ROLE OF AMINERGIC FIBERS IN CI/Akiyoshi et al.

SUMMARY Respiring rhesus monkeys with 2.5 or 4.5% oxygen greatly decreased their cardiac contractility, stroke volume and blood pressure but altered their total peripheral vascular resistance only slightly and inconsistently. All monkeys exposed to 15 minutes and 2 of 4 exposed to 30 minutes of hypoxia recovered and survived without brain injury. Though all animals recovered full cardiovascular function immediately after they were reoxygenated, 2 respired with 4.5% oxygen for 30 minutes began showing declines in blood pressure after a delay of 1 to 2 hours and both subsequently died in shock. Their reductions in blood pressure were associated with reductions in cardiac contractility and stroke volume. The hypotension the animals exhibited both during hypoxia and during development of shock afterwards resulted from pump failure rather than a reduced vascular resistance or an inadequate venous return.

Methods

Ten fasted 4.5 to 6.5 kg monkeys (M. mulatta) anesthetized with i.v. pentobarbital, 35 mg/kg, were intubated and ventilated with a Harvard respirator. Catheter-tip micromanometers (Millar Instruments, Houston, TX), positioned so their tips lay in the left ventricle and thoracic aorta, recorded the left ventricular pressure and systemic blood pressures. Lead II of the ECG was also recorded while samples of arterial blood were analysed for Po2, Pco2, and pH. The respiratory gas values of arterial blood were brought within normal limits by regulating the respirator settings. Body temperature was maintained at 38°C.

Three animals were ventilated with 4.5 and 2.5% oxygen for 15 minutes and 4 animals with 4.5% oxygen for 30 minutes. Left ventricular pressure, central aortic pressure, ECG, and heart rate were recorded. Cardiac output, cardiac contractility as reflected in Vmax values, and total peripheral vascular resistance were calculated at 3-minute intervals throughout the control, the hypoxic, and the recovery periods. Hypoxic exposure was terminated by substituting 100% oxygen and, later, room air for the hypoxic gas mixture in the respiratory stream. The animals also were injected with 10 µg epinephrine and 10 mEq sodium bicarbonate. Additional sodium bicarbonate was administered to treat persisting acidosis.

The physiologic data were recorded on FM magnetic tape. Analogs were converted to digital data and stored on a magnetic tape. Physiologic parameters including stroke volume, heart rate, arterial blood pressure, and aortic pressure were recorded continuously on FM magnetic tape. The physiologic data were transferred to a computer for analysis of the changes in cardiac contractility and the total peripheral vascular resistance.
off-line using a MAC-16 computer system and an A-to-D conversion rate of 500 samples per channel per second. Digital data were processed on an IBM 370 system using Fortran programs.

Stroke volume was calculated from Warner's equation:

\[ \text{SV/K} = \frac{P_{\text{md}}}{1 + \frac{S_a}{D_a}} \]

where \( \text{SV} \) is stroke volume; \( K \), a calibration constant; \( P_{\text{md}} \), the mean pressure difference between the last Tw msec of systole and the last Tw msec of diastole; \( Tw \), the transit time of the left ventricular pressure waveform to the site of pressure recording; \( S_a \), the integrated pressure above 20 mm Hg from Tw msec before systole to Tw msec before diastole; and \( D_a \), the integrated pressure above 20 mm Hg from Tw msec before diastole to Tw msec before the onset of systole. \( Tw \) was calculated as a second order function of the instantaneous mean blood pressure based on Remington and Hamilton.

The proportionality constant, \( K \), in the Warner equation was assumed constant for each animal. The values of stroke volume and total peripheral resistance were computed using actual data substituted into the equations and divided by \( K \). The changes reported are based upon computations of the specific values at the different times and related to the corresponding control values.

The rate of LV pressure increase (dP/dt) was computed numerically at every datum point using a 7 point, second order routine. The values of contractile element velocity (\( V_{c_{\text{m}}} \)) were derived following a three element Maxwell model and force-velocity curves were constructed. \( V_{c_{\text{m}}} \), a measure of contractility, was defined from a linear extrapolation of \( V_{c_{\text{m}}} \) to a theoretical zero load.

Results

Animals Exposed to 15 Minutes of 2.5% and 4.5% Oxygen Breathing

The blood pH, \( P_{\text{CO}_2} \), and \( P_{\text{O}_2} \) values before and after 5, 10, and 15 minutes of hypoxia and 2 and 30 minutes of recovery are presented in figure 1 for each of 6 animals ventilated with 2.5% (fig. 1-A) or 4.5% (fig. 1-B) oxygen. The 15 minute blood samples exhibited average \( P_{\text{O}_2} \) values of 15 and 21 mm Hg; average \( P_{\text{CO}_2} \) values of 24 and 25 mm Hg; and pH ranges of 7.15 to 7.22 and 7.26 to 7.40, respectively.

