ACUTE CLOSED-CHEST CANINE MODEL FOR ANAESTHESIA RESEARCH

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The choice of a particular model for investigative work is determined by a number of factors, including the interests and background of the investigators, the research hypotheses being tested, as well as the resources available in the laboratory and those available in the institution of which it is a part. In this review of a closed-chest model used in the cardiopulmonary research laboratory of the Department of Anesthesiology at the University of California, Los Angeles, I will discuss the points in favour of such a model, its limitations, the types of instrumentation possible with a closed-chest preparation, aspects of the technique as practised, and actual data obtained with this model.

First, why choose a closed-chest model for cardiovascular research? After all, with a closed-chest preparation, one has to approach the heart from the periphery, without direct access to the organ and tissues one is studying. As can be seen in table I, there are a number of reasons why such a model may be chosen. First, it is closer than many other models to the clinical situation, since the subjects are intact with functioning neural and humoral influences. Second, there are minimal perturbations of the intact subject by the methods used, notably, an absence of surgical stress and the attendant physiological alterations of an open chest, that may result in neural interruptions, hormonal alterations, fluid shifts, temperature differentials, dessication of organ surfaces, tissue disruption, and so on. Merin [14] has recently summarized available work on the interactions of calcium channel blocking drugs during anaesthesia, and came to the conclusion that the effects of such drugs were indeed different in the intact subject compared with the effects observed in open-chest preparations. In comparison with chronically instrumented preparations, the acute closed-chest model is not exposed to chronic catheters as sources of infection, clot, adhesions and the like. Investigations using chronically instrumented animals may not be able to report a full set of data points for the different parameters measured because of malfunction or other difficulties associated with chronic catheters [1,15,17]. In some types of experiment this could possibly lead to misinterpretation of results as some animals are represented for one variable and not for another.

As a result of minimal perturbations, not only of the physiology of the subject, but also to the anatomy, by a closed-chest preparation, frequently the animal subject may be allowed to recover after an experiment, if suitable limitations to the procedure have been observed. The animal can therefore serve as its own control for subsequent aspects of a study. This not only mimics the clinical situation, where patients recover after an anaesthetic, but also contributes to the conservation of animal resources and serves to emphasize meticulous and humane treatment of animal subjects. Variability of experimental results may be reduced by utilizing the same subjects as their own controls.

In addition, and not to be taken lightly, is the fact that the use of acute closed-chest preparations minimizes the animal maintenance procedures

<table>
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<th>TABLE 1. Advantages of an acute closed-chest animal model for anaesthesia research</th>
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<td>Similar to the clinical situation.</td>
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<td>Minimal perturbation of the intact subject by the method:</td>
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<td>Absence of surgical stress.</td>
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<td>Absence of physiological alterations of an open chest.</td>
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<td>No chronic catheters as sources of infection, clot, adhesions, etc.</td>
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<tr>
<td>Conservation of animal resources.</td>
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<td>Minimized animal maintenance.</td>
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required when compared with a chronically instrumented preparation. The latter requires exceptional animal quarters in order to maintain patency and asepsis of the catheters. Furthermore, personnel must be available every day of the week to flush the catheters several times daily with heparinized saline solution. Many centres have neither ideal settings nor sufficient personnel for continuous care of chronically instrumented animals. An acute model then is an alternative.

Accepting that one has chosen an acute closed-chest model for study, one must recognize the limitations of the model and choose appropriate research hypotheses for testing. An obvious limitation is that methods must not require a thoracotomy or laparotomy. Thus much of the data will be collected from catheters placed by way of peripherally accessible vessels, with their attendant limitations. The availability of fluoroscopy can be extremely helpful at times, for example for the placement of a coronary sinus catheter. Nuclear methods for evaluating aspects of cardiac function or the presence of myocardial ischaemia are increasingly becoming available as productive collaborations develop between nuclear radiologists and anaesthesia investigators. Echocardiography and colour Doppler techniques are also relatively new additions to the investigative armamentarium which can be fairly simply applied to a closed-chest preparation.

