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Baseline Hemodynamics in Anesthetized Landrace–Large White Swine: Reference Values for Research in Cardiac Arrest and Cardiopulmonary Resuscitation Models

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The use of swine in cardiopulmonary resuscitation (CPR) research has increased in the last decades. Landrace–Large White (LLW) swine are a farm breed of pigs. The aims of the present study were to describe the baseline hemodynamics of this breed and to demonstrate that it is suitable for CPR research. The systolic and diastolic pressures of the descending aorta (mean ± 1 standard deviation; n = 29) were 111.72 ± 13.61 and 79.03 ± 12.08 mm Hg, respectively, whereas the mean systolic and diastolic pressures of the left ventricle were 108.97 ± 12.06 and 8.88 ± 1.81 mm Hg, respectively. The mean pressures of the right atrium were 10.93 ± 1.36 mm Hg (systolic) and 4.10 ± 1.01 mm Hg (diastolic), whereas the value obtained by using near-infrared spectroscopy to determine brain regional oxygen saturation was 64.55% ± 3.88%. LLW can be considered a suitable breed for CPR research because of the close similarity of its hemodynamic values to those of humans.

Abbreviations: CA, Cardiac arrest; CPR, cardiopulmonary resuscitation; LLW, Landrace–Large White

The use of swine in biomedical and cardiovascular research has increased in the last decades, particularly in the United States.[22] The various breeds of swine are classified into 2 large categories: farm pigs and minipigs. Landrace–Large White (LLW) swine are crossbred pigs that belong among the farm breeds.

Cardiac arrest (CA) is a daunting medical emergency, affecting 700,000 Europeans annually.[17] Swine have been used extensively as animal models in CA and cardiopulmonary resuscitation (CPR) research.[14,24] Experimentation in this field has contributed to the formation of guidelines on resuscitation by the European Resuscitation Council, the American Heart Association, and the International Liaison Committee on Resuscitation.[18] Current guidelines on resuscitation suggest effective thoracic compressions, positive-pressure ventilation, and electric defibrillation. Electrical defibrillation is the only definitive treatment for ventricular fibrillation, the most common CA arrhythmia outside of the hospital setting.

Although swine are used increasingly in CPR research, information regarding their hemodynamic reference values are lacking in the international literature. The aims of the present study were to provide baseline hemodynamic values for LLW swine and to show that it is a suitable breed for use in CPR research.

Materials and Methods

The experimental protocol was approved by the General Directorate of Veterinary Services (permit no. K/2262/27-3-2006), according to Greek legislation, regarding ethical and experimental procedures (Presidential Decree 160/1991, in compliance to the EEC Directive 86/609, and Law 2015/1992, in conformance with the European Convention "for the protection of vertebrate animals used for experimental or other scientific purposes, 123/1986"). A total of 29 Landrace–Large White piglets (*Sus scrofa domestica*; 15 female; 14 male), aged 10 to 15 wk, with an average weight 19 ± 2 kg, and of conventional microbiologic status were obtained from a single breeder (Validakis, Athens, Greece).

All animals were housed in single cages. The conditions in the animal house were 15 air changes hourly, 22 ± 2 °C, 55% relative humidity, lights on at 0600, and lights off at 1800. The animals were acclimated to the laboratory conditions for 1 wk prior to the experiment and were fed a standard commercial food (Biozokat, Ekaterinis-Larissis, Greece) (Table 1). The pigs were fasted overnight, but access to water was ad libitum.

Each animal was premedicated with an intramuscular injection of ketamine hydrochloride (10 mg/kg), midazolam (0.5 mg/kg), and atropine sulfate (0.05 mg/kg); 15 min later, the pigs were transported to the operating theatre.

Aseptic procedures were followed throughout the protocol. Intravenous access was achieved via an auricular vein, and anesthesia was induced with an intravenous bolus propofol (2.0 mg/kg). While spontaneously breathing, each animal was intubated with an endotracheal tube (inner diameter, 4.5 mm; MLT 4.5 Oral 27 mm, Mallinckrodt Medical, Athlone, Ireland). Auscultation of both lungs confirmed correct placement of the tracheal tube, which was then secured on the upper jaw. Hair was clipped from the ventral thorax and head to facilitate the use of self-adhesive electrodes.

