Can the Right Ventricle Support the Failing Left Ventricle?

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Abstract

Ventricular failure, from cardiomyopathy or adverse loading, is the leading cause of cardiac death in children. In severe pediatric dilated cardiomyopathy of the left ventricle, heart transplant is the only life-saving option, but is limited by donor availability, cost and relatively poor survival. Alternatives are clearly needed. We have made a series of observations regarding therapeutic modification of ventricular afterload to improve contra-lateral ventricular function. These findings demonstrate novel mechanisms of ventricular–ventricular interactions (VVI), the potential to harness them for therapeutic benefit, and may constitute a paradigm shift in the treatment of pediatric heart failure. The pathophysiological rationale is that although left (LV) and right (RV) ventricular function are usually considered separately, they are inextricably linked through a common septum, shared myofibers and pericardium. Using the Anrep effect induced by banding of the pulmonary artery, LV function can be enhanced via VVI. Thus, VVI may hold great potential for treatment of LV failure. Future studies are needed to further delineate the geometrical, temporal and molecular mechanisms of PA-banding-induced ventricular crosstalk; and to examine their potential modulation through mechanical, electrophysiological and pharmacological interventions.

Keywords

Right ventricle • Failing left ventricle • Support • Ventricular–ventricular interactions

Dilated cardiomyopathy (DCM) is a leading cause of cardiac death in children [1, 2]. 'Traditional' medical therapies proven to be of benefit in adults with heart failure such as beta-blockers, ACE inhibitors and angiotensin receptor blockers have failed to benefit children with acquired and congenital heart failure in random-

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ized clinical trials [3, 4]. Currently, patients diagnosed with end-stage heart failure despite maximal medical therapy may be listed for heart transplantation (HTx) with or without prior support with a ventricular assist device. While heart transplantation is currently the only proven viable life-saving option, it is limited by donor availability, cost and reduced long-term survival [6, 7]; from a global health perspective, HTx is available to only a very small minority of affected children. Therefore, there is a pressing need for alternative therapies. Indeed, the report from a recent working group of the National Institutes of Health, calls for major new initiatives for the development of new therapies in children with heart failure [5].

Although left (LV) and right (RV) ventricular function is usually considered separately, they are inextricably linked through a common septum, shared myofibers and pericardial space [8]. Consequently it has been shown that LV contraction contributes more than 50% of RV work [9]. However, the full portfolio of ventricular–ventricular (V–V) interactions in either LV or RV failure is incompletely understood and has not been harnessed for therapeutic benefit. Based on novel experimental and clinical observations [9–14], we hypothesized that V–V interactions may have therapeutic potential in general, but in particular for the LV with systolic failure. Therefore, the introduction of reversible pulmonary artery banding (rPAB) to the therapeutic arsenal in left heart failure constitutes a paradigm shift, particularly for infants and children with end-stage DCM [15, 16]. The surgical technique of PAB has a low risk, and is usually used to restrict pulmonary artery blood flow to balance systemic-pulmonary circulations in cases of complex ventricular shunts and, for example, in patients with congenitally corrected TGA who are candidates for an anatomic biventricular repair. In young children suffering LV-DCM, the initial rationale for development of rPAB was leftward mechanical shift of the interventricular septum; thereby improving LV end-diastolic volume and pressure via improved Frank-Starling effects and filling dynamics, respectively (Fig. 8.1). Together with restored ventricular

