Brit. J. Anaesth. (1969), **41**, 307

INFLUENCE OF HYPOXIA AND CORONARY LIGATION ON CARDIAC ARREST IN DOGS ANAESTHETIZED WITH PENTOBARBITONE

BY

SURENDRA KUMAR AND SHOBHA SRIVASTAVA

SUMMARY

The response of the heart to ligation of the anterior descending branch of the left coronary artery alone and when followed by exposure to progressive hypoxia was studied in dogs anaesthetized with pentobarbitone. Ligation alone did not have a direct lethal action on the heart whether myocardial infarction developed or not. Dogs in which there was no electrocardiographic evidence of infarction developed cardiac failure concomitant with respiratory failure when exposed to progressive hypoxia. In those showing evidence of infarction, however, exposure to hypoxia led to the development of ventricular fibrillation first, followed by circulatory and respiratory failure.

Of the many possible aetiological factors leading to sudden cardiac failure during general anaesthesia hypoxia has been thought to be important because anaesthetic agents usually cause a certain degree of respiratory depression. However, all cases of sudden cardiac arrest do not appear to be due entirely to hypoxia. Ziegler (1948) reported that in nine patients with cyanotic heart disease dying of cardiac arrest during anaesthesia, the degree of cyanosis was appreciably less just before death in comparison to the pre-anaesthetized state. Kumar and Srivastava (1965) did not observe primary cardiac arrest in severely hypoxic dogs. In their animals cardiac arrest was always secondary to respiratory arrest. Stephenson, Reid and Hinton (1953) suggested that a lesion in heart muscle itself could render it more susceptible to vagal inhibition and that hypoxia accentuated the effect of vagal stimulation. In the light of these findings the intention was to investigate the response of the heart to hypoxia when acute coronary ischaemia was produced during anaesthesia.

MATERIAL AND METHODS

Experiments were performed on 30 unpremedicated healthy dogs of both sexes weighing from 10 to 14 kg. Anaesthesia was induced using pentobarbitone sodium 30 mg/kg injected intravenously. Further doses, up to 10 mg/kg, were given to some dogs 2–3 hours later. Pulmonary ventilation was maintained artificially with air through an endotracheal tube. The heart was exposed through a left thoracotomy. Diaphragmatic movements were recorded kymographically to provide an indication of spontaneous respiratory activity. Blood pressure was recorded from a femoral artery. The electrocardiogram (lead III) was recorded on a Burdick electrocardiograph running at a paper speed of 25 mm/sec, using three bipolar limb leads.

The effect of ligation of the anterior descending branch of the left coronary artery alone was observed for the next 6 hours in 10 dogs. In the remaining 20 dogs hypoxia was induced 1 hour after left coronary ligation by allowing them to rebreathe 7 litres of air through a soda-lime tower contained in a Benedict Roth apparatus. The rate of artificial respiration was synchronized approximately to the diaphragmatic excursions. Arterial blood was collected under liquid paraffin in an oxalated tube before rebreathing was started and then intermittently. The electrocardiogram was recorded at each blood sampling. Blood samples were analysed for oxygen and carbon dioxide content by the method of Peters and Van Slyke (1932). The haemoglobin percentage of each sample was determined by Haldane's method. The percentage saturation of haemoglobin with oxygen was calculated by assuming its oxygen combining capacity to be 1.34 ml/g.

SURENDRA KUMAR, M.D.(HONS.), PH.D.; SHOBHA SRIVASTAVA, M.D.(PHYSIOL.), M.S.(ANAESTH.); Department of Physiology, King George's Medical College, Lucknow-3, India.

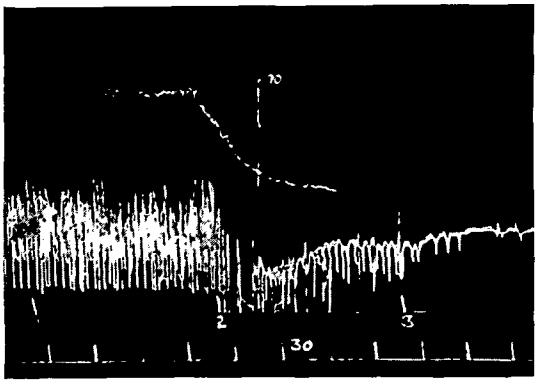

FIG. 1

Dog, anterior descending branch of left coronary artery ligated and animal exposed to hypoxia. Record from above downwards of blood pressure and diaphragmatic excursions. Note sudden fall of blood pressure to zero and continuation of respiration for some time before final apnoea developed. Time signals 30 seconds.

