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Catecholamines restore myocardial contractility in dilated cardiomyopathy at the expense of increased coronary blood flow and myocardial oxygen consumption (MvO_2 cost of catecholamines in heart failure)

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Abstract

To investigate the metabolic cost of catecholamine use in heart failure, we administered intravenous dobutamine or norepinephrine to dogs with moderate and severe LV dysfunction until LV contractile function was restored to normal levels. Both drugs were associated with significant increases in myocardial O_2 consumption, increased coronary blood flow requirements and decreased myocardial mechanical efficiency. These mechanisms may contribute to the deleterious effects of catecholamines in heart failure.

Keywords: Catecholamines; Heart failure; Myocardial oxygen consumption; Myocardial efficiency

1. Introduction

Although catecholamines are used clinically to provide short-term hemodynamic support in decompensated congestive heart failure (CHF), their long-term use has deleterious effects in patients with CHF [1–7], despite progressive desensitization to the inotropic effects of adrenergic stimulation demonstrated in clinical [8,9] and experimental [10,11] studies. Excessive metabolic demands in response to catecholamine administration have been implicated as a possible mechanism [12–14]. We hypothesized that the restoration of LV contractile function attained by using catecholamines in dilated cardiomyopathy (DCM) is accompanied by excessive myocardial O_2 consumption (MvO_2) and greater coronary blood flow (CBF) requirements. The purpose of our study was to investigate the metabolic effects of β1-adrenergic receptor (AR) stimulation (Dobutamine) and combined α- and β-1 AR stimulation (Norepinephrine) at doses required to restore 'normal' contractile function (LV dP/dt) or mean arterial pressure (MAP) in progressive dilated cardiomyopathy

2. Methods

2.1. Instrumentation

Sixteen Mongrel dogs of either sex weighing 15–20 kg were sedated with xylazine (2 mg/kg im) and anesthetized with halothane (1% vol). Using a sterile technique, catheters were implanted in the left atrium (LA), right atrium (RA), descending thoracic aorta (a), and coronary sinus (v) through an incision in the left fifth intercostal space. A solid-state pressure transducer was implanted in the left ventricular (LV) apex to measure LV pressures and LV dP/dt. Transonic flow

Abbreviations: CHF, Congestive heart failure; CO, Cardiac output; SV, Stroke volume; CBF, Coronary blood flow; MvO_2, Myocardial O_2 consumption; MAP, Mean arterial pressure; HR, Heart rate; LVEDP, Left ventricular end-diastolic pressure; LV dP/dt, first derivative of LV pressure; LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter.

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probes were implanted in the ascending aorta and the left circumflex coronary artery, for determination of cardiac output (CO) and coronary blood flow (CBF), respectively. Piezoelectric ultrasonic dimension crystals were implanted on the anterior and posterior endocardial surfaces of the LV to measure the internal short axis diameter in end-diastole (LVEDD) and end-systole (LVESD). Similar piezoelectric crystals on the endocardial and epicardial surfaces of the posterior wall were utilized to measure wall thickening (WTh). A sutureless pacing lead was implanted on the epicardial surface of the right ventricle. All animals received analgesics as needed for the first 72 h following surgery and cephalexin (1 g. IV) daily for seven days. The dogs were allowed to recover from the surgical procedure for 2 weeks, during which time they were trained to lie quietly on the experimental table in a conscious, unrestrained state. All catheters were flushed daily and filled with a 50% heparin solution to maintain patency. Control experiments were initiated 2 weeks after recovery from the surgical instrumentation. Animals used in this study were maintained in accordance with the 'Guide for the Care and Use of Laboratory Animal Resources' [DHHS Publication No (NIH) 86-23, Revised 1996] and the guidelines of the Institutional Animal Care and Use Committee at Allegheny General Hospital.

2.2. Heart failure induction

Following completion of 'control' experiments, rapid RV pacing at 240 min^{-1} was initiated in all dogs. Thereafter, the dogs were reassessed on a daily basis for clinical signs (fatigue, anorexia, tachypnea, tachycardia, edema, ascites) and hemodynamic parameters to establish the progressive development of dilated cardiomyopathy. In addition, all catheters were flushed and all transducers were calibrated daily.

Moderate LV dysfunction was defined as the presence of mild clinical signs and modest hemodynamic perturbations (LV $dP/dt < 2000$ mmHg$\times s^{-1}$, LVEDP > 16 mmHg) without significant LV dilatation. Severe LV dysfunction was defined as more pronounced clinical and hemodynamic deterioration (LV $dP/dt < 1500$ mmHg$\times s^{-1}$, LVEDP > 22 mmHg) as well as significant LV dilatation (LVEDD increase by > 2 mm and LVESD increase by > 4 mm compared to 'control' values) and depressed cardiac output. Consistent with previous studies utilizing this animal model [15,16], moderate heart failure stage (m-CHF) ensued after 10 ± 3 days of pacing and severe heart failure stage (s-CHF) after 27 ± 4 days of pacing in our dogs.

2.3. Hemodynamic measurements

Hemodynamic measurements were made with the dogs fully awake, lying quietly on their right side. A 30-min stabilization period following deactivation of the pacemaker preceded all experiments in CHF. Control experiments consisted of systemic and coronary hemodynamic recordings to determine the 'normal' range values for LV contractility (LV dP/dt), stroke volume (SV), cardiac output (CO), and coronary blood flow (CBF). Coronary arterial (a) and coronary sinus (v) blood samples were obtained to calculate myocardial O_2 extraction [$100 \times$ (a–v)/ (a) O_2 content]. Myocardial oxygen consumption (M_vO_2) was calculated as the product of the left circumflex coronary artery blood flow and the myocardial arterio-coronary sinus O_2 content difference: [$M_vO_2 =$ (CBF $\times$ (a–v) O_2 content]. Coronary sinus pH (Cs-pH) was also measured, using an automatic blood gas analyzer (Radiometer, Inc.).

End-systolic (σ-$_{es}$) and end-diastolic (σ-$_{ed}$) myocardial wall stress was calculated according to Laplace's law [wall stress = (pressure $\times$ radius)/(2 $\times$ wall thickness)] applied to LV end-systolic and end-diastolic values, respectively [14–17]. Myocardial stroke work (SW) and myocardial efficiency index (MEI) were calculated as described by Eichhorn et al. [18]. Stroke work was calculated using the formula SW = $\Delta P \times \Delta V \times 0.0136$, where $\Delta P =$ LVP − LVEDP and $\Delta V =$ LVEDV − LVESV, using sonomicrometry-derived data. Myocardial efficiency was calculated from directly derived hemodynamic parameters, as follows: ME (%) = (SW $\times$ HR)/2.059 $\times$ MvO_2.

