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Effects of Electrical Stimulation of the Carotid Sinus Baroreflex Using the Rheos® Device on Ventricular-Vascular Coupling and Myocardial Efficiency assessed by Pressure-Volume Relations in Non-Vagotomized Anesthetized Dogs

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Abstract— **We investigated the effects of the carotid sinus baroreflex on coupling of the left ventricle (LV) and the arterial system in twelve anesthetized dogs, with all nerves and carotid sinus circulation intact and instrumented to measure LV pressure and volume. The Rheos® device was used to directly electrically stimulate the carotid sinus baroreceptors. Stimulation resulted in a significant reduction in systolic blood pressure (SBP), 95.6±8.1 to 77.3±5.3 mmHg (p<0.0001) and heart rate (HR), 85±13.2 to 67.2±18.8 (p<.001). Cardiac output was unchanged. Ventricular-vascular coupling was determined by the ratio of arterial and ventricular elastance (Ea/Ees). At baseline, Ea/Ees was 1.26±0.27 and after stimulation decreased to 0.51±0.16 (p<0.001), favoring optimization of metabolic efficiency. This decrease was entirely due to a reduction in Ea while Ees was unchanged. The maintenance of end-diastolic volume (EDV) during stimulation allowed stroke work (SW) to remain unchanged as arterial pressure decreased. Thus mechanical efficiency, described as the ratio of stroke work to pressure-volume area (SW/PVA) increased from baseline of 0.51±0.05 to 0.69±0.04 (p<0.0001) during baroreceptor stimulation. We conclude that electrical activation of the carotid sinus baroreceptors results in optimization of both energetic and mechanical efficiency and has no acute effect on LV Ees. These novel findings await confirmation in chronically instrumented animals.**

I. Introduction

To meet the metabolic demands of the tissues, the left ventricle (LV) must perform work to eject an adequate volume of blood into the arterial system. The energy required to perform this work and the resulting pressures generated are critically dependent on both arterial and ventricular properties. This is the fundamental concept of ventricular-vascular coupling, the importance of which has been demonstrated in several pathophysiologic conditions where this coupling is abnormal including hypertension, diabetes, chronic kidney disease and heart failure [1]. Assessment of ventricular-vascular coupling requires independent characterization of cardiac function and arterial load. Since the pioneering work of Sunagawa and colleagues [2], the pressure-volume diagram and the concept of ventricular and arterial elastance has emerged as the most useful framework to assess ventricular-vascular coupling in both basic research and clinical studies [3].

Shown in figure 1 is a schematic of a pressure-volume loop. The integrated (contractile and structural) pump function of the left ventricle is indexed by the end-systolic elastance (Ees), the slope of the end-systolic pressure-volume relationship (ESPVR). The properties of the arterial system are characterized by the effective arterial elastance (Ea), the negative slope of the line connecting the end-diastolic volume (EDV) to the end-systolic pressure (SBP). Traditionally, the properties of the arterial system have been characterized in the frequency domain [4] using Fourier analysis and impedance spectra. However, coupling this type of analysis with cardiac function in the time domain is cumbersome and physiologically difficult to interpret. Although Ea has units of elastance or stiffness, it does not reflect any single property of the arterial system but rather conveys all the information which can be derived from analysis in the frequency domain namely characteristic impedance, peripheral resistance and arterial compliance [2]. In addition, Ea is also influenced by systolic and diastolic intervals determined by heart rate (HR). The derivation of Ea is based upon the three element Windkessel model of the arterial system which has a limitation of not including effects of wave reflections arising in the arterial system due to impedance mismatch between central and distal arteries and arterioles. However, when Ea is derived from pressure-volume loops, the effects of wave reflections are functionally integrated in the measurement [5]. Thus Ea may be used as a surrogate for more rigorous impedance analysis of the arterial system allowing for a simplified assessment of ventricular-vascular coupling.

