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Hormonal modifications in patients admitted to an internal intensive care unit for acute hypoxaemic respiratory failure

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To clarify which endocrine modifications can be observed in acute hypoxaemic respiratory failure, 15 severely ill male patients [PAT; median age: 61 (range: 48 years); median height: 173 (range: 12) cm; median mass: 73 (range 31) kg] were investigated immediately upon admission to an intensive care unit (ICU) for this clinical disorder. Before starting treatment, the blood gases were measured and a number of selected hormones with special relevance for an ICU setting were determined. These are known to be modified by acute hypoxaemia in healthy subjects and to possess glucoregulatory properties, or an influence upon cardiocirculation or the vascular volume regulation: insulin, cortisol, adrenaline, noradrenaline, atrial natriuretic peptide, renin, aldosterone, angiotensin converting enzyme, and endothelin-I (ET). To elucidate whether potential endocrine changes resulted from acute hypoxaemia alone, the underlying disease, or unspecific influences connected with the ICU setting, all measurements were compared to those of a completely healthy reference group (REF) with comparable acute experimental hypoxaemia. The latter state was achieved by having the REF breathe a gas mixture with the oxygen content reduced to 14% (H).

In the REF, neither the medians nor the distribution of endocrinologic measurements were modified significantly by acute hypoxaemia. In the PAT, the medians were increased considerably, yet with a slight diminution of ET. The distribution of individual values was considerably broader than in the REF with H.

In conclusion, considerable increases in the means of the above hormones, with the exception of ET, can be registered in severely ill patients admitted to ICUs with acute hypoxaemic failure. However, such modifications cannot be considered attributable exclusively to acute arterial hypoxaemia. The underlying clinical disorders, such as septicaemia or an unspecific endocrine epiphenomenon, including severe and not only hypoxaemic stress, seem to be predominant.

Introduction

A multitude of recent studies have reported on hormonal modifications associated with various severe non-endocrine clinical disorders, such as cardiocirculatory failure or other forms of shock (1–5).

Acute hypoxaemic respiratory failure, i.e. 'hypoxic' hypoxaemia (Barcroft), is one of the most frequent severe clinical conditions seen in internal intensive care units (ICUs). A wide variety of effects on the cardiopulmonary system, as well as on other organs and tissue, associated with acute arterial hypoxaemia have been reported in the literature (6). Among these, there are also various endocrine modifications (7–11). However, the majority of findings on cardiocirculation and gas exchange, as well as endocrinologic reports, pertaining to acute hypoxaemia have been gathered in healthy subjects at high altitude (12–14). Not surprisingly, the author of a well-known handbook on pulmonary medicine has pointed out that the 'understanding of the effects (of acute hypoxaemia) is derived from studies conducted primarily in normal humans (. . . and that) they may be different in diseased humans' (6).

Aims of the Study

This study intended to clarify whether modifications in the blood levels of the catecholamines, atrial natriuretic peptide, endothelin-I, cortisol, insulin, c-peptide, renin, aldosterone and angiotensin-

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Table 1 Age, physical characteristics and clinical diagnoses of the patients

Patient no.	Age (years)	Mass (kg)	Height (cm)	Clinical diagnoses
1	52	89·2	171	*Hypoxaemia. Pneumonia. Septicaemia.* Reconvalescence phase after chemotherapy for AML.
2	33	58·0	168	*Hypoxaemia. Pneumonia. Septicaemia.* Positive HIV-serology, endocarditis.
3	63	60·1	167	*Hypoxaemia. Pneumonia.* Chronic renal failure.
4	47	67·0	177	*Hypoxaemia. Pneumonia.* Reconvalescence after aortic valvular replacement.
5	73	64·0	173	*Hypoxaemia. Pneumonia.* Intrapulmonary and skeletal metastases of unknown primary tumour.
6	36	64·0	172	*Hypoxaemia. Pneumonia. Septicaemia.* Positive HIV-serology.
7	50	83·0	177	*Hypoxaemia. Pneumonia. Septicaemia.* Diabetes mellitus II.
8	51	75·0	172	*Hypoxaemia. Pneumonia.* Coronary heart disease.
9	69	73·0	170	*Hypoxaemia. Pneumonia.* Intrathoracic aneurysm of the aorta.
10	61	70·0	175	*Hypoxaemia. Pneumonia.*
11	64	92·0	173	*Hypoxaemia. Pneumonia.* Ipsilateral intrapulmonary tumour.
12	41	77·3	175	*Hypoxaemia. Pneumonia. Delirium tremens with alcohol withdrawal.* Congestive cardiomyopathy.
13	67	82·0	178	*Hypoxaemia. Pneumonia.* Coronary heart disease.
14	62	75·6	170	*Hypoxaemia. Pneumonia. Intoxication with a benzodiazepine, aspiration of sputum. Septicaemia.*
15	81	85·0	166	*Hypoxaemia. Pneumonia. Septicaemia. Bleeding from a colonic diverticula.* Coronary heart disease.
$\tilde{x}$	61	73	173	
R	48	31	12	

