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Effects of endotoxic shock on right ventricular systolic function and mechanical efficiency

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Abstract

Objective: To investigate the effects of endotoxin infusion on right ventricular (RV) systolic function and mechanical efficiency. **Methods:** Six anesthetized pigs (Endo group) received a 0.5 mg/kg endotoxin infusion over 30 min and were compared with six other anesthetized pigs (Control group) receiving placebo for 5 h. RV pressure-volume (PV) loops were obtained by the conductance catheter technique and pulmonary artery flow and pressure were measured with high-fidelity transducers. **Results:** RV adaptation to increased afterload during the early phase of endotoxin-induced pulmonary hypertension (T30) was obtained by both homeometric and hetereometric regulations: the slope of the end-systolic PV relationship of the right ventricle increased from 1.4 ± 0.2 mmHg/ml to 2.9 ± 0.4 mmHg/ml (P<0.05) and RV end-diastolic volume increased from 56 ± 6 ml to 64±11 ml (P<0.05). Consequently, right ventricular-vascular coupling was maintained at a maximum efficiency. Ninety minutes later (T120), facing the same increased afterload, the right ventricle failed to maintain its contractility to such an elevated level and, as a consequence, right ventricular-vascular uncoupling occurred. PV loop area, which is known to be highly correlated with oxygen myocardial consumption, increased from 1154 ± 127 mmHg/ml (T0) to 1798±122 mmHg/ml (T180) (P<0.05) while RV mechanical efficiency decreased from 63 ± 2% (T0) to 45 ± 5% (T270) (P<0.05). **Conclusions:** In the very early phase of endotoxinic shock, right ventricular-vascular coupling is preserved by an increase in RV contractility. Later, myocardial oxygen consumption and energetic cost of RV contractility are increased, as evidenced by the decrease in RV efficiency, and right ventricular-vascular uncoupling occurs. Therefore, therapies aiming at restoring right ventricular-vascular coupling in endotoxic shock should attempt to increase RV contractility and to decrease RV afterload but also to preserve RV mechanical efficiency.

Keywords: contractile function ; endotoxins ; hemodynamics ; pulmonary circulation ; septic shock

1. Introduction

Despite advances in supportive care, septic shock remains one of the leading causes of death in critically ill patients [1]. Among the numerous complications of septic shock, right heart failure can be lethal [2], but little is known about dynamic right ventricular (RV) function during septic shock [3]. Indeed, while low peripheral vascular resistance in sepsis decreases left ventricular afterload, increased pulmonary vascular resistance from acute lung injury increases RV afterload [4]. Therefore, RV function must be studied specifically.

In some studies, it was shown that increased RV afterload was not the dominant cause of RV depression in septic shock [2,5]. According to D'Orio et al., however, impaired RV function would rather result from inappropriate matching between ventricular inotropic state and pulmonary vascular impedance [6]. Although such studies have evidenced RV systolic dysfunction in septic conditions, most of them used RV ejection fraction as an index of RV performance [2,7] or RV pressure-length relationship [8-10] as an approximate of RV systolic function.

A better understanding of the mechanisms of RV dysfunction may lead to more effective therapies of myocardial depression in septic shock. Therefore, we investigated in this study the determinants of RV systolic function impairment during endotoxic shock.

In order to investigate accurately RV systolic function, we used the conductance catheter technique to obtain the robust and highly sensitive indices of ventricular function described earlier: the slope (End-systolic elastance, E_{es}) of the end-systolic pressure-volume (PV) relationship (ESPVR) and its volume intercept [11,12].

2. Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Liège. The investigation conforms with the *Guide for the*

Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.1. Surgical preparation

Experiments were performed on 12 healthy pure pietran pigs of either sex weighing from 20 to 30 kg. The animals were premedicated with intramuscular administration of ketamine (20 mg/kg) and diazepam (1 mg/kg). Anesthesia was then induced and maintained by a continuous infusion of sufentanil (0.5 µg/kg/h) and pentobarbital (5 mg/kg/h). Spontaneous movements were prevented by pancuronium bromide (0.2 mg/kg). After endotracheal intubation through a cervical tracheostomy, the pigs were connected to a volume cycled ventilator (Evita 2, Dräger, Lübeck, Germany) set to deliver a tidal volume of 10 ml/kg with a FiO_2 of 0.4 and at a respiratory rate of 20 breaths/min. End-tidal CO_2 ($PETCO_2$) measurements (Capnomac, Datex, Helsinki, Finland) were used to monitor the adequacy of ventilation. Respiratory settings were adjusted to maintain $PETCO_2$ between 30 and 35 mmHg.

