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EFFECT OF A NOVEL THROMBOXANE A_2 INHIBITOR ON RIGHT VENTRICULAR-ARTERIAL COUPLING IN ENDOTOXIC SHOCK

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ABSTRACT—We investigated the effects of a dual thromboxane (TX)A_2 synthase inhibitor and TXA_2 receptor antagonist (BM-573) on right ventricular-arterial coupling in a porcine model of endotoxic shock. Thirty minutes before the onset of 0.5 mg/kg endotoxin infusion, six pigs (Endo group) received an infusion with a placebo solution, and six other pigs (Anta group) with BM-573. Right ventricular pressure–volume loops were obtained by the conductance catheter technique. The slope (E_{es}) of the end-systolic pressure–volume relationship and its volume intercept at 25 mmHg were calculated as measures of right ventricular systolic function. RV afterload was quantified by pulmonary arterial elastance (E_a), and E_{es}/E_a ratio represented right ventricular-arterial coupling. Mechanical efficiency was defined as the ratio of stroke work and pressure-volume area. In this model of endotoxic shock, BM-573 blunted the early phase of pulmonary hypertension, improved arterial oxygenation, and prevented a decrease in right ventricular myocardial efficiency and right ventricular dilatation. However, the drug could not prevent the loss of homeometric regulation and alterations in right ventricular-arterial coupling. In conclusion, dual TXA_2 synthase inhibitor and receptor antagonists such as BM-573 have potential therapeutic applications, improving right ventricular efficiency and arterial oxygenation in endotoxic shock.

KEYWORDS—Hemodynamics, pigs, pulmonary circulation, right ventricular dysfunction, septic shock

INTRODUCTION

Despite tremendous advances in supportive care, septic shock remains one of the leading causes of death in critically ill patients. Among the numerous complications, right heart failure is certainly of the most life-threatening ones (1). In septic shock, impaired right ventricular (RV) function results from an inappropriate matching between the ventricular inotropic state and pulmonary vascular impedance, with secondary altered ventricular–vascular coupling (2).

Thromboxane A_2 (TXA_2) has been reported to be partially responsible for the increase in pulmonary vascular resistance after endotoxin administration (3, 4) leading to ventricular–vascular coupling mismatch (5, 6). To restore coupling, one may aim to increase RV contractility. However, inhibition of TXA_2 in an attempt to blunt the increase in pulmonary vascular resistance seems a more appropriate approach.

Up to now, most studies focused on testing either inhibitors of TXA_2 synthase (6, 7) or receptor antagonists of TXA_2 independently (8, 9). In those studies, TXA_2 synthase inhibitors appeared less effective than anticipated not only because of an incomplete blockage of TXA_2 synthase at the dosage used but also because TXA_2 synthase inhibition induces an accumulation of endoperoxide H_2 (PGH_2), which is a TXA_2 precursor, chemically more stable than TXA_2 itself and with similar biological effects (10). On the other hand, specific inhibitors of TXA_2 synthase are also responsible for increased generation of prostanoids such as prostaglandin I_2 (PGI_2), which is known to possibly exert beneficial effects such as attenuation of platelet activation and decrease in vascular resistance and leukotriene release (6, 8, 10). Nevertheless, it has become clear from these studies that efforts to modulate the actions of TXA_2 should focus on agents able to (a) block the biosynthesis of TXA_2 and (b) to simultaneously antagonize both PGH_2 and TXA_2 at their common receptor.

Torasemide, a loop diuretic, has been shown to have a weak TXA_2 antagonist activity on dog coronary artery (11). Since then, several molecules, chemically related to torasemide, have been designed and studied for their TXA_2 antagonism. Recently, it was demonstrated that BM-573 {*N*-terbutyl-*N*′-[2-(4′-methylphenylamino)-5-nitro-benzenesulfonyl]urea}, a torasemide-related molecule, has a high affinity for the human platelet TXA_2 receptor. It was shown that BM-573 was able to relax a rat aorta that was precontracted with U-46619, a TXA_2 agonist. Moreover, BM-573 prevented human platelet aggregation induced by arachidonic acid and completely inhibited TXA_2 synthase (12). As such, it appears that BM-573 combines both the TXA_2 synthase inhibition and TXA_2 receptor antagonism properties.

