Ventricular Systolic Assessment in Patients With Dilated Cardiomyopathy by Preload-Adjusted Maximal Power
Validation and Noninvasive Application

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**Background** Noninvasive cardiac-specific analysis of contractile function in patients with dilated heart failure remains problematic. This study tests whether maximal power divided by the square of end-diastolic volume (PWR$_{max}$/EDV$^2$, or preload-adjusted PWR$_{max}$) can provide such assessment.

**Methods and Results** To validate the load insensitivity of the PWR$_{max}$ index and determine its response to contractile change, 24 subjects with chronic dilated cardiomyopathy underwent invasive pressure-volume catheterization study using the conductance catheter technique. Preload was transiently reduced by 30% using balloon occlusion of the inferior vena cava, and afterload impedance was lowered by 50%, induced by a bolus injection of nitroglycerin. Contractile state was varied by intravenous dobutamine, verapamil, or esmolol. PWR$_{max}$ was calculated from the simultaneous product of ventricular pressure and rate of volume change (dV/dt), the latter derived from the volume catheter signal. PWR$_{max}$ varied directly with preload but was minimally influenced by afterload. However, PWR$_{max}$/EDV$^2$ was not significantly altered by either loading change. PWR$_{max}$/EDV$^2$ did vary with contractility, correlating closely with changes in the end-systolic pressure-volume relation ($r=91, P<.001$). To test the noninvasive application of this index, 12 additional patients were studied, with PWR$_{max}$/EDV$^2$ derived from nuclear ventriculography combined with a novel method to measure central arterial pressures. Subjects received intravenous nitroprusside or dobutamine in random order. Ejection fraction increased similarly with both agents (+4.29±8.9% for dobutamine and +29.4±5.3% for nitroprusside, both $P<.01$). In contrast, PWR$_{max}$/EDV$^2$ did not significantly change with nitroprusside but increased by 126±16.1% with dobutamine ($P<.01$).

**Conclusions** Preload-adjusted PWR$_{max}$ is a steady-state index of ventricular systolic function that is sensitive to inotropic state and minimally influenced by physiological changes in afterload impedance or volume load. It appears useful for noninvasive cardiac-specific analysis of acute drug effects.

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**Key Words** • cardiomyopathy • ventricle • radionuclides • pressure • volume

Dilated cardiomyopathy is a common but complex disorder with coexisting abnormalities of the heart and peripheral vasculature. Medical therapy targets both aspects, using vasodilators and diuretics to reduce load and inotropic agents to alter contractile strength. Assessment of these various influences in the intact circulation is complicated by the fact that most routine measures of heart function do not adequately differentiate between cardiac and vascular effects. Although approaches based on pressure-volume,$^{1,4}$ stress-ejection,$^{5,6}$ and stress-strain$^7$ relations can provide more cardiac-specific assessments of contractile function, these relations generally require invasive data measured at several chamber loads and thus are difficult to apply in routine or long-term clinical studies. This is an important limitation because heart failure often requires longitudinal evaluation.

One approach to noninvasive cardiac contractile assessment in patients with heart failure may be provided by preload-adjusted maximal power.$^8$ Ventricular power is the instantaneous product of pressure and flow and is analogous to the area under a force-shortening velocity curve for isolated muscle. Thus, power, and in particular maximal power (PWR$_{max}$), varies with contractile strength. Because PWR$_{max}$ can be accurately derived from the central arterial pressure-flow product,$^9$ it is amenable to noninvasive measurement. Calibrated estimates of central arterial pressure can be obtained by recently developed and validated noninvasive methods,$^{9-12}$ whereas volume flow can be assessed by nuclear$^{10}$ or Doppler cardiology.$^{14}$ PWR$_{max}$ by itself is significantly dependent on preload. However, by both theoretical analysis and experimental animal studies, we found that PWR$_{max}$ divided by the square of end-diastolic volume (PWR$_{max}$/EDV$^2$) is minimally influenced by preload or afterload impedance, yet it is very sensitive to contractile change. Importantly, preload-adjusted PWR$_{max}$ is measured at a single steady-state condition, as opposed to the multiple variably loaded cardiac cycles required for many of the other indexes.$^{1,7}$

The present study was undertaken to validate the preload-adjusted PWR$_{max}$ in humans with dilated heart failure and to test its usefulness in noninvasive drug assessment. To determine whether the relative load independence of PWR$_{max}$/EDV$^2$ observed in animals pertained...
to patients with dilated heart failure, invasive studies were performed using pressure-volume analysis to systematically study preload, afterload impedance, and inotropic dependencies. To test whether $PWR_{mx}/EDV^2$ could be used in a noninvasive setting to differentiate between inotropic versus vasodilator drug effects, dobutamine or nitroprusside was administered intravenously in a second group of patients, and drug influences on ejection fraction and $PWR_{mx}/EDV^2$ were compared. The results confirm the relative load independence and inotropic sensitivity of $PWR_{mx}/EDV^2$ in humans with heart failure and suggest its usefulness in noninvasive evaluation of contractile change.

