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Thermodynamic phase plane analysis of ventricular contraction and relaxation

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Abstract

Background: Ventricular function has conventionally been characterized using indexes of systolic (contractile) or diastolic (relaxation/stiffness) function. Systolic indexes include maximum elastance or equivalently the end-systolic pressure volume relation and left ventricular ejection fraction. Diastolic indexes include the time constant of isovolumic relaxation – and the end-diastolic pressure-volume relation. Conceptualization of ventricular contraction/relaxation coupling presents a challenge when mechanical events of the cardiac cycle are depicted in conventional pressure, P, or volume, V, terms. Additional conceptual difficulty arises when ventricular/vascular coupling is considered using P, V variables.

Methods: We introduce the concept of thermodynamic phase-plane, TPP, defined by the PdV and VdP axes.

Results: TPP allows all cardiac mechanical events and their coupling to the vasculature to be geometrically depicted and simultaneously analyzed.

Conclusion: Conventional systolic and diastolic function indexes are easily recovered and novel indexes of contraction-relaxation coupling are discernible.

Introduction

Heart failure (HF) is a common and eventually lethal disease whose incidence is increasing in the population [1,2]. It has only recently been appreciated that in nearly half of patients carrying the diagnosis of HF, left ventricular (LV) contractile function as indicated by LV ejection fraction (EF) is relatively preserved while ventricular diastolic relaxation/stiffness function is compromised and uncoupled [2,3]. In other words, the contraction-relaxation coupling (CRC) is abnormal.

It is established that contraction-relaxation coupling is mediated primarily by intra and extracellular calcium fluxes [4-6]. In the cardiomyocyte, the dominant CRC is via the ionized Ca^{2+} flux cycling between the contractile apparatus and the sarcoplasmic reticulum, SR [4,5,7]. It has been shown that in various cardiomyopathies this cycling is adversely affected [8,9]. Although experimental techniques exist that characterize this uncoupling at the cardiomyocyte level, there is a lack of both a conceptual and an experimental framework by which this type of uncoupling can be characterized at the whole-heart level.

In principle, the Frank-Starling Law, which is an experimentally determined relationship, should characterize contraction-relaxation coupling. Because the Frank-Starling Law is based on experimental observation, rather than being derived from basic laws, there are no explicit mathematical relationships defining CRC using different contraction-relaxation indices. In this study we use a mathematical modeling approach motivated by the historical utility of P and V as variables that define ventricular pump function; the ability of phase-plane methods to characterize the properties of oscillators and the goal to express the macroscopic consequences of contraction-relaxation coupling by introduction of a new concept suitable for derivation of physiologic CRC indexes. The intent is to facilitate quantification of the presence and severity of contractile-relaxation dysfunction by the use of these CRC indexes. We tested our preliminary concepts using conductance catheter derived pressure-volume data from a limited number of human subjects. Results indicate that derived CRC indexes may differentiate between normal and abnormal contraction-relaxation states. Further clinical studies, particularly in selected pathologic subsets, are needed to fully validate the utility of the proposed concepts.

Methods

In proposing our conceptual approach, we assume that analysis of ventricular contraction/relaxation in the P-V plane not only should correlate with the CRC at the cellular level but must also obey the laws of thermodynamics.

First, we note that CRC at the cellular level is measured using features such as the rise and decay of the Ca^{2+} transient. It is known that the upstroke of the Ca^{2+} transient precedes the onset of tension development and starts decaying immediately. Interestingly the Ca^{2+} transient is negligible at the peak of the developed tension and is not affected by inhibition of the net SR Ca^{2+} uptake by 3 mM caffeine [10].

Second, we define a differential relationship that describes the instantaneous power, (erg/s) as the rate of change of energy $\hat{E}$ (ergs), defined as $\hat{E} = PV$. In such a thermodynamic system where the heat losses during contraction are small and are therefore negligible, instantaneous power, $d\hat{E}/dt$, can be written as:

$$d\hat{E} = VdP\text{-}PdV \quad (1)$$

where we denote the time derivatives of $\hat{E}$, P and V as $d\hat{E}$, dP and dV, respectively. In expression (1) the sign of PdV is negative because we chose the system boundary as the LV volume at a given instant. The system loses energy by doing external work during systole when pressure rises and volume falls – hence the negative sign of PdV. This differential relationship defines how the energy contained in this system changes in accordance with the laws of thermodynamics. During each phase of the cardiac cycle the change in energy can be appreciated as illustrated in Figures 1 and 2 (the numbers in *italics* refer to phase of the P-V loop depicted in Figure 2): (*1)* isovolumic contraction when VdP > 0 and *PdV* = 0; (*2* to *3*) early systolic ejection when *VdP* > 0, and *PdV* < 0; (*5* to *6*) late systolic ejection when *VdP* < 0, and *PdV* < 0; (*7*) isovolumic relaxation when *VdP* < 0 and *PdV* = 0; (*8*) rapid filling when *VdP* < 0 initially, then becomes > 0 and *PdV* > 0; (*9*) diastasis when *VdP* = *PdV* = 0; and (*10*) passive filling when *PdV* > 0 *VdP* > 0. Because these macroscopic contraction and relaxation processes are not adiabatic, i.e. the system looses heat and generates external work, they are causally linked to energy consumption at the cardiomyocyte level.