Acute clinical disorders on admission in italic type; chronic diseases in regular type.

converting enzyme were associated with acute arterial hypoxaemia of the 'hypoxic' type (Barcroft), based on respiratory failure in pulmonary intensive care patients. The hormones investigated possess a special relevance for an ICU setting; they are known to be modified by acute hypoxaemia in healthy subjects and to possess either glucoregulatory properties, or an influence upon cardiocirculation or the vascular volume regulation.

In addition, this study intended to clarify whether such endocrine modifications resulted from acute arterial hypoxaemia alone, or could also be attributed directly to the underlying disease or to other unspecific influences connected with admission to the ICU.

Patients, Test Persons and Experimental Procedure

Fifteen male patients (PAT) admitted to an internal ICU for acute hypoxaemic respiratory failure were included in the study. Their age, physical characteristics and clinical diagnoses of acute and chronic diseases are given in Table 1. Physical examination, pulmonary infiltrates in the chest X-rays and microbiological investigations conducted in blood or sputum had indicated that the leading diagnosis was pneumonia. Hypoxaemia was therefore attributed to acute respiratory failure. No recent blood gas measurements had been performed in any of the patients prior to admission to the ICU. Since the leading clinical symptom of dyspnoea had existed for no longer than 24 h prior to clinical admission in every case, arterial desaturation was characterized as *acute* hypoxaemia.

Immediately upon admission to the ICU and well before any treatment was started, including the administration of oxygen, artificial ventilation or sedation, the following diagnostic measurements were performed. The blood gases were measured and a number of selected endocrinologic and metabolic variables were determined in venous blood samples, with the patients breathing normal air (see Methods) and resting in a supine position. In addition, heart rate was registered with an ECG, and blood pressure was measured with a sphygmomanometer. The pertinent results will not be discussed in detail in this paper unless of *immediate* interest for the topic of this investigation.

In order to be able to pursue the second aim of this investigation, a reference group of completely healthy, non-smoking test persons was also investigated. Gender, age and physical characteristics of the reference group [REF; median age: 25 (range: 10) years; median height: 180 (range: 16); median mass: 70 (range: 43) kg] were chosen explicitly to resemble

groups of subjects which had been investigated previously in experiments on acute hypoxaemia at high altitude and upon which the present pertinent knowledge is predominantly based (6). The members of the reference group were free of cardiopulmonary disease and relevant allergies, and had shown normal results in spirometry and blood gas analysis.

In random order and in a single-blind experimental setting, the REF were to breathe normal air on 1 day (N; FiO_2: 0·21) and a gas mixture with reduced oxygen content on another day (H; FiO_2; 0·14) (15). On both test days, the respective inspiratory gases were applied to REF, who also rested in a supine position, in a single-blind fashion under normal ambient pressure over 60 min. For this purpose, a face mask with unidirectional inspiratory and expiratory valves was used. Thus on H day, acute arterial desaturation was produced experimentally and was assigned uniformly to the 'hypoxic' type of acute hypoxaemia (Barcroft classification). In the REF, those laboratory variables which had already been assessed in the patients (see next section) were determined under fasting conditions in the last 10 min of this period.

