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THE ACUTE OPEN-CHEST MODEL

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The acute open-chest animal model is frequently used to assess the effects of anaesthetics on myocardial function. This model, however, requires interventions which by themselves exert important cardiovascular effects and also alter the cardiovascular responses to subsequent physiological or pharmacological interventions. This must necessarily modify the interpretation of data derived from experiments conducted in this model. Accordingly, for the reader of medical literature and for those planning to conduct experiments in the acute open-chest model, the goals of this short overview are: to discuss the physiological consequences of interventions which are unrelated to the actual study procedure but inherent in this experimental model; to suggest ways to reduce the side effects of these unavoidable interventions; and to provide some reasons why the continued use of this experimental model is justified even at a time when great progress has been made in the use of chronically instrumented animals.

BASIC INTERVENTIONS

There are five interventions which disturb normal physiology in the acute open-chest model: anaesthesia, mechanical ventilation, an open thorax, at times, an open pericardium, and surgical manipulation.

Anaesthesia

It is well known that general anaesthesia exerts a profound influence on cardiovascular control. When compared with the conscious animal, the anaesthetized animal responds very differently to a variety of physiological and pharmacological interventions [5]. The principal physiological differences and differences in response to physiological and pharmacological interventions are summarized in tables I and II. Most relevant are the differences in baseline autonomic tone, and the reduced myocardial contractility in the anaesthetized animal. In addition, it can be seen that the anaesthetized animal responds very differently to carotid sinus stimulation, and to changes in heart rate (Bowditch phenomenon), in preload (Bainbridge reflex), and in afterload (Anrep reflex).

Similar differences between the anaesthetized and the conscious animal have been observed in response to pharmacological interventions (table II). These data would suggest that the state of anaesthesia *per se* will substantially modify the cardiovascular response to drugs which themselves have an effect on preload, afterload, contractility, heart rate, and systemic and coronary vascular resistance. However, it remains to be proven that all of these differences are primarily the result of the state of anaesthesia rather than the (inappropriate) choice of baseline anaesthesia. Most of the investigations which seemed to establish the fundamental differences between the anaesthetized and the conscious animal have been carried out under pentobarbitone anaesthesia with baseline heart rates and mean arterial pressures in the range 140–160 beat min^{-1} and 140 mm Hg, respectively. This clearly reflects an unphysiologically increased baseline sympathetic tone which must necessarily modify the cardiovascular response to any subsequent physiological or pharmacological intervention. It has long been felt that "barbiturates render a preparation pathologic rather than physiologic" [3], and only recently has it been shown that pentobarbitone induces an acute cardiomyopathy [1]. This is also suggested by the combination of increased sympathetic tone and reduced baseline myocardial contractility (table I). There is, in fact, mounting evidence that it is not necessarily the state of anaesthesia *per se* that is primarily responsible for the differences between the anaesthetized and the conscious animal, but rather the kind of basal anaesthesia [1]. The appro-

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TABLE I. *Physiological differences and differences in response to physiological interventions between anaesthetized and conscious animals. SVR = Systemic vascular resistance; CVR = coronary vascular resistance. + = Present; (+) = of questionable physiological relevance; − = not present*

	Anaesthetized	Conscious
Predominant autonomic tone	Sympathetic	Parasympathetic
Basal myocardial contractility	Reduced	"Normal"
Effect of carotid sinus reflex on		
Contractility	+	(+)
SVR	(+)	+
Heart rate	(+)	+
CVR	(+)	+
Bowditch phenomenon	+	−
Bainbridge reflex	−	+
Anrep reflex	+	−

TABLE II. *Differences in response to pharmacological interventions between anaesthetized and conscious animals. ↑↑ = Markedly increased; ↑ = increased; (↑) = questionable increase; − = no change; ↓ = decreased*

	Anaesthetized	Conscious
Contractility		
Noradrenaline	↑↑	↑
Dobutamine	↑↑	↑
Dopamine	↑↑	↑
Digitalis	↑	−/(↑)
Cardiac size		
Noradrenaline	↓	−
Dobutamine	↓	−
Heart rate		
Noradrenaline	↑	↓
Coronary vascular resistance:		
Noradrenaline	↓	↑
Dopamine	↓	↑
Digitalis	−	↑
Morphine	↓	↑

TABLE III. *Suggestions for basal anaesthesia*

1. Consider the use of premedication
2. Select anaesthetics with minimal cardiovascular side effects
3. Use only continuous infusions of i.v. drugs
4. Consider the use of a combination of drugs
5. Test for preservation of baroreceptor activity
6. Aim at physiological basal heart rate and arterial pressure

priateness of using pentobarbitone as the basal anaesthetic in cardiovascular investigations must, therefore, seriously be questioned.

An alternative approach to a baseline anaesthetic is proposed in table III. Use of an effective premedication will result in a quiet animal, and a more physiological basal autonomic tone. In addition, the amount of barbiturate needed for induction of anaesthesia can be reduced considerably, and the pain of the surgical preparation (cut-downs, thoracotomy, sternotomy) is in part covered by the analgesic drug. By using continuous infusions we can often reduce the total amount of anaesthetics given, and we can certainly avoid big swings in plasma concentrations with subsequent changes in autonomic tone and cardiovascular function. The use of more than one drug increases the likelihood of additional drug interactions. However, since the dose of each individual drug can be reduced considerably, the overall side effects of the basal anaesthesia may also be reduced this way. Before establishing basal anaesthesia, it is worthwhile to test for preserved baroreceptor activity. This may be done by injecting a short acting vasodilator (e.g. nitroglycerin) and observing whether the change in heart rate in response to the decrease in arterial pressure is similar to that which has been described for the conscious animal. Finally, any basal anaesthesia should produce normal heart rates and arterial pressure.

