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Sildenafil improves the beneficial hemodynamic effects exerted by atorvastatin during acute pulmonary thromboembolism

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A B S T R A C T

We investigated whether atorvastatin has beneficial hemodynamic effects during acute pulmonary thromboembolism (APT) and whether sildenafil improves these effects. We studied the involvement of oxidative stress, matrix metalloproteinases (MMPs), and neutrophil activation. APT was induced with autologous blood clots (500 mg/kg) in anesthetized male lambs pretreated with atorvastatin (10 mg/kg/day, subcutaneously; 1 week) or vehicle (dimethyl sulfoxide 10% subcutaneously). Sildenafil (0.7 mg/kg intravenously) or saline infusions were performed 60 min after APT induction. Non-embolized control animals received saline. APT significantly increased pulmonary vascular resistance index (PVRI) and mean pulmonary artery pressure (MPAP) by approximately 310% and 258% respectively. While atorvastatin pretreatment attenuated these increases (~150% and 153%, respectively; P < 0.05), its combination with sildenafil was associated with lower increases in PVRI and MPAP (~32% and 36%, respectively). Gelatin zymography showed increased MMP-9 and MMP-2 levels in the bronchoalveolar lavage, and increased MMP-9 levels in plasma from embolized animals. Atorvastatin pretreatment attenuated bronchoalveolar lavage MMP-2 increases. The combination of drugs blunted the MMPs increases in bronchoalveolar lavage and plasma (P < 0.05). Neutrophils accumulated in bronchoalveolar lavage after APT, and atorvastatin pretreatment combined with sildenafil (but not atorvastatin alone) attenuated this effect (P < 0.05). APT increased lung lipid peroxidation and total protein concentrations in bronchoalveolar lavage, thus indicating oxidative stress and alveolar-capillary barrier damage, respectively. Both increases were attenuated by atorvastatin pretreatment alone or combined with sildenafil (P < 0.05). We conclude that pretreatment with atorvastatin protects against the pulmonary hypertension associated with APT and that sildenafil improves this response. These findings may reflect antioxidant effects and inhibited neutrophils/MMPs activation.

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1. Introduction

Acute pulmonary thromboembolism is a relatively common complication of deep venous thrombosis (Tapson, 2008). While the mechanical obstruction of pulmonary vessels is the major cause of increased right ventricle overload after acute pulmonary thromboembolism, active vasoconstriction of the pulmonary bed aggravates the increases in pulmonary vascular resistance and may lead to acute right heart failure, circulatory shock, and death (Elliott, 1992). Therefore, the use of selective pulmonary vasodilators has been valued as an important approach to counteract the pulmonary vasoconstriction during acute pulmonary thromboembolism (Smulders, 2000; 2001).

Sildenafil, a specific type 5 phosphodiesterase inhibitor, causes preferential pulmonary vasodilation by activating the nitric oxide-cyclic guanosine monophosphate pathway and attenuates the hemodynamic derangements associated with experimental (Dias-Junior and Tanus-Santos, 2006; Dias-Junior et al., 2005a, 2005b, 2010 Souza-Silva et al., 2005) and clinical (Bonatti et al., 2010a, 2010b; Caniere et al., 2006; Lewis et al., 2004) acute pulmonary thromboembolism. Importantly, in the last few years some authors have suggested that combining statins with sildenafil augments the protective effects exerted by statins alone (Kuang et al., 2010; Rosanio et al., 2006; Zhao et al., 2009). In fact, statins have cholesterol-independent effects including enhanced nitric oxide bioavailability, and therefore sildenafil may have positive pharmacodynamic interactions with statins (Castro et al., 2004). However, although recent studies have examined the beneficial effects exerted by statins in animal models of pulmonary hypertension, which may be improved by combining statins with sildenafil (Kuang et al., 2010; Zhao et al., 2009), no previous study has examined whether...
sildenafil improves the protective effects exerted by statins during acute pulmonary thromboembolism.