Awake controls are possible with many of the measurement techniques used with closed-chest preparations. The animals are trained in advance to lie still in the laboratory setting. On the day of the experiment any required catheters are inserted after infiltration of the site with local anaesthetics. In contrast, if baseline anaesthesia is administered before obtaining the control data, one cannot test any hypothesis that depends upon a comparison between the awake and the anaesthetized state. However, many questions are suitable for an anaesthetized preparation. A few of many examples include: effects of varying anaesthetic concentrations on a particular condition; comparisons of different anaesthetics under the circumstances being studied; effect of any other condition or drug superimposed upon the anaesthetic state; hormonal responses to pharmacological or physiological manoeuvres during anaesthesia and alterations thereof.

Studies undertaken at the cardiopulmonary research laboratory of the Department of Anaesthesiology at the UCLA School of Medicine, have been related to various aspects of the cardiovascular interactions of newer cardioactive drugs with anaesthetics. These have included: arrhythmia studies with verapamil [6, 7], comparison of the influence of the different inhalation anaesthetics upon verapamil pharmacodynamics [3], pharmacodynamic studies of diltiazem with varying anaesthetics [4, 5], interactions of beta-adrenergic blockers with verapamil comparing barbiturate with halothane anaesthesia [8, 18], a series of studies related to the properties of the newer cardiotonic drug amrinone [11-13], and continuing studies of the cardiovascular relationships between local anaesthetic compounds and calcium channel blocking drugs.

In considering the use of the same animal for repeat studies, several important points must be kept in mind. First, it is wise to use conditioned animals for this purpose. Conditioned animals have been under observation for signs of disease, infection or pregnancy for a period of time and have received the appropriate prophylactic immunizations, deworming procedures if indicated, dipping in disinfectant solutions for elimination of external parasites, and so on. In this manner, the contribution to the experimental results of such conditions will be minimized. If the animal is to be allowed to recover between experiments, aseptic techniques should be utilized for catheter placement, parenteral solutions, i.v. tubing, etc. Provision should be made for follow-up antibiotic therapy, catheter site checks and periodic health examinations. The author's laboratory regularly follows and charts the animal's weight and haematocrit. Any animal that does not maintain its weight at or above the initial value or its haematocrit above 30% is withdrawn from further study. Dietary supplements to the standard vivarium fare and oral iron solutions may be given to maintain the animals in good health. To reduce the incidence of a low haematocrit, the amount of blood sampling per experiment is limited consistent with the study data to be obtained. On occasions, if a procedure required a larger number of blood samples, cross-matched donor dog blood has been given to replace the losses. In addition, for survival studies, the experimental procedures are immediately abandoned in the event of hypotension (mean arterial pressure < 50 mm Hg), arrhythmia, etc. The pharmacological effects of the drug under study are antagonized and the animal allowed to recover.

It is also important, in reporting results from an
intact preparation, that the investigators note the
details of the anaesthetic technique, the ventilatory parameters, the acid–base status of the
animal, the body temperature at the time of study,
and blood chemistry or haematocrit values if the
latter are available, so that the reader of the work
may determine that the physiology was indeed being “minimally perturbed” by the technique.

An additional, but by no means mandatory, aspect of the model being discussed is the presence
of a chronic tracheostomy. The technique [16]
results in the skin-covered sternohyoid muscle
covering the permanent tracheostomy when this
is not in use. At the time of an investigation, a
tracheostomy tube is inserted after topical applica-
tion of a small amount of local anaesthetic spray
to the trachea. The tracheostomy allows easy
access to the trachea, even in an awake animal, for
inspired and expired gas sampling and inhalation
anaesthetic inductions. Thus the technique
eliminates the need for adjuvant sedatives, barbiturates or neuromuscular blocking drugs, or
the necessity for a stressful mask induction.
Between investigations the tracheostomy tube is
removed and the animal uses its upper respiratory
tract to provide the normal humidification and
filtering of inspired air, thus minimizing the
incidence of tracheobronchitis. Animals have
been maintained for more than 1 year in good
health.

