The Local Component of the Acute Cardiovascular Response to Simulated Apneas in Brain-Dead Humans*

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**Study objectives:** To investigate the local cardiovascular response to hypoxemia and hypercapnia in a simulated central apnea model in which the central autonomic regulation was absent.

**Design:** Experimental study.

**Setting:** A university hospital.

**Interventions:** A simulated central apnea model achieved by a particular setting of the mechanical ventilator in 10 brain-dead patients.

**Measurements:** Hemodynamic studies using right-heart catheterization and continuous monitoring of arterial blood gas levels.

**Results:** Hypercapnic hypoxic apneas were associated with no change in heart rate, fall in mean systemic arterial pressure and systemic vascular resistance (from 83 ± 9 to 68 ± 7 mm Hg and 1,115 ± 52 to 768 ± 58 dynes·cm⁻², respectively; each p < 0.05), and rise in mean pulmonary artery pressure, pulmonary vascular resistance, and pulmonary capillary wedge pressure (PCWP) [from 17 ± 1.5 to 26 ± 3 mm Hg, 102 ± 27 to 166 ± 43 dynes·cm⁻², and 10 ± 1 to 14 ± 2 mm Hg, respectively; each p < 0.05].

**Conclusion:** Our results suggest that in the absence of central autonomic regulation in humans, apnea-induced hypoxemia and/or hypercapnia are associated with peripheral vasodilatation and pulmonary vasoconstriction, which are probably local in origin, as well as a significant increase in PCWP indicating cardiac dysfunction.

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**Key words:** acute cardiovascular response; brain death; central apnea; hypercapnia; hypoxemia

**Abbreviations:** CaO₂ = arterial oxygen content; CI = cardiac index; CO = cardiac output; Cvo₂ = venous oxygen content; Hb = hemoglobin; HR = heart rate; PAPm = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAPm = mean right atrial pressure; SaO₂ = arterial oxygen saturation; SAPm = mean systemic arterial pressure; SV = stroke volume; Svo₂ = mixed venous oxygen saturation; SVR = systemic vascular resistance; VO₂ = oxygen consumption.

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Among the short-term consequences of sleep apnea are arterial blood gas changes and hemodynamic alterations. During obstructive apnea, hypoxemia and fluctuations in intrathoracic pressure are considered to play prominent roles in mediating the short-term responses of the systemic and pulmonary circulations. The effects of hypoxemia on vascular smooth muscles may occur through neural and local mechanisms.1 During central apneas, no respiratory efforts and fluctuations of intrathoracic pressure are generated because of the transient withdrawal of central respiratory drive.2 Hypoxemia and hypercapnia caused by prolonged central apneas result in synergistic increases in sympathetic activity.3,4 Animal studies5 have shown that there is a primary vasodilatory response to hypoxia that is overridden by autonomic reflexes. During brief apneas in humans, however, it is currently unclear as to what extent hypoxemia and hypercapnia can affect the local control of vascular tone of the systemic and pulmonary circulations.

In the present study, we used a model of central apnea in brain-dead patients. In brain death, the central neural drive to the respiratory muscles, sympathetic neural activity, as well as resting vagal tone are abolished irreversibly.6 We used this model to induce apneas without fluctuations in intrathoracic pressure.
pressure and central autonomic activity and to investigate the local effects of hypoxemia and/or hypercapnia on systemic and pulmonary circulations. We performed hemodynamic studies during apnea-ventilation cycles, and we posed the following questions: (1) what is the local effect of hypoxemia and/or hypercapnia on the systemic and pulmonary circulations during nonobstructive apneas? and (2) in the absence of central autonomic regulation, is there any influence of these stimuli on the heart?

**Materials and Methods**

**Patients**

We studied 10 patients (4 women and 6 men) who had experienced severe head injury who previously had received a clinical diagnosis of brain death and were candidates for organ donation. According to the guidelines for the determination of death,² the clinical diagnosis of brain death was based on the following points: (1) the irreversible and well-defined etiology of unconsciousness; and (2) the absence of clinical evidence of brainstem function. All of the patients were in regular sinus rhythm and hemodynamically stable, as no significant heart dysfunction was observed by echocardiography. Their levels of blood gases, electrolytes, and thyroid hormones, and temperatures were in a normal range. None of the patients were receiving therapy with inotropes, vasopressors, or any medication that might affect cardiovascular function. No adjustment of medication was made during the protocol. None of the patients were morbibly obese or had lung or cardiovascular disease, as determined by their clinical histories. All of the patients received mechanical ventilation (Siemens Servo 300; Siemens; Solna, Sweden) using a tidal volume of 8 to 10 mL/kg and a respiratory rate of 10 to 12 breaths/min in order to keep PaCO₂ within normal values (Table 1). The study protocol was approved by the Scientific Committee of the University Hospital of Ioannina. Informed consent was obtained by each patient’s next of kin.

