The Interventricular Septum

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Vertebrates developed pulmonary circulation and septated the heart into venous and arterial compartments, as the adaptation from aquatic to terrestrial life requires more oxygen and energy. The interventricular septum (IVS) accommodates the ventricular portion of the conduction system and contributes to the mechanical function of both ventricles. Conditions or diseases that affect IVS structure and function (e.g., hypertrophy, defects, other) may lead to ventricular pump failure and/or ventricular arrhythmias with grave consequences. IVS structure and function can be evaluated today using current imaging techniques. Effective therapies can be provided in most cases, although definitions of underlying etiologies may not always be easy, particularly in the elderly due to overlap between genetic and acquired causes of IVS hypertrophy, the most common being IVS abnormality.

Keywords: interventricular septum ; structure ; function ; diseases ; treatment

1. Introduction

Vertebrates changed the structure and function of their hearts in order to adapt to the living environment over the course of evolution. Since adaptation from aquatic to terrestrial life requires more oxygen and energy, vertebrates developed a pulmonary circulation and septated the heart into venous and arterial compartments, allowing the supply of oxygenated blood to peripheral tissues [1]. The formation of the interventricular septum (IVS) initiates at around the fifth week of embryonic development; it involves the sequential fusion of three independent septa: muscular, outlet, and inlet [2]. Cardiac ventricular septation, besides its great intrinsic interest to evolutionary biologists, is also crucial to the physiologist and the clinician. IVS function is important in the healthy heart. IVS contributes to normal left and right ventricular (LV and RV respectively) function, not only via its position and movement, but also through the regulation of RV and LV interaction (ventricular interdependence) [3]. On the other hand, the IVS may become abnormal either from disease of the IVS itself (congenital anomalies, coronary artery disease, cardiomyopathy, hypertension, conduction abnormalities, tumors, etc.) or as a result of abnormalities that involve other structures of the heart that induce abnormal hemodynamics in the IVS (atrial septal defect, valvular heart disease, open heart surgery, etc.) [4].

2. IVS Structure

Traditionally, gross cardiac anatomy has been described mainly based on the findings in the dissection suite. However, imaging with echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR), have fundamentally advanced the understanding of cardiac anatomy in the 21st century [5]. Additionally, CMR is unique for its tissue characterization capabilities, and for the identification of myocardial scar, fibrosis, edema, and inflammation. Diffusion tensor cardiovascular magnetic resonance (DT-CMR) is a noninvasive technique that has been increasingly used to unravel human cardiovascular microstructure in vivo. Finally, it is noteworthy that the IVS thickness prenatally assessed using ultrasound imaging may be a useful diagnostic marker of fetal macrosomia, a common condition affecting approximately 10% of fetuses, and potentially leading to serious complications in both mother and child [6].

The IVS is composed of a muscular and a membranous component. The muscular IVS component arises from the endocardial surface of the common ventricle, and has a normal thickness of approximately 9 mm in women and 10 mm in men [7]. The comparatively diminutive membranous component, the fibrous component of the IVS, is found between the outflow tracts of the LV and RV [8]. Animal studies that examined the transmural features of the IVS reported that the myofiber angle shifted from a longitudinal orientation on the LV-side to a circumferential orientation in the midwall, and then back to a longitudinal orientation on the RV-side of the septum. The main transmural change in the septum was related to the orientation of the myofibers (anisotropy), but not to the mechanical properties or tissue composition [9].

Blood supply to the IVS is predominantly derived from penetrating arteries entering from the left anterior descending artery, whereas branches from the posterior descending artery supply only the posterior third of the IVS [10]. The IVS is a

site of collateral circulatory channels in the human heart. The middle cardiac vein, which empties into the coronary sinus, is responsible for draining the IVS [11].

Cardiac function is controlled by the autonomic nervous system, which consists of the parasympathetic and sympathetic divisions. In addition to the complex integration that occurs in the central nervous system, there is local intracardiac neural regulation brought about by a network of ganglionated plexuses consisting of a large number of intracardiac ganglia, and gathered in specific heart regions including the atria, the sinoatrial and atrioventricular nodes, the IVS, and both ventricles [12].