The primary aim of this study was to evaluate the effects of this novel TXA_2 antagonist, BM-573, on RV performance in a porcine model of endotoxic shock. In addition, however, our

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study may also yield new insights in RV ventricular-arterial coupling in septic shock because only few studies have correctly evaluated RV function in these conditions. In most of these studies, RV systolic function was quantified by RV ejection fraction (1, 6) or RV pressure–length relationship (13–16). In the present work, we make use of the robust and highly sensitive indices of ventricular function described earlier: the slope of the end-systolic pressure–volume (PV) relationship (ESPVR) and its intercept with the volume axis (17, 18). Pulmonary arterial elastance (E_a) was used to describe the load that the RV chamber is facing (13).

MATERIALS AND 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 Liege. They were performed in accordance with the principles of laboratory animal care (NIH publication No. 86–23, revised 1985).

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 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.

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) 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 blood pressure (BP) 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) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a gradual preload reduction.

Experimental protocol

After a 30-min stabilization period (T_0), 12 animals were randomly divided in two groups. Both groups received a 0.5 mg/kg endotoxin (lipopolysaccharide from *Escherichia coli* serotype 0127:B8; Sigma Chemical, St Louis, MO) infusion over 30 min (from T_{30} to T_{60}). In the first group (Endo group, n = 6), the animals were infused with placebo, and in the second group (Anta group, n = 6), they received a 10 mg/kg/h infusion of BM-573 from T_0 to T_{300} to achieve a steady-state concentration of 14.11 ± 3.34 μg/mL. At this concentration, BM-573 completely blocked TXA_2 receptor activation by U-46619, a TXA_2 agonist (unpublished data).

This compound was obtained from the Laboratory of Medicinal Chemistry of our University. It was dissolved in propylene glycol and water to achieve a drug stock solution of 20 mg/mL.

Hemodynamic data included pulmonary artery pressure (PAP) wave, pulmonary blood flow (Q) wave, left atrial pressure, BP, heart rate (HR), RV pressure, RV volume, and RV PV loops. These parameters were recorded every 30 min from T_0 to T_{300} 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). PAP, Q, left atrial pressure, BP, HR, RV volume, RV pressure, and RV PV loops were also monitored on line throughout the experiment. Left atrial pressure was maintained stable throughout the experiment by Ringer-lactate infusion as needed.

RV PV loops were also recorded every 30 min from T_0 to T_{300} during a transient occlusion of the inferior vena cava using the Fogarty balloon (Fig. 1).

Arterial blood was collected every 60 min to measure pH, PO_2, PCO_2, base excess, and bicarbonate standard (288 Blood Gas System, CIBA-Corning, CA).

Data analysis

Pulmonary circulation—E_a, which reflects RV afterload, was calculated using the following equation (13):

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

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

A lumped parameter model, namely the four-element windkessel model, was used to calculate R_1, R_2, and C using an original analytic procedure described previously (19). In this model, R_1 represents the characteristic impedance of the pulmonary circulation, R_2 pulmonary vascular resistance, and C pulmonary artery compliance (20).

Right ventricular function—RV PV loops were obtained using the conductance catheter method as previously described (18).

Before each measurement, parallel conductance was determined with the saline method by injecting 3 mL of NaCl 10% into inferior vena cava (18).

During a rapid inferior vena cava occlusion maneuver, the slope of the ESPVR curve (end-systolic elastance, E_{es}) was determined (18). A volume intercept at a fixed pressure of 25 mmHg (V_{p25}) to quantify the position of the ESPVR was also used. E_{es} and V_{p25} represent load-independent measures of RV contractile performance. An increased E_{es}, a leftward shift indicated by a decreased $V_{p25,}$ or both represent an improved systolic function (17, 18).