**Study Protocol**

During the second apnea testing, as part of the determination of brain death,² a central apnea model was induced. First, preoxygenation with a fraction of inspired oxygen of 1.0 was done, and then an apnea was induced at end-expiration by turning the ventilator off for 2 min. No oxygen was given during the apneic period. Afterward, ventilation resumed with six mechanical breaths using the same tidal volume as before the apnea but with a respiratory rate of 20 to 22 breaths/min to mimic postapnea hyperventilation. We used 2 min of apnea, because the resultant rise in PaCO₂ and fall in PaO₂ mimicked blood gas changes that were observed in typical sleep apneas. During the protocol, lead II of the standard ECG, arterial blood gas levels, and hemodynamic parameters were monitored continuously in all of the studied patients.

Before the beginning of the hemodynamic studies, the assessment of the stability of the apnea model was done by allowing eight apnea-ventilation cycles. The variations in arterial blood gas levels, mean systemic arterial pressure (SAPm), and temperature, as well as cardiac output (CO) and mixed venous oxygen saturation (SvO₂) before and after the apnea-ventilation cycles were monitored. Patients were excluded from the protocol when serious adverse effects, such as cardiac arrhythmia or hemodynamic collapse, were observed.

**Measurements**

Values for arterial blood gases and hemodynamic parameters were obtained during three sequential apnea-ventilation cycles, at the following four specified periods: baseline, before any apneic intervention; late apnea, the last 60 s of the disruption of ventilation; postapnea, the first 60 s following the end of apnea; and recovery, 3 min after stabilization under baseline conditions. Continuous monitoring of PaO₂ and PaCO₂, pH, and arterial oxygen saturation (SaO₂) were obtained by a multiparameter intraarterial fiberoptic sensor that was passed via a 20-gauge catheter in radial artery (Seldinger Paratrend 7 system; Biomedical Sensors; High Wycombe, UK). Concomitantly with the arterial blood gas measurement, the monitoring of SAPm was done through the same artery.

Right-heart catheterization was performed using a standard technique through the subclavian vein. A 7.5F, balloon-tipped, flow-directed continuous CO pulmonary artery catheter catheter (CCOmboV; Edwards Lifesciences LLC; Irvine, CA) was pushed forward under the control of the pressure curve on the screen of a multichannel monitor (HP 78353B; Hewlett-Packard; Palo Alto, CA). Mean right arterial pressure (RAPm), and mean pulmonary artery pressure (PAPm) were recorded on the monitor screen. Mean pressures were obtained by electronic averaging of the values for systolic and diastolic pressures. Pulmonary capillary wedge pressure (PCWP) was measured after inflation of the distal balloon. All of the measurements were obtained at the end of expiration.

Continuous CO monitoring was done using the thermodilution principle by a continuous CO computer (Vigilance Volumetric CEDV; Edwards Life Sciences; Irvine, CA). The values of CO and SvO₂ were presented on the STAT mode screen of the continuous CO computer and were updated every 18 s. We obtained the values of CO that corresponded to the specified periods of the apnea model. The mean average of three recorded values was calculated. Stroke volume (SV), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), arterial oxygen content (CaO₂), venous oxygen content (CvO₂), and oxygen consumption (VO₂) were calculated using the following standard equations: (1) SV = CO/heart rate (HR) × 10³ (mL/beat); (2) CI = CO/body surface area (BSA) (L/min/m²); (3) SVR = (SAPm – RAPm) × 80/CI (dyne cm⁻⁵); (4) PVR = (PAPm – PCWP) × 80/CI (dyne cm⁻⁵); (5) CaO₂ = 1.34 × hemoglobin (Hb) × SaO₂ (mL/100 mL); (6) CvO₂ = 1.34 × Hb × SvO₂ (mL/100 mL); and (7) VO₂ = CO × (CaO₂ – CvO₂) (mL/min).