**Methods**

**Patient Population**

Thirty-six patients with dilated congestive heart failure were studied. Twenty-four patients participated in a cardiac catheterization protocol to test the sensitivity of $PWR_{mx}$ and $PWR_{mx}/EDV^2$ to preload, afterload, impedance, and contractile change. A second group of 12 patients underwent noninvasive study in which the responses to intravenous dobutamine or nitroprusside were compared. The average ejection fraction and EDV for the two study groups were very similar (28±2.7% and 32.0±2.1% and 206.0±17.2 and 236.0±16.8 mL, respectively, *P*=NS). Invasive catheterization studies were performed at the Johns Hopkins Hospital (n=18) and the University of Virginia at Charlottesville (n=6). Noninvasive studies were performed at both the Johns Hopkins Hospital (n=6) and the Rebecca Sieff Hospital, Safed, Israel (n=6). All patients provided informed consent. The protocols were approved by the Joint Committee of Clinical Investigation of the Johns Hopkins Medical Institution and University of Virginia and the Helsinki Committee of Rebecca Zief Hospital, Safed, Israel.

**Study Protocol**

**Invasive Catheterization Study**

Details of the invasive pressure-volume catheterization procedure have been previously reported.14-16 Briefly, all patients underwent routine right- and left-side heart catheterization, coronary angiography, and ventriculography. Subsequently, a conductance catheter was advanced to the left ventricular apex and connected to a stimulator/processor unit (VCU, Cardiac Pacemaker Inc, or Sigma 5, CardioDynamics) for LV volume measurement. LV pressure was obtained by micromanometer catheter (PC-330, Millar Inc) placed within the lumen of the volume catheter. These catheters provided continuous pressure-volume data that were displayed in real-time using custom-designed data-acquisition software. The instantaneous product of chamber pressure and a smoothed derivative of the volume signal yielded power, and the maximal value of this product was $PWR_{mx}$. All analog signals were digitized at 200 Hz and stored on hard disk for subsequent analysis.

Pressure-volume loops and relations were used to determine the preload, afterload, and contractile-state sensitivities of $PWR_{mx}/EDV^2$. The influence of acute preload reduction was evaluated in 8 patients by temporarily impeding inferior vena caval inflow by balloon catheter (Cordis SP-9168). This yielded 15±6 sequential cardiac cycles with progressively smaller EDVs. Arterial afterload sensitivity was tested in 6 additional patients by analyzing data before and after intravenous bolus injection of nitroglycerin (400 µg). This maneuver yielded an average of 19±2 beats at gradually reduced arterial loads. Last, the influence of contractile change was evaluated in 5 patients before and after intravenous administration of dobutamine (5 to 10 µg·kg\(^{-1}\)·min\(^{-1}\)). These contractility data were further expanded by including data from an additional 10 patients with LV hypertrophy who received negative inotropic agents (10 mg verapamil IV or 3 µg·kg\(^{-1}\)·min\(^{-1}\)·esmolol IV).
Noninvasive Pharmacological Study

To evaluate PWR_{max} noninvasively, we combined nuclear ventriculography providing volume and flow data with arterial pressures measured by a newly developed and validated noninvasive technique. Red blood cells were radiolabeled in vivo by injection of 1.2 mg pyrophosphate followed 20 minutes later by 25 mCi Tc-pertechnetate and radionuclide ventriculography performed in a 60° left anterior oblique position. Ventricular volumes and flow signals were derived from the calibrated time-activity curves (see below). Arterial pressures were provided by a recently described novel system. Briefly, this device (CardioSpec 2000, SRD Medical) consists of a sphygmomanometric arm cuff attached to an air pressure unit, a Doppler transducer applied to the brachial artery at the antecubital fossa, and an ECG monitoring system. The cuff is automatically inflated until the Doppler flow signal at the brachial artery disappears. As intracuff pressure is then decreased at a preset rate (2 to 3 mm Hg per beat), the Doppler signal reappears, and the time delay (\Delta T) from the preceding R wave of the ECG to onset of brachial flow is measured as a function of intracuff pressure. \Delta T combines electromechanical delay, pulse wave transit time from aorta to brachial artery, and the delay required for the arterial pressure to rise to the level of the cuff. This last delay shortens as cuff pressure declines, and by plotting cuff pressure versus \Delta T, the upstroke of the arterial waveform is reconstructed (Fig 1, upper left). After resting pressure and nuclear volume data were measured, either dobutamine (starting dose, 5 \mu g \cdot kg^{-1} \cdot min^{-1} IV) or nitroprusside (starting dose, 0.2 \mu g \cdot kg^{-1} \cdot min^{-1} IV) was given. The drugs were titrated to achieve a 10 to 20 mm Hg increase or decrease in systolic blood pressure, respectively. Repeat pressure and nuclear scan data were obtained at peak effect. The infusion was then stopped, and at least 20 to 30 minutes were provided for complete washout. A repeat baseline study was performed, and then the alternative drug was administered. The order of drug administration was randomized.

