Published in final edited form as:

J Am Soc Echocardiogr. 2012 August ; 25(8): . doi:10.1016/j.echo.2012.06.020.

Left Ventricular Function and the Systemic Arterial Vasculature: Remembering What We Have Learned

Brian P. Davidson, MD and George D. Giraud, MD, PhD

Division of Cardiovascular Medicine, Department of Medicine, Oregon Health Sciences University and Portland VA Medical Center, Portland, Oregon.

With each heart beat, the left ventricle moves a volume of blood into the systemic arterial vasculature for distribution to the organs of the body. This interaction between the left ventricle and the systemic arterial vasculature (ventricular-arterial coupling) is an important determinant of left ventricular function. Study of ventricular-arterial coupling once required invasive techniques. However, advances in echocardiography now make it possible to noninvasively assess ventricular-arterial coupling in humans. In this issue of *JASE*, Kuznetsova *et al* use echocardiographic techniques to better understand ventricular-arterial coupling and its effects on left ventricular performance in patients with hypertension.¹ Such studies remind us of the core physiologic concepts pioneering cardiovascular scientists defined many years ago. As we enter an era of increasingly sophisticated noninvasive evaluation of cardiac performance, careful application of these core concepts is essential. These physiologic concepts form the basis for our understanding of the how the heart adapts to hemodynamic challenges during health and disease.

Early researchers worked with both isolated cardiac muscle and the intact heart, using the attributes of each preparation to their advantage. Study of isolated cardiac muscle allowed more strict control of experimental variables to clearly determine the effects of load on muscle function. Researchers found that adding increasing weight to isolated cardiac muscle before contraction results in greater force generation during contraction.² These observations lead to the development of the concept of preload, the force stretching the muscle before the onset of contraction. Researchers also found that adding weight to isolated muscle after the onset of contraction, decreases muscle shortening as the weight increases.² These observations lead to the concept of afterload, the load the muscle must bear after the onset of contraction. In general terms, diastolic filling pressure is widely used as the equivalent of preload while systolic arterial pressure is widely used as the equivalent of afterload in the intact heart. Research at an ultrastructural level found that as cardiac muscle is stretched by increasing preload there is an increasingly favorable overlap of the actin and myosin filaments resulting in increased active tension generation up to the point of maximal overlap, beyond which no additional active tension is generated.³ This length-tension research provided an understanding of the ultra structural basis of the Frank-Starling relationship and complemented the ongoing work in the intact heart. Early researchers also found that increased calcium availability to the contractile apparatus increased the rate and force of contraction.^{4,5} These effects on the rate and force of contraction were defined as a change in contractility, separate from the effects of preload and afterload on cardiac muscle.

Research using the intact heart by Frank,⁶ Starling,⁷ and others that followed showed that cardiac output is the product of stroke volume (end-diastolic volume minus end-systolic volume) and heart rate. From a simplistic point of view, end-diastolic volume is determined by atrial pressure and end-systolic volume determined by both arterial pressure, as well as by contractility. To better understand the effects of diastolic pressure on stroke volume independent of heart rate, the Frank-Starling relationship can be viewed as the filling pressure-stroke volume relationship for the ventricle. This allows us to more easily understand the effects of diastolic ventricular pressure on stroke volume. After accounting for external cardiac restraint, the filling pressure-stroke volume relationship for either the right or left ventricle is characterized by a relatively steep ascending limb and a relatively flat plateau limb. As filling pressure increases stroke volume increases up to a point. Once on the plateau limb of the filling pressure-stroke volume relationship, stroke volume increases very little as filling pressure increases. The filling pressure-stroke volume relationship of the ventricles relates primarily to ventricular diastole or end-diastolic volume.

An equally important but less often used relationship describes the effect of systolic pressure on end-systolic volume. The systolic pressure–end-systolic volume relationship is characterized by a relatively steep descending limb as aortic systolic pressure increases. With any increase in aortic pressure, end-systolic volume is larger with a smaller difference between end-diastolic volume and end-systolic volume resulting in a smaller stroke volume. Changes in myocardial contractility alter the position of both the filling pressure-stroke volume relationship and the aortic systolic pressure-stroke volume relationship with an increase in contractility shifting these relations up to a new relationship with a greater stroke volume at any given pressure.

