Panel discussion

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DR O. HIFZI: Does reserpine cause depletion merely by increasing the release of noradrenaline or also by blocking the uptake of noradrenaline by the nerve ending?

PROFESSOR SHANKS: This is a very good question and there is not a simple answer as we do not know exactly how reserpine works. Guanethidine has the same effect but instead releases the noradrenaline into the circulation and there is an increase in heart rate and arterial pressure. After the administration of reserpine, noradrenaline disappears. No one, as far as I know, has worked out where it goes.

DR HIFZI: Are there any post-capillary sphincters? If their existence is proved, can you explain their control?

PROFESSOR NEIL: The evidence for post-capillary sphincters is very tenuous except in amphibia. I think the post-capillary resistance, which in any case in resting conditions is about one-fiftieth of that of the pre-capillary resistance, is mostly due to ordinary non-organized movements which begin in the smallest venules, affected by transmural pressure.

DR G. E. HALE ENDERBY: What effects has end-tidal positive pressure on pulmonary circulation, dead space, etc.?

DR LEIGH: Positive pressure during expiration tends to reduce cardiac output and blood pressure. It will affect the circulation adversely under conditions of low blood volume. If there is cardiac failure it is positively helpful. (Alveolar dead space increases if pulmonary circulation, i.e. cardiac output decreases.)

DR ENDERBY: In view of the importance of the vertebral venous plexus on circulation why does the Valsalva have such a dramatic effect on blood pressure?

PROFESSOR ECKENHOFF: Because the Valsalva in the presence of hypovolaemia or a ganglionic blockade leads to a marked reduction in cardiac output and reduced venous return.

I would be interested to have Professor Neil's reaction to that?

PROFESSOR NEIL: I entirely agree with that answer.

DR E. HARWICK: What will happen to blood pressure, heart rate and skin blood flow after infiltration of the skin with adrenaline 1 : 200,000 after which 2.5 mg practolol is injected intravenously during halothane anaesthesia and controlled ventilation?

PROFESSOR SHANKS: If only a small amount of adrenaline is infiltrated and none gets into the general circulation this will have no effect on the circulation, and practolol will have little effect. If the adrenaline does get in the circulation we would expect an increase in heart rate, constriction of the skin vessels and an increase in arterial pressure: 2.5 mg is a very small dose of practolol and I doubt if this would have any effect on the increase in heart rate produced by adrenaline. A larger dose of practolol 20 mg intravenously, would probably decrease the adrenaline tachycardia with possibly no change in either blood pressure or skin blood flow. Such observations were described by my colleagues (Brick *et al.*, 1968). On the other hand, a small dose of propranolol would inhibit such an adrenaline tachycardia and convert it to a bradycardia (Brick *et al.*, 1968). This is a response to the greater increase in arterial pressure produced by adrenaline after propranolol as a result of the blockade of the vasodilator action of adrenaline in skeletal muscle vessels.

PROFESSOR E. A. COOPER: Is the fall in PA pressure in hypotension sufficient to explain the large increase in VD/VT?

DR LEIGH: The changes in pulmonary arterial pressure which we saw were very small—this reflects the low resistance of the system. I think the large increase in VD/VT is explained by the reduction of flow through the capillaries.

PROFESSOR ECKENHOFF: I would like to ask a question on this. You mentioned earlier these changes in the VD/VT ratio were in the erect position. Do you think the same occurs with the patient lying flat on an operating table for 2 or 3 hr, breathing relatively smoothly, quietly, or even when controlled quietly?

DR LEIGH: I am pretty sure the same phenomena can be demonstrated.

DR C. PRYS-ROBERTS: Would you please discuss the relevance and limitations of jugular venous PO_2 measurements in the assessment of adequacy of cerebral perfusion during induced hypotension?

