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Pulmonary impedance and right ventricular-vascular coupling in endotoxin shock

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Abstract

Objective: We tested the hypothesis that right heart failure during endotoxin shock may result from altered ventriculovascular coupling responsible for impeding power transfer to the pulmonary circulation. **Methods:** The changes in vascular pulmonary input impedance and right ventricular contractility produced by low-dose endotoxin infusion were studied in 6 intact anesthetized dogs. **Results:** Endotoxin insult resulted in pulmonary hypertension (from 22 ± 2 to 33 ± 3 mmHg) associated with significant decreases in stroke volume (from 26.9 ± 4 to 20.2 ± 3 ml) and right ventricular ejection fraction (from 41 ± 3 to 32 ± 2%). The first minimum of input impedance spectrum and zero phase were shifted towards higher frequencies. Input resistance and characteristic resistance were dramatically increased. The latter change contributed to a significant increase in the pulsatile component of total right ventricular power output from 13 to 21%, indicating a reduction in the hydraulic right ventricle power output delivered into the main pulmonary artery. Overall changes in input pulmonary impedance were indicative of increased afterload facing the right ventricle leading to depressed performance. In contrast, right ventricular systolic elastance was simultaneously increased from 0.56 to 0.93 mmHg/ml indicating an increase in right heart contractility. **Conclusion:** These data suggest that pulmonary hypertension in the setting of experimental endotoxin shock is accompanied by deleterious changes in the pulmonary impedance spectrum, which are responsible for a mismatch of increased contractile state of the right ventricle to the varying hydraulic load ultimately leading to ventricular-vascular uncoupling.

Keywords: blood flow ; hemodynamics ; pulmonary circulation ; septic shock ; ventricular function

1. Introduction

Although septic shock and endotoxin insult share the ability to decrease right heart performance [15,23], both clinical and experimental studies have led to considerable controversy and confusion regarding the true mechanisms of cardiac dysfunction [11,21]. Central to this controversy is the fundamental issue of whether abnormal right ventricular dynamics during sepsis and its experimental counterpart, endotoxemia, are limited by dysfunction intrinsic to the myocardium itself or, alternatively, simply reflect homeometric and heterometric adjustments of an otherwise normal right heart muscle to the abnormal pulmonary vascular environment in which it must pump work. As a matter of fact, some authors claim that right ventricular dysfunction in septic shock, which represents a more common encountered situation than previously suspected, may result from abnormalities in right ventricular afterload [15], eventually aggravated by concomitant poor coronary perfu-sion [23]. Others have proposed that the prominent mechanism of depression regarding both ventricles lies in the effects of a circulating myocardial depressant factor [21]. Beside these mechanisms, attention has been recently focused on the potential role of ventriculovascular coupling in modulating the cardiac performance [2]. The rationale for the present study was to test the hypothesis that how effectively right myocardial performance is transmitted to the pulmonary circulation may be determined to some extent by the vascular bed through the process of ventricular-vascular coupling. Indeed, the pattern of pressure and flow waves measured in the main pulmonary artery represents the result of a collision between a forward wave from the heart with a backward wave reflected from the more peripheral parts of the pulmonary arterial tree. Such a wave reflection phenomenon has a detrimental effect by causing a phase shift between pressure and flow waves that may reduce the hydraulic power output of the right ventricle delivered into the main pulmonary artery. Therefore, we investigated the changes in right ventricular-vascular coupling in dogs with acute pulmonary hypertension produced by low-dose endotoxin infusion. This experimental model was used because of its ability to mimic the clinical septic shock syndrome [8]. The specific aim of this study was to evaluate the right heart operating parameters during experimental septic shock and provide further insight regarding the role of pulmonary vascular load in modulating the right ventricular performance.

2. Methods

All experimental procedures and protocol used in this investigation were reviewed and approved by the Ethical Committee of the Medical Faculty of the University of Liege. All procedures were performed in accordance with

the *Guiding Principles in the Care and Use of Animals* approved by the Council of the American Physiological Society.

Experiments were performed on 6 healthy adult mongrel dogs ranging in weight from 16 to 24 kg. Anesthesia was induced by intravenous injection of sodium pentobarbital (25 mg/kg i.v.). After endotracheal intubation, the dogs were connected to a volume-cycled ventilator set to deliver a tidal volume of 15 ml/kg at a respiratory rate adjusted to maintain an arterial $pC0_2$ between 30 and 35 torr. Arterial oxygen saturation was monitored closely and maintained over 95% throughout experiments by adjusting the F_i0_2. When metabolic acidosis occurred, it was corrected with a slow infusion of sodium bicarbonate. The thorax was opened through a medial sternotomy, the pericardium was opened and the main pulmonary artery was mobilized from the aorta by carefully dissecting the fat between them. An electromagnetic flow probe (Flow unit 3765 M, Cardiovascular-Instruments, UK) was placed around the main pulmonary artery. The probe reduced the diameter by less than 5%, leading to a reduction of the cross-section of the artery, estimated by visual inspection, of around 10% in most cases. Because the frequency response of the flow meter was flat up to and beyond 15 Hz, no correction was applied to the measured flow waves.