Theoretical Basis of Power Index

The notion that PWR_{max}/EDV^2 might serve as a load-independent steady-state contractile index in patients with heart failure is based on a theoretical analysis. Power is the instantaneous product of pressure and flow:

\[
PWR(t) = P(t) \cdot F(t) = P(t) \cdot dV/dt
\]

where dV/dt is rate of ventricular volume change. Using a time-varying elastance model [E(t)] of the heart, one can write:

\[
P(t) = E(t) \cdot [V(t) - V_0]
\]

Thus,

\[
PWR(t) = E(t) \cdot [V(t) - V_0] \cdot dV/dt
\]

TABLE 1. Mean Hemodynamic Parameters at Baseline and at Maximal Preload Reduction (Transient Inferior Vena Cava Balloon Occlusion) or Maximal Afterload Reduction (Nitroglycerin)

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Low</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preload change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>76.2±4.3</td>
<td>77.5±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>EDV</td>
<td>172.2±19.6</td>
<td>137.2±15.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EF</td>
<td>34.8±2.3</td>
<td>30.5±3.2</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ea</td>
<td>2.4±0.4</td>
<td>2.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>PWR_{max}</td>
<td>5.8±0.5</td>
<td>3.4±0.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PWR_{max}/EDV^2</td>
<td>2.3±0.4</td>
<td>2.2±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Afterload change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>81.8±4.8</td>
<td>85.8±3.5</td>
<td>NS</td>
</tr>
<tr>
<td>EDV</td>
<td>251.1±21.2</td>
<td>230.9±27.9</td>
<td>NS</td>
</tr>
<tr>
<td>EF</td>
<td>24.7±4.4</td>
<td>41.4±9.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ea</td>
<td>2.6±0.4</td>
<td>1.4±0.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PWR_{max}</td>
<td>9.4±2.2</td>
<td>8.3±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>PWR_{max}/EDV^2</td>
<td>2.3±1.1</td>
<td>2.7±1.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR indicates heart rate (bpm [beats per minute]); EDV, end-diastolic volume (mL); EF, ejection fraction (%); E_a, effective arterial elastance (mm Hg/mL); PWR_{max}, maximal power (W); PWR_{max}/EDV^2, preload-adjusted PWR_{max} (W/mL^2·10^6). The different baselines reflect two separate although quite similar patient groups.
This means that \( \text{PWR}_{\text{mx}}/\text{EDV}^2 \) has units of \( \text{dE/dt} \), the first derivative of elastance. Prior studies have demonstrated that \( \text{dE/dt} \) (like \( \text{dP/dt} \)) varies with contractile state; indeed, this forms the basis for the \( \text{dP/dt}_{\text{mx}} \)-EDV relation reported by Little et al.\(^4\) Furthermore, \( \text{PWR}_{\text{mx}} \) occurs at or just after peak flow,\(^4\) and because both peak flow and the volume at peak flow vary directly with preload by the Frank-Starling mechanism, Equation 3 suggests a dependence of \( \text{PWR}_{\text{mx}} \), on EDV\(^2\).

A second way to consider the \( \text{PWR}_{\text{mx}} \)-EDV\(^2\) dependence is to examine the analogous relation for stroke work (SW). Power is the rate at which work is performed, with mean power equal to work divided by the systolic period. In the case of SW, one can derive a simple equation relating contractile function, arterial load, and EDV, which predicts a parabolic dependence on EDV\(^2\) ("Appendix"). Although it is difficult to analytically derive a similar relation for \( \text{PWR}_{\text{mx}} \), it can be obtained by computer model using a time-varying elastance simulation of the heart and a three-element Windkessel model of the arterial system. As shown in Fig 2A, the predicted relation is also parabolic, although in the physiological range (above solid horizontal line), this appears linear with a positive axis intercept. This makes \( \text{PWR}_{\text{mx}}/\text{EDV}^2 \) essentially preload independent (Fig 2B).

