Myocardial Contractile Efficiency and Oxygen Cost of Contractility Are Preserved During Transition From Compensated Hypertrophy to Failure in Rats With Salt-Sensitive Hypertension

Isao Morii, Yasuki Kihara, Moriaki Inoko, Shigetake Sasayama

Abstract—In Dahl-Iwai rats, salt-sensitive hypertension causes concentric left ventricular hypertrophy (LVH) at the age of 11 weeks, which is followed by LV dilatation with global hypokinesis and pulmonary congestion, ie, LV failure (LVF), at 16 to 18 weeks of age. To address the question of whether the cardiac remodeling from LVH to LVF is associated with modulations of mechanoenergetic properties, we serially measured the LV pressure-volume area (PVA) and myocardial oxygen consumption (MV\textsubscript{O\textsubscript{2}}) in isolated, isovolumically contracting hearts from this animal model. The end-systolic pressure-volume relationships obtained by stepwise changes of the LV volume were fit into a binominal regression model, which provided a value of LV contractility (E\textsubscript{es}) and a volume intercept (V\textsubscript{0}). A slope (the reciprocal of the LV contractile efficiency) and a PVA-independent MV\textsubscript{O\textsubscript{2}} were determined by a regression analysis of the MV\textsubscript{O\textsubscript{2}}-PVA relation. The procedure was repeated at different Ca\textsuperscript{2+} concentrations in perfusate to estimate the oxygen cost of contractility (dMV\textsubscript{O\textsubscript{2}}/dE\textsubscript{es}). The MV\textsubscript{O\textsubscript{2}} was further evaluated during K\textsuperscript{+}-induced cardiac arrest to delineate the basal metabolism, which was independent of the E-C coupling. During the transition from LVH to LVF, the E\textsubscript{es} was decreased by 50% (from 681 to 338 mm Hg · g · mL\textsuperscript{-1}. P < .001), which was associated with a substantial increase in V\textsubscript{0} (from 0.002 to 0.07 mL, P < .01). These alterations in both the inotropic state and the ventricular shape were associated with a 45% decrease in the PVA-independent MV\textsubscript{O\textsubscript{2}} (from 800 to 440 mL O\textsubscript{2} · beat\textsuperscript{-1} · g\textsuperscript{-1}, P < .01). Despite these marked changes between the two stages, both the LV contractile efficiency and the oxygen cost of contractility remained unchanged. The MV\textsubscript{O\textsubscript{2}} during cardiac arrest also showed an equal level among the groups; hence, from LVH to LVF, the nonmechanical O\textsubscript{2} consumption by the E-C coupling decreased in a manner parallel to the basal contractile state. We conclude that (1) in this animal model, the heart failure transition is associated with a marked decrease in myocardial contractility and with ventricular remodeling; (2) despite these changes, the efficiency of the chemomechanical conversion is highly preserved; and consequently, (3) the total energy consumption per unit of failing myocardium is diminished along with its reduced nonmechanical energy expenditure for E-C coupling. These mechanoenergetic properties might constitute an adaptive mechanism in the energy-starved condition of chronically diseased myocardium. (Hypertension. 1998;31:949-960.)

Key Words: heart failure ■ contractility ■ ventricular function ■ rats, Dahl

In states of chronic heart failure, the biochemical composition of the ventricular wall, the orientation of the cardiac muscle fibers, and the geometry of the ventricular chamber are all altered. LV remodeling is the term used to describe these facets of cardiac adaptation in disease. Some aspects of the remodeling process may be beneficial to overall cardiac function; however, most of the other aspects are maladaptive in the long term. On the basis of a number of recent clinical trials, which consistently reached the conclusions that (1) ventricular remodeling is progressive in nature, (2) the patients show limited survival, and (3) unloading therapies are beneficial for restoring the life expectancy of these patients, it is generally assumed that the ventricle with remodeling not only decreases the myocardial contractility but also wastes excessive energy by producing a unit force resulting in an energy-starved condition. Despite the presence of several established animal models of heart failure, this important issue has been investigated in a very limited number of studies, and the results obtained are inconsistent. The reasons for the inconsistency may be a lack of suitable reference animals, difficulties in documenting the condition before the heart failure transition, or massive fibrosis that makes the accurate normalization of the energy utilization per tissue erroneous.

Recent studies in our laboratory have shown that when the proper timing of the initiation of high salt diet is selected,
Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPP</td>
<td>coronary perfusion pressure</td>
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<tr>
<td>DR</td>
<td>Dahl salt-resistant (rats)</td>
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<tr>
<td>DS</td>
<td>Dahl salt-sensitive (rats)</td>
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<tr>
<td>EDPVR</td>
<td>end-diastolic pressure-volume relationship</td>
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<tr>
<td>ESPVR</td>
<td>end-systolic pressure-volume relationship</td>
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<tr>
<td>LV</td>
<td>left ventricular, left ventricle</td>
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<tr>
<td>LVF</td>
<td>left ventricular failure</td>
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<tr>
<td>LHV</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>MV O₂</td>
<td>myocardial oxygen consumption</td>
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<td>PVA</td>
<td>pressure-volume area</td>
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DS rats show LV concentric hypertrophy with normal mid-wall stress and neurohumoral activities. These findings are soon followed by the dilatation and global hypokinesis of LV with elevated mid-wall stress, augmented hormonal activities, and pulmonary congestion. The alterations of chamber and myocardial contractility have been demonstrated during the transition from compensatory LHV to LVF in both in vivo and in vitro studies. Hence, this animal model might provide an opportunity to investigate the changes in myocardial energetics during the mechanical transition/remodeling process. The concepts of systolic LV elastance (Emax) and PVA proposed by Suga and others have facilitated research on myocardial mechanoenergetics in isolated animal hearts, as well as in vivo human hemodynamics. In the present study, using the PVA versus myocardial MV O₂ framework in hearts isolated from DS rats at different stages, we quantitatively delineated the alteration of myocardial energetics that occurred during the heart failure transition/ventricular remodeling process.

