Advances in cardiac care have allowed the repair of congenital heart defects (CHD) in the neonatal period or in infancy for most patients, before the development of pulmonary arterial hypertension (PAH) and pulmonary vascular disease (PVD) from pulmonary overcirculation. Nonetheless, PAH associated with CHD remains a problem, mainly in patients in whom the left-to-right shunt wasn’t diagnosed until childhood or even adulthood, or in patients who didn’t have access to cardiovascular care and surgical management as infants, particularly in developing countries. The current definition of PAH relies on a pulmonary arterial pressure ≥25 mmHg at rest, a left atrial pressure ≤15 mmHg, and normal resting cardiac output, suggesting a resting pulmonary vascular resistance of ≥3 Woods units. The 2009 European Society of Cardiology (ESC)/European Respiratory Society (ERS)/International Society of Heart and Lung Transplantation (ISHLT) guidelines on the management of PAH subdivided PAH-CHD into 4 clinical groups: (1) Eisenmenger syndrome; (2) PAH associated with systemic-to-pulmonary shunts; (3) PAH with small defects; and (4) PAH after surgical repair. PAH and pulmonary vascular lesions are thought to be reversible after surgery in some patients when operated on early in life. In others, PAH is thought to be irreversible and the prognosis is often worse than without surgery. Patients with persistent or recurrent PAH after surgery have been shown to have worse outcomes than either those with unoperated CHD and PAH or with Eisenmenger’s syndrome in a single-center retrospective review. PAH in CHD is also an increasing problem, with an increasing number and proportion of patients with CHD reported in PAH registries both in adults and children. For example, in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry, CHD patients represent 40% of included patients, 35% of which previously had surgical repair. With improvement in pulmonary vasodilators and their more widespread use, it has been possible to reduce pulmonary vascular resistance (PVR) and symptoms in a subset of patients with PAH, and make these patients amenable to surgery. However, most of the results provide only short-term outcomes and immediate post-operative survival does not always translate into long-term success. Given this shifting paradigm, this review focuses on how to assess operability in PAH associated with congenital heart disease, and the possibility of “treat-and-repair” vs. “repair-and-treat” strategies for patients with inoperable or borderline PAH.

Key Words: Congenital; Heart defects; Pediatrics; Pulmonary hypertension

Assessment of Operability of Patients With Pulmonary Arterial Hypertension Associated With Congenital Heart Disease – Do We Have the Good Tools to Predict Success? –

Patrick O. Myers, MD; Cécile Tissot, MD; Maurice Beghetti, MD

Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease, and is now predominantly among patients with uncorrected left-to-right shunts. A growing population is characterized by persistent or recurrent PAH after surgical or interventional correction of left-to-right shunts; the latter having a worse prognosis than other forms of PAH associated with congenital heart disease. New treatments for PAH have been shown to be effective in improving PAH exercise capacity and hemodynamics, raising the hope for making previously inoperable congenital heart defects operable and shifting the framework for the assessment of operability. This review focuses on current methods for assessing operability in PAH associated with congenital heart disease, and the possibility of "treat-and-repair" vs. "repair-and-treat" strategies for patients with inoperable or borderline PAH. (Circ J 2014; 78: 4–11)
following terms: pulmonary arterial hypertension, congenital heart defects, assessment, operability, pulmonary vascular disease, Eisenmenger, pulmonary vasodilator, pretreatment, post-treatment. Broad search terms ensured that no papers were excluded inadvertently. The bibliographic references in all the literature retrieved were examined for potential secondary sources.

### Assessment of Operability of Patients With PAH Associated With CHD

Clinical examination and hemodynamic assessments form the basis of evaluating patients for operability.

Clinical examination is conducted for signs of congestive heart failure and cyanosis. Clinical signs of advanced PAH-CHD may include central cyanosis (due to a reversed shunt), clubbing, peripheral edema, abdominal tenderness, right ventricular heave, a loud pulmonary ejection click and an accentuated pulmonary component of the second heart sound. Murmurs associated with valvar regurgitation might be present, but typical murmurs, due to previous left-to-right shunts at the ventricular or arterial level, might disappear upon the development of Eisenmenger syndrome. Echocardiography, although a pivotal screening test for the non-invasive diagnosis of PAH and providing several variables that closely correlate with right heart hemodynamics, for detecting signs of increased pulmonary blood flow, and for showing dilated left heart cavities and pulmonary overcirculation in patients that fit the criteria for operability, is not always sufficient to assess operability in borderline patients. In these patients, right heart catheterization remains the gold standard, and is necessary to assess hemodynamic parameters and vasoreactivity. However, hemodynamic guidelines to ensure postoperative success and long-term survival without pulmonary hypertension are still not precise.

