Contraction-relaxation coupling mechanism characterization in the thermodynamic phase plane: normal vs. impaired left ventricular ejection fraction

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Wu Y, Yu Y, Kovács SJ. Contraction-relaxation coupling mechanism characterization in the thermodynamic phase plane: normal vs. impaired left ventricular ejection fraction. J Appl Physiol 102: 1367–1373, 2007. First published December 21, 2006; doi:10.1152/japplphysiol.00593.2006—Using simultaneous pressure-volume measurements obtained during cardiac catheterization, we employ the thermodynamic phase-plane (TPP) method to characterize global contraction-relaxation coupling (CRC) between normal and impaired left ventricular (LV) ejection fraction (LVEF) groups. The cardiac cycle inscribes a closed loop in the TPP defined by the coordinates “potential” power [V(dP/dt), ergs/s] and “kinetic” power [P(dV/dt), ergs/s]. The TPP-derived indexes κ and ρ define the chamber’s contractile and CRC attributes, respectively. Data from 33 subjects dichotomized as normal control (n = 22, >50% LVEF) and impaired LVEF (n = 11, <50% LVEF) were analyzed. The results were as follows: κ = 3.0 ± 1.1 and ρ = −0.38 ± 0.21 for controls and κ = 5.4 ± 1.6 and ρ = −1.14 ± 0.47 for the impaired LVEF group; κ and ρ are significantly higher for impaired LVEF than for control (P < 0.001 for both). As κ increased, ρ decreased (r = −0.69) for all subjects. Hence, ventricles with impaired LVEF are thermodynamically less efficient because they require more potential power per unit of delivered kinetic power than controls. We conclude that TPP-derived indexes of CRC facilitate assessment of chamber efficiency in thermodynamic terms and elucidate the dominant differentiating features in terms of CRC indexes.

A persistent challenge in cardiovascular physiology and cardiology is the elucidation of contraction-relaxation coupling (CRC) in theoretical/conceptual terms that are translatable and applicable in vivo. The need to address this challenge is further underscored by the increasing recognition that, relative to systolic dysfunction with impaired left ventricular (LV) ejection fraction (LVEF), diastolic dysfunction has become an epidemiologically significant cause of heart failure (21) with normal LVEF, associated with delayed relaxation and/or increased stiffness. Because diastolic early rapid filling is powered by stored elastic potential energy from the previous systole, it is necessary to better understand and quantitatively characterize CRC mechanisms.

The pressure-volume (P-V) loop is a well-established modality through which systolic function (LVEF and the end-systolic P-V relation) and diastolic function (the end-diastolic P-V relation) can be assessed (16). Since the P-V loop covers the entire cardiac cycle, it necessarily includes information regarding CRC, although CRC may not be easily discernible from the geometry of the P-V loop. The P-V loop area [∫P(dV)] represents the external work of the chamber during each beat (18). In an effort to more fully characterize the work of the chamber from a thermodynamic perspective and stemming from prior “pressure phase plane” (6) and “physiological hyperspace” (5)-based characterization of ventricular function, Karamanoglu and Kovács (9) proposed the thermodynamic phase plane (TPP) method. Compared with the loop in the P-V plane, the TPP method further clarifies, in geometric terms, the thermodynamic work and energy-related events during the entire cardiac cycle, including the isometric work during isovolumic intervals. Moreover, because sequestration of Ca2+ in the sarcoplasmic reticulum to maintain a concentration gradient of 10,000:1 relative to the cytosol is a continuous, energy (ATP)-requiring process, in thermodynamic terms, diastole constitutes the high-energy state (10) of the cardiac cycle. The thermodynamic low-energy state is systole, when Ca2+ runs down its concentration gradient and generates contraction. Any impairment of the ATP-dependent pumps to fully reestablish the high-energy (diastolic) state results in a variable, spatially inhomogeneous, but persistent, state of residual muscular contraction (tone) that necessarily affects function. To more fully characterize the transition between these low (systole)- and high (diastole)-energy thermodynamic states in quantitative terms, we enter the TPP arena and consider the differences between control and impaired LVEF groups in terms of TPP-derived indexes. Our intent is not to use the indexes as a surrogate for LVEF or diastolic function or to clinically differentiate between impaired LVEF and control states but, rather, to gain insight into CRC mechanisms based on thermodynamic concepts and measures of efficiency using the impaired LVEF group, relative to controls, as a working example.