Pressure–Volume loop analysis: In a subset of animals ($n = 7$), simultaneous recordings of LV pressure and ventricular chamber dimensions were digitized at a rate of 200 samples/s using a PC-based data acquisition package (Windaq, Dataq Instruments, Akron, OH) in order to generate pressure–volume (PV) loops for stroke work analyses. For each animal tested, PV data were collected without adrenergic stimulation and in the presence of 'low-dose' and 'high-dose' Dobutamine (2.5 and 10 mg/kg/min) and Norepinephrine (0.1 and 0.4 mg/kg/min). Experiments were conducted in control state and under conditions of moderate and severe heart failure. LV external work (EW)-defined as the area enclosed by the PV loop-was calculated using a single dimension spherical approximation of ventricular volume (CardioSoft software, Sonometrics Corp., London, Ontario, Canada). Data from 5 to 10 consecutive beats per experimental protocol were signal averaged for analysis. The EW/ MvO_2 ratio was used as an index of mechanical efficiency of the LV in this group of animals.

Catecholamine administration: Graded intravenous infusions of dobutamine (1–10 μg/kg/min) and norepinephrine (0.05–0.4 μg/kg/min) were administered to animals with CHF until restoration of normal LV dP/dt. To avoid residual pharmacodynamic effects, the drugs were administered on two consecutive days, in random order. The same hemodynamic and metabolic parameters (CBF, MvO_2, arterial and coronary sinus blood gases)

Table 1
Hemodynamic changes associated with the development of progressive heart failure in conscious dogs with pacing-induced dilated cardiomyopathy

	Control	Moderate CHF	Severe CHF
LVP (mmHg)	121±3	105±5*	100±5*
LVEDP (mmHg)	10±1	18±2*	28±2*
LV dP/dt (mmHg/s)	2586±89	1549±81*	1289±89*
MAP (mmHg)	94±3	84±5*	81±3*
HR (min^{-1})	88±5	101±4*	116±6*
SV (ml)	24±3	18±2*	15±2*
CO (l/min)	2.2±0.2	1.9±0.2	1.7±0.2*
LVEDD (mm)	39±1	40±1	44±1*
LVESD (mm)	33±1	34±1	39±1*
LVEF (%)	44±2	32±2*	26±2*
WTh (mm)	2.9±0.2	2.2±0.2*	1.9±0.3*
SW (g×m)	15±2	9±1*	7±1*
σ-es (g/cm^2)	76±2	79±3	87±3*
σ-ed (g/cm^2)	13±1	24±1*	33±2*
CBF (ml)	24±2	24±2	29±3
MvO_2 (ml O_2/min)	2.3±0.2	2.2±0.1	2.4±0.2

LVP; left ventricular systolic pressure, LVEDP: left ventricular end-diastolic pressure, LV dP/dt: first derivative of LV pressure, MAP: mean arterial pressure, SV: stroke volume, HR: heart rate, CO: cardiac output, LVEDD; left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVEF: left ventricular ejection fraction, WTh: wall thickening, SW: myocardial stroke work, σ-es: end-systolic wall stress, σ-ed: end-diastolic wall stress, CBF: coronary blood flow, MvO_2: myocardial O_2 consumption).

*$P<0.05$ compared to controls.

were obtained in the presence of adrenergic stimulation with either agonist in cardiomyopathic animals, as were obtained in controls. Myocardial contractile efficiency was also calculated in a similar fashion.

In addition, to better simulate the use of catecholamines in the clinical setting of acutely decompensated patients, the infusions were also titrated to restore mean arterial pressure (MAP) to control levels. MvO_2, CBF and myocardial contractile efficiency were recorded in m-CHF and s-CHF animals receiving dobutamine or norepinephrine at doses that resulted in restoration of MAP to levels comparable to controls.

Statistical analysis: Data were expressed as the mean value±S.E.M. Repeated measures analysis of variance (ANOVA), followed by post-hoc paired *t*-tests was performed to compare data obtained in control with respective parameters in m-CHF and s-CHF at matched contractility or blood pressure levels achieved by adrenergic stimulation. Statistical analysis was performed separately for each of the two distinct catecholamine agonists utilized (Dobutamine, Norepinephrine). For each of these drugs, the measurements corresponding to the dose required to attain matched (within±2 S.E.M.) levels of LV contractile indices (LV dP/dt, SV) to those observed in the control state, were entered into the analysis. Linear regression analyses were performed using Sigma Plot software (v. 5.0, SPSS Inc., Chicago, IL). A level of $P<0.05$ was considered statistically significant.

3. Results

Development of progressive dilated cardiomyopathy: Table 1 illustrates the progressive hemodynamic changes associated with the development of moderate (m-CHF) and severe (s-CHF) heart failure in the rapidly paced dogs prior to any pharmacologic stimulation. Moderate CHF was characterized by a significant increase in LVEDP with significant decreases in LV dP/dt, SV and LVEF compared to control values. In severe CHF, there was progressive deterioration in hemodynamics and in addition both LVEDD and LVESD increased significantly over control values, consistent with LV dilatation. Progressive sinus tachycardia was observed and correlated with the degree of heart failure. Resting MvO_2 was not significantly different between control and heart failure animals. Myocardial stroke work at rest was significantly less in CHF. Increases in diastolic wall stress preceded those in systolic wall stress during the course of development of progressive dilated cardiomyopathy (DCM).

Restoration of LV contractility by adrenergic stimulation: Animals with either m-CHF or s-CHF exhibited a desensitized inotropic response to both dobutamine and norepinephrine. The inotropic (LV dP/dt) response to dobutamine is depicted in Fig. 1. To attain myocardial contractility comparable to controls, a dose of 10 μg/kg/min was necessary in both m-CHF and s-CHF. A desensitized dose-response curve was also observed with norepinephrine (Fig. 2). Progressively higher doses of norepinephrine (0.2 μg/kg/min in m-CHF, 0.4 μg/kg/min in s-CHF) were required to accomplish LV contractility indices comparable to control levels.

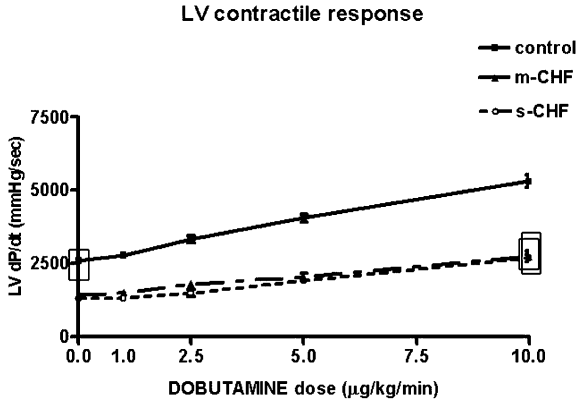

Fig. 1. Inotropic response (LV dP/dt) to Dobutamine (1–10 μg/kg/min) in control (prior to the initiation of rapid pacing) and in moderate (m-CHF) and severe (s-CHF) heart failure. The squares represent the 'matched' levels of LV dP/dt to those of resting, control animals without any pharmacologic stimulation.