The IVS accommodates important parts of the cardiac conduction system. The atrioventricular node is located at the apex of the Koch triangle, whereas the bundle of His divides at the juncture of the fibrous and muscular boundaries of the IVS into the left and right bundle branches (LBB and RBB, respectively). The LBB subsequently divides into anterior and posterior fascicles, which course towards the anterior and posterior papillary muscles of the LV, whereas the RBB courses down the right side of IVS near the endocardium in its upper third, deeper in the muscular portion of the IVS in the middle third, and then again near the endocardium in its lower third [13].

Both ventricles contribute to IVS formation [14]. Cardiomyocyte helical architecture is present as early as the midgestational period [15], whereas cardiomyocyte transformation affecting the IVS initiates in the early postnatal period, whereby the RV origin of the IVS is reduced from 50% in the perinatal period to 25% later in life [15]. A highly echogenic zone seen in the IVS during cardiac ultrasound coursing from base to apex corresponds to the position of the circumferentially orientated cardiomyocytes.

3. IVS Function

During systole the IVS thickens and moves towards the LV after the onset of electrical depolarization followed by a brief ‘shudder’ at end systole, whereas during diastole it returns to its original thickness and position [16]. The IVS sides are significantly softer than their corresponding ventricular free walls, and the collagen content is less than that of the ventricular walls [9]. Moreover, at low strains, there is similar anisotropic behavior between the two sides, whereas at high strains, both sides are isotropic.

Normal septal position and twisting are essential for ventricular function, whereas the functional interaction between the RV and LV via IVS has been termed “ventricular interdependence” [3][17].

3.1. Ventricular Interdependence

Ventricular interdependence describes the influence that each ventricle has to the other as a result of the shared IVS [18], the encircling of the two ventricles by common myocardial fibers, and the pericardial constrain [19]. An intact pericardium enhances ventricular diastolic interdependence but has negligible effect on ventricular systolic interdependence, which is affected by IVS and free wall properties [20]. The RV contributes significantly to the normal cardiac output response to exercise, as demonstrated by the 30–40% decrease in maximum oxygen uptake in young patients with Fontan physiology compared with healthy controls [21]. Ventricular interdependence has also been implicated in the development of RV remodeling in untreated asymptomatic mild hypertensive patients, and has been attributed to changes in IVS structure [22].

3.2. Abnormal IVS Motion

Abnormal, paradoxical septal motion (PSM), is a type of motion abnormality where the IVS movement is atypical for the particular phase of the cardiac cycle.

The most common cause of PSM is left bundle branch block (LBBB) due to periods of asynchrony in contraction, ejection, end-systole, and end-diastole between RV and LV, in addition to decreased regional ejection fraction (EF) of the IVS. The LBBB usually results in two types of PSM, namely septal flash and apical rocking, which are interrelated [23][24]. Septal flash refers to a leftward motion of the IVS associated with a marked pre-ejection shortening; this is mainly due to active IVS contraction, which is followed by immediate re-lengthening (rebound stretch) resulting from contractions in late-activated remote myocardium and subsequent paradoxical rightward IVS motion [25]. Apical rocking, in turn, is characterized by a short septal motion of the apex caused by the contraction of the IVS early in systole, and a subsequent long motion to the lateral side during ejection resulting from the late lateral contraction caused by the LBBB [23].

IVS ischemia/infarction is another common cause of abnormal septal motion. Experi-mental studies have demonstrated that following septal artery ligation, IVS shortening is immediately replaced by systolic lengthening [26]; eventually, IVS

hypokinesia or akinesia develop. The cardiogenic shock, which is frequently due to acute myocardial infarction (AMI), depends on AMI extent and its complications, the most important being mitral regurgitation, IVS rupture, and rupture of the LV free wall [27].