We define the differential thermodynamic energy change dE/dt of the chamber as follows:

\[ dE/dt = V(dP/dt) + P(dV/dt) \]

which makes explicit the two terms that account for how energy varies (9). The V(dP/dt) term (where V is volume and P is pressure) represents the potential power (PP). PP is the instantaneous rate of change of potential energy at any given volume, including during isovolumic intervals. It can be viewed as the ability of the chamber to do work on the blood, including the ability to change potential energy to kinetic energy. This power is generated by molecular motors, which consume ATP to drive the actin-myosin interaction. The po-

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Potential energy generated (i.e., increased pressure) is delivered to the vasculature (usually modeled as a windkessel) and exists as strain energy in the contractile apparatus of the myocyte through deformation of the extracellular connective tissue matrix and in the intracellular components such as the protein titin (3, 4). We refer to the second term \( \text{P}(dV/dt) \) in Eq. 1 as the kinetic power (KP), which represents the instantaneous power transfer from the LV to the periphery. KP is zero during isovolumic intervals. KP can be rewritten as \( \text{PQ} \dot{Q} \) [where \( Q \) is the volumetric blood flow rate (ml/s) leaving the LV and entering the aorta, \( \dot{Q} = -dV/dt \)]. The time integral of this power transfer \((\text{PQ} \dot{Q})\) represents the work done by the LV on the periphery over an ejection period. The majority (85–90%) of this work is devoted to overcoming arterial resistance and storing energy in the elastic arteries, and the remainder (10–15%) accounts for the kinetic energy of blood flow, not to be confused with KP of the ventricle. PP and KP reciprocate continuously throughout the cardiac cycle (Fig. 1). However, the simultaneous pressure and volume variation of the chamber ensures that, rather than being independent, PP and KP are coupled and work continuously to satisfy the requirements placed on the heart. 

Because we view the LV as the boundary of interest and use the convention that a decrease in LV volume represents energy loss, Eq. 1 becomes:

\[
\frac{dE}{dt} = V(dP/dt) - \text{PQ}
\]

By integrating PP and KP independently over time, we obtain the potential energy \( E_p \) and kinetic energy \( E_k \) as functions of time:

\[
E_k = \int (PdV/dr)dr
\]
\[
E_p = \int (VdP/dr)dr
\]
\[
\Delta E = E_k + E_p
\]

In a time-averaged sense, the chamber must return to its original thermodynamic state at the end of each cardiac cycle; i.e., there is no residual accumulation of potential or kinetic work within the chamber. Accordingly, the time-averaged, net potential energy (positive) must equal the net kinetic energy.
(negative), since after each cardiac cycle, the potential energy and kinetic energy are restored (within practical limits) to their original state. This energy exchange (flux) is fueled by the conversion of chemical energy (ATP) to movement of blood from a low-pressure (pulmonary circulation) to a high-pressure (systemic) circuit, where the LV serves as the energy transducer. The change of total thermodynamic energy ($\Delta E = E_k + E_p$) returns to a relative zero point at the end of each beat (Fig. 1). It can be expressed as the product of pressure and volume, or it can be obtained by numerical integration of $P(dV/dt) + V(dp/dt)$. The reciprocating property of total energy mandates the convention of using a plus sign for the $P(dV/dt)$ term in Eq. 1, which modifies the sign convention initially employed (9). Because these processes are essentially isothermal, temperature change is negligible during the process; thus heat loss is small and deemed negligible.