The pulmonary trunk was exposed by means of medial sternotomy. A micromanometer-tipped catheter (Sentron pressure-measuring catheter, Cordis, Miami, FL) was inserted into the main pulmonary artery through a stab wound in the RV outflow tract. A 14 mm diameter perivascular flow probe (Transonic Systems, Ithaca, NY, USA) was closely adjusted around the main pulmonary artery 2 cm downstream of the pulmonary valve. The micromanometer-tipped catheter was manipulated so that the pressure sensor was positioned closely to the flow probe.

Left atrial pressure was measured with a micromanometer-tipped catheter inserted into the cavity through the left atrial appendage. Systemic arterial pressure was monitored with a micromanometer-tipped catheter inserted into the descending thoracic aorta through the right femoral artery.

A 7F, 12-electrode (8 mm interelectrode distance) conductance micromanometer-tipped catheter (CD Leycom, Zoetermeer, The Netherlands) was inserted through the RV infundibulum into the right ventricle and positioned so that all electrodes were in the RV cavity.

A 6F Fogarty balloon catheter (Baxter Healthcare Corp., Oakland, CA, USA) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a titratable gradual preload reduction.

2.2. Experimental protocol and physiologic measurements

After a 30 min stabilization period (T0), 12 animals were randomly divided in two groups.

While in the first group (Control group, n=6) the animals were infused with placebo, in the second group (Endo group, n=6), they received a 0.5 mg/kg endotoxin (lipopolysaccharide from *Escherichia coli* serotype 0127:B8; Sigma Chemical, St Louis, MO, USA) infusion over 30 min (from T0 to T30).

Hemodynamic data included pulmonary artery pressure (PAP) wave, pulmonary blood flow wave, left atrial pressure, systemic arterial pressure, heart rate, RV pressure, RV volume and RV PV loops. These parameters were recorded every 30 min from T30 to T270 during a short apneic phase and stored for subsequent analysis. All analog signals were continuously converted to digital form with an appropriate system (Codas, DataQ Instruments Inc., Akron, OH, USA). Pulmonary artery blood flow, left atrial pressure, systemic arterial pressure, heart rate, PAP, RV volume, RV pressure and RV PV loops, were also monitored on-line throughout the experiment. Systemic arterial pressure, PAP, and pulmonary blood flow waves were integrated to calculate corresponding mean values.

RV PV loops were recorded every 30 min from T30 to T270 during a transient occlusion of the inferior vena cava using the Fogarty balloon.

2.3. Data analysis

2.3.1. Pulmonary circulation

E_a, which reflects RV afterload, was calculated using the following equation [8]:

$$E_a = (R_1 + R_2)/[T_s + R_2C(1 - e^{-R_2C/T_d})] \qquad (1)$$

where T_s and T_d are the systolic and diastolic time intervals, respectively.

A lumped parameter model, namely the four-element windkessel model (WK4), was used to calculate R_1, R_2 and C using an original analytic procedure described previously [13]. In this model, R_1 represents the characteristic impedance of the pulmonary circulation, R_2 pulmonary vascular resistance, and C pulmonary artery compliance

[14]. The fourth element of WK4, an inductance, is used to allow positive phase angles between flow and pressure waves. It corresponds to the inertial properties of the pulmonary vasculature due to the mass of blood [14].

2.3.2. Right ventricular function

Right ventricular PV loops were obtained using the conductance catheter method [12]. Briefly, a multiple-electrode catheter placed in the right ventricle is used to set up an electrical field, and adjacent pairs of electrodes measure the local conductivity of blood, which is proportional to local blood volume [12]. Structures surrounding the blood-filled ventricular cavity also contribute to the overall conductance signal. The resulting off-set, termed parallel conductance, can be estimated by transiently altering the conductivity of blood with hypertonic saline [12]. In addition, the conductance signal must be corrected to represent true volume. Therefore, to determine the gain factor (alpha slope factor), an alternate method of measuring volume is needed [12]. In this study, we used the value of stroke volume measured by the pulmonary artery ultrasonic flow probe.

