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THE ACUTE EFFECTS OF NICOTINE, TOBACCO SMOKE AND CARBON MONOXIDE ON MYOCARDIAL OXYGEN TENSION IN THE ANAESTHETIZED CAT

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1 The acute effects of nicotine, tobacco smoke, and carbon monoxide on myocardial oxygen tension (MPo_2) were estimated amperometrically in 33 anaesthetized open-chest cats with a glass-insulated 25 μm platinum cathode within a 22-gauge needle implanted in the left ventricular wall.

2 MPo_2 was 1.6–60 mmHg (mean 23.5 mmHg) when arterial Po_2 was >80 mmHg. Sequential intravenous infusions of nicotine (2–3 μg/kg every 45 s) or intracheal puffs (3–5 ml) of tobacco smoke commonly produced transitory increases (25–35 mmHg) of arterial pressure and 4–6 mmHg increments of MPo_2. Intratracheal puffs (5 ml) of 5% carbon monoxide sufficient to increase carboxyhaemoglobin from 0.8 to 1.5% to 4–7% had no effect on arterial Po_2 or blood pressure but typically decreased MPo_2 by approximately 1–4 mmHg. Augmentation of MPo_2 often succeeded carbon monoxide administration.

3 Arterial hypoxia (arterial Po_2 < 60 mmHg) reduced mean MPo_2 to 14.4 mmHg but anoxic levels were not observed. Pressor responses to nicotine and tobacco smoke were accompanied by small increases (usually 1–3 mmHg) of MPo_2. Puffs of 5% carbon monoxide had less effect than during normoxia. Locations of low MPo_2 (<10 mmHg) were unaffected as carboxyhaemoglobin was raised to 7–11% during hypoxaemia.

4 It is concluded that nicotine and tobacco smoke cause augmentation of myocardial oxygen supply, even during moderate hypoxaemia. By contrast, smoking dosages of carbon monoxide have the potential of producing a small reduction of MPo_2 during normoxia, but the effect is negligible during moderate hypoxaemia.

Introduction

Nicotine administration in experimental animals increases cardiac work, myocardial oxygen consumption, and coronary blood flow (Forte, Williams, Potgieter, Schmitthenner, Hafkenschiel & Riegel, 1960; Pachinger, Hellberg & Bing, 1972; Ilebekk & Lekven, 1974). Adjustment of the latter is believed to meet or exceed the demands of the myocardium for oxygen (Forte *et al.*, 1960; Leb, Derntl, Robin & Bing, 1970). Cigarette smoke produces similar effects by virtue of its nicotine content (Kien, Lasker & Sherrod, 1959; Aronow & Swanson, 1969; Armitage, Dollery, George, Houseman, Lewis & Turner, 1975). However, since an appreciable level of carbon monoxide also is included in cigarette smoke, tissue oxygenation may be disadvantaged by increased blood carboxyhaemoglobin (Ayres, Gianelli & Mueller, 1970). That this does occur in hearts with restricted coronary blood supply has been suggested in several clinical studies (Goldsmith & Aronow, 1975).

While there is no evidence that cigarette smoke induces myocardial hypoxia in hearts with undiseased vasculature, measurements of myocardial oxygen tension under these circumstances are lacking. Consequently, we have used a platinum cathode to determine the profile of myocardial oxygen tension in anaesthetized cats acutely exposed to nicotine, tobacco smoke, or carbon monoxide. The study was conducted during normoxic and hypoxic ventilation.

Methods

Cats of either sex weighing 2.5–5 kg were anaesthetized with diallylbutyric acid and urethane (Dial, 0.7

ml/kg) intraperitoneally. A femoral artery was cannulated for monitoring blood pressure and heart rate (Physiograph) and withdrawal of blood samples for P_{CO_2}, P_{O_2}, HbO_2, and HbCO estimations (Instrumentation Laboratory Blood Gas Analyzer and CO-oximeter). A cannula in a femoral vein was used for administration of additional anaesthetics, nicotine, or 0.9% w/v NaCl solution (saline) to replace withdrawn blood. Following cannulation of the trachea, cats were paralyzed with gallamine triethiodide (Flaxedil, 10 mg/kg) and artificially ventilated (Harvard Respirator) with a mixture of 77% N_2, 20% O_2 and 3% CO_2. To inhibit atelectasis, lungs were hyperinflated at 10–15 min intervals. Body temperature was monitored by a colonic thermistor (Yellow Springs Telethermometer) and maintained at 37 ± 1°C by a heat lamp. The thorax was entered by a median sternotomy and the wound edges separated by a thyroid retractor. Exposed lung surfaces were covered with Saran to decrease fluid and heat loss by evaporation. The pericardial sac was incised and reflected sufficiently to expose the anterior surface of the left ventricle.