The relative insensitivity of \( \text{PWR}_{\text{mx}} \) to afterload impedance follows from the fact that it combines ejection flow and arterial pressure. Thus, like SW, changes in arterial load (primarily peripheral resistance) generate offsetting effects on flow and pressure, leaving \( \text{PWR}_{\text{mx}} \) minimally altered. At infinite or zero load, \( \text{PWR}_{\text{mx}} \) (like SW) is zero. Theoretically, however, there is

**Table 2. Multiregression Analysis for Preload and Afterload Influences on \( \text{PWR}_{\text{mx}} \) and \( \text{PWR}_{\text{mx}}/\text{EDV}^2 \)**

<table>
<thead>
<tr>
<th></th>
<th>Coefficient±SEM</th>
<th>( r )</th>
<th>( P )</th>
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<tbody>
<tr>
<td><strong>Preload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PWR}_{\text{mx}} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( b_1 ) (EDV)</td>
<td>0.054±0.006</td>
<td>.937</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>( b_2 ) (E(_a))</td>
<td>−0.065±0.94</td>
<td>.493</td>
<td></td>
</tr>
<tr>
<td>( \text{PWR}_{\text{mx}}/\text{EDV}^2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( b_1 ) (EDV)</td>
<td>−0.004±0.003</td>
<td>.961</td>
<td>.084</td>
</tr>
<tr>
<td>( b_2 ) (E(_a))</td>
<td>−0.020±0.039</td>
<td>.603</td>
<td></td>
</tr>
<tr>
<td><strong>Afterload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{PWR}_{\text{mx}}/\text{EDV}^2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( b_1 ) (EDV)</td>
<td>−0.083±0.072</td>
<td>.969</td>
<td>.247</td>
</tr>
<tr>
<td>( b_2 ) (E(_a))</td>
<td>−0.008±0.006</td>
<td>.134</td>
<td></td>
</tr>
</tbody>
</table>

\( \text{PWR}_{\text{mx}} \) indicates maximal power; EDV, end-diastolic volume; and E\(_a\), effective arterial elastance.

Regression model is: \( \text{PWR}_{\text{mx}} \) (or \( \text{PWR}_{\text{mx}}/\text{EDV}^2 \)) = \( b_0 + b_1 \cdot \text{EDV} + b_2 \cdot E_a + \sum d_i \cdot \text{EDV} \), where \( n \) is number of subjects minus 1 and \( d_i \) is 1 for subject \( i \), 0 for subject \( \neq i \), and −1 for subject \( n \).
a broad range of arterial resistance over which PWR\textsubscript{max} is less variable. This is shown in Fig 2C as the range over which PWR\textsubscript{max} is 90% or more of its theoretical maximum (above the horizontal line). Even within this range, there is some nonlinearity, so that small increases or decreases in PWR\textsubscript{max} might be observed depending on the baseline resistance.

**Data Analysis**

**Power Calculation**

PWR\textsubscript{max} was measured from the instantaneous product of pressure and the derivative of volume (dV/dt). dV/dt was determined by fitting the volume waveform [V(t)] (measured by conductance catheter or radionuclide scan) to a four-term Fourier series from which an analytical derivative was obtained. Multiplying P(t) · dV/dt · 1.33 · 10\textsuperscript{-4} yielded power in units of watts, and PWR\textsubscript{max} was the peak instantaneous value.

This method of PWR\textsubscript{max} calculation has been previously described and validated in animals by direct comparison with data obtained using proximal aortic root flow measured by ultrasonic meter.\textsuperscript{9}

**Invasive Studies: Load and Contractility Dependencies**

The preload dependence of PWR\textsubscript{max}/EDV\textsuperscript{2} was tested by analyzing beat-to-beat data during transient balloon occlusion of the inferior vena cava. EDV was determined for each beat by averaging volumes during isovolumic contraction.\textsuperscript{16} Arterial load dependence was examined by calculating effective arterial elastance (E\textsubscript{a}) for each beat after intravenous injection of nitroglycerin. E\textsubscript{a} combines resistive and reactive components of aortic input impedance and can be accurately expressed by the ratio of end-systolic pressure to stroke volume (P\textsubscript{es}/SV).\textsuperscript{18,19} It provides a better index of the effect of arterial load on the heart than mean resistance.\textsuperscript{10} The sensitivity of PWR\textsubscript{max}/EDV\textsuperscript{2} to inotropic change was examined by comparison with two independent measures based on pressure-volume relations. These relations were the end-systolic pressure-volume relation (ESPVR), determined from points of maximal P/(V−Vs), where P and V are instantaneous LV pressure and volume, and Vs is the volume axis intercept,\textsuperscript{16,19} and the SW-EDV relation, determined by linear regression of digitally integrated SW per beat versus EDV.\textsuperscript{9}

