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ORIGINAL ARTICLE

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Altered left ventricular–arterial coupling precedes pump dysfunction in early heart failure

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Abstract The objective of this study was to define alterations in ventricular–arterial (V-A) coupling early in the development of tachycardia-induced heart failure (HF). Although HF is characterized by impaired V-A coupling, the temporal relationship of these derangements to overt left ventricular (LV) dysfunction is unknown. Six anesthetized dogs instrumented with LV manometers and piezoelectric crystals were studied before and after 24 h of rapid ventricular pacing (RVP). V-A coupling was indexed by the ratio between the end-systolic pressure–volume relation slope (endsystolic elastance, E_{ES}) and effective arterial elastance (E_A), and mechanical efficiency by the ratio of stroke work (SW) to pressure–volume area (PVA). After RVP, there was no significant depression of LV function, but E_A and total peripheral resistance (R_T) were increased ($P < 0.05$), indicating increased arterial load. After RVP, E_{ES}/E_A and SW/PVA were maintained during unstressed conditions, but upon changes in load induced by phenylephrine, E_{ES}/E_A declined more precipitously with equivalent increases in R_T (slope E_{ES}/E_A–R_T relation −16.7 ± 4.6 vs −5.8 ± 4.0 ml/mmHg·min, $P < 0.025$). Furthermore, after RVP there was significant ($P < 0.05$) blunting of dobutamine-induced augmentation of E_{ES}, E_{ES}/E_A, and SW/PVA. Thus, after RVP there was a distinct loss of V-A coupling reserve during afterload and catecholamine stress. V-A coupling defects occur early in the development of tachycardia-induced HF prior to significant pump dysfunction, and are manifested primarily during hemodynamic and inotropic stress.

Key words Rapid ventricular pacing · Left ventricular–arterial coupling · Pump dysfunction · Heart failure

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Introduction

Ventricular–arterial (V-A) coupling is an important determinant of cardiovascular function, influencing both the magnitude and efficiency of transfer of left ventricular (LV) stroke work (SW) to the circulation.[1–6] As initially shown by Sunagawa et al.,[1–2] the LV and arterial system can be comparably described and V-A coupling accurately quantified in the pressure–volume (PV) plane. Whereas LV performance can be characterized by the slope (end-systolic elastance, E_{ES}) and relative position of the end-systolic PV (P_{ES}–V_{ES}) relation, the arterial system can be similarly assessed using the slope of the arterial P_{ES}–stroke volume (SV) relation (effective arterial elastance, E_A). In this manner, both the LV and arterial system are considered elastic chambers with known volume elastances, with the E_{ES}/E_A ratio serving as a reliable index of V-A coupling. While E_A is a derived rather than physical parameter, it is dependent on both physical resistance and compliance, and can be predicted analytically using a three-element Windkessel model of the arterial system.[7] Furthermore, E_A as an index of arterial load is virtually identical to that derived from aortic input impedance.[7]

In the intact state under normal conditions, the LV and arterial system are nearly optimally coupled, operating at an E_{ES}/E_A ratio close to one, resulting in maximal SW.[4–6] In contrast, V-A coupling is suboptimal in heart failure (HF), as E_{ES} is decreased and E_A is generally increased, reducing the E_{ES}/E_A ratio.[6,8] Abnormal cardiovascular interaction in HF reflects altered mechanical properties of both of its components (i.e., the LV and the arterial system). Indeed, in addition to pump dysfunction, HF is characterized by several abnormalities of vascular function, including vasoconstriction, impaired exercise-induced vasodilatation, and impaired endothelium-dependent vasodilatation,[9–12] that appear related in part to increased oxidative stress and reduced bioavailability of nitric oxide (NO).[10–12] Also, aortic impedance is increased (both characteristic and low frequency moduli of impedance)[13] and compliance is decreased,[14] contributing to increased LV afterload and

impaired transfer of mechanical work. Although abnormalities in V-A coupling have been well documented in established HF, data regarding the temporal relationship of these derangements to overt LV dysfunction are few. Accordingly, the purpose of this study was to examine the effect of 24 h of rapid ventricular pacing (RVP) on V-A coupling in closed-chest dogs. The central hypothesis was that alterations in V-A interaction, as assessed by the E_{ES}/E_A ratio under stressed and unstressed conditions, would manifest early in the development of tachycardia cardiomyopathy.