A four-lumen Swan-Ganz balloon-tipped catheter equipped with a fast response (50 ms) thermistor (Right ventricular ejection fraction catheter, Edwards Laboratories, Santa Ana, CA, USA) was inserted by using the right jugular vein. The distal port of the catheter was advanced into the main pulmonary artery until its tip was felt just distal to the flow probe, to provide measurements of pulmonary arterial pressure waves (PAP). The intermediate port of the catheter was located in the right ventricle, just downstream to the tricuspid valve to obtain measurements of ventricular pressure waves. The right carotid artery was cannulated for systemic mean blood pressure (BP) and for blood samples. Finally, a balloon-tipped catheter (Pericor 45, Datascope, Paramus, NJ) was advanced into the inferior vena cava through a femoral venotomy. Progressive inflation of this balloon was aimed at producing a titratable decrease in cardiac output by reducing venous return [9].

The deformation of the pressure signal through the fluid-filled Swan-Ganz catheter was evaluated using the linear second-order underdamped model. Determination of the undamped natural frequency ω_n and of the damping coefficient ζ was achieved using the classical pop test [10,16]. The pressure spectrum was then corrected according to the following formula:

$$p(\omega)/p_c(\omega) = \left(\omega_n^2 - \omega^2 + 2i\omega\omega_n\zeta\right)/\omega_n^2,$$

where $\rho(\omega)$ and $p_c(\omega)$ are, respectively, the components at the frequency ω of the corrected pressure and of the measured pressure. Then application of Inverse Fourier Transform allowed us to reconstruct the pressure signal as it was seen at the port of the catheter.

2.1. Physiologic measurements

The dependent level of the right atrium was taken as the hydrostatic baseline for all pressure measurements. Pulmonary and arterial catheters were flushed and filled with normal saline, and connected to transducers (Model 1280C, Hewlett Packard, Palo Alto, CA, USA). Static pressure calibrations of the manometers were made repeatedly throughout the study by providing for each manometer, a low- and high-level signal as reference points.

Heart rate (HR) was determined from a continuously monitored electrocardiographic lead. Cardiac output (CO) and right ventricular ejection fraction (RVEF) were measured by using a rapid computerized thermodilution method (REF-1, Edwards Laboratories, Santa Ana, CA, USA). Serial measurements of RVEF by this method have been shown to be reproducible and have been validated by comparisons with first-pass scintigraphy [3]. A series of 3-5 consecutive CO and RVEF determinations was performed at end-expiration by using 5 ml of 5% dextrose cooled to less than 4°C. The mean of either 3 CO and RVEF values that varied by less than 10% or of 3 close determinations (of 5) after elimination of high and low values were the CO and RVEF recorded for that experimental study point. Right ventricular end-diastolic (RVEDV) and end-systolic volumes (RVESV) were derived from CO, HR, stroke volume (SV) and RVEF by using the following formulae SV = CO/HR, RVEDV = SV/(RVEF) and RVESV = RVEDV - SV.

Pulmonary arterial blood flow was measured continuously with the flow probe. The zero baseline for this device was taken as the signal at the end of diastole and the flowmeter-probe system was calibrated in vivo by recording the flowmeter output during simultaneous thermodilution estimation of cardiac output. Postectopic beats and beats lacking optimal flow velocity configuration were excluded from analysis.

2.2. Computations

All pressure and pulmonary blood flow recordings were performed during a 30-s apneic period in order to eliminate any influence of respiratory cyclic variations. The pressure and flow signals during experiments were

digitized with the use of a high-speed analog-to-digital converter (16/MI CAN, Paris, France) working at a sampling rate of 200 Hz.

