EDITORIAL COMMENT

Chasing the Elusive Pressure–Volume Relationships*

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Quantification of ventricular pump function is fundamental to the practice of cardiology and is required for research into most aspects of cardiac physiology, disease, and therapeutics. Drawing an analogy between the heart and a steam engine, Otto Frank (1) introduced the pressure–volume diagram as a means of characterizing left ventricular properties in the 1890s. Nearly 80 years later, Suga (2) formalized the idea that the relationship between pressure and volume at end systole was relatively independent of loading conditions and that the slope of the curve, called E_{max} or E_{es}, was a sensitive measure of contractility. At nearly the same time,

several investigators demonstrated how the relationship between pressure and volume at end diastole similarly provided the framework for quantifying passive properties of the myocardium (3,4). In the decades to follow, there was intensive research into the characteristics of the end-systolic pressure–volume relation (ESPVR) and end-diastolic pressure–volume relation (EDPVR) and these became the gold standards for quantifying pump function in animal research (5). Despite recognition of the major theoretical advantages of this approach (6), adoption into clinical research was limited, and this approach has not been incorporated into clinical practice.

The major obstacles that have limited more widespread use of the pressure–volume approach include: 1) the need for invasive, high-fidelity pressure monitoring; 2) the need for an accurate means of continuous monitoring of absolute ventricular

volumes; and 3) the need to vary loading conditions, typically by either vena caval occlusion or the use of vasoactive drugs to increase or decrease arterial resistance to obtain pressure and volume over broad ranges of values. It was initially believed that introduction of the conductance catheter for continuous volume measurement (7) would provide the previously missing tool for adoption of pressure–volume analyses into the clinic. However, the other factors remain dominant to this day, especially the invasiveness of the measurements. As a result, despite major theoretic disadvantages, noninvasively measured ejection fraction remains the measures of choice for quantifying systolic properties and a host of Doppler echocardiographic-derived measures of diastolic flow patterns and wall motion are the choice for quantifying diastolic properties. Nevertheless, many investigators remain intent on devising strategies for measuring these elusive pressure–volume relations in ways that are practical for clinical research and for clinical practice. I believe that it is worth the effort, and interesting advances have been made.

For example, the concept of estimating the entire ESPVR (8,9) and entire EDPVR (10,11) from measurements of pressure–volume data from a single steady-state beat have been introduced, validated, and used in some studies. Such approaches are designed to obviate the need to alter the loading conditions on the heart. In some cases, these approaches have been used with data obtained from completely noninvasive measures (12–14). In such case, ventricular volumes have been measured with 2- or 3-dimensional echocardiography (there is no reason why cardiac magnetic resonance [CMR] techniques could not be used for this), estimates of systolic pressure obtained by standard blood pressure cuff and left atrial pressures estimated by Doppler echocardiography of mitral inflow patterns as a surrogate for left ventricular end-diastolic

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pressure. Though the noninvasive nature of this approach is very appealing, there is always a question of accuracy, especially when it comes to the accuracy of the end-diastolic pressure estimates.

In this issue of *iJACC*, Schmitt et al. (15) describe and validate a CMR catheterization based method for estimating the EDPVR and the ESPVR. Very appealing is that the technique can simultaneously be applied to the right and left ventricles. The technique employs invasively measured ventricular pressures and an inferior caval balloon inflation to vary load. Absolute ventricular volumes are measured throughout the cardiac cycle using multislice-multiphase cine magnetic resonance images of steady-state beats. From these data, the ESPVR can be estimated from a previously validated single beat method (9). Then, a vena caval occlusion is performed, and the time course of ejection is determined on a beat-by-beat basis using real-time velocity-encoded cine CMR. Integration of the ejection flow values yields continuous, absolute changes in volume for each beat relative to the as-yet-to-be-defined end-diastolic volume. Thus, for each beat, a pressure–volume loop is obtained (minus the diastolic filling portion), but the starting volume for each beat is unknown. In a post-processing final step, however, each of the loops measured during the vena caval occlusion is shifted so that its end-systolic pressure–volume point falls on the ESPVR established from the steady-state beat and single-beat method. After all beats are appropriately placed, the end-diastolic volumes are defined, and so too is the EDPVR. The pressure–volume relations are shown to behave appropriately in the face of inotropic stimulation.