Before each measurement, parallel conductance was determined with the saline method by injecting 3 ml of NaCl 10% into inferior vena cava [12].

During a rapid inferior vena cava occlusion maneuver, E_{es} was determined [12]. ESPVR was determined by fitting a straight line through the end-systolic PV points. However, these points could show some nonlinearity while ESPVR is calculated by linear regression. To avoid the problem of linear extrapolation to zero pressure, we used a volume intercept at a fixed pressure of 25 mmHg (V_{p25}) to quantify the position of ESPVR. Then, the slope of ESPVR, E_{es}, and its volume position, V_{p25}, represent relatively load-independent indices of ventricular contractility. Any increase in E_{es}, any decrease in V_{p25}, or both changes, suggest an improved contractile state [15].

Stroke work was calculated as the integrated area of each PV loop.

PVA was obtained by measuring the specific area in the PV plane bounded by the end-systolic and end-diastolic PV relationships and the systolic segment of the PV loop and serves as a reliable predictor of myocardial oxygen consumption [8,16].

RV efficiency was calculated as the ratio of stroke work to PVA [8,17].

Additionally, to assess right ventricular-vascular coupling, we examined the E_{es}/E_a ratio. Under normal operating conditions, the right ventricle operates at a maximum efficiency and a submaximal stroke work ($E_{es}/E_a>1$). The maximal stroke work is obtained when $E_{es}/E_a=1$, while uncoupling occurs when E_{es}/E_a is lower than 1 [8,18].

2.4. Statistical analysis

Data are presented as mean ± S.E.M.

Statistical comparison of data over time and between groups was conducted by a two-way analysis of variance for repeated measurements with time and groups as factors, followed by Scheffé's multiple comparisons test if the analysis of variance resulted in *P*-value <0.05 (Statistica°; Statsoft Inc., Tulsa, OK, USA).

$P<0.05$ was considered statistically significant.

3. Results

3.1. Effect of endotoxin infusion on conventional hemodynamic data

The time-course of endotoxin insult on conventional hemodynamic variables is presented in Fig. 1. Mean PAP in Endo group reached a first maximum at T30 (i.e. 30 min after the start of endotoxin infusion), then immediately returned to lower values, and progressively increased until T270. In contrast, mean systemic arterial pressure decreased from 95 ± 5 (T30) to 67 ± 4 mmHg (T60) ($P< 0.05$) and remained below 60 mmHg from T90 until T210. At T240 and T270, mean systemic arterial pressure returned to values greater than 60 mmHg, 63 ± 11 and 74 ± 11 mmHg, respectively.

Evolution of mean pulmonary artery flow remained similar in Control and Endo groups throughout the experiment. Heart rate increased from 115 ± 7 (T0) to 137 ± 12 beats/min (T30) after endotoxin infusion, and remained higher than 150 beats/min throughout the experiment.