Methods

Surgical instrumentation

All animal studies were performed in accordance with guidelines described in the NIH Guide for the Care and Use of Laboratory Animals (DHHS publication No. [NIH] 85-23, revised 1996). Under 1%–2% isoflurane general anesthesia, six mongrel dogs of either sex underwent left thoracotomy and surgical instrumentation for long term monitoring as previously described.[15,16] Instrumentation included a LV apex micromanometer (Konigsberg Instruments, Pasadena, CA, USA), endocardial piezoelectric crystals along the anterior–posterior (D_{AP}), septal–lateral (D_{SL}), and long axis (D_{LA}) diameters, LV epicardial pacing leads, and inferior vena caval pneumatic occluders. Data regarding mechanoenergetics and afterload-induced augmentation of LV performance from these animals have been previously reported.[17]

Experimental protocol

Following a minimum of 2 weeks of recovery after instrumentation, dogs were anesthetized with intravenous thiopental sodium (25–30 mg/kg), droperidol (1.5–3.0 mg/kg), and fentanyl (0.03–0.06 mg/kg), and mechanically ventilated with 100% O_2. To minimize respiratory fluctuations in intrathoracic pressure, data were recorded during 10-s periods of apnea (following brief hyperventilation), during which time the endotracheal tube was held open to the atmosphere. Left ventricular pressure (P), dP/dt, ECG, and the three LV diameters were recorded and digitized (500 Hz). After baseline measurements, intravenous atropine (2 mg) and hexamthonium (20–25 mg/kg) were administered to produce autonomic blockade and obviate reflex effects. After 15 min, data were collected under steady-state conditions and during caval occlusion. Left ventricular afterload was then increased incrementally by graded infusions of phenylephrine (dose range 1–4 μg/kg per minute), and after 10 min of stabilization at each dose, steady-state and caval occlusion measurements were repeated. Phenylephrine was subsequently discontinued for 15 min, a new baseline was recorded, and β-adrenergic stimulation with dobutamine (10 μg/kg per minute) was initiated. Steady-state and caval occlusion measurements were repeated after 10 min in the presence of dobutamine. Two days after the initial experiments, RVP was instituted at a HR of 210 beats/min for 24 h using customized pulse generators (Medtronic Model 5985; Medtronic, Minneapolis, MN, USA). Following this, the pacemaker was turned off for at least 30 min and the entire experimental protocol above was repeated. The animals were then euthanized by lethal KCI injection following deep anesthesia with pentobarbital (50 mg/kg), and proper positioning of the crystals, catheters, and pacing leads was confirmed.

Data analysis

Left ventricular volume (ml), dP/dt (mm Hg/s), end-diastole (ED), and end-systole (ES) were determined as previously described.[15–17] The P_{ES}–V_{ES} relation was determined using the equation: $P_{ES} = E_{ES} \cdot (V_{ES} - V_0)$, where E_{ES} (mmHg/ml) is the slope, and V_0 (ml) is the volume axis intercept. V_{100} was defined as the V_{ES} derived at a P_{ES} of 100 mmHg, to allow for comparisons between animals without excessive extrapolation in the PV plane. SW (mmHg·ml) was defined as the area bounded by the PV loop. The SW–V_{ED} relation was determined using the equation: $SW = M_W \cdot (V_{ED} - V_W)$, where M_W (mmHg) is the slope, and V_W (ml) is the volume axis intercept. V_{W1000} (ml) was defined as V_{ED} derived at a SW of 1000 mmHg·ml. dP/dt_{MAX} – V_{ED} data were fit to the equation: $dP/dt_{max} = dE/dt_{MAX} \cdot (V_{ED} - V_D)$, where dE/dt_{MAX} (mmHg/ml·s) is the slope, and V_D (ml) is the volume axis intercept. The pressure–volume area (PVA, mmHg·ml), or total ventricular mechanical energy, was defined as the area bounded by the P_{ED}–V_{ED} relation, the systolic segment of the PV loop, and the P_{ED}–V_{ED} relation. The mathematical derivation of these parameters has been previously described.[15–17] Both E_A and total peripheral resistance (R_T) were calculated as defined by Sunagawa et al.[2] using: $E_A = P_{ES}/SV$ and $R_T = P_{ES}$ /cardiac output. V-A coupling was quantified by the E_{ES}/E_A ratio, and the efficiency of mechanical energy transfer (i.e., mechanical efficiency) was defined as SW/PVA.[4–6]

Statistical analysis

Comparisons of mechanical parameters prior to and after RVP, or before and after an experimental perturbation, were made using the paired t-test or repeated-measures analysis of variance, as appropriate. A P value of less than 0.05 was considered significant. All group data are expressed as the mean ± SEM.

Results

Rapid ventricular pacing and LV mechanical performance

Table 1 summarizes the mechanical data (after autonomic blockade) at baseline and after RVP. Short-term RVP

resulted in mild but significant reductions in heart rate ($P = 0.047$) and P_{ES} ($P = 0.012$), a trend toward reduction of V_{ED} ($P = 0.075$), with no change in P_{ED} or V_{ES}. As described previously,[17] there were no significant changes in the slopes (E_{ES}, M_W) or the relative positions at physiologic ranges (V_{100}, V_{W1000}) of either the P_{ES}–V_{ES} or SW–V_{ED} relations, indicating no change in overall LV contractile performance. Although dP/dt_{MAX} was significantly decreased after RVP, this reduction was volume related, as dP/dt_{MAX} at a common V_{ED} (defined as the baseline control V_{ED}) calculated from each dP/dt_{MAX}–V_{ED} relation revealed no significant changes. Thus, as related in our previous study,[17] after 24 h of RVP, the LV operated at a lower V_{ED} or preload, but without evidence of circulatory congestion or overt LV dysfunction.