Ten consecutive cardiac cycles were selected from steady-state portions during each experimental period. The digitized data for each group of measurements were analyzed by a computer-assisted system. Pressure and flow waves for each recording period were averaged to produce a mean pressure wave and a mean flow wave. Fourier analysis was subsequently performed on the averaged waves. Frequencies at which the flow modulus was not greater than twice the maximum amplitude for late diastole, taken as the background noise of the flow recording system, were excluded from analysis. The pressure spectrum was then corrected following the above-mentioned formula, to take into account of the catheter distortion. Pop-tests procedure was repeated ten times and gave a mean value of 11.51 ± 0.222 for the undamped natural frequency ω_n and a mean value of 0.43 ± 0.013 for the damping ratio ζ. Taking the value of ω_n into account, spectral analysis was limited to 12 Hz. The modulus of pulmonary vascular input impedance spectrum was derived as the ratio of pressure modulus to flow modulus (per kilo) at a given frequency [1]. The phase angle at a given harmonic was calculated as the difference between pressure and flow phase angles, with the convention that negative phase angle denotes flow leading pressure. In order to avoid any potential errors in the assessment of the phase of impedance, owing to the distance that could set up between the flow and pressure measurement sites during the course of experiments, a systematic correction was introduced by extracting the linear trend from the phase versus frequency diagram. The moduli and phases of the pulmonary vascular input impedance spectrum were then plotted against frequency.

The pulmonary vascular characteristic impedance (Z_c) was derived as the average of moduli for the frequencies above the minimum of the input impedance spectrum. Pulmonary vascular impedance at 0 Hz (Z_o) was calculated as the ratio between mean pulmonary artery pressure and mean blood flow per kilo (indexed input resistance). The extent to which Z_o differs from Z_c was used to quantify wave reflection. The proportion of forward wave at a given frequency ω that was reflected back was expressed as the reflection coefficient ($\Gamma(\omega)$) which was estimated through the following formula:

$$\Gamma(\omega) = (Z(\omega) - Z_c)/(Z(\omega) + Z_c)$$

Oscillatory power per kilo (W_o) was derived from the moduli of pulmonary blood flow and impedance according to the formula:

$$W_o = \frac{1}{2}\Sigma(Q_n)^2 Z_n \cos\theta_n$$

where Q_n is the modulus of flow per kilo, Z_n is the modulus of impedance and θ_n is the phase angle of impedance at the *n*th harmonic [1].

Mean power per kilo (W_M) was calculated as the product of mean pulmonary arterial pressure and mean flow per kilo, and the total hydraulic power (W_T) was obtained by the sum of oscillatory and mean power components.

End-systolic right ventricular pressure/volume points were generated by a four-step inflation of the inferior vena cava balloon to reduce right ventricular preload. In these diagrams, peak systolic pressure was substituted for endsystolic pressure and the inotropic state of the right ventricle was referred to as the slope of the regression line obtained from data collected at end-systolic pressure/volume points (E_s = systolic elastance) [11,17]. Therefore, mean E_s values were computed by averaging individual E_s values obtained as described above, during baseline and after endotoxin challenge.

2.3. Experimental protocol

In order to provide similar states of vascular filling, the dogs were infused, when necessary, with a 10% low molecular weight dextran to increase central venous pressure up to 6-7 mmHg over 30 min. After an additional 30-min period, baseline hemodynamic recording was obtained from simultaneous measurements of pulmonary artery pressure and pulmonary artery blood flow. Thereafter a first four points right ventricular pressure-volume diagram was generated from RVEF, CO, HR and pressure measurements at baseline (1 point) and after stepwise decreases in the cardiac output (3 consecutive points). After deflation of the inferior vena cava balloon, the dogs were allowed to rest for a minimum of 10 min. Before the experiment was continued, hemodynamic measurements were repeated to document return to the baseline position. The dogs were then submitted to a freshly prepared endotoxin solution of *Escherichia coli* endotoxin (0127 B8, Sigma Chemicals, St. Louis, MO, USA) at 0.25 µg/kg/min for 2 h. Hemodynamic measurements including HR, CO, SV, BP (mean systemic blood pressure), PAP (mean pulmonary arterial pressure), RVEF, RVEDV, and RVESV were repeated 30, 60, 90 and 120 min after baseline. Right ventricular pressure-volume points needed for elastance computation were again generated at the end of endotoxin infusion period. Pulmonary arterial input impedance spectra were recorded at baseline and at the end of endotoxin challenge.