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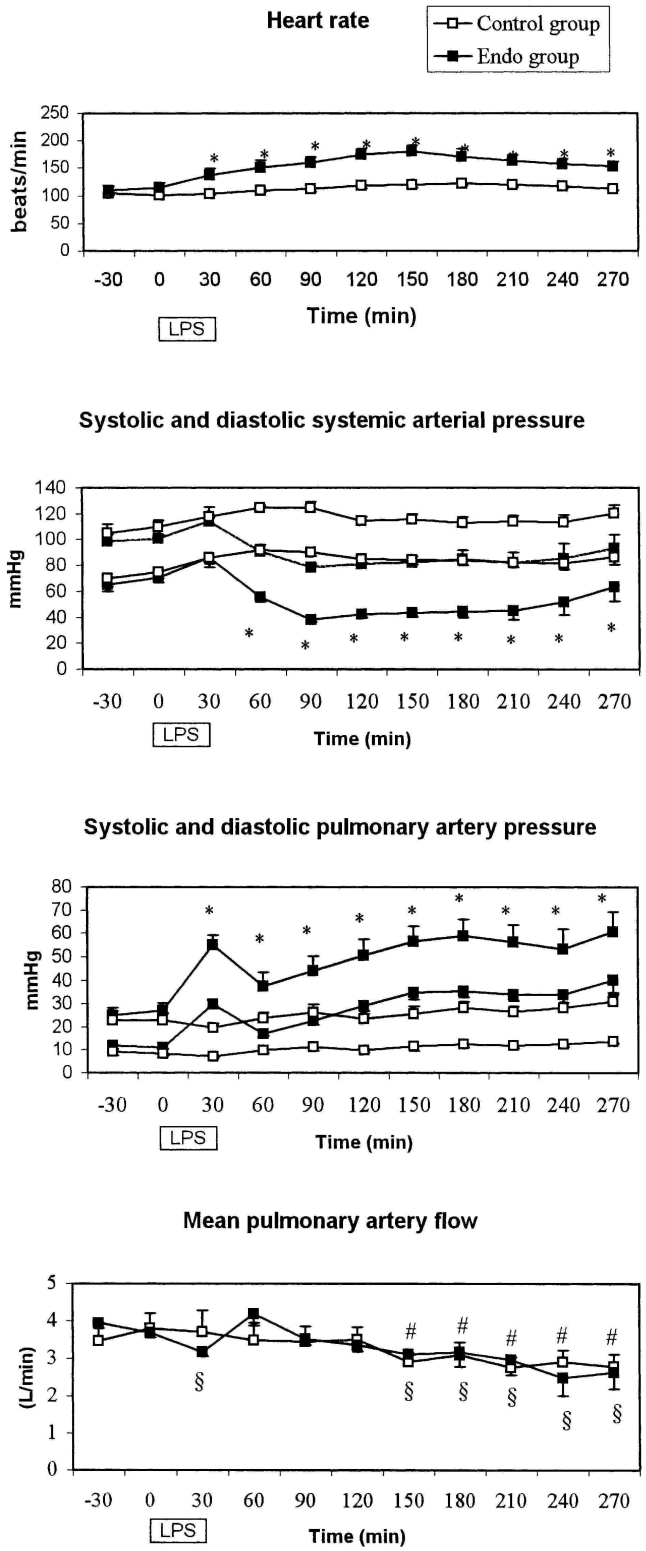
Fig. 1. *Time-course of conventional hemodynamic parameters in Control group (open square) and in Endo group (closed square). LPS indicates endotoxin infusion. Data are presented as mean ± S.E.M. *P<0.05 Endo group vs. T0 and vs. Control group. #P<0.05 Control group vs. T0. §P<0.05 Endo group vs. T0.*



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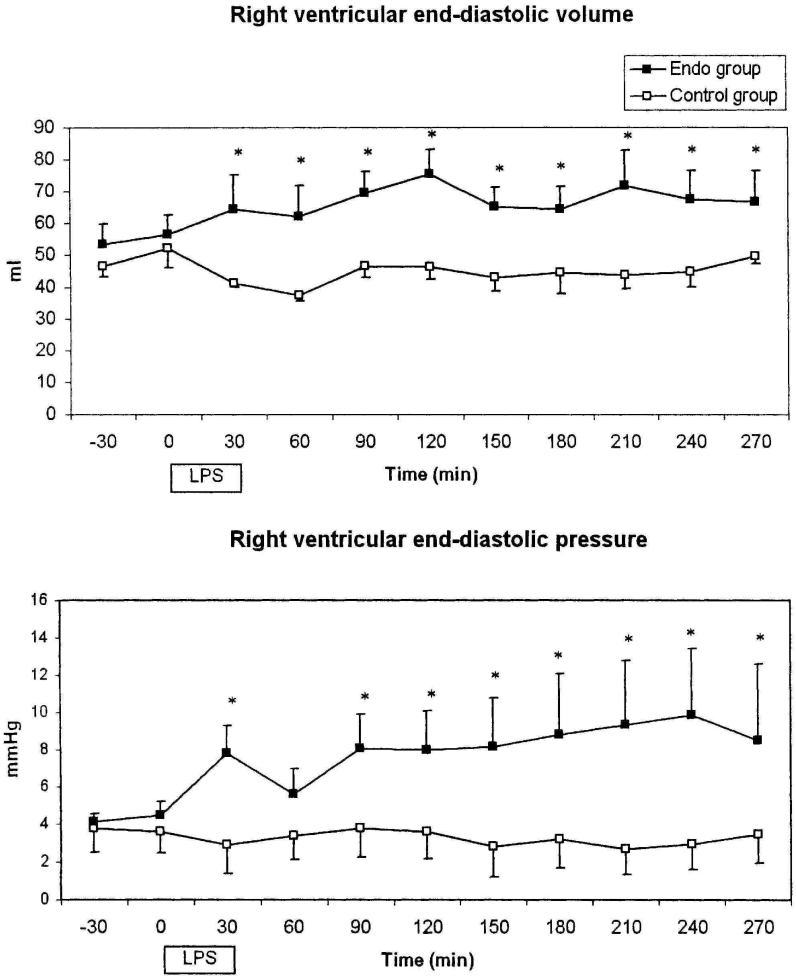
3.2. Effect of endotoxin infusion on right ventricular volumes and end-diastolic pressure