As we use the term contractility it is important that we remember how contractility is defined. Contractility, an often misused term, defines the performance of the heart at a given preload and afterload.⁸ Left ventricular contractility is specifically defined as performance of the ventricle at a given filling pressure and systolic pressure. Myocardial contractility represents the intrinsic ability of the cardiac myocyte to contract independent of preload and afterload. Differences in the ability to produce force during contraction result from alterations in the amount of binding between myosin thick filaments and actin thin filaments. The degree of interaction between these filaments depends on the amount of calcium available for this process. Intrinsic or extrinsic activation of the myocardial beta-1 receptors or inhibition of myocardial phosphodiesterase makes more calcium available during systole to facilitate interaction between myosin and actin filaments; thus, increasing the force of contraction of the cardiac myocytes. With respect to the diastolic filling pressure-stroke volume relationship, end-diastolic pressure is the prime determinant of end-diastolic volume and stroke volume. However, an increase in contractility will shift the filling pressure-stroke volume relationship up and to the left while a decrease in contractility will shift this relationship down and to the right (Figure 1). Acute changes in contractility and its effect on the position of the filling pressure-stroke volume relationship are due to changes in the availability of calcium to the contractile apparatus of the cardiac myocytes. More long-term changes in contractility can result from advantageous or disadvantageous remodeling of the ventricle.

Pressure-volume relationships can also be used to assess ventricular function throughout a series of cardiac cycles.⁹ The ventricular pressure-volume relationship can be plotted as a loop comprised of ventricular systole starting with the isovolumetric contraction phase, then the ejection phase followed by ventricular diastole with the “active” isovolumetric relaxation phase and ending with passive filling of the ventricle. Venous return and ascending aortic pressure can then be varied to generate a series of different pressure-volume loops (Figure

2). Each pressure-volume loop describes a specific point determined by end-systolic pressure and end-systolic volume. As this specific end-systolic pressure-volume point varies with changes in pre-load and afterload, a relationship between these points can be determined. The slope of this relationship is defined as the end-systolic elastance (Ees) of the ventricle.⁹ Ees is a measure of ventricular performance that comprises myocardial contractility as well as geometric and structural components. Any short-term change in this relationship can reasonably be attributed to a change in contractility of the ventricle while long-term changes may reflect change in contractility or ventricular remodeling. Pressure volume loops can also be used to assess left ventricular work as the area enclosed by the left ventricular pressure volume loop.^{10,11} Alternatively, regional myocardial work can be measured noninvasively with strain Doppler echocardiography.¹² This noninvasive method assesses regional myocardial work as the area enclosed in the pressure-myocardial strain loop during the ejection phase of the cardiac cycle.

Arterial load is a powerful stimulant of myocardial hypertrophy. The force the individual cardiomyocyte must generate to shorten is tension, which is an expression of force along the length of the myocyte. The force the intact ventricle must generate to eject blood is wall stress, force per unit area measured as pressure in mmHg. In the heart, wall stress is defined by the Laplace relationship as $(\text{pressure} \times \text{radius}) / 2 \times \text{wall thickness}$, where pressure is the pressure in the ventricle, radius is generally the short axis radius half way between the base and apex of the ventricle and wall thickness is the wall thickness of the ventricle at the same level. Under conditions of increased systolic load the ventricle remodels, undergoing concentric hypertrophy in an effort to normalize wall stress by increasing wall thickness.¹³ Hypertension induced ventricular remodeling can increase left ventricular Ees as a result of myocardial fibrosis and increased myocardial stiffness.¹⁴ Arterial elastance (Ea) can be used as an index of the load placed on the ventricle by the systemic arterial vasculature.¹⁵ Ea is determined from the pressure volume loop as the relationship between end-systolic pressure and stroke volume or end-systolic pressure/stroke volume. Ea represents the composite effects of vascular resistance, arterial compliance, and heart rate. Ventricular-arterial coupling can then be defined as the ratio of Ea/Ees.¹⁶ This ratio, Ea/Ees, provides a useful assessment of left ventricle function under varying loading conditions and inotropic states.¹⁰

Although widely used to describe ventricular function, ejection fraction provides only a limited assessment of ventricular function. Left ventricular ejection fraction can be determined using many techniques including left ventricular angiography, echocardiography, and radionuclide angiography, and measured as the difference between end-diastolic and end-systolic measurements, often volumes, divided by the end-diastolic measurement. Ejection fraction can be an approximate assessment of overall left ventricular function in the absence of mitral regurgitation. However, when mitral regurgitation is present, ejection fraction is not a good assessment of ventricular function because of dynamic changes in wall stress as the radius decreases during the ejection phase. When mitral or aortic regurgitation is present, ejection fraction is not a good assessment of the contribution of left ventricular ejection to cardiac output because the regurgitant fraction does not contribute to cardiac output.

