Intensive Care Med (2000) 26: 292–298

ORIGINAL

M. Wenz
B. Hoffmann
J. Bohlender
G. Kaczmarczyk

Angiotensin II formation and endothelin clearance in ARDS patients in supine and prone positions

Received: 28 May 1999
Final revision received: 1 November 1999
Accepted: 15 December 1999

Supported by a grant of the Deutsche Forschungsgemeinschaft (WE 2326/1–1)

M. Wenz · B. Hoffmann
Clinic of Anesthesiology and Operative Intensive Medicine, Universitätsklinikum Charité Campus Virchow-Klinikum, Berlin, Germany

J. Bohlender
Max Delbrück Center for Molecular Medicine and Franz Volhard Clinic, Virchow-Klinikum, Humboldt-University, Berlin, Germany

G. Kaczmarczyk
AG Experimental Anesthesia, Clinic of Anesthesiology and Operative Intensive Medicine, Universitätsklinikum Charité Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany
e-mail: gabriele.kaczmarczyk@charite.de
Tel.: + 30-450-510 22
Fax: + 30-450-519 02

Abstract *Objective*: In patients with acute respiratory distress syndrome (ARDS), the prone position may enhance oxygenation by changing ventilation/perfusion ratio. In this study, we investigated whether the prone position affects the net balance between pulmonary endothelin (ET-1) and angiotensin II (Ang II) production and clearance, two metabolic functions of lung endothelial cells.
Setting: Anaesthesiological intensive care unit of a university hospital.
Patients: Ten ARDS patients (Murray score > 2.5) were studied in both the supine position (SP) and the prone position (PP).
Measurements and design: Blood samples were taken simultaneously from the patient in SP for assessment of mixed venous and arterial ET-1 and Ang II concentrations, and plasma renin concentration (PRC). This was repeated after 60 min in SP, immediately after turning the patient into PP, and 60 min thereafter. Net arterial/mixed venous ET-1 clearances and net Ang II formations were calculated.
Results: arterial oxygen tension increased from SP to PP by an average of 60 mmHg, about 20 %. Arterial ET-1 concentrations of ARDS patients were 1.57 ± 1.1 pg/ml (mean ± SD) and within the range of healthy persons. Net ET-1 clearances were negative in SP, indicating pulmonary release of ET-1, and did not change in PP. Arterial Ang II concentrations (73 ± 56 pg/ml) as well as PRC (126 ± 85 pg/ml) were markedly elevated. Net transpulmonary Ang II formation did not change.
Conclusion: Acute changes of oxygenation in ARDS patients by positioning do not induce any short-term effects on pulmonary ET-1 net clearance or Ang II net formation.

Key words ARDS (acute respiratory distress syndrome) · Angiotensin II (Ang II) · Renin-angiotensin system (RAS) · Endothelin (ET-1) · Prone position · ICU patients

Introduction

The clearance of endothelin-1 (ET-1) and the formation of angiotensin II (Ang II) are important metabolic functions of lung endothelial cells. ET-1 and Ang II are both strong endogenous vasoconstrictors. Angiotensin I is converted into Ang II by the pulmonary endothelial converting enzyme (ACE) [1]. Endothelin I–III are mainly expressed [2] and removed [3, 4] in the lung. In the acute respiratory distress syndrome (ARDS), pulmonary ET-1 extraction has been reported to be impaired and ET-1 to be released from the injured lung [5, 6], while Ang II formation is claimed to remain unchanged [7]. The prone position enhances oxygenation in approximately 75 % of ARDS patients by improving the distribution of ventilation-perfusion ratios through-

Table 1 Clinical characteristics of study patients

Patients	age	sex	diagnosis or risk factor for ARDS	additional organ failures	Murray Score[a]	SAPS Score[b]	outcome
1	26	f	pneumonia (Staphylococcus aureus)	none	3.75	17	survived
2	54	m	pneumonia (Legionella)	none	2.75	15	survived
3	31	m	pneumonia (Pneumococcus)	none	3.75	18	survived
4	43	m	pneumonia (Varicella)	kidney	3.75	21	died
5	21	m	multiple trauma, lung contusion	none	2.5	20	survived
6	23	f	multiple trauma, lung contusion	kidney	3.75	16	survived
7	34	m	pneumonia, sepsis	none	3.0	23	survived
8	59	f	multiple trauma, lung contusion	kidney, liver	2.75	16	survived
9	32	f	peritonitis, sepsis	none	3.5	15	survived
10	39	f	pneumonia, sepsis	liver	3.25	19	survived