Right ventricular end-diastolic volume evolution is depicted in Fig. 2. In Endo group, end-diastolic volume increased from 56 ± 6 ml (T0) to 64 ± 11 ml (P<0.05) at the end of endotoxin infusion (T30) and remained thereafter at higher values throughout the experiment. In contrast, stroke volume decreased progressively from 31 ± 5 ml (T0) to 21 ± 4 ml (T270) (P<0.05). As a consequence, ejection fraction progressively decreased from 54 ± 2% (T0) to 33 ± 5% (T270) (P<0.05).

Right ventricular end-diastolic pressure increased from 5 ± 1 mmHg at baseline (T0) to 8 ± 2 mmHg (T30) after the end of endotoxin infusion (P<0.05 vs. T0 and vs. Control group) and remained close to 8 mmHg from T90 to T270. These latter values were significantly greater than those obtained in the Control group (P<0.05).

Fig. 2. *Time-course of end-diastolic volume and end-diastolic pressure in Control group and in Endo group. LPS indicates endotoxin infusion. Data are presented as mean±S.E.M. *P<0.05 Endo group vs. T0 and vs. Control group.*



3.3. Effect of endotoxin infusion on derived hemodynamic data

E_a in Endo group expressed a profile that was similar to the changes observed in PAP (Fig. 3). It showed a first peak at T30 and, after a drop, increased again from T90 until the end of the experiment. E_{es} values in Endo group increased from 1.4 ± 0.2 mmHg/ml (T0) to 2.9 ± 0.4 mmHg/ml (T30) (P<0.05) and remained higher than basal values from T60 to T150. From T180, E_{es} values in Endo group were similar to Control group (Fig. 3).

E_{es}/E_a remained at an optimal level of 2 from T0 to T60. At T120, right ventricular-vascular coupling reached a value of 0.9 ± 0.1 and deteriorated progressively reaching a value of 0.5 (T270) at the end of the experiment (Fig. 3).

V_{p25} decreased from a basal value of 20 ± 8 ml to 2 ± 2 ml at T30 (P<0.05) and thereafter remained lower than basal values (P<0.05).

