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NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

Pressure Volume System for Management of Heart Failure and Valvular Heart Disease

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Abstract

Purpose of Review To introduce the reader to the basics of pressure-volume (PV) analysis, its current role in management of heart failure and valvular disease, and the possibilities for future use.

Recent Findings The recent introduction of FDA-approved miniaturized conductance catheters that can produce PV loops in the clinical setting has set the stage for the translation of this important research technique into clinical practice. The use of these catheters has shed important insights into the pathophysiology of many common conditions associated with heart failure including heart failure with preserved ejection fraction and right heart failure and has been utilized to assist in optimization of lead placement during cardiac resynchronization therapy.

Summary The use of PV loops has enhanced our understanding and diagnosis of common conditions associated with heart failure. In addition, it has shown promise as an adjunct to therapeutic procedures. Future directions may include the use of PV loops in the management of patients with heart failure requiring mechanical circulatory support and to help predict the utility of percutaneous valvular interventions.

Keywords Pressure volume loops · Cardiac hemodynamics · Heart failure · Valvular heart disease

Introduction

Hemodynamic assessment of the cardiovascular system is fundamental to the discipline of cardiovascular medicine and surgery. In hemodynamic research, pressure-volume loops have long been understood to provide a much more complete understanding of cardiac performance due to the range of cardiac indices that can be measured beat-to-beat, the ability to measure pressure and volume simultaneously with great fidelity, and the characterization of cardiac performance relative to vascular function.

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However, in clinical practice, hemodynamic assessment has been limited to either pressure or volume measurements in the time domain, e.g., systolic or diastolic filling pressures in the cath lab or systolic or diastolic volumes in the echo lab. Rarely are the two measurements combined in real time. Moreover, cardiac performance is generally assessed with only crude simultaneous measures of vascular function, e.g., blood pressure. The recent introduction of FDA-approved miniaturized conductance catheters that can produce pressure-volume (PV) loops in the clinical setting without the need for extraordinary technical support has set the stage for the translation of this important research technique into clinical practice. This technologic advance has great promise to provide unique diagnostic insights and guide nuanced therapeutic decision-making in patients with complex cardiovascular disease.

PV Loops

The fundamentals of PV loop analysis require the beat-to-beat instantaneous high-fidelity measurement of pressure and volume. There are several excellent resources for the reader that review the theory, principles, and practices [1•, 2]. Table 1 lists

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Table 1 A partial list of hemodynamic parameters available from PV loop analysis

	Parameters from PV loops
Ventricular output	Cardiac output (L/min)
	Cardiac index (L/min/m^2)
	Ejection fraction (%)
	Stroke volume (mL/beat)
	Heart rate (beats/min)
Pressures	End-systolic pressure (mmHg)
	End-diastolic pressure (mmHg)
Volumes	End-systolic volume (mL)
	End-diastolic volume (mL)
Preload and afterload	End-systolic wall stress (mmHg); ESWS = ESP*(1 + 3*ESV)/Vwall; Vwall = ventricular wall volume
	End-diastolic wall stress (mmHg); EDWS = EDP*(1 + 3*EDV)/Vwall; Vwall = ventricular wall volume
Contractility (load independent)	Starling contractile index (mmHg/mL*s)
	Starling contractile index (slope)*
	ESPVR (mmHg/mL); one point measurement
	ESPVR (slope)*
	ESPVR (R^2 correlation coefficient for the straight line fit for ESPVR)*
	Preload recruitable stroke work (mmHg)
	Preload recruitable stroke work (slope)*
	Preload recruitable stroke work (R^2 correlation coefficient for the straight line fit for PRSW)*
Contractility (load dependent)	Maximum dP/dt (mmHg/s)
Diastolic function (load independent)	Tau (ms)
	EDPVR (mmHg/mL); one point measurement
	EDPVR/end-systolic elastance (slope)*
	EDPVR (R^2 correlation coefficient for the straight line fit for ESPVR)*
Diastolic function (load dependent)	Minimum dP/dt (− mmHg/s)
Myocardial Energetics	Stroke work (mL × mmHg)
	Pressure volume area (mL × mmHg)
	Elastic potential energy (mL × mmHg)
	Cardiac work ((mL × mmHg)/min)