Lung biopsy for the histopathological evaluation of changes to the pulmonary vasculature used to be routinely used to assess operability. However, this is now less frequently done in clinical practice, as the results aren’t sufficiently reliable and not without risk, as it provides only one randomly selected area of the lung and does not represent a comprehensive evaluation of the nature and extent of lesions throughout the lungs. Some patients develop advanced PVD although histology suspected mild lesions, while PAH and lesions are often reversible in infants and young children after surgical repair of CHD, despite advanced changes on biopsy.

Empirical thresholds using right heart catheterization hemodynamics and vasoreactivity are best used to predict surgical outcome in patients with PAH. It has not proved possible to validate an index for the precise selection of patients with congenital cardiac shunts who will be free of significant pulmonary hypertension postoperatively. Operability is thus defined on the basis of the likelihood of a favorable vs. an unfavorable outcome. In addition, all the operability thresholds are defined to predict short-term success, which is immediate post-operative survival. PVR and the ratio of PVR to systemic vascular resistance (SVR), and the way they change during an acute vasodilator challenge, have been suggested as predictors of surgical outcomes after biventricular repair (Table).

### Table. Suggested Hemodynamic Criteria for Assessment of Operability in Patients With PAH-CHD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hemodynamics</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>PVR &lt;6 WU/m², PVR:SVR ratio &lt;0.3</td>
</tr>
<tr>
<td>Acute vasodilator challenge (O₂, NO)</td>
<td>Baseline PVR 6–9 WU/m², PVR:SVR 0.3–0.5</td>
</tr>
<tr>
<td></td>
<td>• Decrease in PVR index of 20%</td>
</tr>
<tr>
<td></td>
<td>• PVR:SVR decrease of 20%</td>
</tr>
<tr>
<td></td>
<td>• Final PVR index &lt;6 WU/m²</td>
</tr>
<tr>
<td></td>
<td>• Final PVR:SVR &lt;0.3</td>
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</table>

Criteria suggestive of a favorable outcome after operation with biventricular circulation.

PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; NO, nitric oxide; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Operability is thus defined on the basis of the likelihood of a favorable vs. an unfavorable outcome. In addition, all the operability thresholds are defined to predict short-term success, which is immediate post-operative survival. PVR and the ratio of PVR to systemic vascular resistance (SVR), and the way they change during an acute vasodilator challenge, have been suggested as predictors of surgical outcomes after biventricular repair (Table). A baseline PVR index of <6 WU/m² and a resistance ratio <0.3 has been used as an indicator of favorable outcome following biventricular repair, with no need for vasoreactivity testing. Vasoreactivity testing is encouraged if the baseline PVR is between 6 and 9 WU/m² and there is a resistance ratio of 0.3–0.5. Although these are the best current proposals on assessing operability in CHD and PAH, there is no consensus as to whether vasoreactivity testing is accurate enough to discriminate between patients who will or will not have a good long-term outcome. Some authors consider that precise values of hemodynamic measures of PVD to determine level of risk of death or persistent PVR following biventricular repair cannot be derived, as individual patient factors such as cardiac lesion type and genetic predisposition may alter the hemodynamic testing or have an impact on outcome after surgical repair. Nonetheless, conventional hemodynamic evaluation is far from optimal. In a single-center retrospective review, Kann et al showed that, among 38 patients with unrestricted Ventricular Septal Defect (VSD) and severe PAH (>6 WU, actual mean 7.6±1.8 WU) who underwent surgical VSD repair, 8 (21%) either died or had persistent postoperative severe PAH, suggesting that 30 “inoperable” patients (79%) had a short- or medium-term favorable outcome after repair. To be as certain as possible of a good outcome, limits of a “safe” PVR have to be within a restrictive range, which excludes many patients from surgical repair. Alternative non-invasive imaging, such as cardiac magnetic resonance imaging (CMR), is reliable in evaluating biventricular dimensions, geometry and function. Phase contrast-MRI can be used to derive velocity and flow measurements in the pulmonary arteries and other regions of interest. An algorithm for estimating mean pulmonary artery pressure on CMR, although initially showing promising correlation with hemodynamic parameters derived from right heart catheterization (r=0.92), showed poor correlation in a follow-up study in patients with established PAH. Given these limitations and the acquisition time necessary, functional testing and response to pulmonary vasodilators isn’t currently realistically feasible using CMR. This imaging modality has been used extensively to study right ventricular (RV) remodeling after the introduction of pulmonary vasodilators; however, it hasn’t been assessed in predicting operability in patients with PAH associated with CHD. Finally, a non-invasive
method of estimating cardiac output and PVR using impedance cardiography, Non Invasive Cardiac System (NICaS) and echocardiography was shown to have a good correlation with right heart catheterization Fick-calculated PVR (receiver-operating characteristic area under the curve (ROC AUC) 0.92, sensitivity 80.3%, specificity 100%) but not with thermodilution (ROC AUC 0.84, sensitivity 81.3%, specificity 75%).

