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Respiratory function and carbonic anhydrase inhibition

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Abstract. Acetazolamide (Diamox) induced carbonic anhydrase inhibition is an efficient means of eliminating surplus water and bicarbonate in the overhydrated and alkalotic patient. Previous studies have demonstrated an unexpected and unexplained increase in arterial and venous oxygenation during acute carbonic anhydrase inhibition. In the present investigation we assessed the effect of acetazolamide 15 mg kg^{-1} on pulmonary gas exchange in 10 critically ill, mechanically ventilated patients. Median arterial oxygen tension increased by 0.9 kPa and central venous oxygen tension and content by 16–18% and 6–8% respectively. The improved oxygenation could, however, not be attributed to an improved pulmonary oxygen exchange as both pulmonary venous admixture ($\dot{Q}_s\dot{Q}_t^{-1}$) and physiological dead space ventilation ($V_D V_T^{-1}$) increased. The increase in arterial oxygen tension can be explained by a rightward shift of the oxyhemoglobin dissociation curve due to the increased acidity of the blood during carbonic anhydrase inhibition (Bohr effect). Acetazolamide does not depress oxygen consumption, so the increase in central venous oxygen content probably reflects an improved cardiac performance. This could conceivably be mediated via sympathetic activation in response to acetazolamide induced carbon dioxide retention.

Key words: Acetazolamide – Arterial oxygen tension – Venous oxygen tension – Pulmonary function – Bohr effect – Haldane effect

Carbonic anhydrase inhibition with acetazolamide is an efficient means of eliminating surplus water and bicarbonate in the critically ill patient [1–4].

An unexpected, unexplained but clinically significant rise in arterial oxygen tension (P_aO_2), central venous oxygen tension (P_vO_2), and saturation (S_vO_2) have been noted in previous studies of acetazolamide in mechanically ventilated, overhydrated, alkalotic patients [5–7].

The present investigation was undertaken to elucidate the physiological events behind the improved oxygenation seen after an almost complete inhibition of the carbonic anhydrase activity in the erythrocytes.

Theoretically, the following mechanisms could be involved: a decrease in oxygen consumption ($\dot{V}O_2$) without changes in cardiac output could explain the increase in P_aO_2, P_vO_2 and S_vO_2. It has, however, repeatedly been shown that acetazolamide and carbonic anhydrase inhibition do not diminish oxygen uptake in the ventilated unconscious patient [5–6] or in healthy males [8–10].

An increase in cardiac output with a constant peripheral oxygen utilization is also an unlikely explanation of the improved oxygenation [5].

This leaves two possible unexplored mechanisms:
a) Acetazolamide and carbonic anhydrase inhibition improve the matching of ventilation and perfusion in the lungs. Alveolar-arterial oxygen tension difference ($A-aDO_2$), pulmonary venous admixture ($\dot{Q}_s/\dot{Q}_t$) and physiological dead space (V_D/V_T) are the parameters we determined to explore this possibility.
b) The increases in P_aO_2, P_vO_2 and S_vO_2 are artifacticial. Numerous investigators with different techniques have demonstrated a 50–75% increase in cerebral blood flow after acetazolamide [11–13]. In previous studies we have predominantly utilized central venous blood sampled from the superior caval vein [6–7]. Although this is normally a satisfactory method it can lead to fallacious results. If the peripheral blood flow is redistributed in such a way that the perfusion of areas drained via the superior caval vein increases, the determination of P_vO_2 and S_vO_2 in blood from the superior caval vein would

seriously overestimate the true oxygen content of mixed venous blood. In the present investigation we tried to quantitate a possible change in the distribution of cardiac output by measuring the oxygen content of blood both from the superior and the inferior caval veins during carbonic anhydrase inhibition.