*Requires loading condition changes for measurement

many of the hemodynamic parameters that can be measured or calculated from PV loops. Figure 1 a shows the basic single-beat PV loop. If there is no change in loading conditions, time interval between beats, or contractility, the cycle, or loop, will be repeated and the measurements should be nearly identical. The width of the loop is the stroke volume; the area of the loop represents the stroke work performed by the ventricle.

Changing either preload or afterload will produce a family of loops (Fig. 1b), which define two intrinsic properties of the heart, contractility, and ventricular compliance. Contractility is defined by the slope of the end-systolic pressure-volume relationship (ESPVR) (which is derived from a line that connects the end-systolic pressure points of family of loops) and the X intercept of that line, V_0. The slope of ESPVR is also termed end-systolic elastance (Ees). Changes in contractility will be reflected in the slope of the ESPVR: rightward and flatter for decreased contractility (green in Fig. 1b) and leftward and steeper for increased contractility (red in Fig. 1b).

Ventricular compliance is described by the curvilinear shape of the end-diastolic pressure-volume relationship (EDPVR) created by a series of end-diastolic volume points of the family of loops. Changes in compliance are represented by shifts in the EDPVR relationship; stiffer, less compliant ventricles produce an EDPVR that is shifted up and to the left; a more compliant ventricle shifts this curve down and to the right.

In a PV loop, the impedance or pulsatile afterload, also known as end-arterial elastance, Ea, is best characterized by the slope of the line that connects the end-diastolic volume on the X intercept with the end-systolic pressure (Fig. 1c). Ea is