RESULTS

In the 10 dogs subjected to coronary artery ligation only, the mean arterial pressure was maintained at about 100 mm/Hg during the 6-hour observation period. The saturation of haemoglobin with oxygen varied between 86 and 100 per cent (mean 94.1 ± 5.4). In 8 dogs no electrocardiographic abnormality was observed whilst in 2 there was elevation of the ST segment in leads II and III, indicating development of myocardial infarction.

Of the 20 dogs subjected, in addition, to progressive hypoxia for periods of 25–30 minutes, no electrocardiographic abnormality was observed in 17. Gradual respiratory failure was associated with the progressive hypoxia as judged from cessation of diaphragmatic movements, which after a further period of about 5 minutes was followed by cardiac asystole or ventricular fibrillation. Death usually took place half an hour after commencement of exposure to hypoxia. The lowest percentage of oxygen in arterial blood recorded in this group was 3 per cent (saturation 21 per cent) at the time of asystole or fibrillation. In the remaining 3 dogs in this group coronary ligation was followed by ST segment depression in leads II and III with or without corresponding elevation in lead I. Progressive hypoxia in the 3 dogs resulted in sudden onset of ventricular fibrillation within 4–6 minutes, leading to circulatory and then to respiratory failure and death (fig. 1). In 2 of these the oxygen saturation of haemoglobin was found to be 41 and 28 per cent just before the onset of ventricular fibrillation.

DISCUSSION

The fact that none of the dogs in the first group died shows that ligation of the anterior descending branch of the left coronary artery alone need not have an immediately lethal action as long as adequate pulmonary ventilation with air is maintained. Mathur and Sapru (1962, 1963) studied the electrocardiographic changes as a result of such a ligation in the dog. Nydick and associates (1957) and Mathur and Sapru (1963) observed ST segment and T wave changes almost consistently. In the present study only 2 of the dogs of the control group showed electrocardiographic evidence of myocardial infarction and these dogs survived the 6-hour post-ligation period. In the remaining dogs of this group ligation did not result in myocardial infarction, possibly due to effective collateral circulation.

In the second group, subjected to progressive hypoxia, myocardial infarction after coronary ligation was observed in only 3 dogs. In these animals ventricular fibrillation suddenly developed within 4–6 minutes which was followed by a respiratory failure after 2–3 minutes. Primary cardiac failure therefore occurred in these cases which then resulted in circulatory and respiratory failure. In the remaining 17 dogs of this series, myocardial infarction did not occur and death was primarily due to respiratory failure. Whilst studying the effect of hypoxia, Kumar and Srivastava (1965) in dogs, and De Haan and Field (1959) in rats, reported that cardiac asystole occurs as a secondary but inevitable consequence of respiratory arrest. In the dogs in which the coronary artery was ligated but in which infarction did not develop, hypoxia as low as 3 per cent oxygen (saturation 21 per cent) was enough to sustain heart beat and circulation. The 2 non-hypoxic dogs in which signs of myocardial infarction developed survived as long as normal ventilation was maintained. However, in the animals developing myocardial infarction, as hypoxia was induced (and the arterial oxygen saturation fell below 41 per cent and 28 per cent in 2) sudden ventricular fibrillation occurred.

Gilbert, Leroy and Fenn (1940) found in dogs that distension of the stomach or gall bladder reduced coronary blood flow and suggested that the reduction was the result of reflex coronary constriction. Eckenhoff, Hafkenschiel and Landmesser (1947) and Winbury and Green (1952) failed to confirm the reflex nature of this response. Winbury and Green (1952) also suggested that the reduction in coronary blood flow is secondary to fall in systemic blood pressure. Eckenhoff, Hafkenschiel and Landmesser (1947) further found that anoxia increased the rate of coronary blood flow. Coronary ligation and hypoxia therefore appear to produce opposite effects on coronary blood flow. Possibly this accounts for our finding that in 17 of 20 dogs of the second group, even during severe hypoxia, the heart did not stop until apnoea developed. This was reported earlier by Kumar and Srivastava (1965) who observed in dogs subjected to hypoxia that the blood pressure was sustained until the development of apnoea. In some susceptible animals in which coronary ischaemia results in myocardial infarction, as exemplified by 3 out of the 20 dogs, even moderate hypoxia may lead to ventricular fibrillation before apnoea develops. Cross and associates (1963) observed that the contractile strength and performance of an isolated dog heart was affected severely when the oxygen saturation of the perfusing blood was below 25 per cent. Hypoxia therefore appears to have precipitated primary cardiac failure. Sudden standstill or asystole was never observed.

On the basis of these experiments it is therefore suggested that patients in whom primary cardiac arrest occurs during surgery might actually be developing ventricular fibrillation. This could, however, be confirmed only if continuous electrocardiographic monitoring of all cases undergoing surgery were undertaken.

