EFFECTS OF BASAL ANAESTHESIA ON CARDIAC FUNCTION

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Schmidt's work in 1938 was considered to be the first to recognize that anaesthesia may influence physiological and pharmacological responses [7]. Despite this early warning, Olmsted and Page [17] reported that, between 1962 and 1964, 90–94 % of cardiovascular studies were still using anaesthetized animals. Although the proportion of investigations performed today in anaesthetized animals is not established, anaesthetized, acutely-instrumented animals are the model most often used. Frequently, concepts are proposed on the basis of data collected in these experimental conditions. Yet the limitations of such an approach are rarely considered. On the contrary, it may be claimed that basal anaesthesia does not interfere with cardiovascular function. Although there were earlier attempts to understand the consequences of general anaesthesia for cardiovascular function, for technical reasons most of the knowledge in this field has been collected only in the past 3 decades. For example, the instruments permitting the development of chronically-implanted animal models for the study of cardiovascular function were developed in the late 1960s. As is often the case, a limited number of groups contributed most to current knowledge.

The effects of anaesthesia on cardiac function have been discussed in a number of reviews. Although humans were the main focus [2, 11, 18], in a few cases other species have also been considered [19]. However, little consideration has been given to the potential effects of basal anaesthesia on cardiac function in animals. Vatner and Braunwald [23] provided an important review of the mechanisms by which general anaesthesia affects cardiovascular function. The consequences of basal anaesthesia have to be evaluated in terms of additive, synergistic and antagonistic effects.

What makes this problem even more complex is that, in most cases, it is not possible to predict the nature of the interaction on the basis of data already available. Briefly, basal anaesthesia may affect cardiac function by its direct effects on the cardiovascular system and by its effects on the remote and local control of circulation. In addition, basal anaesthesia may significantly alter the disposition of endogenously, as well as exogenously, administered substances and drug effects which may also interfere with the responses recorded.

DIRECT EFFECTS OF BASAL ANAESTHESIA ON CARDIAC FUNCTION

In vivo, cardiac function is dependent not only upon the direct cardiac effects of anaesthetics, but also on the anaesthetic-mediated changes in pre- or afterload. Consequently, the direct cardiac effects of anaesthetics may be balanced by simultaneous effects on the remote and local control of circulation.

Anaesthetics such as diazepam, chloralose, pentobarbitone, thiopentone, thiamylal, ether, halothane and methoxyflurane are potent direct negative inotropic drugs; this also applies to ketamine which, in vivo, increases cardiac output as a result of a reflex cardiac stimulation. This concept is based mainly on experiments performed in vitro using papillary muscle [9] and isolated heart preparations, and in vivo using heart–lung preparations [20]. Without questioning the value of these experiments, it must be recognized that—except when decapitation is used as in rabbits, guinea pigs and rats—hearts are obtained from anaesthetized animals. When isolated heart–lung preparations are used, the role of basal anaesthesia may be even more important since, in order to set up the preparations, the animals have to be anaesthetized. Thus even in these experimental conditions, the data recorded...
may be at least partly dependent on the anaesthetic used before the experiment.

Although it appears that general anaesthetics have less direct effects on vascular smooth muscle, barbiturates and inhalation anaesthetics—especially isoflurane—have been demonstrated to possess direct vasodilator properties. As with most vasodilators, their potency varies with the specific vascular beds [3].

EFFECTS OF BASAL ANAESTHESIA ON THE CENTRAL AND AUTONOMIC NERVOUS SYSTEMS

Although general anaesthetics obviously have profound effects on the central nervous system, it is difficult to assess their role in the overall cardiovascular consequences of basal anaesthesia. For barbiturates it is established that a relationship exists between the concentration of drugs in the plasma and the brain. However, the relationship between the anaesthetic concentration threshold and the concentration which affects the cardiovascular centre remains unknown. Thus it is not possible to determine the nature of the interrelation between general anaesthesia and centrally-mediated cardiovascular function. Recovery from general anaesthesia is unrelated to its duration. In this regard the study performed by Sawyer, Lumb and Stone [22] provides important data. They demonstrated that, following recovery from anaesthesia, cardiovascular and neurological functions are altered for several hours after halothane and methoxyflurane exposure and pentobarbitone injection. Similar effects can be seen with the short-acting barbiturates thiopentone and thiamylal. The mechanisms of these interactions probably include drug accumulation in the heart, vessels and peripheral and central nervous systems. Goldstein and Aronow [10] reported parallel changes in pentobarbitone and thiopentone concentrations in plasma and brain. Although it is possible to define an anaesthetic threshold in terms of a plasma concentration, the relationship between the centrally-mediated cardiovascular changes and the anaesthetic threshold is unknown. One of the few studies to document the effects of anaesthetics on centrally-mediated cardiovascular changes in chronically instrumented dogs was reported by Ngai and Bolme [15]. They demonstrated that barbiturates and halothane depressed responses obtained after stimulation of hypothalamic and mesencephalic vasoactive areas.

