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Analysis of endotoxin effects on the intact pulmonary circulation

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Abstract

Objective: The mechanism of sustained alterations in pulmonary hemodynamics during endotoxin shock remains unclear. To gain more detailed knowledge we used the four-element windkessel model as a descriptor of the pulmonary circuit. **Methods:** Consecutive changes in characteristic resistance (R_1), vascular compliance (C), input resistance (R_2) and inductance (L) were continuously assessed following injection of endotoxin in 6 anaesthetised pigs, and were compared with the corresponding values measured in a similar group of sham-operated animals. **Results:** Endotoxin challenge resulted in a biphasic pulmonary artery pressure response. Blood flow decreased progressively from 2.8 ± 0.2 l/min to 2 ± 0.2 l/min. Ohmic pulmonary vascular resistance (PVR) increased gradually from 0.2 ± 0.04 to 0.76 ± 0.1 mm Hg s ml^{-1}. The early increase in PAP (from 14 ± 2 to 27 ± 4 mm Hg) was mediated by changes in both R_1 (from 0.04 ± 0.01 to 0.06 ± 0.01 mm Hg s ml^{-1}) and R_2 (from 0.16 ± 0.04 to 0.61 ± 0.2 mm Hg s ml^{-1}). These responses, in turn, altered the proximal vascular compliance. A subsequent increase in PAP (from 27 ± 2 to 32 ± 3 mm Hg) paralleled the specific decline in distal pulmonary vasculature compliance from 0.84 ± 0.1 to 0.65 ± 0.1 ml/mmHg. Analysis of the time course of PVR did not allow us to distinguish between vasoconstriction and stiffening of the vascular tree as mechanisms accounting for PAP changes. **Conclusions:** Endotoxemia leads to pulmonary hypertension, which is a result of constriction of proximal pulmonary arteries during the early phase, whereas the late phase is characterised by a decline in distal pulmonary vasculature compliance.

Keywords: pig ; pulmonary circulation ; septic shock ; endotoxin ; models ; vascular resistance ; vascular compliance

1. Introduction

The pulmonary hypertensive response to endotoxin is usually accounted for by vasoconstriction of the pulmonary bed. Although there is some question as to the exact magnitude of arterial and venous resistance ratios in the pulmonary circulation [3,16], even more uncertainty exists with regard to how vascular compliance and resistance vary simultaneously during endotoxin insult. Indeed, this knowledge is not only important from a theoretical, pathophysiological viewpoint, but also in terms of the potential for therapeutic interventions. The lack of detailed data may reflect the paucity of simple hemodynamic methods capable of clearly distinguishing the portion of the total pressure drop required to open or distend pulmonary vessels from the pressure drop related to flow resistance itself.

Most studies examining the response of the pulmonary circulation to endotoxin administration have been flawed by an approach which calculates changes in pulmonary vascular resistance using an ohmic formula that divides the pressure gradient (the difference between input and output pressures) by flow [3,5,11,14-16,20,21]. Unfortunately, while such a calculation may give insight into the total energy loss required for a given flow through the system, it does not provide detailed knowledge of the system's fundamental mechanical properties, i.e., the compliance and resistance of the vascular tree. More recently, it has been postulated that more detailed knowledge of the functional state of the pulmonary circulation could be achieved by describing the relationship between pulmonary input pressure and flow [6,7]. Over the physiological range of flows, this relationship is essentially linear and can be characterised by a slope and a pressure intercept referred to as a Starling resistor effect [2,6,7]. Unfortunately, several problems associated with the determination of pressure-flow relationships remain to be solved. First, the Starling resistor model ignores the compliant property of the pulmonary vessels. Second, application of such an hemodynamic approach is very difficult because it requires generating pressure-flow plots under very rigorous conditions; in particular, the level of left atrial pressure must remain unchanged during flow manipulations [8]. Finally, experimental use of pressure-flow plots is hampered by the shifting to different curves that occurs during hemodynamic manipulations. The utility of pressure-flow plots is therefore potentially reduced because of these considerable technical limitations. In contrast, growing evidence is being gathered to favor the use of lumped parameter models to describe the global behavior of the pulmonary circulation [12]. The most significant reason for using such models is that changes in both vascular resistance and compliance may be assessed without the necessity for specific manipulations of the circulatory system under investigation. In order to obtain this more detailed knowledge, the effects of endotoxin on the pulmonary

vasculature were investigated in intact animals by application of the four-element windkessel model to the pulmonary circulation.

2. Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the ethical committee of the Medical Faculty of the University of Liege. They were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Council of the American Physiological Society. Experiments were performed on 12 healthy pure pietran pigs of either sex weighing from 16 to 28 kg. The animals were premedicated with intramuscular administration of ketamine (20 mg/kg) and diazepam (1 mg/kg). Anaesthesia was then induced and maintained by a continuous infusion of sufentanil (0.5 µg/kg/h) and propofol (7.5 mg/kg/h). Spontaneous movements were prevented by pancuronium bromide (0.2 mg/kg/h). After endotracheal intubation via a cervical tracheostomy, the pigs were connected to a volume-cycled ventilator (Evita 2, Dräger, Lübeck, Germany) set to deliver a tidal volume of 15 ml/kg at a respiratory rate of 20/min. End-tidal CO_2 measurements (Capnomac, Datex, Helsinki, Finland) were used to monitor the adequacy of ventilation. Respiratory settings were adjusted to maintain end-tidal CO_2 between 30 and 35 mmHg. Arterial oxygen saturation was monitored and maintained above 95% by adjusting the FiO_2 as necessary.

The pulmonary trunk was exposed via a median sternotomy. A micromanometer-tipped catheter (Sentron pressure measuring catheter, Cordis, Miami, FL, USA) was inserted into the main pulmonary artery through a stab wound in the right ventricular outflow tract. A 14 mm diameter perivascular flow-probe (Transonic Systems, Ithaca, NY, USA) was snugly fitted around the main pulmonary artery 2 cm downstream to the pulmonary valve. The micromanometer-tipped catheter was manipulated so that the pressure sensor was finally positioned at the level of the flow-probe.

Left atrial pressure was measured with a micromanometer-tipped catheter inserted into the cavity through the left atrial appendage. Finally, systemic blood pressure was monitored via a micromanometer-tipped catheter inserted into the abdominal aorta through the left femoral artery.

Total effective dynamic lung compliance (C_{eff}), a parameter reflecting the pulmonary compliance and resistance to gas flow together, was calculated as the ratio of tidal volume to peak tracheal pressure. Airway pressure was measured from a sideline connected to the inspiratory circuit and connected to a transducer. This was calibrated with a water manometer. Both inspiratory and expiratory gas flows were measured with a Fleisch pneumo-tachograph. Tidal volumes were obtained by integration of the expiratory flow signal (Capnomac, Datex, Helsinki, Finland). These values were not adjusted for the compression volume and breathing circuit expansion.

2.1. Experimental protocol

After surgical preparation, the animals were allowed to stabilise for 30 min. After an initial 30 min of baseline hemodynamic recording which included mean pulmonary artery pressure (PAP), pulmonary blood flow (Q), left atrial pressure (LAP), mean arterial blood pressure (BP), and heart rate (HR), the animals were then divided into two equal groups (n=6 each). In one group (endotoxin group) the animals had an intravenous infusion of 0.5 mg/kg of a freshly prepared endotoxin solution (lipopolysaccharide from *E. coli* serotype 0127:B8, Sigma, St Louis, MO, USA) over 30 min at T0. The other group of animals (control group) served as control animals and were submitted to the same protocol, using an equivalent volume of saline infusion instead of endotoxin.

Hemodynamics and blood gases were then sequentially measured (T_{30}, T_{60}, T_{90}, T_{120}, and T_{150} min) to characterise the progression of shock in this model.

2.2. Data collection

All analog signals were continuously digitalised with an appropriate system (Codas, DataQ, Akron, OH, USA). The pulmonary pressure and flow waves were sampled at 200 Hz and stored. Cardiac cycles were defined by *R* wave detection provided by a permanent recording of a one lead electrocardiogram. Ten consecutive cycles were recorded during apnea and were numerically averaged to obtain representative diagrams of pressure and flow waves corresponding to specific experimental conditions.

2.3. Data analysis

We used a lumped parameter model, i.e. the four-element windkessel model (WK4), in order to analyse the flow conditions in the pulmonary circulation throughout the experimental protocol. An electrical representation of the WK4 is displayed in Fig. 1.