Acute vasodilator testing is used to test the reactivity of the pulmonary vascular bed, either with oxygen or inhaled nitric oxide (iNO). Berner et al showed that, among patients with long-standing large left-to-right shunts and elevated PVR, there is a marked heterogeneity of response to acute vasodilator challenge with iNO, ranging from a marked pulmonary vasodilatation to a complete lack of vascular reactivity. The Inhaled Nitric Oxide as a Preoperative Test (INOP) test I trial further showed that with an acute vasodilator challenge with oxygen and iNO using a criterium of pulmonary to systemic vascular resistance ratio of <0.33 conferred a sensitivity of 97% and an accuracy of 90% at predicting “operability”, while the same challenge with oxygen only had a sensitivity of 64% and an accuracy of 68%. Using an empirical decrease of 20% in pulmonary-to-systemic resistance ratio from baseline with iNO was a poor predictor of operability (specificity 8%). There is, however, no consensus as to whether vasoreactivity testing is accurate enough to discriminate between patients who will or will not have a good long-term surgical outcome, and in particular if pulmonary arterial pressure will normalize and stay normal. In addition, technical difficulties leading to calculation errors and other medical conditions need to be considered when undertaking vasodilatory testing. Finally, despite the general opinion that oxygen and iNO are the most appropriate agents for testing pulmonary vasoreactivity, there exists considerable debate whether testing at maximal stimulation (90% O₂ and 80 parts per million of iNO) is an accurate predictor of operability, or if more conservative intermediate protocols (O₂: 21–30%, iNO 40 PPM) or gradual increases in vasodilator challenge would be better predictors.

Biomarkers capable of defining the degree of PVD, potential for reversal and confirming operability represent the next breakthrough in the decision-making process for the management of patients with PAH-CHD. Many different pathways are involved in PAH, and multiple biomarkers for PAH have been described, including atrial natriuretic peptide and brain natriuretic peptide (BNP), N-terminal pro-BNP, cardiac troponin T, uric acid, urinary prostaglandin metabolites, endothelial NO synthase (eNOS) and dimethylarginines, ET-1 and ET-1:ET3 ratio, circulating von Willebrand factor, biomarkers of inflammation and oxidative stress such as cytokines (IL-1a, -2, -4, -6, -8, -10 and 12p70, TNF-b, MCP-1 and osteopontin), C-reactive protein, urinary F2-isoprostanes and metabolites, HbA1c, etc. More recently, circulating endothelial cells and micro-RNAs have also been identified as biomarkers in PAH, with possible implications on outcomes. It is of importance to differentiate markers that indeed reflect right ventricular dysfunction from markers of endothelial dysfunction and finally markers that might predict potential reversibility of the pulmonary vascular lesions; the latter being the one that will discriminate operable vs. inoperable patients.