Diastolic and systolic ventricular interactions are negatively affected in pulmonary arterial hypertension (PAH) and result in PSM. In the early stages of PAH, a rapid leftward IVS motion occurs during early LV diastole which is most likely due to prolonged RV myocardial activation [28]. Severe PAH results in RV failure with RV eccentric remodeling and contractile dysfunction, and has an important impact on the geometry, structure, and function of the LV. RV volume and pressure increases cause mechanical IVS flattening and shifting towards the LV, leading to LV compression visualized by paradoxical IVS motion, a “D-shaped” LV, and an increased LV eccentricity index [29]. RV systolic and biventricular diastolic dysfunction result in a reduction of cardiac output and coronary blood flow, both of which may exacerbate congestion [30].

A common cause of PSM is constrictive pericarditis, which is characterized by dissociation of intrathoracic from intracardiac diastolic pressures; it exaggerates diastolic ventricular interdependence due to the fixed volume in the pericardial sack resulting from the thickened, fibrotic, and/or calcified non-compliant pericardium [31]. With inspiration, the RV cannot expand to accommodate increased venous return and encroaches into the LV space, via a shift of the IVS; this results in decreased LV filling and output. The preferential filling of the right heart chambers during inspiration subsequently gives way to preferential left heart filling with expiration, when increased intrathoracic pressure decreases systemic venous return to the right heart, restores the filling gradient between the pulmonary veins and left heart chambers, and shifts the IVS towards the RV [32].

PSM may also occur after uncomplicated cardiac surgery resulting from an increase in RV transverse shortening (free wall to septal fibers), in order to compensate for the reduced RV longitudinal shortening [33], atrial septal defect (ASD) to accommodate the increased RV volume [34], and mitral stenosis reflecting an abnormal transseptal gradient [35].

4. Treatment Modalities Targeting Diseases of the IVS

4.1. Cardiac Resynchronization Therapy (CRT)

CRT is an established treatment in selected patients with heart failure [36]. CRT in most cases is achieved by adding a LV pacing lead (lateral or posterolateral wall of the LV) to a standard pacemaker or defibrillator system that generally includes only an RV lead (RV apex) and—in cases of sinus rhythm—a right atrial lead [37]. The mechanisms of action of CRT in this setting include correction of IVS abnormal systolic motion and restoration of LV electrical and mechanical synchrony [38]. Circumferential contraction of IVS myocardial fibers is improved with CRT, and it is strongly correlated with an increase in aortic velocity time integral (VTI) and shortening of QRS duration [39]. Therefore, not surprisingly, CRT improves cardiac function and symptoms, as well as reduces morbidity and mortality in a specific group of heart failure patients with abnormal LVEF and QRS duration. Nevertheless, approximately 20–40% of the abovementioned patients may not respond to CRT (non-responders) [40].

4.2. Mavacamten

Mavacamten is a small molecule that belongs to the myosin modulators, a novel class of pharmaceutical agents that are being developed to treat patients with a range of cardio-myopathies. Myosin modulators are often classified as either “myosin activators” (omecamtiv, danicamtiv) or “myosin inhibitors” (mavacamten, aficamten) [41]. The therapeutic goal of these drugs is to target cardiac myosins directly to modulate contractility and cardiac power output, in order to alleviate symptoms that lead to heart failure and arrhythmias without changes in calcium signaling [42].

In the recently completed EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy), about one-third of patients on mavacamten, a myosin inhibitor that reduces myocardial contractility, achieved the primary end-point of subjective symptomatic improvement and increased functional capacity assessed by peak VO2 [43]. This beneficial effect has been attributed to mavacamten-induced decrease in LVOT gradients and resolution of mitral valve systolic anterior motion in most HCM patients [44].

4.3. Septal Reduction Therapy (SRT)

SRT reduces LVOT obstruction in patients with HCM and includes surgical IVS myectomy and transcoronary alcohol IVS ablation. The role of surgical IVS myectomy in HCM is well established. Transcoronary alcohol IVS ablation provides a less invasive approach to septal reduction in HCM. Both surgical IVS myectomy and transcoronary alcohol IVS ablation

may improve HCM patients' functional status, with low periprocedural mortality and excellent long-term survival [45]. As the results of these two treatment options seem to be comparable in experienced centers, selection depends on the anatomical findings, concomitant cardiac and non-cardiac morbidities, technical issues, the operator's expertise and availability, and patient's choice [46].

