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Endogenous angiotensin II in the regulation of hypoxic pulmonary vasoconstriction in anaesthetized dogs

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Abstract

Introduction The role played by several vasoactive mediators that are synthesized and released by the pulmonary vascular endothelium in the regulation of hypoxic pulmonary vasoconstriction (HPV) remains unclear. As a potent vasoconstrictor, angiotensin II could be involved. We tested the hypothesis that angiotensin-converting enzyme inhibition by enalaprilat and type 1 angiotensin II receptor blockade by candesartan would inhibit HPV.

Methods HPV was evaluated in anaesthetized dogs, with an intact pulmonary circulation, by examining the increase in the Ppa–Ppao gradient (mean pulmonary artery pressure minus occluded pulmonary artery pressure) that occurred in response to hypoxia (inspiratory oxygen fraction of 0.1) at constant pulmonary blood flow. Plasma renin activity and angiotensin II immunoreactivity were measured to determine whether activation or inhibition of the renin–angiotensin system was present.

Results Administration of enalaprilat and candesartan did not affect the Ppa–Ppao gradient at baseline or during hypoxia. Plasma renin activity and angiotensin II immunoreactivity increased during hypoxia, and subsequent measurements were consistent with effective angiotensin-converting enzyme inhibition after administration of enalaprilat, and with angiotensin receptor blockade after administration of candesartan.

Conclusion These results suggest that, although the renin–angiotensin system was activated in hypoxia, angiotensin II is not normally involved in mediating acute HPV.

Keywords: angiotensin II, angiotensin-converting enzyme inhibition, angiotensin receptor antagonism, hypoxic pulmonary vasoconstriction, renin–angiotensin system

Introduction

Hypoxic pulmonary vasoconstriction (HPV) is a physiological response mechanism in the lung whereby circulating blood is driven away from hypoxic alveoli in order to optimize the matching of perfusion and ventilation and to maximize arterial oxygenation [1,2]. Because it is unique and perhaps the most powerful active control mechanism in the pulmonary circulation, HPV has been an area of intensive investigation and debate since it was first described by von Euler and Liljestrand in 1947 [3]. This physiological hypoxic response mechanism has been found in all mammalian species but it varies in expression from one species to another, from absent (in rabbits and guinea pigs), through moderate (in humans and dogs), to vigourous (in cattle and cats) [1,2,4]. The presence

ACE = angiotensin-converting enzyme; AT_1 = type 1 angiotensin II receptor; AT_2 = type 2 angiotensin II receptor; FiO_2 = fractional inspired oxygen; HPV = hypoxic pulmonary vasoconstriction; Ppa = mean pulmonary artery pressure; Ppao = occluded pulmonary artery pressure; Psa = systemic artery pressure; PVR = pulmonary vascular resistance; Q = cardiac output.

of HPV in critically ill mechanically ventilated patients can be observed in routine clinical practice because these patients present with acute pulmonary hypertension if artificial ventilation is accidentally interrupted, and with severe hypoxaemia if drugs are administered that inhibit HPV [2]. As a potent vasoconstrictor and growth promotor, angiotensin II could play a role in HPV and pulmonary vascular remodelling [4,5]. There exists a variety of conflicting data concerning the possible role of angiotensin II in HPV. Some studies showed that inhibition of the renin–angiotensin cascade, by means of angiotensin-converting enzyme (ACE) inhibition [6-10] or angiotensin II receptor blockade [9,11-14], reduces pulmonary vascular tone in normoxia [6,7] and hypoxia [8-14]. However, other studies did not confirm the pulmonary vasodilating effect of an ACE inhibitor [15,16] and of an angiotensin II receptor antagonist [17,18]. This controversy in the reported data can be explained in part by an important variability in hypoxic response between the different species in these studies and by differences in the experimental models employed (acute versus chronic HPV, *in vivo* versus *in vitro*).

In the context of previous experiments from our laboratory, studying the possible role of endothelial mediators (endothelins, nitric oxide and thromboxane A_2) in the same anaesthetized dog model [19-21], we studied the effects of endogenous angiotensin II on pulmonary vascular tone in conditions of increased fractional inspired oxygen (FiO_2; 0.4) and hypoxia. This model may reflect the clinical condition of mechanically ventilated patients, and the canine pulmonary vascular response to hypoxia is considered to be a good model of human HPV [2,4]. Furthermore, we evaluated the functional status of the pulmonary vascular system by measuring pulmonary vascular pressures at constant cardiac output (Q) in order to avoid flow-dependent changes in mediator release and in pulmonary vascular pressures [19-21].