Using the concept of ventricular and arterial elastance, ventricular-vascular coupling has been assessed as the ratio Ea/Ees. Theoretical analysis has shown that optimal

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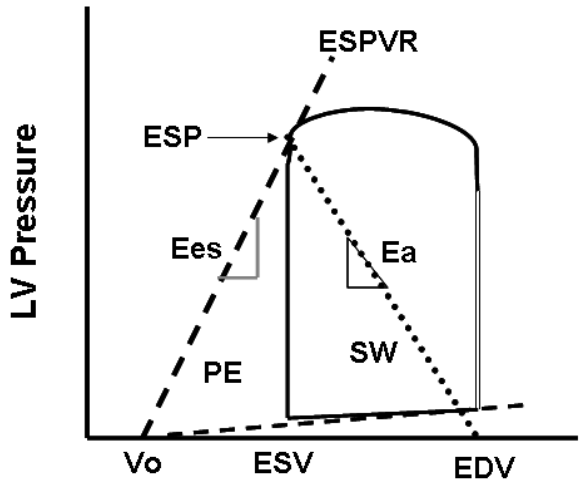

Figure1.Ventricular pressure-volume diagram used to derive effective arterial elastance, Ea and ventricular elastance (Ees). Ea is the negative slope of the line joining the end-diastolic volume (EDV) to the end-systolic pressure (ESP). Ees is the slope of the end-systolic pressure-volume relationship (ESPVR) which passes through the end-systolic pressure and the volume axis intercept Vo. Ees is calculated as ESP/(ESV-Vo). The area contained within the pressure-volume loop is the stroke work (SW) and the triangular area bound by Vo, ESV and and ESP is the potential energy (PE) stored in the ventricle at end-systole. Pressure-volume area (PVA) is the sum of SW and PE and represents the total energy expended by the heart per beat for a given EDV, Ees and Ea.

mechanical efficiency which is the maximum SW from the LV to the arterial system occurs when Ea=Ees and thus Ea/Ees =1 while optimal energetic efficiency measured as the amount of oxygen consumed to perform a given stroke work (SW) is when Ea=0.5 Ees [6]. In normal experimental animals and patients, coupling is typically biased towards optimal mechanical efficiency, Ea/Ees=1 [7]. In systolic heart failure, this ratio is increased to values near 2.5 due to the decrease in Ees and increase in Ea [8]. In patients with hypertension, and heart failure with preserved ejection fraction, both Ees and Ea are increased above normal controls however there is a disproportionate increase in LV stiffness (Ees), likely due to hypertrophy, resulting in an Ea/Ees near 0.6-0.7 [9]. Analysis of mechanical or energetic efficiency and it's relation to the Ea/Ees ratio can also be determined from the pressure-volume diagram (figure 1). The area contained within the pressure-volume loop is the stroke work (SW) which is the work the heart performs to eject blood into the arterial system. The triangular area denoted by PE, is the potential energy stored in the ventricle at end-systole and is released as heat if not converted to stroke work. The sum of SW and PE is the pressure-volume area (PVA) and is the total energy available for a given EDV, Ea and Ees. There is a direct and linear correlation between PVA and myocardial oxygen utilization [2].The carotid sinus baroreflex is a negative feedback system which acts to restore arterial pressure through changes in sympathetic and parasympathetic activity when there is a disturbance in pressure. The reflex has been shown to affect cardiac, arterial and venous properties [10] and thus may affect ventricular-vascular coupling. Only one study has directly assessed the effect of the carotid sinus baroreflex on ventricular-vascular coupling [11]. Kubota et al used a white noise approach to alter pressure in the isolated carotid sinus and found that during pressure perturbations, the baroreflex altered both Ees and Ea equally so that mechanical efficiency was optimized. While the effect of the baroreflex on arterial load, or Ea, has been well characterized, the effect on cardiac contractile properties is controversial [12,13]. Kubota et al. used a single beat approach to estimate Ees based on the peak isovolumic pressure. Furthermore, a bilateral vagotomy was performed which may have led to an increased Ees due to the high basal heart rate (165±20 beats/min) and the elimination of the parasympathetic limb of the baroreflex.

