CHAPTER I

EFFECT OF HYPERCAPNIA AND ITS WITHDRAWAL ON BLOOD PRESSURE AND HEART.
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Despite the voluminous literature devoted to carbon dioxide, widely varying conclusions have been attained concerning the basic cardiovascular effects of the gas. Relatively low concentrations (5-10%) of carbon dioxide have caused either increase (13, 38, 99, 103, 112, 155), or decrease (14) of blood pressure. Similarly, higher concentrations of the gas (15% and above) have been shown to have both pressor (178) and depressor responses (13, 92, 155, 216).

There has been general agreement that carbon dioxide gas in high concentrations reduces the force of myocardial contraction in both the intact heart (14, 141) and the isolated heart (133, 143). All observers have noted a pronounced bradycardia following the administration of high carbon dioxide to either intact or isolated preparation, but little correlation has been made in between the heart contractility changes and the blood pressure responses to hypercapnia. In order to learn more of the physiological mechanism brought into play by hypercapnia, the experiments were designed by maintaining the duration of carbon dioxide induction constant in all phases for reevaluating the effects of hypercapnia on mean arterial pressure, heart rate and force of myocardial contraction, utilizing various animal preparations subjected to pharmacological and surgical modifications. It was of particular interest that during withdrawal of high concentration of carbon dioxide bradycardia was quickly replaced by marked augmentation in force and rate of the heart, but little change was noted in blood pressure response. This
Table 1

Changes of cardiovascular functions in cats during ventilation of 30% carbon dioxide and after washout of the gas mixture

A. Mean arterial pressure in mm Hg.

<table>
<thead>
<tr>
<th></th>
<th>Basal pressure</th>
<th>During carbon dioxide induction</th>
<th>After carbon dioxide withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneously breathing:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>118 ± 4</td>
<td>124 ± 2</td>
<td>120 ± 5</td>
</tr>
<tr>
<td>Atropinized</td>
<td>120 ± 2</td>
<td>132 ± 5</td>
<td>120 ± 2</td>
</tr>
<tr>
<td>Reserpinized</td>
<td>82 ± 4</td>
<td>76 ± 6</td>
<td>84 ± 3</td>
</tr>
<tr>
<td><strong>Open-chest force ventilated:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>84 ± 4</td>
<td>56 ± 8</td>
<td>100 ± 4</td>
</tr>
<tr>
<td>Atropinized</td>
<td>86 ± 2</td>
<td>58 ± 3</td>
<td>90 ± 6</td>
</tr>
</tbody>
</table>

B. Cardiac contractile amplitude (force) and frequency in open-chest preparations expressed as percentage of the pre-CO₂-induction control

<table>
<thead>
<tr>
<th></th>
<th><strong>FORCE</strong></th>
<th><strong>FREQUENCY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>DURING induction</strong></td>
<td><strong>AFTER withdrawal</strong></td>
</tr>
<tr>
<td>Control</td>
<td>30 ± 2</td>
<td>135 ± 5</td>
</tr>
<tr>
<td>Atropinized</td>
<td>75 ± 8</td>
<td>158 ± 5</td>
</tr>
<tr>
<td>Reserpinized</td>
<td>18 ± 4</td>
<td>180 ± 2</td>
</tr>
</tbody>
</table>

Control means normal animal which has not been treated with any drug.
Depletion of oat animals with reserpine, lx (0.1 mg/kg 48 hours, and (This dosage of reserpine depleted catecholamine stores (65.
In order to assess and after hypercapnia, saline was administered in three of the experiment phases of hypercapnia. The saline prior to administration.

Results

Effect of Carbox

The basal blood from 115 to 120 mm Hg while concentrations of carbon dioxide elevation of arterial blood this raised pressure was mostly reversible. The rise of pressure was mostly low or high. When the pressure was raised for more than 5 minutes there was a significant alteration. These were reversible responses. This was also associated with mostly reversible. After inhalation returned to the
Fig. 1. Blood pressure breathing uncat (2.8 kg carbon diox)
Top (R): Reartery blood T (time sign of CO2 inhal)
arrow (start
Fig. 2. Blood pressure responses in spontaneously breathing, urethane anesthetized, bilateral vagotomized (at the cervical region) male cat (3.2 kg) to high concentration of carbon dioxide (30%) in oxygen.

Top (R): Respiration; BE: Control carotid artery blood pressure in mm Hg; T: Time signals in 6 secs.

