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Minireview

Left intraventricular diastolic and systolic pressure gradients

Miguel Guerra1,2, Francisco Sampaio3, Carmen Brás-Silva1,4 and Adelino F Leite-Moreira1,5

1Department of Physiology and Cardiothoracic Surgery, Cardiovascular R&D Unit, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto; 2Department of Cardiothoracic Surgery; 3Department of Cardiology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceiçao Fernandes, Vila Nova de Gaia 4434-502; 4Faculty of Nutrition and Food Sciences, University of Porto, Rua Dr. Roberto Frias, 4200-465 Porto; 5Centre of Thoracic Surgery, Hospital São João, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

Corresponding authors: Miguel Guerra and Adelino Leite-Moreira. Emails: migueldavidguerra@yahoo.com and amoreira@med.up.pt

Abstract

To describe left ventricular (LV) function comprehensively, it is crucial to characterize precisely transmitral, intraventricular and transaortic pressure–flow relations. The site of measurement is important; as the measurement location is moved from the mitral valve toward the apex and the outflow tract, important regional pressure differences are recorded inside the LV. These intraventricular pressure gradients (IVPGs) play an important role in ventricular filling in the normal heart and may be abolished by systolic or diastolic dysfunction. Despite their apparent importance in ventricular filling and diastolic function, IVPGs have never been utilized in clinical cardiology, due to the complexity of their acquisition. The application of Doppler echocardiography allows the reconstruction of diastolic IVPGs completely non-invasively, thus avoiding the risk and expense of a cardiac catheterization. Regional pressure gradients are also present during ventricular emptying but their correlation with systolic function is not so clear. The current minireview highlights theories and experimental data on invasive and non-invasive assessment of diastolic and systolic IVPGs and their role in LV filling and emptying. We also review the pathophysiological modulation of regional gradients, their importance in understanding and evaluating the complex phenomena underlying ventricular filling, as well as their potential clinical application.

Keywords: intraventricular pressure gradients, diastolic suction, dysfunction, ischemia, physiology, echocardiography


Introduction

The hallmark of diastolic dysfunction is the impaired capacity to fill or maintain stroke volume without a compensatory increase in filling pressures.1–3 Measurements made during diastole are very complex, because they are determined both by relaxation and chamber stiffness, with the latter becoming increasingly important toward the end of ventricular filling.4 Despite the fact that in 1896, Porter5 described a method which at the time seemed to secure ‘a correct record of any part of intracardiac pressure curve’, the perfect method for diastolic function evaluation has still not been found. Therefore, intracardiac hemodynamics remains an area of required research. Whereas regional pressure differences between the left ventricle (LV), the LV outflow tract and the aorta during ejection6 or between the left atrium, the LV inflow tract and the LV7 have been recognized for some time, the potential clinical importance of regional pressure differences within the LV during diastole and systole have only more recently8–10 gained attention.

To describe LV diastolic function comprehensively, it is crucial to have a precise characterization of the transmitral pressure–flow relation. Original Courtois et al.7 recordings showed profound differences in the transmitral pressure relation at different sites inside the LV. During early rapid filling, minimum LV pressure increased from 1.6 ± 0.7 to 3.1 ± 0.8 mmHg (mean ± SD), in measurements from apex to base. During atrial contraction, significant regional ventricular apex-to-base gradients were also noted. LV end-diastolic pressure decreased (8.1 ± 2.0 to 7.4 ± 2.0 mmHg), and the upstroke of the LV filling (A-wave) near the base was recorded earlier than near the apex. These recordings reveal a consistent intraventricular pressure pattern that can easily be missed when a dual-micromanometer catheter is not used.

The presence of regional pressure differences strongly suggests the occurrence of intraventricular pressure gradients (IVPGs) between the LV inflow tract, the LV apex and the LV outflow tract. These diastolic IVPGs may play an important role in ventricular filling and emptying in the normal heart.11–13 Systolic IVPGs have also been observed6
between the LV apex and the subaortic area, but there is lack of data on their magnitude and on their behavior in the presence of systolic or diastolic dysfunction. As regional dyskinetics interferes with the normal sequence of ventricular contraction and relaxation, it might be expected to alter the physiological diastolic and systolic IVPGs, although a systematic analysis of its impact on IVPGs along the entire cardiac cycle has not yet been performed.