In Equation 1, the *VdP* term denotes the potential power that is stored as potential energy in the contractile apparatus of the cardiomyocyte and in the extra-cellular connective tissue matrix and intracellularly in titin as strain energy [11,12]. Note that VdP is uniquely different from the conventionally used indexes to describe contractility dP/dt_{max} or relaxation, dP/dt_{min}. This potential power is generated by the strong interaction of the actin-myosin complex and thus should be dependent on fiber length, Ca^{2+} concentration and the Ca^{2+} sensitivity. The second term in the instantaneous power expression, *PdV*, is the kinetic power which accounts for shortening of the contractile apparatus and is the source of external work. It is a function of the weak interaction of the actin-myosin complex. Both the potential and kinetic power production terminates as Ca^{2+} is sequestered back into SR. Thus, it is possible to follow the course of Ca^{2+} cycling by considering the magnitude and time dependence of potential and kinetic power generated by the contractile apparatus. Thereby we obtain an index of contraction/relaxation coupling (Figure 2).

To derive physiologic indexes of systolic-diastolic coupling, we review the components of the cardiac cycle using *PdV* and *VdP* as coordinates in the thermodynamic phase plane.

The potential power becomes maximal *(1)* after the onset of contraction and before aortic valve opening *(2)* During the first part of ejection the potential power decreases and kinetic power increases until kinetic. power becomes maximal. *(3)* The exchange between potential and kinetic power during phase *(2)* and *(3)* occurs at a constant rate, κ. After phase *(3)* both kinetic power and potential power decline at constant but different rates, ρ. At peak systolic pressure (dP = 0) *(4)* potential power becomes zero but the net power output from the contractile apparatus is still positive until the phase *(5)* where the contractile

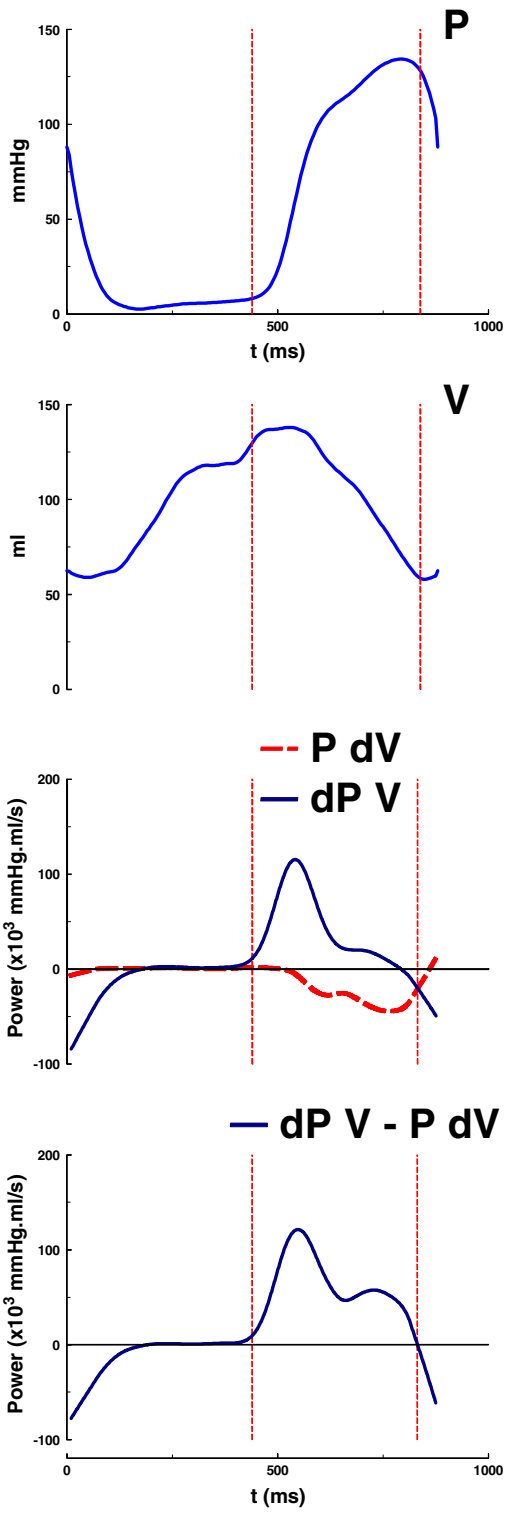

Figure 1
The cardiac cycle in thermodynamic space. Vertical lines depict the beginning and end of systole (end systolic elastance), respectively.

apparatus is incapable of delivering any further power. At aortic valve closure, the kinetic power becomes zero and the potential power becomes negative *(6)*. The potential power decreases to a minimum at peak negative dP and then increases again *(7)*. At mitral valve opening, the Doppler E-wave is inscribed *(8)* when kinetic power is positive, followed by diastasis *(9)*. Diastasis is the only point, where both the potential power and the kinetic power (dP = dV = 0) simultaneously become zero during the cardiac cycle. This is followed by atrial contraction, the Doppler A-wave, when both potential and kinetic power is positive and the cycle repeats itself *(10)*.