Materials and methods

Ten heavily sedated, curarized and mechanically ventilated critically ill patients were investigated [mean age 43 (22–80) years, mean weight 65 (55–100) kg]. All had stable and adequate cardiovascular and renal function (normal s-creatinine concentration) throughout the study. The patients were overhydrated and alkalotic [mean BE_{ECF} 4.5 (3.6–7.3) mmol l^{-1}].

The lungs were ventilated with a Servo 900 C ventilator and expiratory carbon dioxide concentration was measured by a Siemens-Elema 930 infrared carbon dioxide analyzer. Carbon dioxide elimination per min ($\dot{V}CO_2$) was calculated by the instrument from the carbon dioxide signal and the expiratory flow signal from the ventilator [16]. The accuracy of the end-tidal carbon dioxide reading is $\pm 0.05\%$ CO_2 and of the $\dot{V}CO_2$ reading ± 10 ml min^{-1} in the 200 ml min^{-1} range. The main sources of error are rebreathing and compression of gas in the tubings, both of which lead to an overestimation of the expired carbon dioxide concentration [17]. No corrections for these errors or for the day-to-day variation in barometric pressure were considered necessary as all comparisons in this study were within the single patient.

The patients were monitored with a radial artery cannula and catheters in the superior and inferior caval veins. Blood samples were withdrawn anaerobically and simultaneously from the three catheters. Blood gases and acid-base-balance were measured and calculated in duplicate (Radiometer ABL4 blood gas analyzer). The analyses were performed after equilibrium in the CO_2/HCO_3^- system had been reached. The results would, however, only be marginally different if it were possible to determine the values in the capillaries before complete equilibration was achieved [10]. Hemoglobin concentration and oxygen saturation were measured spectrophotometrically (Radiometer OSM2 Haemoximeter).

Transcutaneous oxygen tension $TcPO_2$ was monitored continuously (Radiometer TCM2). The electrode was positioned in the infraclavicular fossa. An electrode temperature of 43 °C and a 30 min stabilization period was used [18].

Calculations

Alveolar oxygen tension was calculated from the alveolar gas equation:

$$P_AO_2 = P_iO_2 - \frac{P_ACO_2}{R} + \left(P_ACO_2 \cdot F_iO_2 \cdot \frac{1-R}{R}\right)$$

where

P_iO_2 = tension of inspired oxygen
F_iO_2 = fraction of inspired oxygen
P_ACO_2 = tension of alveolar carbon dioxide
R = respiratory gas exchange ratio.

Normally, the last factor in the equation is small, but because respiratory carbon dioxide elimination is impeded during carbonic anhydrase inhibition and a high F_iO_2 (mean 0.5) is imployed it is mandatory to use the complete alveolar gas equation to obtain an accurate estimate of P_AO_2. In a similar group of patients R was 0.77 [6], and we used this value together with the measured control $\dot{V}CO_2$ from the present study to calculate $\dot{V}O_2$ (acetazolamide does not change $\dot{V}O_2$ [5–6]). The R value, at a given time, could then be calculated from this $\dot{V}O_2$ and the measured $\dot{V}CO_2$.

Pulmonary venous admixture:

$$\dot{Q}_s\dot{Q}_t^{-1} = (C_cO_2 - C_aO_2)\ (C_cO_2 - C_vO_2)^{-1}$$

where C_cO_2, C_aO_2 and C_vO_2 are the oxygen contents of pulmonary capillary, arterial and central venous blood.

Oxygen tension corrected for the Bohr effect:

$$PO_2(corr) = \text{antilog}\ (\log PO_2 - 0.37\ (pH_{control} - pH) \quad (19)$$

Physiological deadspace:

$$V_DV_T^{-1} = \frac{F_{ET}CO_2 - (\dot{V}CO_2)/(\dot{V}_E)}{F_{ET}CO_2}$$

where $F_{ET}CO_2$ = end tidal carbon dioxide fraction and $\dot{V}_E$ = expiratory minute volume.