The resistor R_2 represents the resistive properties of the pulmonary vasculature, which are considered to reside primarily in the arteriolar system. The capacitor C, placed in parallel with R_2, represents the compliant properties of the pulmonary arterial tree [12].

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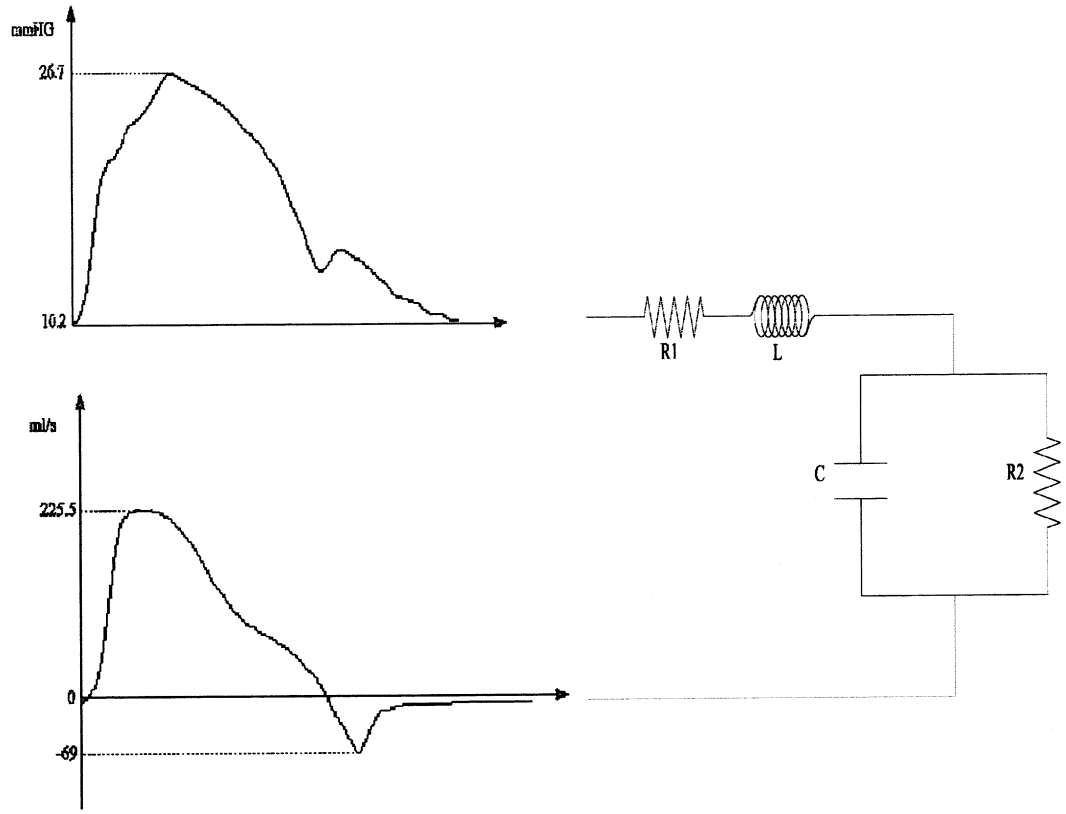
The resistor R_1 is used to reflect characteristic resistance, the value of which depends principally on the inertance and compliance of the main pulmonary artery. Finally, an inductance L is used to allow positive phase angles between flow and pressure waves. It corresponds to the inertial properties of the pulmonary vasculature due to the mass of blood [12].

The four elements of the model were simultaneously calculated by using an original analytic procedure as described previously [17]. Details of this analysis are provided in Appendix A.

Fig. 1. *Representation of the four element windkessel model with an example of computer record used to obtain averaged pulmonary pressure (upper panel) and flow (lower panel) waveforms from ten consecutive systoles. Key to symbols used: R_1, characteristic vascular resistance; L, vascular inductance; C, vascular compliance; R_2, peripheral vascular resistance.*



2.4. Statistical evaluation.

Data are expressed as mean ± standard error of the mean (SEM).