[a] The severity of ARDS was determined immediately before the study as described by Murray et al. [13]
[b] The simplified APACHE II Score was determined also before the study as described by LeGall et al. [14]

out the lung [8] and by a reduction of the pulmonary shunt [9]. In this study, we investigated whether the prone position affects the net balances between pulmonary ET-1 synthesis and clearance and Ang II production and clearance. This was done in order to find out whether a change in position alters the pattern of vascular perfusion modifying the amount of vascular surface areas available for interaction with ET-1 and Ang II. The hypothesis was that improved oxygenation may be paralleled by improved metabolic lung function. As the plasma renin activity has been reported to be increased in intensive care unit (ICU) patients [10, 11, 12], we also investigated whether the high renin in these patients may be due to a decreased Ang II formation by pulmonary disease.

Methods

The following studies were done with approval by the institutional ethics committee. The ten study patients were transferred from other hospitals to our unit for therapy of severe ARDS. None of the patients had a history of previous lung disease. The events which had led to the development of the ARDS as well as additional demographic data are shown in Table 1. The time intervals between the acute onset of the disease and the study period differed from 48 h to 33 days. Diagnosis of severe ARDS was obtained by clinical and radiological signs, using the Murray score [13]. For general classification, SAPS was used (Table 1) [14].

After transfer to the ICU, all patients received standard treatment as described elsewhere [15] including continuous infusion of furosemide. Monitoring of patients included a thermodilution pulmonary artery catheter (Model 93A-431–7.5F, Baxter Healthcare, Irvine, Calif.). Systemic arterial pressure and pulmonary arterial pressure were measured with disposable quartz transducers (Abbott Laboratories, Chicago, Ill.) and monitored (Model 66 S, Hewlett Packard, Böblingen, Germany). Heart rate was measured by ECG (Hewlett Packard). Cardiac output was measured by thermodilution (Baxter Explorer, Cardiac Output Computer, Baxter Healthcare) and taken as the mean value of four measurements. Cardiac output measurements were performed in the supine position 60 min before positioning (SP–60), immediately before (SP 0), and immediately after the positioning manoeuvre to the prone position (PP 0), and after 60 min in the prone position (PP + 60). Systemic and pulmonary vascular resistances were calculated using standard formulas. Pressure-controlled mechanical ventilation with 10–17 cm H_2O positive end-expiratory pressure (PEEP) and a maximum inspiratory peak pressure less than 40 cm H_2O was performed with a Servo 900 C ventilator. Ventilator settings were kept constant. After each measurement in the supine and prone positions, arterial and mixed venous blood samples for blood gas and hormonal analyses were taken, strictly simultaneously. We measured plasma concentrations of ET-1, renin (PRC), angiotensinogen (Ao), Ang II, and blood gases. Arterial blood gas analyses were performed by measuring the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), and pH using standard blood gas electrodes (ABL 300, Radiometer Copenhagen, Denmark). For PRC, Ao, Ang II and ET-1 measurements, blood was collected in precooled Na-EDTA tubes, centrifuged at 4 °C, and stored until analysis. Commercially available radioimmunoassay kits were used to measure PRC (Renin aktiv III. Generation, Sanofi Diagnostics Pasteur, Freiburg, Germany) (intra-assay coefficient of variation 0.6–4.5 % and inter-assay coefficient of variation 2.7–14.5 %), and Ang II (Euro-Diagnostica, Arnhem, Netherlands) (intra-assay coefficient of variation 3.9–8.6 % and inter-assay coefficient of variation 2.5–8.3 %). ET-1 was measured by a commercially available ELISA (Biomedica, Vienna, Austria) (intra-assay coefficient of variation 13.5 % and inter-assay coefficient of variation 15 %).

In the ELISA used in the present study, ET-1 does not need to be extracted (in comparison to a conventional RIA). The cross reactivity is 100 % for ET-1, 100 % for ET-2, < 5 % for ET-3, < 1 % for Big Endothelin (1–38), and < 1 % for Big Endothelin (22–38). The assays were run in duplicate, but values exceeding the assay variability were repeated. Ao was measured by a modified Tree method described elsewhere in detail [16]. Intra-assay and inter-assay coefficient of variation were 10–15 %. The transpulmonary plasma Ang II concentration gradient was defined as the difference between arterial and mixed venous plasma Ang II concentrations (pg/ml). The net transpulmonary Ang II formation (ng/min)