Kuznetsova *et al*¹ have used advanced echocardiographic techniques to study the interaction between the left ventricle and the systemic arterial vasculature. They provide new insight into left ventricular performance in patients with hypertension. The authors demonstrated differences in left ventricular performance at rest and during handgrip exercise in hypertensive patients compared to normotensive subjects. The hypertensive hearts had been exposed to the increased left ventricular systolic load of hypertension over time and had higher systolic load at rest, before handgrip exercise, compared with the normotensive

hearts. Handgrip exercise was used to acutely increase left ventricular systolic load in both the hypertensive patients and the normotensive subjects. Hearts exposed to the increased systolic load of hypertension had greater left ventricular wall thickness and mass than hearts in normotensive patients. This observation suggests an adaptive hypertrophic response striving to normalize wall stress in the hypertensive hearts. At rest, both Ea and left ventricular Ees were higher in hypertensive patients compared to normotensive subjects. However, Ea/Ees was lower in hypertensive patients. During handgrip exercise end-systolic volume, Ea and Ea/Ees increased in both normotensive and hypertensive subjects. Both normotensive and hypertensive participants had similar longitudinal tissue Doppler imaging strain measured at basal-mid left ventricle wall segments. Regional myocardial work density during ejection at rest was higher in hypertensive patients than in normotensive subjects. During the handgrip exercise, regional myocardial work density increased in normotensive subjects but did not in hypertensive patients. The exercised-induced increase in regional work density in normotensive participants suggests contractile reserve in normotensive subjects. End-systolic volume increased with handgrip exercise in the normotensive subjects, with stroke volume maintained by a matched increase in end-diastolic volume, resulting in no change in stroke volume. In hypertensive subjects, end-systolic volume similarly increased with handgrip exercise but end-diastolic volume did not increase. As a result stroke volume decreased. This observation suggests the hypertensive patients are on the plateau limb of the filling pressure-stroke volume relationship. These observations taken together also suggest that hypertensive patients do not have stroke volume reserve by either an end-diastolic or an end-systolic mechanism. Caution should be used when considering potential changes during diastole. Diastolic filling pressures of the left ventricle were not measured. This is not a criticism of the study since it is difficult to detect small changes in filling pressures using non-invasive methods. Noninvasive estimates of diastolic filling have been used. However, recent studies show that noninvasive estimates of diastolic filling pressures are not as useful as some have hoped.^{17,18} The authors have appropriately avoided using diastolic parameters in interpreting their primary findings.

This is an exciting time for echocardiography and for noninvasive evaluation of cardiac function as a whole. The work of Kuznetsova and colleagues adds to the growing body of literature¹⁹⁻²² using advanced echocardiographic techniques to study ventricular function in humans with a level of sophistication that has previously been reserved for invasive hemodynamic studies. The authors show that the left ventricle of hypertensive patients adapts to increased systolic pressure load as it is coupled to the systemic arterial vasculature. This adaptation however, appears to come at the expense of increased regional myocardial work at rest and diminished ability to augment work in response to increased arterial load during handgrip exercise. The use of noninvasive techniques to carefully study left ventricular adaptation to disease has the potential to detect preclinical left ventricle dysfunction. This in turn will guide therapy and be of great value in caring for patients with cardiovascular disease. However, we cannot forget the core physiologic concepts developed over decades, which underlie these evolving techniques and remind us to never look upon the any part of the cardiovascular system in isolation.

Acknowledgments

Research supported by funds from U.S. National Institute of Child Health and Human Development grant P01 HD 34430, National Heart, Lung, and Blood Institute grant R21 HL093617 and National Institutes of Health grant R01 HL102763. B.P.D. was supported by NHLBI training grant T32HL094294.