Changes in hemodynamics and in WK4 parameters within each group were evaluated by a repeated-measures analysis of variance. When necessary, a Scheffé's test was used for multiple comparisons. A *t*-test was used to evaluate statistical differences in behaviour between groups. A *P* value of less than 0.05 was considered as statistically significant.

3. Results

The time course of conventional hemodynamic variables for both groups during both the baseline period and the experimental period is presented in Fig. 2. During the baseline period, no statistical differences were noted in the hemodynamic variables between the two groups.

In the endotoxin group, PAP showed a biphasic, roughly M-shaped response following endotoxin infusion. After 1 h, PAP reached its first maximum, while at 90 min it had decreased to immediate post endotoxin infusion values. It then increased once again at 150 min.

In contrast, BP decreased gradually during the entire experimental period and paralleled the changes observed in blood flow. PVR showed a profile similar to that of PAP.

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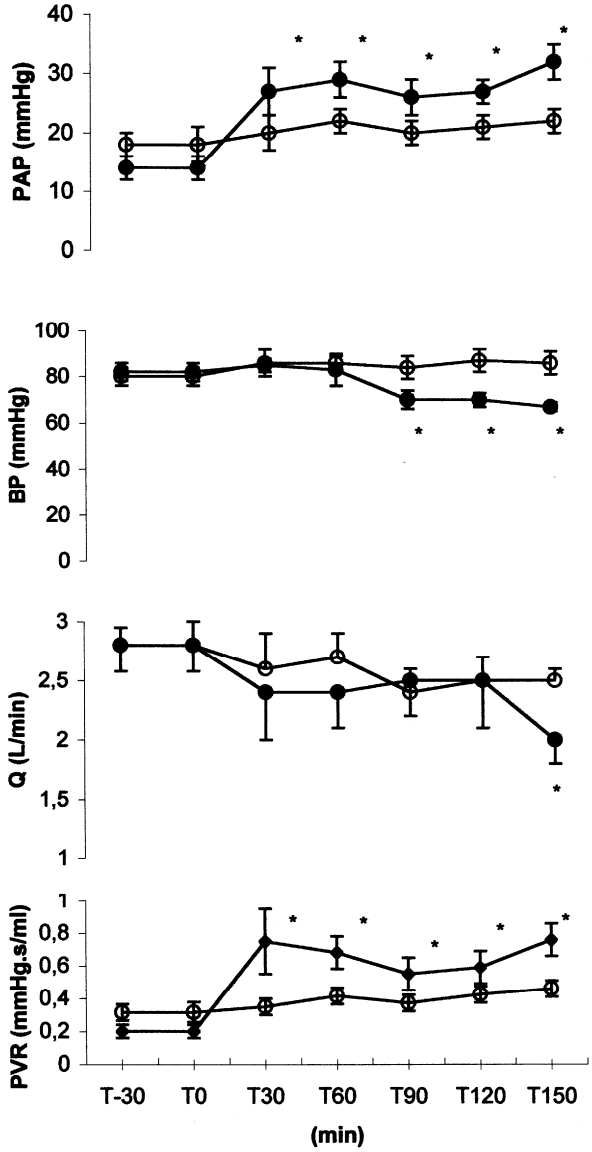
HR increased gradually from 103 ± 13 to 153 ± 13 during the course of the experiment ($P<0.05$). LAP remained almost unchanged at 6 mmHg.

During the same period, we recorded no significant hemodynamic changes in the control group. There were no statistical differences in the dose of anaesthetic or pancuronium administered during the protocol between endotoxin-treated and in control animals.

Fig. 2. *Time course of conventional hemodynamic variables in the control group (open circles) and endotoxin group (closed circles). Endotoxin solution was infused from T_0 to T_{30}. Key to symbols used: PAP, mean pulmonary artery pressure; BP, mean arterial blood pressure; Q, pulmonary blood flow; PVR, pulmonary vascular resistance. PVR was referred to as the ratio between pulmonary pressure gradient (PAP—LAP) and pulmonary blood flow. * indicates significant changes from baseline values ($P<0.05$).*



