Left ventricular ejection fraction (EF) depends on ventricular contractility, afterload, and preload. Preload is related to end-diastolic volume (EDV) and pressure; the relationship between these 2 parameters (the end-diastolic pressure-volume relationship, EDPVR) indexes the degree of ventricular remodeling. Although EF is known to correlate with mortality in the subset of heart failure patients with reduced EF, it is previously unknown which of its determining factors contribute most importantly to prognosis. In this issue of the Journal, Ky et al. (1) set out to address this fundamental question using pressure-volume (PV) analysis, the most powerful approach for addressing such a problem.

They conclude that the extent of ventricular remodeling (indexed by a number of different parameters) and the degree of ventricular-arterial mismatching indexed by the ratio of end-systolic elastance (Ees, an index of ventricular contractility [2,3]), to effective arterial elastance (Ea, an index of afterload [4]), are the most important determinants of prognosis. They also showed that Ees by itself was not prognostic, the implication being that ventricular chamber contractility is not a determinant of prognosis. The methods, findings, and interpretations described in this study deserve further consideration.

The utility of PV loops and PV relationships to characterize and quantify the mechanical properties of the left ventricle was demonstrated by Otto Frank in 1895 (5). After significant research in the early part of the 20th century culminating in the development of the time-varying elastance theory of ventricular contraction by Suga (6,7) and Ees as a load-independent index of contractility by Suga and Sagawa (2) and Suga et al. (3), basic and clinical physiologists considered PV analysis to be the gold standard for assessing ventricular properties by the early 1980s (8). Yet, this approach has yet to become the gold standard in clinical practice or in clinical research. This is mainly because the invasive techniques generally required for measurement of pressure and volume render them impractical on a routine basis. However, with recent technological and conceptual advances that allow noninvasive estimation of these relationships (9–11), this situation is changing. Originally validated (9–11) and used (12–14) in studies involving small numbers of patients, reports have started appearing in which these noninvasive approaches are being used in relatively large numbers of patients (15,16).

Ky et al. (1) report results from 466 patients using noninvasive PV analysis. One major advantage of the PV approach is revealed when the average results of this study are presented graphically and preload, contractility and remodeling can be viewed so that the physiological meaning of changes in these parameters can be readily and simultaneously appreciated. Using the data from Table 2 of Ky et al. (1) (with a few reasonable assumptions), it is possible to plot average estimated PV loops and estimated end-systolic pressure-volume relationships (ESPVRs). Results for patients with New York Heart Association (NYHA) functional class I symptoms are shown in Figure 1A. In patients with progressively worse clinical heart failure (NYHA functional class II [Fig. 1B]; NYHA functional class III, [Fig. 1C]; NYHA functional class IV [Fig. 1D]), the loops shift progressively to the right toward larger volumes; a sign of progressive remodeling.

Concomitantly, the width of the loop decreases (i.e., decreased stroke volume) and the height of the loop decreases (i.e., decreased pressure generation). There is a relatively subtle increase in afterload as indexed by the Ea, the index of afterload (4). Regarding the estimated ESPVR, the main change is a progressive rightward shift toward larger volumes (again, a manifestation of progressive remodeling) with a statistically nonsignificant decrease in the slope, estimated by the “single beat method” (Eesab) (9). To the best of my knowledge, this is the first time that these fundamental relationships between symptom severity and all aspects of progressive remodeling and ventricular-arterial mismatching has been demonstrated so clearly.

In general, a thorough assessment of remodeling should involve estimation of the end-diastolic pressure-volume relationship (EDPVR). This is also possible noninvasively if an estimate of ventricular end-diastolic pressure is available (10,11) (not available in the present study). Evaluation of the EDPVR is required to ensure that shifts of the EDV are not simply related to changes in filling pressure, but reflect true changes in heart structure. Nevertheless, with changes in volumes as large as those reported by Ky et al. (1), it is assured that the results reflect progressive remodeling, especially in the NYHA functional class III and IV patients.
The progressively reduced EF (i.e., the ratio of stroke volume [SV] to EDV; EF = SV/EDV) seen by Ky et al. (1) with worsening NYHA functional class is readily appreciated from the graphs to be mainly due to the increase in EDV (remodeling) and, to a lesser extent, a reduction in SV. The reduction in SV, in turn, is mainly due to an increase in \( E_a \) (the major determinant of which is total peripheral resistance) with no significant change in \( E_{es,b} \).

Ky et al. (1) further show that in patients with reduced EF heart failure, the composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation is most strongly associated with the degree of ventricular remodeling, as indexed by any parameter related to the size of the heart, including EDV, volume at an end-systolic pressure of 100 mm Hg (\( V_{100} \)) and the volume axis intercept of the ESPVR (\( V_0 \)). Not surprisingly, because EF is mainly determined by EDV, outcomes also correlated very strongly with EF, as shown in previous studies. A totally new finding is that outcomes are also determined by abnormally high \( E_a \) and even more so by abnormal ventricular-vascular coupling indexed by the \( E_a/E_{es,b} \) ratio.