Myocardial P_{O_2} (MP_{O_2}) measurements were made amperometrically by a glass insulated platinum cathode 25 μm in diameter, within a 22-gauge stainless steel tube with a bevelled tip (Transidyne). A silver wire with a chlorided tip served as reference electrode. The cathode was polarized with −0.6 V direct current, and resulting currents were measured with a Keithley 410A picoammeter. Preceding the initial calibration the cathode and reference electrode were inserted for 5–10 min in the cat's gracilis muscle for 'conditioning.' This procedure reduced the current recorded during subsequent *in vitro* calibrations in known concentrations of oxygen bubbled through saline at 37°C and virtually eliminated calibration drift (<5%) during 3 h of MP_{O_2} measurement. Gas flows through saline were interrupted at the moment of calibration to remove the 'stirring' artifact. Currents were in the range of 10^{-8} A in air and decreased to less than 5% of that value in 95% N_2 and 5% CO_2. Calibration gases included the latter and 5% O_2 with 5% CO_2 and 90% N_2. Following the initial calibration, small tissue forceps were used to grasp gently 1–2 mm of surface tissue of the left ventricle, and the tip of the oxygen electrode was implanted to the depth allowed by a rubber bumper, positioned a selected distance along the electrode shaft. The electrode assembly was supported perpendicular to the ventricular surface by a Teflon ring which allowed the assembly to follow excursions of the ventricular wall. Remaining ventricle still exposed was covered with Saran.

Once relative stability of the MP_{O_2} recording was attained (15–30 min) one of the following was administered at 30–60 s intervals: (1) intravenous infusions of nicotine (1–4 μg/kg in saline); (2) puffs (2–5 ml) of freshly drawn tobacco smoke from an IRI reference cigarette (Atkinson, 1970), or (3) puffs (5 ml) of 5% carbon monoxide. Puffs were introduced into the trachea at the moment of inspiration by a syringe connected to a side port of the tracheal cannula. Infusions of a volume of saline similar to that of the nicotine solution (~0.1 ml/infusion) or insufflations of 5 ml puffs of air were also made to determine if technique *per se* affected MP_{O_2}.

Following administration of one or more of the above under normoxic conditions (arterial P_{O_2} > 80 mmHg) the protocol was repeated after the cats were made hypoxaemic (arterial P_{O_2} < 60 mmHg) by allowing the animals to breath a mixture of 12% O_2, 3% CO_2 and 85% N_2. When exposures were completed the cat was killed with an overdose of anaesthetic and arrested ventilation, and *post mortem* MP_{O_2} was compared to the final *in vitro* calibration in 95% N_2 and 5% CO_2. The value in the dead animal was consistently lower by approximately 3 mmHg and was used as the zero value in calculations of MP_{O_2} (Lösse, Schuchhardt & Niederle, 1975).

Results

Thirty-three cats were used in this study. Arterial P_{CO_2} was maintained at 30–35 mmHg which corresponds to levels in conscious unrestrained cats (Herbert & Mitchell, 1971). During normoxic ventilation, arterial P_{O_2} was >80 mmHg, and oxyhaemoglobin saturation was 94–98% preceding tobacco smoke or carbon monoxide inhalation. The thickness of the anterior wall of the left ventricle proximal to the apex was usually 4–5 mm (*post mortem* examination). MP_{O_2} measured in a single location 1–4 mm deep in each cat heart was 1.6 to 60 mmHg (mean 23.5 mmHg).

Typically a value close to zero was recorded immediately after implantation, followed by a gradual rise until relative stability was reached. Generally, lower MP_{O_2} was recorded in the deeper half of the ventricular wall, but values above the mean were also found there.

To insure that the electrode was responsive to changes of MP_{O_2}, ventilation was arrested for 20–30 s or the respiratory mixture was switched to 95% O_2 and 5% CO_2. Arrested ventilation caused MP_{O_2} to begin a steep decline within 5–15 s while the high oxygen mixture commonly raised MP_{O_2} by 12–17 mmHg as arterial P_{O_2} increased to over 500 mmHg.