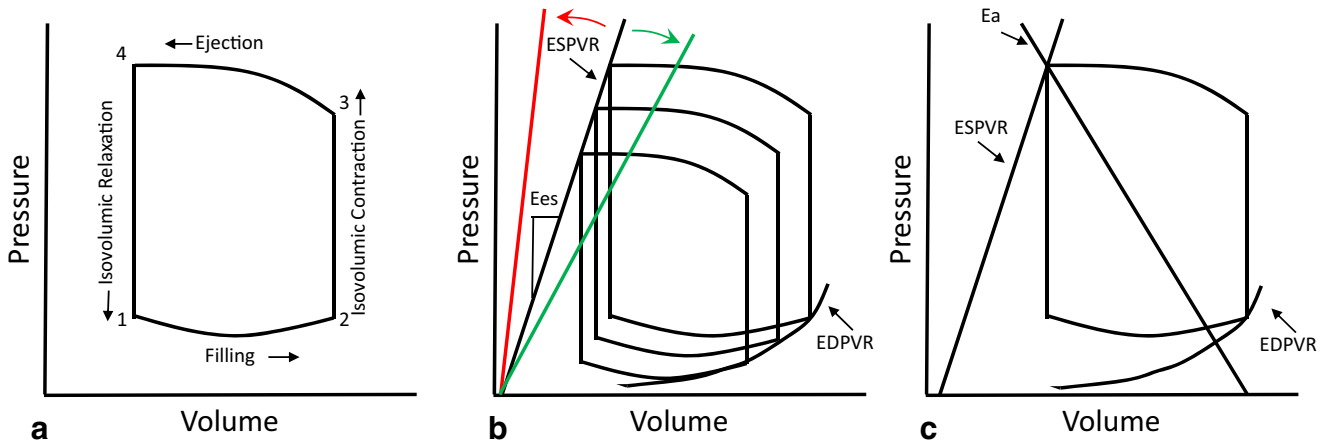

Fig. 1 **a** Shows the single PV loop. At the point where atrial pressure exceeds ventricular pressure (point 1), filling of the ventricle occurs. From end diastole (point 2), there is isovolumic contraction (assuming no valvular regurgitation). At the point where ventricular pressure exceeds aortic pressure (point 3), the aortic valve opens and ejection occurs. At end systole (point 4), the ventricle undergoes isovolumic relaxation (assuming no valvular regurgitation). **b** Shows a family of loops derived from changes in loading conditions. Contractility can be derived by the slope of the ESPVR, also termed end-systolic elastance (Ees). Changes in contractility are reflected by changes in the slope of the ESPVR (green line represents decreased contractility and the red line increased contractility). The ventricular compliance is reflected by the EDPVR. **c** Illustrates the calculation of end-arterial elastance (Ea), a measure of pulsatile afterload

determined by heart rate and vascular compliance. The ratio of the Ees to Ea characterizes the "coupling" or matching of ventricular performance to vascular impedance and is normally close to 1. The measurement of coupling represents a mathematical way to describe systemic cardiovascular efficiency. In a patient with heart failure, Ees will typically fall and Ea will typically rise resulting in a Ea/Ees of > 1.0, an uncoupled relationship. Vasodilator therapy, as an example, can decrease Ea and return this relationship to a more favorable state. Therefore, for any given ventricle with a specific intrinsic contractility (Ees) and passive compliance (EDPVR) contracting against a given impedance (Ea), the resulting beat-to-beat stroke volume is represented by the width of the loop, which must lie between the two boundaries of the Ea and the EDPVR. Thus, the PV loop analysis can provide information on the resulting stroke volume and stroke work to variable loads. The degree of VA uncoupling or "mismatching" can also be quantified, which can have prognostic implications in HFrEF [3].

The measurement of instantaneous pressure can be readily accomplished by either fluid-filled catheters or high-fidelity electronic transducers at the tip of invasive catheters. The most practical method for measuring simultaneous ventricular volumes is the use of electrical conductance using the same catheter. In brief, conductance methodology relies on the measurement of electrical conductance of blood contained in the cavity being studied. Conductance catheters contain multiple electrodes to generate an intra-cavitary electric field and to receive the resulting voltage gradients as a measure of instantaneous volume.

The behavior of the ventricle to changes in preload (or end-diastolic volume) is quantified by varying the venous return by inflating a balloon in the IVC to diminish venous return; alternatively, leg raises or external hepatic pressure can be used to influence the venous return. Afterload can be manipulated by interventions such as hand grip, valsalva, or nitroprusside. Methods for single-beat estimation of end-systolic elastance have been developed that can theoretically avoid the need for these maneuvers [4]. Several imaging techniques (i.e., MRI and echocardiography) can reliably measure volume changes throughout the cardiac cycle but require simultaneous invasive high-fidelity pressure measurements to create such loops, which are generally impractical in the clinical setting.

Current Use

Heart Failure with Preserved Ejection Fraction

Approximately 50% of patients with heart failure have heart failure with preserved ejection fraction (HFpEF). According to the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, the ejection fraction should be > 50% and there should be signs and symptoms of HF. Other specific echocardiographic features (e.g., left ventricular hypertrophy, diastolic dysfunction, and left atrial enlargement) are supportive of the diagnosis, but are neither sufficient nor necessary; biomarkers are similarly useful but not required. Therefore, the diagnosis can be difficult to establish and often becomes a diagnosis of exclusion. Clinical criteria can be useful; for example, the H2FPEF score can help clinicians pursue more invasive diagnostic strategies if the probability of the diagnosis is sufficient [5].