The fact that hypoxia produced ventricular fibrillation in dogs developing myocardial infarction suggests that the foci for fibrillation must be starting within the dying infarcted muscle. Ng and associates (1966) observed that mild hypoxia produced significant stimulation of the ventricle. Wollenberger and Shahab (1965) demonstrated the release of noradrenaline by anoxia in the rabbit heart. Both these factors are known to produce ventricular fibrillation. In the present study, however, hypoxia down to 3 per cent oxygen did not cause ventricular fibrillation after coronary ligation without subsequent myocardial infarction. Cross and associates (1963) have further observed that reflexes originating from the carotid artery territory due to hypoxic stimulation result in heart failure. These impulses also possibly contribute to the factors mentioned above in precipitating a primary cardiac failure due to ventricular fibrillation in an acutely infarcted heart.

REFERENCES

Cross, C. E., Rieben, P. A., Barron, C. I., and Salisbury, P. F. (1963). Effect of arterial hypoxia on the heart and circulation: an integrative study. *Amer. J. Physiol.*, **205**, 963.

De Haan, R. L., and Field, J. (1959). Anoxic endurance of cardiac and respiratory function in adult and infant rat. *Amer. J. Physiol.*, **197**, 445.

Eckenhoff, J. E., Hafkenschiel, J. H., and Landmesser, C. M. (1947). The coronary circulation in the dog. *Amer. J. Physiol.*, **148**, 582.

Gilbert, N. C., Leroy, G. V., and Fenn, G. K. (1940). Effect of distension of abdominal viscera on blood flow in circumflex left coronary artery of dog. *Amer. Heart J.*, **20**, 519.

Kumar, S., and Srivastava, S. (1965). Evaluation of hypoxia, hypercarbia and asphyxia in the production of cardiac arrest during surgical anaesthesia. *Indian J. Physiol. Pharmacol.*, **9**, 173.

Mathur, K. S., and Sapru, R. P. (1962). Electrocardiographic changes after experimental ligature of the anterior descending branch of left coronary artery in dogs (Part I). *Indian Heart J.*, **14**, 142.

—— —— (1963). Electrocardiographic changes after experimental ligature of the anterior descending branch of left coronary artery in dogs (Part II). *Indian Heart J.*, **15**, 5.

Ng, M. L., Levy, M. N., De Geest, H., and Zieske, H. (1966). Effect of myocardial hypoxia on left ventricular performance. *Amer. J. Physiol.*, **211**, 43.

Nydick, I., Ruegsegger, P., Worbleweski, F., and La Due, J. S. (1957). Variations in serum glutamic oxaloacetic transaminase activity in experimental and clinical coronary insufficiency, pericarditis and pulmonary infarction. *Circulation*, **15**, 324.

Peters, J. P., and Van Slyke, D. D. (1932). *Quantitative Clinical Chemistry*, Vol. II. Baltimore: Williams & Wilkins.

Stephenson, H. E., Reid, L. C., and Hinton, J. W. (1953). Some common denominators in 1200 cases of cardiac arrest. *Ann. Surg.*, **137**, 731.

Winbury, M. M., and Green, D. M. (1952). Studies on the nervous and humoral control of coronary circulation. *Amer. J. Physiol.*, **170**, 555.

Wollenberger, A., and Shahab, L. (1965). Anoxia induced release of noradrenaline from isolated perfused heart. *Nature*, **207**, 88.

Ziegler, R. F. (1948). Cardiac mechanism during anesthesia and operation in patients with congenital heart disease and cyanosis. *Bull. Johns Hopk. Hosp.*, **83**, 237.

L'INFLUENCE DE L'HYPOXIE ET DE LA LIGATURE CORONAIRE SUR L'ARRET CARDIAQUE CHEZ LE CHIEN, ANESTHESIE AU PENTOBARBITONE

SOMMAIRE

La réaction du coeur après ligature de la branche descendante antérieure de l'artère coronaire gauche, seul et préalablement à l'exposition à une hypoxie progressive, a été étudiée chez des chiens, anesthésiés au pentobarbitone. La ligature seule n'exerça aucun effet léthal sur le coeur, qu'un infarctus du myocarde se soit développé ou pas. Les chiens signes électrocardiographiques d'infarctus développèrent une insuffisance du coeur et de la respiration, lorsqu'ils furent soumis à une hypoxie progressive. Mais l'exposition à l'hypoxie mena chez les animaux avec signes d'infarctus en première instance au développement de fibrillation ventriculaire, suive d'insuffisance circulatoire et respiratoire.