In accordance with previously reported data [8-10], we started from the hypothesis that the ACE inhibitor enalaprilat would inhibit HPV. Whether this pulmonary haemodynamic effect could be a consequence of reduced angiotensin II levels is unknown because ACE inhibition increases bradykinin levels [22], which may dilate pulmonary vessels [23]. We therefore performed the same experiments using the type 1 angiotensin II receptor (AT_1) antagonist candesartan, which to our knowledge has never been used in this setting – in order to avoid possible effects of bradykinin resulting from ACE inhibition and to provide a more robust interpretation of the possible role played by angiotensin II in HPV. Few studies have been reported on the effects of both drugs on the renin–angiotensin system in this model [9]. Results from these experiments could influence the choice of whether to use or avoid ACE inhibitors and/or angiotensin II receptor antagonists in critically ill patients in certain conditions.

Methods

The experiments were conducted in agreement with the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health, and were approved by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine, Brussels, Belgium.

Animal preparation

Sixteen mongrel dogs (16–38 kg) were anaesthetized with pentobarbital sodium (25 mg/kg intravenously), paralyzed with pancuronium bromide (0.2 mg/kg intravenously), intubated and ventilated (Elema 900 B Servo ventilator; Siemens, Sölna, Sweden) with a tidal volume of 15–20 ml/kg (adjusted to maintain arterial partial CO_2 tension between 35 and 45 mmHg), a respiratory rate of 12 breaths/min and a FiO_2 of 0.4. This higher than normal FiO_2 was selected to maintain the lungs above the threshold for HPV [19-21]. Anaesthesia and lack of pain sensation were assessed before muscular paralysis was induced; they were judged to be complete if there were no movements or haemodynamic changes (heart rate, systemic arterial pressure) during insertion of the catheters. Pentobarbital (2 mg/kg intravenously) was repeated hourly to maintain anaesthesia. Pancuronium (0.2 mg/kg intravenously) was repeated before each haemodynamic measurement. Femoral and pulmonary artery catheters were inserted for measurements of systemic and pulmonary vascular pressures, and Q, and for sampling of arterial and mixed venous blood. A balloon catheter was advanced in the inferior vena cava through a right femoral venotomy, and a large bore cannula was inserted into the left femoral artery and vein to act as an arteriovenous bypass. Stepwise inflations of the balloon catheter or opening of the bypass decreased or increased Q [19-21]. A left jugular catheter was placed for fluid and drug administration. Thrombus formation along the catheters was prevented by administration of heparin (100 U/kg intravenously).

Measurements

Vascular pressures were recorded and measured at end-expiration and at constant Q. Heart rate was determined from a continuously monitored electrocardiographic lead. Q was measured by thermodilution. Arterial and mixed venous blood gases were measured immediately after drawing the samples using a tonometered automated analyzer (ABL2; Radiometer, Copenhagen, Denmark) and corrected for temperature. When excessive metabolic acidosis occurred, it was corrected by a slow infusion of sodium bicarbonate. Temperature was kept constant using an electric heating blanket.

Plasma renin activity and angiotensin II immunoreactivity were measured in arterial and mixed venous blood at baseline, and after ACE inhibition and after angiotensin II receptor blockade during increased inspired oxygen (FiO_2 0.4) and hypoxia. Samples of 10 ml arterial and mixed venous blood were simultaneously and directly withdrawn into polysterene tubes containing disodium salt of ethylenediaminetetraacetic acid (4.64 mg/ml)

and 1–10 phenantroline (0.5 mg/ml), which act as inhibitors of ACE and angiotensinase. Tubes containing blood were immediately centrifuged at 3000 *g* for 10 min. Supernatants were frozen at -20°C until they were assayed.

Plasma renin activity was measured from the generation rate of angiotensin I at 37°C and pH 6. A set of samples kept at 0°C during the same period served as a control. Angiotensin I was quantified by direct radioimmunoassay using rabbit anti-angiotensin I antiserum and ^{125}I-labelled angiotensin I produced according to the method of Waite [24]. Cross-reactivity of the antiserum with angiotensin II was under 0.1%. The intra-assay variation was 11%, and the interassay variation was 10%.