Methods

Dahl Rat Heart Failure Model

Male inbred DS and DR rats that were obtained from Brookhaven National Laboratories (Upton, NY) were bred and supplied by Eisai Co (Tokyo, Japan). The rats were fed a 0.3% NaCl (low salt) diet after weaning until the age of 6 weeks, after which they were fed an 8% NaCl (high salt) diet. The special diet and tap water were given ad libitum throughout the experiment. As we reported previously, under this protocol, DS rats develop concentric LVH at the age of 11 weeks (LVH-DS) followed by marked LV dilatation at the age of 16 to 20 weeks (LVF-DS). During the latter stage, DS rats show the labored respiration with LV global hypokinesis and enlargement that is characteristic of congestive heart failure. After the onset of respiratory distress, these rats die within 30 minutes, during which time the LVP, CPP, and the O₂ yield a maximal oxygen tension. The heart was allowed to stabilize for at least 30 minutes, during which time the LVP, CPP, and the O₂ were measured at the same time of the EDD measurement. For each measurement, data from five repeated records were averaged. From these measurements, the LV fractional shortening (FS) and LV end-systolic meridional wall stress (σₚ) were calculated according to the following formulas:

\[
\text{LV FS} = \frac{(\text{EDD} - \text{ESD})}{\text{EDD}} \times 100
\]

\[
\text{LV } \sigmaₚ (\text{dyn/cm}²) = 0.33 \times \text{SBP} \times \text{ESD} \times \frac{25}{(1 + \text{PWT}/\text{ESD})}
\]

The peak systolic blood pressure (SBP) in Equation 2 was obtained noninvasively from the tail-cuff pressure measurement.

Isolated Heart Preparation

In each experiment, a rat was heparinized (2000 U/kg IP) and then anesthetized with sodium pentobarbital (100 mg/kg IP). A midline sternotomy was performed, and the inferior and superior venae cavae were ligated near their insertions into the right atrium. The heart was rapidly excised and submerged into oxygenated perfusate (37°C, composition provided below). The severed end of the ascending aorta was immediately fed over a 16-gauge needle (covered with silicone tubing) that was connected to a Langendorff coronary perfusion system. The perfusate flow was initially adjusted to provide a mean CPP of 100 to 120 mm Hg. The CPP was readjusted to 140 mm Hg at the end of preparation. The coronary flow rate was kept constant during the experiment. This relatively high CPP was used because of the systemic hypertension in DS rats. In preliminary experiments, hearts isolated from DR rats showed the typical Gregg’s phenomenon in the range of 80 to 150 mm Hg and were stable in this perfusion range.

The LV apex was punctured with a thin piece of Tygon tubing to discharge the Thesbian drainage. Another piece of soft silicone tubing with a fenestrated tip was advanced into the right ventricle via the main pulmonary artery and then held in place by suturing it securely at its base. The opposite end of this tube was placed 5 cm below the position of the heart, and the collected fluid (all perfusate through the coronary sinus and the right ventricular Thesbian veins) was passed down the tube by siphoning.

The left atrial appendage was opened, and a thin latex balloon that was attached to the end of a 10-cm piece of stiff polyethylene tubing was inserted into the LV cavity through the mitral valves. The balloon was held in place by a purse-string suture around the mitral annulus, ensuring that the circumflex coronary artery was not damaged. The balloon and tubing were filled with water and connected to a pressure transducer (Hewlett-Packard 1280A) for measurement of the isovolumic LV pressure. The balloon volume was controlled using a calibrated 0.5-ML gas-tight Hamilton syringe. To prevent contamination of the latex balloon elastance in the LV pressure measurement, the balloon was tested before each experiment and used only when it did not generate any pressure until the intraballoonal volume exceeded 0.5 mL. The volume of the balloon plus the tip of the tubing within the balloon (range, 0.12 to 0.18 mL) was measured by water displacement after all fluid was withdrawn from inside the balloon; this value was added to the volume infused inside the balloon to obtain the total LV volume.

A bipolar pacing catheter was inserted into the right ventricle through the right atrium and then connected to an electronic stimulator (SEN-3201, Nihon-Kohden) that was paced at 10% above the threshold at 3.33 Hz (200 bpm).

The heart was submerged into the heat-jacketed organ bath at 37°C. The flow rate of the coronary perfusion was kept constant by an adjustable-speed rotary pump (Masterflex model 7523-10, Cole-Parmer Instruments Co), and the CPP was continuously monitored from the sidearm of the perfusion line that was attached to another perfusion system. The perfusate was composed of (in mmol/L) NaCl 135.0, KCl 5.0, Na₂HPO₄ 0.33, MgCl₂ 1.0, CaCl₂ 1.7, dextrose 10.0, and HEPES 5.0. The pH was adjusted to 7.40 with NaOH at 37°C, and the solution was continuously bubbled with 100% O₂ to yield a maximal oxygen tension. The heart was allowed to stabilize for at least 30 minutes, during which time the LVP, CPP, and the O₂ tension of the coronary effluent (vide infra) were monitored.
MVO₂ Measurement

The O₂ contents of the coronary perfusate and the effluent were continuously monitored with a pair of O₂ electrodes (Clark type, Unique Medical Co.), one of which was inserted to the perfusion line at the level of the ascending aorta and the other of which was positioned inside the pulmonary arterial drain tubing. Sodium dithionite was used to determine the baseline of the electrodes at the beginning of each experiment. The gains of the electrodes were calibrated against the perfusate solution, which had been equilibrated with 100% O₂. The O₂ content was referred to a Lex-O₂-CON blood gas analyzer. The MVO₂ was determined as the difference of O₂ contents between the two electrodes (A-VDO₂) times the coronary flow (CF) rate. The CF rate was measured by the timed collection of the pulmonary effluent in a calibrated cylinder.

Experimental Protocols

In all preparations, the LV mechanical performance and MVO₂ were studied while the workloads were varied by stepwise increments of the LV volume. The pacing rate (3.33 Hz) and the CF rate (adjusted to 140 mm Hg at the end of preparation) were kept unchanged. The measurements were repeated when the LVP and A-VDO₂ reached a steady state at each LV volume. One series of the volume run was usually completed within 30 minutes. The reproducibility of the maneuver was checked by observing that the values of the ESPVR (vide infra) were always within 95% confidence limits in the DR maneuver was checked by observing that the values of the ESPVR usually completed within 30 minutes. The reproducibility of the strain (n=6) after multiple volume runs. On the basis of this observation, we set a criterion that the data would be discarded when the LVP after a run had not returned to a level >90% of the control LV volume.