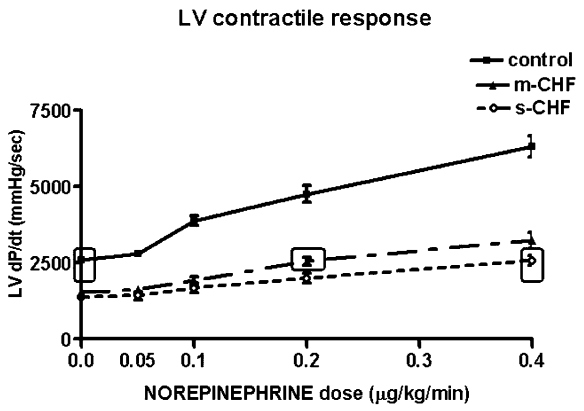

Fig. 2. Inotropic response (LV dP/dt) to Norepinephrine (0.05–0.4 μg/kg/min) in control (prior to the initiation of rapid pacing) and in moderate (m-CHF) and severe (s-CHF) heart failure. The squares represent 'matched' levels of myocardial contractility (LV dP/dt).

3.1. Effects of dobutamine on myocardial O_2 requirements

Although designed to restore LV contractility to normal levels, the use of dobutamine (10 μg/kg/min) at either stage of CHF was associated with significantly higher MvO_2 to achieve LV dP/dt comparable to controls (Table 2). Myocardial O_2 extraction increased early in the process between control and moderate CHF, but there was no further significant change between m-CHF and s-CHF. In contrast, CBF requirements continued to increase further as the animals progressed from moderate to severe CHF. Myocardial SW did not change in m-CHF and tended to decrease in s-CHF animals receiving dobutamine vs. control animals. Myocardial energy efficiency was significantly reduced even at the m-CHF stage. Coronary sinus pH declined progressively as the dogs developed more advanced CHF. A significant determinant of higher metabolic demand (MvO_2) associated with dobutamine use in heart failure was the development of progressive heart rate increases, while MAP remained constant. Significant incremental increases in LVEDP were also observed with the use of dobutamine in progressively worsening CHF. These perturbations were reflected in early increases in diastolic wall stress with dobutamine administration that progressed further in s-CHF. In contrast, systolic wall stress remained unchanged in m-CHF, but increased significantly in s-CHF animals receiving dobutamine. (Table 2). Fig. 3 summarizes the salient metabolic perturbations associated with the use of dobutamine to restore LV contractile dysfunction to normal in CHF.

3.2. Effects of norepinephrine on myocardial O_2 requirements

Conscious dogs with m-CHF required a lower dose of norepinephrine (0.2 μg/kg/min) to restore normal contractile function than the same dogs when they developed s-CHF (0.4 μg/kg/min). A progressive increase in MvO_2 at comparable LV contractile function was observed with norepinephrine use. Similar to the findings observed with dobutamine, norepinephrine administration progressively increased CBF requirements, as CHF became more severe, although myocardial O_2 extraction increased early to help meet additional metabolic demands in m-CHF. The inability to further augment O_2 extraction in s-CHF was associated with a decline in Cs-pH, which was somewhat more pronounced with norepinephrine administration. Myocardial SW was unchanged, but contractile efficiency was

Table 2
The impact of dobutamine utilization at a dose required to restore LV contractility in dogs with moderate and severe heart failure

	Control	Moderate CHF	Severe CHF
Dobutamine (μg/kg/min)	**0**	**10**	**10**
LV dP/dt (mmHg/s)	2586±89	2744±114	2679±132
SV (ml)	24±3	28±3	25±3
SW (g×m)	15±2	14±2	12±2
HR (min^{-1})	88±5	113±7*	129±5*
MAP (mmHg)	94±3	88±4	92±5
LVEDP (mmHg)	10±1	20±2*	29±2*
σ-es (g/cm^2)	76±2	78±4	94±7*
σ-ed (g/cm^2)	13±1	29±4*	40±3*
MvO_2 (ml O_2/min)	2.3±0.2	3.6±0.3*	4.4±0.4*
CBF (ml)	24±2	36±2*	43±3*
(a–v) O_2 extraction (%)	65±2	69.5±3*	71.2±2*
Cs- pH	7.39±0.01	7.36±0.01*	7.35±0.01*
Myocardial efficiency (%)	40±3	23±3*	20±2*

(LV$dP/dt$: first derivative of LV pressure, SV: stroke volume, HR: heart rate, MAP: mean arterial pressure, LVEDP: left ventricular end-diastolic pressure, SW: myocardial stroke work, σ-es: end-systolic wall stress, σ-ed: end-diastolic wall stress, CBF: coronary blood flow, MvO_2: myocardial O_2 consumption, (a–v) O_2 (%) coronary arterio-venous O_2 extraction, Cs-pH: coronary sinus pH.)

*$P<0.05$ compared to controls.

