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THRESHOLDS OF RESPONSE OF THE PERIPHERAL VESSELS OF MAN TO INCREASE IN FLIGHT CARBON DIOXIDE

PROJECT NO. NA 001-032-01-09

RESEARCH REPORT

OF THE

U.S. NAVAL SCHOOL OF AVIATION MEDICINE

NAVAL AIR STATION

PENSACOLA FLORIDA
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11 pp. 2 tables 2 figures UNCLASSIFIED

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THRESHOLDS OF RESPONSE OF THE CEREBRAL VESSELS OF MAN TO INCREASE IN BLOOD CARBON DIOXIDE

Report by

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Commanding Officer

5 January 1954

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SUMMARY

1. The cerebral vascular responses in man to inhalation of 2.5% and 3.5% CO₂ have been studied in 21 subjects. The findings are compared with those obtained by others with higher concentrations of carbon dioxide.

2. The vasodilator response to increase in arterial CO₂ tension appears to be a threshold type of phenomenon. A mean increase in arterial CO₂ tension of less than 4.7 mm. Hg does not affect cerebral blood vessels; each increase above this value is associated with progressive vasodilatation. No data is available beyond an increase in pCO₂ of 14 mm. Hg. A mean increase in arterial pCO₂ of 5.5 mm. Hg produced a slight but, it is believed, physiologically significant vasodilatation.

3. With constant cerebral metabolism, a reduction in cerebral blood flow of approximately 30% would be required to raise end-capillary and venous CO₂ tension to the vasodilator threshold. It is probable that cerebral vessels dilate with a smaller reduction in blood flow, owing to the combined effects of increased pCO₂ and reduced pO₂.

4. Carbon dioxide in 3.5% concentration has little effect on the blood pressure in most patients when inhaled for periods up to 30 minutes. It produces considerably less dyspnea than 5% CO₂ and may have applications in the treatment of certain states of cerebral vascular insufficiency.

INTRODUCTION

The level of carbon dioxide in the blood is now generally accepted as one of the major factors in the regulation of the cerebral circulation. It was first shown in experimental animals that increase in blood carbon dioxide exerts a vasodilator effect on cerebral blood vessels (1,2). Similar effects were postulated in man by Lennox and Gibbs (3) on the basis of decrease in the cerebral arteriovenous oxygen difference. Conclusive evidence of the effects of carbon dioxide on cerebral blood flow in man was provided by the experiments of Kety and Schmidt with the nitrous oxide method. Reduction in arterial CO₂ through hyperventilation was shown to produce a decrease in blood flow (4), whereas increase in arterial CO₂ through inhalation of 5% and 7% carbon dioxide was found to cause a striking increase in blood flow (5).

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\(^1\)This report was supported in part by the Department of Physiology and Medicine, Emory University School of Medicine under Contract N 900-92500, Department of Medicine, Medical College of Virginia, under Contract No. HR-1134(61) and in part by a grant from the National Institutes of Health, U. S. Public Health Service. Acknowledgement also goes to the Medical Service of Grady Memorial Hospital, Atlanta, Ga.
The above observations on man, which were concerned with large-scale effects, do not in themselves permit a precise formulation of the role of carbon dioxide in the control of the cerebral circulation. The minimal changes in blood CO₂ which will evoke vascular responses must be known, together with the degrees of response which are produced by given increments of change in CO₂ beyond these threshold values. Knowledge of the minimal increase in arterial CO₂ required to dilate cerebral vessels has potential therapeutic application in the treatment of certain states of severe impairment of blood flow to the brain. Carbon dioxide in 5% or greater concentration has the disadvantages of raising blood pressure (5, 6) and producing uncomfortable dyspnea within a relatively few minutes (7). It appeared possible, however, that some lower concentration of carbon dioxide might prove more tolerable, while still retaining vasodilator properties.

The present studies were concerned with the thresholds of response of the cerebral vessels of man to increase in blood carbon dioxide. Cerebral blood flow determinations were made with the nitrous oxide method, employing concentrations of 2.5% and 3.5% CO₂ in the inspired gas. Data on the associated changes in blood gases and pH are given.