In the present study, we hypothesized that sildenafil could improve the protective effects exerted by atorvastatin against the hemodynamic derangements associated with acute pulmonary thromboembolism. In addition, increased matrix metalloproteinases (MMPs) activities contribute to the increases in pulmonary vascular resistance (Fortuna et al., 2007; Souza-Costa et al., 2005, 2007) and right ventricle cardiomyocyte injury (Neto-Neves et al., 2011) associated with acute pulmonary thromboembolism, and both sildenafil (Dias-Junior et al., 2009) and atorvastatin (Souza-Costa et al., 2007) blunted MMPs release during acute pulmonary thromboembolism. Therefore, we examined whether sildenafil improves the effects of atorvastatin on acute pulmonary thromboembolism-induced increases in MMP levels and oxidative stress, which is a major factor controlling MMPs activation (Castro et al., 2009).

2. Materials and methods

2.1. Animal model and hemodynamic measurements

The study complied with the international guidelines of the European Community for the use of experimental animal and was approved by the institutional ethics committee.

Twenty two male mixed-bred lambs (17.8 ± 2.9 kg) were randomly assigned to pretreatment with atorvastatin (10 mg/kg/day) (Ozturk and Uma, 2010; Rosanio et al., 2006) subcutaneously or vehicle (2 ml of dimethyl sulfoxide 10% in saline) for 1 week. After this pre-treatment, the animals were anesthetized with ketamine (15 mg/kg, i.m.), xylazine (0.1 mg/kg, i.m.) and relaxed with pancuronium (0.1 mg/kg), tracheally intubated, and their lungs were mechanically ventilated with room air using a volume-cycled respirator (C. F. Palmer, London, UK). The tidal volume was set at 15 ml/kg and the respiratory rate was adjusted to maintain a baseline physiologic arterial carbon dioxide tension. Anesthesia was maintained with intramuscular injections of ketamine (5–7 mg/kg) and midazolam (0.5–1 mg/kg) every 30 min.

Saline-filled catheters were placed into the left femoral artery and right femoral vein for mean systemic arterial pressure monitoring via a pressure transducer and fluid administration, respectively. A 7.5F balloon-tipped Swan-Ganz thermodilution catheter was placed into the pulmonary artery via the left femoral vein. The catheter was connected to pressure transducers to allow the monitoring of mean pulmonary artery pressure, central venous pressure, and pulmonary artery occlusion pressure. Thermodilution cardiac output measurements were determined in triplicate by injecting 3 ml of saline and the results recorded (DX2010 Monitor, Dixtal do Brasil, Manaus, Brazil). The heart rate was measured using a surface electrocardiogram (lead I).

A venous blood sample (5 ml/kg) was collected and allowed to clot for at least 60 min, then cut into 2- to 3-mm cubes. In the present study, acute pulmonary thromboembolism was induced by infusing the autologous clots (250 mg/kg) for 5–10 min via a large-bore cannula placed in the right atrium. This model of acute pulmonary thromboembolism is very similar to that previously reported (Dias-Junior et al., 2009) or saline infusions (S15, S30, S60, and S90 time points respectively). The cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index were calculated by standard formula.

Arterial blood samples were collected at BL and S90 time points and plasma samples were stored at −70 °C until used for gelatin zymography of MMP-2 and MMP-9 as described below. The animals were euthanized with an overdose of anesthetics, and the bronchoalveolar lavage was performed. Lung samples were collected, snap frozen, and stored at −70 °C until used to assess lipid peroxidation levels.

2.2. Bronchoalveolar lavage

Bronchoalveolar lavage was performed six times by instilling 20 ml of phosphate-buffered saline containing 1 mM EDTA. Total cell counts in the bronchoalveolar lavage were performed with a cell counter (Coulter AC T series analyzer; Coulter Corp., Miami, USA), and differential cell counts were carried out on cytocentrifuge slides (Cytospin 3; Shandon Southern Products, Astmoore, UK) stained by the May–Grünwald–Giemsa (Rosenfeld) method (Souza-Costa et al., 2007). The protein concentration in the bronchoalveolar lavage supernatant was measured as an index of alveolar–capillary barrier damage by the Bradford assay using bovine serum albumin as the standard, and the results were expressed as μg/ml. Another aliquot was stored at −70 °C until used for gelatin zymography of MMP-2 and MMP-9 as described below.