EINFLUSS VON HYPOXIE UND KORONARLIGATUR AUF DEN HERZSTILLSTAND BEI HUNDEN UNTER PHENOBARBITAL-ANÄSTHESIE

ZUSAMMENFASSUNG

Bei Hunden, die mit Phenobarbital anästhesiert waren, wurde die Reaktion des Herzens auf die Ligatur des vorderen absteigenden Astes der linken Koronararterie sowohl allein als auch, wenn der Ligatur eine progressive Hypoxie folgte, untersucht. Die Ligatur allein hatte keine unmittelbar letale Auswirkung auf das Herz, gleichgültig ob es zur Entwicklung eines Herzmuskelinfarktes kam oder nicht. Bei Hunden ohne elektrokardiographisch nachweisbare Anzeichen für einen Infarkt entwickelte sich parallel zum Versagen der Atmung ein Herzversagen, wenn sie einer progressiven Hypoxie ausgesetzt wurden. Bei den Tieren mit Anzeichen für einen Myokardinfarkt jedoch führte die Hypoxie-Exposition zuerst zur Entwicklung von Kammerflimmern, dem ein Versagen von Kreislauf und Atmung folgte.

CORRESPONDENCE

AN IMPROVED ELECTRONIC SIMULATOR FOR THE STUDY OF THE DISTRIBUTION OF ANAESTHETIC AGENTS

Sir,—I read the above paper by Crane, Yates and Steen (*Brit. J. Anaesth.* (1968), **40**, 936) with great interest. The general burden of the paper is that an "active" analogue computer (incorporating operational amplifiers) is better at simulating the distribution of anaesthetic agents in the body than the simple, passive, condenser-resistor networks such as those of Severinghaus, of McKrell and of Mapleson (Papper and Kitz, 1963). While agreeing with this general proposition a number of detailed points in the paper call for comment.

Most of the criticisms of the simple passive analogues are not valid. I cannot speak in detail of the analogues built by others but, so far as my own version is concerned, study of the detailed description (Mapleson, 1963) will reveal that the problem of leakage of charge from condensers can be overcome; that the venous return to the lungs *is* represented, although indirectly (see the mathematical part of the paper); and that "variations of morphological structure" can be arranged by plugging various condensers into a skeleton circuit and by switching in various resistors. Even a right-to-left shunt could be represented by an extreme version of Eger and Severinghaus's (1964) uneven-distribution analogue, although here leakage of charge might become a problem.

However, much more important than any possible limitations of the passive analogues is a major flaw in the arrangement of the active analogue of Crane and his colleagues. From both circuit diagrams it is evident that the venous return is connected, not to the alveoli of the lungs, but to the mouth. Therefore, the circuit is not an analogue of any normal animal!

The authors also seem to confuse venous return with rebreathing when they compare the effects of "80 per cent venous gas (rebreathing inhalation anaesthetic technique) and 20 per cent venous gas (non-rebreathing anaesthetic technique)"—their parentheses. The authors use the term "venous gas" to mean anaesthetic gas brought back to the lungs in the venous return. All venous blood must always go, either to the alveoli, or through the right-to-left shunt. To take account of rebreathing requires some representation of the anaesthetic circuit. This has been attempted in the simple analogue of Severinghaus (1963) but is not done in Crane's analogue.

Problems which could readily be handled by an active analogue are the concentration effect and the second-gas effect. These can be represented only with difficulty in the simple passive analogue (Mapleson, 1964). It is to be hoped that the authors will elaborate their model to do this, but only after they have corrected their present version.

W. W. MAPLESON *Cardiff*

REFERENCES

Eger, E. I. II, and Severinghaus, J. W. (1964). Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. *Anesthesiology*, **25**, 620.

Mapleson, W. W. (1963). An electric analogue for uptake and exchange of inert gases and other agents. *J. appl. Physiol.*, **18**, 197.

—— (1964). Inert gas-exchange theory using an electric analogue. J. *appl. Physiol.*, **19**, 1193.

Papper, E. M., and Kitz, R. J. (eds.) (1963). *Uptake and Distribution of Anesthetic Agents*. New York: McGraw-Hill.

Severinghaus, J. W. (1963). Role of lung factors; in Papper, E. M., and Kitz, R. J. (eds.), *Uptake and Distribution of Anesthetic Agents*, p. 59. New York: McGraw-Hill.

Sir,—In my article published in the December 1968 number (*Brit. J. Anaesth.*, **40**, 936) the curves depicting concentration versus time in figures 5 and 6 show relative responses with all scales identical except for fat which has been magnified for clarity by a factor of 10.

STEPHEN N. STEEN *New York*