By using $P(dV/dt)$ and $V(dp/dt)$ as TPP coordinates (Fig. 2), the cardiac cycle can be characterized in thermodynamic terms, and novel characteristics of the cycle manifest themselves (9). For each beat, the closed-loop trajectory in the TPP is inscribed approximately as a triangle with one side on the V(dp) axis. There are generally two distinct phases during which KP is negative, revealing the coupling between potential and kinetic terms. The first phase is from aortic valve opening to early systole (segment a-b in Fig. 2). $PP$ decreases as $KP$ increases in magnitude, and their changing rates maintain an essentially constant ratio $\kappa$. In the second phase (segment b-d in Fig. 2), systole continues until closure of the aortic valve, during which the kinetic and potential terms are numerically decreasing, with their rates maintaining another essentially constant ratio $\rho$. The turning point, $b$, where the magnitude of the KP begins to decline, occurs before peak LV pressure and indicates the thermodynamically defined onset of relaxation. Accordingly, the interaction between contraction (continued shortening of myocardites and decreasing LV volume) and relaxation (decreasing LV pressure) is simultaneously present while the aortic valve is open and strongly influences the overall performance of the heart (15, 17). Hence, $\kappa$ and $\rho$, as TPP-based indexes of heart function, specifically provide information regarding energy input-output as well as CRC. Points $e$ and $j$ are peak negative $dp/dt$ during isovolumic relaxation and peak positive $dp/dt$ during isovolumic contraction, respectively. Since there is no volume change, they reside on the V(dp) axis, with $P(dV/dt) = 0$. Point $f$ depicts mitral valve opening and start of the Doppler E wave. The TPP loop has a small positive bump of positive $P(dV/dt)$ below the $V(dp/dt)$ axis. Point $g$ is at minimum LV pressure. Point $h$ is diastasis and resides at the origin, where pressure and volume change are simultaneously zero. Segment $h-i$, which corresponds to atrial contraction (transmitral Doppler A wave), inscribes a bump with positive $P(dV/dt)$ above the $V(dp/dt)$ axis and ends with mitral valve closure and onset of isovolumic contraction (segment i-j).

**METHODS**

Inclusion criteria. We selected 33 subjects (34–73 yr old) from our existing Cardiovascular Biophysics Laboratory database of high-fidelity LV pressure and simultaneous chamber volume/transmural flow measurements (11, 19). Pressure and volume data were acquired from pressure transducer-tipped 6-F pigtail micromanometric P-V catheters at the commencement of elective, diagnostic cardiac catheterization. Informed consent approved by Institutional Review Board of Washington University Medical Center was obtained from all subjects before data acquisition. The criteria for data selection were as follows: normal sinus rhythm, normal valvular function, and no myocardial infarction or significant ($>$50% luminal narrowing) coronary artery disease or active ischemia. Subjects were dichotomized into a control group ($n = 22, >50%$ LVEF) and an impaired LVEF group ($n = 11, <50%$ LVEF, including a symptom- and sign-based clinical diagnosis of heart failure).

Data acquisition. The method by which pressure and volume data were acquired has been previously described (11, 19). Briefly, after appropriate sterile skin preparation and local anesthesia (1% xylocaine), a valved femoral arterial sheath (6-F, Arrow, Reading, PA) was placed in the artery. A 6-F micromanometer-tipped pigtail P-V (conductance) catheter (model SPC-560-1, Millar Instruments, Houston, TX) was advanced through the sheath and then retrogradely through the aortic valve into the LV under fluoroscopic control. The ventricular pressures were fed to the catheterization laboratory amplifier (Quinton Diagnostics, Bothell, WA). The conductance volume signal was transformed using Sigma 5 DF (CD Leycom, Zoetermeer, The Netherlands). The ventricular pressure and conductance volume were output into a digital converter connected to a customized personal computer. Analysis was performed offline in the Cardiovascular Biophysics Laboratory.

Data analysis. For each subject, data from 10–30 continuous beats were analyzed. Minimal-noise volume data provided by the catheter’s five conductance channels were selected, summed, and smoothed by Savitzky-Golay filters (i.e., digital smoothing polynomial filters or least-squares smoothing filters) and calibrated using suitably calibrated ventriculogram-derived end-diastolic and end-systolic vol-

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**Fig. 2.** Comparison of a typical cardiac cycle in the pressure-volume (P-V) plane vs. the TPP. Both loops are inscribed counterclockwise. A: P-V loop indicating selected thermodynamic events (aortic valve opening ($a$), peak kinetic power ($b$), peak pressure ($dp/dr = 0$), $c$, aortic valve closure ($d$), peak negative dp/dr ($e$), mitral valve opening ($f$), minimum LVp ($g$), diastasis ($h$), mitral valve closure ($i$), and peak positive dp/dr ($j$)). B: actual TPP loop from a control subject. C: idealized (noise-free) TPP loop defining parameters $\kappa$ and $\rho$. **A** and **B** were obtained during a control cardiac cycle. **C** is a computer-generated idealized (noise-free) TPP loop with the same $\kappa$ and $\rho$ as **A** and **B**.
impaired LVEF groups were compared by ANOVA. Results for the two groups are shown in Table 2. Significant differences were observed for $\kappa$ and $\rho$ from control and impaired LVEF groups were compared by ANOVA.