The changes produced in mean blood pressure, cardiac stroke volume, total peripheral resistance, \( V_{\text{max}} \), heart rate, and left ventricular end-diastolic pressure (LVEDP) are illustrated in figures 2 and 3. Respiring the animals with 2.5% and 4.5% oxygen generally produced similar changes except the more marked exposure caused greater reductions in stroke volume and cardiac contractility (\( V_{\text{max}} \)). All animals rapidly increased their mean blood pressure, \( V_{\text{max}} \), heart rate, and total peripheral resistance from sympathetic nervous system stimulation. These early stimulatory changes were followed after 3 to 5 minutes by rapid reductions in all parameters of cardiovascular function except peripheral resistance. The total peripheral resistance, after its early stimulatory increase, merely returned to its preexposure values.

The mean blood pressure, after an initial rise above the control values of 110 to 120 mm Hg, lowered after 15 minutes to measurements as low as 40 mm Hg in both groups. These blood pressure reductions were associated with proportionate declines in \( V_{\text{max}} \) values. The changes in heart rate varied more and were less marked. Of the hemodynamic functions studied only \( V_{\text{max}} \) and stroke volume differed among the animals exposed to 2.5% and 4.5% oxygen breathing. The animals of the 2 groups decreased their stroke volumes from 10 to 5.0 and to 7.5 ml, respectively. All animals increased their LVEDP from control values of 5 to 10 to values as high as 20 mm Hg. However, they failed to respond to their elevated LVEDPs by increasing cardiac output through the Starling principle, but, rather, they reduced their stroke volumes. The animals showed only slight and variable changes in peripheral vascular resistance which correlated poorly with changes in blood pressure. In contrast, they consistently showed marked changes in cardiac contractility and stroke volume and both of these values correlated closely with changes in blood pressure.

All animals exposed to 15 minutes of hypoxia restored their mean blood pressure, stroke volume, \( V_{\text{max}} \), and heart rate to values close to normal within minutes after they were reoxygenated. They all survived long term and failed to show any neurologic or neuropathologic abnormalities.
HEMODYNAMIC RESPONSE TO HYPOXIA/Myers et al.

ANIMAL #N812, N809, N
4.5% Oxygen 15 Minutes

MEAN BLOOD PRESSURE (mmHg)
STROKE VOLUME (cc)
TOTAL PERIPHERAL RESISTANCE (mmHg/mln)
Vmax (sec^-1)
HEART RATE (beats/min)
LVEDP (mmHg)

ANIMAL #0709, M418, 0357
2.5% Oxygen 15 Minutes

MEAN BLOOD PRESSURE (mmHg)
STROKE VOLUME (cc)
TOTAL PERIPHERAL RESISTANCE (mmHg/mln)
Vmax (sec^-1)
HEART RATE (beats/min)
LVEDP (mmHg)

Figure 2. Effects of breathing 4.5% oxygen in nitrogen for 15 minutes on mean blood pressure, stroke volume, total peripheral resistance, \( V_{\text{max}} \), heart rate, and LVEDP of 3 rhesus monkeys.

Figure 3. Effects of breathing 2.5% oxygen in nitrogen for 15 minutes on mean blood pressure, stroke volume, total peripheral resistance, \( V_{\text{max}} \), heart rate, and LVEDP of 3 monkeys.

Animals Ventilated with 4.5% Oxygen for 30 Minutes

Two animals tolerated exposure to 4.5% oxygen for 30 minutes and recovered fully while 2 others died in shock many hours after they were reoxygenated and they had recovered a full cardiovascular function. These 2 sets of animals exhibited the blood compositional changes depicted in figure 1-C. The animals that survived and those that died in delayed shock exhibited average \( P_O_2 \) and \( P_C_o_2 \) values during hypoxia of 23 and 22 and 32 and 39 mm Hg, respectively. Those that survived showed pH values during hypoxia of 7.28 and 7.32 while those that later died of shock showed values of 7.20 and 7.24. Thus, the animals that later succumbed were distinctly more acidotic and hypercarbic during hypoxia than were those that survived.

The animals exposed to 30 minutes of hypoxia showed the mean arterial blood pressure, stroke volume, total peripheral resistance, \( V_{\text{max}} \), heart rate and LVEDP changes illustrated in figures 4 and 5. The animals that survived and those that died showed similar control values for all parameters studied and during hypoxia they also showed similar changes in mean blood pressure, stroke volume, \( V_{\text{max}} \), heart rate, and LVEDP.

The more prolonged hypoxia reduced the vigor of recovery of cardiovascular function at the time the animals were reoxygenated. However, the indices of cardiovascular function stabilized sufficiently well in 2 animals that they were returned to their cages 6 hours into recovery. The remaining 2 animals began to reduce their indices of cardiovascular function several hours into the recovery period. Though they maintained their stroke volume, their blood pressure, heart rate and \( V_{\text{max}} \) values gradually declined taking several hours to reach markedly low values. Throughout all these changes their LVEDPs generally remained high.