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Table 1 *Effects of endotoxin infusion on systemic and pulmonary hemodynamics*

	Baseline	T_{30}	T_{60}	T_{90}	End of endotoxin challenge
HR (beats/min)	145 ± 10	163 ± 7	174 ± 7[a]	185 ± 8[a]	186 ± 8[a]
CO (l/min)	3.9 ± 0.21	4 ± 0.3	3.9 ± 0.25	3.7 ± 0.18	3.76 ± 0.25
SV (ml)	26.9 ± 4	24.6 ± 3	22.3 ± 4	20.3 ± 4[a]	20.2 ± 3[a]
BP (mmHg)	132 ± 14	126 ± 8	108 ± 5[a]	88 ± 8[a]	84 ± 10[a]
PAP (mmHg)	22 ± 2	24 ± 3	30 ± 4[a]	34 ± 5[a]	33 ± 3[a]
RVEF (%)	41 ± 3	39 ± 2	35 ± 3	32 ± 3[a]	32 ± 2[a]
RVED (ml)	64.5 ± 4	62.8 ± 3	62 ± 5	62.6 ± 3	62.5 ± 3
RVES (ml)	37.6 ± 4	38.2 ± 3	40.3 ± 2	42.4 ± 3[a]	42.7 ± 3[a]

Values are means ± s.e.m. HR, heart rate; CO, cardiac output; SV, stroke volume; BP, mean blood pressure; PAP, mean pulmonary artery pressure; RVEF, right ventricular ejection fraction; RVED, end-diastolic volume; RVES, end-systolic volume.
[a] $P < 0.05$.

2.4. Statistical evaluation

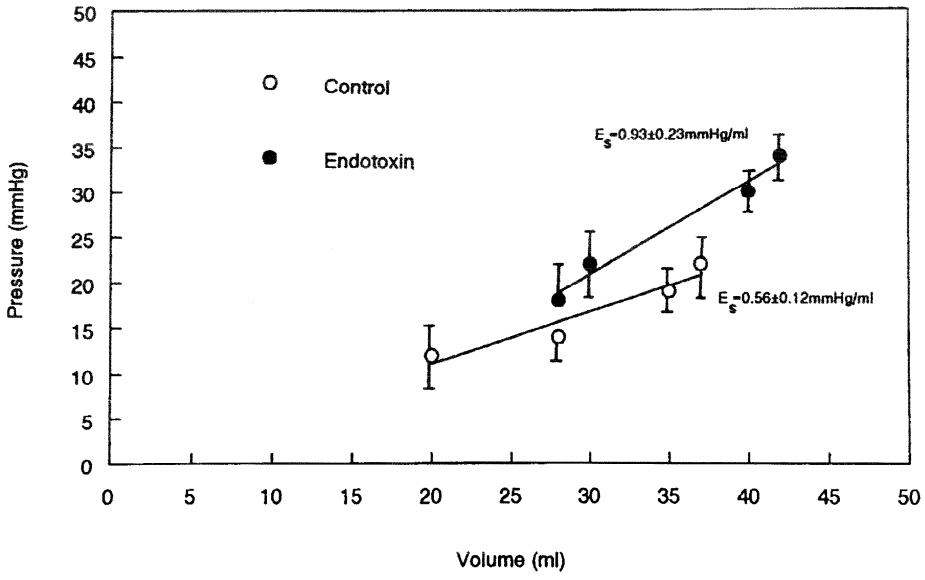
Values were summarized by their mean and standard error of the mean (mean ± s.e.m.). Least-squares linear regression analysis was used to compute slopes of right ventricular end-systolic pressure volume relationships. A regression line was fitted for each dog at baseline and after 120 min of endotoxin infusion to obtain corresponding systolic elastance values.

Two-way analysis of variance in which $n = 6$ dogs represented the levels of the first classification factor and $n = 5$ represented the levels of the second classification factor corresponding to the five experimental periods which were tested (baseline, 30, 60, 90, and 120 min after starting endotoxin infusion), were used to assess the effects of endotoxin on the following hemodynamic parameters: HR, CO, SV, BP, PAP, RVEF, RVEDV, and RVESV. When the analysis of variance evidenced a significant effect of endotoxin on hemodynamic variables, the Scheffe simultaneous 95% confidence intervals were used to determine which values differed significantly from baseline.

A classical *t*-test for paired data was used to compare means before endotoxin insult and at the end of endotoxin infusion for the following variables: input impedance, characteristic impedance, reflection coefficient, right ventricular power output and right ventricular systolic elastance.

P-values < 0.05 were accepted as indicating statistical significance.

Fig. 1. *Composite right ventricular end-systolic pressure-volume plots for dogs as a group at baseline and after endotoxin infusion period. E_s (systolic elastance) is displayed for both experimental conditions.*



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3. Results

3.1. Effects of endotoxin infusion on systemic and pulmonary hemodynamics

Table 1 summarizes the systemic and pulmonary data at baseline and during progression of shock.