RESULTS

The relevant clinical parameters are listed in Table 1. Sexes were well matched in the control group, while males were predominant in the impaired LVEF group. The groups were otherwise well matched with respect to age and heart rate. The results for $\kappa$ and $\rho$ for the two groups are shown in Table 2. Significant differences were observed for $\kappa$ and $\rho$ between the control and the impaired LVEF group. The parameter $\kappa$, as determined from segment a-b of the loop, was smaller in the control than in the impaired LVEF group: $\sim 3.0$ vs. $\sim 5.4$, respectively. Similarly, $\rho$ was much smaller in the control than in the impaired LVEF group: $-0.38$ vs. $-1.14$, respectively. The different shapes in the TPP characteristic of control and impaired LVEF subjects are shown in Fig. 3. Because $\kappa$ is greater in the impaired LVEF group, segment a-b of the loop is necessarily steeper and the P(dV/dt) dimension of the loop is smaller than in controls, while the V(dP/dt) dimension of the loop tends to be similar to that in controls. Figure 4A shows the $\kappa$-$\rho$ relation and elucidates the relation of contractile function to contraction-relaxation. Although the interval that generates $\kappa$ and $\rho$ is systole, from aortic valve opening to aortic valve closure, systolic-diastolic coupling (15, 17) ensures that $\kappa$ and $\rho$ must contain information relevant to the phase of the cardiac cycle beyond systole. Specifically, $\kappa$, measured during early ejection, correlates with LVEF ($r = -0.63$), encompassing an entire ejection (Fig. 4B). The late-ejection parameter $\rho$ also correlates with LVEF ($r = 0.79$; Fig. 4C) and with the isovolumic relaxation time constant $\tau$ ($r = -0.63$; Fig. 4D). There is no significant correlation between $\kappa$ and $\tau$ (data not shown).

DISCUSSION

Phase-plane methodology is widely utilized in applied mathematics, engineering, and nonlinear dynamics to characterize implicit relations that eliminate time as an explicit variable. Phase-plane methods have also been applied in physiology and medicine. In investigations regarding gaze stabilization to high-acceleration head thrusts, for example, phase-plane analysis of head rotation allows simultaneous display of gaze velocity and gaze position and, therefore, facilitates discernment of different head movement patterns in accordance with the degree of vestibular loss and compensation (14). Phase-plane analysis can quantitatively characterize specific components of ventricular systolic and diastolic function, elucidate

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Values are means (SD) of 22 controls (11 male and 11 female) and 11 subjects (8 male and 3 female) with impaired left ventricular (LV) ejection fraction (LVEF). EDV and ESV, end-diastolic and end-systolic volume; LVEDP, LV end-diastolic pressure; HR, heart rate; $\tau$, isovolumic relaxation time constant; NS, not significant.

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Values are means (SD).
novel physiological relations (5, 6), and be considered a two-dimensional embedding in four-dimensional physiological hyperspace spanned by $P$, $V$, $dP$, and $dV$ axes (5). The most frequently encountered phase-plane analog in cardiovascular physiology is the P-V loop (16).

The TPP concept, defined by ventricular PP and KP and their interaction, was introduced and applied to cardiac physiology by Karamanoglu and Kovács (9). The differential $V(dP/dt)$ term is named PP, since it is associated with the potential energy/pressure change of the LV chamber, including pressure changes during isovolumic intervals. In contrast, we opted to refer to $P(dV/dt)$ as KP, since it reflects the consequences of kinetic events such as wall motion and associated volume change. The integral of $P(dV/dt)$ is the area of the P-V loop and represents the external work done by the ventricle. The work done by the LV to eject blood into the aorta is driven by the pressure gradient and is $\int(P_{LV} - P_{ao})dV$, where $P_{LV}$ is LV pressure and $P_{ao}$ is aortic pressure. In contrast, the total external work done by the LV during contraction is $P_{LV}dV$. The former expression for work results in ejection of blood through the aortic valve, whereas the latter includes the work of the chamber starting at a low pressure at the same volume.