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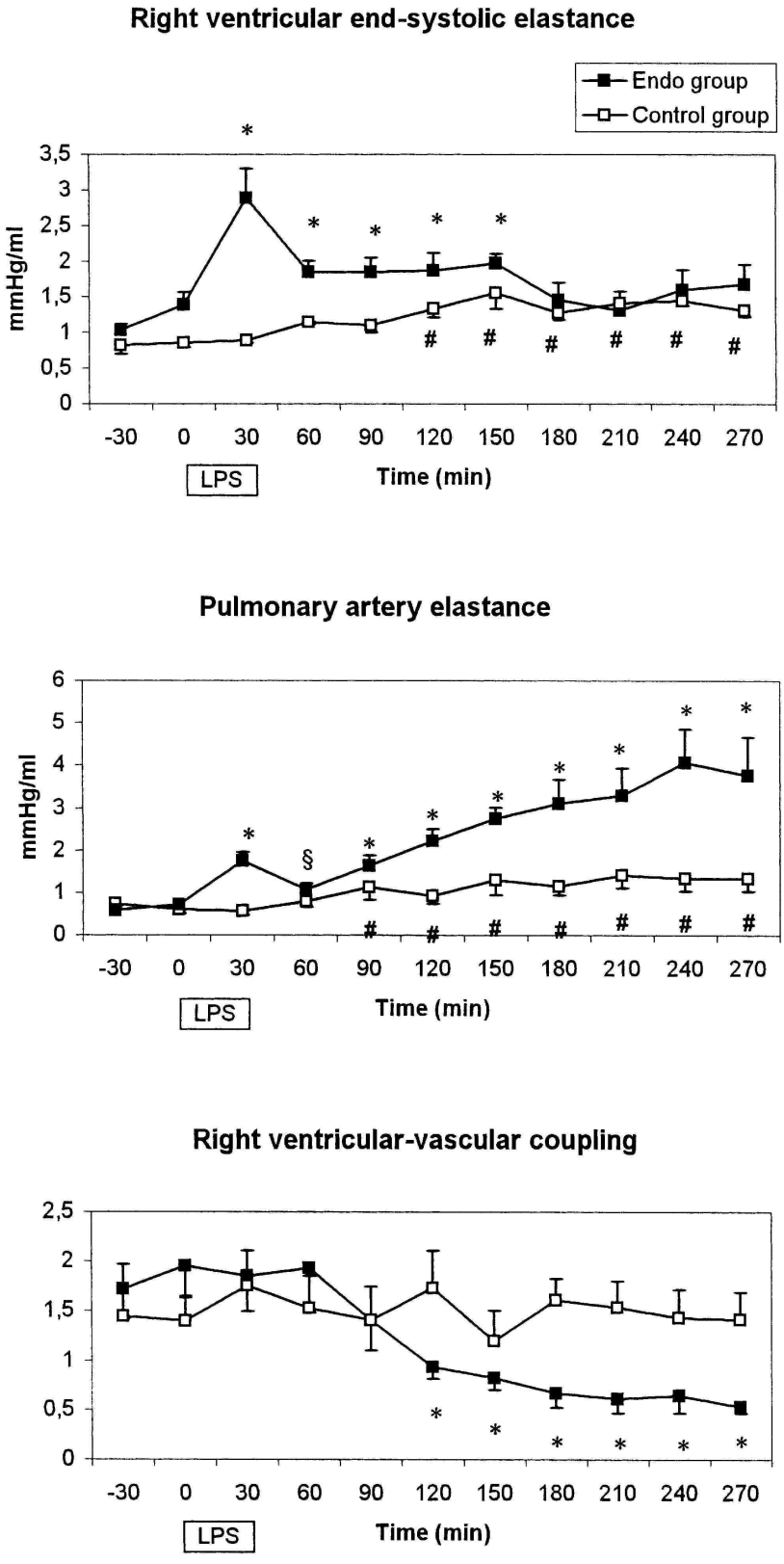
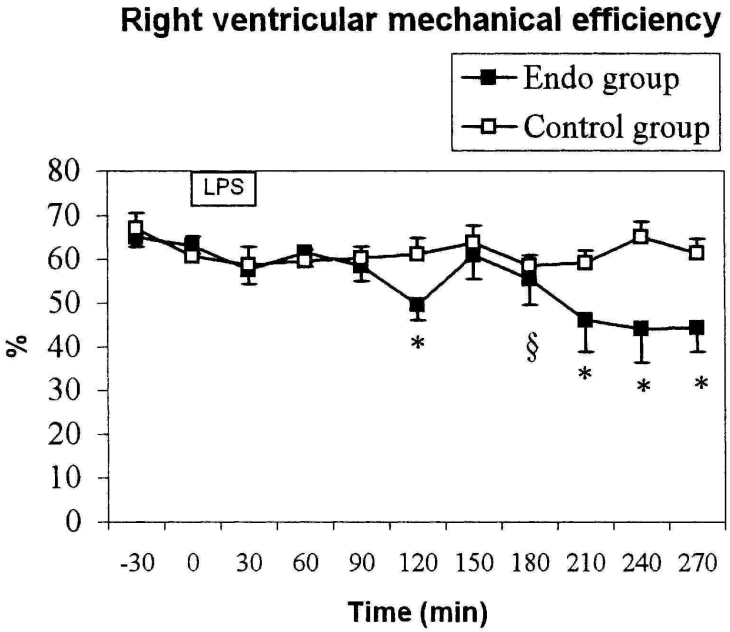
PVA progressively increased from 1154 ± 127 mmHg/ml (T0) to 1475 ± 152 (T90) (P<0.05). It reached a value of 1798 ± 122 mmHg/ml at T180 (P<0.05) and remained elevated until the end of the experimental period.