2.3. Assessment of MMP-2 and MMP-9 in plasma and in bronchoalveolar lavage samples by SDS-polyacrylamide gel electrophoresis (PAGE) gelatin zymography

Gelatin zymography of MMP-9 and MMP-2 of plasma and bronchoalveolar lavage samples was performed as previously described (Dias-Junior et al., 2009; Neto-Neves et al., 2011). Briefly, plasma and bronchoalveolar lavage samples were subjected to electrophoresis on 7% SDS-PAGE co-polymerized with gelatin (1%) as the substrate (at 150 V for approximately 4 h). After electrophoresis was complete, the gels were incubated for 1 h at room temperature in a 2% Triton X-100 solution, and incubated at 37 °C for 16 h in Tris–HCl buffer, pH 7.4, containing 10 mmol/l CaCl2. The gels were stained with 0.05% Coomassie Brilliant Blue G-250 for 3 h, and then destained with 30% methanol and 10% acetic acid. Gelatinolytic activities were detected as unstained bands against the background of Coomassie blue-stained gelatin. The gelatinolytic activities were normalized with respect to an internal standard (bovine fetal serum) to allow intergel analysis and comparison. The forms of MMP-2 and MMP-9 were identified as bands at 72 and 92 kDa, respectively (Dias-Junior et al., 2009; Neto-Neves et al., 2011).

2.4. Assessment of lipid peroxidation levels in the lung

Lung lipid peroxidation levels were determined by measuring thio-barbituric acid reactive substances using a spectrophotometric method as previously described (Ohkawa et al., 1979). The lipid peroxidation levels were expressed in terms of malondialdehyde (nmol/g).

2.5. Statistical analysis

The results are expressed as means ± S.E.M. Two-way (treatments × time) analysis of variance for repeated measures and Bonferroni post-test were used to compare hemodynamic parameters. Biochemical parameters were compared between groups by one-way analysis of
variance followed by the Dunnett multiple comparisons test. A probability value $<0.05$ was considered the minimum level of statistical significance.

3. Results

3.1. Hemodynamic responses

We found no significant hemodynamic changes in the Sham group (Figs. 1–3). Acute pulmonary thromboembolism increased the pulmonary vascular resistance index by approximately 310% and the mean pulmonary arterial pressure by 258% ($P<0.05$; Fig. 1). While acute pulmonary thromboembolism had no significant effects on the mean arterial pressure and cardiac index, it increased the heart rate by approximately 70% ($P<0.05$; Fig. 3). The systemic vascular resistance index increased slightly in the Emb group compared with the Sham group at the S90 time point ($P<0.05$, Fig. 2).

Pretreatment with atorvastatin attenuated the increases in the pulmonary vascular resistance index and in the mean pulmonary arterial pressure (by 150% and 153%, respectively; both $P<0.05$; Fig. 1) associated with acute pulmonary thromboembolism, without significant effects on the mean arterial pressure and systemic vascular resistance index (Fig. 2). Interestingly, the infusion of sildenafil decreased the mean pulmonary arterial pressure and the pulmonary vascular resistance index (by 32% and 36%, respectively; both $P<0.05$; Fig. 1) in the Ator + Emb + Sil group at the S15, S30, S60 and S90 time points. However, the administration of sildenafil decreased the mean arterial pressure and the systemic vascular resistance index at S30 and S90 time points ($P<0.05$, Fig. 2).

Fig. 1. Pulmonary vascular resistance index (PVRI) and mean pulmonary arterial pressure (MPAP) at baseline (BL), 15 min, 30 min, 45 min, and 60 min (E15, E45, and E60, respectively) after acute pulmonary thromboembolism (APT) or saline infusion, and 15 min, 30 min, 60 min, and 90 min (S15, S30, S60, and S90, respectively) after sildenafil or saline infusion in the Sham (n=4), Emb (n=6), Ator + Emb (n=6) and Ator + Emb + Sil (n=6) groups. Values are the mean±S.E.M. * $P<0.05$ for Emb group versus Sham, Ator + Emb and Ator + Emb + Sil groups. ** $P<0.05$ for Emb group versus Sham group.

Fig. 2. Systemic vascular resistance index (SVRI) and mean arterial pressure (MAP) at baseline (BL), 15 min, 30 min, 45 min, and 60 min (E15, E45, and E60, respectively) after acute pulmonary thromboembolism (APT) or saline infusion, and 15 min, 30 min, 60 min, and 90 min (S15, S30, S60, and S90, respectively) after sildenafil or saline infusion in the Sham (n=4), Emb (n=6), Ator + Emb (n=6) and Ator + Emb + Sil (n=6) groups. Values are the mean±S.E.M. * $P<0.05$ for Ator + Emb group versus Ator + Emb + Sil group. ** $P<0.05$ for Emb group versus Sham group.