Table 1. Left ventricular mechanical performance

	Baseline	RVP
HR (bpm)	129 ± 7	114 ± 6*
P_{ES} (mm Hg)	99 ± 5	80 ± 2*
P_{ED} (mm Hg)	4 ± 1	6 ± 2
V_{ES} (ml)	37 ± 3	36 ± 4
V_{ED} (ml)	53 ± 3	45 ± 3$^+$
dP/dt_{MAX} (mm Hg/s)	2240 ± 92	1557 ± 127*
Matched dP/dt_{MAX} (mm Hg/s)	2206 ± 100	2005 ± 275
E_{ES} (mm Hg/ml)	6.6 ± 0.8	8.6 ± 1.3
V_{100} (ml)	36.0 ± 2.6	39.6 ± 4.2
M_w (mm Hg)	70.4 ± 2.4	61.9 ± 5.2
V_{W1000} (ml)	45.6 ± 2.8	51.4 ± 4.8

All values are mean ± SEM, measured after autonomic blockade
RVP, rapid ventricular pacing; HR, heart rate; P_{ES} and P_{ED}, end-systolic and end-diastolic pressure; V_{ES} and V_{ED}, end-systolic and end-diastolic volume; matched dP/dt_{MAX}, value derived from the dP/dt_{MAX}–V_{ED} relation at baseline V_{ED}; E_{ES}, end-systolic elastance; V_{100}, P_{ES}–V_{ES} relation volume intercept at 100 mm Hg; M_W, slope of the stroke work (SW)–V_{ED} relation; V_{W1000}, SW–V_{ED} relation volume intercept at 1000 mm Hg·ml
* $P < 0.05$, $^+P = 0.075$ vs baseline

Rapid ventricular pacing and V-A coupling and the influence of load

Little and Cheng[4] have shown that at a given V_{ED} and contractile state in the conscious dog, SW is within 95% of its maximum value with an E_{ES}/E_A ratio between 0.74 and 1.2. We initially examined whether 24 h of RVP would alters E_{ES}/E_A to a value outside this range. Figure 1 shows steady-state PV loops, and corresponding LV P_{ES}–V_{ES} and arterial P_{ES}–SV relations from two representative animals at baseline and after RVP. In Fig. 1A, E_{ES} and E_A at baseline are nearly equal with and E_{ES}/E_A ratio of 1.23. After 24 h of RVP, E_A is mildly increased, with an attendant mild reduction in the E_{ES}/E_A ratio (to 1.07) and SW, although still well within the range of optimal V-A coupling. The animal in Fig. 1B also shows near optimal V-A interaction at baseline with an E_{ES}/E_A ratio of 0.95. After RVP, however, there was a much greater increase in E_A and a marked reduction in the E_{ES}/E_A ratio to 0.40, indicating significantly impaired VA coupling. In this animal, there was a large reduction in SW, as would be predicted by the magnitude of change in the E_{ES}/E_A ratio. Table 2 shows group data for V-A coupling parameters before and after RVP. E_A and R_T were both significantly increased after RVP, indicating increased arterial load and resistance. The changes in E_A and R_T in this model may well reflect vasoconstriction as a result of the reduced SV during tachypacing. SW was also reduced, however, even when matched for preload (V_{ED}). Since overall LV chamber performance was not reduced (Table 1), the reduction in SW was likely due to increased arterial load. Despite significant changes in E_A, V-A coupling was maintained under unstimulated conditions, with maintenance of E_{ES}/E_A and SW/PVA ratios.

We next evaluated whether V-A coupling alterations were uncovered upon changes in load induced by graded infusions of phenylephrine. For this analysis, we examined