This is explained by the fact that as heart failure worsens, afterload (\( E_a \)) increases and the ESPVR slope (\( E_{es,b} \)) tends to decrease; taking the ratio of these 2 parameters therefore amplifies the impact of either alone.

Although \( E_{es} \), the slope of the presumed linear ESPVR, is considered to be the most reliable index of ventricular contractility, the implications of deviations from ideal behavior need to be considered (17). Specifically, when extreme changes in contractility and extreme degrees of remodeling are involved, as are present in the current study of patients with severe (NYHA functional classes III and IV) heart failure (Fig. 2), several factors must be considered when interpreting \( E_{es} \) as an index of contractility. First, with significant remodeling, true \( V_0 \) (the ESPVR volume axis intercept) may increase. Second, the ESPVR can become nonlinear (18,19). To evaluate for this, PV data must be obtained over a fairly wide range of pressures, which is not usually possible in patients. This is illustrated by data from ex vivo blood perfused, beating human hearts obtained at the time of transplantation (Fig. 2A) (19). The curvilinear nature of the ESPVR seen in the largest, most remodeled hearts is readily apparent; the slope of a straight line drawn through the data cannot, by itself, capture the changes in the relationship. In addition, the ESPVR can become nonlinear in normal hearts operating at significantly reduced or significantly increased levels of contractility (Fig. 2B) (18). Thus, although the ESPVR may be well approximated by a straight line over a limited working range of pressures and volumes, in such cases, extrapolation to the low pressure...
range is not likely to be accurate (Fig. 2C). Therefore, it must be recognized that when the ESPVR is assessed over a limited PV range or when a single beat method is used, the low pressure range of the extrapolated ESPVR may not reflect reality. Therefore, it is important to consider shifts of the extrapolated ESPVR in the assessment of changes in contractility, which requires that changes in the extrapolated \( V_0 \) be accounted for.

One approach for combining information about local \( E_{es} \) and extrapolated \( V_0 \) is to calculate the volume at a given pressure on the ESPVR (17). For example, Ky et al. (1) calculated end-systolic volume at an end-systolic pressure of 100 mm Hg (i.e., \( V_{100} = 100/E_{es} + V_0 \)); in this case \( V_{100} \) may be considered a contractility index surrogate (the larger the \( V_{100} \), the lower the contractility). Although this is imperfect, it does offer a practical solution to the problem.

The implication for interpretation of the results of Ky et al. is that, although \( E_{es,b} \) did not change significantly with progressive worsening of heart failure, reductions in chamber contractility are clearly illustrated by the rightward shifts of the ESPVR as captured by changes in \( V_{100} \). If this premise is accepted, it should therefore be concluded from the data (1) that ventricular chamber contractility is indeed a strong statistical determinant of prognosis in reduced EF heart failure.

It is also important to note that the current study used a single-beat approach to estimating \( E_{es} \). The more traditional approach requires measurement of pressures and volumes over a significant change in load, most typically achieved by preload reduction via inferior vena caval occlusion. However, that approach can only be used with invasive methods, which renders it impractical for large-scale clinical studies. Although the single-beat method has been validated (9) and has opened important opportunities for noninvasive application of PV analysis, potential inaccuracies may exist. It is also noteworthy that invasive techniques for measuring PV loops and relationships are becoming easier to perform and analyze as newer devices and software become available (many recent references have appeared; see as just one example [20]).

In summary, noninvasive PV analysis is feasible in large-scale studies, provides clinically meaningful results, and has the potential to provide more information than measures of volumes alone. PV analysis as used by Ky et al. (1) in a population of reduced EF heart failure shows the following new and important findings:

- With worsening degrees of heart failure symptoms, there are greater degrees of remodeling.
- The more remodeling that has occurred, the worse the prognosis.
- The greater the mismatch is between ventricular and vascular properties, the worse the prognosis.
- The data emphasize the point that \( E_{es} \) (or \( E_{es,b} \)) should be considered the slope of the ESPVR in the working PV range of the heart. Full assessment of changes in contractility requires accounting for changes in both \( E_{es} \) and extrapolated \( V_0 \), especially at

![Figure 2 Implications of Nonlinear ESPVR](image-url)
markedly reduced levels of contractility and in hearts that have undergone extreme degrees of remodeling.

- Accepting that V100 is an index of ventricular chamber contractility, the data also show that ventricular contractility is an important determinant of prognosis.

Although we tend to think of remodeling and changes in contractility as different aspects of ventricular properties, if one digs just a little deeper into the points listed above, one arrives at the understanding that, in practical terms, for patients with reduced EF heart failure, a remodeled heart is intrinsically a heart with reduced contractility. Remodeling and reduction in chamber contractility are intimately linked and, in the end, inseparable phenomena.

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