Fig. 3. Cardiac index (CI) and heart rate (HR) at baseline (BL), 15 min, 30 min, 45 min, and 60 min (E15, E45, and E60, respectively) after acute pulmonary thromboembolism (APT) or saline infusion, and 15 min, 30 min, 60 min, and 90 min (S15, S30, S60, and S90, respectively) after sildenafil or saline infusion in the Sham (n=4), Emb (n=6), Ator + Emb (n=6) and Ator + Emb + Sil (n=6) groups. Values are the mean±S.E.M. * $P<0.05$ for Emb group versus Sham group.
3.2. MMPs levels in plasma and bronchoalveolar lavage samples

We examined the effects of pretreatment with atorvastatin and sildenafil infusion on the increases in MMPs associated with acute pulmonary thromboembolism. Fig. 4A shows a representative zymogram of plasma samples. Acute pulmonary thromboembolism increased plasma MMP-9 levels by >250% (P<0.05). While no significant changes were found in the Ator + Emb group, animals in Ator + Emb + Sild group presented minor, not statistically significant increases in plasma MMP-9 levels after acute pulmonary thromboembolism (P>0.05, Fig. 4A and B). We found no significant increases in plasma MMP-2 levels (Fig. 4C).

In parallel with these results, we found that acute pulmonary thromboembolism caused major increases in MMP-9 and MMP-2 levels in BAL samples (P<0.05), which were blunted in the Ator + Emb + Sild group (P<0.05, Fig. 5A–D). Atorvastatin pretreatment was associated with significant reductions in MMP-2 levels (P<0.05, Fig. 5D), but not with significant reductions in MMP-9 levels (Fig. 5B).

3.3. Neutrophils and protein concentrations in bronchoalveolar lavage samples

Fig. 6 shows that the increases in MMPs levels after acute pulmonary thromboembolism were associated with major increases in the number of neutrophils and in protein concentrations (which reflect alveolar–capillary barrier damage) measured in the bronchoalveolar lavage from embolized animals (P<0.05, Fig. 6A and B, respectively). While atorvastatin pretreatment alone did not significantly reduce the numbers of neutrophils in the bronchoalveolar lavage, the number of neutrophils was significantly lower in the Ator + Emb + Sild group compared with the Emb group (P<0.05, Fig. 6A). Moreover, lower protein concentrations were found in the Ator + Emb and in the Ator + Emb + Sild groups compared with the Emb group (P<0.05, Fig. 6B).

3.4. Lipid peroxidation levels in the lung

We measured thiobarbituric acid reactive substances concentrations in the lungs from animals to assess oxidative stress. As expected, acute pulmonary thromboembolism was associated with increased oxidative stress (128% higher thiobarbituric acid reactive substances levels; P<0.05; Fig. 7). Both atorvastatin pretreatment alone or combined with sildenafil attenuated the increases in lipid peroxidation associated with acute pulmonary thromboembolism (P<0.05; Fig. 7).

4. Discussion

This is the first study to demonstrate that pretreatment with atorvastatin attenuates the pulmonary hypertension associated with acute pulmonary thromboembolism in a whole animal model. More importantly, we showed for the first time that sildenafil improves the beneficial hemodynamic effects exerted by atorvastatin during acute pulmonary thromboembolism. These protective effects were associated with reduced lung lipid peroxidation, plasma MMP-9 levels, bronchoalveolar lavage MMPs levels, and neutrophils/protein leakage into the bronchoalveolar lavage after acute pulmonary thromboembolism. Our findings suggest that atorvastatin + sildenafil is an interesting combination of drugs that could be used in the therapy of acute pulmonary thromboembolism.

An important mechanism that may explain how sildenafil improves the beneficial hemodynamic effects exerted by atorvastatin is that this statin may have increased the sensitivity of vascular tissues to sildenafil as a result of increased vascular NO bioavailability (Castro et al., 2004). In fact, statins upregulate endogenous NO.