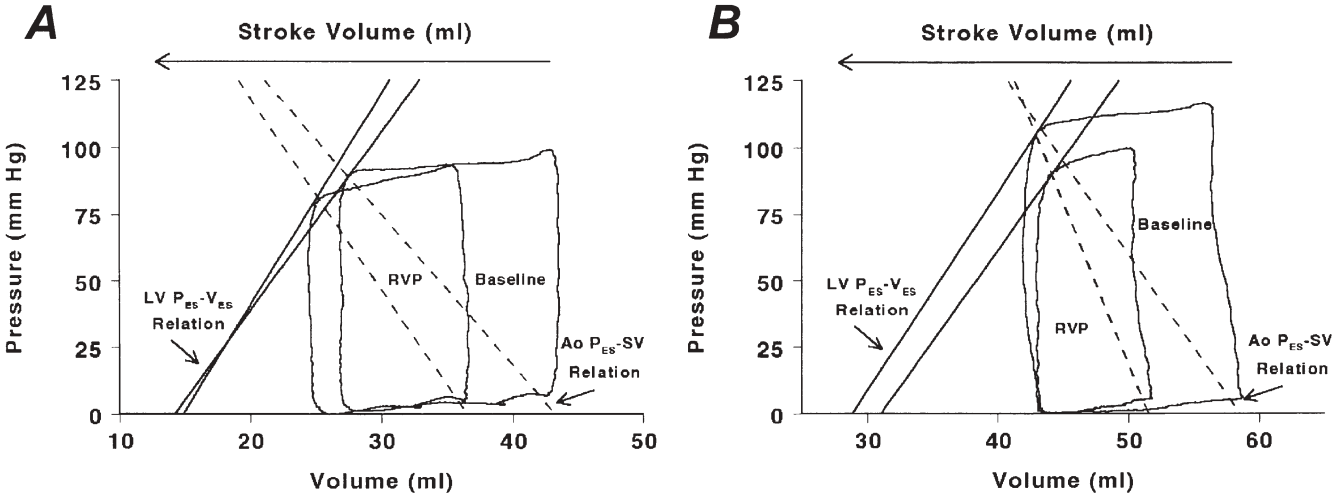

Fig. 1A,B. Steady-state pressure–volume loops from two representative animals before and after 24 h of rapid ventricular pacing (*RVP*). The corresponding P_{ES}–V_{ES} and arterial P_{ES}-SV relations are also shown. Baseline E_{ES} and E_A are well matched in both animals, with an E_{ES}/E_A ratio of 1.23 in **A** and 0.95 in **B**. After RVP changes in the E_{ES}/E_A ratio were variable, with relative maintenance of the ratio (1.07) in the animal in **A** but marked reduction of the ratio (0.40) in the animal in **B**. For definitions see text. *LV*, left ventricular; *Ao*, arterial

the relationship between E_{ES}/E_A and R_T. Figure 2A shows an example of the E_{ES}/E_A–R_T relation from one animal before and after RVP. Under both conditions a linear relationship between E_{ES}/E_A and R_T was observed, with reductions in the E_{ES}/E_A ratio upon augmentation of arterial resistance, and deviation from optimal V-A coupling at higher levels of load. After RVP, however, the slope of this relationship was increased, such that for any given increase in arterial resistance, there was greater proportional reduction of the E_{ES}/E_A ratio and earlier manifestation of suboptimal V-A coupling. Figure 2B shows group data for the slope of the E_{ES}/E_A–R_T relation. After RVP there was a significant increase in the absolute value of the slope ($P = 0.022$ vs baseline), indicating diminished V-A coupling reserve in the face of increased afterload.

Table 2. Left ventricular–arterial coupling

	Baseline	RVP
E_A (mm Hg/ml)	7.8 ± 1.2	11.2 ± 1.2*
E_A/E_{ES}	0.91 ± 0.13	0.86 ± 0.18
R_T (mm Hg·ml·min)	0.059 ± 0.007	0.097 ± 0.007*
SW (mm Hg·ml)	1530 ± 160	654 ± 90*
Matched SW (mm Hg·ml)	1505 ± 164	1152 ± 263*
PVA (mm Hg·ml)	2217 ± 291	972 ± 100*
SW/PVA	0.65 ± 0.03	0.62 ± 0.04

All values are mean ± SEM
RVP, rapid ventricular pacing; E_A and E_{ES}, effective arterial and end-systolic elastance, respectively; R_T, total peripheral resistance; SW, stroke work; Matched SW, value derived from the SW–V_{ED} relation at baseline V_{ED}; PVA, pressure–volume area
* $P < 0.05$ vs baseline

Raid ventricular pacing and V-A coupling during β-adrenergic stimulation

Figure 3 illustrates the effect of dobutamine stimulation on V-A coupling in a representative animal at baseline and after RVP. As shown in Fig. 3A and B, at baseline, dobutamine markedly increased E_{ES} with minimal absolute change in E_A. After RVP the increase in E_{ES} was blunted, whereas the E_A response was unchanged. As shown in Fig. 3C and D, this resulted in a large increase in the E_{ES}/E_A and SW/PVA ratios at baseline that were markedly attenuated after RVP. Table 3 shows group data for dobutamine-induced changes. At baseline, dobutamine: (1) significantly increased contractility (E_{ES}, dP/dt_{MAX}), (2) shifted the P_{ES}–V_{ES} relation to the left (V_{100}), and (3) and improved V-A coupling and mechanical energy transfer as shown by the marked increase in the E_{ES}/E_A and SW/PVA ratios. After RVP, while dobutamine still increased contractility, the degree of change was markedly attenuated (ΔE_{ES}) consistent with desensitization of the catecholamine inotropic response. Accompanying this blunted inotropic response was a significant reduction in dobutamine-induced augmentation of V-A coupling, such that there were much smaller increases in both the E_{ES}/E_A ratio and mechanical efficiency. Dobutamine did not acutely change E_A either at baseline or after RVP. Thus, 24 h of tachypacing altered β-adrenergic-dependent functional responses in the myocardium, thereby reducing V-A coupling reserve available upon inotropic stimulation.