**Noninvasive Studies: Radionuclide Volume Calibration and Indexes**

Radionuclide time-activity curves were generated using automatic or semiautomatic edge-detection algorithms at identified regions of interest. These curves were calibrated using either the count-based method, with peripheral blood sampling to determine counts per milliliter of a reference volume and correction for attenuation of left ventricular counts (n=6),\textsuperscript{20} or a count-based ratio method (n=5).\textsuperscript{21} In addition to obtaining PWR\textsubscript{max}, radionuclide volumes were used in calculations of ejection fraction, preload (EDV), and estimated afterload (E\textsubscript{a}).

For the invasive data, simultaneous digital recording of pressure and volume (and thus flow) signals directly facilitated power calculation. However, noninvasive signals had to first be synchronized and curve fit to calculate power. To synchronize these data, both volume and pressure waveforms were fit and then interpolated to yield temporally matched points (Fig 1). Noninvasive pressures were fit by a running linear interpolation, smoothed with a high-frequency digital filter, and then synchronized to the volume waveform so that both the onset of pressure rise and volume ejection occurred at time=0. The
TABLE 3. Hemodynamic Responses Before and After Nitroprusside and Dobutamine in Subjects During Noninvasive PWRmx Protocol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Nitroprusside</th>
<th>P</th>
<th>Baseline 2</th>
<th>Dobutamine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV</td>
<td>236.0±16.8</td>
<td>204.6±20.2</td>
<td>&lt;.05</td>
<td>236.6±15.9</td>
<td>205.9±18.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Psys</td>
<td>138.7±4.1</td>
<td>106.5±4.8</td>
<td>&lt;.01</td>
<td>134.6±4.3</td>
<td>151.2±3.9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ea</td>
<td>1.7±0.12</td>
<td>1.2±0.89</td>
<td>&lt;.01</td>
<td>1.6±0.18</td>
<td>1.4±0.11</td>
<td>NS</td>
</tr>
<tr>
<td>HR</td>
<td>80.2±4.9</td>
<td>85±4.9</td>
<td>NS</td>
<td>76.2±4.9</td>
<td>98.2±5.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>EF</td>
<td>32.3±3.3</td>
<td>41.8±3.6</td>
<td>&lt;.01</td>
<td>36.3±3.6</td>
<td>49.8±3.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>PWRmx/EDV^2</td>
<td>1.85±0.24</td>
<td>2.02±0.26</td>
<td>NS</td>
<td>1.80±0.22</td>
<td>4.2±0.69</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

EDV indicates end-diastolic volume; Psys, systolic pressure; Ea, effective arterial elastance; HR, heart rate; EF, ejection fraction; and PWRmx, maximal power.

smoothed pressure waveform was divided into 100 equally spaced points, and flows at matched times were analytically calculated. The instantaneous product of pressure and flow yielded power, and its maximal value was PWRmx.

As with the invasive data, preload was defined as EDV for each steady-state condition. Arterial load defined by Ea=Psys/SV could not be directly measured noninvasively. However, we recently demonstrated that Ea can be accurately approximated from arterial systolic and diastolic pressures (Psys and Pnums), given by the ratio: (2Psys+Pnums)/3·SV.19 This formula is similar to one used to estimate mean arterial pressure, with the weighing for systolic versus diastolic pressures reversed. In humans, linear regression of this ratio against Psys/SV yields a slope of 1.0 (r=.98, P<.0001). This approximation was used for the noninvasive analysis.

Statistical Analysis

Data are presented as mean±SEM. The dependence of PWRmx and PWRmx/EDV^2 on EDV or Ea was performed using a multivariate linear regression model.22 This model contained EDV, Ea, and dummy variables encoding patient variation of the PWRmx-EDV and PWRmx-Ea relations. Sensitivity of PWRmx to inotropic change and its correlation with ESPVR and SW-EDV relation changes were based on Student’s paired t tests and linear least-squares regression. Differences in noninvasive drug-induced changes were analyzed by paired t tests. Statistical significance is reported at P<.05.