Figure 1 is a representative example of the effects of sequential intravenous infusions of nicotine. Rapid, transitory, dose-dependent increases of systolic and diastolic blood pressure followed each infusion. In cats receiving nicotine 2–3 μg/kg, increases of mean

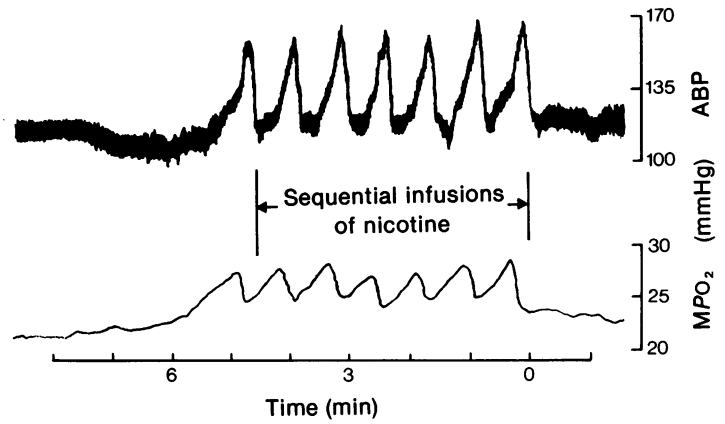

Figure 1 Typical effects of sequential intravenous infusions of nicotine (2 μg/kg every 45 s) on arterial blood pressure (ABP) and myocardial oxygen tension (MPO_2) in the normoxic (arterial PO_2 81 mmHg) cat. Tracing of the original record.

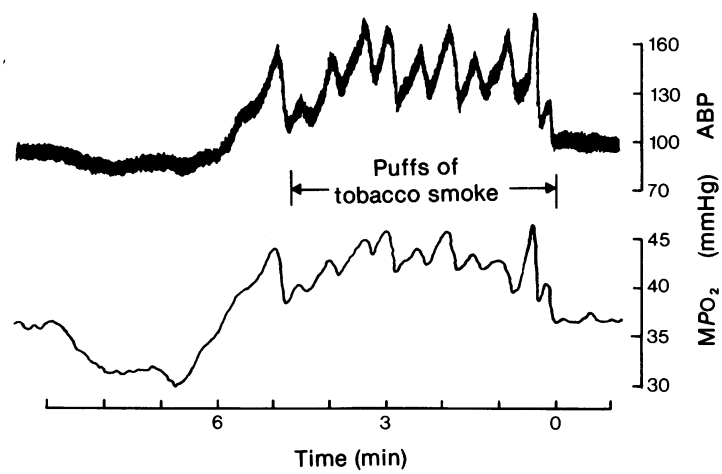

Figure 2 Typical effects of intratracheal puffs (3 ml, every 30 s) of tobacco smoke on arterial blood pressure (ABP) and myocardial oxygen tension (MPO_2) in the normoxic (arterial PO_2 99 mmHg) cat. Tracing of the original record.

arterial pressure generally were 25–35 mmHg, and a temporary 'afterfall' of arterial pressure often followed completion of the sequence. Heart rate was unaltered throughout or showed a small increase (3–4%) coinciding with peaks of arterial pressure. The profile of MPO_2 during nicotine infusions was like that of arterial pressure, i.e. oscillatory, with the difference that peak MPO_2 occurred during the declining phase of each pressor response. Elevations of MPO_2 were most often 4–6 mmHg above the level preceding nicotine infusion. There were a few instances in which augmentation of MPO_2 was marginal, or very large (>10 mmHg). The depth at which MPO_2 was measured appeared to have no relationship to the degree of response. When arterial pressure was temporarily decreased subsequent to nicotine infusions, MPO_2 commonly declined a few millimeters of mercury except in locations where existing MPO_2 was relatively low.