Plasma angiotensin II immunoreactivity was measured by the method of Düsterdieck [25]. Briefly, each sample was extracted by using Dowex H^+ ion exchange resin. After washing with water, peptides were eluted from the column with 2 ml of a solution of ammonia–methanol (90:10, vol:vol). The extracts were dried and redissolved in 50 mmol/l Tris buffer (pH 7.5) for radioimmunoassay with ^{125}I-labelled angiotensin II and a rabbit anti-angiotensin II antiserum. Cross-reactivity of the antiserum with angiotensin I was 0.4%. The intra-assay and interassay variations with repeated extractions were 17% and 13%, respectively.

Effects of enalaprilat

First the dogs ($n = 10$) were subjected to two hypoxic challenges, consisting of a decrease in FiO_2 from 0.4 to 0.1 for 6 min to allow stabilization. They then received 1 mg/kg enalaprilat (Merck & Co. Inc., Whitehouse Station New Jersey, USA; intravenously) and two additional hypoxic challenges were performed thereafter. This dose of enalaprilat results in maximal ACE inhibition in dogs [26]. It is also known that maximal blockade of angiotensin II pressor response is achieved with 0.25 mg/kg enalaprilat [27]. In these experiments enalaprilat was given as an intravenous bolus of 0.5 mg/kg followed by a constant infusion of 0.5 mg/kg. The infusion rate was adjusted so that at the end of the experiments all dogs received the total dose. We additionally checked the effectiveness of this dosage regimen in pilot experiments conducted in three dogs receiving an intravenous bolus of 0.25, 0.50 and 1 mg/kg^{-1} (data not shown). Q was kept constant by opening the femoral bypass or by inflating the inferior vena caval balloon. In each experimental condition mean pulmonary artery pressure (Ppa), occluded pulmonary artery pressure (Ppao), systemic artery pressure (Psa) and Q were recorded, and blood was drawn after 3 min of steady state, as assessed by stability of continuously monitored Psa, Ppa and heart rate [19-21].

Effects of candesartan

A similar series of experiments were conducted with candesartan (AstraZeneca, Mölndal, Sweden). Recommendations from the AstraZeneca Research Department for preparation and dosing of an intravenous solution of candesartan were followed. Candesartan is slightly soluble in water or physiological saline, but it is completely soluble in a 1 N Na_2CO_3 solution. The neutrality of this vehicle was assessed in three anaesthetized dogs, in which no effects on Ppa, Psa and Q were observed either in the absence or presence of increased inspired oxygen or hypoxia (data not shown).

The recommended dose for effective AT_1 receptor blockade in dogs of 1 mg/kg produced a 17% decrease in mean Psa, which is comparable with the change observed after administration of enalaprilat. In addition, elevations in plasma renin activity and in immunoreactive angiotensin II after candesartan administration were consistent with AT_1 receptor antagonism. In the experiments candesartan was given as an intravenous bolus of 0.5 mg/kg followed by a constant infusion of 0.5 mg/kg. The infusion rate was adjusted so that at the end of the experiments all dogs received the total dose. We also checked the effectiveness of this dosage regimen in three pilot experiments in dogs receiving an intravenous bolus of 0.25, 0.50 and 1 mg/kg candesartan. Evidence for maximal AT_1 receptor blockade (also measured by means of systemic hypotension and generation of plasma renin activity and angiotensin II immunoreactivity) occurred at a dose of 0.5 mg/kg (data not shown).

Analysis of the data

Results are expressed as means ± standard error of the mean. Body surface area (m^2) was calculated as 0.112 × weight $(kg)^{2/3}$. A two-factor analysis of variance for multiple measurements was used to assess the effects of both medications on haemodynamics. When the F ratio of the analysis of variance reached $P < 0.05$, modified Student's t-tests were used to determine which means differed [28].

Results

Effects of enalaprilat

Haemodynamic data

Enalaprilat decreased mean Psa by 15% during FiO_2 0.4 (Table 1). Hypoxia increased the Ppa–Ppao gradient (i.e. mean Ppa minus Ppao) measured at constant Q (Fig. 1a). Enalaprilat did not affect Ppa–Ppao gradient in the presence of increased FiO_2 or in hypoxia (Fig. 1a) and had no effect on hypoxic response (Fig. 1b).

Plasma renin activity and angiotensin II immunoreactivity

Plasma renin activity increased in the systemic as well as in the pulmonary circulation during hypoxia and after enalaprilat during FiO_2 0.4 (Fig. 2a). Angiotensin II immunoreactivity increased during hypoxia in the systemic and pulmonary circulations before enalaprilat administration, but it was not detectable after enalaprilat administration (Fig. 2b).