Figure 2 provides a geometric perspective of the method of CRC index derivation. Specifically the angles κ, ρ and δ define the contraction, relaxation and contraction/relaxation coupling behavior of a given ventricle, respectively. These angles in the TPP provide information about the intensity and duration of peaking and decaying of the Ca^{2+} transient, respectively. Therefore the mapping of Ca^{2+} transient to the TPP is important. Accordingly, nearly the entire Ca^{2+} transient maps to points *(1)* to *(7)* in Figure 2.

One of the unique aspects of thermodynamic phase plane analysis is that it depicts contraction and relaxation events simultaneously and includes the way they are coupled. In this phase plane, load dependence is easy to specify. We propose that the parameters κ, ρ and δ define the contraction, relaxation and coupling properties of a given ventricle. From this definition it follows that changes in (a) preload will alter the peak potential power, peak kinetic power but will not affect the angles κ, ρ and δ; (b) afterload will alter the potential power at the peak kinetic power without changes in κ, ρ and δ; (c) LV contractile properties will alter only κ; (d) LV relaxation properties will alter only ρ; and (e) contraction/relaxation coupling will alter the angle δ. Note also that κ, ρ and δ are inherently independent of the LV mass because these indexes describe the ratio of the instantaneous potential to kinetic power, which may be dependent on the LV mass.

Depiction of the cardiac cycle, including contraction/relaxation cycling using these expressions of power in the TPP, makes it possible to better understand the physical and thermodynamic meaning of some contractility indexes used widely in the past.

External Power Normalized to V²

Consider the maximal external power normalized to the volume squared, $(PdV)_{max}/ V^2$ [13]. Note that during phase *(2)* and *(3)* the kinetic power and potential power are linearly related, hence one can write $PdV = \kappa VdP + b_\kappa$ (Figure 2). Because $(dP/V)_{max}$ has been shown to be an index of ventricular contractility [14], it follows that