PROFESSOR ECKENHOFF: The usual cerebral venous measurements are made in the jugular bulb and so far as I am concerned they are only reliable when conditions

remain static in the control versus the observation period. If the position of the patient is changed, or if blood pressure is changed, I am not sure that the measurements made in the jugular bulb are applicable to whole brain changes. What you get in a sample from the jugular bulb is an average of blood that perfuses the entire brain and it does not necessarily indicate what is happening in the various areas of the brain. There is also some evidence to suggest that there is a difference in cerebral outflow systems when blood pressure or body position is changed. Professor Neil, would you care to comment on the cerebral measurement problem?

PROFESSOR NEIL: I agree with you that the jugular bulb measurements are only comparable when the same position is maintained. In all cerebral blood flow discussion I am reminded of a quotation from Seymour Kety that if you do a tremendous amount of mental activity it is equivalent to eating one or two peanuts. I think this is stuff for the birds myself; my brain gets something of the order of 800 ml of blood and it weighs perhaps 1400 g. In the average 1400 g brain—60% is white matter and 40% (roughly) grey matter. For the white matter we do not really know the oxygen usage, but in the peripheral axons the oxygen usage is only 0.3 ml/100 g a min. Now the brain, as Professor Eckenhoff said, is using something of the order of 45 ml of oxygen per min, so when you begin to work it out you have got 600 g of grey matter—that is less than 0.9% of the body weight—using one-fifth of the oxygen usage of the total body. It is the grey matter that is doing it. The point I was seeking to establish was made by Seymour, Kety and Sokolov (1960) that when you take precautions to get an idea about regional cerebral flow you have a different picture. Carl Schmidt and Hendrix in Philadelphia in 1937 showed that if you flash a light at an animal (it happened to be a rabbit) you get a rise of temperature in the occipital lobe. There was a rise in the cerebral blood flow. At that time they could not measure it quantitatively and that is why Schmidt later developed the technique of measuring the total flow. But once you begin to measure total flow in animals and get evidence of regional flow as well, although total flow is regulated or autoregulated, you find striking regional changes within that total. So I do think that before you say that the extra oxygen usage of thinking out the theory of relativity would not light a 15 W bulb one should consider regional changes.

PROFESSOR ECKENHOFF: You have made me feel better.

DR HAYEM: What is the rationale of using propranolol in the treatment of essential hypertension clinically? How should side effects compare with those of earlier forms of treatment?

PROFESSOR SHANKS: The effectiveness of propranolol was found largely by accident. I think that the hypotensive effect of propranolol was probably first noticed by Dr B. N. E. Prichard when he was treating patients for angina. The precise mode of action of propranolol in hypertension has not been worked out. If propranolol is given by intravenous injection there is a small fall in pressure in the hypertensive patients but much less than that which occurs when the drug is given orally over a long period of time. It has been suggested that when propranolol is given orally there is an initial fall in pressure

followed by a much slower progressive fall over weeks and the mechanism of this fall is not really understood. The side effects are less common after propranolol than after other hypotensive drugs, with two exceptions. In patients with asthma, propranolol may produce bronchospasm, and in patients with depressed cardiac function propranolol may produce cardiac failure.

PROFESSOR E. A. COOPER: In the hemi-sectioned cats of Mellander is it reasonable to attribute all the changes to the venous side rather than pre-capillary?

PROFESSOR NEIL: The answer is a bit like 'What, never?' 'Well, hardly ever'. 'All', of course, is an over-estimate, but I should think about 95% of the effect is venous, because that is where the blood is, so to speak. The rapid change in volume occurs here because that is where the blood capacity is. There may be a small pre-capillary force which drives some of the blood out of the capillary part, but the great majority is due to venular change and I think it is wise to ignore the capacity side of the pre-capillary section.

I was astounded one day when doing experiments on hypothermia with the circulation shut off that a big greyhound dog, from the thoracic aorta to the bifurcation of the common iliac and down to the knee, when dissected had a capacity of only 5 ml. I think the amount of blood that is in the pre-capillary section can be ignored. The interesting change in limb volume is due to alterations in capillary transfer which is, however, slower.

PROFESSOR ECKENHOFF: Would you comment upon what one needs to do to compensate for the changes in the VD/VT ratio that occur during hypotension?

