Tachycardia exacerbates abnormal left ventricular–arterial coupling in heart failure

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Abstract The purpose of this study was to assess the effect of heart rate on left ventricular (LV)–arterial coupling and LV mechanical efficiency before and after heart failure (CHF). The production of LV stroke work (SW) and mechanical efficiency depends on the coupling of the LV and arterial system. The response of LV–arterial coupling to tachycardia may be altered in heart failure. We compared mechanical efficiency before CHF and after CHF, with increased heart rate to 180 min⁻¹. Before CHF, E_{ES}/E_A increased similarly with increased heart rate to 180 min⁻¹. Thus, E_{ES}/E_A remained unaltered (0.96 ± 0.08 vs 0.94 ± 0.35), and SW/PVA was unchanged (6.2 ± 0.03 vs 5.9 ± 0.06). Compared with the results prior to CHF and after CHF the resting E_{ES} was decreased, thus both E_{ES}/E_A (0.58 ± 0.09) and SW/PVA (0.48 ± 0.06) were less (P < 0.05) than baseline. After CHF, an increase in HR to 180 min⁻¹ increased E_A but not E_{ES}, thus E_{ES}/E_A fell to 0.44 ± 0.06 (P < 0.05) and SW/PVA fell to 0.41 ± 0.05 (P < 0.05). Under normal conditions, LV–arterial coupling remains optimal during increases in HR. After CHF, tachycardia exacerbates the suboptimal baseline LV–arterial coupling, reducing the efficiency of producing SW.

Key words Conscious dog · Congestive heart failure · Force–frequency relation · Left ventricular–arterial coupling

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Introduction

The performance of the cardiovascular system depends on the interaction of its components. The left ventricle (LV) pumps the stroke volume (SV) into the arterial system that delivers the flow to the tissues. Thus, optimal cardiovascular function requires appropriate coupling of the LV and the arterial system. Functional analysis of this interaction requires that the LV and arterial system be described in similar terms. Sunagawa et al. and Burkhoff and Sagawa proposed that LV–arterial coupling could be analyzed in the pressure–volume (P–V) plane. The intersection of the LV end-systolic pressure (P_{ES})–volume (V_{ES}) relation and the arterial P_{ES}–SV relation determines the SV. The slope of the P_{ES}–V_{ES} relation is the end-systolic elastance (E_{ES}) of the LV, whereas the slope of the arterial P_{ES}–SV relation represents the effective arterial end-systolic elastance (E_A). If the ejection portion of the LV P–V loop is assumed to be flat and the end-diastolic pressure is negligible, this analysis predicts that stroke work (SW) should be maximized when E_A equals E_{ES}. The efficiency of producing SW is predicted to decline as E_{ES}/E_A is reduced. Despite the limitations of the required simplifying assumptions, these predictions are correct in conscious animals. Furthermore, at rest, the LV and arterial system operate close to this point that produces optimal SW.

Furthermore, SW is within 95% of its maximum value when E_{ES}/E_A is between 0.9 and 1.3. During exercise in normal animals, the E_{ES}/E_A ratio remains in this range, indicating that the LV and arterial system are nearly optimally coupled to produce SW, both at rest and during exercise.

We hypothesized that heart failure (CHF) should adversely alter LV–arterial coupling as E_{ES} is reduced and E_A may be increased, thus reducing E_{ES}/E_A to below 0.9 where SW rapidly declines with decreasing E_{ES}/E_A. Normally, E_{ES} increases with higher heart rates, which would be expected to match the increase in E_A. This manifestation of the force–frequency response is lost in CHF due to changes in sarcoplasmic reticular calcium handling. In addition,
there is autonomic dysfunction and reduced adrenergic sensitivity in CHF. Thus, we hypothesized that tachycardia would further exacerbate the abnormal LV–arterial coupling in CHF, reducing both SW and LV efficiency. Accordingly, we undertook this study to test these hypotheses by evaluating the alteration of LV–arterial coupling in response to increasing heart rate before and after pacing-induced CHF.