As mentioned, quite a variety of techniques are
applicable to the acute closed-chest model (table
II). Inspired and expired gas sampling can be
used to determine oxygen consumption and
carbon dioxide production, as well as to regulate
anaesthetic depth (end-tidal concentrations). Arterial access for measurement of pressures and
blood sampling is possible percutaneously by way
of the femoral artery to the aorta. In addition, a
carotid artery loop may be located superficially for
chronic needle sampling or, alternatively, a very
careful small cutdown to reach the carotid artery
can then be closed at the end of the procedure.
Other major vessels that arise from the aorta are
accessible from the femoral vessels using fluoro-
sopic control. Venous access for measurement of
pressures, blood sampling, or drug administration
is available percutaneously by way of the external
jugular veins (which are quite large in the dog),
yielding access to the superior and inferior vena
cavae, the right heart (atrium, ventricle), pul-
monary arteries (pressures, thermodilution car-
diac output), and the coronary sinus (pressures,
coronary blood flow, myocardial oxygen con-
sumption, myocardial drug and metabolite extrac-
tion); the femoral veins; or peripheral extremity
veins.

In the closed-chest model various electro-
physiological measurements may also be made. Surface or oesophageal electrocardiograms can
be obtained. Specialized catheters may be placed by
way of percutaneous introducers to the right heart for intracardiac recording (bundle of His, etc.). Transvenous pacing catheters may also be used. Left heart catheterization may be achieved from the femoral artery for measurement of pressures by using a fluid-filled catheter, a micromanometer-tipped catheter, or one of the newer fibreoptic catheters, and left ventricular dP/dt may be differentiated therefrom. Cardiac ejection fractions may be estimated by a rapid-response thermistor-tipped catheter [9], by angiographic methods, or by nuclear methods. Ventricular volumes may be estimated in the closed-chest subject by use of echocardiographic techniques, a catheter that senses changes in electrical impedance in the blood in the ventricle chamber [10] or from the rapid-response thermistor-tipped catheter.

Other techniques of interest to cardiovascular investigators that are possible in the closed-chest animal include thallium scanning to evaluate areas of myocardial ischaemia, nuclear magnetic resonance and positron emission scanning for changes in the metabolism and biochemistry of the heart, coronary artery catheterization, and endocardial biopsy using the transvenous technique. If the animal is not needed for subsequent investigations, then regional blood flows by microsphere techniques and pathological examination of tissues are also possible.

Regardless of the techniques chosen, recognition of the limitations of the data obtained and rigorous attention to the details of the technique are necessary. For the sake of discussion we will consider the thermodilution coronary sinus catheter technique as advanced by Ganz and colleagues [2]. The coronary sinus catheter can be used only to measure global left ventricular function. Although newer versions now have a second orifice to determine great cardiac vein blood flow, specific information about multiple zones of the ventricle cannot be obtained with this technique. In addition, proper location of the catheter tip is essential. The proper location can be confirmed by use of fluoroscopy with small injections of dilute dye solutions and observation of the proper coronary sinus wave form and PO2. When doubts occur, cold saline can be injected to the right atrium while checking the thermistor temperature of the catheter. Since any of these manoeuvres may transiently affect haemodynamics, they must be performed with several minutes separation from data collection times.

There must also be uniform mixing and delivery of the thermal indicator. Precautions in this regard include continuous infusion for at least 1 min before measurement, transient cessation of ventilation, recording the temperature curves, and taking all measurements in duplicate. Thus the critical evaluation of a research report that incorporates this technique depends upon the inclusion by the investigators of as much information as possible about how the limitations of the technique in question were minimized and what assumptions have been made in interpreting the results.

**SUMMARY**

An acute closed-chest canine model may be useful to study a wide variety of hypotheses relevant to cardiovascular physiology and pharmacology in circumstances which are clinically relevant. The absence of anatomical perturbations allows recovery of the subjects for conservation of animal resources and to serve as their own controls. The use of a chronic tracheostomy has facilitated inhalation anaesthesia without the use of other agents and allows easy access to the trachea in awake animals with minimal adverse effects. A thorough understanding of the techniques utilized aids in the interpretation of results obtained with this as with any other model.

**REFERENCES**