Table 1

Effects of enalaprilat in 10 dogs

Parameter	Baseline		Enalaprilat	
FiO_2	0.4	0.1	0.4	0.1
Q (l/min per m^2)	3.4 ± 0.1	3.5 ± 0.2	3.5 ± 0.1	3.4 ± 0.1
Ppa (mmHg)	14 ± 1	24 ± 2*	15 ± 2	28 ± 2*†
Ppao (mmHg)	6 ± 1	5 ± 1	5 ± 1	6 ± 1
Psa (mmHg)	119 ± 4	123 ± 8	101 ± 3†	102 ± 10†
HR (beats/min)	169 ± 6	189 ± 8*	166 ± 5	183 ± 8*
pHa	7.34 ± 0.01	7.37 ± 0.01	7.34 ± 0.01	7.36 ± 0.02
PaO_2 (mmHg [kPa])	172 ± 15 (23 ± 2)	30 ± 2* (4 ± 0.3)	168 ± 12 (22 ± 2)	29 ± 1* (4 ± 0.1)
$PaCO_2$ (mmHg [kPa])	38 ± 1 (5 ± 0.1)	37 ± 1 (5 ± 0.1)	37 ± 1 (5 ± 0.1)	37 ± 1 (5 ± 0.1)
PvO_2 (mmHg [kPa])	50 ± 2 (7 ± 0.1)	20 ± 2* (3 ± 0.3)	50 ± 2 (7 ± 0.3)	19 ± 2* (3 ± 0.3)

Data are presented as mean ± standard error of the mean. FiO_2, fraction of inspired oxygen; HR, heart rate; $PaCO_2$, carbon dioxide tension in arterial blood; PaO_2, oxygen tension in arterial blood; pHa, arterial pH; Ppa, mean pulmonary artery pressure; Ppao, pulmonary artery occluded pressure; Pra, right atrial pressure; Psa, mean systemic artery pressure; PvO_2, oxygen tension in mixed venous blood; Q, cardiac index. *$P < 0.01$ versus FiO_2 0.4, same drug condition; †$P < 0.01$ versus baseline, same FiO_2.

Effects of candesartan

Haemodynamic data

There was a 17% decrease of mean Psa during FiO_2 0.4 after candesartan administration (Table 2). There was an increase in Ppa–Ppao gradient after hypoxia (Fig. 3a). Ppa–Ppao gradient was not influenced after candesartan during increased FiO_2 or in hypoxia (Fig. 3a). Hypoxic response was not influenced after candesartan (Fig. 3b).

Plasma renin activity and angiotensin II immunoreactivity

Plasma renin activity and angiotensin II immunoreactivity increased in the systemic and pulmonary circulations during hypoxia and after candesartan during FiO_2 0.4 (Fig. 4).

Discussion

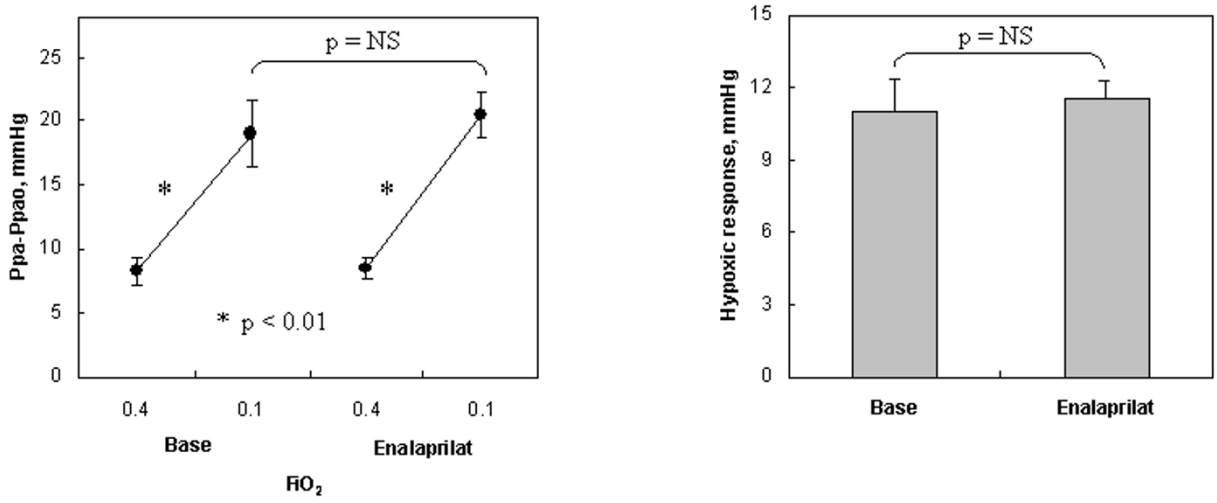
The present results show that, in anaesthetized dogs, ACE inhibition or AT_1 receptor blockade did not affect pulmonary vascular tone during increased FiO_2 or in hypoxia, although measurements of plasma renin activity and angiotensin II immunoreactivity suggested activation of the rennin-angiotensin system during hypoxia and effective blockade of the renin-angiotensin cascade with enalaprilat and candesartan. These data do not support a role for endogenous angiotensin II in acute HPV in intact dogs.