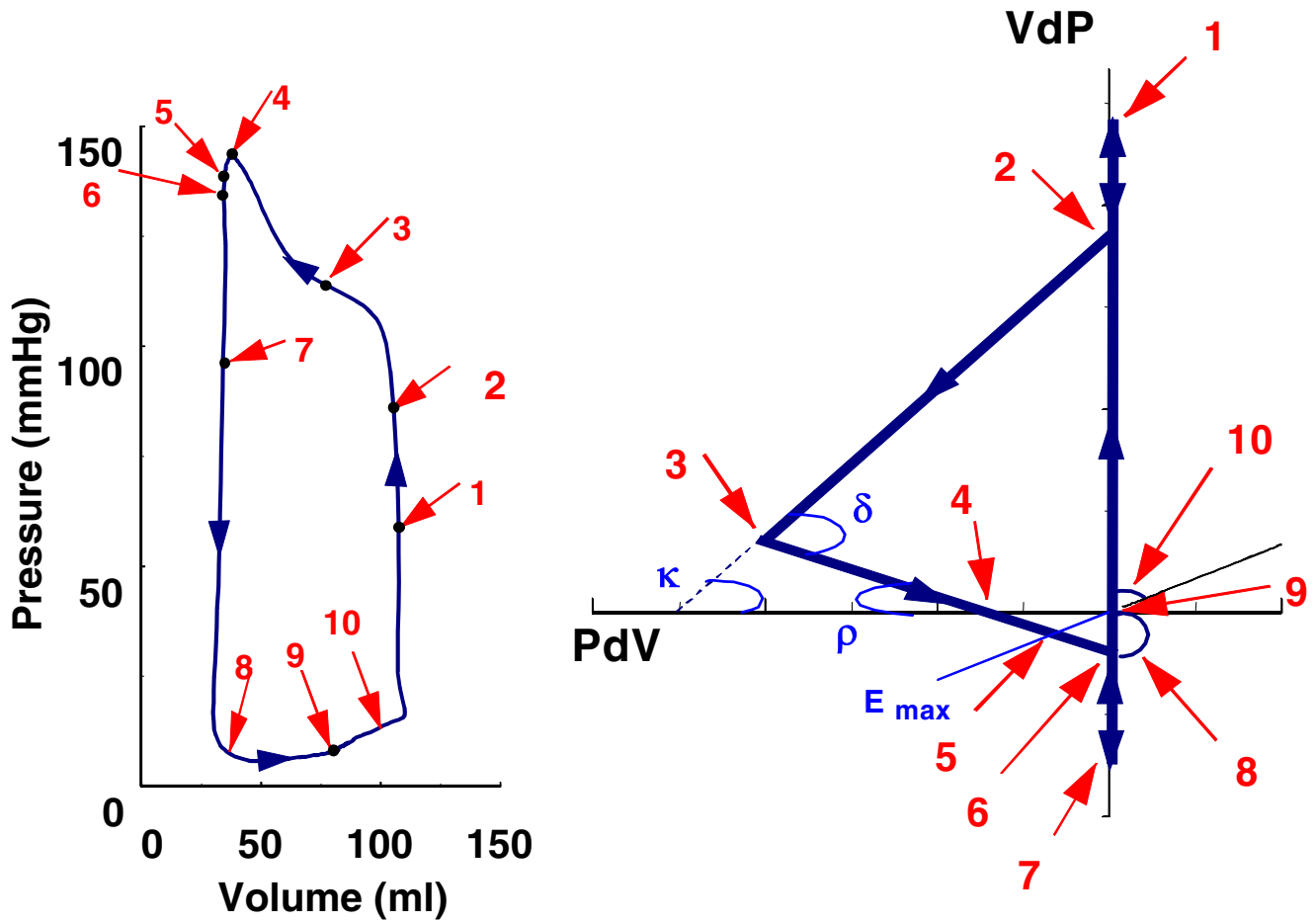

Figure 2
The cardiac cycle depicted in the thermodynamic phase plane. Arrows indicate the direction of time from the onset of systole.

$$(PdV)_{max}/\,V^2 \approx \kappa\,(dP/V)_{max} + b_\kappa / V^2 \quad (2)$$

This novel finding indicates that previously obtained empirical findings have a solid, and deeper thermodynamic foundation.

Maximal elastance

End-systolic elastance had been shown to be the maximal elastance that the ventricle can attain [15]. But, a deeper thermodynamic explanation for this behavior has been lacking. Noting that instantaneous elastance, E(t), is defined as $P(t)/(V(t)-V_o)$, the maximum of this function, E_{max}, occurs when $dE(t) = (V-V_o)dP-PdV = 0$, or without loss of generality i.e. by a change of variable $(V-V_o) \rightarrow V$, or by assuming the ventricular slack volume, V_o, is small and is therefore negligible:

$$VdP = PdV \quad (3)$$

This indicates that the E_{max} point is defined not only mechanistically as the maximal stiffness but also thermodynamically as the point when kinetic and potential powers are equal such that the left ventricular total thermodynamic power output is zero. This novel consequence of our approach has not been previously appreciated.

Time constant of isovolumic relaxation, τ

It is interesting to note that during isovolumic relaxation [16] the index characterizing the relationship between dP and P, is referred to as the '*time-constant of isovolumic relaxation*', [17]. Noting in Figure 2 that after the maximal kinetic power *(3)* and before aortic valve closure *(6)* one can write

Table 1: Patient Characteristics. [a] = $p < 0.05$, [b] = $p < 0.01$ Impaired Relaxation vs Normal, [d] = $p < 0.01$ Heart Failure vs Normal, [e] = $p < 0.05$, [f] = $p < 0.01$ Heart Failure vs Impaired Relaxation.

		Normal	Impaired Relaxation	Heart Failure
Age	years	53.5 ± 7.6	61.3 ± 7.8	59 ± 6.6
Sex		4M 2F	3M 3F	4M 2F
EF	percent	68.8 ± 8. 6	69.5 ± 7.8	37.5 ± 6.4[d,f]
LVEDP	mmHg	7.0 ± 3.0	17.5 ± 1.4[b]	22.4 ± 8.7[d]
τ	ms	41.9 ± 5.2	73.4 ± 14.3[b]	86.3 ± 25.6[d]
ESV	ml	41.0 ± 15.7	51.5 ± 15.7	139.5 ± 30.7[d,f]
EDV	ml	129.9 ± 34.3	173.0 ± 48.9	223.7 ± 46.8[d]
$\mathbf{E_{es}}$	mmHg/ml	3.5 ± 1.8	2.93 ± 0.9	0.96 ± 0.3[d,e]
$\mathbf{M_{sw}}$	mmHg	0.87 ± 0.19	0.89 ± 0.20	0.39 ± 0.18[d,f]
$\mathbf{dP/dt_{max}}$	mmHg/s	1207 ± 124	1102 ± 129	1070 ± 185
$\mathbf{dP/dt_{min}}$	mmHg/s	-1536 ± 193	-1256 ± 78[a]	-1095 ± 204[d]
Hr	beats/min	73.9 ± 7.1	61.7 ± 8.6	71.3 ± 12.5
SP	mmHg	129.5 ± 18.6	151.2 ± 28.0	135.3 ± 20.3
DP	mmHg	67.7 ± 6.7	79.4 ± 10.5[a]	80.7 ± 8.8

$PdV = \rho\ VdP + b_\rho$ and dV/V constant. Because $dP/P \approx -1/\tau$ then

$$\tau \approx -\rho \quad (4)$$

This linear relationship between ρ and τ suggests that τ is a rate constant depicting the proportional decrease of both potential and kinetic power.