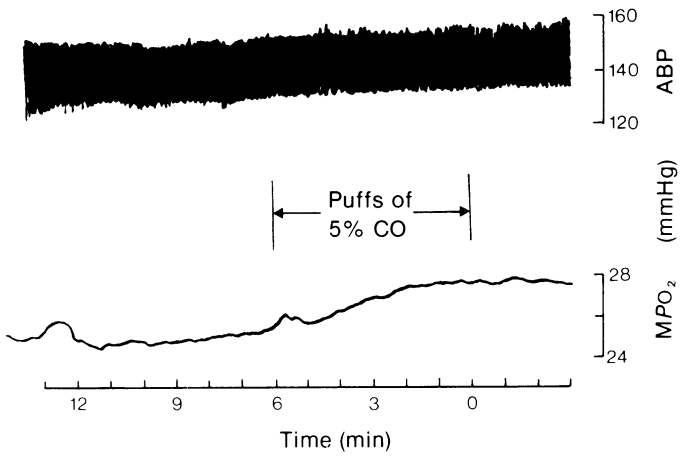

Figure 3 Typical effects of 12 intratracheal puffs (4 ml, every 30 s) of 5% carbon monoxide on arterial blood pressure (ABP) and myocardial oxygen tension (MPO_2) in the normoxic cat (arterial PO_2 90 mmHg). Carboxyhaemoglobin was increased from 0.7% to 4.8%. Tracing of the original record.

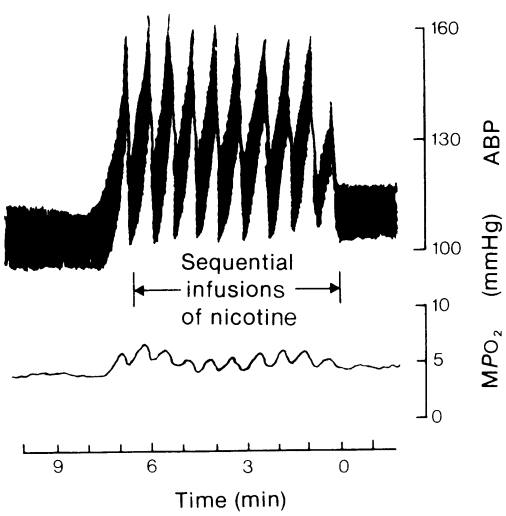

Figure 4 Typical effects of sequential intravenous infusions of nicotine (1 μg/kg every 45 s) on arterial blood pressure (ABP) and myocardial oxygen tension (MPO_2) in the hypoxic (arterial PO_2 52 mmHg) cat. Tracing of the original record.

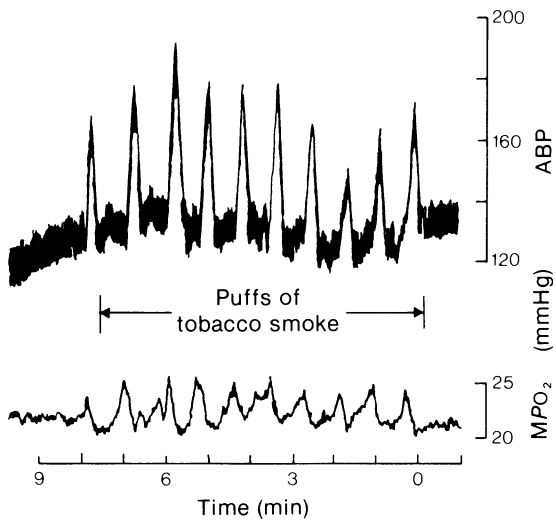

Figure 5 Typical effects of intratracheal puffs (4 ml/every 30 s) of tobacco smoke on arterial blood pressure (ABP) and myocardial oxygen tension (MPO_2) in the hypoxic (arterial PO_2 52 mmHg) cat. Tracing of the original record.

Here arterial afterfall had no appreciable effect on MPO_2. Sequential infusions of small volumes of saline did not influence myocardial oxygen tension.

Intratracheal puffs of freshly drawn tobacco smoke produced responses like those of nicotine (Figure 2). Concomitantly, carboxyhaemoglobin levels increased from 0.7–1.5% during control to 2–3% following 10 puffs or 4–5% following 20 puffs (two cigarettes in succession). Oxyhaemoglobin saturation was decreased by a similar percent. Puffs of air had no effects.

The effects on MPO_2 of puffs of 5% carbon monoxide in air were difficult to assess because of the tendency for MPO_2 to fluctuate slightly with time. In 15

cats in which MPo_2 was stable during administration of air puffs, substitution of the 5% carbon monoxide mixture reduced MPo_2 by approximately 1–4 mmHg as carboxyhaemoglobin increased from control levels to 4–7% (Figure 3). Oxyhaemoglobin saturation declined by a similar amount. Heart rate, blood pressure, and arterial Po_2 were unchanged. During a 5 min period subsequent to carbon monoxide administration the MPo_2 remained relatively stable in approximately half the cats, while in the other half MPo_2 returned toward pre-exposure levels.