Procedure

After baseline determinations of hemoglobin, $F_{ET}CO_2$, $\dot{V}CO_2$, $TcPO_2$, arterial and venous blood gases and acid-base status, 15 mg kg^{-1} of acetazolamide was injected i.v. as a bolus. All measurements were repeated after 10, 20, 30, and 60 min.

Statistics

The Wilcoxon non-parametric test for paired differences was used. $p < 0.05$ was accepted as indicating a statistically significant difference.

Ethics

The rules of the Declaration of Helsinki were followed, and the investigation was approved by the Copenhagen City Ethical Committee.

Results

Arterial oxygen tension increased in all but one of the patients ($p<0.01$, Table 1) after acetazolamide, while S_aO_2 remained unchanged. Correction of the P_aO_2 values to the control pH abolished the statistically significant increase in P_aO_2 (Table 1).

The venous oxygen tension increased by 0.9 kPa ($p<0.01$) and the oxygen saturation by 6–8% ($p<0.01$) after carbonic anhydrase inhibition. The increases were equal in blood sampled from the superior and inferior caval veins (Table 1).

A-aDO_2 decreased statistically significantly by 12–19% (Table 2). $\dot{Q}_s\dot{Q}_t^{-1}$ calculated from the superior caval blood increased by 25% (statistically insignificant), while $\dot{Q}_s\dot{Q}_t^{-1}$ estimated from the inferior caval blood was constant during carbonic anhydrase inhibition (Table 2).

Transcutaneous oxygen tension increased in all patients. The median increase was maximally 3.4 kPa 30 min after acetazolamide.

End-tidal carbon dioxide concentration and $\dot{V}CO_2$ decreased in every instance (Table 3). The nadir was reached after 10 min, and the reductions amounted to 16% and 13%, respectively.

Physiological deadspace ventilation increased significantly (11–14%) in all patients after the enzyme blockade (Table 3).

Table 1. Oxygen tension (P_aO_2, P_vO_2 sup, P_vO_2 inf), oxygen saturation (S_aO_2, S_vO_2 sup, S_vO_2 inf) and arterial oxygen tension corrected for changes in pH after acetazolamide 15 mg kg^{-1} i.v.

Min	Control	10	20	30	60
	15.9	16.5[b]	16.4[b]	16.8[a]	16.5
P_aO_2 kPa	10.0–24.2	11.4–27.3	13.4–29.5	12.5–28.1	10.9–25.9
	15.9	16.0	15.4	15.8	15.6
P_aO_2 kPa corrected	10.0–24.2	10.9–26.5	12.5–28.1	11.6–26.6	9.9–24.4
	0.981	0.982	0.982	0.983	0.974
S_aO_2	0.912–0.998	0.915–0.997	0.940–0.994	0.928–0.994	0.912–0.993
	5.6	6.3[b]	6.5[b]	6.3[b]	6.6[b]
P_vO_2 sup kPa	3.8–8.3	4.5–9.4	4.7–9.8	4.4–10.1	4.2–9.1
	0.761	0.821[b]	0.815[b]	0.810[a]	0.813[a]
S_vO_2 sup	0.535–0.876	0.563–0.902	0.587–0.901	0.587–0.904	0.604–0.906
	5.0	5.5[a]	5.7[b]	5.9[b]	5.9[a]
P_vO_2 inf kPa	3.0–7.2	3.4–7.7	3.4–7.5	3.3–7.5	3.1–7.5
	0.671	0.704[a]	0.701[b]	0.713[b]	0.696
S_vO_2 inf	0.429–0.888	0.466–0.865	0.446–0.884	0.431–0.890	0.379–0.880

[a, b] significant difference from control value ([a] $p\leq0.05$, [b] $p\leq0.01$), $n = 10$. Median and range

Table 2. Alveolar oxygen tension (P_AO_2), alveolar-arterial oxygen tension difference (A-aDO_2) pulmonary venous admixture ($\dot{Q}_s\,\dot{Q}_T^{-1}$) and transcutaneous oxygen tension ($TcPO_2$) after acetazolamide 15 mg kg^{-1} i.v.