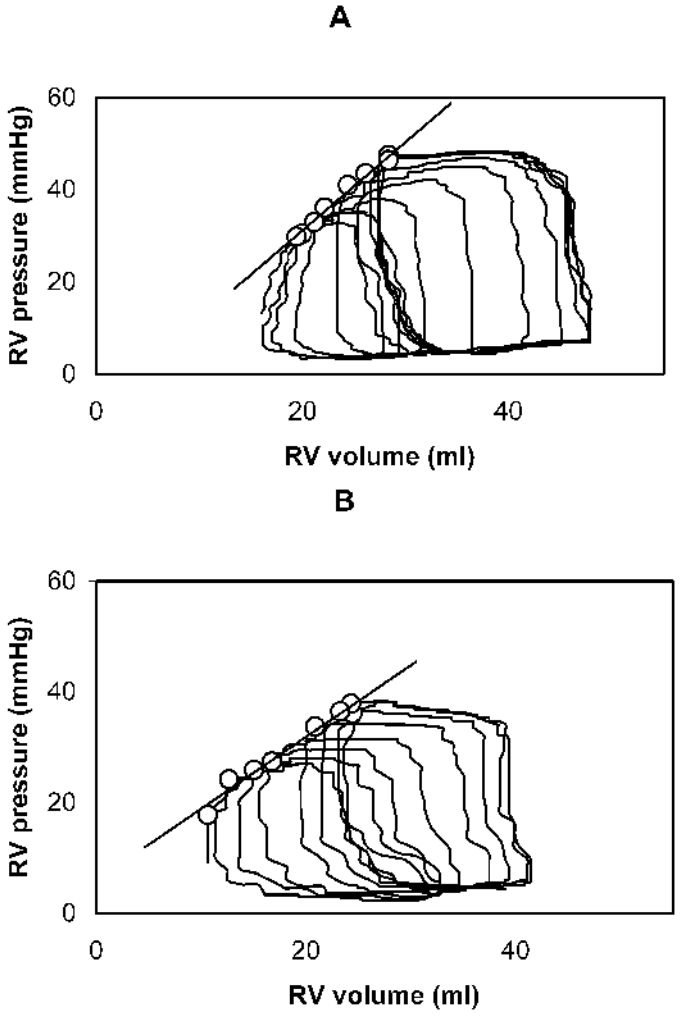

FIG. 1. **Typical example of right ventricular (RV) pressure–volume loops and end-systolic pressure–volume relationship during inferior vena cava occlusion in one animal at T_{60} in the Endo (A) and in the Anta group (B).** Open circles are end-systolic points.

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

The specific area in the PV plane bounded by the end-systolic and end-diastolic pressure–volume lines and the systolic segment of the PV loop (pressure–volume area, PVA) serves as a reliable predictor of myocardial oxygen consumption (13, 21).

RV efficiency was calculated as the ratio of stroke work to PVA (13, 22).

Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volume (EDV).

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 $E_{es}/E_a = 1$, and uncoupling occurs when E_{es}/E_a is lower than 1 (13).

Statistical analysis

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

A two-way ANOVA for repeated measures during early (T_{30}–T_{60}) and late (from T_{90}) phases of endotoxic shock gives *P* value for time, group, and time–group interaction (Statistica®, Statsoft Inc, Tulsa, OK).

$P < 0.05$ was considered statistically significant.

RESULTS

Conventional hemodynamic data

As shown in Figure 2, the time evolution of BP, Q, and HR values did not differ between Endo and Anta groups.

Mean PAP in the Endo group reached a first maximum at T_{60} ($P < 0.05$) (i.e., 30 min after the onset of endotoxin infusion). In the Anta group, in contrast, mean PAP values at T_{60} were not different from their basal values. The difference in mean PAP values between the two groups was statistically significant at T_{60} ($P < 0.05$). After T_{90}, mean PAP increased progressively ($P < 0.05$) and similarly in the two groups.

Right ventricular volumes

The evolution in time of RV EDV is depicted in Figure 3. In the Endo group, EDV increased from 53 ± 6 mL (T_0) to 64 ± 11 mL ($P < 0.05$) at the end of endotoxin infusion (T_{60}) and further remained unchanged throughout the experiment. In the Anta group, EDV was lower than in the Endo group at T_{90} and thereafter ($P < 0.05$). Ejection fraction progressively decreased in both groups throughout the experiment ($P < 0.05$). However, ejection fraction remained higher in the Anta than in the Endo group ($P < 0.05$) (Fig. 3).

Derived hemodynamic data

E_a and R_2 in the Endo group expressed a profile similar to the time evolution of PAP (Fig. 4). As was found for PAP, E_a and R_2 did not significantly increase between T_{30} and T_{60} in the Anta group. From T_{90} until the end of the experimental protocol, there was no difference in E_a and R_2 values between the two groups (Fig. 4).

R_1 increased rapidly from 0.033 ± 0.006 to 0.055 ± 0.010 $mmHg \cdot s \cdot ml^{-1}$ after the onset of endotoxin infusion and remained unchanged during the late phase of endotoxic shock. C decreased rapidly from 1.5 ± 0.2 to 0.7 ± 0.1 mL/mmHg after the start of endotoxin infusion and then remained unchanged until the end of the experimental period. The evolution of R_1 and C in the Anta group paralleled that observed in the Endo group. There were no statistically significant differences in the evolution of R_1 and C between the two groups.