REFERENCES

1. Kuznetsova T, D'hooge J, Kloch-Badelek M, Sakiewicz, Thijs L, Staessen J. The impact of hypertension on ventricular-arterial coupling and regional myocardial work at rest and during isometric exercise. *J Am Soc Echocardiogr.* 2012; 25:882–90. [PubMed: 22622108]
2. Downing SE, Sonnenblick EH. Cardiac muscle mechanics and ventricular performance: force and time parameters. *Am J Physiol.* 1964; 207:705–15. [PubMed: 14220048]
3. Spotnitz HM, Sonnenblick EH, Spiro D. Relation of ultrastructure to function in the intact heart: sarcomere structure relative to pressure volume curves of intact left ventricles of dog and cat. *Circ Res.* 1966; 18:49–66. [PubMed: 5901488]
4. Sonnenblick EH, Rots J, Covell JW, Braunwald E. Alterations en resting length-tension relations of cardiac muscle induced by changes in contractile force. *Circ Res.* 1966; 19:980–8. [PubMed: 5954130]
5. Covell JW, Ross J, Sonnenblick EH, Braunwald E. Comparison of the force-velocity relation and the ventricular function curve as measures of the contractile state of the intact heart. *Circ Res.* 1966; 19:364–72. [PubMed: 5914848]
6. Frank O. Zur Dynamik des Herznuskels. *Zeitschrift fur Biologie.* 1895; 32:370–447.
7. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. *J Physiol.* 1914; 48:357–79. [PubMed: 16993262]
8. Berne, R.; Levy, MN.; Koeppen, BM.; Stanton, A. *Physiology.* 5th ed.. Mosby; St. Louis: 2004.
9. Suga H, Sagawa K. Instantaneous Pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res.* 1974; 35:117–26. [PubMed: 4841253]
10. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J.* 1993; 125:1659–66. [PubMed: 8498308]
11. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. *Am J Physiol.* 1986; 250:R1021–7. [PubMed: 3717375]
12. Urheim S, Rabben SI, Skulstad H, Lyseggen E, Ihlen H, Smiseth OA. Regional myocardial work by strain Doppler echocardiography and LV pressure: a new method for quantifying myocardial function. *Am J Physiol.* 2005; 288:H2375–80.
13. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest.* 1975; 56:56–64. [PubMed: 124746]
14. Pak P, Maughan W, Baughman K, Kieval R, Kass D. Mechanism of acute mechanical benefit from VDD pacing in hypertrophied heart: similarity of responses in hypertrophic cardiomyopathy and hypertensive heart disease. *Circulation.* 1998; 98:242–8. [PubMed: 9697824]
15. Kelly RP, Ting C-T, Yang T-M, Liu C-P, Maughan WL, Chang M-S, et al. Effective arterial elastance as index of arterial vascular load in humans. *Circulation.* 1992; 86:513–21. [PubMed: 1638719]
16. Sunagawa K, Maughan W, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol.* 1983; 245:H773–80. [PubMed: 6638199]
17. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation.* 2009; 119:62–70. [PubMed: 19075104]
18. Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD, et al. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging.* 2011; 4:482–9. [PubMed: 21788358]
19. Koopman LP, McCrindle BW, Slorach C, Chahal N, Hui W, Sarkola T, et al. Interaction between myocardial and vascular changes in obese children: a pilot study. *J Am Soc Echocardiogr.* 2012; 25:401–10. [PubMed: 22265457]
20. Borlaug BA, Olson TP, Lam CSP, Flood KS, Lerman A, Johnson BD, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am College Cardiol.* 2012; 56:845–54.

21. Tartièrre-Kesri L, Tartièrre J-M, Logeart D, Beauvais F, Solal AC. Increased proximal arterial stiffness and cardiac response with moderate exercise in patients with heart failure and preserved ejection fraction. *J Am College Cardiol.* 2012; 59:455–61.
22. Giannini C, Petronio AS, Carlo MD, Guarracino F, Benedetti G, Donne MGD, et al. The incremental value of valvuloarterial impedance in evaluating the results of transcatheter aortic valve implantation in symptomatic aortic stenosis. *J Am Soc Echocardiogr.* 2012; 25:444–53. [PubMed: 22244001]

Figure 1.

Effects of increased contractility on (A) the left atrial pressure-stroke volume relationship and (B) the aortic systolic pressure-stroke volume relationship. An increase in contractility shifts these relationships up (*arrows*), while decrease in contractility shifts these relationships in the opposite direction.

Figure 2.

Pressure-volume loops in series (A) under varying aortic systolic pressures. The slope of the relationship between end-systolic points (*red dots*) defines ventricular elastance (E_{es}), while end-systolic pressure/stroke volume (SV) defines arterial elastance (E_a). Pressure-volume loops (B) before (*solid blue*) and after (*dashed red*) an acute increase in contractility resulting in increased ventricular elastance (E_{es}').