Subjects and study protocol

Subjects

After obtaining informed consent, in accordance with Washington University Medical Center Human Studies committee criteria, we recruited 18 subjects (aged 42–73 years) from referrals scheduled for elective cardiac catheterization for clinical reasons at the request of the referring cardiologist. Subjects were enrolled if they met the following criteria: (i) scheduled for elective left or right/left heart catheterization, in a fasting, non-sedated state, (ii) judged to be clinically stable (iii) willing to participate and able to give informed consent, (iv) have no mitral valve disease, atrial fibrillation, or permanent pacemakers. Clinical status at enrollment was recorded. Subjects were divided into three groups: (i) normal group (n = 6) (τ < 50 ms; LVEF > 60% and LVEDP < 12 mmHg); (ii) impaired relaxation group (n = 6) with normal or mildly reduced left ventricular systolic function (EF > 50%) and evidence of abnormal left ventricular relaxation (τ > 50 ms) and diastolic distensibility (LVEDP > 16 mmHg) [18] and (iii) heart failure group (n = 6) (τ > 50 ms; LVEF < 45% and LVEDP > 16 mmHg).

Pressure volume loops were recorded using a 6F, 10-electrode pressure-volume conductance pigtail catheter (Millar Instruments, Dallas, TX). Briefly, using 62 cm 6F femoral arterial sheath (Arrow, San Leandro CA) the conductance catheter was advanced through the sheath into the central aorta, and then advanced retrogradely across the aortic valve with the pigtail tip positioned near the left ventricular apex. The conductance catheter was used with a simulator-microprocessor unit (Leycom Sigma-5, CardioDynamics, Rijnsburg, The Netherlands) in dual-field stimulation mode. Pressure-volume loops were displayed on a personal computer to allow on-line signal acquisition and real-time display. The pressure and volume data was digitized on-line at a rate of 200 Hz and was stored on a computer hard disk for subsequent off-line analysis. The baseline conductance volume data was calibrated using ventriculogram-derived end-diastolic and end-systolic volumes [19].

From P-V data obtained according to the above criteria, we determined if the three groups were distinguishable using thermodynamic phase plane analysis derived indexes. Hence, we calculated τ, chamber contractility using end-systolic elastance, E_{es}, and integrated ventricular function using the slope of preload-recruitable stroke work relationship, M_{sw}. All analyses were performed off-line in the Cardiovascular Biophysics Laboratory. Pressure-volume loops were analyzed for derivation of contractile-relaxation indexes using a custom written software in Visual Basic. The angles κ and ρ were estimated using the best linear relationship between VdP_{max} and PdV_{max}

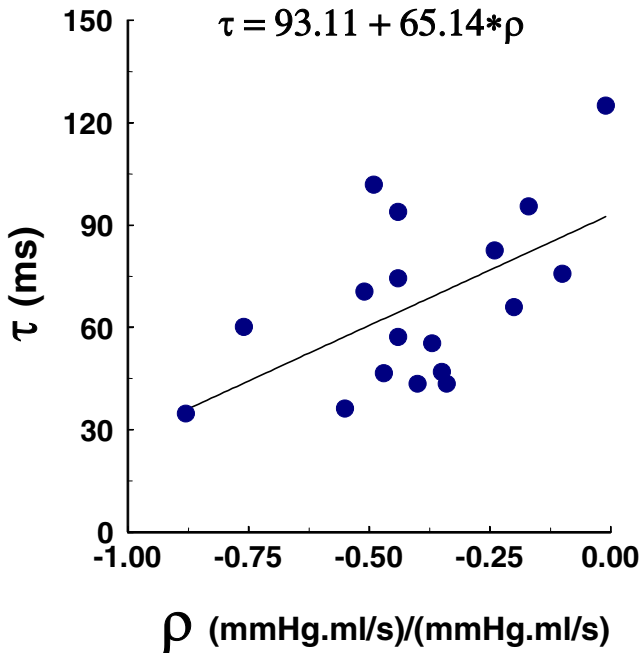

Figure 3
The relationship between diastolic power conversion ratio, ρ, and isovolumic time constant τ, $r^2 = 0.27$, $p < 0.05$

and PdV_{max} and VdP_{min}, respectively. The angle δ was calculated geometrically by considering δ = κ + ρ. Data were analyzed using ANOVA followed by Student-Newman-Keuls multiple comparison post significance test using a commercially available software (Instat, Graphpad). Data are expressed as mean ± SD. and $p < 0.05$ level was considered statistically significant.

Results

As expected from the inclusion criteria, other differences in these study groups were present (Table 1). Despite contractility indexes similar to the normal group, the impaired relaxation group had lower heart rates, higher blood pressure and decreased dP/dt_{min}. The heart failure group had lower contractility and relaxation indexes.