During the early phase of endotoxic shock, E_{es} increased from 1.0 ± 0.1 mmHg/mL (T_0) to 2.9 ± 0.4 mmHg/mL (T_{60}) ($P < 0.05$) in the Endo group and was significantly higher than E_{es} in the Anta group ($P < 0.05$). During the late endotoxic phase, E_{es} remained unchanged and similar in both groups (Fig. 5).

V_{p25} decreased from a basal value of 20 ± 8 mL to 2 ± 2 mL at T_{60} ($P < 0.05$) in the Endo group, but it remained unchanged

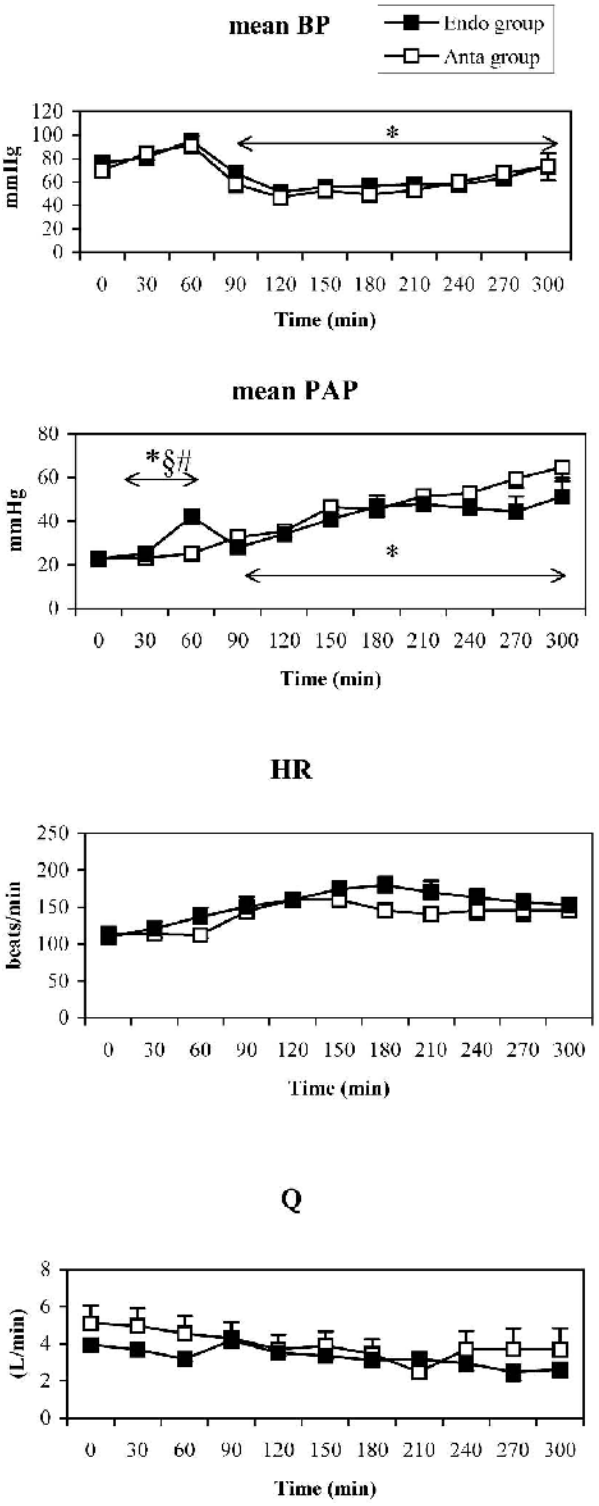

FIG. 2. **Time course of mean systemic arterial pressure (BP), mean pulmonary arterial pressure (PAP), heart rate (HR), and cardiac output (Q) in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{*}P < 0.05$ for time effect. $^{\S}P < 0.05$ for group effect. $^{\#}P < 0.05$ for time–group interaction.