The pigs were immobilized in a supine posture on the operating table, and fentanyl (4 µg/kg) and cis-atracurium (0.15 mg/kg) were administered before the animals were connected to the automatic ventilator (ventiPac, Sims pneuPac, Luton, UK) using 21% oxygen. Anesthesia was maintained by inhalation of isoflurane (1.75% to 2%) delivered with 100% oxygen. Additional doses of

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Table 1. Nutrient contents of the commercial diet (3.5-mm pellets)

Total nitrogenous content	28.0%	Vitamin A	1280 IU/kg
Fiber	3.5%	Vitamin D3	1570 IU/kg
Fat	5.0%	Vitamin E	51 mg/kg
Moisture	11.5%	Vitamin B12	24 mg/kg
Ash	5.0%	Biotin	99 mg/kg
Calcium	1.2%	Pantothenic acid	13 mg/kg
Phosphorus	0.8%	Nicotinic acid	17 mg/kg
Sodium	0.4%	Phyllic acid	1.2 mg/kg
Lysine	0.9%	Vitamin C	19 mg/kg
Sulfurous amino acids	0.5%	Magnesium	65mg/kg
		Iron	113 mg/kg
		Iodine	1500 µg/kg
		Selinium	150 µg/kg
		Copper	135 mg/kg
		Cobalt	1125 µg/kg

fentanyl and cis-atracurium were administered as required. The respiratory frequency of the automatic ventilator was adjusted to maintain end-tidal CO_2 at 35 to 40 mm Hg.

Three adhesive electrodes were attached to the ventral thorax to accommodate electrocardiographic monitoring (Mennen Medical, Envoy, Papapostolou, Greece) using leads I, II, and III. This configuration displayed the most prominent P wave with sufficient QRS amplitude and allowed accurate and continuous determination of heart rate. All tracings were recorded on thermographic paper; heart rate was calculated electronically. Peripheral tissue oxygenation was recorded by pulse oximetry (Vet/Ox Plus 4700, Heska, Fort Collins, CO), the sensor of which was placed on the tongue of the animal.

To continuously and noninvasively detect changes in cerebral oxygenation, near-infrared spectroscopy (Somanetics INVOS Cerebral Oximeter, Model SPFB Pediatric Somasensor, Somanetics, Papapostolou, Greece) was used. The spectroscopy optodes were mounted on the intact skin covering each cerebral hemisphere slightly anterior to the coronal suture (to avoid the frontal sinus) and to the strong musculature of the neck. For optimal spatial resolution, the interoptode distance was set at 5 cm. The path length was adjusted according to the manufacturer's instructions for measurements on an intact human skull. Data were recorded every 10 s after induction of anesthesia, and the device automatically calculated the percentage brain regional oxygen saturation.

A fluid-filled femoral arterial catheter (model 6523, USCI CR, Bart, Greece) was inserted and forwarded into the descending aorta under fluoroscopic examination. The systolic and diastolic pressures of the aorta were recorded simultaneously, whereas mean arterial pressure was determined by the electronic integration of the aortic blood pressure waveform. The left carotid artery was dissected, and a 6-French tipped catheter (Abbott Critical Care, Athens, Greece) was advanced into the left ventricle. The right jugular vein was surgically prepared, and a 5-French Swan-Ganz catheter was advanced into the right heart. Correct placement of all catheters was confirmed fluoroscopically. All hemodynamic measurements were performed after allowing the animals to stabilize from the surgical manipulation for 20 min.

After data collection, all catheters were removed carefully, and the carotid arterial wall was sutured (6-0 Prolene, Ethicon, Athens, Greece). The jugular vein was ligated, and the subcutaneous tissue (3-0 Vicryl, Ethicon) and skin (3-0 Polyamide, Medipac, Athens, Greece) were sutured. The administration of cis-atracurium and isoflurane was discontinued. The ventilator was switched to manual mode, and the animal was ventilated with the use of the reservoir bag. Neostigmine (0.04 mg/kg) was administered to reverse cis-atracurium. When the first spontaneous swallowing reflex was detected, atropine (0.01 mg/kg) was administered to prevent the anticholinesterase action of neostigmine. After adequate inspiration depth was ascertained and peripheral oxygenation exceeded 97%, the animal was extubated. Monitoring of vital signs continued throughout recovery. After appearance of the righting reflex, pigs were returned to their cages.