Figure 3 depicts the overall relationship between the diastolic power conversion ratio ρ and the isovolumic time constant, τ. As predicted by Equation 4, there was good correlation between ρ and τ. Note that τ was calculated during the isovolumic relaxation period while ρ was calculated during the ejection period. This finding, which confirms prediction (d), also provides strong evidence that ventricular relaxation begins not at the end of ejection but immediately after peak ejection [20].

As predicted by Equation 2, there was a close relationship between the systolic power conversion ratio κ and contractility indexes, M_{sw} and E_{es} (Figure 4).

Figure 5 depicts pressure-volume loops and thermodynamic phase plane analysis for a representative subject from each group. The normal and the impaired relaxation group had similar values for κ, ρ, δ and potential power at end ejection (Table 2). In contrast, the heart failure group had a higher κ and lower potential power at end ejection but similar ρ and δ. This finding confirms predictions (a), (b) and (c) and suggests that in this select group of heart failure patients, not only the power generation capacity of the ventricle is diminished but also the potential to kinetic power conversion rate, κ.

Discussion

It is well known that the contractile and relaxation performance of the left ventricle is coupled in healthy subjects through the Frank-Starling mechanism. Accordingly, altered contractile performance is met by altered relaxation properties of the ventricle causing rapid adaptation (within one beat) to changes in demand. It is accepted that this behavior is not a result of how the ventricle itself is geometrically constructed but an attribute intrinsic to the Ca^{2+} cycling and contractile apparatus within the cardiomyocytes [5,21] themselves. Through increased sensitivity of actin-myosin interaction to calcium and through the SR Ca^{2+} fluxes, the contractile force and period of relaxation is modulated. This form of contraction-relaxation coupling at the cellular level is essential for normal function at the whole heart level. There is evidence that in dilated cardiomyopathy and ischemic cardiomyopathy contraction-relaxation coupling is altered at the cellular level [9]. In the former case, there are adverse changes in the Ca^{2+} flux from the SR leading to slower shortening velocity. In the latter case the speed of Ca^{2+} re-uptake into SR is reduced causing delayed relaxation. Changes in Ca^{2+} sensitivity of the actin-myosin interaction, on the other hand, alters the speed and extent of both the contraction and relaxation events, thus preserving the contraction-relaxation coupling [8].

Whether all aspects of normal contraction-relaxation coupling are preserved at the organ level in these two and other forms of HF such as cardiomyopathy is unknown. Existing experimental methods do not allow observation of in vivo Ca^{2+} fluxes in humans, thus only approximate inferences using gross macroscopic mechanical behavior can be made. In the systolic failure model for example, diastolic performance is somewhat preserved through utilization of full Frank-Starling mechanism [22]. The converse may not be true. For example in long standing hypertension where contractile function is preserved (EF > 50%) through hypertrophic remodeling, an increased

