# Metabolic acidosis and ventilatory response

Langbroek, Aart Jan Mattheüs

## SUMMARY

In terrestrial vertebrates lung ventilation is necessary to accomplish exchange of oxygen ($O_2$) and carbon dioxide ($CO_2$) between the gas phase (lung alveoli) and the fluid phase (the blood flowing through the lung capillaries). The ventilatory control system adjusts the arterial carbon dioxide tension ($P_{CO2}$) and oxygen tension ($P_{O2}$) to normal values. Carbon dioxide being a volatile acid challenges the acid balance of the body and the acid-base state of the blood. The acid balance of the body and acid-base state of the blood are also challenged by non-volatile acids. These are mainly end products of metabolism: phosphoric acid ($H_3PO_4$), sulphuric acid ($H_2SO_4$) and organic acids. The acid-base state of the blood is determined by pH, $P_{CO2}$ and the bicarbonate concentration of plasma ($c^p_{HCO3^-}$); the three quantities are interrelated according to the Henderson-Hasselbalch equation (eq. [1.1]) (chapter I).

The ventilatory control system includes the respiratory centre that generates the cyclic respiratory movements. This centre receives signals from the peripheral and central chemosensors in order to be able to respond to changes in the composition of the milieu intérieur. The peripheral chemosensors respond to changes in arterial $P_{CO2}$, $P_{O2}$ and pH. The central chemosensors respond to changes in $P_{CO2}$ and pH of the extracellular fluid of the brain.

Loading the body with an excess of non-volatile acids results in a decrease in arterial pH and $c^p_{HCO3^-}$. This state is called metabolic acidosis. The decrease in pH increases ventilation, through which the arterial $P_{CO2}$ decreases and pH is moved towards normal. This adjustment is called respiratory compensation of a metabolic acidosis. Our research deals with the time course of the respiratory compensation of a metabolic acidosis. The blood-brain barrier is a complicating factor in this compensation; this structure separates the cerebral fluid compartment from the blood compartment. Hence, metabolic changes in the acid-base state of the blood could be accompanied by delayed changes in the acid-base state of the extracellular fluid of the brain. Therefore, the blood-brain barrier might influence the time course of the ventilatory compensation during metabolic acidosis. Literature studies on this

subject point at the excistence of a delayed ventilatory response to a metabolic acidosis, but this seems to be at variance with fast transport of $H^+$ and $HCO_3^-$ across the blood-brain barrier, as is also reported in recent studies.

All experiments were carried out with unanesthetized dogs, each dog equipped with two permanent catheters: the one inserted in the aorta, the other in the pulmonary artery. This made it possible to sample blood from the aorta and to infuse fluid intravenously without disturbing the animal (chapter II). In our study the arterial $P_{CO2}$ was taken as a measure for the ventilatory adjustment. To determine ventilatory responses to disturbances of the acid-base state of the blood, the use of conscious animals is preferable, because it avoids undesired effects of narcotics on the ventilatory control system (ventilatory depression). External stimuli, however, may then disturb the experiment. In chapter III we demonstrated that renewed contact of the dogs with their keeper excited them, which leads to a higher sympathetic activation. This was concluded from the high arterial blood pressure and the high hemoglobin concentration, both decreasing when the animals calmed down. Furthermore, we showed that excitement in animals both with normal acid-base state and during metabolic acidosis was accompanied by a high arterial $P_{O2}$ and oxygen saturation ($S_{O2}$) and in acidotic dogs also with a lower arterial $P_{CO2}$. Therefore, a period of habituation was included in the protocol of each experiment. It was also shown that the time of feeding the animals is important: two hours after the intake of food a slight but significant metabolic alkalosis ($\Delta c^{p}_{HCO3^-}$ = 1.3-2.8 mmol/l) was found. This was taken into account in the protocols of the experiments described in chapters IV-VI: blood samples were taken before feeding. To avoid undesired effects of variations in the composition of the diet on the acid-base state of the blood, the animals were fed a semi-synthetic, electrolyte-poor diet (SSF), based on casein as a protein source. As the effect of this diet on the acid balance of the body and the acid-base state of the blood was not yet known, this was also investigated in this study.

The effect of administration of the semi-synthetic food, including various additions, on the acid balance of the body and the acid-base state of the blood was studied in chapter IV. In comparison to normal dog food (NAE = 1.82 $mmol \cdot kg^{-1} \cdot d^{-1}$), the semi-synthetic food exerted

a significantly larger acid load on the body, as shown by the larger net-acid excretion (NAE = 5.08 mmol·kg$^{-1}$·d$^{-1}$). This larger net-acid excretion was accompanied by a metabolic acidosis ($\Delta c^{p}_{HCO3^-}$ = -3.8 mmol/l; $\Delta$BE = -4.5 mmol/l) when no neutral sodium and potassium salts (NaCl and KCl) were added to the diet. Addition of NaCl and KCl did not result in a change in net acid excretion. However, a smaller metabolic acidosis was developed. The effect of $Na^+$ and $K^+$ on the development of the metabolic acidosis was different from what had been expected. According to the conventional theory, $Na^+$ would prevent a metabolic acidosis through exchange of $Na^+$ and $H^+$ in the distal tubules of the kidney. However, we found that the development of a metabolic acidosis was better prevented by addition of $K^+$ to the diet. On closer examination of literature data on this subject, it turned out that it has been described before that addition of $K^+$ to an intrinsically acidogenic diet may prevent the development of a metabolic acidosis and would even lead to a metabolic alkalosis. When $Na^+$ is added this alkalosis seems to disappear (fig. 4.10).