DR LEIGH: The increase in VD/VT potentially causes an increase in CO_2 which, to a certain extent, can be compensated for by the spontaneously breathing patient. However, if they are relatively deeply anaesthetized, the respiratory response to CO_2 diminishes and it is unlikely that compensation, by increasing rate or depth of ventilation, will occur. The disadvantage of the resulting CO_2 rise would be increased cardiac output and more bleeding. On the other hand, the high CO_2 level would protect the cerebral circulation. If you choose to compensate for the increase in VD/VT by instituting IPPV you will firstly, remove the sign of spontaneous respiration, which some people rely upon as a sign of adequate medullary perfusion and secondly—if you permit hyperventilation and a fall in CO_2 —you will embarrass the cerebral circulation. Probably the best compromise is to use artificial ventilation but to keep PCO_2 normal to protect the cerebral circulation.

PROFESSOR ECKENHOFF: Are you implying that every time you use the technique you ought to have an arterial line and measure blood gases? That is about the only implication I can draw from this.

DR LEIGH: That is obviously impractical all the time. I think one should use one's experience of ventilation patterns in order to achieve what one hopes to be a normal PCO_2 . Personally, I use arterial blood gases as often as I can. Perhaps I am in a somewhat privileged position.

PROFESSOR ECKENHOFF: I am in a privileged position, too, and I can use similar techniques—and for those of you who happen to know that I am, for better or for worse, a Dean of a medical school, I still manage to get

several hours of work in the operating theatre, and any time a deliberate hypotension comes along I am usually the one to do it. I find that the best guide to what you are doing is to stand and keep my eyes on the surgical field and on the colour of the blood, particularly the venous blood compared with the arterial blood. If the arterial blood is well oxygenated, as is evidenced by nice bright red blood, I think pulmonary ventilation is adequate. If the venous blood is black I think there is something wrong with the circulation as a whole. This to me is the best clinical guide. Would Dr Leigh like to comment?

DR LEIGH: The colour of arterial blood will be, I would suggest should be, very little affected over quite a wide range of blood pressure and cardiac output because the lungs are still working, unless there is a tremendous increase in shunt. Although there is often a small increase in shunt during hypotension, it is not sufficient to impair the oxygenation of arterial blood. In any case, the anaesthetist is in a position to keep up arterial oxygenation because of control over the inspired oxygen. However, I certainly agree with you about the colour of venous blood at low cardiac output—but CO₂ does not produce any colour change!

PROFESSOR ECKENHOFF: How concerned are you if the PCO₂ is 50 or 55 compared with the normal 40 mmHg? I think we pay too much attention to it.

DR LEIGH: I am sure you are right in some respects, bearing in mind that CO₂ in itself exerts first a stimulant and then a depressant effect on the heart. The depressant effect is particularly exacerbated by age; the older the person, the lower the CO₂ level that will have a depressant effect on the heart. But I would agree with you that the difference between 20 and 40 mmHg is probably more important as regards cerebral blood flow. A PCO₂ of 20 mmHg during controlled ventilation (as practised routinely) is most common and we should make sure that patients undergoing hypotension are not hyper-ventilated in this manner.

PROFESSOR ECKENHOFF: That is reasonable. I have a particular concern about keeping on one's feet and watching the colour of the blood. Whenever I see an anaesthetist sitting on his rear behind the screen, it is time he should be run through again!

PROFESSOR ECKENHOFF: In your experience or your knowledge, is there a linear relationship between PCO₂ and adrenergic stimulation?

PROFESSOR NEIL: In my experience, no.

I am not convinced that CO₂ has much effect on cardiac output and adrenergic stimulation. If there is you should tell me, because I have just written a chapter on catecholamines and the circulation for the Handbook of the American Physiological Society and the effect of CO₂ did not come into it!

DR LEIGH: It is not too late to change it if it is still 'in press'! Work done by Millar about 10 years ago on cardiac output, and work by Prys-Roberts, shows that CO₂ produces a rise in cardiac output. At the Westminster Hospital we have also demonstrated this response. When CO₂ is increased from a starting level of 20 mmHg cardiac output rises.

