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Survey of Effects of Anesthesia Protocols on Hemodynamic Variables in Porcine Cardiopulmonary Resuscitation Laboratory Models Before Induction of Cardiac Arrest

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Objective: **An advantage of animal models in cardiopulmonary resuscitation (CPR) research is the possibility to control confounding variables that may be impossible to standardize in clinical trials. A neglected effect of the anesthesia protocol in porcine CPR studies may be its impact on hemodynamic variables before induction of cardiac arrest. Accordingly, the purpose of the study reported here was to evaluate published CPR reports with regard to their anesthesia protocol.**

Methods: **Of 100 articles that reported on laboratory models simulating cardiac arrest between 1987 and 1997 in peer-reviewed journals, 25 met inclusion criteria and were analyzed for values of coronary perfusion pressure, mean arterial pressure, heart rate, temperature, and cardiac index before induction of cardiac arrest. Subsequently, mean values for all animals in a given report were calculated and corrected for group size; statistical analysis was not performed since this was a survey only.**

Results: **Different anesthesia protocols resulted in a widely distributed pattern of hemodynamic variables prior to induction of cardiac arrest. Ranges compared with reference values were: heart rate, 100 to 122 beats/min versus 105 ± 11 beats/min; mean arterial pressure, 68 to 130 mm Hg versus 102 ± 9 mm Hg; coronary perfusion pressure, 55 to 114 mm Hg (no reference value); cardiac index, 69 to 152 ml/kg/min versus 147 ± 22 ml/kg/min; body temperature, 37 to 38.5°C versus 38.5 ± 0.7°C.**

Conclusion: **The anesthesia protocol may have an impact on hemodynamic variables before induction of cardiac arrest in CPR studies.**

Over the past ten years, there has been a transition from the classic canine model to swine for laboratory evaluation of human cardiovascular physiology and pathophysiology (1). The similar phylogenetic development of people and swine, both consuming an omnivorous diet and having a sedentary life style and relative lack of daily aerobic exercise, define animals that are prone to cardiovascular disease. In contrast, canine evolution included a carnivorous diet and the ability to perform substantial amounts of continuous aerobic exercise, resulting in coronary artery anatomy, coronary vasodilator function, and cardiac metabolism differing from that of humans and pigs. Accordingly, due to the similar coronary anatomy and lack of native collateral cardiac blood vessels in humans and swine, pigs may be the model of choice in ischemia/reperfusion investigations for evaluation of cardiac pathophysiology, such as sudden cardiac death (2).

An advantage of animal models in cardiopulmonary resuscitation (CPR) research is the possibility to better control confounding variables that may be impossible to standardize in clinical trials. Accordingly, when using a well established anesthesia protocol, and careful surgical instrumentation, hemodynamic variables before induction of cardiac arrest may not differ more than 10 to 20% among all animals being enrolled in the study. Although Utstein-style guidelines exist to standardize CPR laboratory studies, the effect of different anesthesia regimens on hemodynamic variables was not discussed in detail (3). Different anesthesia protocols may, by themselves, favor certain end points of a study. For example, when using a muscle relaxant prior to inducing cardiac arrest in laboratory animals, ventilation during CPR was a critical component to achieve return of spontaneous circulation (4). When pigs were not paralyzed, gasping resulted in sufficient ventilation, rendering artificial ventilation unnecessary.

A neglected effect of the anesthesia protocol may be its impact on hemodynamic variables before induction of cardiac arrest in a CPR experiment. For example, if an animal is accidentally anesthetized too lightly, the adrenal glands may discharge epinephrine and norepinephrine due to surgery-related stress and/or insufficient amounts of anesthetic, which may subsequently alter vasculature tone (5). In this instance, administration of a vasopressor during CPR may not result in the anticipated effect, or the effect may be altered due to an altered or down-regulated status of stress hormone receptors. Thus, an investigator may not be aware that the experiment being conducted does not reflect an

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animal suffering sudden cardiac arrest, such as a victim with sudden ventricular fibrillation, but a creature with peri-arrest alteration of neuroendocrine regulation (6).

Accordingly, the purpose of the study reported here was to evaluate published CPR reports with regard to their anesthesia protocol. Our hypothesis was that different anesthetic protocols may cause different hemodynamic variable responses before induction of cardiac arrest.