Materials and methods

Instrumentation

Six healthy, adult, heart-worm-negative mongrel dogs (weight 25–36 kg) were instrumented under anesthesia after induction with xylazine (2 mg/kg i.m.) and sodium thiopental (6 mg/kg i.v.), and maintained with halothane (0.5%–2.0%). Micromanometer pressure transducers (Konigsberg Instruments, Pasadena, CA, USA) and polyvinyl catheters (1.1 mm i.d.) for transducer calibration were inserted into the LV through an apical stab wound and into the left atrium from the left atrial appendage. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the LV to measure the anterior-to-posterior, septal-to-lateral, and base-to-apex (long-axis) dimensions, using methods previously described from our laboratory. Hydraulic oculder cuffs were placed around the inferior and superior venae cavae. Pacing leads were attached to the right atrium and right ventricle and connected to programmable pacemakers (Model 8329, Medtronic, Minneapolis, MN, USA) implanted subcutaneously. All wires and tubing were exteriorized through the posterior neck.

Data collection

Studies were performed after full recovery from instrumentation (from 10 days to 2 weeks after surgery) with the dogs standing. The LV catheter was connected to a pressure transducer (Statham P23Db, Gould, Cleveland, OH, USA) calibrated with a mercury manometer. The signal from the micromanometer was adjusted to match that of the catheter. The analog signals were recorded on an eight-channel chart recorder (Astro-Med, West Warwick, RI, USA), digitized with an online analog-to-digital converter (Data Translation Devices, Marlboro, MA, USA) at 200 Hz.

Experimental protocol

Studies before CHF

Steady-state data and data during transient caval occlusion were recorded at rest while the animals were standing. Three sets of variably-loaded pressure–volume loops were generated by caval occlusion. We analyzed the data recorded at control and at 3 min after each stage of increased heart rate by right atrial pacing. The heart rates of 140, 160, and 180 min⁻¹ were adjusted using an external magnetic control unit. Atropine was not required to produce ventricular capture.

Studies during the development of CHF

After the completion of the baseline study, the right ventricular pacemaker rate was adjusted to 220–250 beats/min. Three times per week, the pacemaker rate was adjusted to below the spontaneous rate. The animal was allowed to equilibrate for 30 min and then data were collected. After each study, the pacing rate was returned to 220–250 min⁻¹. After pacing for 4–5 weeks, when the LV end-diastolic pressure (P_{ED}) during the nonpaced period had increased by more than 15 mmHg over the prepping control level, the animals had begun to show clinical evidence of CHF (anorexia, mild ascites, and pulmonary congestion).

Studies after the onset of CHF

The pacemaker was turned off, and the animal was allowed to stabilize for at least 30 min. Steady-state data and data during transient caval occlusion were collected with the animal standing as in the protocol performed in dogs before CHF.

Data processing and analysis

The LV volume (V_{LV}) was calculated as a modified general ellipsoid using the following formula:

\[
V_{LV} = \frac{(\pi/6)D_{AP} \cdot D_{SL} \cdot D_{LA}}{}
\]

where \(D_{AP}\) is the anterior to posterior LV diameter, \(D_{SL}\) is the septal to lateral LV diameter, and \(D_{LA}\) is the long-axis LV diameter. This method gives a consistent measure of \(V_{LV}\) (\(r = 0.97\); standard estimated error (SEE) < 2 ml) despite changes in LV loading conditions, configurations, and heart rate. To account for respiratory changes in intrathoracic pressure, steady-state measurements were averaged over the 12–15-s recording period that spanned multiple respiratory cycles. End-diastole was defined as the relative minimum of LV pressure occurring after the A wave. End-systole was defined as the upper left corner of the LV P–V loop.

Stroke volume was calculated as \(V_{ED} \text{ min} V_{ED} \text{ min}\). LV stroke work was also calculated by point-by-point integration of the LV P–V loop for each beat as described by Glower et al. The rate of LV relaxation was analyzed by determining the time constant of the isovolumic fall in LV pressure. LV pressure from the time of minimum dP/dt until mitral valve opening was fit to an exponential equation:

\[
P = P_a \exp(-t/T) + P_b
\]

where \(P\) is LV pressure, \(t\) is time, and \(P_a, P_b,\) and \(T\) are constants determined by data. Although the fall in isovolumic pressure is not exactly exponential, the time