Thus, diastole is not amenable to analysis with simple passive-filling models and any complete description of diastole must account for ventricular suction and regional gradients. Because different regions of the LV are subjected to different pressures, and thus different wall stresses at different time points, an ideal description of LV diastolic function must be regional in nature. The presence of regional pressures and gradients indicates that studies with techniques for assessment of LV compliance by curve-fitting LV diastolic pressure-dimension data should use a standardized catheter position, particularly if serial measurements are involved. However, the technical difficulties involved in multisite measurement of pressure within the ventricle, coupled with the observation that regional variations in pericardial constraint may also exist, make regional stress-strain measurements a challenge. In fact, invasive pressure measurements in the LV using fluid-filled catheters with external transducers, instead of tip pressure micromanometers, as commonly happens for clinical studies in cath labs, are much too inaccurate to measure with precision very low pressures and gradients. Catheter-based measurements with micromanometers are usually not available and therefore rarely performed in clinical practice, having in addition the difficulties of aligning microcatheters in the direction of flow. In these circumstances, color Doppler M-mode measurements may be much more accurate, taking into account the spatial, temporal and velocity characteristics and resolution of echo that makes it suited for this type of work. Recently, it has been proposed that IVPGs, as derived by color M-mode echocardiography, correlate with LV elastic recoil and LV contractility, and that IVPGs could be a useful method to improve the assessment of LV diastolic function using Doppler echocardiography. The current minireview highlights theories and experimental data on invasive and non-invasive assessment of diastolic and systolic pressure gradients and their role in LV filling and emptying. We also review pathophysiological modulation of regional gradients, their importance and potential clinical application.

**Normal IVPGs**

**Diastole**

As early as 1930, Katz was speculating that diastole was not an entirely passive process and that the LV had the ability to ‘exert a sucking action to draw blood into its chamber’. Nevertheless, it was only in 1979 that Ling et al. first described, in a canine model, a 2–5 mmHg pressure gradient from the midventricle to the apex during the rapid phase of diastolic filling. In 1988, Courtois et al. observed, also in a canine model, a significant early diastolic pressure gradient along the LV inflow tract with minimum pressure in the apex suggesting suction of the blood toward the LV apex. When it was subsequently shown that these gradients were diminished by ischemia and related to systolic function, the concept that they could reflect ventricular filling and emptying was born. Moreover, when Nikolic et al. demonstrated IVPGs during early diastole in filling as well as in non-filling heart beats, the hope that IVPGs would become an index for isovolumic and early ventricular relaxation was substantiated.

Later, Smiseth et al. demonstrated, also in humans, the presence of a diastolic IVPG between the apex and outflow tract. They showed that when apical pressure started to rise, outflow pressure continued to fall, thus creating an apex-to-outflow tract pressure gradient in early diastole. The peak gradient was $3.5 \pm 0.3$ mmHg and it had occurred $57 \pm 7$ ms after apical pressure nadir. It was preceded by a small opposite gradient of $1.0 \pm 0.2$ mmHg. In late diastole, during atrial contraction, there was also a gradient from the apex-to-outflow tract; its peak value was $1.8 \pm 0.2$ mmHg. More recently, we were able to confirm and extend their results (Figure 1 and Table 1).

The observation that the apical region fills first and begins to oscillate while filling is still occurring in the basal region is consistent with a model of diastolic function that treats the apex as recoiling during early diastole and contributing to filling by actively drawing blood into the LV. The timing during early diastolic filling at which LV pressure begins to increase after its nadir would mark the completion of ventricular suction. Because such an increase in pressure occurs earlier in the apex than in the base of the heart, it can be inferred that filling is completed first in the apex and only then in the base. It is now well recognized that the driving force for early diastolic transmitral flow is the atrioventricular pressure gradient. This gradient is created, in part, by elastic properties of the ventricle that allow for the storage of potential energy in the myocardium during systole that is released during diastole. Recent experiments indicate that proteins such as titin, acting as a bidirectional, linear spring, together with the extracellular matrix and microtubules, play a role in generating elastic recoil. It is noteworthy that the regional pressure-wave pattern recorded during atrial contraction is exactly opposite to the pattern recorded during the early rapid-filling phase. In this phase the upstroke of the LV rapid-filling (E-wave) occurs first near the apex and last near the base of the heart, suggesting a mechanism, other than passive filling.