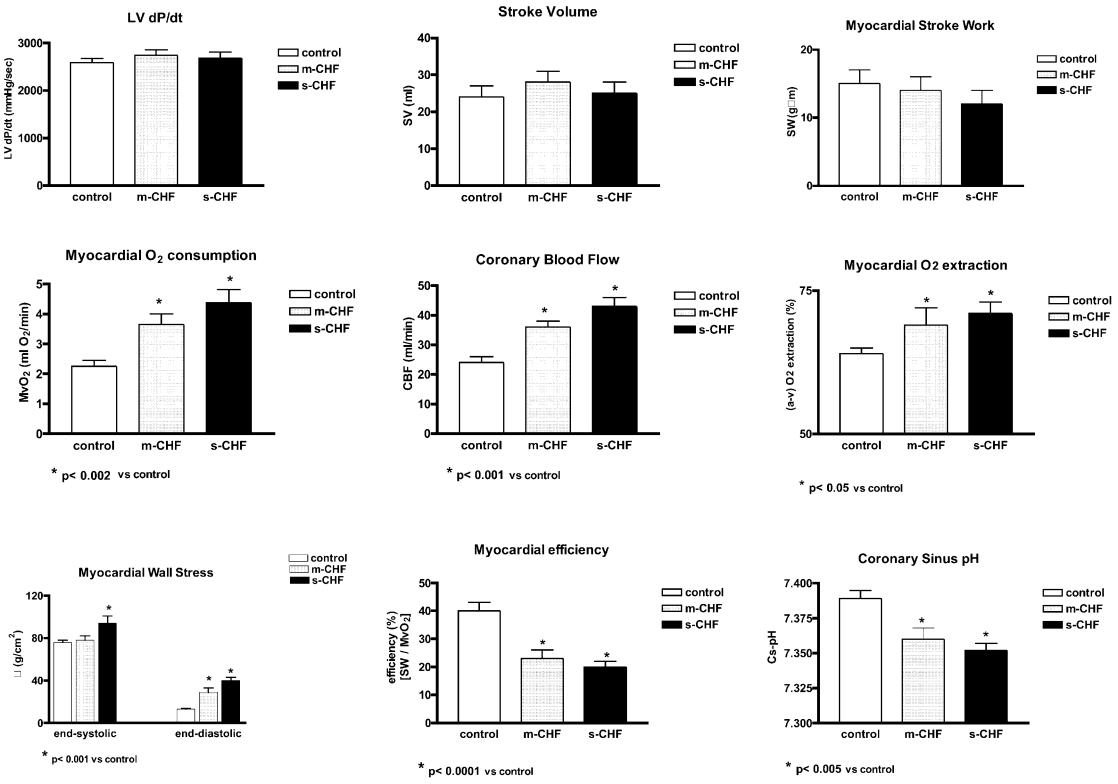

Fig. 3. Hemodynamic and metabolic consequences of Dobutamine use in heart failure. To attain similar levels of myocardial contractility (LV dP/dt, stroke volume: SV) to those observed in normal controls, the use of Dobutamine in animals with moderate (m-CHF) or severe heart failure (s-CHF) resulted in progressive increases in myocardial O_2 consumption (MvO_2), coronary blood flow demands (CBF) and myocardial O_2 extraction and associated decreases in coronary sinus pH (Cs-pH) and myocardial efficiency. ($P<0.05$ compared to controls).

Table 3
The impact of norepinephrine utilization at the respective doses required to restore LV contractility in dogs with moderate and severe heart failure

	Control	Moderate CHF	Severe CHF
Norepinephrine (μg/kg/min)	**0**	**0.2**	**0.4**
LV dP/dt (mmHg/s)	2586±89	2545±120	2573±166
SV (ml)	24±3	23±3	22±2
SW (g×m)	15±2	15±2	14±1
HR (min^{-1})	88±5	97±9	102±6
MAP (mmHg)	94±3	112±8*	132±6*
LVEDP (mmHg)	10±1	27±3*	34±3*
σ-es (g/cm^2)	76±2	99±8*	127±7*
σ-ed (g/cm^2)	13±1	35±4*	51±3*
MvO_2 (ml O_2/ min)	2.3±0.2	3.7±0.4*	4±0.3*
CBF (ml)	24±2	36±4*	44±3*
(a–v) O_2 extraction (%)	65±2	77±2*	74±2*
Cs- pH	7.39±0.01	7.35±0.01*	7.34±0.01*
Myocardial efficiency (%)	40±3	27±3*	23±2*

LV$dP/dt$: first derivative of LV pressure, SV: stroke volume, HR: heart rate, MAP: mean arterial pressure, LVEDP: left ventricular end-diastolic pressure, SW: myocardial stroke work, σ-es: end-systolic wall stress, σ-ed: end-diastolic wall stress, CBF: coronary blood flow, MvO_2: myocardial O_2 consumption, (a–v) O_2 (%) coronary arterio-venous O_2 extraction, Cs-pH: coronary sinus pH.
*$P<0.05$ compared to controls.

depressed when norepinephrine was used to restore myocardial contractility in either stage of CHF. Unlike dobutamine, norepinephrine used in heart failure resulted in significant raises in MAP, thus contributing to increased afterload, in addition to increased LV preload (LVEDP). Although a trend toward increases in heart rate was observed with norepinephrine, this was not statistically significant. The impact of these hemodyn-

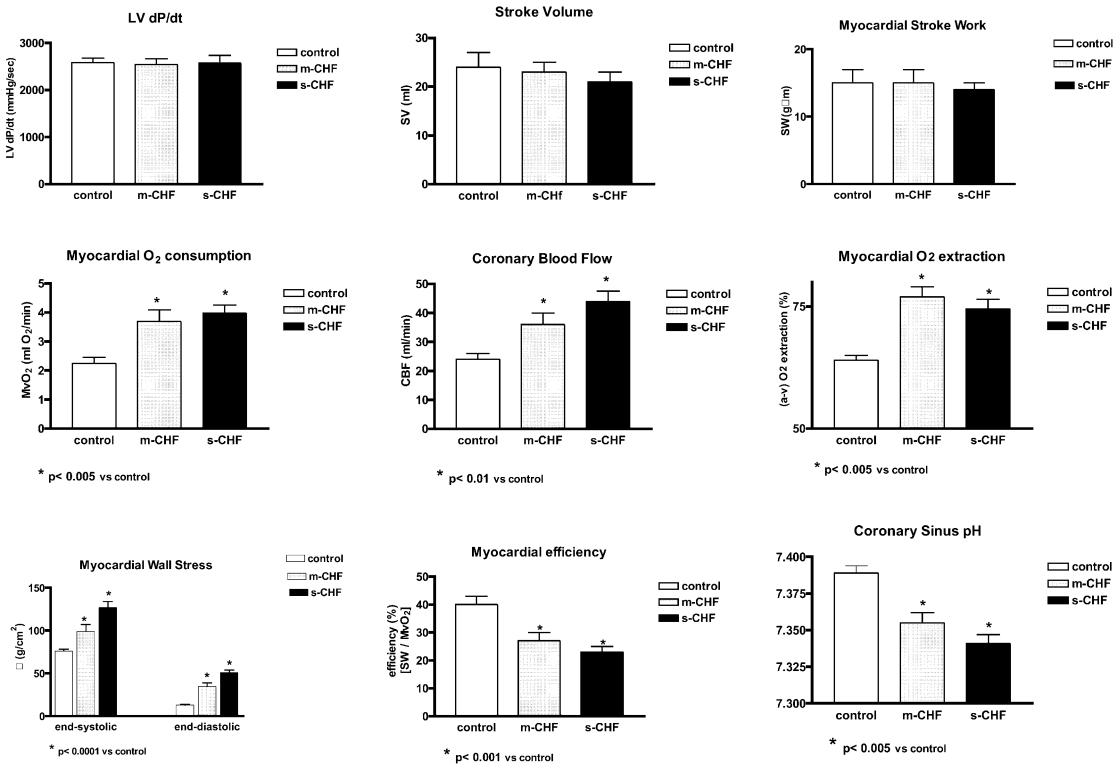

Fig. 4. Hemodynamic and metabolic consequences of Norepinephrine use in heart failure. To attain similar levels of myocardial contractility (LV *dP/dt*, stroke volume: SV) to those observed in normal controls, the use of progressively higher doses of Norepinephrine in animals with moderate (m-CHF) or severe heart failure (s-CHF) similarly resulted in significant increases in myocardial O_2 consumption (MvO_2), coronary blood flow demands (CBF) and myocardial O_2 extraction and associated decreases in coronary sinus pH (Cs-pH) and myocardial efficiency. (*$P<0.05$ compared to controls).

amic responses was associated with progressive increases in both systolic and diastolic wall stress requirements, to achieve matched contractile state using norepinephrine (Table 3). Fig. 4 summarizes the salient metabolic perturbations associated with the use of norepinephrine to restore LV contractile function in CHF.