Methods

In 5-μl samples of arterial blood from the a. radialis or the a. brachialis ('Arterial canula with FloSwitch®', Ohmeda; Swindon, U.K.), the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), and pH values were determined, taking into consideration the individual body temperature and using a polarographic microanalyser (AVL 939; Bad Homburg, Germany).

Duplicate measurements of the following hormones were performed in blood samples taken from the antecubital vein through an indwelling catheter (Abbocath®), using commercially available radioimmunoassays: Insulin (INS; Pharmacia, Freiburg, Germany), C-peptide (CP; Diagnostic Products, Los Angeles, U.S.A.), cortisol (CORT; Travenol Baxter, Unterschleissheim, Germany) (16), atrial natriuretic peptide (ANP, ITS, Wijchen, The Netherlands) (17), renin (PRA; Serono, Freiburg, Germany) and aldosterone (PA; Biermann, Bad Nauheim, Germany). For the determination of endothelin-I (ET), blood from the cubital vein was collected in ice-chilled ethylenediaminetetraacetate-coated tubes, centrifuged at 1500 *g* for 20 min, and the plasma frozen at − 70°C until analysis. Endothelin-I was extracted via SepPak C18 cartridges (Waters, Millipore; Marlboro, U.S.A.) and measured with an endothelin-sensitive radioimmunoassay (Biomedica, Vienna, Austria). The ET antibody has a cross-reactivity <1% with its precursors, big endothelin, C-terminal hexapeptide or sarofotoxin. The activity of the angiotensin-converting enzyme (ACE) was assessed with a colorimetric assay (18). In addition, adrenaline (ADR) and noradrenaline (NOR) were determined radioenzymatically (19).

The intra-assay coefficients of variation were 7·0% for the ADR method, 5·0% for NOR, 8·0% for the CORT assay, 5·8% for the INS assay, 2·0% for the CP assay, 8·6% for the ANP assay, 12·0% for the PRA assay, 9·8% for the PA assay, 8·2% for the ACE method and 10·0% for the ET assay. Blood counts were also performed in the venous blood samples for the determination of the leucocyte count. Lactate (LA) and glucose (GLU) were determined enzymatically in the arterial blood samples (20).

All data were calculated as medians ($\tilde{x}$) and ranges (R). In a descriptive, explorative approach, non-parametrical statistical comparisons were conducted between the medians of the measurements referring to the PAT and the REF using U-tests. Measurements in the REF were compared between N day and H day using Wilcoxon's matched pairs signed rank tests. The level of statistical significance was set at $a=0{\cdot}05$. Statistical symbols: $*P<0{\cdot}05$; $**P<0{\cdot}01$; $***P<0{\cdot}001$.

The experiments were approved by the Committee for Ethics in Medicine of Frankfurt University and informed consent was obtained from the subjects.

Results

In the PAT, the median of PaO_2 amounted to 58·0 (range: 31·6) mmHg and differed significantly, yet only by a slight margin, from the medians of the REF on H day with 50·6 (range: 11·5) mmHg (**), but was clearly reduced compared to the normal median values of the REF on N day with 95·2 (range: 16·0) mmHg (***) (21). The corresponding median values of the haemoglobin-O_2-saturation (SaO_2) were 87·2 (range: 37·4) % in the PAT and 85·3 (range: 8·7) % in the REF on H day, and 97·8 (range: 2·1) % on N day. The medians for PaO_2 and SaO_2 in the REF seen on H day were reduced significantly compared to N day (***, respectively), and corresponded to prior measurements conducted under similar experimental conditions (22). The median of the $PaCO_2$ in the PAT was 38·9 (range: 17·2) mmHg and did not differ significantly from the medians in the REF group, which were almost similar between both test days with 39·2 (range: 13·3) mmHg during H and 40·3 (range: 12·0) mmHg during N. In the REF, one individual measurement was lower than 35 mmHg on