Rapid ventricular pacing and the relationship between V-A coupling and mechanical efficiency

Prior studies have demonstrated that while SW at a constant V_{ED} is maximal over a broad range of E_{ES}/E_A ratios,

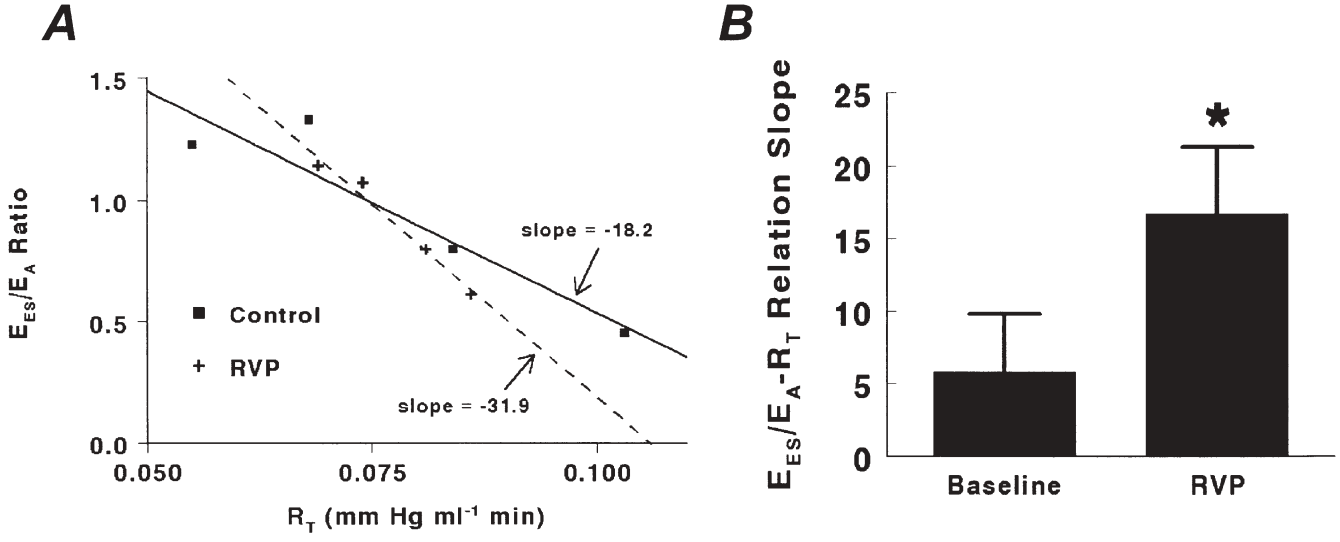

Fig. 2A,B. Relationship between the E_{ES}/E_A ratio and R_T at different levels of afterload induced by graded infusions of phenylephrine. Data from a representative animal are shown in **A** and group data for the slope of this relation are shown in **B**. E_{ES}/E_A and R_T were inversely and linearly correlated with reductions in E_{ES}/E_A upon augmentation of arterial resistance. After 24 h of rapid ventricular pacing (*RVP*), the absolute value of the slope of this relationship significantly increased, such that for any given increase in arterial resistance there was greater proportional reduction of the E_{ES}/E_A ratio. For definitions see text