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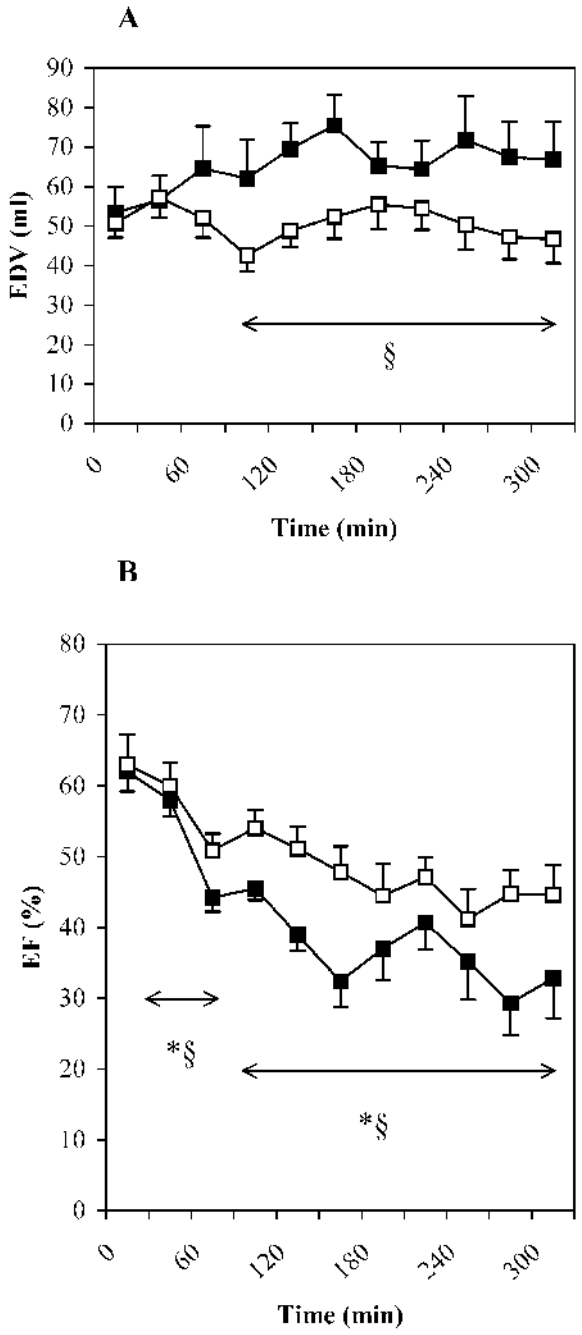

FIG. 3. **Time course of end-diastolic volume (EDV) (A) and right ventricular ejection fraction (EF) (B) in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{*}P < 0.05$ for time effect. $^{\S}P < 0.05$ for group effect.

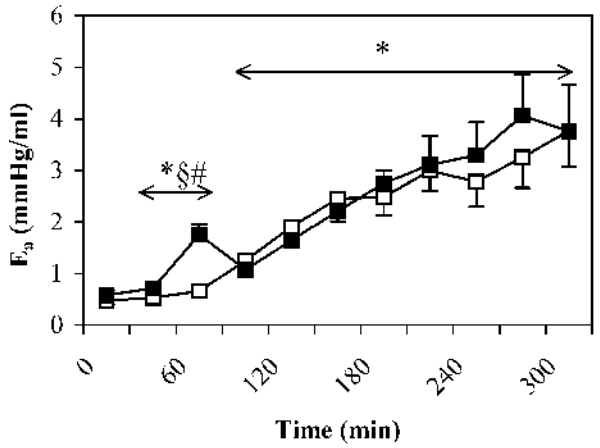

FIG. 4. **Time course of pulmonary arterial elastance (E_a) in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{*}P < 0.05$ for time effect. $^{\S}P < 0.05$ for group effect. $^{\#}P < 0.05$ for time–group interaction.

in the Anta group. During the late phase of endotoxic shock, V_{p25} remained constant in both groups.

During the early phase of endotoxic shock, E_{es}/E_a remained at an optimal level of 2 from T_0 to T_{90} in both groups. During the late phase of endotoxic shock, right ventricular–arterial coupling deteriorated progressively in both groups ($P < 0.05$) (Fig. 5).

RV efficiency remained unchanged in both groups during the early phase of endotoxic shock. In contrast, during the late phase of endotoxic shock, RV efficiency in the Endo group decreased significantly ($P < 0.05$) and differed from the value calculated in the Anta group (Fig. 6).

