CEREBRAL BLOOD FLOW DURING CARDIOPULMONARY RESUSCITATION

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ABSTRACT

Introduction: Cardiopulmonary resuscitation (CPR) is a standard treatment for cardiac arrest. A major goal of CPR is to maintain blood flow to the brain. Compared with standard chest compression (SCC), performed in the centre of the chest, left ventricle chest compression (LVCC) has been shown to improve end-tidal CO_2 ($ETCO_2$) and arterial blood pressure (BP). Using a porcine model, we hypothesized that, consistent with improved $ETCO_2$ and BP, LVCC will promote greater cerebral blood flow (CBF) than SCC.

Methods: Female pigs (N=32; 35±2 kg) were systematically assigned to receive either SCC (n=14) or LVCC (n=18) following 2 minutes of untreated asphyxiated cardiac arrest. Transthoracic echocardiography was used to identify and externally mark the midline at the level of the aortic root (SCC) or the intersection of the long and short axis of the left ventricle (LVCC) for mechanical chest compressions (LUCAS III). $ETCO_2$, BP (arterial catheter line), and CBF velocity (CBF_v; transcranial Doppler) were measured pre-cardiac arrest, during cardiac arrest, and through three rounds of basic life support (BLS) CPR. Data were analyzed using a mixed model RM ANOVA.

Results*:* $ETCO_2$, BP, and CBF_v were similar between the SCC and LVCC groups at baseline ($P \geq 0.224$) and during untreated cardiac arrest ($P \geq 0.216$). $ETCO_2$ (SCC=24±10 versus LVCC=36±6 mmHg; $P<0.001$) was significantly elevated throughout CPR in the LVCC versus SCC group. Systolic BP (SCC=45±10 versus LVCC=61±10 mmHg; $P<0.001$), Diastolic BP (SCC=33±10 versus LVCC=41±8 mmHg; $P<0.001$), and Mean BP (SCC=33±9 versus LVCC=49±9 mmHg; $P<0.001$) were significantly elevated throughout CPR in the LVCC versus SCC group. Peak CBF_v (SCC=19±6 versus LVCC=37±6 cm/s; $P<0.001$) and Mean CBF_v (SCC=5±2 versus LVCC=11±5 cm/s; $P<0.001$), but not Minimum CBF_v ($P \geq 0.249$), were significantly elevated throughout CPR in the LVCC versus SCC group.

Conclusion*:* LVCC improved $ETCO_2$, BP, and CBF_v throughout BLS in a porcine model of cardiac arrest.

New and Noteworthy*:* This is the first study to provide evidence that compared with mechanical compressions performed over the middle of the chest, compressions performed over the left ventricle promote greater CBF during BLS CPR. Clinical validation of these results may improve survival rates and attenuate neurological deficits following cardiac arrest.

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To my Father, Barry Marshall, Mother, Teresa Marshall, and Sister, Helen Marshall, your unwavering love and support provides me with the strength to move forward. I am and will be forever grateful for you and all that you do for me. I hope to one day be able to return the favour.

DEDICATION

I dedicate this thesis to my Grandfather, Keith Thorpe, and late Grandmother, Jill Thorpe. As role models, you have shown me what it means to share truly unconditional love and joy with the world. You have been foundational in shaping me into the person I am today. Thinking of you both reminds me how truly lucky I am, always. I am beyond grateful to have had you both in my corner, cheering me on in life. I do not know exactly what trouble I will be getting into next, but I do know you will be right there with me.

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GLOSSARY OF TERMS

Term	Definition
Blood Pressure	Circulating pressure against arterial walls
Cardiac Arrest	Loss and sustained absence of rhythmic heart contraction
Cardiac Output	Volume of blood pumped by the heart per minute
Cardiopulmonary Resuscitation	Chest compression and ventilations to treat cardiac arrest
Cerebral Blood Flow	Volume of blood supplied to the brain