Accordingly, to evaluate the effects of the baroreflex on ventricular-vascular coupling in a more intact preparation, we used a using a novel medical device, Rheos® Baroreflex Activation Therapy (BAT) which is currently undergoing clinical investigation for the treatment of resistant hypertension, to electrically stimulate baroreceptors through electrodes placed directly on the carotid sinus. This obviated the need for isolation of the carotid sinus region with a separate perfusion circuit and all nerves were left intact. Pressure-volume data were recorded continuously, beat by beat with a conductance-micromanometer catheter placed in the LV. The results indicate that electrical activation of the baroreflex, equivalent to a rise in arterial pressure, causes a reduction in Ea with no change in Ees, thereby maximizing energetic efficiency of contraction. A further novel finding is that mechanical efficiency is equally maximized as stroke work is unchanged while PVA is decreased, thereby extracting more potential energy.

II. METHODS

A. *Animal Preparation*

Twelve (n=12) healthy, adult mongrel dogs weighing 24.8±2.9 kg were studied. Animals were induced with intravenous propofol or fentanyl, intubated and placed on a mechanical, positive pressure ventilator and ventilated with room air. Anesthesia was maintained with intravenous fentanyl (20µg/kg/min) and isoflurane (1-1.5%). Arterial blood was regularly sampled for blood gas and pH analysis. Adjustment to physiologic pH was accomplished through changes in ventilation or bicarbonate infusion. The left and right carotid sinuses were exposed through a single, midline neck incision and custom fabricated canine electrodes were wrapped around the carotid bifurcation and sutured in place.

Stimulation parameters were chosen to obtain a 20-25 mmHg drop in arterial systolic pressure. Typical stimulation settings were 4-6 Volts pulse amplitude, 480μs pulse width and 20 Hz frequency delivered continuously using the Rheos® system. In seven animals unilateral stimulation was used (4 right, 3 left) and bilateral in the remainder. Baseline was defined as the steady state immediately preceding the onset of stimulation. Stimulation resulted in an immediate fall in arterial and ventricular pressure and heart rate, with a steady state being achieved in approximately 30 seconds.

Left ventricular pressure and volume were measured using a 6F dual-pressure, 8-electrode conductance-micromanometer catheter (SPR-921, Millar Instruments, Houston TX) advanced retrograde to the heart through a left femoral artery incision. Correct placement of the catheter was verified using flouroscopy. In a subset of animals (n=3), a Fogarty balloon occluder catheter (Edwards Lifesciences, CA) was advanced to the junction of the inferior vena cava and right atrium through a right femoral vein incision and was used to obstruct vena caval flow. The conductance catheter was connected to a volumetric system (Ultra MPVS, Millar Instruments, Houston TX) or a custom designed system both delivering a constant current of 30μA at a frequency of 20kHz. No attempt was made to calibrate the conductance catheter to obtain absolute volumes or stoke volume, however the main thesis of this paper does not rely on absolute volume calibration since Ea/Ees and SW/PVA are dimensionless. Thus LV volume was expressed in arbitrary conductance units and values dependent on absolute volumes will be expressed as percent change from baseline. Left ventricular pressure, left ventricular volume and central arterial pressure signals were digitized at 1kHz (Powerlab, ADInstruments, Bella Vista, Australia) and stored on a local computer for offline analysis using custom software. All protocols were approved by an Animal Care and Use Committee.

B. Data Analysis

For each condition, hemodynamic variables were determined at steady state from the average of 20-25 beats. Ea was determined as SBP/(EDV-ESV), where end-diastole was defined as the peak of the R-wave on electrocardiographic lead II. Ees was determined from the least squares linear regression of the upper left-hand corner of the pressure-volume loops identified using the iterative method of Kono et al. [14] derived during stimulation (figure 2). Caval occlusions to reduce preload were not performed after stimulation to avoid any potential coronary ischemia due to the reduced arterial pressure below 60 mmHg which would alter the slope of the ESPVR. Stroke Work (SW) was determined as SBP*(EDV-ESV) and PVA was calculated as SW+(SBP^2/Ees)/2. Cardiac output (CO) was (EDV-ESV)*HR and total peripheral resistance (TPR) was MBP/CO.