Van de Werf et al. showed that a reversed gradient between the atrium and the ventricle during early diastolic filling is a normal physiological event which corresponds to the deceleration of the transmitral E-wave. This biphasic IVPG may play an important role in intraventricular flow and vortex formation and it is probably related to intraventricular propagation of the early transmitral flow pulse, following myocardial segment asynchrony during relaxation. In fact, while outflow tract segments re-extend during the entire diastole, apical segments lengthen first and then shorten in the late phase of diastole.
Figure 1  Left ventricular apical (—) and outflow tract (— —) pressures and simultaneous recording of apex-to-outflow tract IVPG (gray) along the cardiac cycle in a representative animal are displayed. Experiments were performed in open-chest anesthetized rabbits, instrumented with pressure tip micromanometers placed in the apex and outflow tract of the left ventricle.25,26 Systolic phase: During early systole, we recorded an IVPG from apex-to-outflow (a) which inverts during late systole (b).

Diastolic phase: During diastole, we observed a significant outflow tract-to-apex IVPG in the early diastole (c) and an apex-to-outflow tract IVPG in the late diastole. IVPG, intraventricular pressure gradient; LV, left ventricular; LVP, left ventricular pressure.

Table 1  Intraventricular pressure gradients (mean; mmHg)

<table>
<thead>
<tr>
<th>Experimental protocol</th>
<th>Diastole</th>
<th>Systole</th>
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<tr>
<td></td>
<td>Early diastole</td>
<td>Ventricular filling</td>
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<tr>
<td>Ling et al.21</td>
<td>Dog</td>
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<tr>
<td>Falsetti et al.27</td>
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<td>Pasipoularides et al.</td>
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<td>Firstenberg et al.8</td>
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<td>Yotti et al.30</td>
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<td>Guerra et al.25</td>
<td>Rabbit</td>
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+, apex-to-base gradient direction; −, base-to-apex gradient direction.
This complex torsion and untwisting reveals the physiological IVPGs observed during ventricular filling. It improves myocardial relaxation, contributing first to filling of the LV outflow tract and then preparing ventricular emptying. Smiseth et al. showed that both in animals and humans, the pressure gradient between the ventricular apex and the outflow tract strongly correlated not only with peak early transmitral flow and early ventricular filling, but also with stroke volume. These observations suggest the crucial importance of IVPGs to ensure efficient LV diastolic filling and emptying and therefore its close association with LV diastolic and systolic function.

In terms of flow-driving energy expenditure, diastolic suction contributes to filling more than one order of magnitude above passive atrial decompression. Temporal analysis conducted by Yotti et al. confirmed that in humans, suction is initiated during isovolumetric ventricular relaxation and continues during rapid filling. During early ventricular filling, suction causes pressure to fall despite filling. Therefore, reduced suction shifts the left corner of the pressure–volume loop toward a higher diastolic pressure and diastolic suction is directly related to the apex-to-base IVPG. Pressure gradients and redistribution of blood flow create a ring vortex, which results from the acceleration of blood along the inflow tract, and represents a force applied on quiescent blood already in the ventricle. The ring vortex will first appear at the cardiac base, at the level of the mitral valve tips, with subsequent propagation toward the apex during the deceleration phase of transmitral flow.

**Systole**

A characteristic pattern of systolic IVPGs has also been described in humans within the LV. A 3.7 ± 0.4 mmHg gradient between the LV apex and the subaortic outflow tract was recorded in early systole, while an outflow tract-to-apex 3.9 ± 0.5 mmHg gradient was observed in late systole. The physiological significance of that gradient is still unclear. More recently, we studied IVPGs along the cardiac cycle in an animal model (Figure 1 and Table 1). We recorded a gradient from the apex to the outflow tract during the rapid ejection phase, which inverted during the slow ejection phase. This gradient continued into the first part of the isovolumic relaxation period. We speculated that systolic apex-to-outflow gradient along the ejection phase, which parallels the aortic-ventricular pressure gradients, probably reflects earlier and faster shortening of apical rather than basal segments. This might favor ventricular emptying during systole and mitral-apical flow during diastole. However, the significance of this gradient for intraventricular flow propagation in the normal and the diseased heart remains to be determined. Generated by the active force of the contracting ventricle, the systolic IVPG between the LV apex and the outflow tract has shown to be related to the inotropic state. In the absence of outflow obstruction, the systolic IVPG reaches its peak early during systole and is fundamentally caused by impulsive forces. The magnitude of the systolic IVPG has been shown to increase with exercise and adrenergic stimulation and to decrease with β-blocking agents in invasive studies. Furthermore, the peak systolic IVPG has shown to be relatively load-independent and to have a greater sensitivity than the first time derivative of pressure for changes in the inotropic state assessment.