PROFESSOR ECKENHOFF: From 40 to 60 mmHg?

DR LEIGH: No. You get a small increase in cardiac output as you get into the mid-forties. In the fifties you

get a greater increase, whilst at a PCO₂ of 70 mmHg you start to get the depressant effect. There is much confusion on the effect of CO₂ on the heart because of this dual response. The initial response can be blocked with propranolol, thus indicating that it is due to sympathetic stimulation.

PROFESSOR NEIL: What is the order of increase as compared with sympathetic effects on the central venous conduits. What, seriously, do you think is the important contribution in a system in which you also have a general sympathetic discharge. Which has the first and foremost effect on cardiac function?

PROFESSOR ECKENHOFF: Would Dr Prys-Roberts like to comment on this?

DR PRYS-ROBERTS: The thing that should be said about CO₂ and cardiac output is it does matter very considerably under what conditions the experiments are performed. All our studies have been done during anaesthesia, either in man or in animals. In awake conscious man changes in CO₂ have relatively little effect on cardiac output. In other words taking CO₂ down from 40 to 20 or less has very little effect. However, ventilation increases cardiac output and if conscious man breathes CO₂ cardiac output will rise and with it there will be tachycardia.

PROFESSOR ECKENHOFF: What strength CO₂?

DR PRYS-ROBERTS: Even 5%. You cannot breathe more than 10%.

PROFESSOR J. E. ECKENHOFF: That is conscious man. Is he getting some other effect than CO₂? Is he becoming apprehensive—because one does get apprehensive breathing 5% CO₂?

DR PRYS-ROBERTS: I have done it myself.

PROFESSOR ECKENHOFF: You did not get apprehensive?

DR PRYS-ROBERTS: No. But there is certainly an increase in cardiac output, a sympathetic response overlaid on another response. If you look at anaesthetized man, it depends on the type of anaesthesia you use, because the greater the depth of anaesthesia the less the effect of CO₂ rise, the greater the effect of CO₂ fall. Thus, during ether anaesthesia you get quite a marked response, but with halothane very little response to hypercarbia and quite a marked response to hypocarbia. The crux of it, what matters, is not sympathetic stimulation but what effect CO₂ has on the peripheral vessels. I do not think the effect on the depressed myocardium matters a great deal.

PROFESSOR ECKENHOFF: Would Professor Neil care to comment?

PROFESSOR NEIL: Yes. In conscious man, there is obviously respiratory stimulation, and this makes quite a large contribution to increased cardiac output. In animal experiments, you said that high PCO₂ produces a vasodilation, in many vessels certainly, but you said there was also a depressed myocardium implying that this is a direct effect?

DR PRYS-ROBERTS: That is the combination of the effects of high CO₂ and deep anaesthesia.

PROFESSOR NEIL: How high a CO₂ tension?

DR PRYS-ROBERTS: Oh, 70 to 80 mmHg. That is not uncommon during straightforward clinical anaesthesia.

PROFESSOR ECKENHOFF: I think the point to be taken from the discussion is that it is very difficult to extrapolate data obtained in normal, awake man to man in the

anaesthetized state or in man who has had a series of pre-operative medications with variable effects. Which has the most profound effect—let's not worry about the relatively minor ones?

DR HIFZI: Would you explain the mechanism involved in tachyphylaxis following intravenous noradrenaline drip?

PROFESSOR SHANKS: In my experience you do not get tachyphylaxis to noradrenaline, at least not in animals. There has been a lot of interest in the subject recently. The death rate from asthma increased dramatically in this country between 1960 and 1966 and this increase coincided with a marked increase in the amount of isoprenaline used. Studies were carried out to find if isoprenaline was contributing to this increase and if so how it produced death. One view was that tachyphylaxis occurred with isoprenaline, but several lots of experts have looked at this, in animals and in man, and cannot find any tachyphylaxis in response to isoprenaline. Professor Neil referred to the reduction in the patient's response to noradrenaline intravenously. Whether this is tachyphylaxis or not I am not sure.