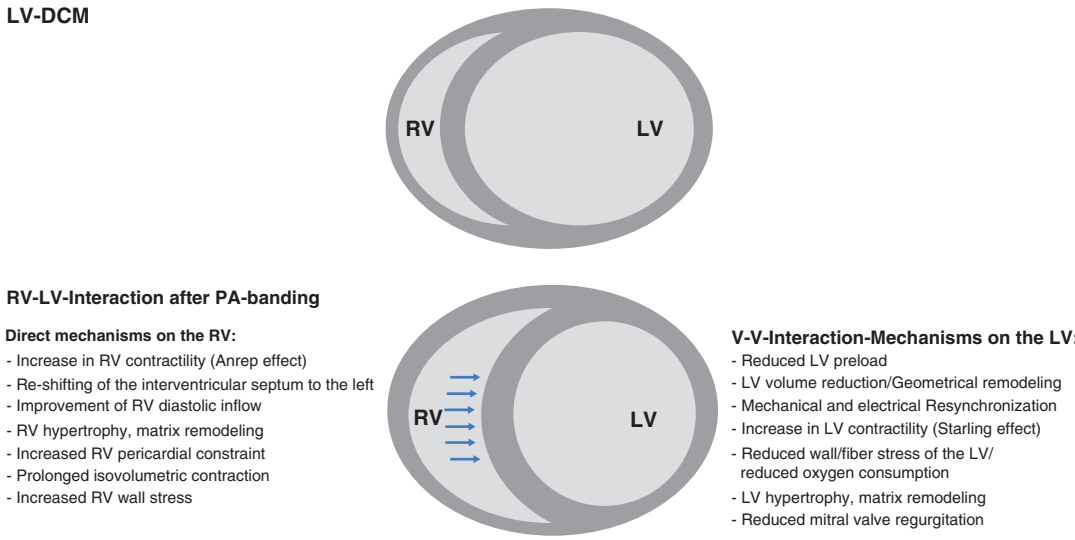

Fig. 8.1 Schematic transverse sectional view on the left (LV) and right (RV) ventricle. The upper panel is showing the changes in LV dilated cardiomyopathy (DCM), leading to LV failure and dilation, bulging of the interventricular septum to the right, thus resulting in impaired RV filling. The lower panel is showing the potential mechanisms how an increase in RV afterload induced by pulmonary banding might modify adverse ventricular–ventricular interactions for therapeutic benefit. We hypothesize that beyond the pure mechanical shift of the interventricular septum (*arrows*) corresponding mechanisms on cellular and molecular levels i.e. neuro-humoral and immunological activation, altered bioenergetics (mitochondrial remodeling) may play an important role

electromechanical synchrony, increased LV ejection fraction led to clinical improvement at rest and during exercise. In this context, rPAB is a promising therapeutic option with the potential to be a clinical 'game changer' [17]. The first rPAB approach in a DCM patient was performed eight years ago in a newborn listed for HTX 2-months after birth without a realistic chance to receive donor heart in a timely manner [15]. By the end of 2014, 26 infants and young children had undergone rPAB with end-stage DCM; six of them during open-heart surgery for concomitant repair of additional cardiac lesions; twenty patients received isolated surgical-PAB by an off-pump open-chest approach. In all patients surgery was well tolerated without perioperative mortality. Remarkable clinical improvements and significant improvements in LV cardiac function and reverse remodeling including LV-size, LV-ejection fraction, and mitral valve regurgitation have been observed (Fig. 8.2). Twenty one of 26 patients could be de-listed from transplant list. Following further improvement in their clinical and hemodynamic status, complete or partial pulmonary artery de-banding was performed by transcatheter technique in 17 patients. Two of 26 patients (8%), both with LV non-compaction morphology, decompensated 4 and 6 months after complete transcatheter de-banding and died 6 and 9 months later, one following complications during support with a ventricular assist device.

These 'proof-of-principle' results imply that rPAB in LV failure provides a novel alternative 'bridge-to-transplant' or destination therapy in children with advanced LV-DCM. Technically rPAB is simple, safe, effective and affordable making it a realistic option for children worldwide, especially where transplant is not an option. However, to date, the pediatric DCM population who may benefit from V–V interaction therapy has not been defined, and we have demonstrated therapeutic benefit only in infants and children whose myocardium may have greater potential for recovery [18, 19]. Therefore, there is a need for a prospective, randomized study of rPAB in LV-DCM, including older children up to 12-years of age. In addition, biochemical profiling is warranted as part of a comprehensive strategy to define patient characteristics, thereby defining mechanisms of response and allowing future prediction and augmentation of response [20].

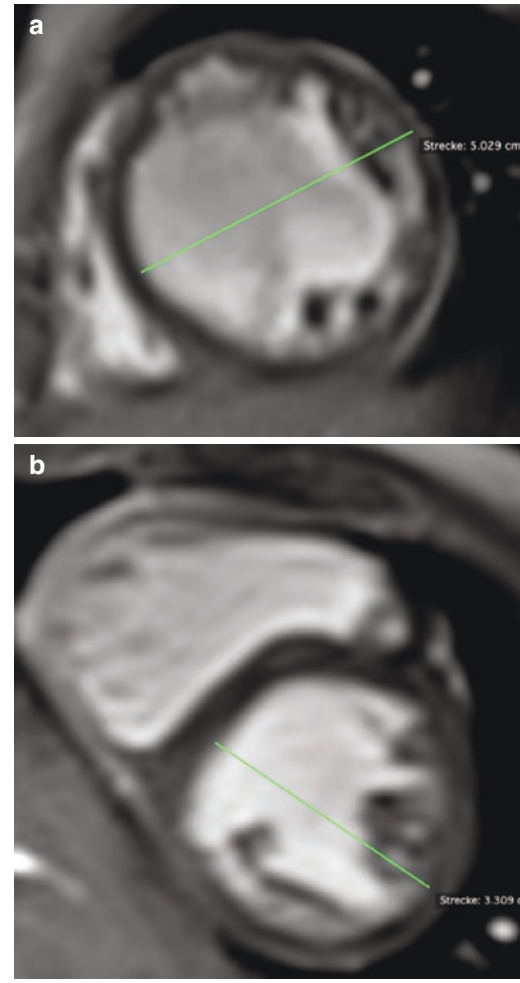

Fig. 8.2 (**a**, **b**) Magnetic resonance tomography in a 15 months old boy with LV-DCM who was admitted to our hospital for heart transplantation. The *upper panel* shows in a short axis view the severe dilation (z-score of left ventricular enddiastolic diameter, LVEDD +7.5) of the LV and the compressed RV. The left ventricular ejection fraction (LV-EF) was only 23%. The *lower panel* demonstrates the remarkable findings 4 months after the PA-banding operation: LV-size (LVEDD z-score + 1.2), geometry and LV-EF (52%) fundamentally improved, respectively

Although anecdotal, based on our single center experience we would emphasize that rPAB needs to be supported by concomitant anticongestive therapy. Considering the neuro-humoral activation

in patients with DCM in general and specifically the beta-adrenergic-receptor-pathophysiological response of pediatric DCM [21], we have treated infants and children who received a rPAB, using a ß1-specific beta-blocker (Bisoprolol), a tissue ACE-inhibitor (Lisinopril) and a mineralocorticoid-blocker (spironolactone) [22].