Increasingly, it is accepted that HFpEF is a heterogeneous syndrome of exertional intolerance with multiple putative mechanisms. This observation is also true hemodynamically

and PV loop characterization may better define the specific type of HFpEF present. Although a number of investigators have been able to demonstrate decreases in ventricular compliance with PV loops [6, 7], which were previously thought to be critical to the diagnosis and pathophysiology of HFpEF, other investigators have not found a uniform hemodynamic picture. For example, Mauer and his colleagues have shown a variety of PV loop characterizations of HFpEF [8]. In their series, the "purest" form of diastolic dysfunction and decreased ventricular compliance was seen with restrictive cardiomyopathies. In states associated with hypertension, changes in EDPVR were coincident with either increases in Ees or an overfilled, overdistended ventricle. An overfilled ventricular and vascular system is consistent with recent observations that the HFpEF of obesity is a high-output state where increased metabolic needs and inappropriate vasoplegia lead to salt and water avidity [9].

Detailed hemodynamic assessment using PV loops may also exclude the diagnosis of HFpEF or uncover atypical expressions of the disease. Penicka et al. examined 30 patients with unexplained dyspnea with both standard non-invasive studies and invasive hemodynamic studies utilizing PV loops [10]. They found that only 25% of patients with PV loop-established HFpEF had non-invasive measures that would qualify as a diagnosis utilizing ESC HFpEF diagnostic guidelines.

Ultimately, more detailed hemodynamic characterization using PV loops may allow more specific targeted therapies to address the specific hemodynamic profile of a given HFpEF patient.

Right Heart Failure

Right ventricular dysfunction is common in clinical practice and frequently accompanies conditions such as pulmonary hypertension, acute MI, and non-ischemic cardiomyopathy. In advanced heart failure, a thorough hemodynamic understanding of RV function and VA coupling is critical to mechanical circulatory support and heart transplant planning in order to avoid the high morbidity and mortality of postoperative RV failure. To date, hemodynamic assessment of RV function in clinical practice has been limited to pressure assessment in the time domain; load-independent assessment of RV performance has not been possible. For example, RA/PCWP ratio, pulmonary artery pulsatility index (PAPi) ($[PA_{sys}-PA_{dia}]$)/RA), and RV stroke work have been used to quantify the severity of RV dysfunction or describe static RV-PA coupling. In most instances, these measures have been limited by the inability to take volume over time into account. Moreover, the load dependency of these measurements limits the ability to characterize intrinsic RV contractility, which is critical to predicting the RV's performance in a high-impedance environment.

The crescentic shape of the RV makes determinations of volume and contractility challenging using traditional imaging techniques, making conductance catheters perhaps better suited to quantify RV volumes in real time. However, there are important differences between the assessment of RV and LV PV loops [11, 12]. For example, estimation of the RV Ees is challenging in a RV PV loop due to the trapezoidal shape. This issue becomes critical since an important advantage of the PV loop to RV assessment is the measurement of Ees or intrinsic load-independent contractility.

RV-PA coupling is also quantifiable using PV loops and can help distinguish intrinsic RV dysfunction from impedance mismatching. McCabe et al. investigated the utility of this method in patients with chronic thromboembolic arterial disease and PAH (CTEPH), chronic thromboembolic disease without PAH (CTED), and controls. They found clear evidence of reduced efficiency of coupling between the RV and PA in the CTEPH group compared with those in the CTED and control groups [13]. Perhaps more importantly, the technique has been utilized by others to identify occult dysfunction in patients with CTED possibly identifying a group in whom earlier therapy may be beneficial [14]. Tello and colleagues recently extended these observations to quantify the reserve in RV-PA coupling in chronic RV overload using PV loop and CMR data in PH and CTEPH patients in the Right Heart I and Giessen PH Registry. These investigators found that a fall in the Ees/Ea from a normal range of 1.5–2.0 to < 0.8 was associated with RV dysfunction (e.g., RVEF < 35%), enlargement, and diastolic stiffness as well as a decrease in PA compliance. They also suggested that Ees/Ea could be estimated from SV/ESV, which could be used clinically to predict RV failure [15].