All data are reported as mean ± 1 standard deviation. Normality was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. All parameters measured followed the normal distribution curve, from which the distribution among different percentiles was derived. All analyses were conducted using SPSS version 13.00 (SPSS, Chicago, IL).

Results

After stabilization, the average heart rate was 116.41 ± 8.11 beats/min. The systolic and diastolic pressures of the descending aorta were 111.72 ± 13.61 and 79.03 ± 12.08 mm Hg respectively, whereas the systolic and diastolic pressures of the left ventricle were 108.97 ± 12.06 and 8.88 ± 1.81 mm Hg, respectively. Figure 1 illustrates the pressures of the descending aorta, whereas Figure 2 shows the scattering of the values for the pressures of the left ventricle.

The mean pressures of the right atrium were 10.93 ± 1.36 mm Hg (systolic) and 4.10 ± 1.01 mm Hg (diastolic). The systolic and diastolic pressures of the right ventricle were 21.24 ± 2.16 and 4.20 ± 0.72 mm Hg, respectively. Table 2 shows the distribution of the hemodynamic variables of the right heart among different percentiles.

The value obtained by using near-infrared spectroscopy to determine brain regional oxygen saturation was 64.55% ± 3.88%, and Table 3 gives the distribution of values among different percentiles.

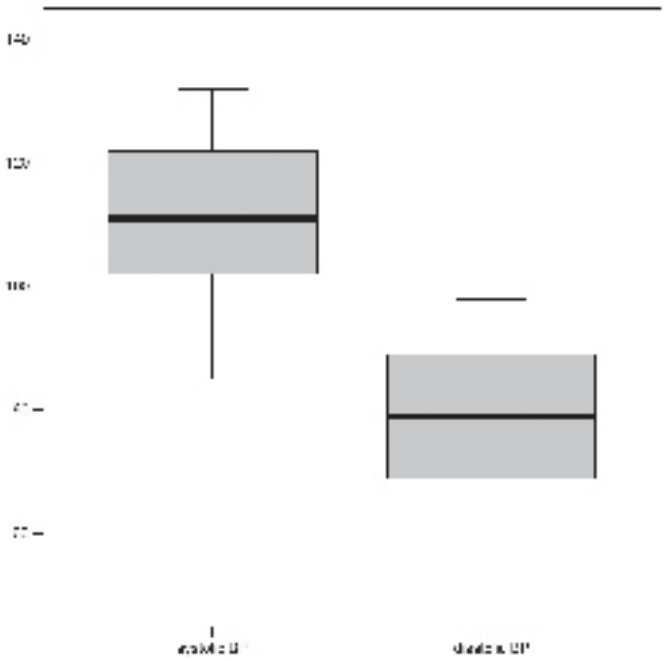

Figure 1. Boxplots of the systolic and diastolic blood pressures (BP) of the descending aorta. The dark line represents the median value, the shaded area indicates the standard deviation (SD), and the horizontal lines above and below the shaded area represent the maximal and minimal values, respectively.

Discussion

To appropriately extrapolate the findings from experimental studies of CA and CPR in pigs to humans, researchers should bear in mind the similarities and differences between the human and porcine hearts.

Similarities between humans and swine in their cardiac anatomy and physiology have been established on the basis of their common characteristics.[9,28] The coronary blood distribution, blood supply to the conduction system, and the histologic appearance of the myocardium in pigs are almost exactly analogous to those in humans.[26] In addition, pre-existing collateral channels and anastomoses are nonexistent in swine, whereas their myocardial, biochemical, and metabolic characteristics in response to ischemic injury are similar to those of humans.[26,27] For these reasons, the swine has often been used as an experimental model for ischemic heart disease.[8]

However important differences exist. Comparing the swine and human myocardial conduction systems, Bharati and colleagues found that the pig atrioventricular bundle is shorter, with a more proximal bifurcation of the bundle branches, more connective tissue, and less elastic tissue. In addition, there are copious amounts of nerve fibers, implicating an important neurogenic component for conduction in the pig.[4] Similar findings have been reported recently, suggesting that pigs should be used with caution as a model system in arrhythmia studies.[6,7]

