Supplemental Materials

Detailed Methods

ESPDR derived based on maximum myocardial stiffness

Mirsky et al. demonstrated that the maximal stress-strain ratio (i.e., myocardial stiffness) attained during end-systole is constant throughout the acute change in the preload and that the ESPVR derived from the myocardial stress-strain relationship is curvilinear and represents a more physiologic ESPVR than a linear ESPVR.[1] The average fiber stress (σ): $\sigma = (3/2) \times P \times V_m/V_w$, where P is the left ventricular pressure and V_m and V_w are the midwall volume and the wall volume, respectively. The midwall volume is defined as the logarithmic mean of the cavity volume (V_{in}) and the outer volume (V_{out}), $(V_{out}-V_{in}) / (\ln V_{out} - \ln V_{in})$.[2]

The average natural strain (ε): $\varepsilon = (1/3)\ln (V_m/V_{0m})$, where V_{0m} is the midwall volume at zero stress. We set the systolic zero-stress volume as a reference distension as described by Mirsky et al.[1] The average systolic myocardial stiffness (E_{av}): $E_{av} = \sigma/\varepsilon$. End-systole was defined as the latest time at which systolic myocardial stiffness attains its maximum value (max E_{av}). The end-systolic, stress-strain relations (σ_{es} vs. ε_{es}) based on the maximal stiffness concept is represented in the form:

$$\mathrm{Max}E_{\mathrm{av}} = \sigma_{\mathrm{es}}/\varepsilon_{\mathrm{es}} = (\frac{9}{2}) \times P_{\mathrm{es}} \times V_{\mathrm{mes}}/(V_{\mathrm{w}} \times \ln(\frac{V_{\mathrm{mes}}}{V_{0\mathrm{m}}})) \qquad \text{[equation A1]}$$

where P_{es} and V_{mes} are left ventricular pressure and midwall volume at end systole.

Rearranging equation A1,

$$P_{\mathrm{es}} = \left(\frac{2}{9}\right) \times \max E_{\mathrm{av}} \times \ln\left(\frac{V_{\mathrm{mes}}}{V_{0\mathrm{m}}}\right) \times V_{\mathrm{w}} / V_{\mathrm{mes}} \qquad \text{[equation A2]}$$

Transformation of the midwall volume into cavity dimension (D) was performed using geometric factors, α, β and γ, and midwall dimension (D_m), which is defined as the logarithmic mean of the cavity dimension (D) and the outer dimension (D_{out}), (D_{out}-D) /(ln D_{out}-ln D):[1]

$$V_{\mathrm{m}} = \alpha \times {D_{\mathrm{m}}}^{3} \qquad \text{[equation A3]}$$

$$D_{\mathrm{m}} = \beta \times D^{\gamma} \qquad \text{[equation A4]}$$

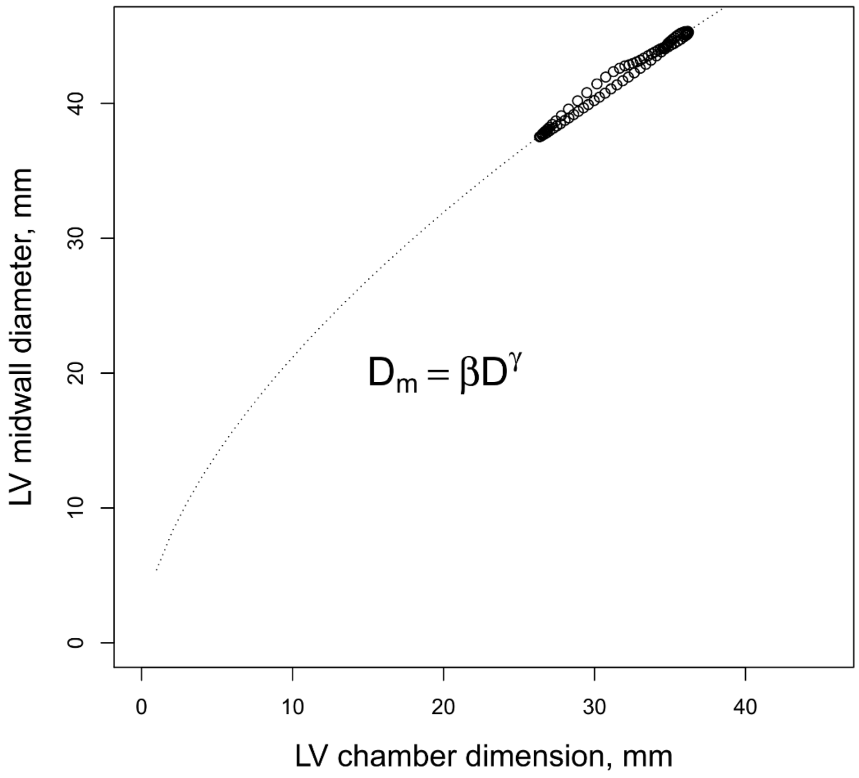
Note that the annotations are different from Mirsky's article.[2] Substituting equations A3 and A4 into equation A2 yields

$$P_{\mathrm{es}} = \left[\left(\frac{2}{3}\right) \times \max E_{\mathrm{av}} \times V_{\mathrm{w}} \times V_{0\mathrm{m}} \times \gamma\right] \times \ln\left(\frac{D_{\mathrm{es}}}{D_0}\right) / \left(\frac{D_{\mathrm{es}}}{D_0}\right)^{3\gamma} \qquad \text{[equation A5]}$$