The time course of calculated pulmonary vascular parameters as provided by the WK4 model is presented in Fig. 3. In the control group, the characteristic resistance R_1 and the peripheral resistance R_2 remained remarkably stable. On the other hand, the vascular compliance C tended to decrease over time; these changes were, however, minor and failed to reach statistical significance. In contrast, R_1 and R_2 showed specific changes in the endotoxin group. R_2 increased significantly immediately following endotoxin insult and remained elevated thereafter. R_1 increased rapidly, subsequently returned baseline values, and then showed a secondary rise between T_{90} and T_{120} min. The vascular compliance C decreased immediately after endotoxin insult, remaining at the same low level between T_{60} and T_{120}, and then decreased significantly again at the end of the experiment. In contrast, inductance

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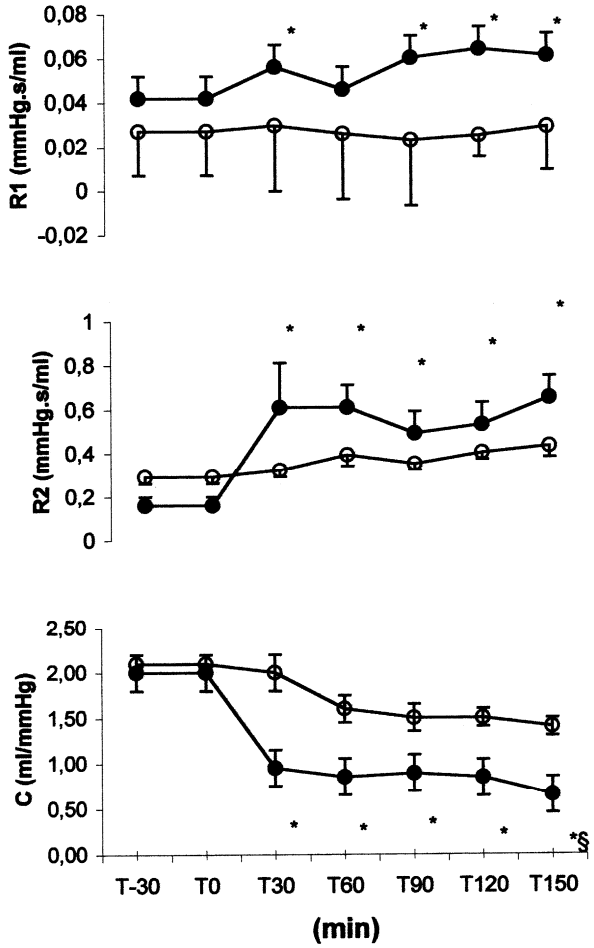
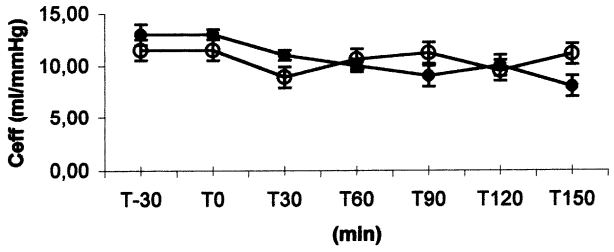
L remained essentially unchanged throughout the experiment when compared to baseline values in both groups of animals.

Fig. 3. *Changes in detailed pulmonary vascular parameters as obtained by the four element windkessel model of the pulmonary circulation, in the control (open circle) and endotoxin groups (closed circles). Key to symbols used: R_1, characteristic vascular resistance; R_2, peripheral vascular resistance; C, global vascular compliance. Endotoxin solution was infused from T_0 to T_{30}. * indicates significant changes from baseline values ($P<0.05$); § indicates significant difference from T_{30} values ($P<0.05$).*



Analysis of variance showed that dynamic lung compliance remained unchanged throughout the experiment in both groups, as illustrated in Fig. 4.

Fig. 4. *Time course of effective dynamic lung compliance (C_{eff}) in the control group (open circles) and in endotoxin-injured animals (closed circles). Endotoxin infusion was started at T_0 and stopped at T_{30}. No statistical change occurred during the experimental period.*



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4. Discussion

Our laboratory has previously investigated effects of continuous endotoxin infusion, as this situation is more likely to reflect human sepsis [2,3]. Clinical sepsis would appear more likely be associated with a continuous or repeated release of endotoxin, rather than a single bolus [4]. The absence of a clinical hyperdynamic circulatory state in the present experiment is explained by the fact that peripheral blood pooling was not compensated by fluid loading. In contrast, fluid challenge is initiated early in the clinical setting and allows expression of an hyperdynamic state.