Min	Control	10	20	30	60
	38.0	38.1	37.9	37.3	38.0
P_AO_2 kPa	23.0–53.5	22.8–53.7	22.7–53.6	22.6–53.6	23.3–53.4
	19.9	17.6[b]	16.2[a]	16.6[a]	17.5
A-aDO_2 kPa	7.8–43.1	6.4–42.2	6.9–40.1	6.3–39.9	6.3–41.7
$\dot{Q}_s\cdot\dot{Q}_T^{-1}$	0.105	0.133	0.129	0.140	0.133
cava superior	0.054–0.249	0.058–0.411	0.050–0.356	0.041–0.339	0.044–0.374
$\dot{Q}_s\cdot\dot{Q}_T^{-1}$	0.085	0.081	0.085	0.085	0.080
cava inferior	0.032–0.252	0.028–0.256	0.031–0.220	0.041–0.214	0.029–0.239
	8.7	9.9[b]	11.8[b]	12.1[b]	10.0[b]
$TcPO_2$ kPa	6.1–19.8	7.1–25.3	8.0–25.0	8.3–24.1	8.0–21.8

[a, b] Significant difference from control value ([a] $p\leq0.05$, [b] $p\leq0.01$), $n = 10$. Median and range

Table 3. End-tidal carbon dioxide concentration ($F_{ET}CO_2$), carbon dioxide elimination ($\dot{V}CO_2$) and physiological dead space ($V_D \cdot V_T^{-1}$) after acetazolamide 15 mg kg^{-1} i.v.

Min	Control	10	20	30	60
	3.96	3.53[b]	3.72[a]	3.77[a]	3.96
$F_{ET}CO_2 \times 100$	3.37–4.86	2.84–4.60	3.21–5.20	3.20–5.16	3.36–5.24
	288	250[b]	260[a]	271[a]	282
$\dot{V}CO_2$ ml min^{-1}	190–371	170–317	185–374	185–351	180–350
	0.257	0.294[b]	0.285[a]	0.287[b]	0.289[b]
$V_D \cdot V_T^{-1}$	0.225–0.462	0.231–0.463	0.228–0.459	0.237–0.468	0.229–0.464

[a, b] Significant difference from control value ([a] $p \leq 0.05$, [b] $p \leq 0.01$), $n = 10$. Median and range

Discussion

The present investigation confirms that an acute and almost complete blockade (>99.8%) [10] of human carbonic anhydrase C augments arterial and venous oxygen tension and the venous oxygen content [5–7]. A decrease in A-aDO_2 normally indicates an improved matching of pulmonary blood flow and ventilation [14, 15]. However, when the oxygen content difference between arterial and venous blood is changed the shunting of venous blood through the lungs is not truthfully represented by the A-aDO_2 [20]. In our study mixed venous oxygen saturation increased by 6–8%, and in spite of this arterial oxygen saturation was constant (0.98). Furthermore, calculation of $\dot{Q}_s\dot{Q}_t^{-1}$ on the basis of central venous blood from either the inferior or the superior caval veins demonstrated that a diminished pulmonary venous admixture is unlikely.

Another index of pulmonary ventilation/perfusion matching is $\dot{V}_D\dot{V}_T^{-1}$. This parameter has not been evaluated before in patients after carbonic anhydrase inhibition. A modest but statistically significant increase in deadspace ventilation was found.

Acetazolamide does not change hemoglobin-oxygen binding characteristics [5] but a decrease in blood pH displaces the oxyhemoglobin dissociation curve to the right, and thereby increases oxygen tension at a constant oxygen saturation. This Bohr shift could explain most, if not all, of the increase in arterial oxygen tension (Table 1) but not the increase in venous oxygen content. In short it is unlikely that acetazolamide improves oxygen exchange in the lungs.