Before introduction and application of the TPP concept to cardiac physiology, the theoretical basis of characterizing cardiac energy consumption and work output was P-V analysis (PVA) established by Suga (18). The PVA approach was based on a time-varying elastance model (16), in which the LV is modeled kinematically as a stretched spring. The elastance of the LV, equivalent to the spring with time-varying stiffness, was defined as follows

$$\text{elastance} = P(V - V_0)$$

where $P$ is pressure, $V$ is volume, and $V_0$ is the empirically determined “unstressed” volume. In analogy to a “spring constant” being determined by the slope of the force-displacement relation, the chamber is modeled as a “three-dimensional” spring in which the stretch (displacement) of the “spring” is $V - V_0$, the pressure is the “force,” and the elastance is the time-varying spring constant. In the time-varying elastance model, the slope of the line, with one end fixed at $V_0$ and the other end moving along the P-V loop, determines the instantaneous elastance. The triangular differential area swept out by the line connecting $V_0$ to any P-V point of interest is the differential mechanical potential energy $dE_m$. During LV ejection, the mechanical potential power $dE_m$ is

$$dE_m = \frac{1}{2} P(dV)$$

During ejection, $dE_m$ is independent of $V_0$. This is not the case for the isovolumic relaxation-contraction phase, when $dE_m$ is

$$dE_m = \frac{1}{2} (V - V_0)dP$$

Hence, the distinction between TPP (Eq. 1) and PVA is that TPP simultaneously includes KP and PP, while PVA includes mechanical PP only. When integrated over one cardiac cycle, the kinetic energy in the TPP and mechanical potential energy in the PVA yield the same effective external work, i.e., the P-V loop area. Integrating the TPP-derived $V(dp/dt)$ term over one cardiac cycle generates the same value of the $P(dV/dt)$ term but with a minus sign, which, when added to the integral of $P(dV/dt)$, makes the total energy change zero at the end of one cycle. This is reasonable, since after one cardiac cycle the LV returns to its initial state. This method of accounting for energy/work highlights the role of the LV as an energy converter, converting potential energy (ATP) to external work.

Portions of the phase-plane loop (Figs. 2 and 3) can be well approximated by linear relations that express the rate of change between PP and KP in terms of $\kappa$ and $\rho$. To facilitate comparison of CRC mechanisms, we express $\kappa$ and $\rho$ as dimensionless parameters (rather than angles, as in Ref. 9) that measure the slopes of (regression) lines, rather than the angles relative to the horizontal. This allows for a more direct visual comparison of quantitative relations. The obviously higher magnitude of $\kappa$ and $\rho$ for impaired LVEF subjects indicates abnormal coupling of PP and KP. Specifically, conversion of a greater amount of PP per unit of KP is required in impaired LVEF subjects than in controls. In Fig. 3, this difference between the indexes for the impaired LVEF group is accounted for by the lower KP [thinner triangles, below the $P(dV/dt)$ baseline], since the heights [$V(dp/dt)$] of the triangles are approximately similar. This indicates that to deliver similar amounts of external work, as reflected by $P(dp/dt)$, ventricles in the impaired LVEF group utilize a greater amount of potential energy and, therefore, are less efficient. Although control vs. impaired LVEF groups are easily differentiated by LVEF or other clinical parameters, conventional measures cannot elucidate differences between groups utilizing these thermodynamic efficiency mechanisms.