At the left: A - elevation of control blood pressure after bilateral vagotomy (indicated by arrow, \( V \)); Middle: B - Blood pressure responses to hypercapnia, duration of CO\(_2\) inhalation is indicated by arrow.

Time between panels A and B: 12 minutes; between B and C: 15 minutes.
with transient fall below the baseline compensated shortly by a rise of the gas.

In bilaterally vagotomized animals, induction of carbon dioxide inhalation of high concentration led to a vasodepressor pattern as observed in the normal animals. Although the basal pressure was slightly higher (8-10% above the control values) of carbon dioxide the blood pressure was observed to be 80-90 mm Hg. Induction of hypercapnia instead of a rise as observed after atropinization (F) was very often delayed (6-8 minutes) after atropinization (F) although the basal pressure was 70-80 mm Hg, and this fall persisted being reached within one minute after the basal value was high or low. The small rise of blood pressure at induction, followed by a gradual blood pressure was increasing gradually being reached within one minute after induction. The fall of pressure was about 10% of the baseline value within one minute, after which the pressure returned slowly. In bilaterally vagotomized group, induction of carbon dioxide
Fig. 3. Comparison of cardiac contractile responses and blood pressure responses of male urethane anesthetized and thoracotomized cat (3.2 kg) to high concentration of carbon dioxide (30%) in oxygen administered by forced ventilation.

Top (Heart): Contractile response; Middle (BP): Carotid artery blood pressure in mm Hg; Bottom (T): Time intervals in 6 secs.

Duration of carbon dioxide administration is indicated by arrows. Panel A shows the depression of blood pressure and cardiac contractility during CO₂ induction and a gradual increase in the cardiac contractions along with elevation of blood pressure after the withdrawal of CO₂ induction. Panel B shows the augmented cardiac contractility after 10 minutes of withdrawal of CO₂.
Effect of Carbon Dioxide Ventilation on the Contractile Force and Rate of Heart, in situ

In the open-chest artificially ventilated animals, introduction of high concentrations of carbon dioxide (30% CO₂) caused a gradual depression of cardiac force of contraction demarcated by diminution of the amplitude of contraction as demonstrated in the Figure 3. Immediately after the carbon dioxide induction, there was a temporary tachycardia for few seconds (average mean increase being 20 beats/minute, maximum being 30 beats/min). This tachycardia in response to carbon dioxide induction was reversible. Thereafter there was gradual slowing of the heart. This depression in force and frequency of the contraction of heart continued throughout the period of carbon dioxide induction ultimately attaining about 30% value of the control after 2-3 minutes and maintained at that level during the rest of the exposure period. No irregularity in rhythm was observed during the five minutes' duration of hypercapnia. On prolonged administration of the gas mixture beyond five minutes, however, the force of contraction was slightly increased attaining about a 40% value of the control, the rate and rhythm showing no significant alteration. The higher concentrations of carbon dioxide up to 50% with 50% oxygen did not appear to depress the heart to any greater extent than did the 30% concentration.

After the withdrawal of carbon dioxide mixture, the cardiac force was revived and attained an augmented value of 130-140% of the control within 2 minutes of the withdrawal. Then the force became less gradually, but the heightened force of contraction beyond the control value was maintained even after ten minutes of the withdrawal. The heart returned to its original contractile force at about fifteen minutes after the carbon dioxide withdrawal. The frequency of cardiac contraction was also increased considerably to about 150% of the control in the first minute and 120-130% after the fifth minute.
of the withdrawal. No significant change in the rhythm was observed except in very few cases where there were some idioventricular rhythms for a few seconds just after the withdrawal of the gas mixture. Thus, all the animals responded to the termination of carbon dioxide induction with a marked rebound of contractile force and rate of cardiac activity (Fig. 3).

In the atropine pretreated animals, the cardiac force showed a depression in a less degree than in the nontreated controls. The depression in the contractile amplitude was 20-25% of the control value. The rebound phenomenon during withdrawal was markedly augmented. The contractile force reached a value of 160% of the control as compared to the value of 130-140% in the control nonatropinized cases. The rate and rhythm followed almost the same sequences as in the nontreated animals.

The reserpinized animals exhibited more marked depression (upto about 80% of the control value) during carbon dioxide induction, but after withdrawal of carbon dioxide, the rebound effect was much greater, the contractile force and rate attaining a value of about 180% of the control excursions.