Restoring MAP by adrenergic stimulation in CHF: Restoration of MAP in dogs with m-CHF or s-CHF was accomplished using 0.1 μg/kg/min of Norepinephrine. Progressively higher doses of Dobutamine (5 μg/kg/min in m-CHF, 10 μg/kg/min in s-CHF) were required to attain the same hemodynamic effect. At comparable MAP levels, MvO_2 and CBF requirements were higher and contractile efficiency was significantly lower when catecholamines were used in CHF compared to controls (Table 4).

Effects of catecholamines on the EW-MvO_2 relationship: In the group of animals ($n=7$) that underwent

Table 4
Effect of Dobutamine and Norepinephrine on MvO_2 and CBF requirements and myocardial efficiency when these adrenergic agonists are used in dogs with progressive degrees of CHF to restore mean arterial pressure to levels comparable to controls

	Control	Moderate CHF		Severe CHF	
		m-CHF + **DOB (5)**	m-CHF + **NE (0.1)**	s-CHF + **DOB (10)**	s-CHF + **NE (0.1)**
SBP (mmHg)	121±4	119±6	125±8	113±6	118±7
MAP (mmHg)	94±3	92±4	99±7	92±5	95±6
MvO_2 (ml O_2/min)	2.3±0.2	3.2±0.3*	2.6±0.3	4±0.3*	3±0.2*
CBF (ml/min)	24±2	33±2*	32±4*	43±3*	42±4*
Myocardial efficiency (%)	40±3	23±2*	27±3*	19±2*	22±3*

SBP: systolic blood pressure, MAP: mean arterial pressure, CBF: coronary blood flow, MvO_2: myocardial O_2 consumption, m-CHF: moderate congestive heart failure, s-CHF: severe congestive heart failure, DOB: dobutamine, NE: norepinephrine. Drug doses in parentheses are in μg/kg/min.

*$P<0.05$ compared to controls.

additional experiments to generate PV loops (Fig. 5), the area enclosed by the PV loop was calculated as an index of external work (EW) performed by the left ventricle during a cardiac cycle. The ratio of EW/MvO_2 was computed as an estimate of mechanical contractile efficiency of the LV [19,20]. Table 5 demonstrates that animals with m-CHF required high doses of either dobutamine or norepinephrine to accomplish total EW comparable to that of a normal dog in the control state (prior to pacing). This was associated with a significantly higher MvO_2 and lower EW/MvO_2 ratio consistent with the reduced mechanical efficiency of the failing myocardium. Animals with s-CHF were unable to accomplish EW comparable to controls, even when they were stimulated with high doses of agonists, thus resulting at even lower efficiency.

4. Discussion

Our study demonstrated that pharmacologic restoration of normal LV contractile performance in CHF by either dobutamine or norepinephrine is associated with greater MvO_2 requirements and greater dependence on CBF to meet these demands. These excessive demands increased as dilated cardiomyopathy progressed from a stage of moderate to severe CHF. Myocardial O_2 extraction increased early in the evolution of CHF, but could not increase further as the dogs developed severe CHF. In contrast, CBF requirements continued to increase as the animals progressed to severe CHF. Restoration of LV contractility by means of either sympathomimetic agonist led to significantly reduced myocardial efficiency, calculated by two different methods.

4.1. Hemodynamic determinants

We also demonstrated that sinus tachycardia and increased preload were significant contributors to the excessive O_2 requirements associated with dobutamine (β1-AR) use in dilated cardiomyopathy. In contrast, increased preload and increased afterload characterized the effect of norepinephrine. These mechanistic differences between the two agonists can be explained by their different affinities for α- and β1- adrenergic receptors. Restoration of LV contractility comparable to normal levels by means of sympathomimetic administration in CHF was attained at significantly increased LV filling pressures compared to controls. End-diastolic wall stress increased similarly in an incremental fashion with either agonist. Earlier and more robust increases in end-systolic wall stress were observed with norepinephrine, reflecting the α- adrenergic mediated augmentation in systemic afterload.

These pharmacologic manipulations, when employed clinically in decompensated heart failure may 'restore' MAP, yet at a high price, in terms of MvO_2. While