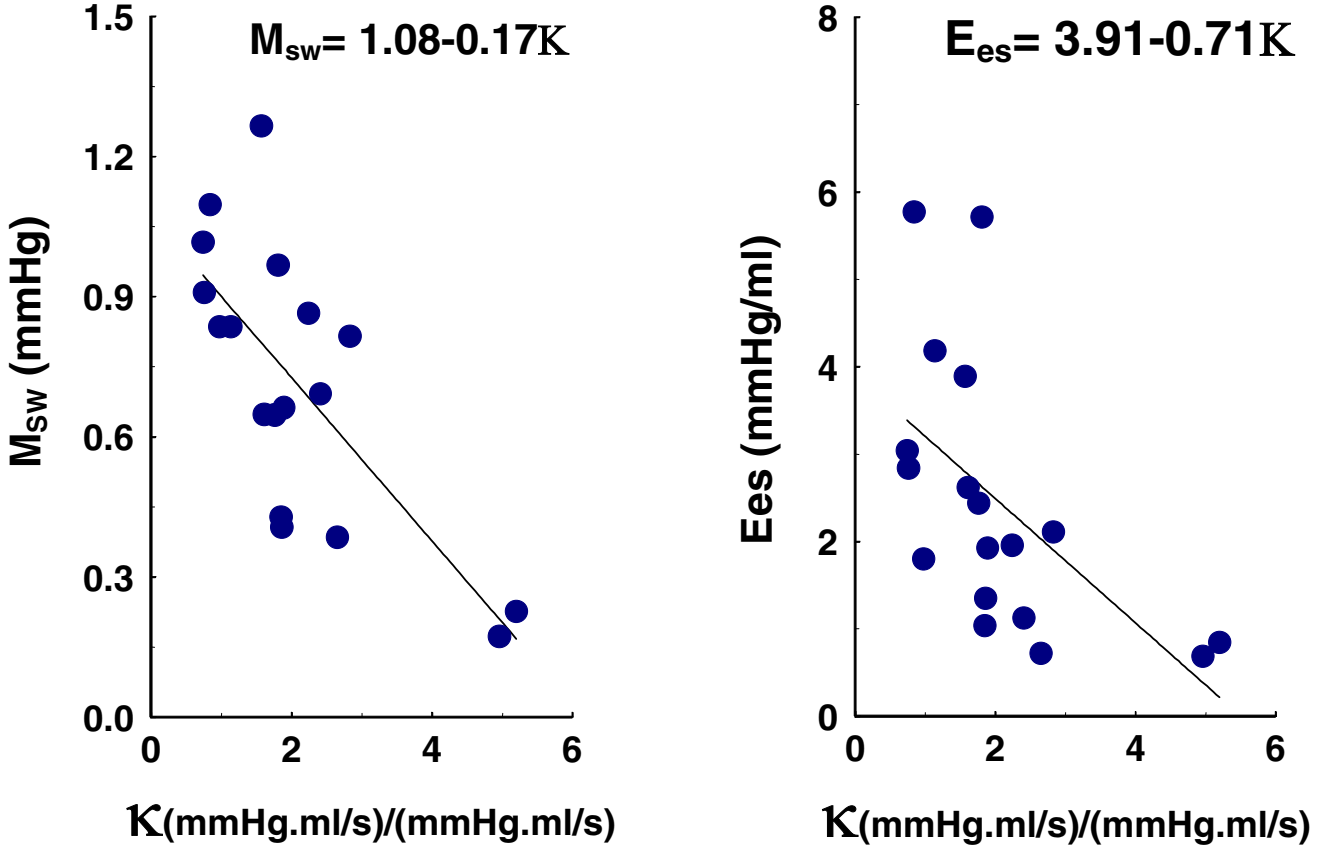

Figure 4
The relationship between systolic power conversion ratio, κ, and contractility indexes: (Left) M_{sw}, $r^2 = 0.51$, $p < 0.001$, (Right) E_{es}, $r^2 = 0.28$, $p < 0.01$

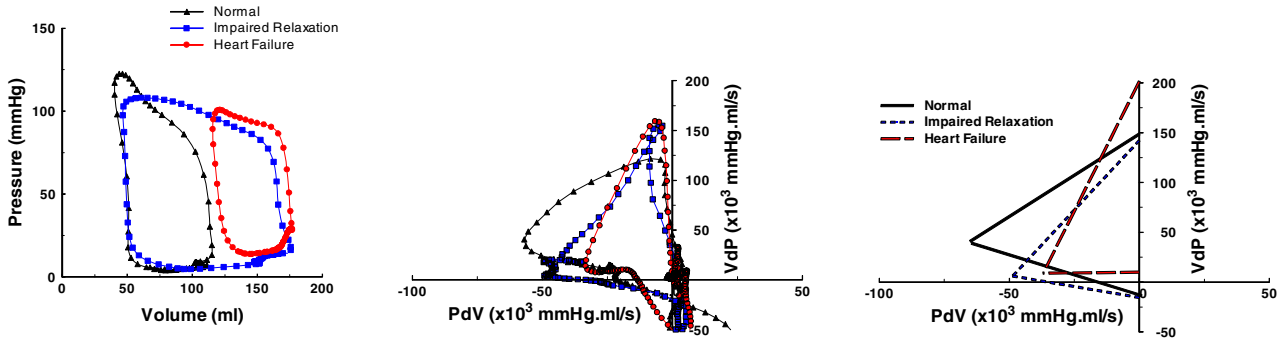

Figure 5
Typical pressure-volume loops (left), thermodynamic phase-plane plots (middle) and (right) best linear fits for the TPP plots from normal, impaired relaxation and heart failure subjects.

Table 2: TPP parameters calculated. [a] = p < 0.05, [b] = p < 0.01 Heart Failure vs Normal, [c] = p < 0.01 Heart Failure vs Impaired Relaxation

		Normal	Impaired Relaxation	Heart Failure
κ	degrees	50.8 ± 11.7	56.4 ± 12.0	69.6 ± 7.8[a]
b_κ ($\times 10^3$)	mmHg.ml/s	108.4 ± 51.3	148.0 ± 90.9	188.0 ± 35.9
ρ	degrees	-25.9 ± 8.5	-22.5 ± 9.9	-14.6 ± 10.4
b_ρ ($\times 10^3$)	mmHg.ml/s	-13.5 ± 3.8	-10.4 ± 4.2	12.1 ± 6.2[b,c]
δ	degrees	76.6 ± 15.7	78.8 ± 13.5	89.8 ± 9.1

incidence of diastolic failure has been observed particularly in elderly women [23]. This dichotomy suggests that contraction-relaxation abnormalities associated with remodeling may be a dominant feature in the latter case. Unfortunately, at the organ level the mechanisms that may account for this uncoupling of systolic and diastolic function are not well understood. The derivation and in-vivo validation of indexes that are specific and sensitive to contraction-relaxation coupling at the organ level will help elucidate and characterize the state of coupling.