**Pathological IVPGs**

Several studies have shown marked changes in the intraventricular filling pattern and the diastolic IVPG in patients with myocardial ischemia and in those with congestive heart failure. Courtois et al. found, in an animal model, that the diastolic IVPG disappeared during acute ischemia and demonstrated a relationship between the decrease in IVPG and LV systolic dysfunction. Later, it was speculated that during systole, some elastic potential energy could be stored in the dyskinetic segment and then released, when LV intracavitary pressure declines to low levels during the late isovolumic relaxation and early diastolic filling phases. Such inward diastolic movement of the dyskinetic segment could impart some motion to blood pooled in the apical and anterior regions of the ventricle and thus contribute to the alteration of the normal early diastolic IVPG. Thus, acute regional myocardial ischemia, by diminishing the amount of ventricular myocardium available for contraction and subsequent elastic recoil in one region of the ventricle, should result in loss or attenuation of the diastolic IVPG in that region.

Firstenberg et al. complemented previous animal experiments. They showed the presence of IVPGs in humans and demonstrated that improvements in LV systolic and diastolic function correlate directly with the recovery of the diastolic IVPG. Their findings suggest that improvements in ventricular relaxation, through surgical myocardial revascularization, are related to LV remodelling and to changes in LV elastic recoil. More else, the lack of a relationship shown between IVPGs and left atrial pressures suggests that IVPGs occur even in the absence of LV filling. In fact, using a non-filling LV model, suggested that the diastolic IVPG could reflect intrinsic properties of the LV and not only transmural pressure gradients.

Beppu et al. also showed that after coronary artery ligation in dogs with consequent apical akinesia or dyskinesias, the normal apical diastolic pressure differentials are attenuated. The absence or decrease of IVPGs during both the filling and ejection phases can contribute to the relative stasis of blood throughout the cardiac cycle, predisposing to thrombus formation. During mitral to apical flow acceleration, the IVPG is directed toward the apex, and during the subsequent flow deceleration, the pressure gradient reverses. Such pressure gradients observed from the apex to the subaortic region and from the mitral tip to the subaortic region can play an important role in intraventricular flow. Therefore, in dogs with relatively large infarcted area and apical dyskinesis, distribution of the inflow blood toward the infarcted area is absent or extremely small, and blood stagnation develops in the apex. Using a different approach, Smiseth et al. also demonstrated a marked increase in the early diastolic IVPG during
volume loading and a marked decrease during reduced LV filling by caval constriction, showing a strong correlation of the IVPG with peak rate of transmural filling and with stroke volume. Diastolic IVPGs therefore appear to reflect mass and velocity of global LV filling, being correlated with peak apex-outflow tract velocities and presumably playing a role in the redistribution of the early filling wave toward the LV outflow region.24 Actually, Falsetti et al.27 observed a gradual increase in the magnitude of the IVPG during β-stimulation and a decrease during β-blockade and during myocardial ischemia, suggesting the close association between LV relaxation rate and the magnitude of the IVPG. The decrease in the mitral to apical pressure gradient during myocardial ischemia or β-blockage was attributed to marked prolongation of tau, a loss of non-uniformity of tau between the apex and base, and a marked increase in end-systolic volume.9

Rovner et al.57 demonstrated an increase in LV relaxation and the IVPG during diastole with exercise in both normal subjects and in patients with heart failure. However, this mechanism was significantly impaired in the heart failure group compared with normal subjects. In patients with heart failure, the decreased ability to augment ventricular relaxation and diastolic IVPG is responsible for the inability to accommodate the increase in estimated preload during exercise, resulting in higher filling pressures.58–61 In contrast to what is seen in normal hearts, minimum diastolic pressure of failing ventricles rises during exercise.62 It is very likely that the limited suction reserve recruitable by inotropic stimulation is a major determinant of this abnormal behavior induced by exercise. Also, uncoordinated regional ventricular function is a major cause of prolonged ventricular relaxation and abnormal diastolic IVPG.63 These observations suggest an additional mechanism by which cardiac resynchronization therapy can hypothetically improve filling of dilated cardiomyopathy ventricles. If true, IVPG evaluation could be potentially helpful to analyze regional ventricular filling and to optimize or to predict the response to resynchronization therapy.