Results

Preload Sensitivity of PWRmx and PWRmx/EDV^2

Occlusion of inferior vena caval inflow induced a maximal fall in EDV of 20.0±2.5% with minimal simultaneous change in heart rate or arterial load (Ea). There was a small but significant decline in ejection fraction (Table 1). Fig 3A displays pressure-volume loops for a representative patient during preload reduction, and Fig 3B displays the PWRmx-EDV data derived from these loops. Consistent with prior animal results,8 PWRmx decreased markedly with reduced preload volume, and in the measured range, these data were reasonably fit by a linear relation with a positive volume axis intercept. The same data were also well fit by a parabolic relation with an intercept at EDV=0, indicating that PWRmx/EDV^2 was near constant despite preload variation consistent with model prediction. Fig 3C shows this result, with both PWRmx/EDV^2 and EDV normalized to the initial baseline. This result was typical for the group overall (Table 1).

Fig 4 displays group results for PWRmx and PWRmx/EDV^2 preload dependence. To combine individual patient data, both absissa and ordinate variables for each patient were normalized to their respective baseline before preload reduction (as in Fig 3C). The results were then averaged over equally spaced ranges. PWRmx was highly dependent on preload (95% confidence limits for virtually all the points did not include 1.0), whereas PWRmx/EDV^2 was essentially unchanged despite a near-30% reduction in EDV. This graphic analysis was corroborated by multivariate regression. Combining PWRmx, PWRmx/EDV^2, and EDV data from all patients revealed a significant direct correlation between PWRmx and EDV (slope=.51, P<.001) compared with an insignificant correlation between PWRmx/EDV^2 and EDV (slope=.003, P=1.2) (Table 2).

Arterial Load Sensitivity of PWRmx/EDV^2

Fig 5A displays an example of pressure-volume data after nitroglycerin injection in a patient, and Fig 5B displays the PWRmx/EDV^2-Ea data from these loops. The loop display demonstrates an increase in SV and decline in systolic pressure induced by the vasodilator. The combined effect was a near-50% decrease in Ea, yet despite this marked afterload decline, PWRmx/EDV^2 was little altered. Table 1 provides the average maximal responses...
to nitroglycerin. Arterial load ($E_a$) was reduced by $-43.6\pm2.6\%$ ($P<.001$). Smaller changes in EDV and heart rate fell short of statistical significance. Importantly, despite the marked fall in arterial load, $\text{PWR}_{\text{mx}}/\text{EDV}^2$ did not significantly change. In contrast, ejection fraction rose by $60.3\pm12\%$ ($P<.01$). Fig 5C displays the group results, with $E_a$, $\text{PWR}_{\text{mx}}/\text{EDV}^2$, and ejection fraction were all first normalized to baseline. Although ejection fraction rose markedly with reduced $E_a$, there was minimal change in $\text{PWR}_{\text{mx}}/\text{EDV}^2$. Consistent with theory (Fig 2C), the $\text{PWR}_{\text{mx}}/\text{EDV}^2$ data displayed minimal afterload dependence, with slight nonlinear curvature. Two of the individual means fell significantly above 1.0, although even these changes were fairly small in magnitude. These graphic results were further confirmed by multivariate regression analysis (Table 2).

**Sensitivity to Inotropic State**

Although $\text{PWR}_{\text{mx}}/\text{EDV}^2$ was minimally influenced by 40% to 50% reductions in either preload or arterial afterload, the index was very sensitive to inotropic change. Fig 6 displays individual percent changes in power index versus the ESPVR slope ($E_a$) due to the various positive and negative inotropes. There was a significant correlation, with a linear regression given by: $\%\Delta E_a = -0.91 \cdot \%\Delta \text{PWR}_{\text{mx}}/\text{EDV}^2 + 5.8$ ($r=.9$, $P<.001$, $\text{SEE}=25.7\%$). Similar correlations were obtained comparing the power index to the slope of the SW-EDV relation ($r=.67$, $P=.002$, data not shown).

**Noninvasive Study: Response to Nitroprusside Versus Dobutamine**

The preceding studies verified that in patients with dilated cardiomyopathy, $\text{PWR}_{\text{mx}}/\text{EDV}^2$ could reliably index contractile change with minimal alteration from acute changes in chamber preload or arterial afterload. To explore how this parameter might be clinically applied, we studied a second patient group using noninvasive techniques and assessed whether the index could differentiate between a prototypic vasodilator (nitroprusside) and a positive inotropic agent (dobutamine). Results are provided in Table 3. Dobutamine increased heart rate by 28.4±6.1% and systolic blood pressure by 12.8±2.2% and lowered EDV by $-13.7\pm3.5\%$ (all $P<.01$). In contrast, nitroprusside lowered systolic pressure by 23.2±2.5%, as well as EDV ($-14.0\pm4.9\%$, both $P<.05$), but heart rate was not significantly altered. Arterial load ($E_a$) was reduced in all patients during nitroprusside administration ($-27.1\pm4.6\%$, $P=.001$), whereas it was variably and insignificantly influenced by dobutamine.