Anaesthetics also affect the function of the autonomic nervous system, both centrally and peripherally. Depression of ganglionic transmission appears to be an important mechanism by which anaesthetics alter the function of the autonomic nervous system. Such a depression has been reported with oxybarbiturates [8, 13] and inhalation anaesthetics [21]. Conversely, it seems that thiopentone [8, 13] and urethane [14] have little or no effect on ganglionic transmission. In this respect it is interesting to note that tubocurarine may also affect ganglionic transmission, even at doses lower than its therapeutic threshold [16]. However, the magnitude of the block depends upon the species—it is minimal in dogs [1, 12], while more marked in cats. In addition, tubocurarine appears to have more pronounced effects on the parasympathetic than on the sympathetic system [18].

Another important mechanism by which anaesthetics alter cardiovascular function is their effect on reflex pathways. The baroreflex pathway has been extensively investigated, especially after Vercauteren and Heymans [25] noted that baroreflex function was depressed in the presence of barbiturate anaesthesia. These results were later confirmed by Brown and Hilton [4]. Vatner, Franklin and Braunwald [24] demonstrated that pentobarbitone alters responses from carotid sinus nerve stimulation; in the conscious state the bradycardia induced by stimulation of the carotid sinus nerve is mediated by the parasympathetic system, whereas it is dependent upon a sympathetic withdrawal after administration of pentobarbitone. In addition, recovery from the stimulation is prolonged during pentobarbitone anaesthesia. Other characteristic examples are the effects of such anaesthetics as chloralose and pentobarbitone on chemoreflex-mediated haemodynamic changes [27]. In the awake state, stimulation of the chemoreceptors leads to increases in arterial pressure and iliac vasoconstriction. Although haemodynamic values are similar during pentobarbitone and chloralose anaesthesia, haemodynamic responses to chemoreceptor stimulation are abolished. These findings are of especial interest when considering that anaesthetics alter differently the respiratory response to chemoreflex pathway stimulation. Chloralose and pentobarbitone decrease the centrally-mediated responses, whereas they potentiate the peripheral responses [7].
CONSEQUENCES OF BASAL ANAESTHESIA FOR THE
EXPERIMENTAL DESIGN

As stated earlier, the problem of basal anaesthesia is not its relation to the properties of drugs per se; its problems are the consequences of carrying out investigations in the presence of anaesthetics and mechanical ventilation and in surgically-stressed, possibly open-chest animals. In these conditions it is not possible to disassociate the role of each factor. The situation is made even more complex by the existence of species specificities in the cardiovascular consequences of basal anaesthesia. Furthermore, the use of anaesthetics differs, depending upon the species. Barbiturates—including pentobarbitone, thiopentone and thiamylal—are often used in dogs, cats and rats for cardiovascular physiology and pharmacology experiments, whereas chloralose is often used in the same species for neurological experiments, discrimination between these two indications being based on the theoretical absence of interference with the corresponding system used. We know that both types of anaesthetic interfere with the cardiovascular and nervous systems. However, the consequences of basal anaesthesia must also be evaluated in relationship with the rationale behind the experimental design. If the procedure is designed toward the assessment of drug effects on cardiac function or on the interactions between vasoactive drugs and anaesthetics, then basal anaesthesia is not suitable. If the goal is to mimic clinical situations, or to assess the drug effects during anaesthesia, then the use of basal anaesthesia may be justified. Even more important seems to be the method by which steady-state conditions can be verified. The use of basal anaesthesia for which a steady state is demonstrated (temperature, fluid balance, haemodynamic and respiratory functions, etc.) is preferable to uncontrolled conditions in awake animals.

EFFECTS OF BASAL ANAESTHESIA ON DRUG
DISPOSITION

Although it is established that changes in drug distribution and elimination may affect cardiovascular pharmacology, the effect of basal anaesthesia on drug disposition is not especially considered in its consequences on cardiovascular function. Anaesthetics, surgical stress, carbon dioxide [19] and acid–base balance status are factors which may alter drug disposition. Pento-

barbitone alters catecholamine metabolism. Inhalation anaesthetics affect hepatic clearance of antipyrine, verapamil [5], nicardipine, plasma protein binding of lignocaine, propranolol, diazepam [6], and oxidative biotransformation of aminopyrine [26], fentanyl and propranolol. Chloralose displaces warfarin from its protein binding site. In most cases, the consequences of basal anaesthesia on drug disposition are difficult to predict and are consequently ignored.

CONCLUSION

Basal anaesthesia includes not only the use of premedication and general anaesthetics, but also the physiological and pharmacological disturbances (acute instrumentation, mechanical ventilation, alteration of acid–base balance, etc.) related to the preparation of the experimental model. Except for a limited number of designs in well-controlled conditions, the physiological as well as the pharmacological consequences of basal anaesthesia on cardiac function are unpredictable. Basal anaesthesia not only directly interferes with cardiac function, but also affects the cardiovascular system by effects on vessels and on the central and peripheral nervous systems. Furthermore, basal anaesthesia may have important effects on drug distribution. Hence, investigations conducted in anaesthetized animals are of limited value, since it is not known what interactions will be introduced to the system. In this respect, each experimental design represents a condition which must be studied in itself.

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