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**Table 1—Clinical Characteristics of All Study Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>14</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Age, yr</td>
<td>55 ± 12</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.6 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.78</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.87 ± 0.3</td>
</tr>
<tr>
<td>T, °C</td>
<td>36.8 ± 0.6</td>
</tr>
<tr>
<td>T4, ng/mL</td>
<td>8.5 ± 3.6</td>
</tr>
<tr>
<td>TSH, IU/dL</td>
<td>0.36 ± 0.1</td>
</tr>
</tbody>
</table>

*Data are presented as the mean ± SD or No., unless otherwise indicated. T = temperature; T4 = thyroxine; TSH = thyroid stimulating hormone.
Statistics

Data are presented as mean ± SD. Statistical comparisons between groups were performed using two-way analysis of variance for repeated measurements. The significance of differences between the values was determined with the Bonferroni correction for multiple comparisons. A p value of < 0.05 was considered to be significant.

Results

Patient Stability

No spontaneous respiratory movements were noticed in any patient during apneas. All of the apneas were performed without serious adverse effects, such as severe hypoxemia, acidosis, cardiac arrhythmia, cardiac asystole, and hemodynamic collapse. There were no significant differences in any parameter between preapnea (baseline) values and postapnea (recovery) values. Furthermore, temperature and HR were stable throughout the apnea-ventilation cycles. In addition, no significant variations were noticed in VO₂ throughout the apnea-ventilation cycles.

Blood Gases

In comparison with baseline and recovery, apneas led to a statistically significant decrease in PaO₂ and arterial pH, and an increase in PaCO₂. At postapnea, hypoxemia was corrected, but mild hypercapnia persisted (Table 2).

Hemodynamics

Table 3 summarizes the hemodynamic findings throughout the apnea-ventilation cycles.

Late Apnea vs Baseline: From baseline to late apnea, HR and RAPm did not change. Mean SAPm and SVR were significantly lower at late apnea than in baseline (68 ± 7 vs 83 ± 9 mm Hg, respectively [p < 0.05]; and 768 ± 58 vs 1,115 ± 82 dyne·cm⁻⁵, respectively [p < 0.05]). Mean PAPm, PVR, and PCWP increased significantly during late apnea in comparison with baseline (26 ± 3 vs 17 ± 1.5 mm Hg, respectively; 166 ± 43 vs 102 ± 26 dyne·cm⁻⁵, respectively; and 14 ± 2 vs 10 ± 1 mm Hg, respectively [each p < 0.05]).

Postapnea vs Late Apnea: At postapnea, mean SAPm and SVR were significantly greater in comparison with late apnea (82 ± 9 vs 68 ± 7 mm Hg, respectively; and 1,128 ± 94 vs 768 ± 58 dyne·cm⁻⁵, respectively [each p < 0.05]). When compared with late apnea, mean CO and SV were significantly lower (5.1 ± 1 vs 6.2 ± 1 L/min, respectively; and from 73 ± 14 vs 90 ± 15 mL/beat, respectively [each p < 0.05]). Mean SAPm, PVR, and PCWP were found significantly lower at postapnea than in late apnea (19 ± 2 vs 26 ± 3 mm Hg, respectively; 126 ± 27 vs 166 ± 43 dyne·cm⁻⁵, respectively; and 11 ± 3 vs 14 ± 2 mm Hg, respectively [each p < 0.05]).

Postapnea vs Baseline: Although PVR decreased at postapnea in comparison with late apnea (126 ± 27 vs 166 ± 43 dyne·cm⁻⁵, respectively [p < 0.05]), it remained higher compared with baseline values (126 ± 27 vs 102 ± 26 dyne·cm⁻⁵, respectively [p < 0.05]). At postapnea, PAPm was higher than at baseline but not significantly.

Recovery: The values of all of the hemodynamic parameters in recovery were not different from those at baseline.