Effect of Vagus Stimulation during Induction of Carbon Dioxide

Stimulation of vagus with submaximal strength under control condition caused a fall of blood pressure of 6-10 mm Hg. During inhalation of carbon dioxide gas mixture, when the blood pressure was raised to a higher level, stimulation of the vagus with the same parameters of electrical current caused a greater fall of pressure of 25-35 mm Hg. The vagal vasodepression was significantly augmented, i.e. from 6% in the control to 20% during hypercapnia (Fig. 4). This potentiation of vagal effect was not observed during withdrawal phase.
Fig. 4. Vasodepressor responses to vagal stimulation (at the cervical region) before and during hypercapnia in spontaneously breathing urethane anesthetized male cat (2.78 kg).

Top (R): Respiration;
Middle (BP): Carotid artery blood pressure in mm Hg;
Bottom (T): Time intervals in 6 secs.

$V_1$ and $V_1'$ indicate the vasodepressor responses to stimulation of peripheral cut end of right vagus at 6 volts, 60 cps and 1 mSec duration, for 10 secs and $V_2$ and $V_2'$ indicate those of the left vagus with same parameters.

Duration of carbon dioxide induction is indicated by upward arrow (CO$_2$) and downward arrow (Off). Note the vagal depressor action is potentiated during the hypercapnic period.
Fig. 5. Comparison of epinephrine vasopressor and cardiac responses of urethane anesthetized thoracotomized male cat (3.1 kg) to high concentration of carbon dioxide (30%) in oxygen.

Top (Heart): Contractile response of heart;
Middle (BP): Carotid artery blood pressure in mm Hg;
Bottom: Time intervals in 6 secs.

Induction of carbon dioxide is indicated by upward and downward arrow (CO₂) and epinephrine is administered I.V. at 50 μg/kg at the arrow. Note the elevation of blood pressure by epinephrine during hypercapnia while the cardiac contractile response remained depressed inspite of blood pressure rise. Epinephrine has got no positive inotropic or chronotropic responses on heart during severe hypercapnia.
Effect of the Exogenous Catecholamines During Hypercapnia

In the open-chest preparations, during carbon dioxide induction when the blood pressure was at a lower level than the pre-exposure value, administration of adrenaline caused the usual rise of blood pressure. The cardiac excursion in these cases, when depressed by carbon dioxide induction, was only slightly increased in response to adrenaline administration. After the withdrawal of carbon dioxide, there was further augmentation of the cardiac force, though the blood pressure gradually came down to the basal level (Fig. 5).

Discussion

The results of the above experiments indicate that during administration of high concentration of carbon dioxide, the blood pressure is elevated slightly in spontaneously breathing animals, but depressed during forced ventilation in open-chest preparations. This depression reaches a maximum within 1 minute of carbon dioxide ventilation and often followed by compensation of blood pressure towards the control level.

In spontaneously breathing animals, the cause of slight elevation during carbon dioxide induction is possibly related with the sympathetic activation. The vasodepression during forced ventilation in thoracotomised preparations cannot be attributed to parasympathetic activation as atropinization or vagotomy did not reduce this response.

Reports of rise of systolic and diastolic blood pressure (112) and peripheral vasoconstriction (103) during hypercapnia are available. Fall of blood pressure during hypercapnia was also noted by Mosley and Spitzer (134) in dogs inhaling 30% carbon dioxide, and by Yamoto and Edwards (216) in rats having intravenous infusion of blood enriched extracorporeally by 100% carbon dioxide. Post-hypercapnic hypotension has also been reported by Clowes et al (15) in anesthetised patients. Our results
Curiously enough, the vagal vasodepressor response is potentiated during hypercapnia and the compensation to the vasodepression during withdrawal of carbon dioxide treatment is not facilitated by parasympathetic blockade with atropine. It may be assumed that the sympathetic activation immediately after carbon dioxide induction plays an important role in elevating the blood pressure as well as in returning the blood pressure towards control. But during forced ventilation this sympathetic activity may be masked by the direct vasodilator action of carbon dioxide on the wall of the blood vessels. Further, pretreatment with reserpine reduced considerably the return of blood pressure towards control level. The vasoconstrictor responses induced by carbon dioxide administration in spontaneously breathing animals may be related with liberation of catecholamines along with peripheral vasoconstriction, and the vasodepression observed by carbon dioxide induction in artificially maintained respiration is perhaps induced by acidosis, as amount of carbon dioxide administered is much higher and has a greater chance of producing acidosis. Role of epinephrine in maintaining cardiovascular homeostasis during respiratory acidosis has been stressed by Tenney (191, 193). The blood pressure response to raised carbon dioxide level is probably maintained by the balance between the catecholamines liberated by carbon dioxide stress (165, 197) and the degree of acidosis produced. Thus it may be suggested that rise of blood pressure during hypercapnia in spontaneously breathing animals or the compensation to hypercapnic cardiovascular depression in the thoracotomized animals may be attributed primarily to sympathetic postganglionic release of catecholamines.