When arterial Po_2 was reduced to 45–55 mmHg, MPo_2 decreased to a mean of 14.4 mmHg (range 1–31 mmHg). Oxyhaemoglobin saturation was 74–83%. Heart rate increased by 4–5% and arterial pressure rose slightly in most cats. Quantities of nicotine and smoke equal to those administered during normoxia produced slightly larger increases of blood pressure under hypoxaemic conditions. Heart rate during peak arterial pressure was either unchanged or variably increased or decreased by approximately 4%. MPo_2 commonly increased by 1–3 mmHg during the declining phase of each arterial peak (Figures 4 and 5). Administration of puffs of 5% carbon monoxide to 12 cats in which carboxyhaemoglobin had decreased to $<3\%$ from the higher levels established during normoxia had little effect on MPo_2. As carboxyhaemoglobin increased to 7–11% and oxyhaemoglobin saturation declined similarly, MPo_2 was either unaffected or decreased by 1–2 mmHg. Sites of low MPo_2 (<10 mmHg) typically showed no changes. Blood gases, heart rate, and arterial pressure were likewise unaffected.

Discussion

Of special importance in studies with acutely implanted electrodes is the effect of concomitant tissue trauma. Since the present investigation employed a relatively large electrode we were concerned about the degree to which our results might be spurious. In soft highly vascular tissues such as liver, kidney, and spleen large electrodes (330 μm) may induce appreciable tissue damage upon insertion (Jamieson & van den Brenk, 1965). Nevertheless, Po_2 responses obtained during differing procedures were qualitatively similar to those recorded with smaller (60 μm) electrodes, and absolute Po_2, while usually higher, was not significantly different statistically in most cases. The damage produced by large electrodes in less friable tissues, e.g. muscle, may be comparatively minor since Moss (1968) and van der Laarse & Freud (1975) observed only slight cellular trauma and a small number of free red blood cells in the myocardium adjacent to electrode tips. The tip of our electrode was bevelled to reduce displacement and compression of tissue adjoining the platinum cathode. *Post mortem* examination with a dissecting microscope of myocardium incised along the path of the electrode revealed no discernible blood clots. In addition, the rapid responses of MPo_2 to arrested ventilation and the modulated effect of 95% O_2 and 5% CO_2 suggests that microcirculation neighbouring the electrode tip was intact and functional. Thus we believe that tissue trauma did not materially affect our results. The range of MPo_2 recorded in the cat was generally similar to that reported for the canine myocardium (Moss, 1968; Winbury, Howe & Weiss, 1971; van der Laarse & Freud (1975).

The infusion of nicotine into experimental animals commonly has a positive inotropic effect accompanied by increased arterial blood pressure and coronary blood flow (Forte *et al.*, 1960; Pachinger *et al.*, 1972; Ilebekk & Lekven, 1974). Although cardiac work and oxygen consumption are also increased by nicotine, our MPo_2 measurements suggest that there is a net increase in the myocardial oxygenation during nicotinic stimulation. That peaks of MPo_2 occurred during the declining phase of each pressor response may reflect decreased oxygen consumption concomitant to decreasing work load. In addition, ventricular intramural pressure may be expected to decrease as systolic pressure falls (Brandi & McGregor, 1969), and perhaps this has a salutary effect on microcirculation. Increased concentrations of metabolites may also follow each pressor response and promote vasodilatation (Rubio & Berne, 1969).

Assuming that the effects of nicotine are mediated largely by the release of catecholamines from sympathetic ganglia (Burn, 1960) our observations are consistent with those of Säyen, Sheldon, Horwitz, Kuo, Peirce, Zinsser & Mead (1951), who saw that the administration of adrenaline to dogs increased myocardial oxygen availability.