PO_2 decreased from 131 ± 21 mmHg (T_0) to 74 ± 12 mmHg (T_{300}) ($P < 0.05$) in the Endo group (Fig. 7), while PO_2 progressively increased from 140 ± 88 mmHg (T_0) to 241 ± 31 mmHg (T_{300}) in the Anta group. The difference between the Endo and Anta groups reached statistical significance ($P < 0.05$) during the late phase of endotoxic shock.

Arterial pH, arterial PCO_2, ionogram, and hematocrit remained within the normal range in both groups throughout the experimental period.

DISCUSSION

Our data show that, in a porcine model of endotoxic shock, administration of BM-573 blunts the early phase of pulmonary hypertension, improves arterial oxygenation, and preserves right ventricular efficiency. During the early phase of endotoxic shock, beneficial effects are obtained by a decrease in right ventricular afterload, and in the later phase BM-573 mainly results in an improved arterial oxygenation.

The effects of endotoxin infusion on pulmonary hemodynamics and right ventricular–vascular coupling have been previously studied in our laboratory (2, 19). It has been suggested that the early changes in PAP resulting from endotoxin insult are associated with the release of TXA_2, whereas later changes could be related to injury of the vascular wall and subsequent decrease in NO production (2, 3, 23, 24). Our present study confirms that TXA_2 is indeed responsible for the early vasopressive response of the pulmonary circulation during endotoxin infusion, as evidenced by the prevention of the abrupt increase in R_2 by BM-573 infusion.

Theoretically, blocking the action of TXA_2 can be achieved by two different types of molecules: TXA_2 synthase inhibitors (blocking the production of TXA_2) and TXA_2 receptor antagonists (preventing its action). It was earlier demonstrated in a sheep model that inhibition of TXA_2 synthase still led to an increase in PAP 30 min after endotoxin infusion, although PAP values during the first 2 h of the experiment were significantly

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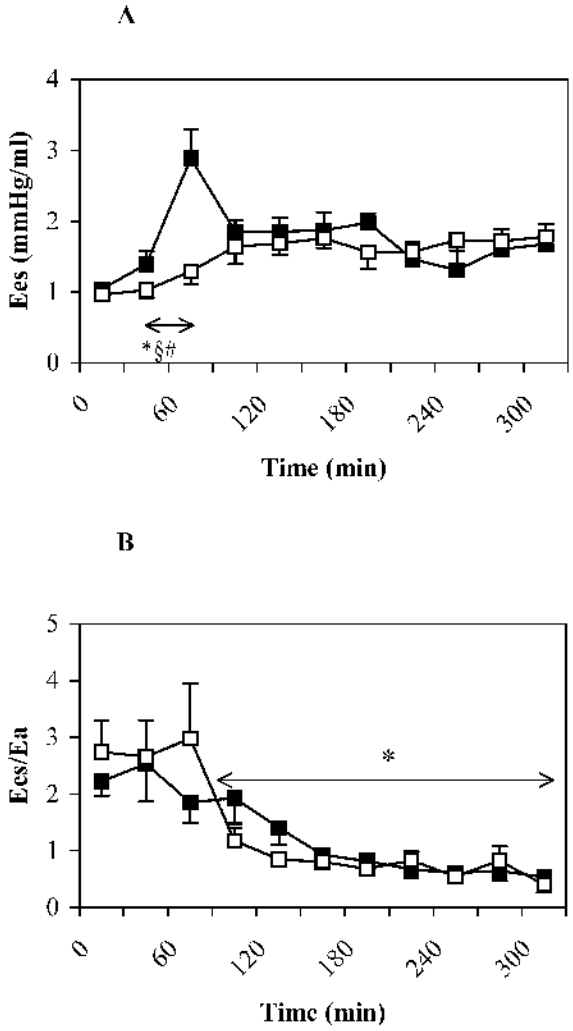

FIG. 5. **Time course of end-systolic elastance of the right ventricle (E_{es}) (A) and right ventricular–vascular coupling (E_{es}/E_a) (B) in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{*}P < 0.05$ for time effect. $^{\S}P < 0.05$ for group effect. $^{\#}P < 0.05$ for time–group interaction.

