Left-to-Right Shunts
Is There No Window for Repair Before Pulmonary Vascular Disease and Myocardial Fibrotic Remodeling Develop?

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Contrary to the opinion of French pediatrician Henri-Louis,1 that isolated ventricular septal defects (VSDs) are universally well tolerated, the subsequent discoveries of Eisenmenger,2 Abbott,3 Wood,4 and others have taught us that the prognosis of left-to-right shunt lesions is not always benign. After more than a century of research, as pediatric cardiologists and congenital heart surgeons, we claim that we know what happens in the lungs and the hearts of these patients and when these changes occur. The repair of VSDs has become routine since Lillehei’s, Warden’s, and Kirklin’s5,6 pioneering work in the 1950s, and we feel that we know in whom, at what age, and for which signs and symptoms to intervene. In reality, significant heterogeneity prevails between different centers and among individual physicians with regard to whether and when to close an isolated moderately restrictive VSD or patent arterial duct. Conceptually, we agree to occlude left-to-right shunts for one or both of the 2 reasons: to treat heart failure and to prevent irreversible pulmonary vascular damage, both of which have been identified as important risk factors in congenital heart disease. The study by Pereda et al7 from Madrid and Barcelona, published in this issue of Circulation: Cardiovascular Imaging, leads us to consider the fate of the myocardium as well. When counseling parents, we point out the low operative mortality and excellent long-term prognosis after successful VSD or patent arterial duct closure. Indeed, postoperative pulmonary hypertensive crises and more than transient and mild ventricular dysfunction are rare occurrences after shunt repair in infancy in the current era. Nonetheless, most of us vividly remember the stormy early postoperative course in the occasional patient who experienced these complications. Somewhat troublesome, we do not always know, even in hindsight, what sets these patients apart from the great majority who have an uncomplicated perioperative course. In the study by Pereda et al7 (and by other groups), structural pulmonary vascular and myocardial changes, resulting in elevated pulmonary vascular resistance and ventricular dysfunction, respectively, occurred at a strikingly young age, suggesting that there is essentially no surgical window during which these consequences can be completely prevented.

See Article by Pereda et al

As far as long-term outcomes are concerned, recent data comparing Dutch patients who underwent VSD closure with the general population in The Netherlands suggests that, after an average of nearly 4 decades, the event-free survival rate in patients with VSD is abnormally low.8 These individuals carried a 13% risk of symptomatic arrhythmias and a 4% risk of heart failure.

The study by Pereda et al7 follows in the great tradition of groundbreaking experimental physiology studies of the 1960s and 1970s: the seminal studies from that era, like Pereda et al’s today, isolated a research question, applied the technology necessary to answer it, meticulously controlling for confounders, both of which often meant working with animals instead of humans. As such, this study from Spain sets an example on how we can use modern technology to unveil the answers to old questions. The work by Pereda et al7 and by other groups on what we call ventricular remodeling defines a new standard that combines innovative cardiovascular imaging, typically coupled with invasive barometry, with a molecular genetic exploration.

Cardiac magnetic resonance (CMR) techniques have come a long way since the early 1980s, forwarding our understanding of the hemodynamic effects of left-to-right shunt lesions. Beerbaum et al9 demonstrated that Qp/Qs by phase contrast CMR is accurate in comparison to the gold standard of invasive oximetry, using the Fick principle. A decade and a half later, this landmark study can be considered a historical document because CMR is today’s gold standard of blood flow assessment as it overcomes many of the technical challenges associated with and assumptions made when using invasive oximetry. CMR is also the reference method of ventricular volume, ejection fraction, and myocardial mass quantification. Myocardial deformation imaging using tagging and, more recently, feature tracking provides additional insights into myocardial mechanics and contractility. Fibrosis imaging with late gadolinium enhancement and T1 relaxometry (aka T1 mapping) are noninvasive windows into myocardial health at a tissue level. Combining these techniques, CMR offers a comprehensive evaluation of left-to-right shunts, but it is not a one-stop-shop on the way to a hemodynamic assessment of shunt lesions. Pulmonary arterial pressures still need to be measured invasively for the determination of pulmonary vascular resistance, and echocardiography remains the standard imaging modality for diastolic function assessment.
Myocardial Fibrosis in Left-to-Right Shunts