A significant effect of endotoxin was revealed by the analysis of variance for the following variables: HR, SV, BP, PAP, RVEF and RVESV. The Scheffe simultaneous 95% confidence intervals for the difference between the means before endotoxin infusion and after endotoxin insult, evidenced that a significant difference appeared 120 min after starting the endotoxin infusion. No significant effect was pointed out regarding CO and RVEDV.

Low-dose endotoxin infusion induced a classic response of aortic hypotension. BP decreased gradually from 132 to 84 mmHg, this difference was significant. CO decreased over time, but the change failed to reach statistical significance. Pulmonary hemodynamic variables indicate that PAP tended to increase and became significantly different from baseline after 90 and 120 min. There was a statistically significant increase in HR from the baseline value of 145-186 beats/min after 120 min. This increase was associated with a significant decline in SV from 26.9 to 20.2 ml.

3.2. Right ventricular operating parameters

In all dogs, endotoxin insult was responsible for a statistically significant reduction in RVEF from 41 to 32%. RVEDV remained statistically unchanged during the all course of the experiment whereas RVESV increased significantly from 37.6 to 42.7 ml.

Rectilinearity of the pressure-volume plots was a general finding in all dogs during the two experimental conditions with correlation coefficients very near 1 (ranging from 0.90 to 0.96).

Endotoxin caused a significant upward and leftward shift in such individual pressure-volume relationships. To obtain composite right ventricular end-systolic pressure-volume plots for the dogs as a group, respectively, at baseline and after endotoxin insult, peak ventricular pressures interpolated from the regression equations from individual dogs were averaged at identical intervals of RVESV and presented in Fig. 1. Averaged slope E_s was significantly increased from 0.56 ± 0.12 at baseline to 0.93 ± 0.23 mmHg/ml after endotoxin infusion.

3.3. Pulmonary arterial input impedance spectra and efficiency of power transfer

Pooled impedance spectra obtained before and after the endotoxin infusion period are depicted in Fig. 2. Impedance moduli increased at all frequencies as a result of endotoxin insult. Fig. 2 shows that the spectrum of pulmonary vascular input impedance was affected by displacement of the first minimum modulus towards a higher frequency from 2.5 ± 0.3 to 7.5 ± 0.6 Hz. A similar change was induced on zero phase crossing which was shifted to the right from 3.9 ± 0.4 to 5 ± 0.8 Hz after endotoxin insult.

Parallel to these changes, there was a progressive and significant increase in characteristic impedance and input resistance from 2730 ± 120 to 4040 ± 70 dyn · s · cm^{-5} · kg and from 6560 ± 210 to 12108 ± 282 dyn · s · cm^{-5} · kg, respectively (Fig. 3). Reflection coefficient at frequency 0 ($\Gamma(0)$) increased significantly with endotoxin infusion from a baseline value of 0.46 ± 0.04 to 0.65 ± 0.05. For the first harmonic, the reflection coefficient decreased significantly from 0.59 ± 0.04 to 0.46 ± 0.04. For the second harmonic, the reflection coefficient increased significantly from 0.37 ± 0.04 to 0.45 ± 0.04.

A significant increase in steady-flow, pulsatile and total power output was noted with endotoxin infusion (Fig. 3).

The ratio of pulsatile power output to total power output (which constitutes an index of dissipated energy) showed a significant increase from a baseline value of 13 ± 2 to 21 ± 3%.

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Fig. 2. *Composite pulmonary input impedance spectra before and after endotoxin insult are depicted in the upper panel. Pulmonary hypertension was associated with an increase in input resistance (Z_o) and a shift to the right of the first minimum. Endotoxin effects on phase angle are displayed in the lower panel. A less negative phase angle at low frequencies and a displacement to the right of zero crossing were the most prominent effects of endotoxin.*