Pulmonary vascular resistance (PVR) in intact animals and in humans is commonly evaluated by the calculation of Ppa minus Ppao divided by Q. This method is based on the assumptions that the Ppa–Ppao/Q relationship is linear and passes through the origin. The latter is in fact incorrect when the lungs are diseased and/or hypoxic [19-21]. When the extrapolated pressure intercept of the Ppa/Q plots (i.e. the closing pressure of the pulmonary vessels or their effective downstream pressure) exceeds Ppao, the calculation of PVR cannot discriminate between passive (flow dependent) and active changes in Ppa. We should like to stress that, as in previous experiments, we took great care to maintain Q constant in the present study. When Q is kept constant, PVR is directly proportional to the Ppa–Ppao gradient [19-21]. In contrast, in the large series of published studies on angiotensin II in HPV, this methodology was used only by Murray and coworkers [6,7]. Whether angiotensin II is a mediator of HPV is controversial. Berkov [29] found that angiotensin II was the only mediator involved in HPV in isolated rat lungs, whereas McMurtry [30] showed in the same model that angiotensin II was not required for HPV. Furthermore, the renin–angiotensin system has been shown to be activated [31,32], unaltered [10,13], and depressed [18] during hypoxia. Finally, inhibition of the renin–angiotensin cascade inhibited HPV in some [8,10,13] but not all [15,17,18] studies.

As mentioned in the Introduction section (see above), part of the controversial variety in the reported data concerning the possible role of angiotensin II in HPV can be accounted for by the important variability in hypoxic response between the studied species (mice, rat, cat, dog and human) [1,2,4]. There also exists a large variety in the experimental models used to study the pulmonary vasoreactive response. The experimental model itself is a key factor in interpreting findings: intact animals are different from isolated organs and more so from isolated vessels. In this regard, additional weight is given to our data because of the use of the intact dog model, which reflects in a realistic manner the hypoxic pulmonary vascular response in humans [2,4]

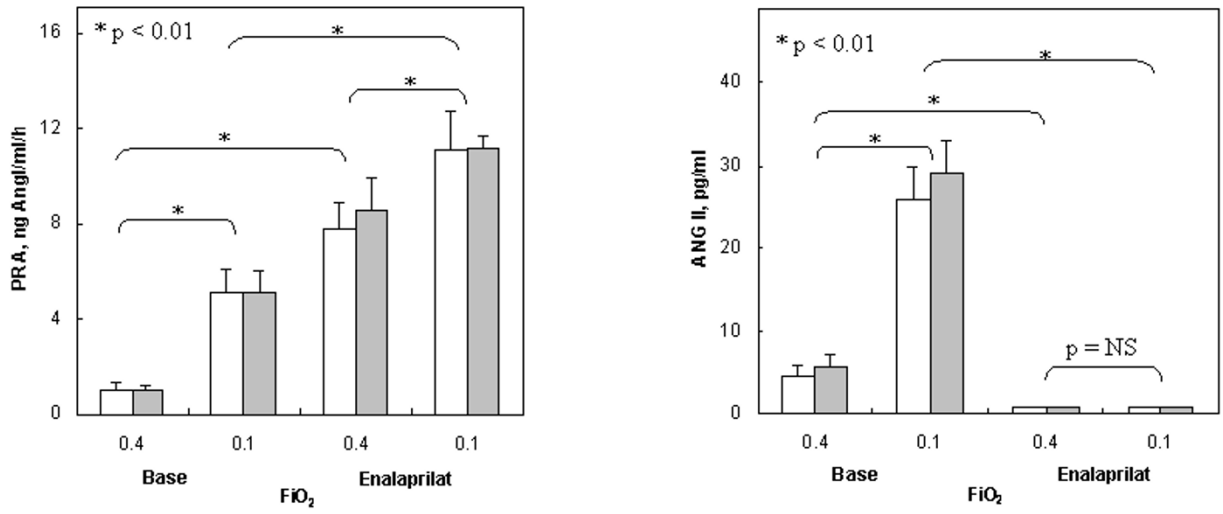
Our findings clearly show that neither ACE inhibition nor AT_1 receptor antagonism attenuated HPV, which is in accordance with previous studies using captopril [15], saralasin [17] and