References

1. Katano, W.; Moriyama, Y.; Takeuchi, J.K.; Koshiba-Takeuchi, K. Cardiac septation in heart development and evolution. Dev. Growth Differ. 2019, 61, 114–123.
2. Rojas, C.A.; Jaimes, C.; Abbara, S. Ventricular septal defects: Embryology and imaging findings. J. Thorac. Imaging 20 13, 28, W28–W34.
3. Buckberg, G.; Hoffman, J.I. Right ventricular architecture responsible for mechanical performance: Unifying role of vent ricular septum. J. Thorac. Cardiovasc. Surg. 2014, 148, 3166–3171.
4. Kaul, S. The interventricular septum in health and disease. Am. Heart J. 1986, 112, 568–581.
5. Daubert, M.A.; Tailor, T.; James, O.; Shaw, L.J.; Douglas, P.S.; Koweek, L. Multimodality cardiac imaging in the 21st ce ntury: Evolution, advances and future opportunities for innovation. Br. J. Radiol. 2021, 94, 20200780.
6. Szmyd, B.; Biedrzycka, M.; Karuga, F.F.; Rogut, M.; Strzelecka, I.; Respondek-Liberska, M. Interventricular Septal Thic kness as a Diagnostic Marker of Fetal Macrosomia. J. Clin. Med. 2021, 10, 949.
7. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An up date from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 2015, 28, 1–39.e14.
8. De Almeida, M.C.; Sanchez-Quintana, D.; Anderson, R.H. The membranous septum revisited: A glimpse of our anatomi cal past. Clin. Anat. 2021, 34, 178–186.
9. Nguyen-Truong, M.; Liu, W.; Doherty, C.; LeBar, K.; Labus, K.M.; Puttlitz, C.M.; Easley, J.; Monnet, E.; Chicco, A.; Wan g, Z. The Interventricular Septum Is Biomechanically Distinct from the Ventricular Free Walls. Bioengineering 2021, 8, 2 16.
10. Kim, S.D. Anatomy of the septal perforating arteries of the heart. Anat. Cell Biol. 2019, 52, 236–241.
11. Kassem, M.W.; Lake, S.; Roberts, W.; Salandy, S.; Loukas, M. Cardiac veins, an anatomical review. Transl. Res. Anat. 2021, 23, 100096.
12. Duraes Campos, I.; Pinto, V.; Sousa, N.; Pereira, V.H. A brain within the heart: A review on the intracardiac nervous sys tem. J. Mol. Cell Cardiol. 2018, 119, 1–9.
13. De Almeida, M.C.; Mori, S.; Anderson, R.H. Three-dimensional visualization of the bovine cardiac conduction system a nd surrounding structures compared to the arrangements in the human heart. J. Anat. 2021, 238, 1359–1370.
14. Franco, D.; Meilhac, S.M.; Christoffels, V.M.; Kispert, A.; Buckingham, M.; Kelly, R.G. Left and right ventricular contribut ions to the formation of the interventricular septum in the mouse heart. Dev. Biol. 2006, 294, 366–375.
15. Zhang, L.; Allen, J.; Hu, L.; Caruthers, S.D.; Wickline, S.A.; Chen, J. Cardiomyocyte architectural plasticity in fetal, neon atal, and adult pig hearts delineated with diffusion tensor MRI. Am. J. Physiol. Heart Circ. Physiol. 2013, 304, H246–H2 52.
16. Clancy, D.J.; McLean, A.; Slama, M.; Orde, S.R. Paradoxical septal motion: A diagnostic approach and clinical relevanc e. Australas J. Ultrasound Med. 2018, 21, 79–86.
17. Santamore, W.P.; Dell'Italia, L.J. Ventricular interdependence: Significant left ventricular contributions to right ventricula r systolic function. Prog. Cardiovasc. Dis. 1998, 40, 289–308.
18. Wanner, P.M.; Filipovic, M. The Right Ventricle-You May Forget it, but It Will Not Forget You. J. Clin. Med. 2020, 9, 432.
19. Borlaug, B.A.; Reddy, Y.N.V. The Role of the Pericardium in Heart Failure: Implications for Pathophysiology and Treatm ent. JACC Heart Fail. 2019, 7, 574–585.
20. Naeije, R.; Badagliacca, R. The overloaded right heart and ventricular interdependence. Cardiovasc. Res. 2017, 113, 1 474–1485.
21. Paridon, S.M.; Mitchell, P.D.; Colan, S.D.; Williams, R.V.; Blaufox, A.; Li, J.S.; Margossian, R.; Mital, S.; Russell, J.; Rho des, J.; et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operatio n. J. Am. Coll. Cardiol. 2008, 52, 99–107.