The biphasic course of PAP, as well as the pattern of decrease in blood flow after endotoxin insult are quite similar to the observations of other authors. Such endotoxin effects are clearly different from the evolution of hemodynamics in sham-operated animals, as previously shown by others [5,9,15,21].

According to Ohm's law, decreases in blood flow associated with concomitant increases in the pulmonary pressure gradient imply that increases in PVR occurred. In our experiments, endotoxin insult resulted in a gradual increase in PVR. This is classically interpreted as being caused by vasoconstriction, without regard to predominant effects on either the arterial or venous side of the pulmonary circulation. In fact, several explanations, invoked separately or in association, are able to account for increases in PAP in presence of decreased blood flow. These include: (1) increase in the distal vascular resistance provoked by an elevation in vascular tone, (2) alteration of the vascular compliance of the pulmonary bed, or (3) increase in the characteristic resistance secondary to an endotoxin-induced stiffening of the proximal arterial tree.

Previous studies in which pulmonary hypertension has been reported to result from endotoxin challenge have not been able to differentiate among these possibilities [3,5,11,14,16,20,21]. Our results suggest that the lumped parameter model provides relevant information regarding the vascular properties that govern pulmonary blood flow during basal conditions and endotoxin shock. Our results for characteristic resistance R_1, total pulmonary vascular compliance C, and input resistance R_2 were comparable to values obtained in previous studies of animals of comparable size under baseline conditions [10,18]. It should be emphasised, however, that all existing methods of estimating total pulmonary vascular compliance are based on windkessel models; it is therefore impossible to validate these model-derived estimates using alternative, in vivo approaches, which are unable to provide definitive values for compliance. To our knowledge, there have been no previous measurements of compliance changes in the intact pulmonary circulation in response to endotoxic shock. Therefore, comparison of our results with those of other workers is fraught with difficulty. The present data suggest that endotoxin insult leads to a complex pulmonary vascular response involving a dynamic, time-dependent interplay between R_1, C and R_2. During early endotoxemia, the increase in PAP and the rise in PVR may be attributed to alterations in R_1 and R_2 and a decline in vascular compliance. It is of interest to note that the transient improvement in pulmonary hemodynamics appears to parallel changes in R_1. This may result from the fact that the portion of the pulmonary circulation most affected during early endotoxemia is the proximal arterial segment. An increase of R_1 may be interpreted as reflecting a reduction in the compliance of the main pulmonary artery and/or a decrease of vessel radius, indicating that selective stiffening was produced by an increase in smooth muscle tone in the main pulmonary artery. On the other hand, the terminal phase of the biphasic PAP response appears to be accounted for by a selective decline in compliance of the distal pulmonary vasculature, since both R_1 and R_2 did not show further changes during this time interval. This feature is of particular interest, as it clearly shows that PAP and PVR may be increased in the absence of further alterations in the resistive properties of the vessels, but may, in fact, parallel changes in distal vascular compliance. The mechanism whereby endotoxin challenge leads to sequential effects on resistive and compliance properties of the various segments of the pulmonary vasculature remains unclear. To further complicate matters, increased interstitial fluid or pulmonary air trapping would both tend to increase perivascular pressure in distal vessels, adding to the effects of increased vascular wall tone. Thus, the occurrence of perivascular cuffing as well as bronchoconstriction could lead to exagerrated estimates of either the increase in vascular resistance or the decrease of vascular compliance. The degree of pulmonary interstitial edema was not directly measured in the present study. However, total effective dynamic compliance is generally assumed, in open-chest animals, to reflect combined effects of parenchymal compliance plus the pressure required to overcome airway resistance. To test the hypothesis of the occurence of air trapping and/or interstitial edema accumulation, we used an analysis of variance for the interaction between airway pressures and either air flow or volume. This showed that there were no significant differences in peak inspiratory pressures caused by corresponding flow nor volume changes in controls and after endotoxin insult. Although we were able to rule out the occurrence of both significant edema and bronchoconstriction to explain peripheral vascular narrowing, we cannot be entirely certain that lung volume remained constant during endotoxin infusion, because functional residual capacity was not measured in the present study. In contrast, convincing evidence has been accumulated to suggest that early changes in PAP are associated with the release of thromboxane A2, whereas later changes could be related to injury of the vascular wall and subsequent decrease in local NO production [1,13,21]. This is consistent with the loss of elastic properties of distal vessels. Our results raise questions that