The major advantages of this approach include: 1) that it takes advantage of the high accuracy of CMR-determined continuous volumes and flows; 2) it readily allows simultaneous assessment of both right and left ventricles; and 3) that it uses invasively measured pressures, taking away uncertainty about the accuracy of end-diastolic and -systolic pressures. The last point also represents one of the potential limitations, which, as with the traditional approach, makes the technique invasive. Other limitations include: 1) that a catheter is required for vena caval occlusion; 2) it assumes that there is no mitral or tricuspid regurgitation (which is very frequently present, especially in heart failure); 3) it cannot be performed in patients with contraindication for CMR; and 4) there is also the need to transfer the patient from the cardiac catheterization laboratory to the CMR suite with pressure and

caval occluding catheters in place, which could pose logistical issues at some institutions. Thus, compared with the traditional approach, the important differences are: 1) substitution of CMR-based estimates of volume for conductance catheter-based measurements; 2) estimation of the ESPVR using single beat methods instead of direct measurements during caval occlusion; and 3) ease of obtaining biventricular data. Since CMR machines are more readily available than conductance catheter equipment, it is possible that the current approach could facilitate estimation of pressure–volume loops in centers interested in their measurement that have heretofore shied away. The merits of this approach are clear, and it will be very interesting to see how many studies emerge using this technique. The authors are to be congratulated for arriving at this interesting and creative approach.

There are a few further technical comments concerning the interpretation of parameters derived from pressure–volume analysis. In most studies, the ESPVR is assumed to be linear, and thus described by a slope (E_{es}) and intercept value; the volume-axis intercept, V_o, is used for this throughout the literature. Since, in reality, the ESPVR is not generally linear over the entire range of pressures and volumes, it is important to report and account for changes in *both* E_{es} and V_o values, especially when describing differences in the ESPVR between groups of patients or when describing changes in the ESPVR in response to an intervention. At the extreme, an intervention for which E_{es} does not change and V_o is shifted to lower values signifies an increase in contractility, just as an intervention during which E_{es} increases and there is no change in V_o. Similarly, when considering the EDPVR, it is important to report and account for changes in all parameters of the equation used. So, for example, while Schmitt et al. (15) reported that the values of β were decreased during dobutamine infusion in pigs (although not humans) and there is a temptation to conclude that dobutamine increases compliance, it would be incorrect to make such a conclusion without also reporting and considering the impact on "A," the other parameter in the equation used ($EDP = Ae^{\beta \cdot EDV}$). As seen in Figure 7 of the accompanying report (15) showing typical examples, the EDPVR is hardly changed by dobutamine (<0.5 mm Hg shifts, which could easily be accounted for by minor differences in volume estimations) even though the values of β decreased by ~30%. Furthermore, for both ESPVR and EDPVR, it is most appropriate to use an analysis of

covariance, which accounts for changes in all parameters of the relevant equation, rather than a simple paired t test on individual parameters. The interested reader is referred to a relatively recent review article on this topic, which goes into greater detail (6).

In summary, Schmitt et al. (15) describe a very interesting approach to assess EDPVR and ESPVR of both ventricles. The advantage is that the equipment used is now standard in all hospitals. Although the requirements for invasive pressure monitoring and vena caval occlusions will likely continue to limit widespread adoption, this appears to be a viable approach, especially for animal and clinical research. Particularly appealing is that measurements can be made for both ventricles, which has been completely lacking in the literatures. Many longstanding questions whose answers may rely on understanding of the relative impairment of right versus left ventricular systolic and diastolic properties could potentially be addressed.

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