As shown in Fig 7, EF increased with both drugs ($+42.9\pm8.9\%$ for dobutamine and $+29.4\pm5.3\%$ for nitroprusside, both $P<.001$), but these changes were not statistically distinguishable. In contrast, $\text{PWR}_{\text{mx}}/\text{EDV}^2$ increased only with dobutamine and by nearly three times as much as the change in EF ($+126.58\pm14.68\%$, $P<.02$). There was no significant change in $\text{PWR}_{\text{mx}}/\text{EDV}^2$ induced by nitroprusside. Furthermore, although there was a strong negative correlation between percent afterload reduction and ejection fraction change after nitroprusside: $\%\Delta EF = -0.92 \cdot \%\Delta E_a + 4.5$ ($r=.8$, $\text{SEE}=11.6$, $P<.001$), $\text{PWR}_{\text{mx}}/\text{EDV}^2$ did not significantly correlate with $E_a$ reduction.

**Discussion**

The power of the LV chamber is the rate at which it performs work. It bears close correspondence with the area under a force–velocity of shortening relation for cardiac muscle. In the 1970s, indexes based on $\text{PWR}_{\text{mx}}$ and maximal rate of change of $\text{PWR}_{\text{mx}}$ were proposed as improved methods to assess ventricular systolic performance. However, these earlier studies did not or could not systematically evaluate loading influences on $\text{PWR}_{\text{mx}}$ or compare its inotropic response with independent meaningful standards. Furthermore, because $\text{PWR}_{\text{mx}}$ measurement required invasive data, it offered no particular advantage over other approaches. The recent development of techniques to measure central aortic pressure and flow now enables noninvasive assessment of $\text{PWR}_{\text{mx}}$, and this has renewed interest in power-based indexes. In an earlier animal study, we demonstrated that $\text{PWR}_{\text{mx}}$ was marked and directly dependent on preload volume, minimally altered by afterload impedance, and sensitive to inotropic change. Furthermore, theoretical analysis suggested that $\text{PWR}_{\text{mx}}/\text{EDV}^2$ would adjust for preload dependence, and this was experimentally confirmed. Based on this finding, the present study sought to determine if a similar load insensitivity for $\text{PWR}_{\text{mx}}/\text{EDV}^2$ held in human patients with dilated heart failure. The present results derived from invasive catheterization pressure-volume data confirm both the relative load independence and inotropic sensitivity of this index. In a test of the applicability of this index to noninvasive drug assessment, we found that although ejection fraction could not differentiate between afterload reduction due to nitroprusside versus inotropic enhancement from dobutamine, $\text{PWR}_{\text{mx}}/\text{EDV}^2$ clearly discriminated between these effects. These data support use of this relatively simple steady-state index and noninvasive approach for drug testing and contractile assessment in human heart failure.

**Noninvasive Usefulness of $\text{PWR}_{\text{mx}}/\text{EDV}^2$**

Our primary impetus for reinvestigating $\text{PWR}_{\text{mx}}$ was its potential as a steady-state, noninvasive, and reasonably cardiac-specific index of contractile function in humans. Despite numerous approaches, the question of whether a given drug does or does not have inotropic effects remains difficult to answer noninvasively. This has impeded the evaluation of agents with simultaneous cardiac and vascular effects, as well as those with which the onset to peak effect is delayed, necessitating longitudinal evaluation. The present data suggest that $\text{PWR}_{\text{mx}}/\text{EDV}^2$ may be used in patients with heart failure to address such questions. This ratio can be measured noninvasively and provides excellent discrimination between vasodilation and inotropic change.