Established indexes of contraction(systole) and of relaxation(diastole) in the left ventricle

Apart from the gross anatomical features such as the large-scale fiber direction and orientation [24], the left ventricle can be thought of as an assembly of cardiomyocytes that are arranged and work in parallel and in series. It is therefore reasonable to assume that the simplest model for left ventricle entails the main features of the cardiomyocyte itself. Similar to models (Maxwell, Voigt) of the single cardiomyocyte [25], various simplified approximations and parameters have also been developed to quantify cardiac mechanical events. Contraction indexes include: ejection fraction, the time-varying elastance [15]; maximal rate of rise of pressure [14], maximal external power [13]; and preload recruitable stroke work [14]. Diastolic function indexes include: the isovolumic relaxation time constant, τ, for ventricular relaxation [17], end-diastolic pressure-volume relationship for passive left ventricular properties [26], conventional E-and A-wave derived indexes [27] and the parameterized diastolic filling, (PDF), formalism derived indexes of ventricular filling [28,29]

Despite the success of these conceptual and experimental descriptions of distinct phases of the cardiac cycle, a deficiency exists in that a comprehensive description applicable to the entire cardiac cycle is absent. Specifically, these paradigms and indexes were not specifically intended for deriving indexes of contraction-relaxation coupling in the intact left ventricle.

Existing indexes of contraction and relaxation coupling

The two gold standard indexes that independently describe left ventricular contraction and relaxation properties respectively, are the end-systolic elastance, E_{es}, and the isovolumic relaxation time constant, τ. Although scant animal data indicates that E_{es} and τ may be inversely related [30], the data do not explain why it is possible to have preserved contractile (systolic) function with concomitant relaxation (diastolic) dysfunction. It is also known that E_{es} is relatively load-independent but τ is sensitive to the timing and the amplitude of the imposed load. Early systolic load decreases τ but late systolic load increases τ [20]. Increased afterload initially decreases τ but if the systolic pressure reaches 80% of isovolumic maximum pressure, τ is increased [20,30]. Whether the reported load sensitivity of τ is caused by methodological details [32,33] remains an issue. Other relationships should exist. Starting from a time-varying compliance concept Palladino et al also derived energy-exchange equations between the biochemical processes, mechanical work, potential energy and heat during contraction with considerable success [34]. We have previously shown that SW and dP-P phase plane areas and dP_{min} and dP_{max} are correlated [16]. This former finding constitutes preliminary data to support the concept that a coupling between the dP-P limit cycle area generated by each cardiac cycle and EDV exists because SW is related to EDV through PRSWR. This state of affairs underscores the need for better indexes by which contraction-relaxation coupling can be quantified.

Limitations

Movement and positioning uncertainties of the conductance catheter introduces noise into the data. We have found that this could be addressed in part by recording longer periods, (30 seconds), of continuous data while the hemodynamics are in steady state. Beat averaging of data eliminates most of the movement and respiratory artifacts. Although the derivatives of conductance signals amplify noise, this does not adversely affect our TPP analysis because: (a) we average data for 10–16 beats, (b) conductance signals are usually free from artifacts between

phases (*2*) and (*6*) (Figure 5), and (c) because the way the VdP and PdV are depicted in TPP analysis, the impact of noise due to derivatives is reduced.

Based on the inclusion criteria, we considered a high EF, increased LVEDP and increased τ would suffice to classify the impaired relaxation group. Because passive diastolic properties of the LV chamber also contributes to the LVEDP, the discrimination between the normal and impaired relaxation group may not be powerful. Other factors which directly affect P and V, such as underlying pathology, heart rate, medications, preload, contractility and afterload could modulate the CRC indexes. We have, however, found a significant correlation between τ and ρ suggesting active relaxation processes are indeed reflected in ρ. Our analysis suggests that in this select group of subjects the magnitude of relaxation impairment was not sufficient to be detectable, although a trend suggesting that ρ was lower was present. Further studies, involving larger number of subjects with documented diastolic heart failure will be carried out to determine if this trend is significant.

Conclusion

The proposed thermodynamic phase plane analysis method presented forms the basis of an evolving conceptual approach for quantitative contraction-relaxation assessment. Additional work in well-defined clinical pathophysiologic subsets as well as experimental animal models will aid in defining its full potential. Utilization in the aforementioned settings will facilitate complete determination of the relationship between current ventricular systolic and diastolic function assessment methods and the thermodynamic phase plane analysis method. Although our work is preliminary, and in a modest number of subjects, we found that the thermodynamic phase plane analysis method can not only quantitatively characterize the standard clinical systolic and diastolic ventricular function indexes but is able to elucidate their deeper thermodynamic basis. Our results justify further studies in order to extend these findings to subjects and animal models with and without impaired contraction/relaxation states due to various clinical (diabetes, hypertension, obesity etc) and specific molecular-cellular (titionopathies, myosinopathies, etc) etiologies.

Authors' contributions

MK and SK jointly conceived the 'thermodynamic phase plane" concept in terms of PdV and VdP coordinates, MK performed the data analysis and participated in study design and coordination. SK participated in study design and coordination and carried out the cardiac catheterizations. All authors read and approved the final manuscript.

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