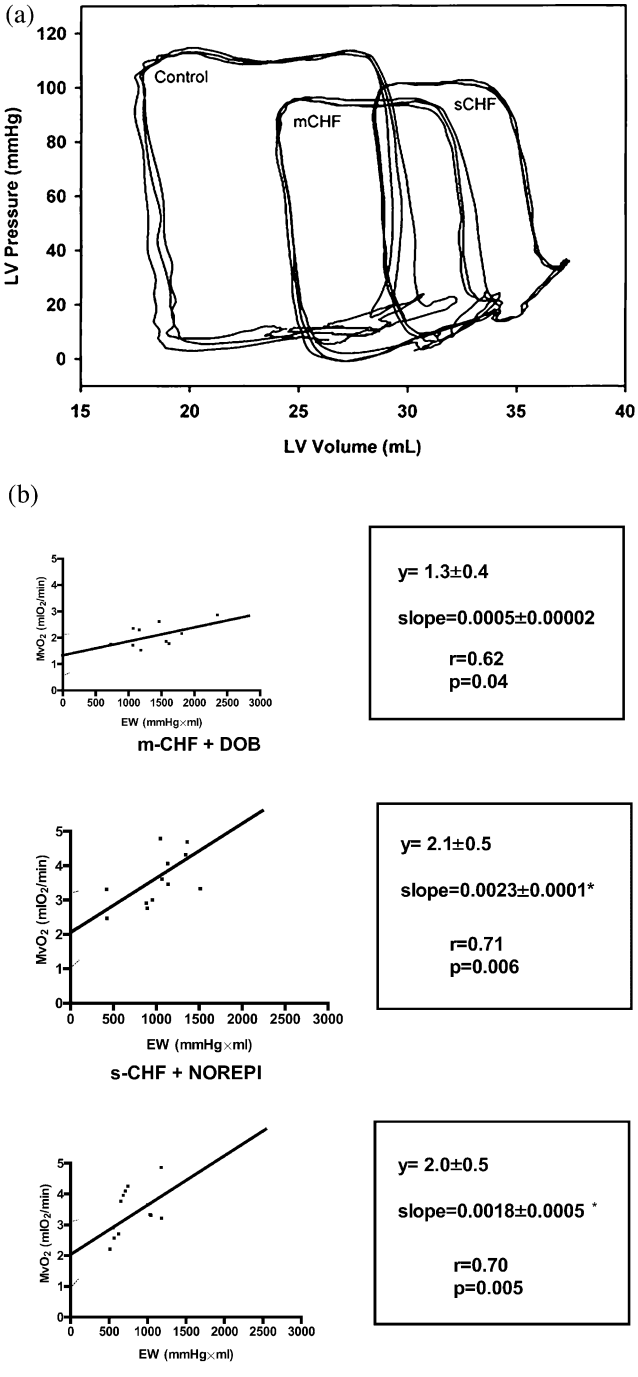

Fig. 5. An example of a P–V loop generated using sonomicrometry and pressure manometry data in the same dog in control, moderate and severe CHF (5a). Fig. 5b describes the relationship between external myocardial work (EW) as calculated from the PV area (in the abscissa) and MvO_2 (in the ordinate) in control animals, m-CHF animals receiving Dobutamine and s-CHF animals receiving Norepinephrine. The slope of these curves has an inverse relationship to myocardial mechanical efficiency. The y-intercept represents MvO_2 unrelated to external mechanical work (potential energy and basal 'internal' work). (*$P < 0.05$ compared to controls).

Table 5
Effect of Dobutamine and Norepinephrine on ventricular mechanical efficiency using pressure-volume loop derived external work (EW)

	Control	Moderate CHF	Severe CHF
Dobutamine			
EW area (mmHg×ml)	**1411±182**	835±90*	537±72*
+2.5 μg/kg/min DOB	1768±362	1089±183	640±102*
+10 μg/kg/min DOB	2346±579	**1217±181**	**781±103***
MvO_2 (ml O_2/min)	**2.3±0.2**	2.3±0.2	2.5±0.3
+2.5 μg/kg/min DOB	3.2±0.4	3±0.3*	2.7±0.3
+10 μg/kg/min DOB	5.7±0.4	**3.2±0.3***	**4±0.3***
EW/ MvO_2 ratio ($\times 10^{-3}$)	**0.71±0.08**	0.34±0.03*	0.22±0.03*
+2.5 μg/kg/min DOB	0.63±0.10	0.36±0.08*	0.22±0.02*
+10 μg/kg/min DOB	0.46±0.08	**0.28±0.03***	**0.19±0.02***
Norepinephrine			
EW area (mmHg×ml)	**1382±191**	772±9790*	621±78*
+0.1 μg/kg/min NE	1893±418	898±105*	762±96*
+0.4 μg/kg/min NE	2513±739	**1213±198**	**991±159***
MvO_2 (ml O_2/min)	**2.3±0.1**	2.5±0.2	2.4±0.3
+0.1 μg/kg/min NE	3.6±0.4	2.7±0.3	3±0.3*
+0.4 μg/kg/min NE	6.3±0.8	**3.9±0.3***	**3.9±0.3***
EW/MvO_2 ratio ($\times 10^{-3}$)	**0.62±0.07**	0.29±0.04*	0.26±0.04*
+0.1 μg/kg/min NE	0.57±0.10	0.33±0.05*	0.24±0.04*
+0.4 μg/kg/min NE	0.48±0.12	**0.32±0.06***	**0.25±0.03***

MvO_2: myocardial O_2 consumption, EW: external work, DOB: Dobutamine, NE: Norepinephrine.
*$P<0.05$ compared to controls. The bold fonts represent the comparison between controls on no drugs, and moderate or severe CHF animals receiving high-dose catecholamine infusions.

these demands can be partially compensated by increased myocardial O_2 extraction in moderate CHF, this mechanism becomes exhausted in severe stages. Thus, in severe CHF requiring 'inotropic support' to restore LV contractile function, increased CBF remains the sole mechanism available to meet the excessive metabolic demands associated with the utilization of adrenergic agonists.

4.2. Coronary blood flow demands

Our study observed a near -doubling in CBF demand in association with the use of either agonist to restore LV contractility or MAP in severe CHF. Previously reported studies from our laboratory and others [21–23] have demonstrated a significant impairment in coronary flow reserve in advanced dilated cardiomyopathy. The imposition of such excessive demands upon an already limited CBF reserve in DCM can be implicated as a deleterious mechanism of catecholamines. The decrease in coronary sinus pH is suggestive of a supply-demand imbalance. The limitation in CBF reserve in DCM is largely confined to the sub-endocardium [21], making this myocardial tissue a vulnerable target for ischemic events. Although our study did not address regional distribution of myocardial perfusion in response to adrenergic agonists, it is reasonable to speculate that prolonged administration of these drugs in s-CHF may predispose to subendocardial ischemia. Such phenomena can contribute to the increased morbidity and mortality associated with the clinical use of these drugs in CHF.

4.3. Prior experimental studies

Prior studies in experimental animal models examining the effects of catecholamines, particularly dobutamine, on myocardial efficiency have yielded conflicting results. Wolf et al. [24] performed pharmacologic stimulation experiments in isolated, perfused hearts explanted from dogs with pacing-induced DCM, and compared to control canine hearts. They reported significant increases in MvO_2, accompanied by a parallel, although desensitized inotropic response to dobutamine, resulting in unchanged contractile efficiency, as measured by the MvO_2–PVA slope. The discrepancies can be explained by the differences in experimental conditions between isolated perfused hearts and in-vivo conscious animals. In addition, these experiments were conducted with fixed heart rate and ventricular preload. We have found that these very same factors constitute significant determinants of dobutamine-induced myocardial metabolic demands. While control of these parameters may be appropriate from the pure mechanistic standpoint, our methodology to aim at restoring normal contractility or MAP simulates clinical practice in a more relevant way.