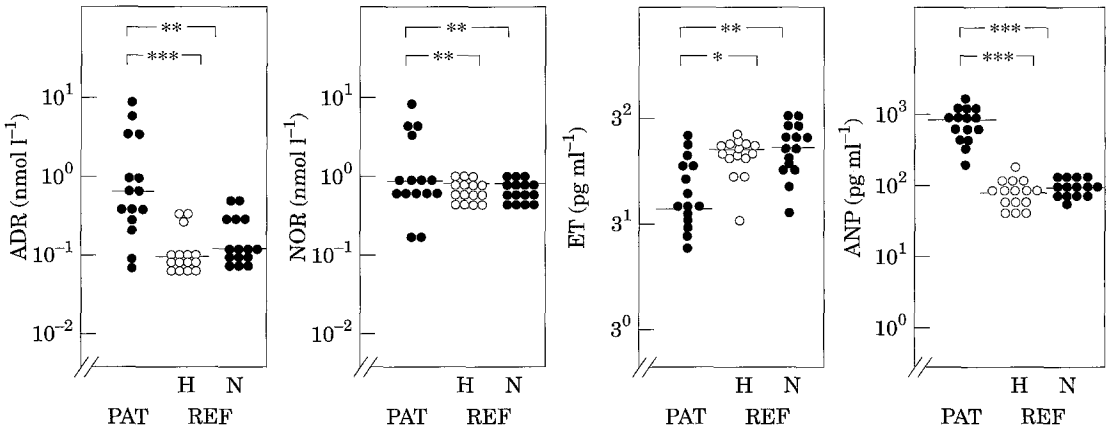

Fig. 1 Comparisons of adrenaline (ADR), noradrenaline (NOR), endothelin-I (ET) and atrial natriuretic peptide (ANP) between the groups of the acutely hypoxaemic patients (PAT) and the reference group (REF) on H day (H) and on N day (N), respectively. The horizontal lines in the scatter plots indicate the positions of the medians. See text for statistical symbols. Note that logarithmic scales were used on the ordinate.

each test day. The median pH values were normal and did not differ significantly between the PAT with 7·435 (range: 0·280) and the values of the REF with 7·435 (range: 0·108) on H day, nor with 7·410 (range: 0·088) on N day (21). The variability of the blood gas measurements in the PAT was higher than in the REF.

In the REF, all endocrinologic measurements were within the normal limits of the authors' laboratory and none of the hormones nor ACE was modified by H (Figs 1 and 2). In contrast, in the PAT, the medians of all endocrinologic measurements, with one exception, were elevated significantly when compared to those of the REF on either test day (Figs 1 and 2). The augmentations of the medians were 1·8-fold for ADR, 1·3-fold for NOR, 5·4-fold for INS, 18·8-fold for CP, 11·9-fold for ANP, 9·0-fold for PRA, 3·0-fold for PA, 8-fold for ACE and 1·9-fold for CORT compared to the REF on H day (at least * for all comparisons; Figs 1 and 2). The only exception was ET, whose median concentration in peripheral venous blood was diminished in the PAT by about 40% compared to the hypoxic REF (**); (Fig. 1). All individual endocrinologic measurements referring to the PAT group were considerably broader spread than those on the REF group. This necessitated the use of logarithmic scales in Figs 1 and 2, which tends to diminish the differences between the PAT and the REF optically.

Glucose in the PAT amounted to 157 (range: 426) mg dl^{-1} and differed significantly from the measurements in the REF with 88 (range: 27) mg dl^{-1} on N day (***) and 87 (range: 63) mg dl^{-1} (***) on H day. The median of lactate was still in the range of normality but was increased significantly in the PAT with 1·36 (range 2·93) mmol l^{-1} compared to the REF with 1·01 (range: 1·21) mmol l^{-1} on N day (***) and with 0·86 (range: 1·11) mmol l^{-1} on H day (***). The leucocytes were elevated significantly in the PAT with 16·3 (range: 18·0) μl^{-1} compared to the REF with 5·5 (range: 3·9) μl^{-1} on N day (***) and with 5·9 (range: 4·2) μl^{-1} on H day (***).