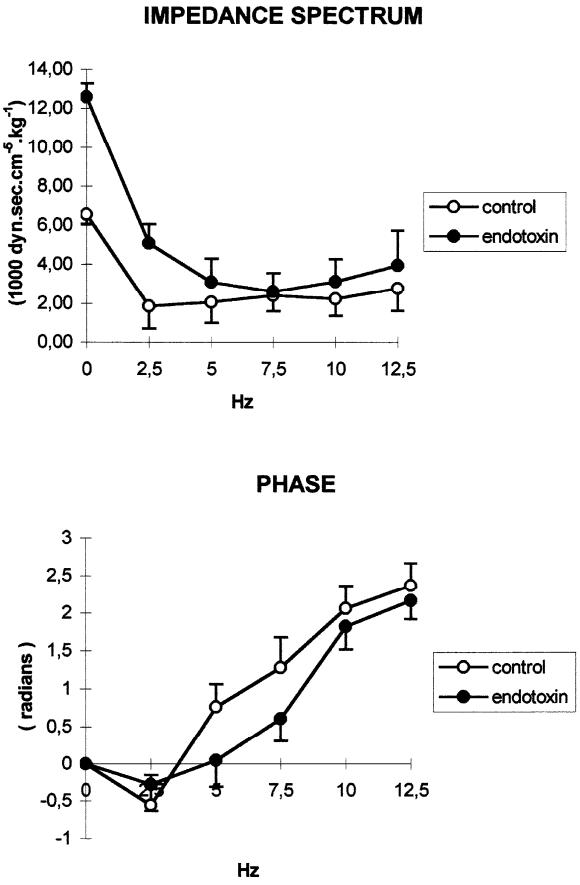

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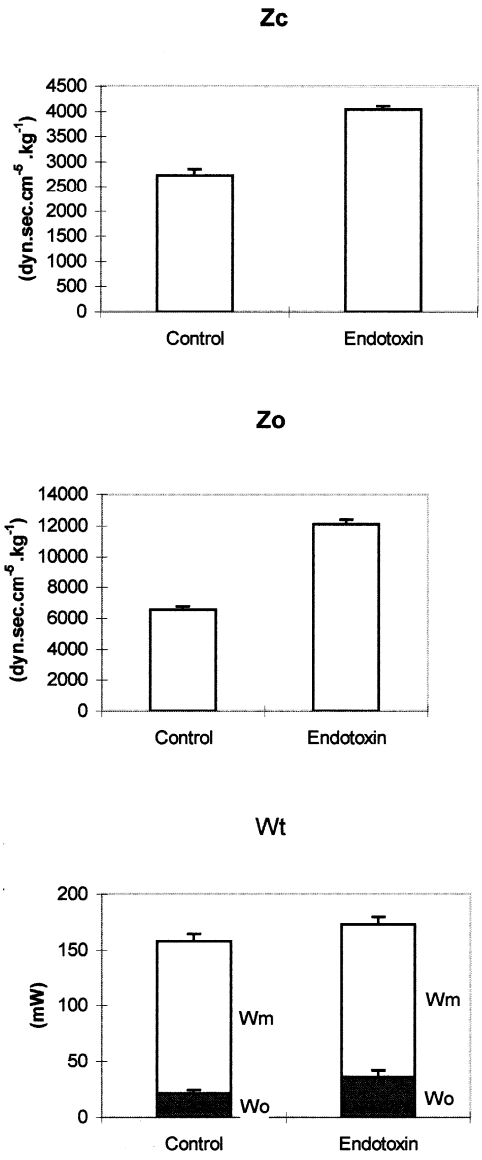
Fig. 3. *Mean values ± s.e.m. of characteristic impedance (Zc), input resistance (Zo), as well as of oscillatory (Wo) and mean power (Wm) components of total right ventricular power (Wt), before and after endotoxin insult.*



4. Discussion

Our data show that hyperdynamic endotoxin-induced shock resulted in decreases in right ventricular performance as evidenced by reductions in both stroke volume and ejection fraction. Reports from Schneider et al. [24] and Natanson et al. [19] have shown similar reductions during infusion of endotoxin either in pigs or beagle dogs, respectively. The initial report by Goldfarb et al. [12], who have used the pressure-volume relationship to investigate the role of the heart during endotoxin shock, indicated decreased myocardial contractility throughout the time course of the experiment, whereas our data show increased right heart contractility following the induction of endotoxin shock. In fact, the cardiovascular severity and lethality reported in the Goldfarb et al. study [12] was higher, resulting in a hypodynamic endotoxin shock as opposed to hyperdynamic state of shock without any early agonal event in our study. Thus, these divergent results can be explained on the basis of a fundamental difference in the endotoxin models used in these studies. In contrast, our data agree with earlier reports by Goodyer [13] and Raymond [22] who showed that contractility was increased in dogs during endotoxin shock. Although previous data from our laboratory [4] did not evidence any toxic actions by a sustained low-dose endotoxin infusion on myocardial ox-idative metabolism in intact dogs, we cannot speak of the late depression of myocardial contractility described by others [12,21], since our study did not extend beyond 2 h. Because we did not presently attempt to measure either the direct effects of endotoxin or the proper role played by changing afterload on right heart contractile state, we had to assume that the actual performance was the end result of endotoxin influence on two prominent factors that changed in opposite directions: increased afterload combined with relative hypovolemia on the one hand, and enhanced contractility

on the other hand. The net result of these effects produced a deterioration in right heart performance as judged by the reduction in both ejection fraction and stroke volume. Therefore, our results would indicate that shortly after the endotoxin insult, alteration in cardiac performance may be due to a direct result of the pulmonary vascular environment to which the right ventricle is subjected.