After the initial volume run (Ca²⁺ 0.7 mmol/L), the Ca²⁺ concentration in the perfusate was increased to 1.0 mmol/L and then to 2.0 mmol/L. At each Ca²⁺ level, the volume run was repeated using the same incremental protocol. Recordings at the Ca²⁺ concentration of 1.0 mmol/L were taken as the standard. Along with the exclusion criterion, the results of the following animals were not included in the data analysis because of their incomplete recovery after each of three serial volume runs: 6 of the 12 LVH-DS rats, 5 of the 11 DR rats at 11 weeks, 5 of the 11 LVF-DS rats, and 4 of the 10 DR rats at 18 weeks. Subsequently, 6 animals from each group were subjected to the data analysis (vide infra). The stability of the preparations and the reproducibility of responses to the workloads appeared not to differ among these groups.

At the end of the study, the heart was arrested by replacing the perfusate with that containing 30 mmol/L KCl (NaCl was reduced to 110 mmol/L). The LV balloon volume was gradually reduced to 140 mm Hg at the end of preparation) were kept unchanged. The reproducibility of the contractile state of the LV, pressures were plotted against the LV volume (V) to construct the pressure-volume diagram. To assess the contractile state of the LV, the ESPVRs were fit into a nonlinear regression analysis:

\[
P_{es} = \frac{P_v}{(V_v - V_0) + \alpha (V_v - V_0)^2}
\]

where \(P_v\) is the volume axis-intercept of the ESPVR and \(E_s\) is the slope of the extrapolated ESPVR at the volume of \(V_v\). \(\alpha\) is the index of the degree of ESPVR curvilinearity. The significance of \(\alpha\) that represented the curvilinearity of ESPVR was determined by Student’s \(t\) test.

The EDPVRs were fit to a monoequation:

\[
P_{es} = P_{es} + \beta (e^{x+y} - 1)
\]

where \(V_o\) is the end-diastolic volume, \(P_{es}\) is the pressure at \(V_o=0\), and \(\beta\) and \(\gamma\) are nonlinear fit parameters. Diastolic chamber stiffness (dP/dV₁) was calculated from the first derivative of Equation 4.

The pressure-volume relationships have limitations in the assessment of the contractile state of the unit myocardium because of their dependence on chamber size and ventricular mass. To further quantify the myocardial contractile state, a stress-strain analysis with a thick-walled spherical ventricular model was used (see Appendix for details). The end-systolic circumferential wall stress-strain relation was fit by the following equation:

\[
\sigma_{es} = A \times \epsilon_{es} + B
\]

where \(\sigma_{es}\) is the end-systolic stress, \(\epsilon_{es}\) is the end-systolic strain, and \(A\) and \(B\) are fit parameters.

The total energy liberated by the ventricle under the isovolumic conditions was quantified by the PVA. The PVA was defined as the area circumscribed by the ESPVR, EDVPR, and the systolic portion of the pressure-volume trajectory. The PVA was normalized by the LV mass to 1 g. The value of MVO₂ was reported as milliliters of O₂ per beat per gram LV after the estimated right ventricular MVO₂ was subtracted. The MVO₂ by an unloaded right ventricle might consist of a small part of the measured MVO₂; hence, it was approximated by multiplying the MVO₂ value at unloaded contractions (the intercept of MVO₂ axis at estimated zero PVA) by the ratio of the right ventricular mass to the total heart mass. To assess the contractile efficiency, a linear regression analysis was then performed to quantify the slope (\(C\)) and intercept (\(D\)) parameters of the relationship:

\[
MVO₂ = C \times PVA + D
\]

The enhancement of \(E_s\) by increasing the Ca²⁺ concentration in the perfusate shifted the MVO₂-PVA relationship in a parallel manner (increases in the intercept \(D\) whereas the slope \(C\) was unaffected). Therefore, the relationship between \(E_s\) and the corresponding PVA-independent MVO₂ (intercept D) was plotted to the following equation:

\[
D = E \times E_s + F
\]

where the slope of this regression line, \(E\), represents the oxygen cost of contractility.

Statistics

Data are presented as mean±SEM unless indicated otherwise. Comparisons of variables among the groups were made by one-way ANOVA. When the F test indicated a significant difference among the groups, the difference in mean values was tested by Fisher’s protected least-significant difference method. Comparisons of the MVO₂-PVA regression lines and comparisons of the regression lines of PVA-independent MVO₂ on \(E_s\) among the groups were performed by ANCOVA. Significant differences were determined by F test. Values of \(P<.05\) were considered significant.

Results

Transition from LVH to LVF in Dahl Rats

Table 1 summarizes the hemodynamic and pathological profiles of the Dahl rats enrolled in the data analysis. The LVH-DS and LVF-DS groups showed systemic hypertension to the same extent. Despite the excessive afterload, the systolic wall stress of the LVH-DS remained within the normal range because of a 53% increase in the wall thickness. In contrast, in the LVF-DS, the wall stress increased to a level four times greater than that in the age-matched controls. This was associated with a marked increase in the chamber diameter and a decrease in the fractional shortening. The unstressed LV volume (V₀) in the LVF-DS rats also showed a 58% increase. This set of changes seen in DS rats during a short period provides a paradigm of the transition from LV compensatory hypertrophy to decompensated failure with the typical features of LV remodeling.
control animals, DR rats fed the same high salt diet, did not develop systemic hypertension and maintained a normal hemodynamic profile with no increase in the LV to body weight ratio.

Changes of Systolic Ventricular Mechanics During Transition to Heart Failure

Fig 1 presents the pressure-volume relationships plotted from the representative hearts. During each volume run, five to eight points at end systole and at end diastole were plotted. We observed that both the ESPVR and the EDPVR in the LVH-DS group were consistently shifted to the left (upward) of those in the 11-week-DR group. In contrast, both the ESPVR and EDPVR in the LVF-DS rats were located to the right (downward) of those in the 18-week-DR group.