The cardiac force and frequency of contraction during carbon dioxide induction showed a marked depression and after withdrawal a marked augmentation above the control value maintaining for a period of about 10 minutes was observed in all preparations regardless of experimental conditions. The blood...
pressure in these cases showed depression during hypercapnia and a transient elevation after withdrawal of the gas but was not maintained for so long as ten minutes.

It is of interest to recall the lack of compensation to this depression of heart, whatever mechanism returned the pressure toward control level or maintained above the basal value during carbon dioxide induction appeared to have little influence on heart's excursion.

Injected epinephrine failed to increase the heart rate and force of contraction during carbon dioxide induction and thus the expected rise of cardiac force and frequency by endogenously liberated catecholamines during carbon dioxide induction could not be seen whereas the vasopressor response was noted. After the withdrawal of carbon dioxide cardiac force was increasing gradually reaching beyond the control value, but the blood pressure showed no such parallel rebound, instead there was gradual fall. It seems that the peripheral vasculature remains dilated owing to direct action of carbon dioxide and less responsive to sympathetic activation until the carbon dioxide reduction is more complete.

It has been reported that under conditions of hypercapnia acidosis there is a rise in plasma catecholamine level and a rise in blood pressure (144, 145, 166, 174). Forced ventilation with high concentration of carbon dioxide (30%) for 5 minutes obviously caused a drop of blood pH and from the review of literature (145) it is reported that as the pCO₂ increases in the blood, the blood pH shifts to the acidic range (from 7.4 to 7.16) along with the rise of plasma catecholamine level from a control level of 0.6 ±0.3 μg/l for epinephrine and 28 ±12 μg/l for norepinephrine. It would be of interest to see the effect of exogenously administered epinephrine during hypercapnia. The magnitude of epinephrine pressor response during hypercapnia or its withdrawal phase in the dosage of 25 μg/kg did not differ markedly from that
of the control cases. This suggests that the plasma catecholamines as
liberated during hypercapnic acidosis did not exert their full activity on
the blood pressure responses, whereas there was depression of cardiac activity.
The magnitude of epinephrine pressure response was also related to the amount
of epinephrine administered and no significant difference was observed in
cases of hypercapnia than in case of control animals. But if the carbon dioxide
induction is prolonged for lowering the blood pH, there is a decreased
epinephrine pressure response though on the basis of present experiments it
is not possible to determine whether the depression of pressure response
to epinephrine is due to change of pH to acid range, or due to general
depression of metabolism by carbon dioxide, or to a blockade of the sites
of action of the effector organs of catecholamines. This finding should have
been elucidated more in order to relate the clinical use of prolonged
epinephrine infusion in cases of shock associated with apnea or hypercapnia
where arterial blood pH is low. It has been reported that the infusion of
1 µg/kg/min of epinephrine would produce a significant increase of blood
pressure in apneic dog when the arterial blood pH is maintained normal or
alkaline but the same dose of epinephrine fails to change significantly the
blood pressure when arterial blood pH is maintained acidic (145).

Although the marked rebound of myocardial contractile force and
rate during withdrawal of hypercapnia is difficult to explain at this phase,
it is apparent that during blowing off of carbon dioxide, when the direct
depressant action of the gas is gradually removed, the endogenously liberated
catecholamines are there free to elicit their usual inotropic and chronotropic
effect on the heart. The reserpinized animals showed considerable increase
in the rebound phenomenon of carbon dioxide withdrawal along with usual
depression during induction. This may be related to the supersensitivity
phenomenon of endogenously liberated catecholamines from adrenals of
reserpinized animals by the intense carbon dioxide stress. But in cases
where the adrenals were tied before, carbon dioxide exposure caused
similar changes in heart along with posthypercapnic augmentation phenomena.
Thus, within the limits of these experiments, the data show a significant
increase in contractile amplitude and rate of heart following the withdrawal
of high concentration of carbon dioxide and this 'withdrawal augmentation'
of cardiac force and rate appears more likely to be related to a peripheral
cardiac phenomenon. Therefore, the high concentrations of carbon dioxide
during induction and its withdrawal seem to have more pronounced effect on
the cardiac muscles than on the blood pressure, and the experiments should
be extended more for elaborating the mechanism of such action on heart.