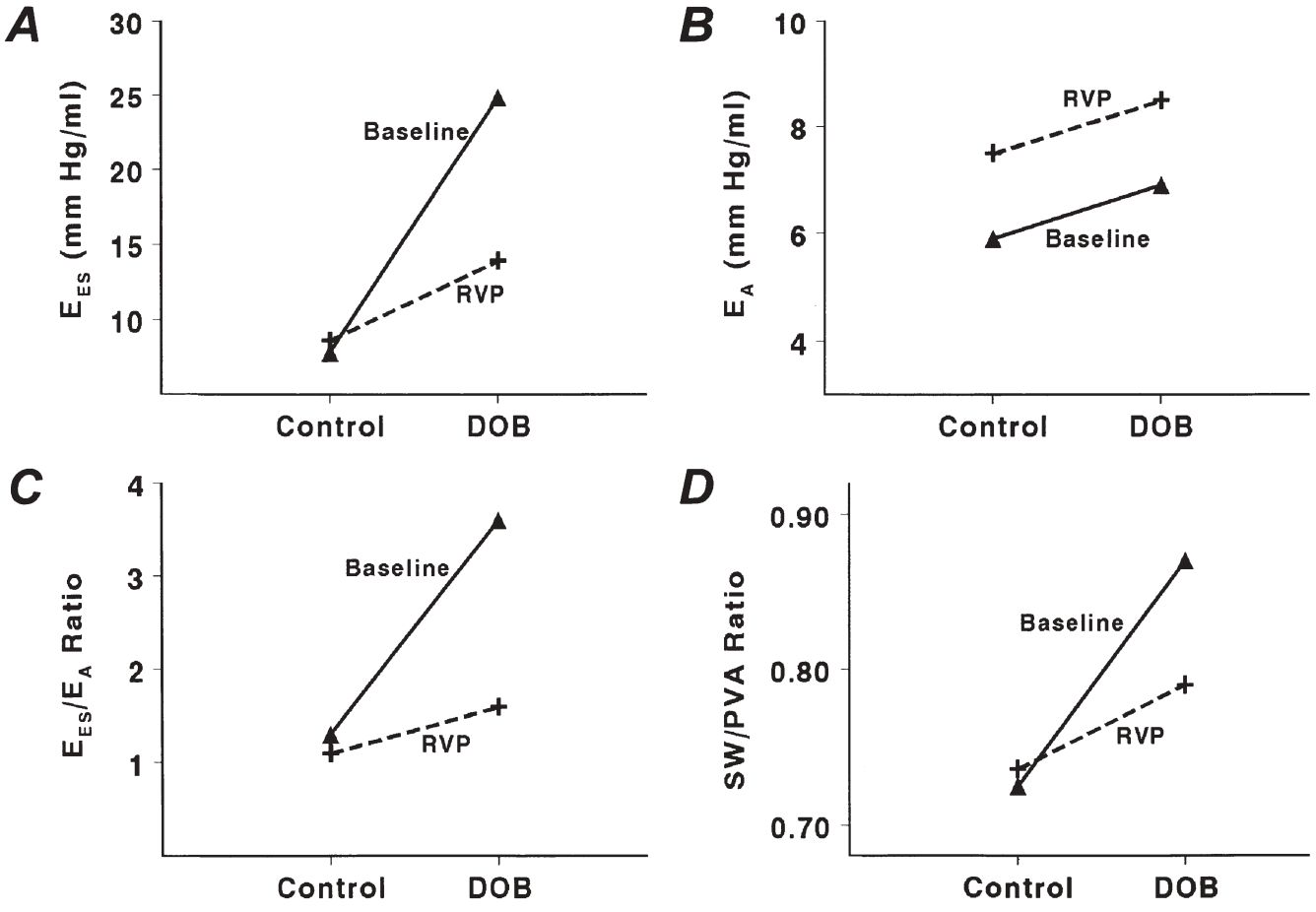

Fig. 3A–D. Dobutamine (*DOB*)-induced changes in ventricular–arterial (V-A) coupling before and after 24 h of rapid ventricular pacing (*RVP*). The augmentation of E_{ES}, E_{ES}/E_A ratio, and SW/PVA (mechanical efficiency) induced by dobutamine was markedly blunted after RVP. *SW*, stroke work; *PVA*, pressure–volume area

Table 3. β-Adrenergic stimulation and left ventricular–arterial coupling

	Baseline		RVP	
	Control	DOB	Control	DOB
E_{ES} (mm Hg/ml)	7.5 ± 0.9	21.1± 4.7*	8.4 ± 1.2	13.3 ± 2.3*#
V_{100} (ml)	34.2 ± 3.3	29.2 ± 3.0*	35.7 ± 4.8	31.6 ± 3.9*
dP/dt_{MAX} (mm Hg/s)	2213 ± 179	3411 ± 200*	1819 ± 146#	2290 ± 131*#
E_A (mm Hg/ml)	8.6 ± 1.1	9.1 ± 1.5	11.6 ± 1.1#	10.9 ± 0.7
E_{ES}/E_A	0.97 ± 0.16	2.40 ± 0.38*	0.84 ± 0.14	1.25 ± 0.22*#
SW/PVA	0.65 ± 0.04	0.80 ± 0.03*	0.62 ± 0.04	0.74 ± 0.04*#
DOB vs Control				
ΔE_{ES} (%)		171 ± 41		61 ± 15#
$\Delta E_{ES}/E_A$ (%)		154 ± 28		76 ± 24#

All parameters mean ± SEM, measured after autonomic blockade
RVP, rapid ventricular pacing; DOB, dobutamine 10 μg/kg/min; E_{ES}, end-systolic elastance; V_{100}, end-systolic pressure–volume (P_{ES}–V_{ES}) relation volume intercept at 100 mm Hg; dP/dt_{MAX}, maximum rate of LVP rise; E_A, effective arterial elastance; SW, stroke work; PVA, pressure–volume area
* $P < 0.05$ versus respective control; # $P < 0.05$ vs respective baseline

the conversion of PVA to SW consistently increases with increases in E_{ES}/E_A.[4] We examined whether this relationship was altered after short-term RVP. Figure 4 demonstrates the SW/PVA–E_{ES}/E_A relations at baseline and after RVP. In both experimental conditions, the SW/PVA ratio steadily increased with enhancement of the E_{ES}/E_A ratio in a monoexponential fashion, and the curves were superimposable before and after RVP. This indicated a similar impact of V-A coupling on the transformation of PVA, an index of total mechanical energy,[18] into useful external