Because acetazolamide increases cerebral blood flow [11–13], without augmenting cardiac output [5], our second hypothesis was that the oxygen content of blood sampled from the superior caval vein is not representative of mixed venous blood. A decrease in perfusion of the lower part of the body would result in a decrease in venous oxygen content in the inferior caval vein and consequently the total mixed venous oxygenation would be normal.

The present investigation, however, demonstrated significant and equal increases in oxygen content in both superior and inferior caval blood (Table 1). The inferior caval catheters were placed distally to the renal and hepatic veins. Renal blood flow is not altered by acetazolamide [21]. Hepatic blood flow has not been measured during human carbonic anhydrase inhibition, but carbonic anhydrase has not been demonstrated in hepatic tissues. So the omittance of renal and hepatic venous blood in our measurements can not change the fact that mixed venous oxygen content does increase, at least temporarily, during carbonic anhydrase blockade.

The increase in mixed venous oxygen content reflects either an increase in cardiac output or the incurment of an oxygen debt. Previous studies have demonstrated a normal $\dot{V}O_2$ [5, 6] and a nearly normal maximal exercise capability [10, 22] during carbonic anhydrase inhibition, so it seems improbable that acetazolamide interferes with oxygen utilization. Cardiac output has only been estimated in one study. In six patients studied after coronary artery bypass surgery, cardiac output (thermodilution) was constant after acetazolamide [5]. All the patients were on β-blockers preoperatively, and in retrospect it can not be excluded that the apparent stability of cardiac output was due to residual β-blockade.

Transcutaneous oxygen tension increased significantly (Table 2) and much more than arterial oxygen tension (3.4 kPa vs 0.9 kPa 30 min after acetazolamide). This also clearly indicates that peripheral oxygen supply is adequate and that peripheral perfusion is enhanced.

The balance of the evidence suggests that acetazolamide increases cardiac output and consequently mixed venous oxygenation. The change could probably be mediated via sympathetic activation in response to acetazolamide induced carbon dioxide retention [23].

Carbon dioxide production in this series of patients was high. This reflects primarily the hypercatabolic state of the posttraumatic patient but also a general overestimation of $\dot{V}CO_2$ by the CO_2 analyzer

[17]. The maximum depression of median carbon dioxide elimination was 13% 10 min after acetazolamide. Until now, this has been attributed solely to the slowing of carbon dioxide hydration/dehydration after inhibition of intraerythrocytic carbonic anhydrase B and C. The present study, however, suggests an additive mechanism behind the reduction in carbon dioxide transport. The increase in mixed venous oxygen content must reduce the Haldane effect and thereby decrease carbon dioxide pickup, by the blood, from the tissues and carbon dioxide release in the lungs. One more factor should be considered. If the increase in mixed venous oxygen content is an indication of an increased cardiac performance, transport of CO_2 from the tissues would be enhanced [24]. This would, at least partially, counteract the diminished Haldane effect.

Sixty min after acetazolamide carbon dioxide elimination proceeded at a normal pace, but at the expense of an increase in the body stores of carbon dioxide and an augmented CO_2 gradient between the tissues and the alveolar air.

This study was initiated before human studies had clarified the renal and the respiratory dose-response relationships of acetazolamide. It is now clear that a dose of 5 mg kg^{-1} of acetazolamide secures maximal renal bicarbonate and water excretion and almost no interference with carbon dioxide elimination [1].

In conclusion: the injection of high doses of acetazolamide

1. increases P_aO_2 (Bohr effect),
2. decreases A-aDO_2, but oxygen exchange in the lungs is not improved,
3. increases P_vO_2 and S_vO_2 possibly due to an increase in cardiac performance,
4. causes carbon dioxide retention by the combined effects of delayed CO_2 hydration/dehydration, a diminished Haldane mechanism and increased dead space ventilation.

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