The median heart rate amounted to 115 (range: 62) beats min^{-1} in the PAT and was elevated significantly compared to the REF with 68 (range: 51) beats min^{-1} on N day and 71 (range: 35) beats min^{-1} on H day (*** for both comparisons). Systolic blood pressure amounted to 120 (range: 85) mmHg in the PAT and 125 (range: 30) mmHg in the REF on N day, as well as 130 (range: 10) on H day, without any statistically significant differences between the medians. In the PAT, the lowest measurement was 95 mmHg. Diastolic blood pressure was 80 (range: 64) mmHg in the PAT and 80 (range: 20) mmHg in the REF on N day and 85 (range: 10) mmHg on H day, again without any significant differences between the medians. The median values in the REF of glucose, lactate, the leucoytes, body temperature, heart rate, and systolic and diastolic blood pressure did not differ significantly between N day and H day.

Body temperature in the PAT was 39·4 (range: 1·4) °C, contrasting to normal values in the REF on both test days, without exception.

Discussion

The findings in the patients of this investigation essentially corroborate the observation that critical

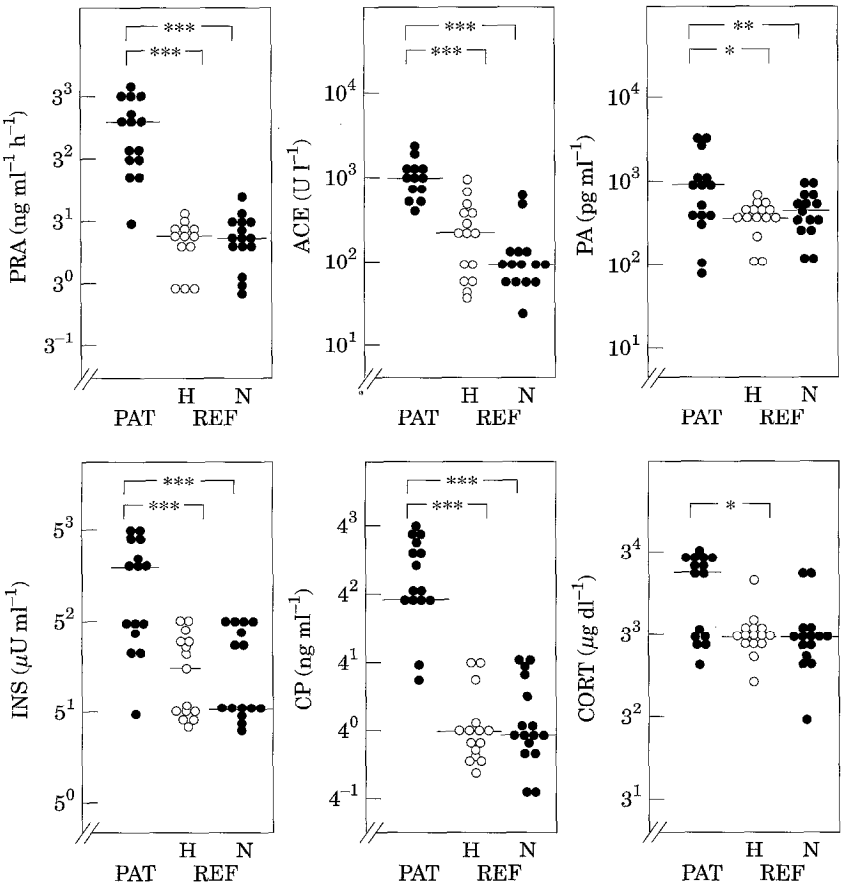

Fig. 2 Comparisons of renin (PRA), angiotensin-converting enzyme (ACE), aldosterone (PA), insulin (INS), c-peptide (CP) and cortisol (CORT) between the groups of the acutely hypoxaemic patients (PAT) and the reference group (REF) on H day (H) and on N day (N), respectively. The horizontal lines in the scatter plots indicate the positions of the medians. See text for statistical symbols. Note that logarithmic scales were used on the ordinate.

illness can be associated with sizeable modifications in the circulating hormones (23,24). However, the extent of the endocrine modifications in this study made the authors doubt that these changes could be attributed exclusively to acute hypoxaemia. In order to clarify this problem, a healthy reference group was investigated additionally with experimentally-induced acute hypoxaemia. A synoptical comparative analysis of the endocrinologic measurements in both groups investigated does not imply that the relevant modifications in the patients are attributable predominantly to acute arterial desaturation. However, since no previous endocrinologic measurements in the patients had been conducted, the data of this study do not exclude the possibility that the hormonal changes registered reflect a specific pathophysiological characteristic of the group of individuals investigated, and not of the clinical disorder its members were selected to represent. But even assuming that a pathological reaction to acute hypoxaemia might have been present in the patients, other influences, first those connected with various aspects of the *methodology* and the *experimental circumstances* of this clinical investigation, need to be considered.