METHODS

The subjects for these studies were hospital patients convalescing from a variety of illnesses in which the brain was not involved. Seven patients were given 2.5% CO₂ and 14 patients 3.5% CO₂ in the inspired gas. The mean ages of these two groups were 32 and 36 years, respectively. Cerebral blood flow (CBF) before and during carbon dioxide inhalations was determined by the nitrous oxide method (8) with slight modifications (9). Six of the 21 patients were studied by measurements of cerebral arteriovenous gas differences alone. Cerebral oxygen consumption (CMR₂O₂) was determined from the cerebral blood flow multiplied by the cerebral arteriovenous oxygen difference, (A-V)O₂. The values for (A-V)O₂ were obtained from analyses of arterial and internal jugular blood samples drawn just before and just after the cerebral blood flow procedure and pooled. The cerebral vascular resistance (CVR) was calculated by dividing the blood flow into the mean arterial pressure, measured from either the femoral or brachial arteries with a damped mercury manometer.

Control observations of the cerebral circulation were made with the standard gas mixture for the nitrous oxide method (15% N₂O, 21% O₂, 64% N₂). Following this the patient was given a mixture containing either 2.5% or 3.5% CO₂, with 21% O₂ and the remainder N₂. At the end of 15 to 20 minutes this mixture was changed to gas containing the same percentages of CO₂ and O₂, together with 15% N₂O, and the experimental blood flow determination carried out.

The pooled blood samples of arterial and venous blood were analyzed for oxygen and carbon dioxide content by the combined procedure for these gases described by Peters and Van Slyke (10), as modified for the presence of nitrous oxide by Kety and Schmidt (8). Oxygen capacity of the blood samples was determined by the method of Roughton and Darling (11). Blood
pH was measured with a Cambridge Model R pH meter, with appropriate corrections to body temperature (12). Carbon dioxide tensions (pCO\(_2\)) were obtained from the pH, CO\(_2\) content and hematocrit by means of the nomogram of Singer and Hastings (13). Venous oxygen tension was determined from the pH and the percent of oxygen saturation, using the oxygen-hemoglobin dissociation curves of Dill (14). Observations were made on the character of the subject's breathing, but respiratory minute volumes were not measured.

**RESULTS**

Inhalation of 2.5% carbon dioxide produced very little change in the mean values of the cerebral blood flow, oxygen consumption or vascular resistance (Table I). The blood pH and gas tensions were not determined in this group, but a comparable group of 7 subjects given 2.5% CO\(_2\) for 15 minutes showed a decrease in the mean value for arterial pH from 7.37 to 7.34 and an increase in arterial pCO\(_2\) from 41.3 to 45.6 mm. Hg. Dyspnea and increase in rate or depth of the subjects' breathing were either slight or not detectable. The same concentration of carbon dioxide was also well tolerated by 10 patients with cerebral vascular accidents (7) for periods of 30 minutes to one hour.

Carbon dioxide in 3.5% concentration was associated with small but statistically insignificant increase in the cerebral blood flow (Table I). There was almost no change in either the cerebral oxygen consumption or cerebral vascular resistance. There were, however, decreases in the cerebral arteriovenous oxygen difference. The mean values of (A-V)O\(_2\) for air and CO\(_2\) breathing in the patients studied by the nitrous oxide method were 5.8 and 5.3 volumes percent, respectively. In the larger group of 14 subjects the mean value for (A-V)O\(_2\) was 6.3 volumes percent with air and 5.3 volumes percent with CO\(_2\) breathing (p = .1). Nine of these subjects showed a fall in (A-V)O\(_2\) of 0.5 volumes percent or more; four showed little change; and only one subject had an increase in this function (Table II). Changes in the blood gas tensions and pH in the five patients of the nitrous oxide group in whom these functions were studied differed only slightly from those in the larger group of nine subjects (Table II). In these nine individuals 3.5% carbon dioxide produced the following increases: arterial pCO\(_2\), 5.5 mm. Hg; jugular venous pCO\(_2\), 4.2 mm. Hg; jugular venous pO\(_2\), 4.1 mm. Hg. Arterial pH fell .04 units and jugular venous pH .03 units with this concentration of carbon dioxide.