The deleterious effect of chronic pulmonary hypertension on right ventricular (RV) performance has long been recognized. It is becoming increasingly clear that inflammation and an activation of apoptosis occur within the myocardium of RVs with increased afterload\(^1\) from a left-to-right shunt. Ultimately, these events lead to accelerated myocardial fibrosis, although we are only beginning to unveil the precise mechanisms by which this occurs. Similarly, the triggers of inflammation, cell death, and replacement fibrosis remain incompletely understood: abnormal loading conditions, chronic hypoxia, the effects of cardiopulmonary bypass, and genetic constitution have all been implicated in a cascade of events that we call fibrotic remodeling.

Pereda et al\(^2\) confirmed the presence of fibrosis and dysfunction histologically and by CMR in the RV, but they also detected fibrotic remodeling on the left side. Whether the causes of right and left ventricular fibrosis are independent (ie, the result of pressure overload on the right side and volume overload on the left side) or whether the involvement of both ventricles indicates ventriculo–ventricular interactions on a tissue level through molecular pathways that are shared between them\(^3\) is unclear. Pereda et al\(^2\)'s data suggest that the compromise of myocardial health is underappreciated by the traditional functional parameters and that CMR fibrosis markers may be useful as early indicators: in their study, expansion of extracellular volume preceded the increase in left ventricular end-diastolic pressure; left ventricular ejection fraction never fell significantly beneath that in controls. Whether CMR markers of fibrosis will indeed be able to signal morphological remodeling before a decline in function has occurred remains to be seen.

On the basis of what we learn from Pereda et al\(^2\)'s study about early pulmonary vascular and myocardial changes, should we close left-to-right shunts more aggressively and earlier? Pereda et al\(^2\)'s findings in pigs cannot be extrapolated 100% to humans who have much slower somatic growth rates and different trajectories with which irreversible vascular changes and myocardial remodeling occur.\(^4\) After all, most patients after closure of a large left-to-right shunt do well. A modest cohort of 24 patients who were catheterized within a year after VSD repair in the 1970s had normal pulmonary vascular resistance.\(^5\) However, Pereda et al\(^2\)'s and other data suggest that we perhaps need to look more closely, for longer periods of time, and under load: while not uncontested, recent studies suggest reduced cardiopulmonary exercise tolerance in adults after repair of VSD.\(^1,0\) Up to one third of patients after VSD repair show evidence of exercise-induced pulmonary hypertension, although most are normotensive at rest. Studies based on both CMR and echocardiography found persistent right and left ventricular dilatation and RV hypertrophy in 5% to 15% of patients after VSD repair.\(^6,7\) The force–frequency relationship of the RV, which is responsible for 40% of the increase in cardiac output during exercise, is impaired in patients after VSD repair.\(^8\) Although overt congestive heart failure is rare, elevated levels of N-terminal pro-B type natriuretic peptide are found in 38% of long-term survivors.\(^8\)

It is possible but speculative at this time that the persistent ventricular dysfunction and pulmonary hypertension that we observe occasionally represent the clinically manifest tip of the iceberg, whereas the structural changes in the lungs and myocardium that Pereda et al\(^2\) found remain subclinical in most patients. Although these discoveries are concerning a potential change in clinical practice must be based on equivalent data in humans. Given the advances in cardiovascular imaging, this information is obtainable. In the meantime, as clinicians, we need to stay alert to the subtle signs of functional impairment that some of our patients after repair of a simple left-to-right shunt lesion may be experiencing after the operation.

Disclosures

None.

References


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