Fig. 3. *Time-course of right ventricular end-systolic elastance (E_{es}), pulmonary arterial elastance (E_a), and right ventricular-vascular coupling (E_{es}/E_a) in Control group (open square) and in Endo group (closed square). LPS indicates endotoxin infusion. Data are presented as mean ± S.E.M. *P<0.05 Endo group vs. T0 and vs. Control group. $^{\#}P<0.05$ Control group vs. T0. $^{\S}P<0.05$ Endo group vs. T0.*



Right ventricular efficiency decreased significantly ($P< 0.05$) from 6 3± 2% (T0) to 45 ± 5% at the end of the experimental period (T270) (Fig. 4).

Fig. 4. *Time-course of right ventricular mechanical efficiency in Control group (open square) and in Endo group (closed square). LPS indicates endotoxin infusion. Data are presented as mean±S.E.M. *P<0.05 Endo group vs. T0 and vs. Control group. §P<0.05 Endo group vs. T0.*



4. Discussion

The effects of endotoxin infusion on pulmonary hemodynamics and right ventricular-vascular coupling have been studied previously in our laboratory [6,13]. In the present study, using a more reliable technique, i.e. the conductance catheter technique, we confirm these data, and improve the understanding of right ventricular dysfunction mechanism by demonstrating that endotoxin infusion induced a decrease in RV mechanical efficiency.

RV adaptation to an increase in afterload can be obtained by two different, but complementary, mechanisms: heterometric (the Frank-Starling mechanism) and homeometric regulations. During heterometric regulation, stroke volume is maintained owing to changes in RV preload, i.e. end-diastolic volume, while contractility, per se, remains unchanged. In contrast, during homeometric regulation, RV contractility, i.e. E_{es}, increases to maintain stroke volume while end-diastolic volume remains unchanged. Previous studies performed in sheep, have suggested that the RV response to acute pressure overload consisted in both enhanced contractility and the Frank-Starling mechanism [19]. However in newborn lambs, RV output in the face of increased afterload seems regulated only through homeometric regulation [11,15,20]. In endotoxic dogs, D'Orio et al. evidenced that the impairment of cardiovascular performance is due to inappropriate matching between ventricular inotropic state and RV afterload, with secondary altered ventricular-vascular coupling [6].

In the present study, RV adaptation during the early phase of endotoxin-induced pulmonary hypertension (T30) was obtained by both homeometric and hetereometric regulations. Indeed, both E_{es} and end-diastolic volume increased and right ventricular-vascular coupling was maintained at a maximum efficiency [8]. Surprisingly, 90 min after the end of endotoxin infusion (T120), facing the same increased afterload (E_a), the right ventricle failed to maintain its contractility to such an elevated level and, as a consequence, right ventricular-vascular coupling decreased from values close to 2 to values lower than 1. These results thus suggest an impairment of homeometric regulation at T120.

During increased left ventricle afterload, homeometric regulation is explained by an increase in coronary perfusion secondary to the increased aortic pressure. However, in our study, because of systemic hypotension, RV homeometric regulation cannot be induced by increased coronary perfusion but rather could be related to mechanisms such as mechanical stretch-activated channels, release of endogenous catecholamines, or release of stimulating factors from the endocardial endothelium [15].

In the present work, PVA, which is known to be highly correlated with myocardial oxygen consumption even in the presence of marked changes in preload, afterload, and cardiac contractility [16], increased significantly at T120, as compared to T0. This suggests that the right ventricle requires significantly more oxygen in sepsis than during normal condition.