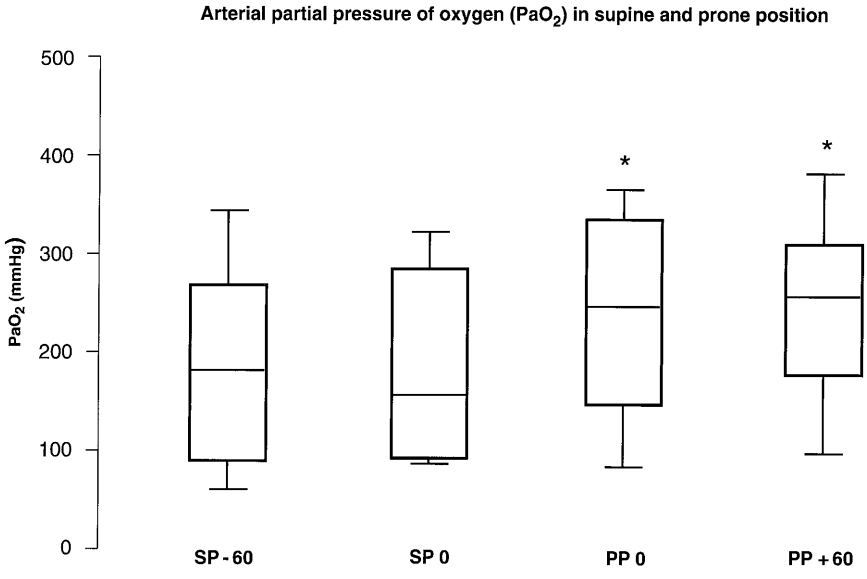

Fig. 1 Arterial partial pressure of oxygen (PaO_2) in the supine and prone positions. Box plots ± SD, $n = 10$ ARDS patients. * $P < 0.05$ refers to SP 0. *SP–60*, *SP 0* supine position 60 min and 0 min before positioning, respectively; *PP 0*, *PP + 60*, prone position 0 min and 60 min after positioning, respectively

was calculated by the transpulmonary Ang II gradient multiplied with the cardiac output (l/min). The transpulmonary plasma ET-1 concentration gradient was defined as the difference between mixed venous and arterial plasma ET-1 concentrations (pg/ml). The net transpulmonary ET-1 clearance (ng/min) was calculated by the transpulmonary ET-1 gradient multiplied with the cardiac output (l/min). Hemodynamic data were monitored continuously and sampled every 20 s (CMS Patient Monitoring System, Hewlett Packard, Bad Homburg, Germany). Pulmonary capillary wedge pressure was measured 60 min before, immediately before, immediately after and 60 min after positioning.

For statistical analysis, *t*-tests for paired samples were used to compare PRC and Ao in SP–60 and PP + 60. An analysis of variance (ANOVA) for correlating samples (repeated measurements) was used to compare blood gases, hormonal data and hemodynamics before (SP 0) and after positioning (PP 0 and PP + 60). Then, *t*-tests for paired samples were performed to compare SP 0 and PP 0 and SP 0 and PP + 60, respectively, with Bonferroni corrections for *P* values. Bivariate correlations were performed with Pearson's correlation coefficient. *P* values less than 0.05 were regarded as statistically significant. All statistics were done by means of the superior performing software systems (SPSS version 7.5).

Results

Hemodynamics and blood gases

Heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), and systemic vascular resistance (SVR) did not change (Table 2). Mean pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) increased in PP, whereas pulmonary vascular resistance (PVR) did not change (Table 2). PaO_2 increased considerably in PP 0 and PP + 60 (Fig. 1), PvO2 showed a tendency to increase in PP 0 and PP + 60 (n. s., Table 2). $PaCO_2$ increased and pH decreased in PP + 60 due to a decrease in tidal volume (VT) and in minute volume (MV) (Table 2). Peak airway pressure (PIP), mean airway pressure (MIP), and PEEP did not change (Table 2). Calculated total compliance (C) and pulmonary shunt (Qs/Qt) did not change (Table 2).

Angiotensin II

Arterial Ang II ranged between 20 and 269 pg/ml and did not change in PP. Mixed venous Ang II ranged from 14 to 172 pg/ml in SP and did not change in PP. Arterial Ang II values were at all times higher than mixed venous values (Table 3). Ang II gradients and cardiac output (CO) did not change (Table 3). Net Ang II formations did not change (Table 3; for individual values see Fig. 2).