22. Maresca, A.M.; Mongiardi, C.; Corso, R.; Robustelli Test, L.; Lippi, A.; Montalbetti, L.; Campiotti, L.; Moretti, S.; Tandurella, N.; Agostinis, M.; et al. Right ventricular remodelling in mild hypertensive patients: Role of left ventricular morpho-functional parameters. J. Hum. Hypertens. 2020, 34, 293–300.
23. Stankovic, I.; Prinz, C.; Ciarka, A.; Daraban, A.M.; Kotrc, M.; Aarones, M.; Szulik, M.; Winter, S.; Belmans, A.; Neskovic, A.N.; et al. Relationship of visually assessed apical rocking and septal flash to response and long-term survival following cardiac resynchronization therapy (PREDICT-CRT). Eur. Heart J. Cardiovasc. Imaging 2016, 17, 262–269.
24. Mele, D.; Luisi, G.A.; Malagu, M.; Laterza, A.; Ferrari, R.; Bertini, M. Echocardiographic evaluation of cardiac dyssynchrony: Does it still matter? Echocardiography 2018, 35, 707–715.
25. Calle, S.; Delens, C.; Kamoen, V.; De Pooter, J.; Timmermans, F. Septal flash: At the heart of cardiac dyssynchrony. Trends Cardiovasc. Med. 2020, 30, 115–122.
26. Agarwal, J.B.; Yamazaki, H.; Bodenheimer, M.M.; Banka, V.S.; Helfant, R.H. Effects of isolated interventricular septal ischemia on global and segmental function of the canine right and left ventricle. Am. Heart J. 1981, 102, 654–658.
27. Braile-Sternieri, M.; Mustafa, E.M.; Ferreira, V.R.R.; Braile Sabino, S.; Braile Sternieri, G.; Buffulin de Faria, L.A.; Sbardellini, B.C.; Vianna Queiroz, C.O.; Braile, D.M.; Zotarelli Filho, I.J. Main Considerations of Cardiogenic Shock and Its Predictors: Systematic Review. Cardiol. Res. 2018, 9, 75–82.
28. Palau-Caballero, G.; Walmsley, J.; Van Empel, V.; Lumens, J.; Delhaas, T. Why septal motion is a marker of right ventricular failure in pulmonary arterial hypertension: Mechanistic analysis using a computer model. Am. J. Physiol. Heart Circ. Physiol. 2017, 312, H691–H700.
29. Bernardo, R.J.; Haddad, F.; Couture, E.J.; Hansmann, G.; de Jesus Perez, V.A.; Denault, A.Y.; de Man, F.S.; Amsallem, M. Mechanics of right ventricular dysfunction in pulmonary arterial hypertension and heart failure with preserved ejection fraction. Cardiovasc. Diagn. Ther. 2020, 10, 1580–1603.
30. Konstam, M.A.; Kiernan, M.S.; Bernstein, D.; Bozkurt, B.; Jacob, M.; Kapur, N.K.; Kociol, R.D.; Lewis, E.F.; Mehra, M.R.; Pagani, F.D.; et al. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement from the American Heart Association. Circulation 2018, 137, e578–e622.
31. Nishimura, R.A. Constrictive pericarditis in the modern era: A diagnostic dilemma. Heart 2001, 86, 619–623.
32. Welch, T.D. Constrictive pericarditis: Diagnosis, management and clinical outcomes. Heart 2018, 104, 725–731.
33. Stanley, A.; Athanasuleas, C. Paradoxical Septal Motion after Uncomplicated Cardiac Surgery: A Consequence of Altered Regional Right Ventricular Contractile Patterns. Curr. Cardiol. Rev. 2022, 18, 9.