A definite deepening and slight increase in rate of respiration was usually observed 10 to 15 minutes after onset of inhalation of 3.5% CO\(_2\). This was associated with slight dyspnea, which in a few patients had become definitely uncomfortable 30 minutes after breathing the gas mixture.

The relation on the concentrations of CO\(_2\) in the inspired gas to the cerebral arteriovenous oxygen difference is shown in Figure 1. The data for 5% and 7% CO\(_2\) are from the work of Kety and Schmidt (5). Supplementary observations made with 5% CO\(_2\) in our laboratory (7) in four patients with cerebral vascular accidents showed a decrease in (A-V)O\(_2\) only slightly less
than that observed by Kety and Schmidt in normal subjects. It is evident in Figure 1 that a rather abrupt change in the slope of the curve occurs between 2.5 and 3.5% carbon dioxide. The striking fall in the arteriovenous oxygen difference with each additional increment in the concentration of inspired CO₂ is also quite apparent.

In the present studies and those of Kety and Schmidt the cerebral oxygen remained unchanged during the inhalation of various concentrations of carbon dioxide. Since \( \text{CBF} = \frac{\text{CMRO}_2}{(A-V)O_2} \), and with \( \text{CMRO}_2 \) a constant, the blood flow in this group of subjects will vary as to reciprocal of the arteriovenous oxygen difference. The relationship between \( \frac{1}{(A-V)O_2} \) and the change in mean arterial CO₂ tension with the different inspired CO₂ concentrations is illustrated in Figure 2. The data of Kety and Schmidt in this figure show a mean increase in arterial pCO₂ of 7 mm. Hg with 5% CO₂, and 14 mm. Hg with 7% carbon dioxide. The value for \( \frac{1}{(A-V)O_2} \) abruptly rises beyond an apparent threshold value and continues to rise rapidly with further increase in pCO₂ up to 14 mm. Hg. A doubling of blood flow is predicted for a 10 to 11 mm. Hg increase in CO₂ tension. If the ascending part of the curve is extrapolated downward, it crosses the horizontal portion of the curve at 4.7 mm. Hg. A similar plot of the cerebral blood flow, determined from the nitrous oxide concentration, as a percentage of its control value yields an S-shaped curve which crosses the control level (100%) at 5.3 mm. Hg. The \( \text{CBF}_{\text{N}_2\text{O}} \) points are lower than the corresponding \( \frac{1}{(A-V)O_2} \) values in the 3.5% and 7% CO₂ observations, and higher in the case of the 5% CO₂ studies.

DISCUSSION

The findings with 2.5% CO₂ clearly indicate that the threshold for cerebral vasodilator effect lies beyond this inspired concentration and its associated mean increase in arterial CO₂ tension of 4.3 mm. Hg. This conclusion is based on the absence of changes in the cerebral blood flow, vascular resistance and arteriovenous oxygen difference.

In regard to 3.5% CO₂ the question must first be considered as to which determination possesses the greater validity, under the conditions of the present experiment, for the detection of small changes in blood flow: the cerebral arteriovenous oxygen difference or the nitrous oxide method. Actually, the validity of change in \( (A-V)O_2 \) as a measure of change in CBF rests upon the demonstration that cerebral oxygen consumption, as determined by the nitrous oxide method, is not altered by inhalation of carbon dioxide over the concentration range of 2.5 to 7%. There seems little reason to
question the constancy of the \( C_M R G_2 \) under these circumstances, since the
number of subjects in the present series combined with those studied by Kety
and Schmidt is relatively large. Random errors would tend to be averaged
out, and even systematic errors would not preclude correct conclusions re-
garding the constancy of cerebral metabolism. If the \( C_M R G_2 \) is a constant,
blood flow will vary as \( \frac{1}{(A-V)_{O_2}} \), and this function may be used as a measure
of change in flow. In a limited series of studies, such as the present
observations with 2.5 or 3.5% \( C_O_2 \), the \( (A-V)_{O_2} \) determined by Van Slyke
gasometric analysis is probably the more accurate measure of small changes
in blood flow. The nitrous oxide method in any given determination contains
more possibilities of error, since it involves multiple analyses, the
assumption of equilibrium in respect to nitrous oxide between the brain and
jugular venous blood, and other potential sources of error. In the present
studies, somewhat greater reliance will be placed on the arteriovenous
oxygen difference, although similar conclusions except for quantitative
differences can be drawn from the nitrous oxide data.