Inhalation of tobacco smoke also produces increments of arterial pressure, cardiac work, and coronary blood flow (Kien *et al.*, 1959). This is generally conceded to be an effect of the nicotine content (Aronow & Swanson, 1969; Armitage *et al.*, 1975). In our investigation, puffs of tobacco smoke produced blood pressure and MPo_2 responses identical to those of sequential infusions of nicotine. Although carboxyhaemoglobin was increased from control levels of 0.8% to 4–5%, a concentration common to human smokers (Goldsmith, 1970), the profile of MPo_2 was not different from that produced by nicotine. By contrast, puffs of 5% carbon monoxide sufficient to produce similar levels of carboxyhaemoglobin had no effect on arterial pressure or heart rate but reduced MPo_2 by approximately 1–4 mmHg. Although carbon monoxide administration has been reported to decrease arterial Po_2 (Ayres *et al.*, 1970; Brody & Coburn, 1969) we recorded no changes. The effect on

tissue oxygen tension is probably best explained by the carbon monoxide-induced shift to the left of the oxygen dissociation curve (Hlastala, McKenna, Franada & Detter, 1976). Presumably this also occurs when carbon monoxide is absorbed as a component of tobacco smoke but its effect on tissue oxygen levels is overshadowed by the actions of nicotine.

The depressant effect of carbon monoxide administration was marginal in sites where existing MPo_2 was low, or was frequently succeeded by increases of MPo_2 in locations of higher oxygen tension. This suggests that tissue blood flow may have been augmented. Low levels of carboxyhaemoglobin increase coronary blood flow in humans (Ayres *et al.*, 1970), and in canine isolated hearts perfused with blood (Scharf, Permutt & Bromberger-Barnea, 1975). Whether the effect is initiated by myocardial hypoxia is not clear. However, as studies with small platinum electrodes have shown, much of the myocardium is characterized by very low oxygen tension (Whalen, 1971; Lösse *et al.*, 1975), and it is reasonable to suggest that increasing levels of carboxyhaemoglobin may have reduced MPo_2 sufficiently in local areas to initiate mechanisms leading to increased tissue blood flow. Significantly, restricted capacity to augment myocardial blood flow, as in patients with coronary artery disease, is associated with more rapid onset of angina and other signs of myocardial hypoxia during exposure to low levels of carbon monoxide (Ayres *et al.*, 1970; Goldsmith & Aronow, 1975).

The increases of heart rate and arterial pressure initiated by moderate hypoxic hypoxaemia are reflexes mediated by the carotid and aortic bodies (Schmidt & Comroe 1940). Although MPo_2 declined from a mean of 23.5 mmHg to 14.4 mmHg we did not record zero levels even in sites where the pre-hypoxaemic MPo_2 was low. Increases in coronary blood flow (Afonso, Ansfield, Berndt & Rowe, 1972) and additional capillary recruitment (Martini & Honig, 1969) undoubtedly moderated the decline. However, we cannot state with certainty that tissue hypoxia did not exist. As Lübbers (1969) has indicated, monitoring tissue Po_2 in a single location does not provide sufficient information to detect hypoxia. Instead, Po_2 must be measured in many sites to establish a frequency distribution curve which effectively characterizes tissue oxygenation. This technique was not feasible in the present study. Significantly, both nicotine and tobacco smoke produced small increments of MPo_2 concomitant to pressor responses equal to those recorded during normoxia. Thus even under conditions of arterial hypoxia the normal circulatory system retained sufficient capacity to augment myocardial oxygen supply during increased work. Säyen, Katcher, Sheldon & Gilbert (1960) recorded a similar effect in hypoxic dogs during noradrenaline administration. The mechanism producing increased tissue oxygen levels probably includes further dilatation of coronary arteries as occurs in hypoxic dogs during adenosine administration (Afonso *et al.*, 1972).

Elevation of carboxyhaemoglobin levels to 7–11% in hypoxaemic cats had little or no depressant effect on MPo_2, as opposed to more definitive reductions during normoxia. This may reflect potentiation of carbon monoxide's effect on coronary arterial flow by the pre-existing hypoxaemia. As noted earlier (Scharf *et al.*, 1975) increasing levels of carboxyhaemoglobin stimulate coronary blood flow. Of special interest in their study was the finding that carbon monoxide stimulated the largest increases of flow as it reduced arterial oxygen content from 15 vol. % to 10 vol. % or less. In the present work hypoxaemia initially reduced arterial oxygen content to 12–13 vol. % (calculation based on a haemoglobin value of 12 g/100 ml blood and oxyhaemoglobin saturation of 74–83%). Assuming that carbon monoxide has a coronary vasodilatory action in the cat, as well as the dog, we suggest that further reductions of arterial oxygen content by carbon monoxide inhalation prompted a larger increase of coronary arterial flow than during normoxic conditions. Presumably, then, microcirculatory flow in hypoxaemic cats was augmented sufficiently to over-ride the effects of declining oxygen content of the blood and a leftward shift of the oxyhaemoglobin dissertation curve.

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