In summary, the failure of pharmacotherapy alone and the limited availability of heart transplantation for heart failure in children mandate a new approach to treatment. V–V interactions represent novel therapeutic targets in both right heart and left heart disease. In particular, we hypothesize that rPAB can benefit LV failure via enhanced Anrep effects and beneficial modification of biventricular geometry in infants and children with LV-DCM. Future studies are required to examine the mechanisms underlying the observed response in the early proof-of-principle reports, and to establish which children are most likely to benefit from this simple intervention.

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References

1. Daubeney PE, Nugent AW, Chondros P, et al. Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. Circulation. 2006;114:2671–8.
2. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006;296:1867–76.
3. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, et al. Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA. 2007;298(10):1171–9.
4. Roche SL, Redington AN. Right ventricle: wrong targets? Another blow for pharmacotherapy in congenital heart diseases. Circulation. 2013;127(3):314–6.
5. Burns KM, Byrne BJ, Gelb BD, Kühn B, et al. New mechanistic and therapeutic targets for pediatric heart failure: report from a national heart, lung, and blood institute working group. Circulation. 2014;130(1):79–86.
6. Alexander PM, Daubeney PE, Nugent AW, et al. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation. 2013;128:2039–46.
7. Canter CE, Shaddy RE, Bernstein D, et al. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;115:658–76.
8. Sanchez-Quintana D, Anderson RH, Ho SY. Ventricular myoarchitecture in tetralogy of Fallot. Heart. 1996;76:280–6.
9. Damiano RJ Jr, La Follette P Jr, Cox JL, Lowe JE, Santamore WP. Significant left ventricular contribution to right ventricular systolic function. Am J Phys. 1991;261:H1514–24.
10. Yamashita H, Onodera S, Imamoto T, et al. Functional and geometrical interference and interdependency between the right and left ventricle in cor pulmonale: an experimental study on simultaneous measurement of biventricular geometry of acute right ventricular pressure overload. Jpn Cir J. 1989;53:1237–44.
11. Belenkie I, Horne SG, Dani R, Smith ER, Tyberg JV. Effects of aortic constriction during experimental acute right ventricular pressure loading. Further insights into diastolic and systolic ventricular interaction. Circulation. 1995;92:546–54.
12. Apitz C, Honjo O, Friedberg MK, et al. Beneficial effects of vasopressors on right ventricular function in experimental acute right ventricular failure in a rabbit model. Thoracic Cardiovasc Surg. 2012;60:17–23.
13. Apitz C, Honjo O, Humpl T, et al. Biventricular structural and functional responses to aortic constriction in a rabbit model of chronic right ventricular pressure overload. J Thoracic Cardiovasc Surg. 2012;144:1494–501.
14. Friedberg M, Cho MY, Li J, et al. Adverse biventricular remodeling in isolated right ventricular hypertension is mediated by increased TGFβ1 signaling and is abrogated by angiotensin receptor blockade. Am J Respir Cell Mol Biol. 2013;49(6):1019–28.
15. Schranz D, Veldman A, Bartram U, Michel-Behnke I, Bauer J, Akinturk H. Pulmonary artery banding for idiopathic dilative cardiomyopathy: a novel therapeutic strategy using an old surgical procedure. J Thoracic Cardiovasc Surg. 2007;134:796–7.
16. Schranz D, Rupp S, Muller M, et al. Pulmonary artery banding in infants and young children with left ventricular dilated cardiomyopathy: A novel therapeutic strategy before heart transplantation. J Heart Lung Transplant. 2013;32:475–81.
17. Bailey LL. Back to the future! Bold new indication for pulmonary artery banding. J Heart Lung Transplant. 2013;32:482–48313.
18. Amir G, Ma X, Reddy VM, et al. Dynamics of human myocardial progenitor cell populations in the neonatal period. Ann Thoracic Surg. 2008;86:1311–9.

19. Mishra R, Vijayan K, Colletti EJ, et al. Characterization and functionality of cardiac progenitor cells in congenital heart patients. Circulation. 2011;123:364–73.
20. Lumens J, Ploux S, Strik M, Gorcsan J 3rd, et al. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure: electrical resynchronization versus left-right ventricular interaction. J Am Coll Cardiol. 2013;62(25):2395–403.
21. Miyamoto SD, Stauffer BL, Nakano S, et al. Beta-adrenergic adaptation in pediatric idiopathic dilated cardiomyopathy. Eur Heart J. 2014;35:33–41.
22. Recla S, Steinbrenner B, Schranz D. Medical therapy in dilated cardiomyopathy and pulmonary arterial banding in children. J Heart Lung Transplant. 2013;32:1045–6.