The relationships shown in Figure 2 indicate that the cerebrovascular
response to increase in arterial \( C_O_2 \) tension is a threshold type of pheno-
menon. This is demonstrated by the absence of change in \( \frac{1}{(A-V)_{O_2}} \) over the
lower range of increase in \( pC_O_2 \), then an abrupt change in the slope of the
curve followed by progressive increase in \( \frac{1}{(A-V)_{O_2}} \) with further increase in
arterial \( C_O_2 \) tension. Since mean arterial blood pressure was unaffected by
3.5% \( C_O_2 \) (Table I) and only slightly to moderately affected by 5 and 7%
\( C_O_2 \) (5), the rising curve of cerebral blood flow with increase in arterial
\( C_O_2 \) tension beyond the threshold value must have been primarily due to pro-
gressive dilatation of cerebral blood vessels.

Two types of threshold can usefully be defined for this phenomenon:
(1) that value for increase in arterial \( pC_O_2 \) below which there is no effect
on cerebral vessels and above which there is increasing cerebral vasodilata-
tion; and (2) that amount of \( pC_O_2 \) increase which is accompanied by changes
in the cerebral circulation of a significant or specified magnitude.

The probable mean threshold in the first sense can be obtained by extra-
polating the rising portion of the curve backward to its intersection with
the control (100%) level, which yields a value of 4.7 mm. Hg. The arterio-
venous \( O_2 \) difference for the 5% \( C_O_2 \) cases (mean increase in arterial \( pC_O_2 
7 \) mm. Hg) is significantly (p < 0.05) different from the control value and
falls just short of significance for the 3.5% \( C_O_2 \) group (mean increase in
arterial \( pC_O_2 \) 5.5 mm. Hg). Obviously, the nearer a point on the curve of
Figure 2 lies to the threshold value of \( pC_O_2 \) change, the less will be the
statistical significance of the corresponding \( (A-V)_{O_2} \) or \( \frac{1}{(A-V)_{O_2}} \) compared
with their control values.
The threshold in the second sense is chosen as the average increase in arterial $pCO_2$, which was produced by 3.5% carbon dioxide, namely, 5.5 mm. Hg. The conclusion that this mean increase of $pCO_2$ produced a slight but physiologically significant vasodilatation is based on several considerations.

As stated earlier, in the 14 subjects given this concentration of 3.5% $CO_2$, the arteriovenous $O_2$ difference showed a decrease in nine instances, was little changed in four, and increased in only one case. The standard errors of $\frac{1}{(A-V)O_2}$ for the points representing the mean increase in arterial $pCO_2$

produced by 2.5 and 3.5% $CO_2$ do not overlap. The p value of 0.1 falls only slightly short of significance ($p \leq 0.05$ or less). A further mean increase of only 1.5 mm. Hg was associated with a statistically significant increase in cerebral blood flow and significant decrease in arteriovenous oxygen difference (5). The 42% increase in $\frac{1}{(A-V)O_2}$ associated with 5% $CO_2$

breathing and its 7 mm. Hg mean increase in arterial $pCO_2$ is beyond the small but physiologically significant change which we are seeking. Internal jugular venous $pO_2$ was raised by 4.1 mm. Hg during the $CO_2$ breathing, a finding consistent with vasodilatation.