Figure 1



(a) Transpulmonary pressure gradient in the enalaprilat group. Mean pulmonary artery pressure (Ppa) minus occluded pulmonary artery pressure (Ppao) at constant cardiac output in 10 dogs as the fractional inspired oxygen (FiO_2) was decreased from 0.4 to 0.1, before (base) and after administration of enalaprilat. **(b)** Hypoxic response in the enalaprilat group. Hypoxic response defined as the increase in the gradient between Ppa and Ppao measured at constant cardiac output in response to a reduction in FiO_2 from 0.4 to 0.1 at baseline (base) and after administration of enalaprilat in 10 dogs. In both panels the vertical bars indicate the standard error of the mean.

Figure 2



(a) Plasma renin activity (PRA) in the enalaprilat group. PRA in mixed venous (white columns) and arterial (gray columns) blood during fractional inspired oxygen (FiO_2) 0.4 and during FiO_2 0.1 before (base) and after administration of enalaprilat in 10 dogs. **(b)** Angiotensin II immunoreactivity in the enalaprilat group. Angiotensin II (ANG II) immunoreactivity in mixed venous (white columns) and arterial (gray columns) blood during FiO_2 0.4 and during FiO_2 0.1 before (base) and after the administration of enalaprilat in 10 dogs. In both panels the vertical bars indicate the standard error of the mean.

Table 2

Effects of candesartan in six dogs

Parameter	Baseline		Candesartan	
FiO_2	0.4	0.1	0.4	0.1
Q (l/min per m^2)	4.1 ± 0.1	4.3 ± 0.3	4.05 ± 0.1	4.4 ± 0.3
Ppa (mmHg)	12 ± 1	21 ± 1*	12 ± 1	22 ± 2*
Ppao (mmHg)	4 ± 1	3 ± 1	4 ± 1	3 ± 1
Psa (mmHg)	121 ± 3	126 ± 4	101 ± 2 +	116 ± 5†
HR (beats/min)	123 ± 8	157 ± 8*	115 ± 6 +	145 ± 8*
pHa	7.39 ± 0.01	7.40 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
PaO_2 (mmHg [kPa])	271 ± 4 (36 ± 0.5)	31 ± 3* (4 ± 0.4)	254 ± 4 (34 ± 0.5)	27 ± 3* (3 ± 0.4)
$PaCO_2$ (mmHg [kPa])	37 ± 1 (5 ± 0.1)	37 ± 1 (5 ± 0.1)	38 ± 1 (5 ± 0.1)	38 ± 1 (5 ± 0.1)
PvO_2 (mmHg [kPa])	52 ± 1 (7 ± 0.1)	22 ± 2* (3 ± 0.3)	50 ± 2 (7 ± 0.3)	21 ± 1* (3 ± 0.1)

Data are presented as mean ± standard error of the mean. FiO_2, fraction of inspired oxygen; HR, heart rate; $PaCO_2$, carbon dioxide tension in arterial blood; PaO_2, oxygen tension in arterial blood; pHa, arterial pH; Ppa, mean pulmonary artery pressure; Ppao, pulmonary artery occluded pressure; Pra, right atrial pressure; Psa, mean systemic artery pressure; PvO_2, oxygen tension in mixed venous blood; Q, cardiac index. *$P < 0.01$ versus FiO_2 0.4, same drug condition; †$P < 0.01$ versus baseline, same FiO_2.

losartan [18] Of note, in the study conducted by Krebs and coworkers [18] plasma renin activity and plasma angiotensin II levels decreased during hypoxia in conscious dogs, which suggests inhibition of the renin–angiotensin system by hypoxia, and might explain the lack of effect of losartan on HPV.

Why enalaprilat and candesartan did not affect HPV, despite evidence of activation of the renin–angiotensin system during hypoxia in our dogs, is not clear. A tentative explanation is that hypoxia stimulates the release of pulmonary vasoconstrictors, but that their effect is largely attenuated by the concomitant release of vasodilators such as nitric oxide and prostacyclin [19-21]. In support of this hypothesis, we recently showed that the dual endothelin receptor antagonist bosentan did not inhibit HPV in dogs, but that it did so after nitric oxide synthase inhibition [21].