Fig. 4. Representative sodium dodecyl sulfate-polyacrylamide gel electrophoresis gelatin zymogram of plasma samples at baseline and S90 time point showing the bands of 92 and 72 kDa corresponding to matrix metalloproteinase-9 and matrix metalloproteinases-2 respectively (Panel A). Each band detected was normalized with regard to an internal standard (bovine fetal serum) to allow intergel analysis and comparison. Percentage of baseline (BL) MMP-9 (Panel B) and MMP-2 (Panel C) levels in the Sham (n=4), Emb (n=6), Ator + Emb (n=6) and Ator + Emb + Sild (n=6) groups. Values are the mean ± S.E.M. STD: internal standard. BL: baseline MMP-2: matrix metalloproteinase-2 MMP-9: matrix metalloproteinase-9 *P<0.05 for Emb group versus Sham and Ator + Emb + Sild groups.
formation (Lacchini et al., 2010; Nagassaki et al., 2006), and sildenafil-induced increases in cyclic guanosine monophosphate levels can be potentiated by increased nitric oxide levels after pretreatment with atorvastatin.

The increases in bronchoalveolar lavage MMP-2 and MMP-9, and in plasma MMP-9 levels that we found after acute pulmonary thromboembolism are supported by previous studies, and suggest a role for MMPs in the pathophysiology of acute pulmonary thromboembolism (Dias-Junior et al., 2009; Souza-Costa et al., 2005, 2007). Atorvastatin or the combination of atorvastatin and sildenafil prevented the increases in MMPs after acute pulmonary thromboembolism, as previously shown in animal models of acute pulmonary thromboembolism (Dias-Junior et al., 2005a; Souza-Costa et al., 2007). The attenuation of MMPs activities after acute pulmonary thromboembolism may explain, at least in part, the beneficial hemodynamic effects of

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**Fig. 5.** Representatives sodium dodecyl sulfate-polyacrylamide gel electrophoresis gelatin zymograms of bronchoalveolar lavage samples showing the bands of 92 and 72 kDa corresponding to matrix metalloproteinase-9 and matrix metalloproteinase-2 respectively (Panels A and C respectively). Percentage of MMP-9 (Panel B) and MMP-2 (Panel D) levels compared with those found in the Sham animals. Sham group (n = 4), Emb group (n = 6), Ator + Emb group (n = 6) and Ator + Emb + Sild group (n = 6). Values are the mean ± S.

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**Fig. 6.** Number of neutrophils (Panel A) and protein concentrations (Panel B) in bronchoalveolar lavage samples from animals in Sham group (n = 4), Emb group (n = 6), Ator + Emb group (n = 6) and Ator + Emb + Sild group (n = 6). Values are the mean ± S.E.M. BAL: bronchoalveolar lavage ⁎ P < 0.05 for Emb group versus Sham and Ator + Emb + Sild groups (Panel A). # P < 0.05 for Emb group versus Sham, Ator + Emb and Ator + Emb + Sild groups (Panel B).

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**Fig. 7.** Thiobarbituric acid reactive substances (TBARS) concentrations expressed in terms of malondialdehyde (MDA) concentrations in lung samples from animals in the Sham (n = 4), Emb (n = 6), Ator + Emb (n = 6) and Ator + Emb + Sild (n = 6) groups. Values are the mean ± S.E.M. ⁎ P < 0.05 for Emb group versus Sham, Ator + Emb and Ator + Emb + Sild groups.
at orvastatin and sildenafil, which are similar to those found when doxycycline (a non selective MMPs inhibitor) was tested in animal models of acute pulmonary thromboembolism (Fortuna et al., 2007; Neto-Neves et al., 2011; Palei et al., 2005). In fact, increased MMP activities may promote vasoconstriction, especially during acute pulmonary thromboembolism, as previously discussed (Fortuna et al., 2007; Neto-Neves et al., 2011; Palei et al., 2005). Moreover, our findings are in line with previous studies showing that statin, combined with sildenafil or not, attenuated the pulmonary hypertension in animal models of lung disease, at least in part, because lower MMP-9 levels were found (Kuang et al., 2010; Lee et al., 2005; Souza-Costa et al., 2007).