Therefore, ESPDR can be expressed in a simple form:

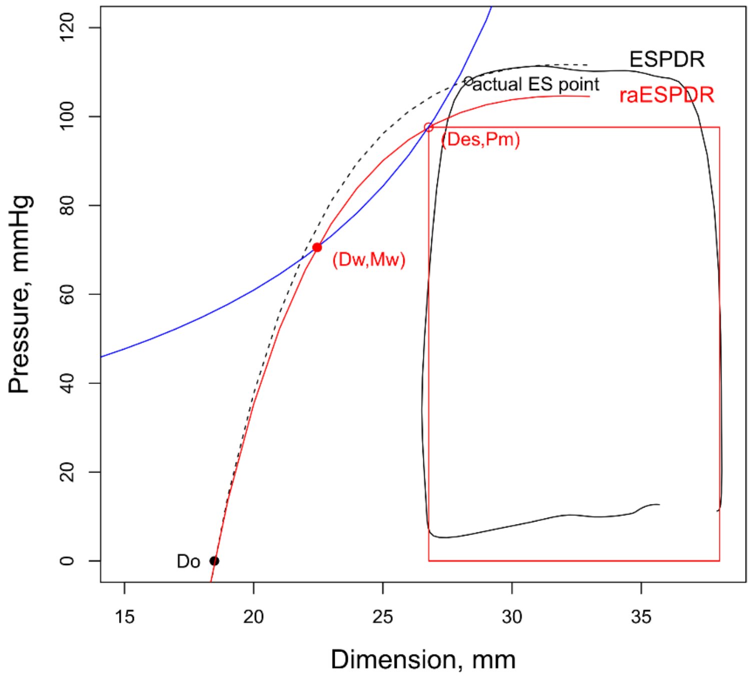
$$P_{\mathrm{es}}(D_{\mathrm{es}}) = \mathrm{A} \times \ln\left(\frac{D_{\mathrm{es}}}{D_0}\right) / \left(\frac{D_{\mathrm{es}}}{D_0}\right)^{3\gamma} \qquad \text{[equation A6]}$$

Supplemental Figures



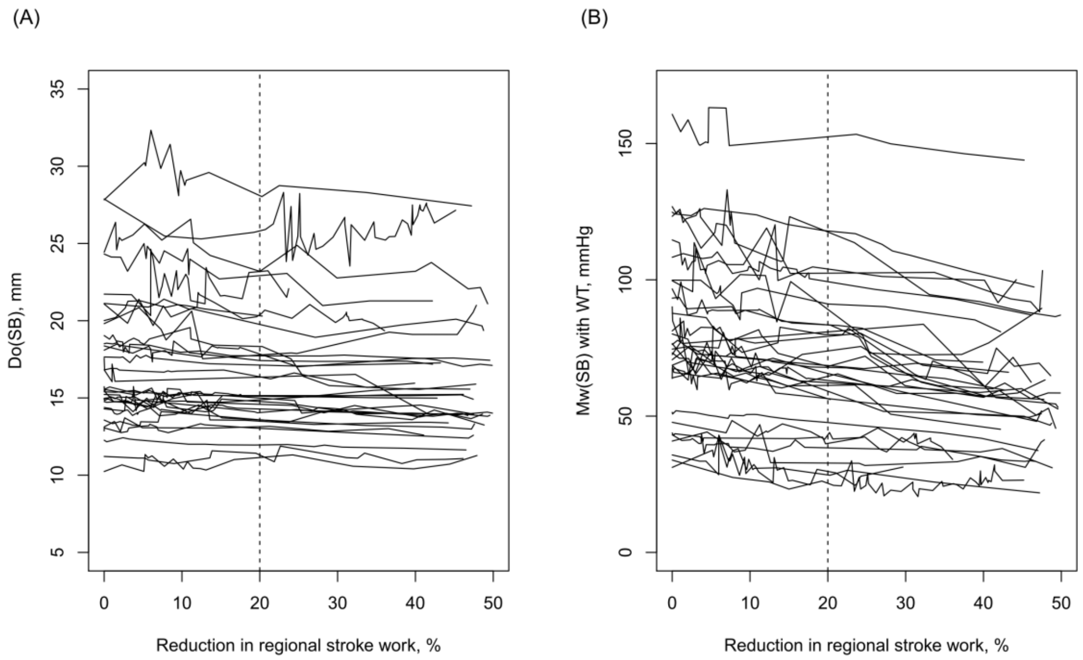
Supplementary Figure 1. Determination of the exponent of ESPDR, γ, from the wall thickness

The midwall dimension (D_m), defined as the logarithmic mean of the chamber's inner dimension (D) and outer dimension (D_{out}), is calculated as (D_{out}-D) /(ln D_{out}-ln D). The left ventricular (LV) inner dimension versus the midwall dimension during an entire cardiac cycle (before vena caval occlusion) is plotted as open black circles. The dotted curve is a regression of these plots to the equation, $D_{\mathrm{m}} = \beta \times D^{\gamma}$, which yields the exponent of the ESPDR, γ .