The absence of effect of enalaprilat and candesartan could be due to an incomplete inhibition of the renin–angiotensin system. We nevertheless believe that this system was effectively blocked, as indicated by the expected changes in plasma renin activity (increased after enalaprilat and candesartan) and in angiotensin II immunoreactivity (abolished after enalaprilat and increased after candesartan), and by the 15–17% reduction in mean aortic pressure. In addition, the results of the pilot experiments examining the dose–effect relationship of both medications support maximal inhibition of the renin–angiotensin cascade. Nyhan and coworkers [7], using pressure–flow plots in normoxic conditions, showed that angiotensin II produced pulmonary vasoconstriction in conscious as well as in dogs anaesthetized with pentobarbital. However, the pulmonary vasodilator response to captopril observed in conscious dogs was reversed to a paradoxical vasoconstriction in pentobarbital anaesthetized dogs. In the present study we cannot exclude that pentobarbital anaesthesia could have altered the response of the pulmonary circulation to enalaprilat and candesartan.

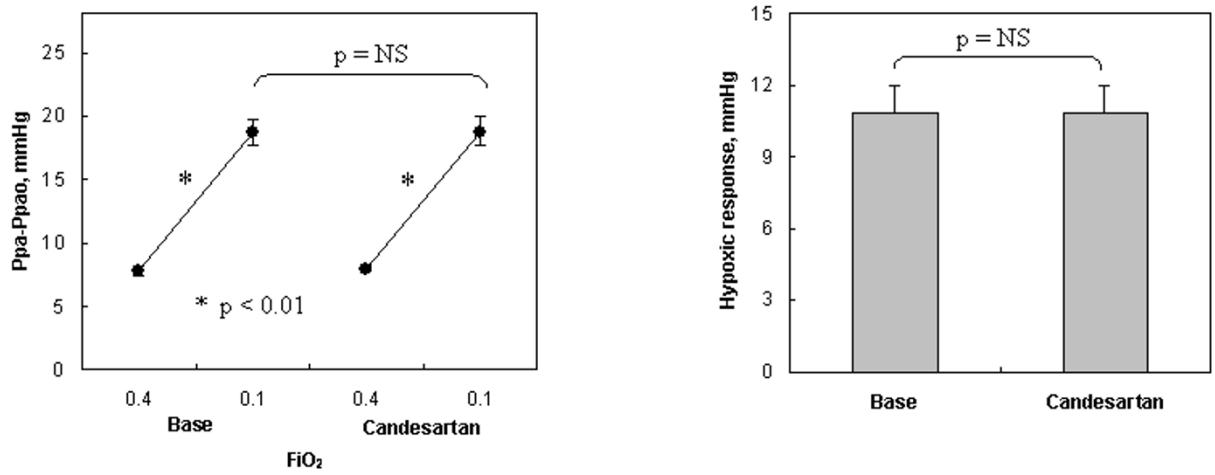
By constructing pulmonary vascular pressure–flow plots in the same experimental preparation, we previously found that the magnitude of hypoxia-induced increase in pulmonary vascular pressures was unchanged after 2 hours of pentobarbital anaesthesia [33].

Angiotensin II binds to AT_1 but also to AT_2 receptors. Absence of pulmonary vascular effect of the AT_1 receptor blocker candesartan could be due to the action of angiotensin II on AT_2 receptors. Although pulmonary and systemic vascular beds may respond differently to the same stimulus, it has been shown in the systemic circulation that none of the established cardiovascular effects of angiotensin II can be attributed to the AT_2 receptor [34]. As a matter of fact, it is well recognized, based on more recent data, that the haemodynamic effects of angiotensin II are mediated via the AT_1 receptors [35]. Moreover, experimental data showed that the AT_1 receptor was the predominant subtype in both normal and hypoxic lungs [11] and that the pulmonary vasotonic response to angiotensin II was mainly due the AT_1 subtype [36].