Because inspections of the ESPVRs suggested that their curvilinearity could alter depending on the stage or the ventricular size, we used a parabolic (binominal) curve fitting (Equation 3) for the analysis, which provided reliable fits in preparations from all four groups (the \( r \) values are presented in Table 2). The coefficient of the second term (\( \alpha \)) was significantly different from the nil value in the LVH-DS and DR groups, indicating their nonlinear relationships. By contrast, in the failing hearts of the LVF-DS, the relationship typically showed a linear fitting, and the value for this group was not significantly different from zero. The result supported the idea that for the comparative analysis of the ESPVR among hearts of different sizes or from different stages such as those examined in this study, the binominal nonlinear fitting might be more suitable than the standard linear regression method.

Table 2 summarizes the data of the ESPVR of the four groups. The LVH-DS group showed a significant increase in \( E_{es} \), whereas the \( V_0 \) was equivalent to that of the age-matched DR rats. In contrast, in the LVF-DS rats, the \( E_{es} \) was markedly reduced to 50% of that of the LVH-DS rats and to 78% of that of the age-matched DR rats, which was associated with a significant increase in \( V_0 \). This change in \( V_0 \) was consistent with the twofold increase in \( V_{ref} \) measured in the \( K^+ \)-arrested condition (Table 1).

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**TABLE 1. Blood Pressure, Echocardiographic, and Pathological Data**

<table>
<thead>
<tr>
<th></th>
<th>11-wk-DR</th>
<th>LVH-DS</th>
<th>18-wk-DR</th>
<th>LVF-DS</th>
</tr>
</thead>
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<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127±3</td>
<td>235±4*</td>
<td>121±5</td>
<td>231±5*</td>
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<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
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<tr>
<td>EDD, mm</td>
<td>6.2±0.1</td>
<td>5.7±0.1*</td>
<td>6.8±0.1‡</td>
<td>9.1±0.2†</td>
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<tr>
<td>ESD, mm</td>
<td>3.3±0.1</td>
<td>2.5±0.1*</td>
<td>3.8±0.1‡</td>
<td>6.5±0.2‡</td>
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<tr>
<td>PWT, mm</td>
<td>1.5±0.02</td>
<td>2.3±0.04*</td>
<td>1.6±0.03</td>
<td>1.6±0.02†</td>
</tr>
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<td>FS, %</td>
<td>47±1</td>
<td>56±1*</td>
<td>45±1</td>
<td>29±1†</td>
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<td>Systolic wall stress, kdyne/cm²</td>
<td>95±2</td>
<td>102±5</td>
<td>105±4</td>
<td>403±13†</td>
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<tr>
<td>Pathological data</td>
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<td>LV, g</td>
<td>0.78±.02</td>
<td>1.14±.04*</td>
<td>0.93±.03‡</td>
<td>1.39±.05†</td>
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<td>RV, g</td>
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<td>0.21±.01</td>
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<tr>
<td>LV/body weight, mg/g</td>
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<td>1.95±.05</td>
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<td>RV/body weight, mg/g</td>
<td>0.51±.03</td>
<td>0.66±.01</td>
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<tr>
<td>V_{ref}, mL</td>
<td>0.095±.002</td>
<td>0.077±.002*</td>
<td>0.109±.002‡</td>
<td>0.172±.002†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. 11-wk-DR and 18-wk-DR indicate Dahl salt-resistant rats at the age of 11 weeks and 18 weeks, respectively; LVH-DS and LVF-DS, Dahl salt-sensitive rats with LVH and LVF, respectively; n, number of rats; SBP, systolic blood pressure; EDD, end-diastolic LV diameter; ESD, end-systolic LV diameter; PWT, posterior wall thickness; FS, fractional shortening; RV, right ventricle; and \( V_{ref} \), LV volume attaining zero pressure during \( K^+ \) arrest.

* \( P<.05 \) compared with age-matched DR; † \( P<.05 \) compared with LVH-DS; ‡ \( P<.05 \) compared with 11-wk-DR.

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**Figure 1.** ESPVR and EDPVR in representative experiments: left, LVH-DS vs 11-week-DR; right, LVF-DS vs 18-week-DR. LVV and LVP represent left ventricular volume and pressure, respectively. The Ca²⁺ concentration in the perfusate was 1.0 mmol/L. Symbols show the individual data, and the superimposed lines show the curve fitting for each group.
Changes of Myocardial Contractility

The contractile states of the unit myocardium in the isolated hearts were estimated independently of the chamber geometry and mass by a stress-strain relationship. In Fig 2, the end-systolic stress-strain relations from all experiments were plotted, and the fitted lines for each group were superimposed on the individual data. The regression line of the LVH-DS group was significantly different from the lines of the other three groups in its shift toward the left. By contrast, the line of the LVF-DS group was located to the right of the others. The relations between the 11-week-DR and the 18-week-DR were superimposable. Hence, the hypercontractile state of the unit myocardium caused the increased \( E_s \) in the LVH-DS rats, whereas it showed a marked decrease during the transition and resulted in the LV hypocontraction in the LVF-DS rats.

Diastolic Ventricular Mechanics

As noted above, the EDPVR in the LVH-DS group was located to the left side of the control, whereas the EDPVR in the LVF-DS group shifted to the right and downward. Despite these alterations, the diastolic chamber stiffness, \( \gamma \), as estimated from the monoexponential fitting, was not significantly different among the groups (Table 2). We further examined the slope of the EDPVR at a common end-diastolic pressure of 15 mm Hg. The values were also similar among the groups (112 and 110 mm Hg/mL in 11-week-DR and 18-week-DR, 127 mm Hg/mL in LVH-DS, and 136 mm Hg/mL in LVF-DS; no significance between any two groups). In crystalloid-perfused preparations, the diastolic chamber characteristics might be affected by the tissue water content. The myocardial flow rates (CF/LV mass), however, were not different among the groups (25 mL/g in both 11-week- and 18-week-DR and 18-week-DR, 127 mm Hg/mL in LVH-DS, and 136 mm Hg/mL in LVF-DS; no significance between any two groups).