Materials and Methods

Selection of articles: To identify articles for inclusion, a Medline literature search encompassing the period 1987 to 1997 was performed using the medical subject headings CPR/cardiopulmonary resuscitation, porcine, swine, and cardiac/heart arrest. Subsequently, more than 100 articles that reported on laboratory models simulating cardiac arrest were identified in peer-reviewed journals; additional reports were identified from citations and collective reviews. From these articles, a set of criteria was developed for inclusion in the study: the report had to simulate cardiac arrest in farm pigs and include CPR as part of the experimental protocol; the anesthesia protocol had to be reported to identify anesthetic agents; and animal weight had to be $\geq 15 \leq 50$ kg. Exclusion criteria were: dog and rat models; articles not reporting numerical values of hemodynamic variables before induction of cardiac arrest, such as coronary perfusion pressure, mean arterial pressure, cardiac index, or heart rate; abstracts, non-resuscitation models, human cardiac arrest investigations, and studies that did not provide sufficient data to evaluate the anesthesia protocol. Breed and age were not reviewed. Frequently, more than one study from a particular CPR working group of investigators was located and all studies meeting the inclusion criteria were reviewed. Twenty-five articles that met these criteria were identified and were included in the study (6–31).

Article review process: An initial review of the 25 articles was performed to define the variables to be evaluated. All articles were evaluated for reporting of data relating to coronary perfusion pressure, mean arterial pressure, heart rate, and cardiac index before induction of cardiac arrest. Each article was reviewed first in a preliminary procedure; second, a blinded review was performed by creating a special copy of the article, in which all titles, names, institutions, and references to the investigators were deleted; and finally, a third review was completed by checking again applicability of a given article to the present study. Areas of discrepancy among the three reviews were specifically reexamined, and a final judgement was made by one investigator.

Calculation of mean data variables: The data for each experimental group of each article were entered into a spreadsheet, using Stat-view 4.5 statistical software (Abacus Concepts, Berkeley, CA) and a personal computer. Subsequently, mean values for all animals in a given report were calculated according to the following formula, using heart rate as an example in a study with two groups: mean heart rate (group 1 + group 2) = [(n) group1 • mean heart rate group1]+ [(n) group2 • mean heart rate group2] / [(n) group1 + (n) group2]. Thus, this calculation allowed us to correct mean values for different group sizes used in one investigation. These mean values were again summarized according to this formula for the following anesthesia protocol categories: Premedication, induction of anesthesia, fluids, temperature, and maintenance of anesthesia.

Statistical analysis: This is a survey only; therefore, statistical analysis was not performed.

Results and Discussion

Different anesthesia protocols resulted in a widely distributed pattern of hemodynamic variables and temperature prior to induction of cardiac arrest (Tables 1–5). No study involved use of minipigs. To determine effects of intervention during CPR in a clinical study is extremely difficult due to confounding variables. For example, a given patient population differs significantly due to past medical history, standard of living, age, race, cardiac rhythm at collapse, and location of cardiac arrest (32). Also, the healthcare system itself may affect CPR outcome fundamentally due to differences in emergency medical services, response time, intensive care unit management, and access to diagnostic technology (33). To detect a significant increase in hospital discharge rates and/or neurologic recovery by use of a new CPR intervention, approximately 15,000 patients, several years, and hundreds of thousands of US dollars would be necessary—a trial that would be substantially bigger than the large Framingham Heart studies, with typically about 3,000 to 5,000 patients (34). In contrast, use of an animal model may enable researchers to more rapidly determine the role of an intervention during CPR with comparatively reasonable financial expense.

The assumption that a laboratory study is simple to conduct is incorrect, since variables such as skill and experience of in-

Table 1. Comparison of fluid management during anesthesia

Fluids	N	MAP (mm Hg)	CPP (mm Hg)	HR (bpm)	CI (ml/kg)
Reference values (mean ± SD)[35]		102 ± 9	. . .	105 ± 11	147 ± 22
Administered	118	100	79	109	144
Not reported	397	98	100	122	116

N = number of animals; bpm = beats per minute; MAP = mean arterial pressure; CPP = coronary perfusion pressure; HR = heart rate; CI = cardiac index; . . . = not reported.

Table 2. Comparison of premedication management

Premedication	N	MAP (mm Hg)	CPP (mm Hg)	HR (bpm)	CI (ml/kg)
Reference values (mean ± SD)[35]		102 ± 9	. . .	105 ± 11	147 ± 22
Azaperone	78	97	82	100	146
Azaperone + atropine	65	103	. . .	111	148
None	372	97	90	122	112

See Table 1 for key.