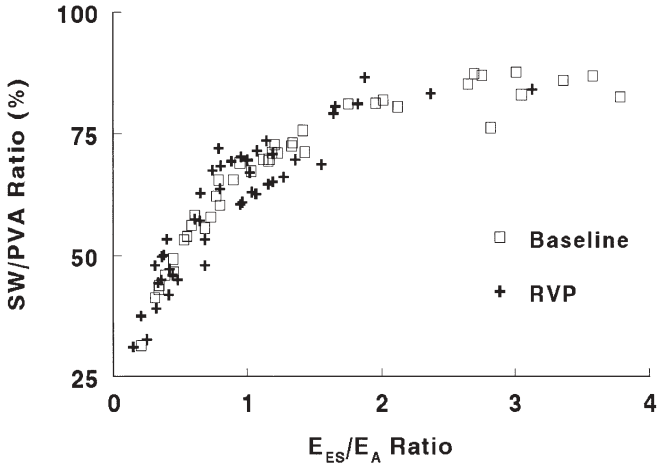

Fig. 4. SW/PVA–E_{ES}/E_A relations at baseline and after RVP. Regardless of experimental condition, the SW/PVA ratio (mechanical efficiency) increased monoexponentially with enhancement of the E_{ES}/E_A ratio and the curves were superimposable before and after RVP

work, and constancy of the fundamental relationship between these variables with or without tachypacing.

Discussion

These are several key findings of this study. First, although short-term RVP did not depress baseline LV contractility, it did significantly increase arterial load and vascular resistance (as indexed by E_A and R_T), establishing that altered vascular mechanical properties occur early in the development of HF prior to significant pump dysfunction. Second, short-term RVP-induced alterations in arterial load did not translate into diminished V-A coupling during unstressed conditions. However, such abnormalities were uncovered during conditions of increased afterload and during inotropic stimulation, indicating an inability of the cardiovascular system to appropriately maintain or augment V-A coupling under stress (i.e., reduced V-A coupling reserve). Third, short-term RVP did not change the basic relationship between V-A coupling and LV mechanical efficiency. These results suggest that in early HF, V-A coupling defects can contribute to impaired mechanical performance during conditions of cardiac stress.

Altered vascular function in early HF

Heart failure is characterized by several abnormalities in vascular function, including heightened vasoconstriction and impaired exercise-induced vasodilatation together with reduced peripheral blood flow at rest and during exercise.[9] Impairment of endothelium-dependent vasodilatation contributes importantly to abnormal vasodilatory capacity, with abnormal responses documented in both the microcirculation and conduit arteries.[10–12,19–21] These abnormalities are thought to be largely related to vascular oxidative stress and reduced bioavailability of NO,[10–12,20,21] a notion further supported by the demonstration of improved endothelial-dependent vascular responses with exercise training,[10–11] antioxidant therapy,[20] and L-arginine supplementation.[21] Other vascular abnormalities reported in HF include increase conduit vessel stiffness and reduced aortic compliance.[14,22] The current study extends these prior findings by demonstrating that increased total arterial load (greater E_A and R_T) occurs at a very early stage in HF, prior to the appearance of overt LV dysfunction or circulatory congestion. The increase in E_A did contribute, however, to a modest decline in SW that was independent of changes in preload (Table 2). This suggests that vascular alterations represent early responses that may contribute to the subsequent decline in cardiovascular function seen at more advanced stages of disease. Indeed, this finding is consistent with data demonstrating that near-maximal endothelial dysfunction is already present in humans with early, mild HF.[23] Although the cellular mechanisms underlying these vascular changes were not directly examined here, in a prior study we demonstrated that myocardial oxidative stress was consistently increased 24 h into the development of tachycardia cardiomyopathy.[24] Analogous augmentation of oxidative stress in the vasculature may contribute to altered arterial mechanical properties in early HF, as oxygen free radicals are known contributors to vascular dysfunction in established disease.

Reduced V-A coupling reserve in early HF

Ventricular–arterial coupling is impacted by both intrinsic myocardial and vascular factors and by the activation of neural reflexes.[25] In this study, reflex effects were minimized by pharmacologic autonomic blockade. Although E_A and arterial load were increased after short-term RVP, V-A coupling (E_{ES}/E_A ratio) was unchanged under baseline conditions, indicating that LV performance was maintained enough to offset the increase in arterial load (Tables 1 and 2). However, impaired V-A coupling responses were uncovered upon augmentation of afterload and inotropic state. As has been shown previously,[4] increasing arterial resistance with phenylephrine increased E_A and reduced the E_{ES}/E_A ratio, indicating depression of V-A coupling. Figure 2 demonstrates that the peripheral resistance and E_{ES}/E_A ratio derived from acutely altering afterload are inversely related in a linear fashion. After short-term RVP, the slope of this relation was significantly increased such that the decline in V-A coupling for any given increase in arterial resistance was augmented. Thus, from a mechanical standpoint, loss of V-A coupling reserve increases the susceptibility of the LV to changes in afterload in early HF.