Discussion

Because after brainstem herniation the sympathetic activity and resting vagal tone were abolished, the central cardiovascular autonomic regulation was

Table 2—Arterial Blood Gases Throughout the Apnea-Ventilation Cycle*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline (Mean ± SD)</th>
<th>Late Apnea (Mean ± SD)</th>
<th>Postapnea (Mean ± SD)</th>
<th>Recovery (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mm Hg</td>
<td>428 ± 46</td>
<td>55 ± 2†</td>
<td>150 ± 19†</td>
<td>365 ± 35</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>49 ± 2</td>
<td>59 ± 6†</td>
<td>52 ± 7†</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
<td>7.33 ± 0.01†</td>
<td>7.35 ± 0.01†</td>
<td>7.36 ± 0.01</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>98 ± 2</td>
<td>86 ± 2†</td>
<td>98 ± 1†</td>
<td>99 ± 1</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>83 ± 3</td>
<td>73 ± 5</td>
<td>82 ± 4</td>
<td>85 ± 6</td>
</tr>
<tr>
<td>VO₂, mL/min</td>
<td>152 ± 16</td>
<td>156 ± 17</td>
<td>153 ± 14</td>
<td>147 ± 10</td>
</tr>
</tbody>
</table>

*Data are presented as the mean ± SD or No., unless otherwise indicated. Significance was set at p value of < 0.05.
†p < 0.05 vs baseline.
‡p < 0.05 vs late apnea.
§p < 0.05 vs postapnea.
||p < 0.05 vs late apnea.
absent in the present model. Hence, this model provided us with the opportunity to evaluate the local effects of hypoxemia, hypercapnia, and/or acidosis on the systemic and pulmonary circulations during nonobstructive apneas in humans. Our main findings demonstrate that during apneas without fluctuations in intrathoracic pressure and autonomic activity, hypoxemia, hypercapnia, and mild acidosis are associated with a fall in SAPm and SVR. At the same time, it was found that PAPm, PVR, and PCWP were increased. After the end of apnea, mild hypercapnia without hypoxemia was associated with high PVR. Despite the fall in SVR, CO and SV did not increase significantly during apnea.

Blood Gases

In this study, hypoxemia and hypercapnia occurred during the last part of apnea. This is not consistent with previous studies in patients with apnea,9 where the changes in arterial blood gas levels were observed after the termination of apnea. A possible reason for this difference could be that, in our study, the continuous arterial blood gas monitoring was done through an intravascular sensor, which is characterized by a fast dynamic response to changes in blood gas tension.10 The ear or finger oximeters that have been used in previous studies had a relatively limited rate of dynamic response to abrupt changes in arterial blood gas levels, which are recorded after a brief circulation delay, estimated at 10 to 35 s.11 We think that our measurements reflect more precisely the changes in arterial blood gas levels during the apnea-ventilation cycle. Another possible reason for this difference could be the longer duration of apnea in our model.

One could argue that the modest changes in blood gas values could be attributed to a reduced metabolic rate. However, the values of calculated VO2 before, during, and after apnea did not shown significant variations. Therefore, we suppose that the metabolic rate did not change during apnea.

HR and Right Arterial Pressure

HR remained unchanged throughout the apnea-ventilation cycle. Additionally, no change in HR was noticed during nonobstructive apneas in vagotomized and chemically sympathectomized pigs.5 This finding is also consistent with data from previous studies in brain-dead patients.12–14

RAPm remained unchanged throughout the apnea-ventilation cycle, possibly because no respiratory movements occurred. Furthermore, RAPm was not significantly affected by the withdrawal and reinstitution of mechanical ventilation. It could be suggested that the intrathoracic pressure did not significantly change throughout the apnea-ventilation cycles. It is probable that the relatively low tidal volume used, in the absence of positive end-expiratory pressure (and/or auto-positive end-expiratory pressure), hardly affected the intrathoracic pressure in hemodynamically stable patients with normal respiratory systems. Therefore, it is quite possible that mechanical ventilation did not influence heart function, in terms of venous return, preload and afterload.

Systemic Arterial Pressure and SVR

In response to apnea, SAPm fell in parallel with a fall in SVR. These findings are consistent with data from animal studies,15,16 in which hypoxemia and hypercapnia caused local vasodilatation in many vascular beds. After apnea termination, mild and nonhypoxic hypercapnia was associated with a rise in SVR and SAPm, suggesting that nonhypoxic mild hypercapnia was not associated with vasodilatation.
Different in patients without brain death.