Similarly to a number of studies on a variety of clinical disorders which were conducted in an intensive care setting, this investigation is afflicted with methodologic problems, in the first place connected with the process of compiling the study groups.

The patients of this investigation reflect the broad scope of cases admitted to an ICU for acute hypoxaemic respiratory failure, although not selected specifically for this purpose. This sample, however, cannot be considered 'representative' in a strict statistical sense, since data on the totality of relevant patients are not available. In contrast, the reference

group was compiled to resemble groups of subjects which had been previously investigated under experimental hypoxaemia, mostly at high altitude, and from which the current knowledge about hypoxaemia was derived. Since the normal values of those hormones which were measured are not influenced by age, or dependent on physical characteristics such as body mass or height, influences of these variables can be excluded as the causes of the endocrinologic modifications seen in the patients of this investigation or the differences between the groups. Moreover, the age characteristics of the healthy reference group primarily ruled out any potential influence of internal diseases upon the endocrine measurements in this group.

Both the raised body temperatures and the elevated white blood cell counts in the group of hypoxaemic patients prove the presence of infection, and confirm the initial radiologic and clinical diagnosis of pneumonia, i.e. a primarily respiratory origin of acute arterial desaturation. In addition, the slightly increased values of lactate in the patients compared to the normal values on both test days in the reference group, despite a comparable severity of hypoxaemia, indicate an increase in anaerobic tissue metabolism in the first group. This supports the notion that sepsis was present in some of the patients. With elevated median values for heart rate (corresponding to the increased catecholamines) in the group of patients as a whole, individual patients with septicaemia exhibited extensive tachycardia together with systolic blood pressure values in the lower range of normality. This seems to indicate that in these persons, an impairment of cardiocirculatory function, most probably of septic origin, was present. In turn, the latter also corroborates the notion of sepsis and might indicate that in these individuals, acute hypoxaemia could not only be attributable to a pulmonary impairment, but also to a cardiocirculatory impairment. The higher variability of the PaO_2 measurements in the patients additionally implies that the severity of hypoxaemia was less homogeneous than in the reference group, despite similarly reduced medians.

Although, on admission, only the clinical anamnesis with respect to the onset of dyspnoea was available to determine the duration of hypoxaemia, a synoptical analysis of other clinical symptoms pertaining to the natural course of the underlying clinical disorder also corroborates that hypoxaemia in the patients had set in acutely, i.e. during the day upon which the investigation was started. The somewhat dissimilar duration of acute hypoxaemia in the patients and the reference group cannot be considered a relevant influence upon the endocrinologic differences between the groups. In particular, those hormones which are known to reflect various kinds of stress, e.g. the catecholamines and cortisol, are known to react very rapidly (within a few minutes) to relevant stimuli. However, in the reference group, these hormones were not modified with acute hypoxaemia of the severity and the duration seen in this investigation.

Moreover, although the median lactate in the reference group on N day was slightly elevated compared to H day, the difference was not statistically significant and thus the result of stochastic variation.

In summary, it seems implausible that differences in the duration or severity of acute hypoxaemia between the test persons and the patients could alone account for the sizeable endocrinologic dissimilarities between the groups.

The measurements of $PaCO_2$ and pH prove that a ventilatory or an acid-based influence upon the medians of the hormones, especially upon the catecholamines (25,26), can be ruled out in the reference group. Neither do ventilatory and acid-base modifications suffice to explain the vast extent of the endocrine modifications seen in the patients.