Conclusion

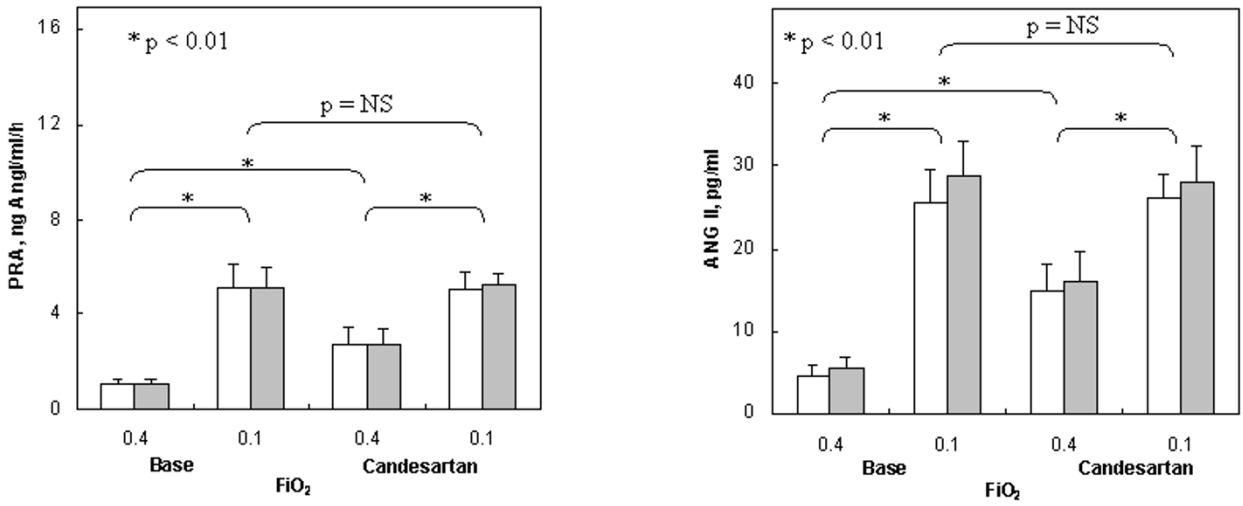
Obtained in anaesthetized dogs with intact pulmonary circulation by measuring pulmonary vascular pressures at constant flow, these data show that, although the renin–angiotensin system seemed activated during hypoxia, ACE inhibition and AT_1 receptor blockade did not attenuate HPV. This suggests that angiotensin II does not play a role in mediating hypoxic pulmonary vascular tone, at least when all counteracting

Figure 3



(a) Transpulmonary pressure gradient in the candesartan group. Mean pulmonary artery pressure (Ppa) minus occluded Ppa (Ppao) at constant cardiac output in six dogs as the fractional inspired oxygen (FiO_2) was decreased from 0.4 to 0.1, before (base) and after administration of candesartan. **(b)** Hypoxic response in the candesartan group. Hypoxic response defined as the increase in the gradient between Ppa and Ppao measured at constant cardiac output in response to a reduction in FiO_2 from 0.4 to 0.1 at baseline (base) and after administration of candesartan in six dogs. In both panels the vertical bars indicate the standard error of the mean.

Figure 4



(a) Plasma renin activity (PRA) in the candesartan group. PRA in mixed venous (white columns) and arterial (gray columns) blood during fractional inspired oxygen (FiO_2) 0.4 and during FiO_2 0.1 before (base) and after administration of candesartan in six dogs. **(b)** Angiotensin II immunoreactivity in the candesartan group. Angiotensin II (ANG II) immunoreactivity in mixed venous (white columns) and arterial (gray columns) blood during FiO_2 0.4 and during FiO_2 0.1 before (base) and after the administration of candesartan in six dogs. In both panels the vertical bars indicate the standard error of the mean.

systems are intact. This conclusion is limited to acute hypoxia, and so our findings do not exclude a role played by angiotensin II in chronic pulmonary hypertension and vascular remodelling [8,11,36,37].

Apart from (patho)physiological interest in identifying different mediators of HPV and pulmonary hypertension, results from these experiments may have clinical implications because enalaprilat and candesartan are available for use in humans.

Many patients admitted into the intensive care department (i.e. after cardiac or vascular surgery) have mild hypoxaemia due to basal atelectasis. If these patients must be treated with vasodilating drugs, which are known to worsen pulmonary gas exchange by inhibiting HPV [2], then ACE inhibitors or angiotensin II receptor blockers are a reasonable choice because these drugs should not affect HPV and hence gas exchange. Although we are not aware of a clinical study examining the effects of these compounds on gas exchange, it has been shown that nifedipine (a calcium channel blocker) but not captopril (another ACE inhibitor) reduced arterial oxygen tension significantly in patients with hypertension after abdominal aortic surgery [38]. It is evident that the results obtained from these animal experiments must be interpreted with caution because they might not fully reflect the human setting.

Key messages

1. Angiotensin II does not play a role in mediating acute hypoxic pulmonary vasoconstriction.

2. ACE inhibitors or angiotensin II receptor blockers might be a reasonale choice for treating hypoxic patients in the critical care setting since they should not affect HPV and hence gas exchange.

Competing interests

None declared.

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