### Table 2: Analysis of ESPVR and EDPVR: Summary of Nonlinear and Monoexponential Curve Fitting

<table>
<thead>
<tr>
<th>Status</th>
<th>No.</th>
<th>( E_s ) (mm Hg·g·mL(^{-1}))</th>
<th>( \alpha )</th>
<th>( V_0 ) (mL)</th>
<th>( r )</th>
<th>( P_0 ) (mm Hg)</th>
<th>( \beta )</th>
<th>( \gamma )</th>
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<td>.99</td>
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<td>−2.08E-8</td>
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<td>.96</td>
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<td>Mean±SEM</td>
<td></td>
<td>681±24*</td>
<td>−688±83*</td>
<td>0.002±.002</td>
<td>.99</td>
<td>−8.4±2.0</td>
<td>99±58</td>
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</table>

\( E_s \) (mm Hg·g·mL\(^{-1}\)), \( \alpha \) (mm Hg·g\(^2\)·mL\(^{-2}\)), and \( V_0 \) (mL) indicate slope, degree of linearity, and volume intercept of ESPVR derived from binominal curve fitting, respectively; \( P_0 \) (mm Hg), \( \beta \) (mm Hg), and \( \gamma \), asymptote LV pressure, amplitude constant, and rate constant of EDPVR derived from exponential curve fitting, respectively; 11-wk-DR and 18-wk-DR, Dahl salt-resistant rats at the age of 11 weeks and 18 weeks, respectively; and LVH-DS and LVF-DS, Dahl salt-sensitive rats with LVH and LVF, respectively.

* \( P<.05 \) compared with age-matched DR; † \( P<.05 \) compared with LVH-DS.
week-DR, 25 mL/g in LVH-DS, and 23 mL/g in LVF-DS; no significant difference between any two groups).

Effects of Inotropic Intervention and Myocardial Energetics

The myocardial contractility was varied by changing the Ca\(^{2+}\) concentration in the perfusate ([Ca\(^{2+}\)]\(_{o}\)) from 0.7 mmol/L to 1 mmol/L and then to 2 mmol/L. As shown in Fig 3A, the end-systolic points at any [Ca\(^{2+}\)]\(_{o}\) level were fit equally well by the binominal regression. The increase in [Ca\(^{2+}\)]\(_{o}\) did not affect the value of V\(_{0}\). In contrast, the levels of E\(_{es}\) were significantly augmented in both the LVH-DS and LVF-DS groups (Fig 3B). It is noteworthy that although the baseline levels of E\(_{es}\) were different by approximately twofold between the two stages, their percentages of augmentation by this increase in [Ca\(^{2+}\)]\(_{o}\) were similar (53% in LVH-DS, 57% in LVF-DS).

Fig 4 shows the grouped data of the M\(\dot{V}\)O\(_2\)-PVA relations from the LVH-DS and 11-week-DR rats (left) and LVF-DS and 18-week-DR rats (right). The M\(\dot{V}\)O\(_2\)-PVA relations were highly linear in the range examined in all groups, and their lines were essentially in parallel. Hence, the slope C was unchanged among the groups. Interestingly, the line of the LVH-DS group was located in a position superior to that of the age-matched controls, whereas the line of the LVF-DS group was located inferior to that of the 18-week-DR rats. This resulted in a 45% reduction of the intercept D during the transition from LVH-DS to LVF-DS. In contrast, between the 11-week-DR and 18-week-DR groups, the intercepts were equal, resulting in their superimposable M\(\dot{V}\)O\(_2\)-PVA relations.

The inotropic run by changing [Ca\(^{2+}\)]\(_{o}\) consistently affected the levels of intercept D in all stages. However, the [Ca\(^{2+}\)]\(_{o}\)
level did not modulate the slope C in any group (Table 3). The changes of intercept D by \([\text{Ca}^{2+}]_0\) were plotted against the concomitant increases in E\(\text{es}\) in Fig 5, and the slopes are presented as E (Equation 7) in Table 3. This value, an index of the oxygen cost of contractility, did not differ significantly among the groups.

To further elucidate what aspect of the cellular oxygen consumption was reduced in the failing myocardium, we

**Figure 4.** PVA-MV\(\dot{O}_2\) relationships in the LVH-DS (left) and LVF-DS (right) rats compared with those of the age-matched DR rats. Each point (closed symbols for the DS rats and open symbols for the age-matched DR rats) was obtained during a stepwise change of the LV volume. Grouped data from 6 animals in each group are presented. Lines show the linear regressions. The Ca\(^{2+}\) concentration in the perfusate was 1.0 mmol/L; the ventricular pacing was set at 3.33 Hz.

**TABLE 3.** Analysis of MV\(\dot{O}_2\) and PVA Relations and E\(\text{es}\) and PVA-Independent MV\(\dot{O}_2\) Relations: Summary of Linear Regression Analysis

<table>
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<tr>
<th>Status</th>
<th>0.7 mmol/L</th>
<th>1.0 mmol/L</th>
<th>2.0 mmol/L</th>
<th>Run</th>
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<tr>
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<td>0.41</td>
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<td>Mean±SEM</td>
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<td>0.80±.04*</td>
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<tr>
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<td>2.16±.07</td>
<td>0.44±.02†</td>
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\(C\) (mL O\(\dot{2}\) · mm Hg\(^{-1}\) · mL\(^{-1}\)· min\(^{-1}\)) and D (mL O\(\dot{2}\) · g\(^{-1}\)· beat\(^{-1}\)· min\(^{-1}\)) indicate slope and intercept of MV\(\dot{O}_2\)-PVA relation with linear regression, respectively; E (mL O\(\dot{2}\) · mL\(^{-1}\)· mm Hg\(^{-1}\)· beat\(^{-1}\)· g\(^{-2}\)· min\(^{-1}\)) slope of \(E_{\text{es}}\)-PVA-independent MV\(\dot{O}_2\) relation extrapolated from the Ca\(^{2+}\) inotropic run.