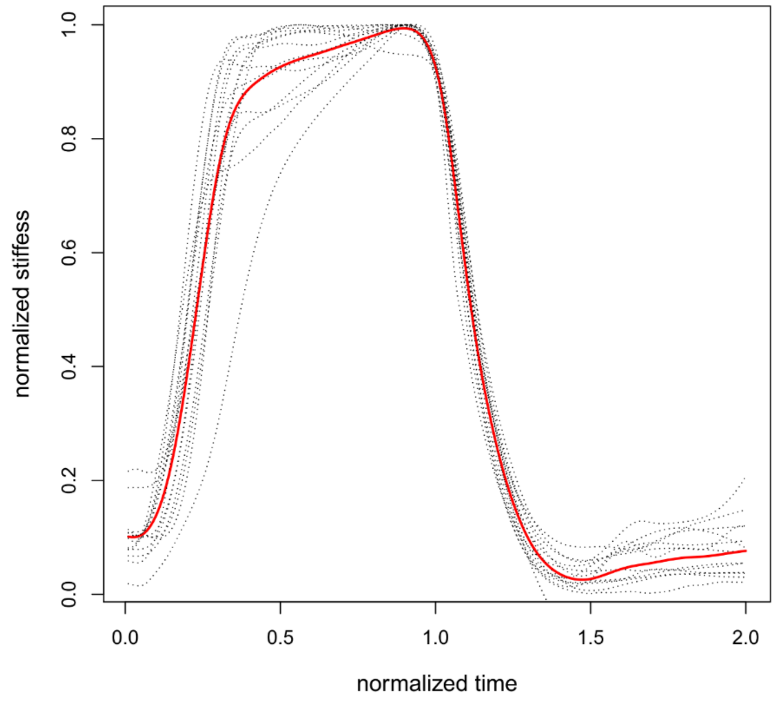
Supplementary Figure 2. The actual ESPDR and the rectangular-approximated ESPDR

An actual P-D loop (black loop) is approximated by a square with the same area with the stroke dimension (SD) in width and the mean ejection pressure (P_m=regional stroke work/SD) in height (red square). Note that the actual end-systolic (ES) point and the left-upper corner of the square (the point (end-systolic dimension (D_{es}), P_m)) are different. While the former follows the ESPDR (black dotted curve), the latter follows the rectangular-approximated ESPDR (raESPDR, red curve). The point (D_w, M_w) is on the raESPDR rather than the actual ESPDR as equation 6 in the main text is accurate for mean ejection pressure (i.e., $P_m(D_w)=M_w$). Once the zero-stress dimension (D_0) is obtained from the ESPDR (dotted curve), the raESPDR can be determined as a curve passing through points (D_o, 0) and (D_{es}, P_m).



Supplementary Figure 3. Preload sensitivity of the single-beat estimation method

The single-beat estimation method was applied to each pressure-dimension loop during inferior vena caval occlusion. The change in (A) the estimated zero-stress dimension ($D_{0(SB)}$) and (B) the estimated preload recruitable stroke work slope ($M_{w(SB)\ with\ WT}$) according to a reduction in regional stroke work from the baseline. Both estimates were robust when the reduction in regional stroke work is less than 20%, within physiological resting conditions.



Supplementary Figure 4. Normalized stiffness curve

The time-course of myocardial stiffness normalized by the maximal myocardial stiffness is plotted for each dog's baseline status (black dotted curves). The systolic myocardial stiffness was calculated using the zero-stress dimension based on the multiple-beat, end-systolic pressure dimension relationship (ESPDR). The red curve represents the averaged curve. To align each curve, the latest point attaining > 90% of maximal stiffness was set to a normalized time of 1. While the shapes of normalized stiffness curves are quite variable among individuals, the curves commonly exhibit small plateaus around the maximal stiffness point (i.e., at end systole), which have been used for the single-beat estimation of the ESPDR.

Supplemental References

1. Mirsky I, Tajimi T, Peterson KL. The development of the entire end-systolic pressure-volume and ejection fraction-afterload relations: A new concept of systolic myocardial stiffness. Circulation. 1987;76:343-356

2. Regen DM. Calculation of left ventricular wall stress. Circ Res. 1990;67:245-252