Although the thresholds defined above have been stated in terms of change in arterial $pCO_2$, it is possible that they actually represent thresholds for the effects of associated change in hydrogen ion or bicarbonate ion concentration. The work of Schieve and Wilson (15) appears to rule out the H-ion as a possible vasodilator, but does not eliminate the $HCO_3^-$-ion. The question must also be raised as to whether we are dealing with a "pure" $CO_2$ threshold or whether an increase in oxygen tension as a result of hyper-ventilation was a factor. Cerebral vessels are only slightly constricted by 50% oxygen (16), which should produce an arterial $pO_2$ of nearly 300 mm. Hg, calculated from the alveolar equation (17) and an assumed alveolar-arterial $pO_2$ gradient of 20 mm. of mercury. Since the inspired $pO_2$ itself was only 159 mm. Hg, the possibility that change in arterial $pO_2$ influenced the results seems remote.

The site of action of the carbon dioxide in these experiments was probably the blood vessels themselves. Although a vasodilator innervation has been demonstrated in the experimental animal (18), its functional significance for man is unknown. It is of interest that recent experiments suggest that a threshold concentration of $CO_2$ is required for respiratory stimulation (19). Observations have been made on the effect of an increase in blood $CO_2$ on other vessels of the body deprived of their vasomotor innervation. The vessels in sympathectomized upper extremities in man (20) and the hind limb vessels in dogs, given ganglionic-blocking doses of tetraethylammonium (21), respond alike by vasodilatation to an increase in blood carbon dioxide.

The $CO_2$ tension thresholds for cerebral vascular effect which have been reported in this paper are non-specific in the sense that they do not indicate which type of vessel is responding: arteries, arterioles, capillaries or venules. Since the increase in venous $pCO_2$ during 3.5% $CO_2$ breathing (4.2 mm. Hg) was almost as great as that of arterial $pCO_2$, the thresholds as
given would not be greatly different, regardless of which type of vessels is dilating. As a corollary we may conclude that, if all of these vessels are responding, the threshold is very nearly the same throughout the group. In the case of arteriosclerotic cerebral blood vessels, it might be anticipated that their threshold of response to CO₂ change is different from normal vessels. They have been shown to respond poorly to 5% CO₂ inhalation (22).

Studies on dogs by Gurdjian and co-workers (23) furnish evidence on the relationship between cerebral (A-V)O₂ and arterial pCO₂ beyond the range of 2 values available for acute experiments in man (Fig. 1). These workers found that an actual value of 70 mm. Hg arterial pCO₂ apparently was sufficient to drive the cerebral vasodilator mechanism close to its limit of response. It seems reasonable to anticipate a similar leveling off of the vasodilator response in man with progressively higher values of arterial CO₂ tension.

In the intrinsic control of the cerebral circulation, carbon dioxide and oxygen tension changes would operate simultaneously, either additively or in competition. The threshold for combined fall in pO₂ and rise in pCO₂, a situation produced by decrease in cerebral blood flow, may occur at a lower pCO₂ than the threshold reported in this paper. From the Fick equation and the blood nomogram (13), it can be shown that cerebral blood flow must fall by approximately 30% to raise venous pCO₂ to the vasodilator threshold. Actually, cerebral vessels dilate with a smaller reduction in blood flow. Studies on such combined thresholds, and on the threshold of cerebral vascular response to reduction in blood CO₂ tension, are obviously needed. The data in the existing literature on the combined effects of arterial pCO₂ and pO₂ on cerebral blood flow has recently been worked into a useful nomogram by Cannon (24).

Therapeutic applications of our findings remain to be explored. It would appear that 3.5% CO₂ may be of value in the treatment of cerebral vascular manifestations produced by a reduction in blood flow. Although more weakly vasodilator than 5% CO₂, it is considerably more tolerable from the standpoint of dyspnea and can be given for 30 minutes in most patients without producing excessive dyspnea or changes in arterial blood pressure. Its use in selected patients with cerebral vascular insufficiency seems indicated.
ACKNOWLEDGEMENTS

The technical assistance of the Misses Mary Ruth Fordham, Mary Bell, Mary Upshaw, Mary Herbert, Sallie Jones, Mrs. Louise Thompson, and Mrs. Marjorie Stephenson is acknowledged with appreciation.
REFERENCES