Cardiac Resynchronization Therapy

Approximately one-third of patients with HFrEF and left bundle branch block are non-responders to cardiac resynchronization therapy (CRT) [16]; in some cases, this lack of benefit is due to inexact lead placement. In such a setting, PV loops could be used to optimize CRT at the time of implantation. Delnoy et al. studied 29 patients with chronic RV pacing being upgraded to biventricular pacing [17]. They positioned the LV leads in a variety of positions to optimize stroke volume and work, ejection fraction, and contractility. In 45% of patients, the initial lead position was changed to optimize performance as measured by the PV loop variables. Importantly, these acute hemodynamic improvements have been shown to be a robust indicator of sustained improvement [18]. The benefits of new technologic advancement in CRT have also been assessed using PV loops. For example, Dutch investigators demonstrated that multipoint pacing using quadripolar LV leads is associated with heterogeneous changes in stroke work and the changes are independently

associated with male gender and lower LV ejection fractions (e.g., LVEF ≤ 26%) [19•].

Mitral Valve Repair

MitraClip is a novel percutaneous method of mitral valvular repair based on the surgical technique of the Alfieri stitch in which the anterior and posterior leaflets of the mitral valve are tethered together creating two orifices. This technique is playing an increasingly important role in therapy for patients with degenerative MV disease who are not good surgical candidates. With the recent publication of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial [20], this technique is poised to become equally important for the large cohort of patients with functional mitral regurgitation (FMR). Gaemperli et al. [21••] recently utilized invasive PV loops to investigate the immediate hemodynamic changes occurring with implantation and to look at the effects on clinical outcomes at ~ 6 months. There has long been a concern in patients with decreased contractility and poor EF, that abrupt increase in afterload could lead to acute hemodynamic worsening in patients with MR. However, these investigators unexpectedly found favorable hemodynamic effects of the device with reduction of the pulmonary capillary wedge pressure, increased cardiac output, and spared contractility despite acute drops in ejection fraction. Increases in afterload and a fall in preload did not predict a fall in cardiac output. Taken together, these findings suggest that acute hemodynamic worsening does not occur and the overall effect of clipping is in fact beneficial to the overall hemodynamic picture.

Recent trials of the MitraClip device in the treatment of severe FMR associated with heart failure and reduced EF have yielded opposing results. In the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation) trial, use of the clip was not associated with reduced mortality or improved rates of hospitalization for heart failure [22]. Conversely, in the COAPT trial, MV repair decreased all-cause mortality as well as the combined risk of death or hospitalization for heart failure [20]. Packer and Grayburn have postulated that the difference lies in the two distinct populations studied in these trials [23]. They suggest that patients can be divided into two groups based on the amount of MR present in relation to the extent of LV remodeling. Those patients with so-called proportionate MR could be distinguished by having severity of MR as measured by effective regurgitant orifice area (EROA) consistent with their degree of LV dilation (LVEDV) as predicted by the Gorlin hydraulic formula. On the other hand, those patients with so-called disproportionate MR had a higher severity of MR than would be predicted by their LVEDV. It is the latter group that was represented in the COAPT trial and in whom the salutary effect of clipping was found. Given the inherent technical challenges with measurement of mitral regurgitant severity and volume by non-invasive methods, PV loop measurement may be an ideal method to more accurately assess these parameters in conjunction with standard PA catheter measurements of cardiac output. In addition, these two groups (proportionate vs disproportionate MR) may have distinct signatures of intrinsic load-independent contractility and VA coupling that could be evaluated with invasive PV loops.

Future Directions

Heart Failure

The use of invasive hemodynamic information to guide therapy of patients with severe heart failure has been a topic of considerable interest and controversy. The seminal ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial found that the addition of pulmonary artery catheter measurements in addition to careful clinical assessment did not improve outcomes in patients with severe heart failure and actually led to an increase in adverse events [24]. However, hemodynamic data from these patients did demonstrate a strong correlation between final PCWP measurements and the composite measure of cardiac hospitalization, death, or transplant [25].