Endothelin-1

Mixed venous ET-1 ranged from 0.58 to 3.66 pg/ml in SP and did not change in PP. Arterial ET-1 ranged from 0.72 to 4.1 pg/ml in SP and did not change in PP. ET-1 gradients, and net ET-1 clearances did not change in PP and SP (Table 3). For individual values of clearances see Fig. 3.

Renin-angiotensin system (RAS)

PRC ranged between 38 and 268 pg/ml in SP (mean 126 ± 85) and did not change in PP. Ao ranged between 1.55 and 5.1 μg Ang I/ml in SP (mean 3.02 ± 1.17) and did not change in PP.

Table 2 Hemodynamic parameters, arterial blood gases, and parameters of mechanical ventilation in supine position 60 min (SP 60) and immediately (SP 0) before turning the patient into the prone position, immediately in prone position (PP 0) and 60 min after positioning manoeuver (PP 60): heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), systemic vascular resistance (SVR), mean pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), partial pressures of mixed venous oxygen (PvO_2), arterial carbon dioxide ($PaCO_2$), pH, tidal volume (VT), minute volume (MV), peak airway pressure (PIP), mean airway pressure (MIP), positive end-expiratory pressure (PEEP), calculated compliance (C), and calculated shunt (Qs/Qt). $\bar{x} \pm SD$, $n = 10$ patients, * $p < 0.05$ refers to SP 0

	SP 60	SP 0	PP 0	PP 60
HR (beats/min)	117 ± 18	115 ± 17	118 ± 17	120 ± 16
MAP (mm Hg)	88 ± 16	88 ± 15	90 ± 14	86 ± 12
CVP (mm Hg)	11 ± 2	11 ± 2	14 ± 3	14 ± 2
SVR ($dyn \cdot s \cdot cm^{-5}$)	786 ± 279	792 ± 307	761 ± 307	729 ± 300
PAP (mm Hg)	33 ± 5	32 ± 5	37 ± 5*	37 ± 4*
PCWP (mm Hg)	12 ± 2	12 ± 2	15 ± 2*	16 ± 2*
PVR ($dyn \cdot s \cdot cm^{-5}$)	219 ± 113	205 ± 109	212 ± 88	217 ± 101
PvO_2 (mm Hg)	44 ± 8	45 ± 8	49 ± 9	51 ± 11
$PaCO_2$ (mm Hg)	51 ± 14	52 ± 14	56 ± 18	60 ± 20*
pH	7.4 ± 0.01	7.37 ± 0.12	7.38 ± 0.11	7.34 ± 0.13*
VT (ml)	680 ± 217	667 ± 197	618 ± 184*	598 ± 179*
MV (ml/min)	10.8 ± 3	10.7 ± 3	9.8 ± 2.8*	9.2 ± 2.6*
PIP (cmH_2O)	35 ± 3	35 ± 3	35 ± 3	35 ± 3
MIP (cmH_2O)	25 ± 3	25 ± 3	25 ± 3	25 ± 3
PEEP (cmH_2O)	16 ± 3	16 ± 3	16 ± 3	16 ± 3
C (ml/cmH_2O)	38 ± 19	38 ± 20	35 ± 18	34 ± 18
Qs/Qt (% of CO)	39 ± 10	39 ± 9	36 ± 9	37 ± 10

Table 3 Arterial (art) and mixed venous (mv) plasma angiotensin II concentrations (Ang II), differences between arterial and mixed venous plasma concentrations (Ang II gradients), cardiac outputs (CO), and net transpulmonary angiotensin II formations (Ang II formations = Ang II gradients multiplied with CO); plasma endothelin concentrations (ET-1), differences between mixed venous and arterial plasma concentrations (ET-1 gradients), and net transpulmonary endothelin clearances (ET-1 clearances = ET-1 gradients multiplied with CO). Values of ARDS patients are given in supine position 60 min (SP-60) and immediately (SP 0) before turning the patient into the prone position, immediately in prone position (PP 0) and 60 min after positioning manoeuver (PP + 60). $\bar{x} \pm SD$, $n = 10$ patients, * $p < 0.05$ refers to arterial values