Circulating endothelial cells, already recognized as a non-invasive marker of vascular damage and remodeling, have recently emerged as a new and particularly interesting biomarker. Patients with irreversible PAH post-surgery, in addition to showing pulmonary arterial intimal thickening and a corresponding high expression of the anti-apoptotic marker, Bcl-2, in the endothelial cells on a lung biopsy, also had significantly higher circulating endothelial cell levels in the peripheral blood than those with reversible PAH. Furthermore, in patients with idiopathic or CHD-associated refractory PAH, circulating endothelial cells were significantly decreased after the introduction of endothelin-receptor antagonists and/or phosphodiesterase 5 inhibitors and/or subcutaneous treprostinil, and rose before clinical deterioration. In contrast, other biomarkers of endothelial activation, regeneration and injury,
have not been able to discriminate between reversible and irreversible PAH following surgery.\(^5\)

Micro-RNAs are small, endogenously expressed non-coding RNAs that regulate gene expression at a post-transcriptional level.\(^6\) Micro-RNAs have been implicated in many different settings of cardiovascular remodeling, including blood vessel development, angiogenesis and vascular injury.\(^7,8\) They have been identified as biomarkers for early diagnosis in acute myocardial infarction and heart failure.\(^9,10\) Wei et al identified a significantly different profile of circulating micro-RNAs in patients with PAH compared to controls,\(^11\) proportional to the degree of PAH. Rhodes et al also showed, more specifically, that downregulation of microRNA-150 is associated with a reduced 2-year survival in patients with established PAH.\(^12\) There currently is no data available in the specific population of patients with PAH-CHD and if the micro-RNA profile differs between reversible and irreversible PAH, although micro-RNAs are potentially a very interesting area of research in terms of circulating biomarkers.

It is hoped that long-term studies will confirm circulating endothelial cells or other biomarkers as appropriate markers for predicting the reversibility of PAH. A simple blood test could replace the need for catheterizations and lung biopsies, or at least simplify risk stratification.

### Outcomes

There is a relative paucity of data on the long-term outcomes of PAH-CHD. In the most complete report available, Manes et al reviewed their single center experience in managing 192 patients with PAH-CHD from 1998 to 2013.\(^13\) This data showed that patients with PAH after surgical cardiac defect repair had a far worse outcome than patients with any other type of PAH-CHD (Figure 1), and it also confirmed the good outcomes of patients with Eisenmenger syndrome (93% at 5 years). Compared to their experience in managing patients with other forms of PAH such as idiopathic or associated PAH, the long-term prognosis of PAH-CHD overall was the best of all PAH etiologies, with survival of patients with PAH-CHD being 91% at 5 years compared to 63% in 278 contemporary patients with idiopathic PAH. Long-term outcomes are the key question to which we have little current data available.

### Surgical Repair of CHD in Borderline Patients With PAH

#### Treat-and-Repair

Eisenmenger syndrome has been synonymous with inoperability, as remodeling of the pulmonary vasculature is considered irreversible, placing these patients at high perioperative risk, at a low likelihood of benefiting from the procedure, and at a high risk of postoperative right ventricular failure.\(^2\) Right-to-left shunting in patients with PAH acts as a safety valve and forms the basis of practising atrial septostomy or Pott’s shunt in patients with PAH with advanced disease.\(^14\)

Nevertheless, despite established, long-standing pulmonary vascular disease with evidence of significant vascular remodeling/obstruction, Eisenmenger syndrome patients often respond favorably to advanced therapy.\(^15\) Almost one-third of Eisenmenger syndrome patients maintain some degree of pulmonary vasoactivity despite the presence of PVD.\(^16\) Many novel treatments have been introduced over the last decade for the medical management of PAH, including prostanooids, endothelin receptor antagonists, and phosphodiesterase-type 5 inhibitors; they work by targeting the obstructive changes of the distal pulmonary arteries. Experimental data has indicated that prostanoids, endothelin receptor antagonists, and phosphodiesterase-type 5 inhibitors exert antiproliferative effects on vascular endothelial and smooth muscle cells.\(^17-19\) Hypothetically, these new treatments could produce reverse or positive remodeling in patients in whom lesions of the pulmonary vascular bed are not fixed or irreversible, thus allowing surgical repair. This approach might be applicable in patients with group B lesions (large shunts), but obviously not Eisenmenger syndrome patients with a right-to-left shunt, who remain inoperable.