III. RESULTS

TABLE 1: HEMODYNAMIC PARAMETERS

Parameter	Baseline	Stimulation	Paired T-Test
HR (beats/min):	85.0±13.2	67.2±18.8	0.001
SBP (mmHg):	95.6±8.1	77.3±5.3	0.000
DBP (mmHg):	67.6±9.1	42.3±5.4	0.000
MAP (mmHg):	81.6±8.2	55.1±4.6	0.000
CO (arb units): %Δ		-3.54±4.97	0.603
SV (arb units): %Δ		21.4± 8.6	0.013
EDV (arb units): %Δ		-4.1±2.2	0.494
ESV (arb units): %Δ		-15.3±5.1	0.015
TPR (arb units): %Δ		-21.3±5.3	0.015
Ea (arb units): %Δ		-36.1±5.6	0.002
Ea/Ees	1.26±0.27	0.51±0.16	0.000
SW (arb units): %Δ		1.3±5.6	0.356
PVA (arb units): %Δ		-26.4±9.9	.003
SW/PVA	0.51±0.05	0.69±0.04	0.000

Summary of hemodynamic changes associated with electrical stimulation of the carotid baroreceptors. Parameters dependent on conductance catheter calibration are expressed in arbitrary units and represented as percentage changes from baseline. Data are mean±s.d. and statistical analysis was performed using a paired t-test. HR, heart rate; SBP, arterial end-systolic blood pressure; DBP, arterial diastolic blood pressure; MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; EDV, end-diastolic volume; ESV, end-systolic volume; TPR, total peripheral resistance; Ea, effective arterial elastance; Ees, LV end-systolic elastance; SW, stroke work; PVA, pressure-volume area.

Hemodynamic parameters are listed in Table 1. With electrical stimulation of the carotid baroreceptors there is a significant and sustained drop in arterial pressure and HR. Despite the reduced HR (85.0±13.2 to 67.2±18.8 beats/min., $p<0.001$), cardiac output was unchanged due to the increase in stroke volume (21.4±8.6%) resulting from the decrease in total peripheral resistance (TPR) (-21.3±5.3%, $p<0.05$). Note that the magnitude of the change in Ea was much greater than the change in TPR since Ea also incorporates changes in HR. This is of primary importance since this significantly reduces the Ea/Ees ratio to 0.51±0.16 ($p<0.001$), favoring optimal energetic efficiency.

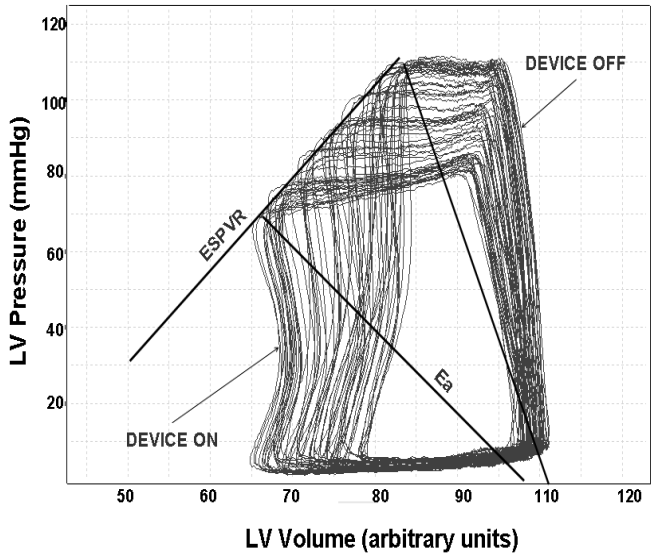

Figure 2. Example of beat-by-beat pressure volume loops at baseline (device off), transient blood pressure reduction, and steady state with electrical stimulation (device on). Note the linearity of the end-systolic pressure volume relationship (ESPVR), increase in stroke volume with constant Ees and reduction in Ea.