To the extent that pulmonary input impedance spectrum provides a complete evaluation of the arterial opposition by the pulmonary vasculature to both pulsatile and steady-state pressure and flow waves it, therefore, represents an ideal model for the description of the coupling of the right ventricle to the pulmonary vascular tree [1]. The pulmonary input impedance spectrum in our dogs before endotoxin insult was in agreement with results in previous studies [18]. It was characterized by a steep fall from a high value at 0 Hz to a minimum located between 3 and 5 Hz, and a negative impedance phase at low frequencies indicating that flow leads pressure. The specific alterations we found after endotoxin insult were: (1) rightward shift of frequencies relative to the minimum of impedance modulus and to the zero-phase crossing; (2) increased impedance moduli, at all frequencies, leading to both increased characteristic impedance and input resistance of the pulmonary vasculature; and (3) increased magnitude of wave reflections at zero frequency.

The rightward shift of the pulmonary input impedance spectrum could be due to either increased pulse-wave velocity or alteration in the site of major reflections [25]. From our data, we were not able to differentiate between these possibilities.

Baseline characteristic impedance, which is largely determined by the elastic and compliance properties of the central pulmonary artery, was in the normal range as defined by previous reports [1,18]. Endotoxin infusion resulted in an increase in characteristic impedance. Since characteristic impedance is not only affected by the compliance of the main pulmonary artery, but also by its cross-sectional area, our results suggest that increased characteristic impedance in endotoxin insult could be the result of cumulative effects of decreased compliance and of pulmonary vasculature constriction. The precise mechanism for the observed changes in pulmonary impedance remains speculative. Low-dose endotoxin infusion is known to increase pulmonary vascular tone, as is manifest by the significant augmentation of pulmonary vascular resistance [6]. Previous data from our laboratory [5] suggest that endotoxin's effects on pulmonary vascular resistance are exerted at two different loci such that these effects are additive. These endotoxin-induced effects consisted of increased vascular resistance of the arteriolar segment and appearance of a Starling resistor at the venous side of the pulmonary circulation, which acted as the relevant back-pressure to flow. The current observations indicate that endotoxin has a similar influence on stiffening of larger vessels, such as the main pulmonary artery. In addition, the increase in mean pulmonary pressure resulting from endotoxin insult may account, in part, for the observed elevation in characteristic impedance occurring by means of a rise in passive distending pressure of the proximal pulmonary vascular tree. Stiffening of the pulmonary artery has also been the explanation for increased characteristic impedance during sympathetic stimulation leading to enhanced pulmonary vascular tone [20], or in pulmonary hypertension secondary to an increase in pulmonary venous pressure [14]. Characteristic impedance is an important determinant of the arterial opposition to pulsatile flow and thereby, a factor determining myocardial performance. An increase in characteristic impedance is responsible for a larger pulse pressure for the same flow wave amplitude.

Because pulmonary reflected pressure waves add to pressure generated by the right ejecting ventricle, whereas reflected flow waves subtract from forward flow, assessment of reflection coefficient magnitude is of prominent importance regarding right ventricular loading conditions or the manner in which appropriate modulation of ventricular-vascular coupling occurs. The increase in pulmonary wave reflection that results from endotoxin insult is an indicator of altered ventricular-vascular coupling. Such a mismatch of pulmonary impedance to the increased contractile state of the right ventricle is finally responsible for reducing the efficiency of power transfer to the pulmonary circulation, as assessed by the ratio of pulsatile to total power output. In our animals with endotoxin-induced pulmonary hypertension, total right ventricular power output increased as well as the absolute level of its pulsatile component leading to a decrease in efficiency. As a consequence, right ventricular performance declined despite of a relative increase in contractility. These observations are consistent with investigations regarding systemic circulation that have indicated that without beneficial matching of increased inotropic state to impedance, there is little, if any, improvement in ventricular performance [2]. Surprisingly, our data show that elevated dynamic afterload was not associated with increased right ventricular end-diastolic volume. This expected increase in preload in response to increased afterload was not present in our shocked animals, due, probably, to a peripheral blood pooling in relation to enhanced venous compliance and moderate fluid loading [7].

In conclusion, our data suggest that early deficits in right cardiovascular performance during endotoxin shock were due to the lack of appropriate matching of the increase in the ventricular inotropic state to pulmonary vascular impedance ultimately leading to altered ventricular-vascular coupling and decreased power transfer to the pulmonary circulation.