Maximum KP ($\text{point } b$ in Fig. 2) defines the limit of increasing $P(dV/dt)$ and, therefore, defines a transition point from $\kappa$ to $\rho$. In impaired LVEF, $\text{point } b$ is located at lower $P(dV/dt)$ values (Fig. 3B) because impaired LV function limits the ability to eject blood and overcome external load. The maximum attained value of KP, $P(dV/dt)$ ($\text{point } b$), tends to be smaller. The decrease in maximum $P(dV/dt)$ is consistent with impaired LV contractility. Segment $a$-$b$ of the loop defines a domain where pressure rises and ejection dominates. At point $b$, pressure continues to rise, but the rate of volume ejection decreases more rapidly; hence, the numerical value of $P(dV/dt)$ decreases and the inscribed loop changes slope (from $\kappa$ to $\rho$) until aortic valve closure. Accordingly, $\kappa$ reflects primarily contractile phenomena. In accordance with a higher $\kappa$, stroke volume is decreased in a subject with impaired LVEF (Fig. 4B). Hence, elevated values of $\kappa$ are associated with generally lower values of $P(dV/dt)$, while $V(dp/dt)$ is relatively preserved. When $\kappa$ is higher than normal, the maximum rate of energy conversion ($\kappa$ vs. $\rho$) is higher by a factor of ~2 in the impaired LVEF versus the control condition (Fig. 3). As a result, more potential energy is required [$(V(dp/dt)$] per unit of kinetic energy for ejection. The parameter $\rho$ characterizes the interval from the onset of relaxation while blood continues to enter the aorta due to inertia. Higher $\rho$ in impaired LVEF subjects indicates that the decrease of peak KP (shift of point $b$ in Fig. 2) results in a steeper slope of the $b$-$d$ segment; i.e., the inertial volume ejection component tends to be decreased. Higher $\rho$ decreases overall stroke volume and contributes to higher end-systolic volume and decreased LVEF (Table 1). Concomitantly, the stored systolic elastic strain energy available for mechanical suction-initiated early rapid filling (Doppler E-wave) tends to be smaller.
Contraction and relaxation attributes of a healthy LV are manifest through its reciprocal pressure and volume cycles and can be appreciated from the cellular to the organ level. At the organ level, the heart maintains the same input and output steady-state volumes. As heart rate increases, stroke volume increases and the ejection and filling rates increase, but the steady-state balance between input and output volume is maintained. In thermodynamic terms, the chamber returns to the same energy level at the same phase; i.e., the consumption of energy keeps pace with the work done. Although it is accepted that, in cardiomyocytes, contraction and relaxation are coupled via Ca$^{2+}$ cycling (10, 12), a full description at the microscopic level is incomplete. Cellular studies of Ca$^{2+}$ fluxes show that the amount of Ca$^{2+}$ leaving the cell during twitch relaxation must be the same as the amount of Ca$^{2+}$ entering the cell for each beat (2). Similarly, the rate of change of Ca$^{2+}$ concentration in cardiomyocytes increases for contraction and relaxation in response to an increase in heart rate or inotropic stimulation in cardiomyocytes increases for contraction and relaxation as an index of LV function is usually regarded as a descriptor of the latter part of systole, during which cardiac valve closure and focuses attention on the latter portion of the cardiac cycle, via the “time constant of isovolumic relaxation” parameter $\tau$. Importantly, the geometry of the loop in the TPP (segment $b$–$d$ in Fig. 2) explicitly elucidates the role of relaxation before aortic valve closure and focuses attention on the latter portion of ejection as a phenomenon determined in part by relaxation. Figure 4D indicates the association between relaxation via $\rho$ before the end of systole and $\tau$ after the end of systole.

Limitations. Micromanometric pressure and conductance volume data are subject to noise. We sought to minimize noise by filtering and averaging beats. Volume data were computed by summing the five volume output measurements from the five channels of the conductance catheter. Usually, one or more of the five volume channels were too noisy for analysis and were excluded. For those subjects whose segments of interest ($a$–$b$ and $b$–$d$ in Fig. 2) were somewhat curved rather than relatively linear, we approximated $\kappa$ with a straight line from start of ejection (point $a$) to maximal KP (point $b$) and $\rho$ with a straight line from maximal KP (point $b$) to the end of ejection (point $d$). An independent (non-conductance catheter-based) method of $P(dV/dt)$ and $V(dP/dt)$ computation is needed to determine the potential issue of physiological importance of the curvatures of these segments.

The TPP approach includes the entire cardiac cycle, the diastolic portion of which is demonstrated in greater detail in Fig. 2. As illustrated in Fig. 3B, point $d$ is lower in a subject with impaired LVEF than in a control subject. The loop of diastolic filling is longer in the vertical direction and shorter in the horizontal direction. Since our focus was based on contraction-relaxation (i.e., systole), we did not explicitly compute or propose TPP-derived diastolic phase indexes. However, using a frequency-based analysis of the physiology of filling, incorporating micromanometric pressure and simultaneous echocardiographic transmural flow measurement for validation, we recently showed (20) that diastolic dysfunction is indeed a thermodynamic state of impaired efficiency in energetic terms. Future work will apply the TPP method to diastole.

In conclusion, TPP-based analysis elucidates contraction-relaxation mechanisms in novel, thermodynamics-based terms. Impaired LVEF subjects were used as a working example to show that $\kappa$ and $\rho$ significantly differentiated ($P < 0.001$) between impaired LVEF and control groups and that the impaired LVEF chambers are less efficient, because they require more PP per unit of delivered KP than controls. This novel approach facilitates quantitative estimation of CRC. The results go beyond the ability of classical indexes (LVEF) to elucidate mechanisms by illustrating the utility of TPP analysis in elucidating novel CRC mechanisms. The method underscores relaxation as a determinant of late systole ($\rho$ vs. $\tau$). Application of the method to selected pathophysiological groups and to the diastolic portion of the cardiac cycle has commenced.

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GRANTS

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