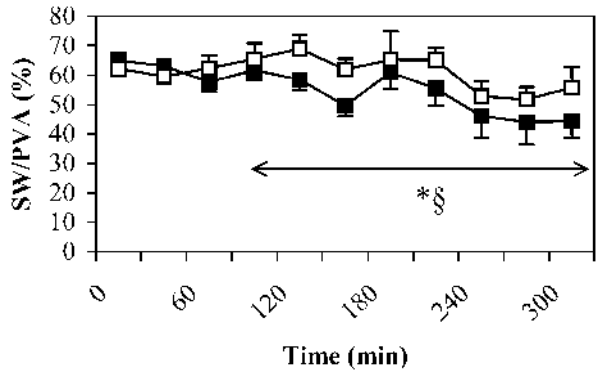

FIG. 6. **Time course of myocardial efficiency (SW/PVA) in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{*}P < 0.05$ for time effect. $^{\S}P < 0.05$ for group effect.

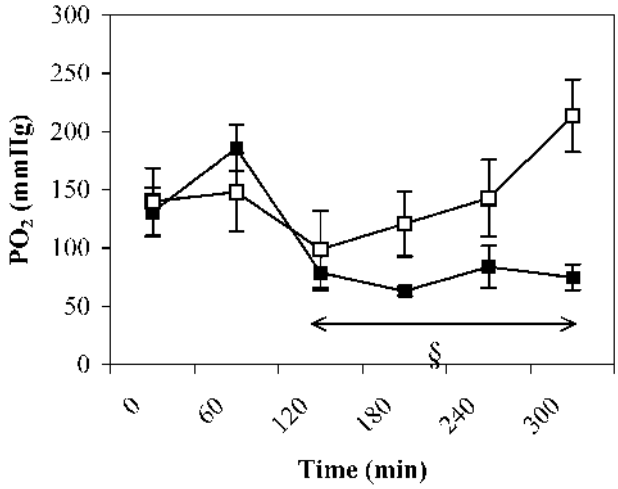

FIG. 7. **Time course of PO_2 in the Endo (■) and Anta groups (□).** Data are presented as mean ± SEM. *P* values for time, group, and time–group interaction are given by a two-way ANOVA for repeated measures: $^{\S}P < 0.05$ for group effect.

lower than in a control group subjected only to endotoxin insult (6). However, pulmonary vascular resistance showed a similar increase in both groups during the following 3- to 6-h period. Using a TXA_2 receptor antagonist during *Escherichia coli* challenge, Jesmok et al. showed that the acute pulmonary hypertensive phase could indeed be inhibited, although the drug did not affect the development of septic shock and subsequent death (9). Accordingly, TXA_2 receptor antagonists could seem more effective than TXA_2 synthase inhibitors in attenuating the early pulmonary response to endotoxin insult. However, these results were not confirmed by the study of Iglesias et al. (25). These authors compared TXA_2 synthase inhibition and TXA_2 receptor antagonism in a porcine burn-injury sepsis model and did not find a significant difference between the two drugs in preventing the occurrence of pulmonary hypertension (25). Moreover, TXA_2 receptor antagonist is associated with cardiac index decrease and pulmonary vasoconstriction in response to PGI_2 blockade. In fact, using only TXA_2 synthase inhibitors increases plasma PGH_2 to levels high enough to stimulate the TXA_2 receptors, whereas using TXA_2 receptor antagonists reduces PGI_2 blood levels. As such, drugs should aim to combine both TXA_2 synthase inhibition and TXA_2 receptor antagonism.

RV adaptation to an increase in its afterload can be obtained by two different, but complementary, mechanisms: heterometric and homeometric regulation. During heterometric regulation, stroke volume is maintained because of changes in RV preload (i.e., EDV), while contractility, as such, remains unchanged (the Frank-Starling mechanism). In contrast, during homeometric regulation, RV contractility (i.e., E_{es}) increases to maintain stroke volume, while EDV remains unchanged. It has been suggested in previous studies in a sheep model of sepsis that the RV response to acute pressure overload consists of both enhanced contractility and the Frank-Starling mechanism (26). In newborn lambs, however, RV output in the face of increased afterload, is regulated only through homeometric regulation (17, 27). In the present study, RV adaptation during the early phase of endotoxin-induced pulmonary hypertension (T_{60}) was obtained by both homeometric and hetereometric regulation. Indeed, both E_{es} and EDV increased, and right ventricular–vascular coupling was maintained at a maximum efficiency. Surprisingly, 1 h later (T_{120}), facing the same

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increased afterload (E_a), the right ventricle failed to maintain its contractility to such an elevated level. As a consequence, right ventricular–vascular coupling decreased from values higher than 2 to values below 1. This confirms earlier findings of D'Orio et al. in endotoxic dogs, which found that the deficit in cardiovascular performance is caused by inappropriate matching between ventricular inotropic state and RV afterload, with secondary altered ventricular-vascular coupling (2).