We added $CaHPO_4$ and $MgHPO_4$ to the semi-synthetic food. It is probable that both phosphate salts load the body with acid, as in the intestinal lumen phosphoric acid ($H_3PO_4$) is formed. Addition of CaO to the diet diminished net acid excretion from 5.08 mmol·kg$^{-1}$·d$^{-1}$ to 3.74 mmol·kg$^{-1}$·d$^{-1}$. This can be ascribed to a diminished formation of phosphoric acid by precipitation of $CaHPO_4$ in the intestinal lumen.

In chapter V we have described the ventilatory response during induction (3 h) and maintenance (12 h) of a metabolic acidosis. In the control experiments, in which isotonic saline solution (NaCl) and glucose were infused, hardly any change in the acid-base state of the blood was found. The stable arterial $P_{CO2}$ level in these experiments indicated that no change in the ventilatory adjustment took place. The coefficients of the fast ventilatory response (b in eq. [5.2]) during induction of the metabolic acidosis by intravenous administration of $NH_4Cl$ (b = 0.51) were not different from those during intravenous administration of HCl (b = 0.52)(table 5.3). According to literature data intravenous administration of $NH_4Cl$ would evoke a smaller ventilatory response, as the liberated $NH_3$ in the blood easily passes through the blood-brain barrier and then as a base, by uptake of $H^+$, increases the pH of the extracellular fluid of the brain. It is probable, however, that

the toxic $NH_3$ does not reach the extracellular fluid of the brain as it is rapidly metabolized with glutamate to glutamine in the astrocytes. In fact, no difference could be demonstrated between the ventilatory response to an acidosis induced by HCl or $NH_4Cl$ administration. The ventilatory response during induction of the metabolic acidosis by oral administration of HCl or $NH_4Cl$ was smaller than the response which resulted from intravenous administration.

A further increase in ventilation took place in the 12-h period after induction, during the maintenance of the metabolic acidosis: in most animals a further decrease in arterial $P_{CO2}$ was found in the same course of time (d is negative in eq. [5.3]) (table 5.5). This is in accordance with the findings of Asch et al. (J Lab Clin Med 73: 610-615, 1969). In the experiments in which the animals were fed the semi-synthetic diet (chapter IV) we demonstrated that ventilation was even more heavily stimulated when the metabolic acidosis persisted for more than 12 h. This was shown by a further decrease in arterial $P_{CO2}$ (f = 0.89, calculated according to eq. [5.4]). These findings seem not to be in accordance with the fast transport of $HCO_3^-$ across the blood-brain barrier reported in literature, which would suggest that the acid-base state of the extracellular fluid of the brain rapidly follows the changes occurring in the blood and thus lead to a fast ventilatory response.

The increase in ventilation during the 12-h period in which the metabolic acidosis persisted in the oral HCl and $NH_4Cl$ experiments and the intravenous $NH_4Cl$ experiments, is in contrast to the decrease in ventilation in that period in the experiments in which HCl was administered intravenously. This decrease in ventilation is not in accordance with the findings of Asch et al. who also induced a metabolic acidosis by intravenous administration of HCl. The discrepancy between our observations and those of Asch et al. could be the result of a single difference in experimental set-up: in our experiments the tip of the catheter was in the pulmonary artery, in the experiments of Asch et al. it was in the jugular vein. Administration of $NH_4Cl$ via the pulmonary artery resulted in the same time course of the ventilatory response as in the experiments carried out by Asch et al.. It may be expected that administration of $NH_4Cl$ is accompanied by a smaller local decrease in pH than administration of HCl. It is conceivable that the larger local decrease in pH after infusion of HCl into the pulmonary artery is the

cause of the discrepancy between our intravenous HCl experiments and those of Asch et al. and also of the discrepancy between our intravenous HCl experiments and our intravenous $NH_4Cl$ experiments.

In humans a metabolic acidosis is accompanied by an increase in plasma potassium concentration. In our dogs a hyperkalemia was also developed during induction of a metabolic acidosis (chapter VI). This increase, however, was rather rapidly followed by a decrease in potassium concentration which resulted from an increase in potassium excretion. Plasma potassium concentration was normal 12 h after induction of the acidosis; when the metabolic acidosis exists for a longer period, hypokalemia will develop. In humans, a hypokalemia is not found during chronic metabolic acidosis.

According to literature data an increase in plasma potassium concentration caused by injection of KCl leads to an increase in ventilation by stimulation of the peripheral chemosensors. This seems to be at variance with our observation that a larger initial increase in plasma potassium concentration leads to a smaller initial ventilatory response to a metabolic acidosis. An interesting observation, moreover, was that potassium depletion as developed in the experiments in which the semi-synthetic food was given without addition of neutral salts (chapter IV), inhibits the ventilatory stimulation of the metabolic acidosis ($f = 0.35$ instead of 0.89 (table 5.7)).

The plasma urea concentration decreased in the 16-h experiments during induction and maintenance of the metabolic acidosis (chapter V). In the control experiments, in which the acid-base state of the blood remained stable, the decrease in plasma urea concentration was even larger. It was also demonstrated in the feeding experiments of chapter IV that excretion of urea was not dependent on the level of acidosis. Therefore, in contrast to what is assumed by some authors, we conclude that urea synthesis is not inhibited by metabolic acidosis.