for example.[27] This is clearly a potentially fruitful area of future research.

The widespread use of pulmonary vasodilators in the early or late postoperative treatment of patients before or after Fontan procedure is not supported by available data. Selected individuals may respond to such treatments if pulmonary arteriolar resistance is a key element in the pathogenesis of Fontan failure.

Class: I. Level of evidence: C.

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