Blood supply to the swine conduction system is achieved by means of the right coronary artery. Unlike humans, however, pigs have a left hemiazygos vein that drains the intercostals vessels into the coronary sinus.[20]

During CA and CPR experiments, the key variables that need to be monitored continuously are the aortic systolic and diastolic pressures, the systolic and diastolic pressures of the right atrium, and the coronary perfusion pressure, which is calculated as the difference between minimal aortic diastolic pressure and the simultaneously measured right atrial diastolic pressure.[13]

Various swine breeds have been studied extensively, especially in CPR research. The LLW breed is easily obtainable and could be a favorable model for CPR research. According to our measurements, the hemodynamic variables of this breed

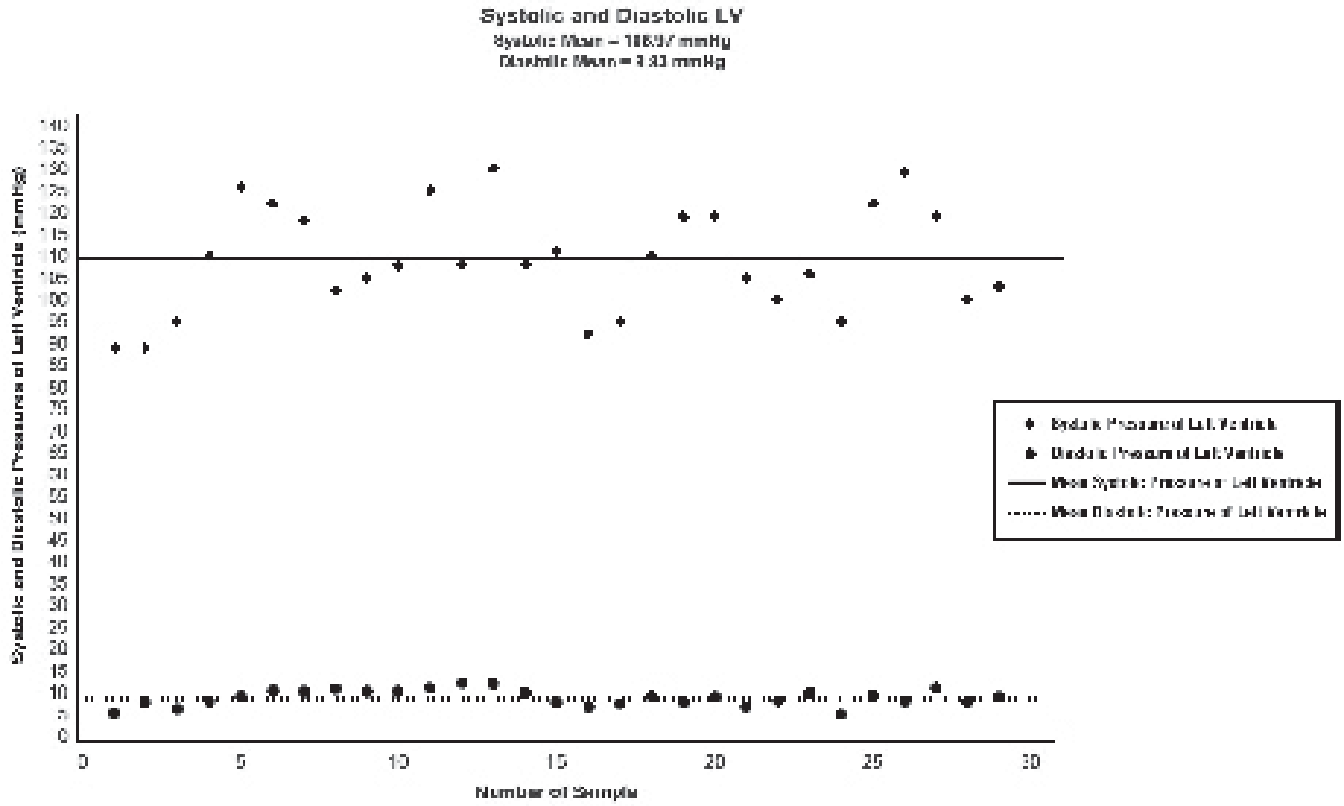

Figure 2. Scattering of values for the systolic and diastolic pressures of the left ventricle.