In the animals of the Anta group, E_{es} did not increase at T_{60} and right ventricular–vascular coupling remained intact because the early pulmonary vasopressive response of the pulmonary circulation was offset by BM-573. However, later in the experiment (T_{120}), E_{es} could not increase enough to maintain right ventricular-vascular coupling at an optimal level, similar to what happened in the Endo group. These results suggest that, 1 h after the end of the endotoxin infusion (T_{120}), homeometric regulation is impaired. This impairment is not prevented by TXA_2 inhibitors because the evolution of right ventricular–vascular coupling is similar in both groups. However, although EDV increased progressively in the Endo group, it remained near basal values in the Anta group. Such an increase in RV EDV and decrease in ejection fraction are hemodynamic signs indicating a decrease in RV mechanical efficiency.

When left ventricular afterload is increased, homeometric regulation can partially be explained by an augmentation 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. It could rather be explained by mechanisms such as mechanical stretch-activated channels, release of endogenous catecholamines, or release of stimulating factors from the endocardial endothelium (27). The precise mechanism by which homeometric regulation appears to be reduced during endotoxin infusion needs further investigation. There is, however, growing evidence that coronary circulation in sepsis is susceptible to maldistribution of regional blood flow (28) and that myocardial blood flow could be unable to augment in response to higher oxygen demands (29). These abnormalities in cardiac performance are largely attributed to TXA_2 formation (28). It is probable that by inhibiting these deleterious effects of TXA_2 on myocardial perfusion, but also by improving arterial oxygenation, the decrease in RV efficiency during endotoxin shock is prevented by BM-573. Nevertheless, because the loss of homeometric regulation was similar in both control (Endo) and treated (Anta) groups, the progressive myocardial depression is not attributable only to the effects of TXA_2.

We estimated ventricular performance by the slope and intercept of the ESPVR, which is obtained by fitting a straight line through the end-systolic PV points. However, these points could show some nonlinearity, and ESPVR is calculated by linear regression. The intercept of ESPVR with the volume axis at zero pressure is thus the result of extrapolating a line far beyond the actual pressure range where the ESPVR could be considered as quasilinear. We therefore used a volume intercept at a fixed pressure, within the pressure range encountered, 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. An increase in E_{es}, a decrease in V_{p25}, or both suggest an improved contractile state (27).

Our results also demonstrated that the use of BM-573 improves arterial oxygenation during endotoxin infusion. In the Endo group, PO_2 decreased throughout the experiment, whereas it increased slightly in the Anta group with a significant difference between the two groups during the late phase of endotoxic shock. These results appear in contradiction with those of Suchner et al., who found that in acute respiratory deficiency syndrome (ARDS), TXA_2 may improve oxygenation by amplifying the efficacy of hypoxic pulmonary vasoconstriction (30). Elevated plasma levels of TXA_2 have been clinically observed in patients with acute lung injury, suggesting that TXA_2 is an important mediator in acute lung injury (31). TXA_2 stimulates platelet activation, promoting the adhesion of platelets to damaged vascular endothelium. Platelet adhesion and degranulation lead to a release of mediators, helping to perpetuate a vicious cycle as granulocyte–endothelial cell adhesion and granulocyte-induced cytotoxicity become enhanced. In turn, activated leukocytes play an important role in acute lung injury through the release of oxygen free-radical species and proteolytic enzymes (32). Our results suggest that inhibition of TXA_2 improves oxygenation by reducing pulmonary vascular inflammatory reactions. Schuster et al. found that inhibition of TXA_2 decreased venous resistance of the pulmonary vascular bed and, hence, pulmonary capillary pressure (33). Imidazole, a TXA_2 inhibitor, has also been suggested to reduce capillary permeability and alveolo-arterial oxygen difference in a model of endotoxic shock in dogs (34). In this way, TXA_2 receptor inhibitors could also diminish the generation of pulmonary edema (33, 35).

In conclusion, BM-573 blunts the early phase of pulmonary hypertension, improves arterial oxygenation, and prevents decrease in RV myocardial efficiency and RV dilatation in a porcine model of endotoxic shock. However, further studies are needed to understand the true mechanism of oxygenation improvement and to test the potential therapeutic benefit of this molecule in septic shock.

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