34. Hung, J.; Uren, R.F.; Richmond, D.R.; Kelly, D.T. The mechanism of abnormal septal motion in atrial septal defect: Pre- and postoperative study by radionuclide ventriculography in adults. Circulation 1981, 63, 142–148.
35. Thompson, C.R.; Kingma, I.; MacDonald, R.P.; Belenkie, I.; Tyberg, J.V.; Smith, E.R. Transseptal pressure gradient and diastolic ventricular septal motion in patients with mitral stenosis. Circulation 1987, 76, 974–980.
36. Glikson, M.; Nielsen, J.C.; Kronborg, M.B.; Michowitz, Y.; Auricchio, A.; Barbash, I.M.; Barrabes, J.A.; Boriani, G.; Braunschweig, F.; Brignole, M.; et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur. Heart J. 2021, 42, 3427–3520.
37. Jaffe, L.M.; Morin, D.P. Cardiac resynchronization therapy: History, present status, and future directions. Ochsner J. 2014, 14, 596–607.
38. Thomas, G.; Kim, J.; Lerman, B.B. Improving Cardiac Resynchronisation Therapy. Arrhythm. Electrophysiol. Rev. 2019, 8, 220–227.
39. Yaman, B.; Kemal, H.S.; Donmez, Y.; Cerit, L.; Usalp, S.; Yuksek, U.; Gunsel, A.; Duygu, H.; Akpinar, O. Improvement of abnormal systolic motion of the interventricular septum with cardiac resynchronization therapy. Pacing Clin. Electrophysiol. 2019, 42, 1213–1218.
40. Prinzen, F.W.; Vernooy, K.; Auricchio, A. Cardiac resynchronization therapy: State-of-the-art of current applications, guidelines, ongoing trials, and areas of controversy. Circulation 2013, 128, 2407–2418.
41. Day, S.M.; Tardiff, J.C.; Ostap, E.M. Myosin modulators: Emerging approaches for the treatment of cardiomyopathies and heart failure. J. Clin. Investig. 2022, 132, e148557.
42. Tower-Rader, A.; Ramchand, J.; Nissen, S.E.; Desai, M.Y. Mavacamten: A novel small molecule modulator of beta-cardiac myosin for treatment of hypertrophic cardiomyopathy. Expert Opin. Investig. Drugs 2020, 29, 1171–1178.
43. Spertus, J.A.; Fine, J.T.; Elliott, P.; Ho, C.Y.; Olivotto, I.; Saberi, S.; Li, W.; Dolan, C.; Reaney, M.; Sehnert, A.J.; et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): Health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021, 397, 2467–2475.

44. Hegde, S.M.; Lester, S.J.; Solomon, S.D.; Michels, M.; Elliott, P.M.; Nagueh, S.F.; Choudhury, L.; Zemanek, D.; Zwas, D.R.; Jacoby, D.; et al. Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy. J. Am. Coll. Cardiol. 2021, 78, 2518–2532.
45. Kimmelstiel, C.; Zisa, D.C.; Kuttab, J.S.; Wells, S.; Udelson, J.E.; Wessler, B.S.; Rastegar, H.; Kapur, N.K.; Weintraub, A.R.; Maron, B.J.; et al. Guideline-Based Referral for Septal Reduction Therapy in Obstructive Hypertrophic Cardiomyopathy Is Associated With Excellent Clinical Outcomes. Circ. Cardiovasc. Interv. 2019, 12, e007673.
46. Batzner, A.; Pfeiffer, B.; Neugebauer, A.; Aicha, D.; Blank, C.; Seggewiss, H. Survival after Alcohol Septal Ablation in Patients with Hypertrophic Obstructive Cardiomyopathy. J. Am. Coll. Cardiol. 2018, 72, 3087–3094.