Although baroreceptor stimulation reduced the ventricular-vascular coupling ratio, baseline SW remained unchanged (1.3±5.6%) thereby also maintaining optimal transfer of work to the arterial system by beat pressure-volume loops at baseline (Rheos OFF), during the transient reduction in arterial pressure and at steady state after stimulation (Rheos ON). The unique ability of the baroreceptors to maintain SW at reduced arterial pressure is due to the fact the reflex alters both cardiac and vascular properties so that end-diastolic volume (EDV) remains relatively constant (-4.1±2.2%) and Ees is not reduced. In a sub-group of dogs, we compared Ees at baseline derived from caval occlusion to Ees also derived from preload reduction after reducing afterload with electrical stimulation and the relations were identical (data not shown). These results together imply that the mechanical efficiency of the heart is increased. Indeed, the ratio SW/PVA was significantly increased from 0.51±0.05 to 0.69±0.04 ($p<0.0001$). This increase was solely from a decrease in PVA (-26.4±9.9%, $p<0.003$).

IV. DISCUSSION

In this study we evaluated how the carotid sinus baroreflex affects ventricular-vascular coupling. We used a novel medical device, Rheos® to electrically stimulate the carotid sinus, where the baroreceptors are located thereby providing an afferent signal to the central nervous system equivalent to an increase in arterial blood pressure. Use of this device obviated the need to isolate the carotid sinus region from the circulation. Furthermore, the vagal pathways remained intact as previous studies using the Rheos® device in chronically instrumented dogs have shown a sustained blood pressure reduction [16], indicating that the aortic baroreceptors, which signal through the vagus nerve, do not restore arterial pressure to baseline.

We report for the first time that baroreflex activation results in a reduction in effective arterial elastance, Ea, without any changes in ventricular elastance, Ees. At the same time stroke work and cardiac output are maintained constant. This results in the maintenance of stable hemodynamics at reduced arterial pressures, and increase in mechanical efficiency. Although we did not measure it, these findings suggests that myocardial oxygen consumption (MVO2) is reduced since it has been shown that there is a linear relationship between PVA and MVO2 [15].

The apparent lack of change in Ees with electrical stimulation is intriguing given the relatively large reduction in HR, as would be postulated through the force-frequency relationship. It has been previously shown in isolated, denervated hearts ejecting into a constant, servo-controlled arterial system that there is a small, but consistent reduction in Ees without a change in Vo for HR 60-80 bpm [2]. It is difficult to extrapolate these data to the more intact preparation used here, where arterial properties are being altered simultaneously such that the large increase in ejection fraction at nearly constant EDV may have positive effects on the ESPVR. Furthermore, the increase in stroke volume and reduction in end-systolic volume, which was observed in each dog is uniquely different from the hemodynamic effects observed with direct stimulation of the vagus nerve where Ees declined and end-systolic volume increased with no change in stroke volume [19]. Since baroreceptor activation also results in increased vagal tone, the disparate effects on hemodynamics and cardiac contractile function observed in this study warrants further investigation.

In aging and disease conditions, including hypertension and heart failure, there is abnormal ventricular-vascular coupling [3] leading to an increase in the Ea/Ees ratio. Elevation of the Ea/Ees ratio results in increased loading conditions on the heart leading to increased oxygen consumption for a given preload, increased lability of systolic blood pressure and reduced exercise capacity [18]. The goal of therapies targeted to treat these conditions is to normalize or reduce this ratio without comprising stroke work and cardiac output and minimizing oxygen consumption. If the effects of electrical stimulation of the baroreceptors observed in this study can be translated to human disease, this may account for the cardiac remodeling and near normalization of the left ventricular mass index recently observed in resistant hypertension patients implanted with the Rheos device [17].

V. CONCLUSION

Electrical stimulation of the carotid baroreceptor has yielded new insight into the control of ventricular-vascular

coupling and optimization of mechanical work and energy consumption. The Rheos device provides a novel approach to the treatment of various cardiovascular diseases, including hypertension and heart failure.

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