	SP-60	SP 0	PP 0	PP + 60
Ang II art (pg/ml)	73 ± 56	87 ± 81	76 ± 55	77 ± 51
Ang II mv (pg/ml)	56 ± 45*	55 ± 36*	53 ± 36*	53 ± 28*
Ang II gradients (pg/ml)	17 ± 15	32 ± 50	23 ± 21	24 ± 25
CO (l/min)	8.4 ± 2.3	8.4 ± 2.4	8.7 ± 2.5	8.7 ± 2.6
Ang II formations (ng/min)	143 ± 139	269 ± 504	200 ± 218	209 ± 289
ET-1 mv (pg/ml)	1.37 ± 0.85	1.73 ± 0.9	1.38 ± 1.02	1.54 ± 0.75
ET-1 art (pg/ml)	1.57 ± 1.1	1.85 ± 1.16	1.6 ± 1	1.58 ± 1.16
ET-1 gradients (pg/ml)	–0.2 ± 0.58	–0.12 ± 0.41	–0.22 ± 0.93	–0.04 ± 0.53
ET-1 clearances (ng/min)	–1.68 ± 6.5	–1.01 ± 2.6	–1.91 ± 7.74	–0.35 ± 5

Statistical correlations

Arterial and mixed venous Ang II showed a positive correlation in supine and prone position (coefficients of correlation 0.92 to 0.98, $P = 0.002$). Arterial Ang II and PRC were positively correlated in supine and prone position (SP 60: 0.85, $P = 0.002$ and PP–60: 0.74, $P = 0.014$; Fig. 4). Mixed venous Ang II and PRC were also positively correlated in supine and prone position (SP–60: 0.79, $P = 0.006$ and PP + 60: 0.77, $P = 0.009$). There were no correlations between ET-1, PaO_2, hemodynamics, or components of the RAS. Neither PRC nor Ang II were correlated with haemodynamics or PaO_2.

Discussion

This study was performed to find out whether net Ang II formation and net ET-1 clearance as components of the metabolic lung function are changed in ARDS patients before and after positioning manoeuvre to the prone position, a standard treatment of severe lung injury. The results show that the prone position has neither influence on plasma concentrations of Ang II and ET-1, nor on net pulmonary Ang II formation or ET-1 clearance.

Arterial/mixed venous ET-1 ratio was greater than unity indicating pulmonary ET-1 production or reduced

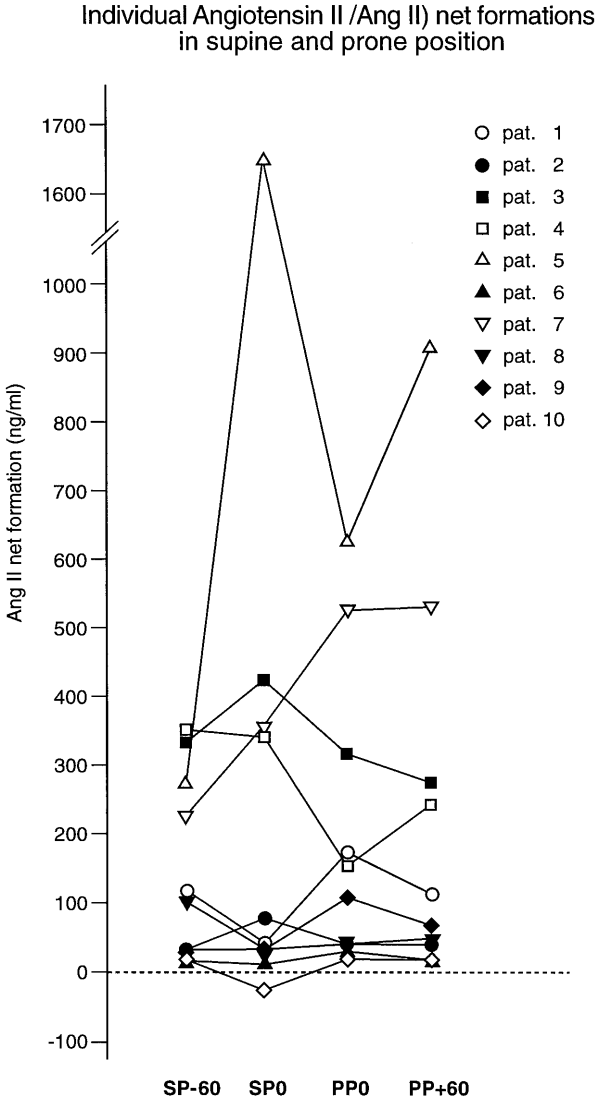

Fig. 2 Individual angiotensin II (Ang II) net formations in the supine and prone position. Values of ten ARDS patients. Ang II net formation (ng/min), the amount of transpulmonary Ang II, is the difference between arterial and mixed venous plasma Ang II concentrations (pg/ml) multiplied with the cardiac output (l/min). *SP–60*, *SP 0* supine position 60 min and 0 min before positioning, respectively; *PP 0*, *PP + 60*, prone position 0 min and 60 min after positioning, respectively