Table 3. Comparison of anesthesia induction management

Induction	N	MAP (mm Hg)	CPP (mm Hg)	HR (bpm)	CI (ml/kg)
Reference values (mean ± SD)[35]		102 ± 9	. . .	105 ± 11	147 ± 22
Halothane	55	119	104	. . .	. . .
Isoflurane	30	75	114	. . .	. . .
Pentobarbital	65	103	. . .	111	148
Metomidate					
Metomidate/ pancuronium	14 21	85 115	. . . 90	100 . . .	141 . . .
Piritramide/ thiopental	29	100	77	. . .	. . .
Isoflurane/N_2O	9	97	86	. . .	. . .
Metomidate/ buprenorphine	14	75	. . .	. . .	152
Ketamine/barbiturate	146	113	109	. . .	124

See Table 1 for key.

Table 4. Comparison of anesthesia maintenance management

Maintenance	N	MAP (mm Hg)	CPP (mm Hg)	HR (bpm)	CI (ml/kg)
Reference values (mean ± SD)[35]		102 ± 9	. . .	105 ± 11	147 ± 22
Halothane	25	123	. . .	. . .	. . .
Isoflurane	110	68	55	122	. . .
Pentobarbiturate/pancuronium	22	130	. . .	. . .	69
Pentobarbiturate/N_2O/buprenorphine	65	103	. . .	111	147
Metomidate/N_2O	35	99	90	. . .	152
Metomidate/N_2O/buprenorphine	14	85	. . .	100	141
a-Chloralose	5	125	107	. . .	. . .
Barbiturate	165	110	92	. . .	124
Halothane/a-chloralose	35	110	97	. . .	. .

See Table 1 for key.

Table 5. Comparison of temperature management during anesthesia

N	Temperature
Reference temperature (mean ± SD)[35]	38.5 ± 0.7°C
257	Not reported
29	37.0–38.0°C[1]
99	37.5–38.5°C[1]
130	38.7°C[2]

[1]Range; [2] mean = exactly reported.
See Table 1 for key.

vestigators, health status of the animals, possible strain differences, conditioning prior to the investigation, diet, housing conditions, and specific-pathogen-free status, may have a fundamental impact on study results. Most of these parameters cannot be assessed or may be unknown; however, comparison of the anesthesia protocols may be a component that is doable.

There is no doubt that a fully instrumented pig must be anesthetized to ensure humane and ethical management during laboratory investigations. In our study, the anesthesia protocol had an impact on hemodynamic variables before induction of cardiac arrest, rendering circulatory status of pigs in some investigations only partially comparable to reference baseline values (35). Some researchers use models of fully anesthetized animals for instrumentation and subsequently induce cardiac arrest while the animal emerges from anesthesia. Although it is possibly meant to simulate a spontaneous breathing human with normal cardiocirculatory parameters, such model may not be able to keep the animal free of stress. Accordingly, if an animal is accidentally anesthetized too lightly, the response to a stress experiment, such as CPR with use of vasopressors, may be altered due to tachyphylaxis and/or down-regulation of receptors. An impressive example may be results from a pediatric porcine model involving the onset of asphyxial cardiac arrest in animals that were anesthetized with ketamine, isoflurane, or pentobarbital (36). As such, cardiopulmonary arrest occurred after 8.4 ± 1.6 minutes in the ketamine group, 7.8 ± 1.2 minutes in the isoflurane group, and 11.1 ± 2.4 minutes in pigs anesthetized with pentobarbital, indicating that the anesthesia protocol may have an important impact.

When a tranquilizer is given as premedication, induction of anesthesia is easier, the dose of anesthetics required and the incidence of vomiting is decreased, and recovery from anesthesia is usually smoother and free of vocalization. It is surprising that only about 25% of the pigs in our study received premedication. Given the fact that routine surgical procedures in patients are almost always started by administration of a premedication due to the aforementioned reasons and further, to reduce perioperative stress and anxiety, this practice may have been deemed unimportant in some laboratories. However, many porcine breeds are extremely sensitive to stress, especially when changing cages, eating and drinking pattern (nonfeeding period before induction of anesthesia), and transportation (37). For example, an unsedated pig is most likely to struggle on being caught and restrained in a transport box before induction of anesthesia, which may result in profound metabolic acidosis, attenuation of appropriate respiratory compensation, and subsequently, restraint-associated cardiac arrest. Interestingly, this problem has been recognized by the emergency medical service in the United States when managing patients such as cocaine addicts who present with combativeness despite restraints, sometimes resulting in fatalities (38). As such, stressful situations should be avoided to spare a laboratory pig unnecessary suffering and distress. We speculate that a possible altered stress hormone balance may exist in animals that do not receive premedication, which subsequently could result in higher heart rate and lower cardiac index compared with that in premedicated pigs.