Acute pulmonary thromboembolism induces acute infiltration of inflammatory cells into the pulmonary artery wall (Eagleton et al., 2002), right ventricle (Neto-Neves et al., 2011; Zagorski et al., 2007) and bronchoalveolar lavage (Souza-Costa et al., 2007; Zagorski et al., 2003). In fact, increased number of neutrophils, lymphocytes, and protein concentrations was found in the bronchoalveolar lavage after pulmonary embolism (Nakos et al., 1998). Therefore, the increased MMPs levels in the bronchoalveolar lavage may reflect activation of neutrophils, which release large amounts of pre-stored inflammatory thromboembolism causes alveolar capillary barrier damage. The increases in MMP-9 levels after acute pulmonary thromboembolism after acute pulmonary thromboembolism-induced oxidative stress by atorvastatin and sildenafil suggest that this combination inhibits neutrophil migration, thus partially protecting against increased proteolytic activity by MMP-9.

The increases in MMP-9 levels after acute pulmonary thromboembolism and the protective effects by the drugs tested in the present study may have important implications. Acute pulmonary thromboembolism increases the expression of chemokines (Zagorski et al., 2003), and MMP-9 regulates the levels of some cytokines and chemokines. For example, MMP-9 activates pro-interleukin-1β into active interleukin-1β and may also potentiate interleukin-8 activity, thus promoting a positive feedback between interleukin-8 and MMP-9 (Opedenaker et al., 2001). In this respect, increased interleukin-1β levels were shown in experimental acute pulmonary thromboembolism (Sun et al., 2011). Although we have not measured the levels of these mediators in the present study, it is highly probable that MMP-9 downregulation by the drugs used in the present study, especially atorvastatin, may have indirectly attenuated neutrophil chemotaxis and inhibited the release of proinflammatory factors, as previously shown (Sun et al., 2011).

Injured pulmonary vasculature and activated neutrophils are important sources of reactive oxygen and nitrogen species which exacerbate lung injury (Grommes and Soehnlein, 2011). Indeed, increased oxidative stress has been reported in clinical (Muhl et al., 2006) and experimental acute pulmonary thromboembolism (Dias-Junior et al., 2005a; Souza-Costa et al., 2005). Supporting this idea, we found increased lung lipid peroxidation after acute pulmonary thromboembolism. Importantly, atorvastatin pretreatment alone or its combination with sildenafil attenuated acute pulmonary thromboembolism-induced oxidative stress, thus confirming previous findings (Dias-Junior et al., 2005a, 2009; Souza-Costa et al., 2005). The antioxidant effect that we found may have prevented MMPs activation and its consequences discussed above. This is because reactive oxygen species, especially peroxynitrite, activate MMPs by non-proteinolytic mechanisms (Chow et al., 2007; Schulz, 2007), and attenuation of acute pulmonary thromboembolism-induced oxidative stress by atorvastatin and sildenafil is another mechanism that may explain how these drugs may have blunted MMPs activation after acute pulmonary thromboembolism.

Our study has some limitations that should be taken into consideration. Firstly, we studied the protective effects exerted by atorvastatin, and not therapeutic effects of this drug after acute pulmonary thromboembolism. It would be interesting to study statins as a rescue treatment. Secondly, we have not included a group of animals treated only with sildenafil. However, the hypothesis being tested here was that sildenafil could improve the beneficial hemodynamic effects exerted by statins, which has been tested by comparing the effects of sildenafil (or vehicle) in animals previously treated with atorvastatin. Moreover, the evidence supporting beneficial effects of sildenafil in acute pulmonary thromboembolism is very strong, and many experimental studies (Dias-Junior and Tanus-Santos, 2006; Dias-Junior et al., 2005a, 2005b, 2010; Souza-Silva et al., 2005) have consistently shown that sildenafil is a very promising drug to be used in the therapy of acute pulmonary thromboembolism, as suggested by clinical reports (Bonatti et al., 2010a, 2010b; Ganiere et al., 2006; Lewis et al., 2004).

In conclusion, our study shows that pretreatment with atorvastatin protects against the pulmonary hypertension associated with acute pulmonary thromboembolism and that sildenafil improves this response. These findings may reflect antioxidant effects and inhibited neutrophils/MMPs activation. Clinical studies should be carried out to validate the beneficial effects exerted by this combination of drugs during acute pulmonary thromboembolism.

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