*\(P<.05\) compared with age-matched DR; †\(P<.05\) compared with LVH-DS.
measured the MV\textsubscript{O2} in the K\textsuperscript{+}-arrested hearts. The remaining MV\textsubscript{O2} in this condition should be derived from subcellular activities that were independent of the E-C coupling.\textsuperscript{13,23,35}

Despite substantial differences in the PVA-independent MV\textsubscript{O2}, the K\textsuperscript{+}-arrested myocardium from any stage consumed the same amount of oxygen (36±5 mL O\textsubscript{2}·g LV\textsuperscript{-1}·min\textsuperscript{-1} in LVH-DS, 37±5 mL O\textsubscript{2}·g LV\textsuperscript{-1}·min\textsuperscript{-1} in LVF-DS, NS, n=6, respectively; Fig 6). This result indicates that the substantial reduction of myocardial oxygen consumption in heart failure transition is primarily due to the diminished subcellular activity regarding the E-C coupling.

Discussion

Heart Failure Transition and Ventricular Remodeling in Dahl Rats

DS rats were developed in 1962 from the Sprague-Dawley strain by Dahl and Iwai.\textsuperscript{36,37} When fed a high salt diet after weaning (5 to 8 weeks), these rats develop marked systemic hypertension and have a limited lifespan; they die by the early stage of their maturity.\textsuperscript{38,39} It was generally assumed that uremia due to hypertensive nephrosclerosis was the cause of the early death.\textsuperscript{38} However, in our previous study,\textsuperscript{16,17} we found that when the high salt regimen was started when these rats were 6 weeks old, they died at 18 weeks of age from typical LV dysfunction with pulmonary congestion. This condition was associated with marked increases in LV systolic wall stress, atrial natriuretic peptide, and plasma catecholamines but with only a modest impairment of renal function.\textsuperscript{16} In contrast to this terminal stage of LV failure, the same animals at 11 weeks of age showed normal to hyperdynamic LV function, normal LV wall stress, and normal neurohumoral conditions despite the presence of the similar afterload stress (compensatory concentric LVH). On the basis of these observations, we have proposed this strain as a new model of heart failure in which investigations could be focused on key factors to initiate the transition toward heart failure. There are several types of animal models of LV failure, including senile spontaneous hypertensive rats,\textsuperscript{40} rats with chronic aortic banding\textsuperscript{41} or coronary-ligated infarction,\textsuperscript{42} cardiomyopathic hamsters,\textsuperscript{43} and dogs with chronic tachycardia–induced heart failure.\textsuperscript{44} Because each animal model, including ours, has both advantages and disadvantages, investigators should select the most appropriate model on the basis of their research needs and purposes. In this regard, the DS rat model provides an opportunity to address questions concerning the pathophysiological changes that occur during heart failure transition.

In the present study, using coronary-perfused hearts isolated from Dahl rats, we confirmed that the marked alteration of chamber contractility in association with changes in the LV mass and geometry occurred during a short period of transition from LVH to LVF. The stress-strain analysis precluded the possible role of the chamber geometry as a major cause of the LV contractile dysfunction and further suggested that a substantial change of the contractile performance of unit myocardium played the critical role in the chamber dysfunction. We demonstrated previously that this transition process to LVF was not associated with the significant loss of contractile elements (in LVF-DS, the fibrosis/cross-sectional area remained <2.0%, and this tissue fibrosis occurred mainly around the epicardial coronary arteries and not in the subendocardial layers).\textsuperscript{16} The present data further indicate that the E-C coupling process in each myocardial cell is responsible for this mechanical deterioration. We also demonstrated here for the first time that the failing myocardium utilized 45% less oxygen for its basal activities (PVA-independent O\textsubscript{2} cost) when compared with the preceding compensatory myocardium. At the same time, both the contractile efficiency and the oxygen cost of contractility remained unchanged. Thus, we confirmed that the efficiency of chemomechanical conversion is highly preserved despite the chronically diseased condition with contractile failure. Consequently, the total oxygen consumption per unit of failing myocardium was diminished along with its reduced activity in the E-C coupling process.
Mechanoenergetics in the Failing Rat Heart

The mechanical characteristics of isolated rat hearts under crystalloid coronary perfusion were extensively evaluated by Wannenburg et al. They reported that the preparations were stable over a period of 60 minutes and that the general characteristics of the ESPVR were similar to those reported for isolated blood-perfused dog and rabbit hearts. They also showed that the ESPVRs were equally well fit to both linear and nonlinear curves and that the presented Ees values were comparable to those in standard blood-perfused hearts.

Our nonlinear regression analysis of ESPVR in the DR and LVH-DS hearts showed that the curvilinearity index α was significantly different from nil. This indicates that the nonlinear regression is more suitable for this analysis than is the linear regression for such minuscule hearts. However, the dilated hearts of the LVF-DS rats presented a linear ESPVR. This stage-dependent difference is not surprising, since as discussed elsewhere, the ESPVR unfolded into a sigmoid shape when the relationship was plotted on a wide range of pressure. The smaller the heart, the closer to the upper corner of the sigmoid configuration the relationship locates and vice versa, as is known for the hearts from larger animals. Hence, along with the progression of remodeling, the apparent relationship might become more linear by shifting the operating range toward the middle portion of the sigmoid curve.

The values of Ees estimated in our control animals (435 to 451 mm Hg · g · mL⁻¹) were lower than those reported by Wannenburg et al (645 mm Hg · g · mL⁻¹). However, this is not discordant when our relatively lower Ca²⁺ concentration in the control perfusate is taken into account (1.5 mmol/L in the Wannenburg et al study versus 1.0 mmol/L in our study). Taken together, the results obtained from our experimental settings were qualitatively and quantitatively consistent with those observed by Wannenburg et al, and they further validated the efficacy of the PVA analysis in such small hearts.