The practical value of IVPGs is enhanced by the recognition of its general applicability and quantification, since diagnosing and quantifying suction via pressure gradients is important in understanding pathophysiology.39,64 In fact, dilated ventricles are poor suction pumps, aspirating a relatively small volume in early filling and compensating with atrial contraction and a resting tachycardia to maintain cardiac output. Healthy ventricles store greater amounts of elastic energy during systole and are therefore more effective suction pumps during diastole. A reduced diastolic IVPG is the consequence not only of a lower impulse due to depressed elastic recoil, but also of relatively higher deleterious convective forces and impaired ventricular relaxation which adversely affects LV filling.39,40,65

**Estimation of IVPGs by Doppler echocardiography**

Doppler echocardiography has been proposed28 as a promising approach to evaluate LV diastolic function and LV filling non-invasively. It provides velocity information, not only at a single location and point in time, but also along the entire inflow tract from the left atrium across the mitral valve into the LV throughout the entire diastolic filling period. Greenberg et al.28 hypothesized that Doppler profiles, representing flow velocities within the ventricle between the base and apex, could provide information on IVPGs. They proposed a novel concept to apply basic hydrodynamic principles to reconstruct non-invasively the IVPG present during LV filling. They used the local spatial and temporal velocity distribution measured by color Doppler M-mode echocardiography to calculate local pressure gradients using the Euler equation, integration of which allows them to calculate a pressure difference between two points along the inflow tract. In their study, they focused on pressure gradients between the base and apex of the LV and compared the results of this estimate with direct catheter measurements. They also showed that this approach not only provides accurate information under baseline conditions, but is also able to detect relatively small changes in transmural and IVPGs induced by pharmacologically altering LV relaxation. Actually, several studies50–53,66,67 observed differences in the LV inflow patterns by Doppler echocardiography in different disease states and physiological conditions. Stugaard et al.51 noticed a significant change in the Doppler inflow pattern with delayed apical filling during ischemia caused by balloon occlusion of the left anterior descending coronary artery. During isoproterenol infusion, Greenberg et al.28 observed an increase in the reconstructed IVPG, similar to the observations of Falsetti et al.27 and consistent with the finding by Brun et al.50 of increased flow propagation into the LV in patients during intracoronary dobutamine infusion.

This application of Doppler echocardiography allows the reconstruction of a small diastolic IVPG completely non-invasively, thus avoiding the risk and expense of a cardiac catheterization. This method also enables the detection of changes in IVPGs induced by alterations in LV relaxation and may help in understanding and evaluating the complex phenomena underlying LV filling.39 The accuracy of pressure difference estimates results in part from the accuracy of color Doppler M-mode velocity data used in the non-invasive calculation of pressure differences.66 In addition to this velocity resolution, the temporal and spatial resolutions of color Doppler M-mode images are important as they determine the degree of accuracy for the partial derivative terms of the Euler equation. The accuracy of the pressure estimate is also related to the degree to which the ultrasound scanline approximates an inflow streamline through the center of the mitral valve. Because color Doppler M-mode velocities are measured as a continuum between the left atrium and the LV apex at 0.5-mm spatial resolution, the derived pressure gradient distribution along a scanline can be integrated over space to produce a pressure map.19,39,66–68 However, this method is limited because the transmitral velocity profile is also affected by several parameters other than LV diastolic function, such as heart rate, atrioventricular conduction interval and left atrial pressure. In fact, a reliable non-invasive method to
characterize the state of LV relaxation is still an unsolved issue and to overcome the limitations of standard Doppler echocardiography, additional techniques are required. Analysis of the pulmonary venous flow patterns, and more recently, the use of tissue Doppler imaging, strain and strain rate imaging have been suggested as promising tools in the evaluation of LV filling using ultrasound-based technology.