Drugs approved for PAH treatment have been extensively tested in patients with idiopathic PAH,\(^20-22\) and there is evidence that some of them are effective in treating PAH-CHD.\(^23-25\) By reducing PVR in patients in whom vascular lesions are not extensive, the possibility arises that pretreatment with PAH-specific drugs can be used to improve a patient’s condition and an inoperable patient could be considered operable. This may not, however, be the case in patients where lesions are extensive and PVD is established. One problem that may arise by decreasing PVR by pretreatment is an increase in shunt volume (by increasing the compliance of the downstream chamber or vascular bed) and a consequent increase in pulmonary blood flow. This may result in a paradoxical increase in pulmonary vascular damage if left unguarded. The timing of surgical repair would thus be of paramount importance, calibrated to when the PVR decreases sufficiently to consider the ideal operable conditions, but before further vascular damage ensues due to the increased pulmonary blood flow.

There is a relative paucity of data on pretreatment with PAH-specific drugs in CHD, and this is mostly limited to individual case reports or case series on patients with CHD and borderline or “inoperable” PAH,\(^26-28\) previously reviewed in detail.\(^29\) When evaluating in detail the hemodynamics of some of these patients, they might indeed be considered operable anyway depending of the threshold used. These initial case reports appear promising, but no conclusions can be drawn until stronger evidence is available. We do not know how many patients with unsuccessful results are not published, as successful case reports are usually presented. Follow up in most cases was relatively short, and the long-term adaptation of the right ventricle to the closure of the defect and normalization of the pulmonary pressures remains unknown. Once the perioperative risk is overcome, right ventricular failure can manifest itself years later. Moreover, a large proportion of these patients might have been within the range of operable values of PAH when using standardized criteria for operability.\(^30\) Patients with less advanced pulmonary vascular disease and those who demonstrate a substantial response to advanced therapy are likely to be considered for this treat-and-repair approach, although there are no studies available to guide management with regards to this.

There are serious concerns when taking into consideration closure of cardiac defects in patients with established PVD. The long-term results and tolerability of pulmonary vasodilators remain unknown. Moreover, no data is available on the long-term response of the right ventricle to closure of intracardiac communications. Once the defect is closed, a pathophysiologic situation more similar to idiopathic PAH is obtained, which is associated with a much worse long-term outcome compared to the outcome of patients with Eisenmenger syndrome (Figure 2). The presence of the shunt, which allows right-to-left shunting in Eisenmenger patients, unloading the right ventricle and preserving it’s function, has been hypothesized to explain the striking difference in survival between patients with Eisenmenger and patients with idiopathic PAH.\(^31\)
CHD have a reduced life expectancy, even if many can survive into their third or fourth decade. Yet patients with Eisenmenger syndrome in adulthood seem to fare far better than patients with all other forms of PAH (Figures 1B, 2B); a fact that is not appreciated by many who care for these patients. The key to the relative longevity of these patients lies in the unique adaptation of the right ventricle.

There are differences, though, between patients with idiopathic PAH and PAH-CHD: the pulmonary circulation in PAH-CHD does not grow normally, intra-acinar arteries are reduced, and endothelial dysfunction and smooth muscle cell hyperplasia are present early after birth. Furthermore, as more patients with PAH after surgical repair of CHD are included in registries and followed, it is increasingly apparent that the prognosis of this group of patients is very poor (Figure 2B).

Patients with Eisenmenger syndrome or “inoperable” PAH-CHD have a reduced life expectancy, even if many can survive into their third or fourth decade. Yet patients with Eisenmenger syndrome in adulthood seem to fare far better than patients with all other forms of PAH (Figures 1B, 2B); a fact that is not appreciated by many who care for these patients. The key to the relative longevity of these patients lies in the unique adaptation of the right ventricle. A positive response to advanced PAH therapies can mean closure of intracardiac defects, but this cannot be generally recommended.