Table 2. Pressures (in mm Hg) of the right atrium and right ventricle and their distribution among different percentiles

	Percentile						
	5	10	25	50	75	90	95
Right atrium							
Systolic	8.50	9.00	9.50	11.00	12.00	12.00	12.50
Diastolic	2.50	3.00	3.00	4.00	5.00	5.00	6.00
Right ventricle							
Systolic	18.00	19.00	19.50	21.00	22.50	24.00	26.00
Diastolic	3.00	3.00	4.00	4.00	5.00	5.00	5.50

Table 3. Normal values (%) of near-infrared spectroscopy (NIRS; for assessment of brain regional oxygen saturation) and their distribution among percentiles

	Percentiles						
	5	10	25	50	75	90	95
NIRS	57.00	60.00	62.00	65.00	67.50	68.00	71.50

are highly similar to those of healthy recumbent adults. In particular, the pressures originating from the left chambers of the porcine heart are directly comparable to those of the human heart. Moreover, the pressures from the right heart that we recorded during our experiments are in the upper normal range for a human adult.[8]

Several researchers favor experimentation on minipigs.[23] However, their baseline hemodynamics differ markedly from those of healthy human adults. Specifically, pressures originating from the left heart of minipigs[21] are almost half those recorded from LLW swine in our experiments. Regarding the pressures of the right heart, minipigs show distinct variation among breeds, with values ranging from 3 to 9 mm Hg.[21] The LLW breed seems to be more similar to the human cardiovascular variables than are other swine breeds, such as Yucatan minipigs, Yucatan micropigs, and Hanford pigs.[21] However, differences among anesthetic regimens and baseline hemodynamic parameters should not be overlooked during interpretation of results.

Needless to say, successful resuscitation means not only the return of spontaneous circulation but also preservation of adequate cerebral oxygenation. One of the ways to monitor cerebral oxygenation is near-infrared spectroscopy.[30] The application of noninvasive tools that provide real-time information on cerebral oxygenation during CA may shed light on the mechanisms responsible for CA-induced brain injury and neurologic recovery. In contrast to pulse oximetry, cerebral oximetry measures the saturation of oxygen of the venous and capillary blood plus the saturation of the arterial blood. Those measurements represent the mean oxygen saturation of all hemoglobin in the peripheral small capillaries. The normal value for humans is approximately 70%;[25] the values we recorded resemble those for humans.

We recognize that the values we measured reflect the effects of the premedication and anesthetic agents we used. Intravenous ketamine is known to increase arterial pressure and heart rate. However, the action of ketamine after intramuscular injection is limited to 25 min,[1] therefore, its action on the hemodynamic parameters measured should be minimal. Midazolam, like all benzodiazepines, produces very modest hemodynamic effects with good preservation of homeostatic reflex mechanisms. Midazolam causes severe hypotension only during situations of hypovolemia or marked vasoconstriction, as confirmed in human and animal studies.[2] Atropine has widespread antimuscarinic effects on parasympathetic functions, resulting in increased heart rate, without any noteworthy effect on systemic pressures. However, the atropine premedication regimen we used is used frequently in various animal CPR models.[11,29] Furthermore, fentanyl remains the drug of choice in cardiosurgery, because it maintains hemodynamic stability.[5] Cis-atracurium is the only paralytic agent that does not affect cardiovascular system.[16] Compared with other sedative drugs, such as propofol, sevoflurane, and desflurane, isoflurane allows better compensation by the circulatory system.[3,12,15] In addition, the agents we used also are used in the majority of the CPR experimental protocols in LLW and Yucatan minipigs.[3,12,19]

We further recognize several limitations of our study in regard to the differences between the conduction systems of swine and human. The distribution of Purkinje fibers in the ventricular free walls and the collateralization between the left and right main bundles in the apical third of the septum of swine produce vastly different pathways of ventricular activation than those in humans.[4,6,7] We conclude that, despite the current experimental shortcomings, the LLW is a favorable breed for CPR research because of the closeness of the resemblance between its hemodynamic variables and those of humans.

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