certainly need further, detailed investigation. The partitioning between resistive and vascular compliance changes revealed by application of our circulatory model may provide support for the idea that increases in PVR can only be counteracted by use of vasodilating drugs under certain circumstances. As long as the pressure response is primarily a result of vasoconstriction, the administration of vasodilators would represent a logical therapeutic step [1,5,14,20,21]. In contrast, the possibility that reduction in vascular compliance contributes to the observed response of PAP would theoretically preclude any success in attempts to restore basal tone by using vasodilators. This problem may be alleviated by reducing the inflammatory response associated with injury of the vascular wall. Previous work has shown that even minor decreases in pulmonary vascular compliance are responsible for marked deleterious effects on right ventricular function [10]. In the face of altered vascular compliance, the right ventricle's functional mode changes, from that of a flow pump to that of a pressure pump. This ventricular accommodation takes place to the detriment of stroke volume [10]. We observed this process during late endotoxemia.

In summary, we have shown that endotoxin infusion leads to a biphasic pulmonary arterial pressure response. Our analysis revealed that early changes are consistent with the occurrence of vasoconstriction, which in turn reduces the global compliance of the pulmonary bed. The PAP response was partially caused by changes in the characteristic resistance of the proximal vascular area. Late changes in PAP resulted from a specific decline in vascular compliance without further alterations in the resistive properties of the pulmonary bed. The present study reveals that analysis of PVR using an ohmic model of the pulmonary circulation fails to provide any substantial insight into the mechanisms responsible for the complex hemodynamic responses seen during endotoxin shock.

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Appendix A

Calculation of WK4 parameters

The relationship between pressure and flow in standard models is described by a second order linear differential equation [19]:

$$a_0 Q + a_1 \frac{\mathrm{d}Q}{\mathrm{d}t} + a_2 \frac{\mathrm{d}^2 Q}{\mathrm{d}^2 t} = b_0 P + b_1 \frac{\mathrm{d}P}{\mathrm{d}t} + b_2 \frac{\mathrm{d}^2 P}{\mathrm{d}t^2} \qquad (1)$$

In order to avoid the use of a second derivative, which decreases signal-to-noise ratio, Eq. (1) is integrated and becomes:

$$\int_{t_0}^{t} Q(\tau)\mathrm{d}\tau = k_1 \int_{t_0}^{t} P(\tau)\mathrm{d}\tau + k_2(P(t) - P(t_0)) + k_3(Q(t) - Q(t_0)) + k_4\left(\frac{\mathrm{d}Q}{\mathrm{d}t}(t) - \frac{\mathrm{d}Q}{\mathrm{d}t}(t_0)\right) \qquad (2)$$

where Q = pulmonary flow, P = pulmonary pressure, and t_0 = the beginning of the cardiac cycle defined as the R wave on the ECG.

The multiple regression technique estimates the constants k_i in order to minimise the residual sum of squares (RSS) i.e., the sum of the squared differences between the observed values of both parts of this equation:

$$RSS = \sum_t \left[\int_{t_0}^{t} Q(\tau)\mathrm{d}\tau - k_1 \int_{t_0}^{t} P(\tau)\mathrm{d}\tau - k_2(P(t) - P(t_0)) - k_3(Q(t) - Q(t_0)) - k_4\left(\frac{\mathrm{d}Q}{\mathrm{d}t}(t) - \frac{dQ}{dt}(t_0)\right) \right]^2 \qquad (3)$$

The parameters k_1, k_2, k_3 and k_4 are the following respective functions of L, R_1, C and R_2:

$$k_1 = \frac{1}{R_1 + R_2} \quad k_2 = \frac{CR^2}{R_1 + R_2} \quad k_3 = -\frac{L + CR_1R_2}{R_1 + R_2} \quad k_4 = -\frac{LCR_2}{R_1 + R_2} \tag{4}$$

L, R_1, R_2 and C values were then derived by solving Eq.(4).

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