Elevated levels of the catecholamines have been registered previously in patients with *chronic* pulmonary failure (27). Since adrenaline and noradrenaline were not modified by acute hypoxaemia in the reference group, it seems implausible that differences between them and the patients could account for the sizeable endocrine dissimilarities between the groups, for example, via hormonal interactions (28). However, the elevated levels of adrenaline in particular, together with the increased concentrations of cortisol in the patients of this study can be interpreted as signifying severe mental, in addition to hypoxaemic, stress. The augmented median concentrations of insulin and c-peptide in this group basically coincide with elevated median concentrations of blood glucose, the main stimulus of basal insulin secretion. The elevated median glucose concentrations in turn can be attributed to the increases in the medians of cortisol and the catecholamines (29). However, the vast increase in the median insulin levels could also be compatible with a resistance to insulin, which has been registered previously with acute infections (30), similar to the one seen in the patients of this study.

The augmentation of the median levels of ANP supports findings on a modification of the peptide's concentrations caused by acute damage to pulmonary tissue as well as reports about modifications of the peptide seen with decompensated obstructive

pulmonary disease (31,32). The sizeable increases in the median of this peptide would also match the increases in the medians of renin and aldosterone, together with those of the median of ACE in the acutely hypoxaemic patients, since a functional interaction of the peptide with these hormones has already been registered in patients with obstructive lung disease (33,34) and in hypoxaemic test persons (35). Therefore, the increases in ACE seen in this investigation reflect the presence of pulmonary inflammation most plausibly (36). Both in contrast to the measurements in the hypoxaemic test persons of this study and to previous clinical observations on acute and serious infections (37), and despite its documented role in the pathophysiology of some pulmonary diseases (38), the concentrations of ET measured in the peripheral venous blood of the hypoxaemic patients of this investigation were not increased. However, about 80% of ET production is supposedly released abluminally, with the peptide acting primarily as an autocrine-signalling factor promoting local vasoconstriction, and 20% is secreted intravasally. Furthermore, there is a high clearance rate of unbound ET in the lung and in the kidneys. Endothelin-I concentrations are highest at their site of secretion and thus are locally active as a vasoconstrictor. Therefore, it must be assumed that ET measured in a peripheral vein only reflects a local spill-over and thus is not representative of the total ET production.

In summary, the endocrine reactions encountered in the hypoxaemic patients of this investigation must be assumed to represent a mixture of various influences. However, the experimental part of this investigation implies that acute hypoxaemia of the severity and duration registered in these patients seems to play a subordinate role, if any at all, for the endocrine modifications. Since the presence of acute infection was proven in the patients, at least some of the endocrine modifications in this group can be attributed directly to septicaemia, which is also the primary cause of the acute arterial hypoxaemia in this investigation (39). However, the above constellation in the hypoxaemic patients, especially with respect to the catecholamines, strongly suggests the additional presence of an unspecific endocrinologic epiphenomenon associated with admission to the ICU, such as severe mental stress. This last condition is one which all endocrinologic investigations on critically ill patients can be assumed to be afflicted. In this investigation, the phenomenon became clearly evident and demonstrable only through the additional investigation of a hypoxaemic reference group under similar experimental conditions.

More indirectly, the results of this clinical investigation suggest that since hormones determined in critically ill patients at an ICU are largely subject to a variety of unspecific influences, their diagnostic value under these circumstances, especially in non-endocrine disease, will have to be critically reappraised. In addition, in this study the endocrinologic measurements conducted in the healthy test persons with acute experimental hypoxaemia cannot serve as a model for the pertinent reactions in the severely ill patients admitted to an ICU for acute hypoxaemia. This study also supports the notion that hormones measured in healthy hypoxaemic subjects can serve only as a yardstick for the normal endocrine acclimatization reaction to acute *pure* 'hypoxic' hypoxaemia.

Conclusions

In conclusion, considerable increases in the catecholamines, ANP, renin, aldosterone, ACE, insulin, c-peptide and cortisol along with a slight decrease in ET levels in peripheral blood can be registered in severely ill patients admitted to an ICU for acute hypoxaemic respiratory failure. However, such modifications cannot be considered to be exclusively attributable to acute arterial hypoxaemia. The underlying clinical disorder, such as septicaemia, or an unspecific endocrine epiphenomenon associated with admission to an ICU, such as severe stress, seem to be of major importance for these endocrine modifications.

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