PROFESSOR ECKENHOFF: How strong is the beta stimulant action of phentolamine?

PROFESSOR SHANKS: My theory is that phentolamine is only an alpha blocking agent. It may produce a tachycardia as a reflex response to the fall in arterial pressure.

PROFESSOR ECKENHOFF: So the response is not very strong at all?

PROFESSOR SHANKS: No it is not.

DR ENDERBY: Does skin vascularity decrease more than that of essential organs when systemic blood pressure falls?

PROFESSOR NEIL: I cannot really answer that, because skin vascularity decreases fantastically when systemic pressure falls. From resting forearm skin level you can get down to less than 0.1 ml/min, just as it can go up in the forearm in heat stress to 150 ml/min. It goes down fantastically in severe haemorrhage, but to say it goes down more or less than essential organs I would not know, because you cannot get at the organs. The kidney cortex, for instance, undergoes a startling amount of constriction.

I have recently been looking at venous sympathetic discharge and the reflexes that affect it—these can be very dramatic in the abdominal viscera.

PROFESSOR ECKENHOFF: Is the change of vascularity of the skin after ganglion block of any significance in so far as accommodation of blood volume is concerned?

PROFESSOR NEIL: Yes, together with the inhibition of tissue flow which falls purely hydrodynamically. Thus there is the extraordinary shrivelling which you see in somebody who has seriously bled. Conversely, if you blockade the sympathetic supply in a man in an equable environmental temperature, there is quite a substantial increase in the subcutaneous venular volume of the skin. I would be interested to hear what Professor Shanks has to say.

PROFESSOR SHANKS: Hypotension occurs because of sympathetic paralysis. There is no reflex vasoconstriction on standing to maintain venous return and cerebral blood flow; and with stress it is exactly the same. When the patient goes into a warmer environment there is a

redistribution of the blood and quite a large volume of blood is in the skin under heat stress and it goes there rather than going into the veins.

PROFESSOR ECKENHOFF: I would like to see data. I do not believe a significant volume of blood can be contained within the skin. Nonetheless, this could be quite right.

PROFESSOR A. CRAMPTON SMITH: Would Professor Eckenhoff comment on the fact that it has recently been shown that quadriplegic patients (who have no sympathetic connection with the brain) do not decrease cerebral blood flow during hyperventilation?

PROFESSOR ECKENHOFF: I said earlier, if you recall, that there was no significant evidence of nervous control over the cerebral circulation in man. Would Professor Neil care to comment?

PROFESSOR NEIL: I think the same but one cannot ignore some of the evidence. Michael Purves inquired into this. There is some sympathetic innervation, though I have always played it down, of the deep cerebral vessels. The trouble is, that the argument proceeds to cerebral vessels in general, and to include the pial vessels which you can watch through a skull window, but which activities have nothing to do with the deep vessels. I was not aware of this, but if hypocapnia produced by artificial hyperventilation does not reduce cerebral flow, I should say there is evidence that the sympathetic is implicated in CO₂ response. The proposition of Purves and others is that it is part of a CO₂ effect on cerebral flow and that it operates via the sympathetic but I was not aware of the fact about the quadriplegics. I believe with Professor Eckenhoff that the sympathetic has not much to do at all with cerebral vascular flow.

PROFESSOR ECKENHOFF: Would Professor McDowall like to comment?

PROFESSOR G. MCDOWALL: I have no direct observational evidence. Many members of the audience will know that a week or two following the publication of that article there was a letter commenting on the methodology involved, casting some suspicion on it, and whether the flow measurements were all cerebral flow or were heavily contaminated with extra-cranial blood. The experiments need to be repeated. There has been the finding that in animals there is no responsiveness after total sympathectomy.

PROFESSOR ECKENHOFF: It should be remembered that because the adrenergic system does not seem to have a significant effect on the cerebral circulation that does not imply that there are not other substances which, working on a different path, may not have a significant effect. For instance, it is well known that direct smooth muscle constrictors have an effect on cerebral vessels. It is well known that angiotensin has a marked effect. There may be other factors. It is a very interesting subject.

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