Such an increase in oxygen consumption by a right ventricle delivering a similar work represents a decrease in RV mechanical efficiency. In our study, RV mechanical efficiency, calculated as the ratio of stroke work to PVA, was decreased from T120: stroke work remained unchanged but PVA increased significantly during endotoxic shock.

Several hypotheses can explain this decrease in RV mechanical efficiency during endotoxic shock.

Although Cunnion et al. demonstrated an increase in coronary sinus blood flow in septic patients [21], there is, however, growing evidence that coronary circulation in sepsis is susceptible to maldistribution of regional blood flow [22] and that myocardial blood flow could be unable to augment sufficiently in response to oxygen demands [23]. Since, in endotoxic condition, the energetic cost of contractility is increased while, in parallel, myocardial blood flow and, consequently, contractility are unable to increase, homeometric regulation cannot occur.

A number of humoral and intracellular mediators have also been implicated in the endotoxemic cardiac dysfunction, and myocardial ischemia is not the only mechanism contributing to myocardial depression [24]. Endotoxin induces the synthesis and release of tumor necrosis factor alpha and interleukin-1 beta by monocytes and macrophages [25]. Consecutive activation of constitutive and inducible nitric oxide synthase increases nitric oxide production [26] which, in turn, stimulates guanylate cyclase and production of cGMP, a nucleotide with known myocardial depressant function [26,27]. Tumor necrosis factor alpha may also impair the adenylate cyclase response to catecholamines and inhibit calcium influx through calcium channel leading to myocardial depression [28]. Alterations of beta receptors may also contribute to myocardial dysfunction and decrease myocardial sensitivity to catecholamines [29]. Finally, increased superoxide, and peroxynitrite generation as well as oxidative stress injury in the myocardium of endotoxemic rats were associated with impaired cardiac contractility and depressed cardiac efficiency [30].

To our knowledge, it is the first study to look at right ventricular-vascular coupling and myocardial energetics by conductance catheter technique during septic shock. Decrease in RV mechanical efficiency during endotoxic shock has never been described previously by the conductance catheter technique in intact animals. However, it has already been observed in the isolated heart of endotoxemic rats and in tumor necrosis factor alpha-infused isolated canine hearts [28,30].

Accurate evaluation of RV performance needs assessment of contractile state, preload and afterload. Determination of preload and afterload can be relatively straightforward by measurements of RV end-diastolic volume and pulmonary artery elastance, respectively. Quantification of contractile state needs analysis of pressure-volume loops under different loading conditions. However, conductance catheter can be inadequate to measure absolute volume. It is an indirect technique and the measured signals (the conductivity of the blood within the ventricle) require calibration (specific resistivity of the blood, parallel conductance and alpha slope factor). Moreover, compared to the left ventricle, the right ventricle has a complex shape and dense trabeculation. Nevertheless, volume measurement provided by this technique allows correct estimation of RV contractile state and RV volume changes, even in closed chest [12].

The major limitation of this study is the use of endotoxin infusion as a model of human septic shock. In this porcine model which mimics the cardiovascular effects of clinical septic shock [13], production of the two key mediators of human septic shock, tumor necrosis factor alpha and interleukin-1 beta, is induced by endotoxin infusion. The dose-response relationship for endotoxin and the onset of cardiovascular effects differ between species and, moreover, animal models take no account of human variability due to age, biological reserve, and genetic factors [31]. Therefore, our data should be viewed in that context.

In conclusion, this is the first report of RV myocardial dysfunction in pigs during sepsis using the conductance catheter. Our data showed that in the very early phase of endotoxinic shock, right ventricular-vascular coupling is preserved by an increase in RV contractility. Later, myocardial oxygen consumption and energetic cost of RV contractility are increased, as evidenced by the decrease in RV efficiency, and right ventricular-vascular uncoupling occurs. Therefore, therapies aiming at restoring right ventricular-vascular coupling in endotoxic shock should attempt to increase RV contractility and to decrease RV afterload but also to preserve RV mechanical efficiency. As the key to future diagnostic and therapeutic interventions in patients with right heart dysfunction relies completely on the availability of a reliable and valid clinical physiologic monitor, conductance catheter technique should become a method of choice in the assessment of RV performance under clinical conditions.

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