Figure 2. Kaplan-Meier estimates of survival in patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD). (A) Global survival curve in 192 patients with PAH-CHD at a single-center. (B) Survival curve stratified by category of PAH-CHD: Eisenmenger syndrome (ES), PAH with systemic-to-pulmonary shunt (PAH-SP), PAH with small defect (PAH-SD) and PAH after cardiac defect correction (PAH-CD). Reproduced with permission from Manes et al.81

Figure 3. Double-flap valve patch for fenestrated ventricular septal defect closure. (A) View from the right atrium, through the tricuspid valve and with a probe through the flapped fenestration. (B) View of the double-flap valve patch in profile with an open valve. Reproduced with permission from Novick et al.89
until hard evidence of its safety, efficacy, and durability becomes available.

**Repair-and-Treat**

Pre-treating borderline PAH patients with advanced pulmonary vasodilators has the potential to demonstrate the reactivity of the pulmonary vascular bed; however, this comes at the risk of an increase in shunt volume, pulmonary blood flow and shear stress. This creates a paradoxical increase in pulmonary vascular damage if left unguarded, and might worsen the patient’s condition before surgical repair. To avoid these potential pitfalls, a “repair-and-treat” approach has been proposed in borderline PAH-CHD patients, essentially relying on advances in anesthesia, cardiac surgery and intensive care, helped with advanced pulmonary vasodilators after surgical repair, to achieve a good perioperative outcome in a high-risk patient. Although this approach might enable a favorable operative or short-term outcome, it remains unclear if it provides any improvement in terms of long-term outcomes. Alternative surgical techniques might be used, such as the fenestrated closure of a ventricular septal defect with a 1-way flap (Figure 3) to allow right-to-left shunting and decompression of the right ventricle during periods of raised pulmonary vascular resistance, especially in the postoperative period, while limiting flow and pressure overload to the pulmonary circulation. Although theoretically interesting, there is currently no data available on this approach of “repair-and-treat”. Closest to patients managed with a “repair-and-treat” approach is the group of PAH-CHD patients with prior surgical correction. This subgroup of PAH-CHD patients had the worst survival of all PAH-CHD (Figure 1B), although these outcomes might improve after the introduction of advanced pulmonary vasodilators. Evidence is mounting that advanced pulmonary vasodilators improve patient survival and their functional tests in diverse settings of PAH, including PAH-CHD, and that novel therapeutic agents might grow the armamentarium of the medical management of PAH after surgical repair.

**Conclusion**

For patients with PAH-CHD considered borderline for surgery, there are no evidence-based recommendations of how best to proceed, and careful evaluation, especially hemodynamic assessment using right heart catheterization, of each patient is required. This evaluation and choosing a management strategy based on conservative “operable” hemodynamic parameters will undoubtedly mark some patients with reversible PVD as inoperable. Novel biomarkers of the reversibility of PVD, such as circulating endothelial cells and micro-RNAs, might ease risk-stratification and response to medical management. A risk–benefit assessment is required for each individual based on the type of defect and the natural course of PAH, risks of surgical repair, and risk of developing right heart failure should a high PVR persist.

While a long-term survival trial is the ideal, we believe that it is an unrealistic primary endpoint. Therefore, we suggest a study that has a short-term primary endpoint of postoperative survival and a PVR <3 Wood units/m²: 1 year postoperatively with or without the need for continued PAH therapy, as previously described. Continuous follow up will still be required to capture patients who present with late recurrent increase in pulmonary arterial pressure. While a trial of this kind is a major undertaking, it is the only way to scientifically answer the question of whether shunt closure, even within conservative preoperative PVR limits, is ultimately the best option for the patient, and requires rigorous continuous follow up in specialized referral centers. This is an important question that needs resolution. Another approach would be to design a registry to collect these patients’ data in order to better define this population. With continued improvements in the diagnosis, management with novel pulmonary vasodilators with possible anti-proliferative and reverse-remodeling effects, refinement in surgical technique and patient selection, patients previously considered borderline or inoperable might be amenable to surgical repair in the current era or near future.

**Disclosures**

Maurice Beghetti has served as a consultant for Actelion Pharmaceuticals, Glaxo Smith Kline and EliLilly, and has received lecture fees from Actelion Pharmaceuticals. Cécile Tessot and Patrick Myers have no disclosures related to this manuscript content.

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Operability and Congenital Heart Disease