Importantly, technologies that provide implantable hemodynamic monitoring do appear to have some clinical utility. In the randomized CHAMPION trial [26], the CARDIOMEMS device decreased heart failure hospitalizations by providing actionable hemodynamic data to the care team. Is it possible that the additional measurements available from PV loop analysis including intrinsic cardiac contractility, and measures of VA coupling could provide information that would allow more effective titration of therapy and show long-term benefit. Ky and her colleagues demonstrated that VA coupling and EDV, but not Ees, predicted outcomes in chronic HF patients; those patients who had a mismatch of contractility (Ees) to afterload (Ea) despite HF medications fared worse over time [3]. In the acute setting, assessing intrinsic myocardial contractility and VA coupling may allow for a more tailored approach to the use of vasoactive and inotropic agents in combination with temporary devices that provide mechanical circulatory support.

Heart Failure Recovery

Durable mechanical circulatory support devices, e.g., left ventricular assist devices (LVAD), are used commonly to bridge patients with advanced heart failure to cardiac transplantation; because they meaningfully extend overall survival, they can also be used as definitive therapy for end-stage heart disease,

e.g., destination therapy. It has also been recognized that a subset of patients supported with LVADs will spontaneously recover myocardial function as assessed by an improvement in LVEF; in selected patients, this recovery of LV function even allows explantation of the devices. However, LVEF integrates a number of variables, including intrinsic myocardial contractility, LV remodeling, and VA coupling; understanding the improvement in EF in these terms is fundamental to the prediction of sustainable LV recovery and successful device removal. In most programs, myocardial recovery is assessed by varying pump speeds and examining the consequences on various load-dependent variables, such as EF, cavity size, PCWP, CO, maximal oxygen consumption, and exercise capacity [27]. However, none of these parameters measure direct LV contractility or the impact of VA coupling. One can envision PV loops being used to evaluate contractility during a controlled turn down of the VAD allowing for a family of loops to be developed that would reflect actual contractility and the performance of the ventricle in relation to current loading conditions.

Aortic Stenosis

Outcomes after AVR for severe AS are recognized to vary depending on a number of clinical factors. Echocardiographic studies have demonstrated that low EF and poor flow as measured by stroke volume index are two of the most predictive of poor outcome [28]. Low flow, low gradient (LFLG) aortic stenosis in the setting of low EF is often misunderstood and remains a challenging entity in terms of prognosis and therapeutic decisions. LFLG AS associated with normal ejection fraction has been more difficult to recognize due to the low gradients associated with small stroke volumes inherent to small ventricles. While SAVR has been shown to be superior to medical therapy in these patients, the outcomes are worse than for patients with normal flow and high gradient [29]. Regardless of EF, low-flow states in the setting of AS have been identified as having a restrictive physiology with more mid-cavitary interstitial fibrosis as measured by both histopathology and MRI late enhancement [30]. PV loops offer the opportunity to look at immediate improvements in ventricular function after TAVI and to assess impedance mismatches that will remain after relief of aortic valve obstruction. The measurement of intrinsic load-independent contractility, VA uncoupling, and poor LV compliance may identify patients who are not likely to gain substantial benefit from the procedure.

Conclusion

Long recognized as the gold standard for defining ventricular hemodynamics, recent advances in technology hold the promise for evaluation of load-independent and load-dependent variables in a variety of human cardiac diseases in routine clinical practice. Much as the pulmonary artery catheter revolutionized the understanding and management of heart failure in its varied forms, PV loop analysis stands poised to further refine and expand our understanding and therapy of these complex conditions.

Compliance with Ethical Standards

Conflict of Interest Frederick G.P. Welt reports being on the Advisory Board of Medtronic Inc.

James C. Fang reports other from Novartis (EVALUATE trial steering committee), Amgen (GALACTIC trial steering committee), AstraZeneca (DELIVER trial national leader), and Johnson & Johnson (SOPRANO trial DSMB chair).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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