Investigations in-vivo in anesthetized dogs [25] or pigs [26] with ischemic LV dysfunction, have demonstrated exaggerated or unchanged MvO_2 responses to dobutamine, respectively. These studies reflect heterogeneous ischemic substrates (acute vs. chronic) and their results may not be directly applicable to non-ischemic DCM. Buser et al. [27] suggested a differential energetic effect of dobutamine (favorable in m-CHF,

Table 6
Comparative effects of a fixed dose of dobutamine or norepinephrine on myocardial O_2 demands and contractile efficiency in control vs. severe CHF. Unlike Tables 2 and 3 that refer to 'matched' contractility levels, this table compares the response to the same dose of each agonist when administered in control vs. severe CHF animals

	Control		Severe CHF	
	Baseline	% change	Baseline	% change
Dobutamine (10 μg/kg/min)				
SW (g×m)	15±2	**71±12**	7±1	**71±11**
MvO_2 (ml O_2/min)	2.3±0.2	144±7	2.4±0.2	63±7*
Myocardial efficiency (%)	40±3	−27±9	19±2	5±10*
Norepinephrine (0.04 μg/kg/min)				
SW (g×m)	15±2	**100±12**	7±1	**100±11**
MvO_2 (ml O_2/min)	2.3±0.2	174±9	2.4±0.2	79±8*
Myocardial efficiency (%)	40±3	−16±10	19±2	15±9*

MvO_2: myocardial O_2 consumption SW: myocardial stroke work.
*$P<0.05$ compared to control responses.

deleterious in s-CHF) on a different animal model of DCM (cardiomyopathic hamster) applying a different approach to quantify myocardial energetics (MR spectroscopy). Few studies of dobutamine administration have been performed in conscious dogs with DCM, yet these are focused on comparing to different inotropic strategies [28,29], rather than per se on the MvO_2 cost of restoring normal hemodynamics during progression of cardiomyopathy. Our current findings are consistent with those of Asai et al. [29] who implied that mechanical efficiency in dogs with severe CHF on dobutamine may be depressed even at comparable LV dP/dt to a control group. We extend these findings to earlier stages of CHF, as well as to the effects of Norepinephrine during progressive development of DCM. Thus, we studied responses to both a synthetic (dobutamine) and an endogenous (norepinephrine) adrenergic agonist serially in moderate and severe CHF in a conscious experimental model of DCM.

4.4. Relevant clinical investigations

There is considerable controversy as to whether and by what mechanisms dobutamine affects mechanical efficiency in the clinical CHF setting. Some investigations have demonstrated that dobutamine decreases mechanical efficiency [30–33] while others suggest that dobutamine preserves [34,35] or improves [36] mechanical efficiency. These discrepancies reflect differences in myopathic substrate (ischemic vs. idiopathic) and the techniques used to assess efficiency and CBF in clinical studies. In addition, concomitant administration of other drugs (ACE inhibitors, β-blockers) with known effects [18,37–39] on myocardial energetics and contractile efficiency may confound the interpretation of clinical studies.

In addition, our different reference point for comparisons can reconcile seemingly contradictory observations. In CHF, the incremental increase in MvO_2 for comparable gains in myocardial work using catecholamines is actually less when compared with the effect on a healthy heart stimulated with the exact same dose to a supra-normal contractile level (Table 6). This could be potentially explained by differences in metabolic substrate utilization patterns. As reported from our laboratory [40] and others [16,33], the function of driving normal myocardium to supra-normal levels is predominantly accomplished through free fatty acid utilization. It is plausible that equivalent increases in myocardial EW from the depressed levels seen in cardiomyopathy to normal levels may rely more upon glucose utilization, at a higher respiratory quotient but lower MvO_2. This is in contrast to studies comparing responses to catecholamines in CHF to responses in normal controls, where 'relative' increases in contractile efficiency of inotropic agents in CHF could be potentially attributable to metabolic substrate shifts.

4.5. Norepinephrine effects

Norepinephrine levels are elevated in clinical [41] and experimental [42] heart failure. This is the first study to confirm the detrimental O_2 wasting effects and contractile inefficiency following exogenous administration of norepinephrine in the setting of dilated cardiomyopathy. In addition, our findings of different myocardial wall stress determinants point toward a possibly synergistic contribution of both α- and β-1

adrenergic mediated mechanisms to myocardial inefficiency in DCM.

4.6. Limitations

Our findings pertain to a model of DCM and may differ from ischemia, infarction, or pressure-overload hypertrophy. We did not address the issue of 'internal' (vs. 'external') ventricular work that is independent of PV area or the 'potential energy' of the myocardium. As other authors have suggested [19,20,24,43], these components could reflect basal metabolism and excitation-contraction coupling that could be conceivably altered by medications. Although the effect of dobutamine on these parameters has not been shown to be significant in isolated perfused hearts [24], the importance of these mechanisms in the failing myocardium in-vivo remains to be elucidated.

5. Conclusions

In summary, while catecholamines are effective in restoring LV performance in both moderate and severe CHF, the cost is significant in terms of MvO_2 and CBF demands. In turn, myocardial efficiency is reduced. While a portion of the increased O_2 requirements when normalizing contractility with dobutamine is due to heart rate increases, increased wall stress accounts for the excess MvO_2 with norepinephrine. These mechanisms contribute to the deleterious effects of normalizing cardiovascular function with catecholamines in clinical heart failure.

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References

[1] O'Connor CM, Gattis WA, Uretsky BF, Adams KF Jr, McNulty SE, Grossman SH, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138:78–86.

[2] Oliva F, Latini R, Politi A, Staszewsky L, Maggioni AP, Nicolis E, Mauri F. Intermittent 6 month low-dose dobutamine infusion in severe heart failure: the DICE multicenter trial. Am. Heart J 1999;138:247–53.

[3] Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. Clin Pharmacol Ther 1998;63:682–5.

[4] Burger AJ, Elkayam U, Neibaur MT, Haught H, Ghali J, Horton DP, Aronson D. Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine vs. nesiretide therapy. Am J Cardiol 2001;88:35–9.

[5] Hampton JR, van Veldhuisen DJ, Kleber FX, Cowley AJ, Ardia A, Block P, et al. Randomized study of effect of ibopamine on survival in patients with advanced severe heart failure. (PRIME II) Investigators. Lancet 1997;349:971–7.

[6] The Xamoterol in Severe Heart Failure Study Group: Xamoterol in severe heart failure. Lancet 1990; 336:1–6.

[7] Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE study research group. NEJM 1991;325:1468–75.

[8] Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Assessment of the β-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and sub-sensitivity to agonist response. Circulation 1986;74:1290–302.

[9] Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and β-adrenergic receptor density in failing human heart. NEJM 1982;307:205–11.

[10] Kiuchi K, Shannon RP, Komamura K, Cohen DJ, Bianchi C, Homcy CJ, et al. Myocardial β-adrenergic receptor function during the development of pacing-induced heart failure. J Clin Invest 1993;91:907–14.

[11] Vatner DE, Sato N, Ishikawa Y, Kiuchi K, Shannon RP, Vatner SF. Beta-adrenergic receptor desensitization during development of canine pacing-induced heart failure. J Clin Exp Pharmacol Physiol 1996;23:688–92.

[12] Katz AM. Is the failing heart energy depleted? Cardiology Clinics 1998;16:633–44.

[13] Ingwall JS. Is cardiac failure a consequence of decreased energy reserve? Circulation 1993;87(suppl. VII):VII 58–VII 62.

[14] Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy. Circulation 2000;102:3053–9.