Mechanical ventilation

The consequences of mechanical ventilation with an open thorax are well known. Venous return may decrease secondary to the decrease in venous filling gradient. This will in turn reduce preload, and stroke volume and the developed systolic pressure may subsequently decrease.

If the chosen tidal volumes are too low or too high, pulmonary vascular resistance (an index of right ventricular afterload), Pa_{CO_2}, Pa_{O_2} and pH may all be adversely affected.

In order to keep those side effects at a minimum, adequate fluid administration, relatively high tidal volumes (preferably with low positive end-expiratory pressure because of the tendency for airway collapse), and frequent monitoring of arterial blood-gases and pH are mandatory.

Open thorax and pericardium

The acute loss of negative intrathoracic pressure will result in reductions of the venous filling gradient, the cardiac filling pressures and of lung volume. Lung–heart interaction will be reduced. The open thorax is certainly one of the main reasons why these animals tend to become hypothermic very readily.

If, in addition to the thorax, the pericardium is also opened, then cardiac geometry, the degree of ventricular interaction, cardiac distensibility, and cardiac filling pressures will be affected further. However, these effects are probably of some physiological relevance only at higher end-diastolic volumes and pressures [2, 6]. Thus if experiments are being performed that are likely to cause significant changes in ventricular volumes and pressures, the pericardium should preferably be kept intact or, at least, re-closed after surgical preparation.

Obviously, some of the changes following the opening of the thorax and pericardium are similar to those following the institution of mechanical ventilation. Preload tends to decrease, which tends to reduce stroke volume and developed systolic pressure. The lungs tend to collapse and this may affect pulmonary vascular resistance and arterial blood-gas tensions. There is also the risk of hypothermia developing so, again, adequate volume replacement, adequate tidal volumes (preferably with low PEEP), and monitoring of body temperature are essential.

Surgery

The potentially adverse effects of acute surgical manipulation consist of increased sympathetic tone as a result of inadequate analgesia, hypovolaemia as a result of inadequate fluid replacement, and trauma to myocardium, coronary vascular endothelium or coronary artery innervation following placement of measuring devices (e.g. piezoelectric crystals, electromagnetic flow probes). As mentioned earlier, increased sympathetic tone will induce a variety of neurohumoral changes which are likely to modify the cardiovascular response to subsequent interventions. Effective premedication or transient deepening of the level of anaesthesia will help to blunt the increase in sympathetic tone.

Trauma can only be kept to a minimum if the preparation is performed by a technically very skilled person. An excessively traumatic preparation or unphysiological baseline signals must not be accepted for subsequent data analysis. The trauma of recent surgery may modify the effects of subsequent interventions [4].

MONITORING

The acute open-chest model carries the potential for many adverse effects which may significantly modify the results independently of the actual study programme. Whenever using this model it is, therefore, imperative to provide a minimum of additional information which allows some estimation of the animal's general homeostasis. Only on such background information is it possible to judge the physiological and clinical significance of data obtained in the acute open-chest model.

Most of the parameters listed in table IV reflect ventilatory and fluid management. Thus the more complicated and potentially more traumatic the preparation becomes, and the longer the experiment lasts, the more we need time controls. This

TABLE IV. *Essential information required when using the acute open-chest model*

Mode of ventilation
Fluid regimen
Urine output
Arterial blood-gas tensions/pH
Haematocrit
Body temperature
Time controls

TABLE V. *Reasons for using the acute open-chest model*

1. Model simulates clinical reality
2. Certain study programmes are facilitated by open-chest
3. More simultaneous measurements possible
4. Less sophisticated animal care facilities required

is the only way to exclude spontaneous deterioration of the preparation with time.

WHY USE THE MODEL?

Despite the drawbacks inherent in the acute open-chest model, there are definite advantages (table V)—provided we take the necessary precautions referred to in this overview. One might very well argue that, in reality, we rarely give a single anaesthetic drug to an unpremedicated patient without any form of surgery going on. What we usually do is add an anaesthetic to some basal anaesthesia while some form of surgery is going on. So, why not test the cardiovascular effects of an anaesthetic under conditions which somehow mimic clinical reality? Of course, the information that we will obtain this way will be different from a "pure" pharmacological approach, but it will still have clinical relevance.

The acute open-chest does not pose the problems of postoperative infections, adhesions and uncorrectable malpositioning or malfunctioning of equipment. This, in general, should allow simultaneous registration of more technically satisfactory signals.

Last, but not least, this model requires less sophisticated animal care facilities compared with those required for chronically instrumented animals. This includes logistic, financial and manpower aspects which may well become the limiting factor. However, I do believe that, if we take the necessary precautions to maintain general homeostasis as well as possible, and if we are aware of the limitations of this model, the use of the acute open-chest model will continue to contribute valuable information on the effects of anaesthetics on myocardial function.

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