Early during the lowering of blood pressure the peripheral vascular resistance was augmented in an effort at compensation. Several measures to treat shock, including infusion of low molecular weight dextran and epinephrine and injection of positive inotropes including ouabain and calcium gluconate, all failed to exert lasting effects. Furthermore, the cardiovascular decompensation appeared and progressed even though all respiratory gas and acid-base values were maintained within their normal ranges. Throughout the
ANIMAL N805  ANIMAL N869
DIED IN SHOCK  DIED IN SHOCK

MEAN BLOOD PRESSURE (mmHg)
0 100

STROKE VOLUME (cc)
0 10

TOTAL PERIPHERAL RESISTANCE (mmHg/min)
0 100

Vmax (sec⁻¹)
0 200

HEART RATE (beats/min)
0 200

LVEDP (mmHg)
0 15

0 2 4 6 8
HYPOXIA
0 2 4 6 8
HYPOXIA

FIGURE 4. Effects of breathing 4.5% oxygen for 30 minutes on mean blood pressure, stroke volume, total peripheral resistance, Vmax, heart rate and LVEDP of two animals. Both of these animals survived the episodes of hypoxia and showed no neurologic abnormalities.

progression of shock, the correlation between Vmax and cardiac output and Vmax and mean arterial blood pressure remained close (R = 0.84 and 0.89, respectively) while that between total peripheral resistance and cardiac output and total peripheral resistance and mean blood pressure never reached significance (R = 0.28 and 0.19, respectively).

The 2 animals that survived long term after exposure to 4.5% oxygen breathing recovered consciousness from barbiturate anesthesia with a normal time course (in 6 to 14 hours). Clinical evaluation prior to their sacrifice 2 weeks later failed to define any neurologic abnormalities while pathologic examination of their brains demonstrated no gross or microscopic damage. The 2 animals that died in cardiogenic shock many hours into the recovery period nonetheless showed a similar time course of recovery of consciousness as those that survived long term. They already had begun to respond to stimulation prior to their death from cardiogenic shock. As in the animals which survived long term, the brain pathologic evaluation of the animals that died in shock showed no gross morphologic evidences of brain edema or gross or microscopic indications of brain tissue injury.

ANIMAL P303  ANIMAL P328
SURVIVOR  SURVIVOR

MEAN BLOOD PRESSURE (mm Hg)
0 100

STROKE VOLUME (cc)
0 10

TOTAL PERIPHERAL RESISTANCE (mm Hg/min)
0 100

Vmax (sec⁻¹)
0 200

HEART RATE (beats /min)
0 200

LVEDP (mmHg)
0 15

0 2 4 6 8
HYPOXIA
0 2 4 6 8
HYPOXIA

FIGURE 5. Effects of breathing 4.5% oxygen for 30 minutes on mean blood pressure, stroke volume, total peripheral resistance, Vmax, heart rate and LVEDP of two animals. Both animals died 10 and 12 hours following exposure to hypoxia with the findings of cardiogenic shock.

Discussion

The effects of hypoxia on the heart have been studied in isolated papillary muscles,4 in detached, perfused hearts,5 and in intact animals.6 The few studies carried out on intact primates have demonstrated profound reductions in blood pressure and heart rate and changes in the electrocardiogram during marked hypoxia.7,8 The present study applies a variety of techniques already developed and described by their originators4-10 to this problem to define those changes in cardiovascular function brought about by marked hypoxia. Separate attention was paid to the development of hypotension that appeared secondarily in several animals during the recovery period.

Earlier investigations in our laboratory have demonstrated the Vmax to be independent of both preload and afterload over the entire range of pressures studied.13 However, cardiac contractility and, hence, Vmax, depends on heart rate.4 Thus, some
part of the decline of $V_{\text{max}}$ that develops during hypoxia and during the recovery period can be attributed to heart rate slowing. A depressed contractility of the heart itself also contributes significantly to the decline of $V_{\text{max}}$ during hypoxia since the stroke volume decreases at the same time that the LVEDP increases. A similar relation between a reduced stroke volume, despite an increased LVEDP, was found in the animals as they lay dying in shock late during the recovery period.

The animals that survived and those that died of cardiogenic shock late during the recovery period showed no definite differences in their arterial blood oxygen tensions during exposure to hypoxia. However, the animals that died of delayed cardiogenic shock developed lower pH, higher carbon dioxide tensions, and greater depressions of their indices of cardiac function during exposure to hypoxia than did the animals that survived. A similar relation between excessive pH lowering and damage to the myocardium has been described by Selkoe and Myers. The same investigations have also included that delayed animal death from cardiogenic shock following exposure to marked circulatory or respiratory insufficiency results from a decreased perfusion in the action of the heart that takes place as a consequence of the antecedent oxygen lack as it acted directly on the myocardium and that the delayed circulatory failure does not depend for its development on any specific concurrent damage to the nervous system.

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