There are few experimental studies regarding the quantitative analysis of mechanoenergetics in the failing heart, and the observations that have been obtained are controversial. Goto et al demonstrated the downward and parallel displacement of the PVA-MVO₂ relationship in isolated hearts from pacing-induced failing dogs. Using the same rapid-pacing dog hearts, however, Wolff et al reported that the slope became steeper in the failing heart while the PVA-independent MVO₂ (intercept) remained unchanged. The causes of these differences have not been elucidated. One major shortcoming of these two studies is that neither of them showed the sequential changes in these relationships before and after the heart failure transition. Using isolated hearts from senile spontaneously hypertensive rats, Brooks et al showed that the systolic stress generation at a given oxygen consumption was depressed in both failing and nonfailing myocardium. They interpreted this result as indicating that the energy utilization of the hypertrophic and failing hearts was less economical. However, the stress-MVO₂ relationship described may lack a conceptual background in chemomechanical theory. In addition, a significant loss of myocardial cells and their replacement with massive fibrosis may complicate the normalization of oxygen consumption per unit of myocardium. In our study, these issues were obviated by a set of serial observations in genetically uniform animal strains and by the established pressure-volume framework. Our results indicated that the parallel and downward shift of the PVA-MVO₂ relation is essential during the heart failure transition, which was consistent with the study in dogs by Goto et al. In a patient group in which the Ees levels were widely scattered in a range from 0.8 to 8.8 mm Hg/mL, Kameyama et al showed a constancy of the slope of PVA-MVO₂ relation (2.46 ± 0.33), whereas their oxygen axis intercepts decreased along with the reduction in Ees. Another clinical study by Takaoka et al also presented a similar distribution of the PVA-MVO₂ diagram among patients with different levels of LV contractility. Taken together, these observations suggest that despite the significant differences in species, heart size, and etiology of the disease, failing hearts in the decompensated state might share the common mechanoenergetic characteristics in that they feature a reduction in the oxygen consumption for the basal metabolism with no remarkable change in contractile efficiency.

Subcellular Mechanisms of Mechanoenergetic Changes in the Failing Heart

The K⁺-arrested heart showed a significant reduction in the PVA-independent MVO₂ (by 55% to 76%). Surprisingly, although the MVO₂ intercept in the beating hearts was different depending on the diseased condition, the levels were equalized after flaccid cardiac arrest (Fig 6). This novel finding clearly indicates that the stage-dependent change in the MVO₂ intercept relates to the activities of subcellular systems that halt when the contraction stops. The energy expenditure for the basal metabolism, in contrast, is independent of the disease conditions.

The contraction-related process, namely the E-C coupling, includes energy-dependent components such as actomyosin ATPase, Ca²⁺- and Mg²⁺-dependent ATPase in the sarcoplasmic reticulum, and sarcosomlemal ATPases for the Ca²⁺ pump and Na⁺ pump. These ATPase activities are tightly coupled with the amount of activator Ca²⁺ released to the cytosolic space during membrane depolarization. The ATP consumption increases along with the increase in the activator Ca²⁺, which is expressed as increases in the MVO₂ intercept on the PVA-MVO₂ framework. This type of change in energy utilization was well characterized during acute inotropic interventions by several inotropic agents. Therefore, the mechano-energetic character of the failing heart appears to be similar with acute interventions with negative inotropic agents. Actually, the reduced MVO₂ intercept in the failing heart was augmented to a level equal to that of the age-matched DR rats when the extracellular Ca²⁺ concentration was increased to 2.0 mmol/L. Such chronic conditions may occur in two ways: one is the reduction of the amount of activator Ca²⁺ due to the loss or inactivation of ATPases in the presence of enough ATP/phosphocreatine; the other is the reduction of cytosolic ATP/phosphocreatine which limits the activities of these enzymes, resulting in a decrease in Ca²⁺. In the present study, we could not dissect these two mechanisms. However, in another series of experiments using the same Dahl rat strains, we demonstrated that the Ca²⁺ uptake was reduced by 41% in the presence of a constant ATP.
concentration in isolated sarcoplasmic reticular vesicles from the failing DS myocardium. In contrast, these values in the LVH-DS rats were equal to those of control strains (unpublished observations, Kihara et al, 1997). Furthermore, in studies using the same animals, the cytosolic Ca\(^{2+}\) transients from the failing DS rats showed a significant reduction in amplitude compared with that in the LVH-DS rats.\(^5\) These independent observations strongly suggest that in this heart failure model, the reduction in the number of ATP-dependent enzymes and the subsequent decrease in the amount of mobilized Ca\(^{2+}\) might contribute to the decrease of energy expenditure for the E-C coupling. These subcellular changes may not be specific to these rat strains because the down-regulation of sarcoplasmic reticular ATPase was demonstrated in several experimental models, as well as in explanted human myocardium, in both protein and mRNA levels.\(^3\) A decrease in actomyosin ATPase was also reported in human failing myocardium.\(^6\)

**Chemomechanical Conversion Efficiency**

We observed that despite a decrease in the energy expenditure for E-C coupling, neither the contractile efficiency nor the oxygen cost of contractility were affected during the transition to heart failure. There was a slight tendency toward a decreased slope of the PVA-M\(\dot{V}O_2\) relationship between the LVH-DS and LVF-DS groups (2.35±0.05×10\(^{-5}\) mL O\(_2\) · mm Hg\(^{-1}\) · mL\(^{-1}\) versus 2.16±0.07×10\(^{-5}\) mL O\(_2\) · mm Hg\(^{-1}\) · mL\(^{-1}\)); however, these values were not significantly different (\(P=0.20\)). In addition, they did not show any significance against the age-matched DR groups. Thus, we concluded that changes in the chemomechanical conversion efficiency were not the essential factor in the heart failure transition.

In hypothyroid animals, the isozyme shift of the myosin heavy chain was associated with increases in contractile efficiency at the expense of decreased contraction velocity.\(^2\) A similar isozyme shift may occur in the rat heart with chronic pressure overload.\(^5\) Our preliminary study showed a 30% increase in the expression of \(\beta\)-myosin heavy chain mRNA in the LVH-DS (in comparison with the age-matched DR), but the increase was by only 24% in the LVF-DS rats (unpublished observations, Kihara et al, 1997). These data suggest that the myosin isozyme shift was in progress in our preparations in both the LVH-DS and the LVF-DS groups. However, these changes appeared not to be sufficient to modulate the slope of the contractile efficiency on the PVA-M\(\dot{V}O_2\) diagram. The cross-bridge cycling rate may also change in the failing heart.\(^2\) However, it was noted that the coupling rate between ATP hydrolysis and cross-bridge cycling is not fixed in a one-to-one relation; rather it varies depending on the loading condition up to 1:6 or more.\(^5\) Hence, these changes may not strictly affect the contractile efficiency.