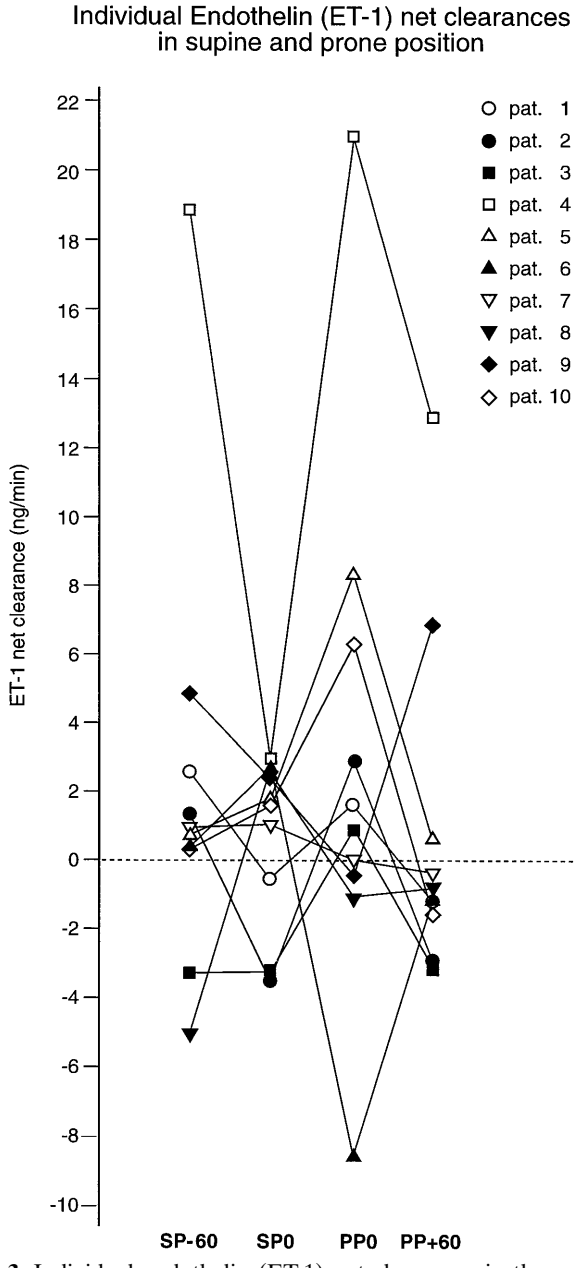

Fig. 3 Individual endothelin (ET-1) net clearances in the supine and prone position. Values of ten ARDS patients. ET-1 net clearance (ng/min) is the difference between mixed venous and arterial plasma ET-1 concentrations (pg/ml) multiplied with the cardiac output (l/min). *SP–60*, *SP 0* supine position 60 min and 0 min before positioning, respectively; *PP 0*, *PP + 60*, prone position 0 min and 60 min after positioning, respectively

clearance function of the damaged lung (Table 3). In our study, one patient had a very high ET-1 clearance (patient 4, Fig. 3) due to an increased mixed venous/arterial ET-1 gradient and increased CO. This patient had a varicella pneumonia, a high SAPS score, and a negative outcome (patient 4, Table 1). Another patient had a lower ET-1 clearance than the others (patient 6, Fig. 3) due to a low mixed venous/arterial ET-1 gradient and low CO. This patient had a multiple trauma with lung contusion, low SAPS score, and survived (patient 6, Table 1). Both patients had high lung injury scores (Table 1), but it cannot be explained why they reacted differently compared to the other patients. However, in contrast to results from another study [5], ET-1 plasma