7. Patterson, J. L., Jr., and Heyman, A., Unpublished observations.


## Table I

Cerebral Functions and B:CO2 Studies during Air and Carbon Dioxide Breathing

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<td>1.9</td>
<td>96</td>
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<td>5.3</td>
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</table>

*Data from 7 other Control Subjects*
TABLE II

ARTERIAL AND INTERNAL JUGULAR VENOUS CARBON DIODE AND OXYGEN TENSIONS AND CEREBRAL

ARTERIOVENOUS OXYGEN DIFFERENCES WITH AIR AND 3.5% CARBON DIODE INHALATION

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Art. pCO₂ (mm. Hg)</th>
<th>Art. pH</th>
<th>Ven. pCO₂ (mm. Hg)</th>
<th>Ven. pH</th>
<th>Ven. PO₂ (mm. Hg)</th>
<th>(A-V) Oxygen Vol. %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Air CO₂</td>
<td>CO₂</td>
<td>Air CO₂</td>
<td>CO₂</td>
<td>Air CO₂</td>
<td>CO₂</td>
</tr>
<tr>
<td>C. C.</td>
<td>33</td>
<td>35 55</td>
<td>7.39</td>
<td>7.32</td>
<td>47</td>
<td>57</td>
<td>7.32  7.26 29</td>
</tr>
<tr>
<td>W. McL.</td>
<td>25</td>
<td>47 55</td>
<td>7.38</td>
<td>7.30</td>
<td>61</td>
<td>70</td>
<td>7.30  7.25 33</td>
</tr>
<tr>
<td>G. G.</td>
<td>40</td>
<td>43 55</td>
<td>7.40</td>
<td>7.36</td>
<td>52</td>
<td>55</td>
<td>7.34  7.32 34</td>
</tr>
<tr>
<td>W. M. J.</td>
<td>36</td>
<td>37 47</td>
<td>7.44</td>
<td>7.40</td>
<td>46</td>
<td>47</td>
<td>7.37  7.36 35</td>
</tr>
<tr>
<td>G. M.</td>
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<td>41 55</td>
<td>7.40</td>
<td>7.35</td>
<td>52</td>
<td>54</td>
<td>7.32  7.29 26</td>
</tr>
<tr>
<td>C. P.</td>
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<td>40 55</td>
<td>7.38</td>
<td>7.38</td>
<td>48</td>
<td>49</td>
<td>7.32  7.32 27</td>
</tr>
<tr>
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<td>42 55</td>
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<td>7.38</td>
<td>51</td>
<td>55</td>
<td>7.35  7.34 35</td>
</tr>
<tr>
<td>C. H.</td>
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<td>48 55</td>
<td>7.31</td>
<td>7.27</td>
<td>58</td>
<td>61</td>
<td>7.28  7.24 30</td>
</tr>
<tr>
<td>E. C.</td>
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<td>37 55</td>
<td>7.43</td>
<td>7.37</td>
<td>52</td>
<td>57</td>
<td>7.35  7.32 24</td>
</tr>
<tr>
<td>H. T.</td>
<td>23</td>
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<tr>
<td>R. L. D.</td>
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<tr>
<td>E. J.</td>
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<tr>
<td>H. E.</td>
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<tr>
<td>F. M.</td>
<td>22</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Mean (of first 9 patients): 36.4 41.1 46.6 7.39 7.35 51.9 56.1 7.33 7.30 30.3 34.4 6.3 5.5

Mean (of all 14): 35.9 -- -- ---- ---- ---- ---- ---- ---- ---- ---- 6.3 5.3 *

* Statistical significance of difference from mean with air: p = .1
THE RELATION BETWEEN THE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE AND THE PERCENTAGE OF CARBON DIOXIDE IN THE INSPIRED GAS
FIGURE 2
RELATION BETWEEN THE RECIPROCAL OF THE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE AND THE INCREASE IN ARTERIAL CARBON DIOXIDE TENSION

PRESENT DATA
DATA OF KETY & SCHMIDT