Noninvasive determination of $\text{PWR}_{\text{mx}}$ depends on techniques for measuring arterial pressure and volume flow. Flow can be assessed either by quantitative Doppler cardiology or radionuclide ventriculography. In this study, the nuclear technique was used as it provided consistency between scans (ie, single injection, no changes in body or scanner position between drug interventions) and directly generated the quantitative output needed for power analysis. There are several approaches to noninvasive pressure determination.
Kelly et al.11,12 recently demonstrated that applanation tonometry of the carotid artery provides a reasonable approximation of the arterial pulse waveform. This signal must be calibrated to systolic and diastolic pressures obtained by an alternative method. More recently, we evaluated a new approach combining a computer-controlled arm cuff with measures of the time delay between the QRS complex of the ECG and the upstroke of brachial artery flow.9 This method yields calibrated pressures during the ascending portion of the arterial waveform, the period during which PWRm occurs. Pressures obtained by this method were compared with simultaneous invasive data, demonstrating excellent correlations. Furthermore, we found that PWRm calculated by substituting pressures obtained by the new noninvasive method for invasive micromanometer ventricular pressures were near identical.9

Caveats and Potential Limitations in the Use of PWRm/EDV2

There are several issues regarding the application of PWRm/EDV2 that should be considered. First, it is an index of chamber function, and like many similar parameters, it does not necessarily reflect properties at the myocardial level. There is increasing recognition that a "load-independent index of contractility" cannot truly exist, because loading itself alters myofilament Ca2+ sensitivity27 and force-generating capacity.28 However, at the level of an intact organism, the ability to identify aspects of hemodynamic function that result and/or are manipulable by changes in venous and arterial loading versus those that are not remains valuable. Preload-adjusted PWRm provides such discrimination, with its chief advantages being that it is measured at a single load and can be assessed noninvasively.

The lack of significant preload or afterload impedance influence on PWRm/EDV2 in patients with heart failure is relative in that it applies to a physiological range of loading changes but is not true at all loads. For example, as afterload resistance is markedly decreased or increased, PWRm will eventually fall as pressure or flow approaches zero. However, as predicted theoretically and demonstrated by the data of Fig 5, afterload can be reduced by nearly 50% with relatively little change in PWRm. We have reported similar findings during isometric handgrip, which increases afterload by about the same amount.29

Autonomic reflexes were not blocked in the present study, as generally is the case for human evaluation; thus, reflex activation may have contributed to preload, afterload, or inotropic drug responses. In patients with heart failure, this effect appeared small as heart rate change to both mechanical preload reduction and to nitroglycerin was minimal. Baroreceptor function may be downregulated with heart failure, and this could have blunted such reflex responses.

Although we reported that PWRm/EDV2 is minimally preload dependent in anesthetized animals9 and now extend this finding to patients with dilated heart failure, one cannot assume that this applies to all forms of human cardiac disease. Unlike experimental animals, human heart geometry in normal and particularly diseased ventricles can vary considerably. Smaller hearts in which EDV and V0 (the volume intercept of the ESPVR) are less disparate or in which V0 appears to be negative,30,31 and stronger hearts in which nonlinear ESPVRs are observed32,33 could negate the simplifying assumptions used in predicting a parabolic dependence between PWRm and EDV2 ("Appendix"). Such hearts will require separate evaluation before a preload-adjusted PWRm index is used.

Conclusions

The diagnosis and management of congestive heart failure and the evaluation of new therapeutic agents require measurements that can identify cardiac contractile versus vascular loading abnormalities and changes. Because both the disease and its treatment are chronic processes, noninvasive methods that can be used serially are highly desirable. The present study has shown that preload-adjusted maximal power in the form of PWRm/EDV2 can serve as such a measurement in patients with heart failure. Because it is obtained at a fixed steady state rather than requiring multiple variably loaded beats, it has clinical appeal. Future studies will need to assess the use of this parameter for improving the targeting and understanding of heart failure therapies.

Appendix

The PWRm-EDV relation is very similar to that derived for SW. If one writes the ESPVR as

\[ P_a = E_a(V_a - V_c) = E_a(EDV - SV - V_c) \]

and Ea as

\[ P_a = E_a \cdot SV \]

then

\[ SV = E_a[(E_a + E_c) \cdot (EDV - V_c)] \]

SW can be approximated by SV \cdot P_a = E_aSV^2. Thus

\[ SW = K \cdot (EDV - V_c)^2 \]

where \( K = E_a[(E_a + E_c)]^2 \).

Thus, at constant arterial load and contractility (ie, E_a and E_c), if EDV >> V_c, then SW varies with EDV^2. This same equation predicts a nonlinear dependence between arterial load and SW, with a broad plateau around the physiological loading range. This has been verified experimentally by us and others in isolated34,35 and intact hearts.36,37

Similar relations between PWRm and both EDV and E_a can be obtained using a computer simulation in which the heart is modeled by a time-varying elastance and the arterial system by a three-element Windkessel model. The results of this simulation (Fig 2) demonstrate a parabolic dependence between PWRm and EDV and a nonlinear afterload relation with a broad plateau.

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