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References

[1] Bergel DH, Milnor WR. Pulmonary vascular impedance in the dog. Circ Res 1979;44:309-315.

[2] Binkley PF, Van Fossen DB, Nunziata E, Unverferth DV, Leier CV. Influence of positive inotropic therapy on pulsatile hydraulic load and ventricular-vascular coupling in congestive heart failure. J Am Coll Cardiol 1990;15:1127-1135.

[3] Dhainaut JF, Brunet F, Monsallier JF, et al. Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. Crit Care Med 1987;15:148-152.

[4] D'Orio V, El Allaf D, Vaira S, et al. Lack of defective cardiac oxidative metabolism in intact dogs subjected to a prolonged low-dose infusion of E. coli endotoxin. Circ Shock 1986;18:43-52.

[5] D'Orio V, Fatemi M, Marnette JM, et al. Pressure-flow relationships of the pulmonary circulation during endotoxin infusion in intact dogs. Crit Care Med 1992;20:1005-1013.

[6] D'Orio V, Halleux J, Rodriguez LM, Wahlen C, Marcelle R. Effects of E. coli endotoxin on pulmonary vascular resistance in intact dogs. Crit Care Med 1986;14:802-806.

[7] D'Orio V, Wahlen C, Naldi M, et al. Contribution of peripheral blood pooling to central hemodynamic disturbances during endotoxin insult in intact dogs. Crit Care Med 1989;17:1314-1319.

[8] D'Orio V, Wahlen C, Rodriguez LM, et al. A comparison of Escherichia coli endotoxin single bolus injection with low-dose endotoxin infusion on pulmonary and systemic vascular changes. Circ Shock 1987;21:207-216.

[9] Fahey JT, Lister G. A simple method for reducing cardiac output in the conscious lamb. Am J Physiol 1985;249:H188-H192.

[10] Glantz SA, Tyberg TV. Determination of frequency response from step response: application to fluid filled catheter. Am J Physiol 1979;263(2):H376-H378.

[11] Goldfarb RD, Lee KJ, Andrejuk T, Dziubian JR. End-systolic elastance as an evaluation of myocardial function in shock. Circ Shock 1990;30:15-26.

[12] Goldfarb RD, Tambolini W, Weiner SM, Weber PB. Canine left ventricular performance during L50 endotoxemia. Am J Physiol 1983;244:H370-H377.

[13] Goodyer AV. Left ventricular function and tissue hypoxia in irreversible hemorrhagic and endotoxin shock. Am J Physiol 1967;212:444-450.

[14] Hopkins RA, Hammon JV, McHale PA, Smith PK, Anderson RW. An analysis of the pulsatile responses of the pulmonary circulation to acute and chronic pulmonary venous hypertension in the awake dog. Circ Res 1980;47:902-910.

[15] Kimchi A, Ellrodt AG, Berman DS, et al. Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. J Am Coll Cardiol 1984;4:945-951.

[16] Kleinman B, Powell S, Kumar P, Gardner RM. The Fast Flush Test measures the dynamic response of the entire blood pressure monitoring system. Anesthesiology 1992;77:1215-1220.

[17] Maughan WL, Shouka S, Sagawa K, Weisfeldt ML. Instantaneous pressure-volume relationship in the canine ventricle. Circ Res 1979;44:309-315.

[18] Naeije R, Maarek JM, Chang HK. Pulmonary vascular impedance in microembolic hypertension: effects of synchronous high-frequency jet ventilation. Respir Physiol 1990;79:29-52.

[19] Natanson C, Danner RL, Fink MP, et al. Cardiovascular performance with E. coli challenges in a canine model of human sepsis. Am J Physiol 1988;254:H558-H569.

[20] Pace JB. Sympathetic control of pulmonary vascular impedance in anesthetized dogs. Circ Res 1971;29:555-567.

[21] Parker M, Parillo JE. Myocardial function in septic shock. J Crit Care 1990;5:47-61.

[22] Raymond RM. When does the heart fail during shock?. Circ Shock 1990;30:27-41.

[23] Schneider AJ, Teule GJ, Groenveld AB, et al. Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. Am Heart J 1988;116:103-112.

[24] Schneider AJ, Teule GJ, Kester AJ, Heindendal GA, Thijs LG. Biventricular function during volume loading in porcine, E. coli septic shock, with emphasis on right ventricular function. Circ Shock 1986;18:53-60.

[25] Taylor MG. The input impedance of an assembly of randomly branching elastic tubes. Biophys J 1966;6:29-52.