The behavior of the cardiovascular system could be altered by these alterations induced by brain death. Therefore, hypoxemia and hypercapnia, furthermore, might enhance cardiovascular and epithelial function altering the release of mediators, such as catecholamines. Hypoxic and hyperoxic. Differences in the PaCO2 level and/or the duration of apnea could be responsible for these different findings. It should be noted that the apneas in those studies were induced in sedated pigs.

CO and SV

Compared with preapnea values, CO and SV values increased only slightly during apnea, but without reaching statistical significance. One could hypothesize that the limited increase in SV and CO in response to peripheral vasodilation could be attributed to diastolic dysfunction of the left ventricle. This hypothesis is supported by the concomitant rise in PCWP, which is an index of left ventricular end-diastolic pressure. At the same time, the increase in PAPm and PVR suggests that pulmonary hypertension-induced right ventricle-septal dysfunction causes diminished left diastolic ventricular function. This hypothesis is consistent with those of previous studies, in which pulmonary hypertension during apnea led to an increase in right ventricle end-diastolic pressure. The latter produces a marked leftward septal shift causing a decrease in left ventricle compliance and left ventricle end-diastolic volume.18,19 On the other hand, the rise in PCWP could be attributed to decreased left ventricular contractility due to hypoxia unopposed by sympathetic stimulation.20,21 However, in other studies in brain-dead patients,13–15,18 CO levels were significantly increased in response to a fall in SVR during long hypercapnic apneas. This difference could be attributed to the absence of hypoxemia during apnea in those studies, as well as to different methods of evaluation of heart function. In our model, hypoxemia could affect the function of both heart ventricles. However, in chemically sympathectomized and vagotomized sedated pigs, CO and SV were increased during brief nonobstructive hypoxic and hypercapnic apneas.5 Differences in the neural state (sedation vs brain death) or in species could be responsible for these different findings. However, we should note that brain death could affect the cardiovascular and epithelial function altering the release of mediators, such as catecholamines. Hypoxia and hypercapnia, furthermore, might enhance these alterations induced by brain death. Therefore, the behavior of the cardiovascular system could be different in patients without brain death.

After the termination of apnea, CO and SV levels were decreased in comparison with the late apnea period. Because HR remained constant, the fall in CO and SV could be attributed to increased SVR and a short-term increase in left ventricular afterload. Also, it is possible that the effect of hypoxemia on the heart was persistent.

Pulmonary Circulation

PAPm and PVR were increased during apnea and fell again in the recovery. These findings indicate that hypoxemia and hypercapnia, when acting locally, cause pulmonary vasoconstriction even in the absence of central autonomic control. This finding is consistent with data from animal studies,22 in which it was observed that hypoxemia acts directly on the smooth muscles of the pulmonary vasculature to produce vasoconstriction.

Although PVR values declined after late apnea termination, they remained higher than those at baseline. Mild hypercapnia without hypoxemia was associated with pulmonary vasoconstriction. These findings indicate that the local effect of carbon dioxide seems to play a significant role in the reaction of the pulmonary vasculature to apnea. Pulmonary circulation is probably more sensitive than the systemic to the local hypercapnic stimulus.

Limitations

A limitation of this study is that our findings could not be extrapolated to real central apneas where central autonomic activity exists. However, it could be suggested that autonomically impaired individuals could be at a significant risk during central sleep apneas because of the local effects of hypoxemia and hypercapnia on the cardiovascular system. Another limitation is the lack of monitoring of heart function during apnea, for example, by echocardiography, hence the direct evaluation of the influences of hypoxemia on the heart.

Conclusion

In brain-dead humans, hypoxemia, and/or hypercapnia during nonobstructive apneas seem to cause a local vasodilator effect on the systemic vasculature. On the other hand, these stimuli are associated with pulmonary vasoconstriction, which is probably local in origin. However, mild and nonhypoxic hypercapnia were associated with pulmonary vasoconstriction, although the same stimulus did not affect systemic vascular resistance. In addition, in the absence of central autonomic activity, the direct effect of hypoxemia on the heart and changes in pulmonary circu-
lation during apnea could cause a degree of cardiac dysfunction. Only limited data exist regarding the hemodynamic response to nonobstructive apneas in humans. Our results confirm in humans some findings from animal studies.

REFERENCES
8 Gillman PH. Continuous measurement of cardiac output: a milestone in hemodynamic monitoring; focus on critical care. Focus Crit Care 1992; 19:155–158