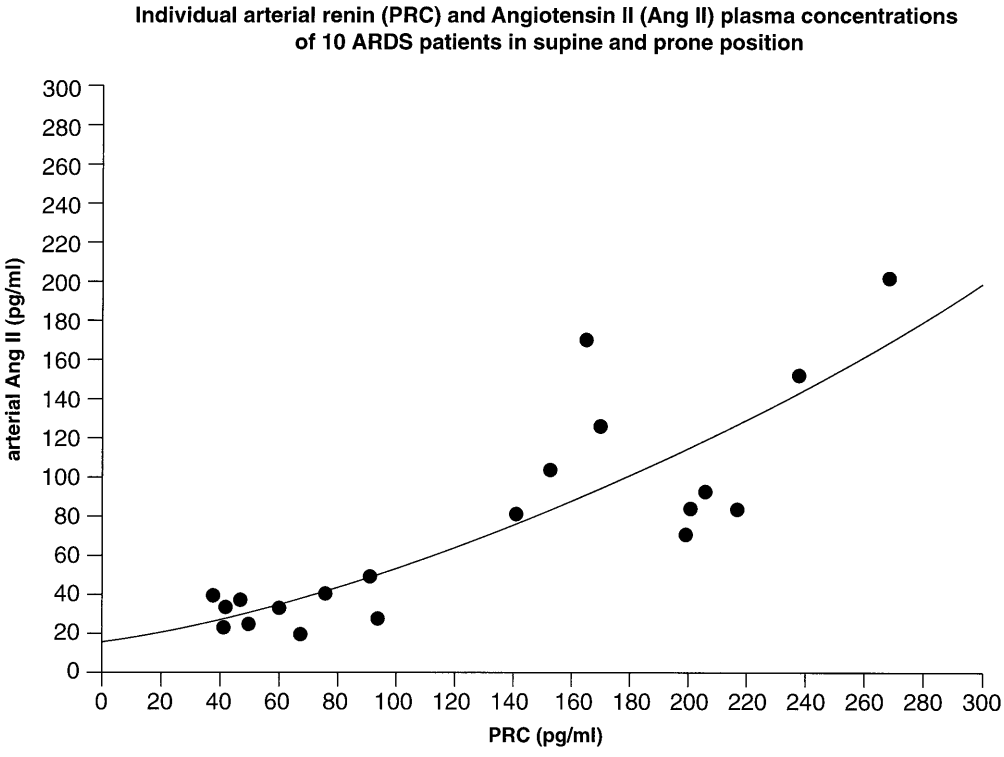

Fig. 4 Individual arterial renin (PRC) and angiotensin II (Ang II) plasma concentrations of ten ARDS patients in the supine and prone position

concentrations were not increased above normal in our ARDS study patients, though the patients in the present and the other study [5] were comparable. The difference between the present and the other study [5] is most likely due to different ET-1 measurement. We used an enzyme-linked immunosorbent assay (ELISA) because this allows, by means of a competitive antibody technique, the measurement of active ET-1 only without inactive metabolites. Therefore our values are most likely lower than the values measured by the radioimmunoassay (RIA) used in the other study [5].

In another study in patients with acute lung injury, the authors used an RIA plus antibody technique and measured elevated ET-1 levels combined with abnormal ET-1 metabolism in the very beginning of the disease and in later normalization in patients who recovered [6]. This may be in line with our data, because all the patients investigated in our study were transferred from other hospitals to our unit. Therefore we were not able to investigate the onset of respiratory failure.

In this study, plasma renin *concentrations* were measured in ARDS patients. The advantage of the direct measurement of renin in comparison to the plasma renin activity, which measures in vitro Ang I, is the quantification of *plasma* renin concentration. PRC and, in accordance, Ang II, were considerably increased: PRC 12-fold and Ang II sevenfold relative to control values of healthy volunteers on a normal dietary salt intake (unpublished data). The most likely mechanisms for extreme renin release in these patients are the increased sympathetic stimulation, catecholamine therapy, and diuretic therapy with furosemide [17] as discussed earlier in detail [18]. The increase in intrathoracic pressure by PEEP ventilation, which is followed by the unloading of intrathoracic baroreceptors, is also a well-known stimulus for the renin-angiotensin system [19]. In the present study, PEEP values between 10 and 17 cm H_2O were most likely a strong stimulus for renin release.

Arterial and mixed venous Ang II plasma concentrations were correlated throughout the study protocol. Arterial Ang II plasma concentrations were always greater than mixed venous concentrations, indicating continuous pulmonary Ang II formation in spite of lung disease as described earlier in respiratory failure [7] and ARDS [18].

In the present study, one patient had an extremely elevated Ang II formation (patient 5, Fig. 2) due to considerably increased Ang II plasma concentrations. This patient had a multiple trauma with lung contusion, a high SAPS score (patient 5, Table 1), and also increased renin values (data not shown) indicating increased activity of the renin-angiotensin system.

PRC and arterial Ang II were significantly correlated in our study (Fig. 4). The positive correlation between PRC and Ang II leads to the conclusion that in these patients reduced Ang II formation is not a stimulus for renin release.

For the first time, Ao was measured systemically in ARDS patients. Ao plasma concentrations were elevated above normal, but less than PRC and Ang II. Therefore neither a lack of Ao, caused for example by liver damage, nor extremely increased Ao plasma concentrations were additional mechanisms for renin release in the ARDS patients investigated.

