ROLE OF AMINERGIC FIBERS IN CI/Akiguchi 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 exposed to 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 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 a mixture in the respirator 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.
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:

$$SV/K = P_{md} (1 + Sa/Da)$$

where SV is stroke volume, K, a calibration constant; P_{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; Sa, the integrated pressure above 20 mm Hg from Tw msec before systole to Tw msec before diastole; and Da, 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_{ce}) were derived following a three element Maxwell model and force-velocity curves were constructed. V_{max}, a measure of contractility, was defined from a linear extrapolation of V_{ce} to a theoretical zero load.

**Results**

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

The blood pH, P_{CO2}, and P_{O2} 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_{O2} values of 15 and 21 mm Hg; average P_{CO2} 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_{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_{max}). All animals rapidly increased their mean blood pressure, V_{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_{max} values. The changes in heart rate varied more and were less marked. Of the hemodynamic functions studied only V_{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_{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.
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 PO₂ and PCO₂ 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 acidic 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_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_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_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
progression of shock, the correlation between $V_{\text{max}}$ and cardiac output and $V_{\text{max}}$ 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.

Discussion

The effects of hypoxia on the heart have been studied in isolated papillary muscles, in detached, perfused hearts, and in intact animals. 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. The present study applies a variety of techniques already developed and described by their originators 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 $V_{\text{max}}$ to be independent of both preload and afterload over the entire range of pressures studied. However, cardiac contractility and, hence, $V_{\text{max}}$, depends on heart rate. 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. Many other examples of the development of circulatory failure have been described in animals exposed to marked hypoxia or anoxia. Thus, asphyxiated monkey newborns frequently die of a circulatory failure refractory to treatment many hours after successful resuscitation. Adult monkeys exposed to circulatory arrest, hypotension, or inhalation of carbon monoxide likewise frequently die from a circulatory failure that takes place many hours after exposure.

In all studies the hypotension that developed during the early hours after oxygenation was restored, progressed relentlessly even though the blood pressure initially was restored to normal or near-normal values and the arterial blood oxygen tension was maintained in the normal range. All efforts at treatment failed to halt the downward trend in blood pressure. Administering positive inotropes failed to alter the $V_{\text{max}}$ values' steady decline while augmenting the venous return through blood volume expansion (preload enhancement) also failed to increase the stroke volume or cardiac output of the affected animals. Thus, the delayed death many animals experienced in all these studies resulted from a decreased contractility of the heart as evidenced by a reduced cardiac stroke volume that appeared despite an increase in preload (LVEDP) and by the decreased $V_{\text{max}}$ even though the peripheral vascular resistance remained unchanged or even increased.

Earlier studies from our laboratory have described the development of a delayed circulatory failure during which the work output of the heart progressively declines over many hours following animal exposure to hypoxia or anoxia. This ultimately leads to animal death in circulatory collapse even though the animals are fully oxygenated throughout their survival. Separate studies have been carried out of the effects of rhesus monkey exposure to marked hypotension for 22 to 75 minutes by exsanguination followed by restoration of blood pressure by infusion of withdrawn blood. These studies have demonstrated that delayed death in cardiogenic shock as described above may take place in animals in which the brain remains entirely intact.

The same investigations have also made the point that changing the conditions of exposure can convert pathologic outcome from damage to the heart to one of marked injury to the brain. The present study further supports the view that hypoxic conditions that alter the functional state of the heart leading to delayed animal death from cardiogenic shock may differ only in a few essential details from similar conditions that injure only the brain. It is concluded that delayed animal death from cardiogenic shock following exposure to marked circulatory or respiratory insufficiency results from a delayed depression 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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Hemodynamic response to profound hypoxia in intact rhesus monkeys.
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