Why should there the exaggerated depression of V-A coupling in the face of augmented afterload in early HF? Previous work in this model[17,26] has shown that in normal hearts, increasing afterload does not alter E_{ES} but does shift the P_{ES}–V_{ES} relation to the left thereby improving LV performance, a phenomenon thought to be due to myocardial length-dependent activation. However, after 24 h of RVP, afterload-induced enhancement of LV performance

was markedly attenuated, with a much smaller leftward shift and overt decline in E_{ES} despite equivalent changes in load (presumably due to reduced length-dependent activation).[17] This loss of inotropic reserve would also impact V-A coupling, as there would be greater reductions in the E_{ES}/E_A ratio with augmented afterload as demonstrated in this study. Thus, loss of inotropic reserve and V-A coupling reserve in early HF are closely inter-related, and the ability of the cardiovascular system to functionally compensate for increased afterload is diminished. This mechanical profile may underlie the increased sensitivity of the dysfunctional heart to elevated blood pressure.

As seen in Fig. 3 and Table 3, loss of V-A coupling reserve was also manifested during catecholamine stress. Under normal conditions, dobutamine augmented E_{ES}, maintained E_A, increased the E_{ES}/E_A ratio, and increased the efficiency of PVA transformation into external SW, as demonstrated in prior studies.[4,27] After 24 h RVP, dobutamine-induced augmentation of LV contractility (E_{ES} increase) was blunted, consistent with β-adrenergic desensitization, which, along with elevated plasma catecholamines, also occurs at this early stage of tachycardia cardiomyopathy.[28] Importantly, attenuation of the E_{ES} increase upon dobutamine stimulation was not offset by reductions in E_A, and thus there was significant blunting of the E_{ES}/E_A ratio and an inability to properly augment V-A coupling after 24 h RVP. From a mechanical standpoint, as the E_A response to dobutamine was unchanged after RVP, loss of V-A coupling reserve was primarily related to depression of stimulated LV contractility, again underscoring the intimate interrelationship between LV chamber performance and V-A interaction.

The net effect of this altered dobutamine response after RVP was a less efficient transfer of LV total mechanical energy (PVA) to stroke work, underscoring the importance of V-A coupling in mechanoenergetic performance. As described by Suga,[18] myocardial oxygen consumption (MVO_2) is linearly related to PVA, and this relation can be described by a slope (termed contractile efficiency) and MVO_2-axis intercept (unloaded MVO_2). Thus, the energy cost of external SW is related to both the SW/PVA ratio (mechanical efficiency) and the MVO_2–PVA relation. Although MVO_2 was not directly measured in this study, we have previously shown that LV mechanoenergetic behavior is altered after 24 h of RVP such that there is increased unloaded (nonmechanical) MVO_2 but no change in contractile efficiency.[17] Since baseline SW/PVA was unchanged and since contractile state was equivalent after RVP (Table 1–3), the oxygen cost of SW at any given PVA would be increased secondary to increased unloaded MVO_2. Also, since there was less augmentation of SW/PVA with dobutamine after RVP (Table 3), and since doubtamine further increases unloaded MVO_2,[18,29] the energy costs of increasing SW with β-adrenergic stimulation would thus also to tend to be exacerbated. Importantly, the relationship between mechanical efficiency and E_{ES}/E_A was identical prior to and after short-term RVP (Fig. 4), indicating preservation of the essential relationship between V-A coupling and LV energetics under either condition.

This study must be examined in the light of potential limitations. First, the analysis above assumes linearity of the P_{ES}–V_{ES} relation. In the intact canine model, Little et al.[30] have shown that although a minor curvilinearity of the P_{ES}–V_{ES} relation exists regardless of inotropic state, this degree of nonlinearly does not prevent the accurate approximation of this relation by a straight line. In our study, the linear regression correlation coefficients were high, lessening the likelihood of significant quantitative error. Second, description of arterial load solely by E_A does not take into account the higher-frequency portions of the aortic impedance spectrum. While these components comprise a minor portion of the energy transfer under normal conditions, their impact may be greater in HF.[13] However, in general, estimates of arterial load by E_A are remarkably similar to that derived by vascular impedance analysis over a wide range of systolic pressures and resistances.[7] This finding together with the ease of integration E_A with LV chamber performance to determine V-A coupling supports the approach used in the current study.

In summary, the results demonstrate that a short-term, 24-h period of RVP in the intact dog significantly increases arterial load and vascular resistance without depression of baseline LV contractility. While V-A coupling was maintained during unstressed conditions, abnormalities in V-A interaction were uncovered during afterload and catecholamine stress, establishing that loss of V-A coupling reserve occurs early in the development of HF. The fundamental relationship between V-A coupling and LV mechanical efficiency did not change. These findings suggest that impaired V-A coupling can impact LV performance in the early formative stages of HF, especially under conditions of cardiac stress.

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