With tissue Doppler imaging, regional LV wall motion dynamics can be sequentially analyzed throughout the cardiac cycle, providing an efficient assessment of the LV relaxation pathophysiology, process and dynamics. The diastolic motion of the mitral annulus, as measured by tissue Doppler imaging, has been used to provide additional information. Mitral annulus velocity reflects the rate of change in LV long-axis dimension and volume. This, in turn, is related to myocardial relaxation, so that impaired relaxation results in a reduced early mitral annulus velocity (e'). Unlike other Doppler parameters of diastolic function, e' velocity appears to be relatively independent of preload, especially when the rate of myocardial relaxation is decreased. In addition, the ratio of early transmitral flow velocity (E) to early diastolic septal mitral annulus velocity (E/e') has been shown to be the most accurate non-invasive predictor of elevated LV filling pressure. With diastolic dysfunction, the LV filling and IVPG pattern are altered. The annular motion away from the apex is coincident with the IVPG in normal LV function but with loss of suction in heart failure, the annular motion is delayed and occurs after the E-wave and after the early diastolic IVPG. In particular, the E/e' is correlated with LV filling pressures and evaluates how much blood enters the ventricle for a given atrium–ventricle pressure gradient. Although its applicability has some limitations, determining this ratio is strongly recommended in the evaluation of diastolic function and LV filling.

The determination of diastolic function using IVPGs offers several advantages over the conventional diastolic parameters that are currently in clinical use. With the advent of ultrasound technology and computer programming, the color M-mode velocity information can be used to determine the diastolic IVPG not only during resting conditions but also during exercise in relation to heart failure patients. The use of newer indexes of diastolic function that are less preload-dependent in patients with heart failure and abnormal preload provide more objective information in the clinical setting. These newer diastolic indexes include transmitral annular flow velocity (Ea) obtained from tissue Doppler and transmitral flow propagation velocity (Vp) obtained from color M-mode Doppler. The ability to integrate the continuum of the velocities from the LV base to the LV apex can produce the pressure maps that allow for a non-invasive determination of LV filling pressures and normal and pathological IVPG patterns. Rovner et al. demonstrated an important relationship between the IVPG and overall clinical status. Improvement in exercise capacity, increase in ejection fraction and decrease in mitral regurgitation severity correlated well with improvement in the IVPG in patients with diastolic dysfunction. Recently, Yotti et al. showed that Doppler-derived measurements of diastolic and systolic IVPGs provide a sensitive, reliable, reproducible and relatively load-independent index of the rate of LV relaxation. When combined with early myocardial lengthening velocity, this method improves the assessment of LV relaxation and LV filling in the clinical setting.

Summary

Accurate diastolic and systolic IVPGs have been identified in the LV since some years ago, but their importance in determining diastolic and systolic function only recently became evident. Significant IVPGs during diastolic filling were described along the inflow tract and directed to the apex. They occur early in diastole and they are probably a marker of diastolic suction and ventricular filling. During late diastole, these IVPGs reverse, directing now from the apex to the outflow tract and preparing the ventricular emptying. In fact, when ventricular emptying is opposed by afterload elevations or after ischemia, the normal IVPG are abolished, indicating ventricular ejection impairment. Regional alterations in these diastolic IVPGs might be an important factor in the characteristic changes that occur in intraventricular flow in specific cardiac disorders. Recently, the early diastolic velocity of the myocardium, as measured by tissue Doppler imaging, and the spatial–temporal distribution of the velocity of blood flow from the annulus to the apex, as measured by M-mode color Doppler, have been used to predict LV filling pressures and gradients. The ability to directly and non-invasively quantify IVPGs in the LV may allow for better assessment of cardiac function in response to interventions, such as pharmacological echocardiographic stress testing or intraoperative assessment of surgical interventions. Moreover, the clinical application and interpretation of IVPGs might contribute to the knowledge of normal intraventricular physiology and to predict LV filling and emptying impairment during specific cardiac disorders.

Author contributions: MG searched the bibliography and prepared the initial manuscript. FS and CB-S did critical revision of the manuscript. MG and AFL-M completed the initial version to its final format and came up with the overall planning.

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