In the present study, the chemomechanical efficiency was quite constant in a narrow range from 44% to 48% despite different disease conditions. In excised dog hearts, the efficiency was reported to be limited to the same range at all loading conditions, heart rates, and inotropic interventions.\(^2\) In vivo human LV in various contractile states, Kameyama et al\(^7\) and Takaoka et al\(^8\) also reported these values to be approximately 41% to 45%. The chemomechanical efficiency represents a product of the chemical conversion rate during mitochondrial respiration and the mechanical conversion rate during ATP consumption for the E-C coupling. The consistency of this surprisingly high efficiency may indicate that these chemomechanical processes are preserved at the optimal level regardless of the contractile state or of the presence of chronic disease conditions.

**Remodeling and Diastolic Chamber Compliance**

Despite the progress of LV chamber remodeling during the heart failure transition, our analysis of passive chamber elastance in the EDPVR did not show significant changes. Our analysis could be biased by the narrow pressure range we measured or by the coronary perfusion with a crystalline solution, in which the tissue water content increased by sixfold to eightfold.\(^9\) However, the values of \(\gamma\) (a nonlinear parameter of chamber stiffness) were comparable to those reported in blood-perfused isolated hearts.\(^5\) In the isolated heart from dogs with pacing-induced heart failure, Wolff et al\(^9\) did not observe changes in the chamber compliance, whereas the chamber showed significant remodeling. This finding is consistent with ours. These observations suggest that the remodeling process is not necessarily associated with the increase in myocardial stiffness unless significant tissue fibrosis occurs during the course, as has been demonstrated in senile spontaneously hypertensive rats.\(^5\) Because diastolic abnormalities repeatedly have been reported as a primary manifestation of heart failure in experimental as well as clinical settings,\(^5\) our data support the hypothesis that the diastolic dysfunction in failing myocardium is critically determined not by the passive tissue architecture but by more dynamic factors such as intracellular Ca\(^{2+}\) handling or cross-bridge cycling.\(^3\)

**Hypercontractile State in LVH-DS Rats**

The present study showed that the LV in the compensatory hypertrophic state in the LVH-DS rats had an increased chamber contractility, above that in the age-matched DR rats. The end-systolic stress-strain relationship indicated that this was not due to the chamber geometry or its loading conditions. At the same time, the level of the PVA-independent M\(\dot{V}O_2\) showed a significant increase above control. This independent measure further supported the presence of the supercontractile state in the hypertrophic myocardium. Therefore, the hypercontractile state preceded the subsequent heart failure transition, which in turn resulted in a marked change to the hypocontractile state below the control level. Accordingly, our previous studies\(^16\) showed that the in vivo measurements of ESPVR in the LVH-DS rats were located to the left side of those in the age-matched DR. Because the hormonal factors such as catecholamines were not elevated in the LVH-DS rats,\(^16\) these factors were not likely the direct cause of the hypercontractile state. Furthermore, in the present study with isolated hearts, we examined the effects of an intrinsic release of tissue catecholamines by adding 3×10\(^{-7}\) mol/L propranolol to the perfusate in two prepara-
tions from the LVH-DS rats. However, the developed pressure was decreased only modestly, and the contractile state remained elevated. Recent studies in hypertrophic myocytes isolated from spontaneously hypertensive rats support our observation.\textsuperscript{55–65} Brooksbys and al\textsuperscript{66} suggested that the increased contractile state was caused by an increase in the Ca\textsuperscript{2+} influx during the prolonged action potential because it disappeared under a membrane voltage clamp. Taken together, these observations suggest that our finding of a hypercontractile state in the LVH-DS rats was not an artificial observation nor was it due to an inappropriate selection of control animals. Rather, such a level of contractility might be required to normalize the wall stress in the presence of excessive afterload. The excessive energy expenditure in this “compensatory” state may provide a detrimental access to the heart failure transition.

**Conclusion**

In conclusion, decreases in myocardial contractility and ventricular remodeling occurred during the transition from LVH to LVF. Despite the marked change in myocardial contractility, both the contractile efficiency and the oxygen cost of contractility of the LV myocardium in these two stages remained unchanged. Thus, the efficiency of chemomechanical conversion was highly preserved even in the chronically diseased myocardium. Consequently, the total energy consumption per unit of failing myocardium showed a decrease in a manner parallel to its contractile state by reflecting the reduced E-C coupling activity. This observation is consistent with our recent findings that the intracellular Ca\textsuperscript{2+} transients and the sarcoplasmic reticular activities of the LV myocardium were decreased (resulting in diminished basal contractility) at the time of heart failure transition.\textsuperscript{49}

**Appendix**

In the balloon-fixed isovolumic heart preparation, instantaneous natural strain (\(\epsilon\)) at the cross-sectional area of the ventricular wall in the equatorial plane was assumed as

\[
\epsilon = \ln(V_{\text{ball}} + V_{\text{wall}})/(V_{\text{wall}} + V_{\text{wall}})^{1/3}
\]

where \(V_{\text{ball}}\) is the latex balloon volume, \(V_{\text{wall}}\) is the ventricular wall volume (1.05 mL/g LV mass), and \(V_{\text{ref}}\) is the K\textsuperscript{-}-arrested LV volume (reference volume).

The end-systolic circumferential wall stress (\(\sigma_{c}\)) was calculated by a balanced-force equation for a thick-walled spherical geometry:\textsuperscript{66}

\[
\sigma_c = \frac{P_s \times (R_i^2 / h) / (2 R_i + h)}{(2 R_i + h)}
\]

where \(P_s\) is the end-systolic LV pressure, \(R_i\) is the internal radius of the LV cavity \((3V_{\text{wall}} / 4 \pi)^{1/3}\), and \(h\) is the LV wall thickness, which was calculated as follows:

\[
h = (V_{\text{ball}} + V_{\text{wall})/4 \pi /3}^{1/3} - R_i
\]

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