It is likely that many researchers administered fluids, but did not report it, which resulted in the comment “fluids not reported” in our database. We have experienced that when pigs are subjected to an overnight nonfeeding period, some swine stop drinking as well. In this instance, these animals require careful balancing of fluid status in the instrumentation and preparation phases of the experiment. Since cardiac arrest and CPR result in hemoconcentration (39), lack of fluid management in the preparation phase may result in decreased perfusion pressures during CPR. Thus, it is important that filling pressures are optimized before induction of cardiac arrest to ensure reproducible results.

Although premedication and fluid administration are important, a bigger impact on the cardiovascular system may be imposed by anesthesia induction and maintenance agents. In clinical anesthesia, drug management consists of use of various agents to provide amnesia, analgesia, and muscular relaxation. Some researchers in our study used single-agent anesthetics in their animals; this may require larger doses, which subsequently renders more side effects than does a combination of anesthetic agents. For example, isoflurane depresses left ventricular function, which is documented by decreased mean arterial pressure and increased heart rate in this study. Also, when a barbiturate was given alone, cardiac index decreased; when the barbiturate was combined with a muscular relaxant, mean arterial pressure increased, and cardiac index decreased.

In another study, anesthesia with barbiturate only was associated with a higher overall complication rate than were the other anesthesia protocols (40). These hemodynamic changes may be indicative of pentobarbital's direct cardiac depressant action and reflex pressor receptor activity, as has been clearly documented in denervated pentobarbital-anesthetized dogs (3). Further, recently published results from use of canine models

involving nuclear magnetic resonance imaging further point out that the left ventricular transmural trend in the creatine phosphate-to-ATP ratio was likely to be a direct reflection of the sodium pentobarbital anesthetic regimen (41). This may indicate the necessity of increased caution in directly extrapolating results from experiments performed on animals under anesthesia. Accordingly, the question arises whether anesthesia protocols should be standardized. An advantage could be that comparing data may be simpler; however, this may obstruct investigators to use specific circumstances, may not be applicable, cannot be enforced, and finally, was not the objective of Utstein-style guidelines for CPR laboratory research. It is also acknowledged that many of the agents included in this survey have multiple systemic side effects on other parameters (i.e., cardiac electrophysiology or coronary vasodilatation); however, animal experimentation without anesthesia would not be ethically justified, and therefore, these side effects need to be tolerated. Without doubt, the best anesthesia protocol for CPR studies would be management that keeps the animal's body function in all aspects as close as possible to normal physiologic values (35) using a minimum of drugs.

Owing to different porcine hemoglobin structure and increased body temperature, compared with that of humans (approx. 38.5°C vs. approx. 37.0°C) (35), proper control of core temperature in porcine studies is extremely important. For example, if the animal's temperature is similar to that of humans, a hypothermia component may be superimposed on the actual experiment. If this is not recognized, oxygen delivery during CPR may be impaired, which may fundamentally alter results of the study. In our study, temperature was not reported in about 50% of the published reports, with the remaining experiments being conducted at temperature values that are either normal or near normal physiologically for pigs.

There were several limitations to this study. Evaluation of articles reporting values in graphs was excluded to avoid incorrect data acquisition. This is a survey only, not a meta analysis. Thus, we did not include standard deviation in the calculation of mean values for a given article for an anesthetic category, and therefore, numerical results are given as mean only. Also, it is impossible to determine the possible role of anesthesia management on study results in the articles. Accordingly, this investigation was meant to point out possible confounding variables in CPR experiments of which investigators need to be aware to ensure that their results are valid. Further, our purpose was not to describe the ideal anesthesia regimen. It seems impossible to incorporate an analysis and/or estimation of cost with regard to anesthetic agents due to different international markets, patents, and delivery conditions. Finally, we were unable to determine the effect of surgical procedures and different doses vs. drug effects; it was impossible to determine whether the anesthesia protocol has an impact on variables measured during CPR.

In conclusion, the anesthesia protocol may have an impact on hemodynamic variables before induction of cardiac arrest in CPR studies.

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