[15] Shannon RP, Komamura K, Stambler BS, Bigaud M, Manders WT, Vatner SF. Alterations in myocardial contractility in conscious dogs with dilated cardiomyopathy. Am J Physiol 1991;260:H1903–H1911.

[16] Recchia FA, McConnell PI, Bernstein RD, Vogel TR, Xu X, Hintze TH. Reduced nitric oxide production and altered myocardial metabolism during the decompensation of pacing-induced heart failure in the conscious dog. Circ Res 1998;83:969–79.

[17] Opie L. 3rd ed. The heart: physiology from cell to circulation. Philadelphia, PA: Lippincott-Raven, 1998. p. 360–4.

[18] Eichhorn EJ, Heesch CM, Barnett JH, Alvarez LG, Fass SM, Grayburn PA, et al. Effects of metoprolol on myocardial function and energetics in patients with non-ischemic dilated cardiomyopathy: a randomized, double- blind, placebo-controlled study. J Am Coll Cardiol 1994;24:1310–20.

[19] Nozawa T, Cheng CP, Noda T, Little WC. Relation between left ventricular oxygen consumption and pressure-volume area in conscious dogs. Circulation 1994;89:810–7.

[20] Westerhof N. Cardiac work and efficiency. Cardiovasc Res 2000;48:4–7.

[21] Shannon RP, Komamura K, Shen YT, Bishop SP, Vatner SF. Impaired regional subendocardial coronary flow reserve in conscious dogs with pacing-induced heart failure. Am J Physiol 1993;265:H801–H809.

[22] van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebelink HM, Vaalburg WM, et al. Regional

myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2000;35:19–28.

[23] Cannon RO 3rd, Cunnion RE, Parrillo JE, Palmeri ST, Tucker EE, Schenke WH, et al. Dynamic limitation of coronary vasodilator reserve in patients with dilated cardiomyopathy and chest pain. J Am Coll Cardiol 1987;10:1190–200.

[24] Wolff MR, de Tombe PP, Harasawa Y, Burkhoff D, Bier S, Hunter WC, et al. Alterations in left ventricular mechanics, energetics and contractile reserve in experimental heart failure. Circ Res 1992;70:516–29.

[25] Abe Y, Kitada Y, Narimatsu A. Effect of MCI-154, a cardiotonic agent, on regional contractile function and myocardial oxygen consumption in the presence and absence of coronary artery stenosis in dogs. J Pharmacol Exp Therap 1993;265:819–25.

[26] Murakami Y, Zhang Y, Cho YK, Mansoor AM, Chung JK, Chu C, et al. Myocardial oxygenation during high work states in hearts with post-infarction remodeling. Circulation 1999;99:942–8.

[27] Buser PT, Camacho SA, Wu ST, Higgins CB, Jasmin G, Parmley WW, et al. The effect of dobutamine on myocardial performance and high-energy phosphate metabolism at different stages of heart failure in cardiomyopathic hamsters. Am Heart J 1989;118:86–91.

[28] Shen W, Gill RM, Jones BD, Zhang JP, Corbly AK, Steinberg MI. Combined inotropic and bradycardic effects of a sodium channel enhancer in conscious dogs with heart failure: a mechanism for improved myocardial efficiency compared with dobutamine. J Pharmacol Exp Ther 2002;303:673–80.

[29] Asai K, Uechi M, Sato N, Shen W, Meguro T, Mathier MA, et al. Lack of desensitization and enhanced efficiency of calcium channel promoter in conscious dogs with heart failure. Am J Physiol Heart Circ Physiol 1998;275:H 2219–H2226.

[30] Hayashi Y, Takeuchi M, Takaoka H, Hata K, Mori M, Yokoyama M. Alteration in energetics in patients with left ventricular dilatation after myocardial infarction. Circulation 1996;93:932–9.

[31] Thierfelder L, Holubarsch CH, Hasenfuss G, Just HJ. Myocardial energetics in dilated cardiomyopathy. Clin Cardiol 1990;13:649–54.

[32] Kanda H, Yokota M, Ishihara H, Nagata K, Kato R, Sobue T. A novel inotropic vasodilator, OPC-18790 reduces myocardial oxygen consumption and improves mechanical efficiency with congestive heart failure. Am Heart J 1996;132:361–8.

[33] Sun KT, Czernin J, Krivokapich J, Lau YK, Bottcher M, Maurer G, et al. Effects of dobutamine stimulation on myocardial blood flow, glucose metabolism and wall motion in normal and dysfunctional myocardium. Circulation 1996;94:3146–54.

[34] Beanlands RS, Bach DS, Raylman R, Armstrong WF, Wilson V, Montieth M, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured by using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. J Am Coll Cardiol 1993;22:1389–98.

[35] Beanlands RSB, Schwaiger M. Changes in myocardial oxygen consumption and efficiency with heart failure therapy measured by carbon-11 acetate PET. Can J Cardiol 1995;11:293–300.

[36] Shinke T, Takaoka H, Takeuchi M, Hata K, Kawai H, Okubo H, et al. Nitric oxide spares myocardial oxygen consumption through attenuation of contractile response to β-adrenergic stimulation in patients with idiopathic dilated cardiomyopathy. Circulation 2001;101:1925–30.

[37] Sabbah HN. The cellular and physiologic effects of beta blockers in heart failure. Clin Cardiol 1999;22:V16–V20.

[38] Sanbe A, Tanonaka K, Kobayasi R, Takeo S. Effects of long-term therapy with ACE inhibitors captopril, enalapril and trandolapril on myocardial energy metabolism in rats with heart failure following myocardial infarction. J Mol Cell Cardiol 1995;27:2209–22.

[39] Zhang X, Xie YW, Nasjletti A, Xu X, Wolin MS, Hintze TH. ACE inhibitors promote nitric oxide accumulation yo modulate myocardial oxygen consumption. Circulation 1997;95:176–82.

[40] Nikolaidis LA, Hentosz T, Doverspike A, Huerbin R, Stolarski C, Shen YT, et al. Mechanisms whereby rapid RV pacing causes LV dysfunction: perfusion-contraction matching and NO. Am J Physiol Heart Circ Physiol 2001;281:H2270–H2281.

[41] Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma rennin activity, and congestive heart failure. Relations to survival and effects of therapy in V-HeFT II study. The V-HeFT VA cooperative studies group. Circulation 1993;87:VI 40–VI 48.

[42] Patel MB, Stewart JM, Loud AV, Anversa P, Wang J, Fiegel L, et al. Altered function and structure of the heart in dogs with chronic elevation in plasma norepinephrine. Circulation 1991;84:2091–100.

[43] Gerber BL, Bernard X, Melin JA, Delestinne T, Vanbutsele R, Goenen M, et al. Exaggerated chronotropic and energetic response to dobutamine after orthotopic cardiac transplantation. J Heart Lung Transplant 2001;20:824–32.