Oxygenation improved in PP in most patients (Fig. 1). $PaCO_2$ increased gradually and pH decreased due to a relative hypoventilation by smaller VT and MV in PP (Table 2). The increases of PAP and PCWP (Table 2) can be explained by the increases of extramural pressures in PP, but were of no haemodynamic relevance, for CO (Tables 2, 3) and PVR (Table 2) did not change. In contrast to results from other authors [9] pulmonary shunt did not change in the present study. It has to be taken into consideration that oxygenation improved in spite of a relative alveolar hypoventilation. The enhancement of oxygenation in PP is therefore most likely due to changes in ventilation–perfusion ratios throughout the lung.

We conclude from the present study that the acute increase of PaO_2 in ARDS patients in the prone position is not paralleled by changes in net Ang II formation and net ET-1 clearance. Improved oxygenation was not paralleled by improved metabolic lung function.

Acknowledgements We thank Birgit Brandt and Daniela Bayerl for technical assistance and the medical staff of the intensive care unit for support.

References

1. Stewart TA, Weare JA, Erdös EG (1981) Purification and characterization of human converting enzyme (kininase II). Peptides 2: 145–152
2. Barnes PJ (1994) Endothelins and pulmonary diseases. Brief review. J Appl Physiol 77(3): 1051–1059
3. De Nucci G, Thomas R, D'Orleans-Juste P, Antunes E, Walder C, Warner TD, Vane JR (1988) Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci USA 85: 9797–9800
4. Dupuis J, Stewart DJ, Cernacek P, Gosselin G (1996) Human pulmonary circulation is an important site for both clearance and production of Endothelin-1. Circulation 94: 1578–1584
5. Druml W, Steltzer H, Waldhäusl W, Lenz K, Hammerle A, Vierhapper H, Gasic S, Wagner OF (1993) Endothelin-1 in adult respiratory distress syndrome. Am Rev Respir Dis 148: 1669–1673
6. Langleben D, Demarchie M, Laporta D, Spanier AH, Schlesinger RD, Stewart DJ (1993) Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. Am Rev Respir Dis 148: 1646–1650
7. Wiberg-Jørgensen F, Klausen NO, Hald A, Quist J, Giese J (1983) Pulmonary angiotensin II production in respiratory failure. Clin Physiol 3: 59–67
8. Pappert D, Rossaint R, Slama K, Grüning T, Falke KJ (1994) Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 106: 1511–1516
9. Lamm WJE, Graham MM, Albert RK (1994) Mechanisms by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 150: 184–193
10. Hilgenfeld U, Kienapfel G, Kellermann W, Schott R, Schmidt M (1987) Renin-angiotensin system in sepsis. Clin Exp Hypertens 9: 1493–1504
11. Marik PE (1993) Low-dose dopamine in critically ill oliguric patients: the influence of the renin-angiotensin system. Heart Lung 22: 171–175
12. Staroukine M, Devriendt J, Decoodt P, Verniory A (1984) Relationships between plasma epinephrine, norepinephrine, dopamine and angiotensin II concentrations, renin activity, hemodynamic state and prognosis in acute heart failure. Acta Cardiol 39: 131–138
13. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138: 720–723
14. LeGall J-R, Loirat P, Alperovich A, Glaser P, Granthil C, Mathieu D, Mercier P, Thomas R, Villers D (1984) A simplified acute physiology score for ICU patients. Crit Care Med 12: 975–977
15. Lewandowski K, Pappert D, Kuhlen R, Rossaint R, Gerlach H, Falke KJ (1996) Klinische Aspekte des akuten Lungenversagens des Erwachsenen (ARDS). Anaesthesist 45: 2–18
16. Bohlender J, Ménard J, Wagner J, Luft FC, Ganten D (1996) Human renin-dependent hypertension in rats transgenic for human angiotensinogen. Hypertension 27: 535–540
17. Waterbury LD, Thayer RR, Roszkowski AP (1980) Drug effects on plasma renin activity in the mouse. J Cardiovasc Pharmacol 2: 165–173
18. Wenz M, Steinau R, Gerlach H, Lange M, Kaczmarczyk G (1997) Inhaled nitric oxide does not change transpulmonary angiotensin II formation in patients with acute respiratory distress syndrome. Chest 112: 478–483
19. Hemmer M, Viquerat CE, Suter PM, Vallotton MB (1980) Urinary antidiuretic hormone excretion during mechanical ventilation and weaning in man. Anesthesiology 52: 395–400