ABBREVIATIONS

Abbreviation	Definition
ALS	Advanced Life Support
AV	Atrioventricular
BLS	Basic Life Support
BP	Blood Pressure
CA	Cardiac Arrest
$CarBF_v$	Carotid Blood Flow Velocity
CBF	Cerebral Blood Flow
CBF_v	Cerebral Blood Flow Velocity
CerePP	Cerebral Perfusion Pressure
CO	Cardiac Output
CO_2	Carbon Dioxide
CorPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CT	Computer Tomography
DBP	Diastolic Blood Pressure
$ETCO_2$	End-Tidal Carbon Dioxide
HR	Heart Rate
IHCA	In-Hospital Cardiac Arrest
LA	Left Atria
LAV	Left Atrioventricular
LDF	Laser Doppler Flowmetry
LV	Left Ventricle
LVCC	Left Ventricle Chest Compression
LVOT	Left Ventricular Outflow Tract
MBP	Mean Blood Pressure
OHCA	Out-of-Hospital Cardiac Arrest
RA	Right Atria
RAV	Right Atrioventricular

ROSC	Return of Spontaneous Circulation
rSO_2	Regional Hemoglobin Oxygen Saturation
RV	Right Ventricle
SBP	Systolic Blood Pressure
SCC	Standard Chest Compression
TEE	Transesophageal Echocardiography
TCD	Transcranial Doppler
TTE	Transthoracic Echocardiography

CHAPTER 1

1. INTRODUCTION

During normal bodily function, the heart contracts and relaxes rhythmically to circulate blood throughout the body.[1] The circulation of blood is essential to supply oxygen and nutrients as well as remove metabolic by-products from organs throughout the body.[1] Some organs, like the brain, have minimal metabolic reserves; thus, a constant supply of blood is required to ensure normal function.[1] Even small interruptions of blood flow to the brain can cause injury or death.[1]

A cardiac arrest (CA) occurs when the abrupt absence of proper heart function causes inadequate perfusion to sustain life.[2] The incidence of CA in Canada totals over 35,000 each year.[3] Cardiopulmonary resuscitation (CPR) is an emergency procedure used to treat CA.[4] The two components of CPR are ventilation, to simulate breathing, and external chest compression, to simulate the heart pumping.[5] Maintaining pumping capacity of the heart is essential to preserve oxygen and nutrient delivery to the brain during CPR. If return of normal heart rhythm does not occur, brain damage and eventually death are inevitable. Unfortunately, less than 10% of people survive a CA, and the likelihood of survival decreases in the setting of absent or delayed CPR.[6–9] Given the prevalence of CA and the dismal survival rate, enhancements to the treatment can have major implications for saving lives.

Effective chest compressions are a vital component of CPR. Laypeople, those who are not trained formally in administering CPR, are no longer advised to administer ventilations, just chest compressions.[10,11] Recommendations from American Heart Association indicate that chest compressions are to be delivered to a depth of 5 cm, a rate of 100-120 compressions per minute, and to allow full recoil of the chest.[12] The current recommended chest compression location is the centre of the chest or inter-nipple line.[12,13] This location overlies the upper third of the heart, which encompasses the ascending aorta, aortic root, left ventricular outflow tract (LVOT; where blood is ejected from the heart into the systemic circulation), or atria in over 80% of patients.[14–20] Of note, the largest width of the heart is closer to the transverse midline of the ventricles, which is

positioned inferior to the current recommended chest compression site.[18] Importantly, the ventricles, which normally contract from the apex to the base of the heart (moving cranially) to propel blood out through the LVOT and aorta, are responsible for pumping blood to the lungs as well as the systemic circulation. Thus, the current chest compression location overlies a submaximal portion of the heart and may not compress the chambers of the heart responsible for pumping blood to peripheral tissues, which could contribute to limited circulation during CPR. Furthermore, by compressing the upper third of the heart, in addition to limiting the potential volume of blood being pumped, the recommended compression location may also impede flow by narrowing of the outflow vessels.[20] Potentially, changing the chest compression location to encompass a larger ventricular area would improve circulation and brain blood flow during CPR by simultaneously increasing the volume of blood being pumped and decreasing flow resistance in the outflow vessels. Improving circulation and brain blood flow could increase survival rates and prognoses following cardiac arrest.

Chest compressions targeting the lower aspect of the sternum or LV have been found to improve some measures of hemodynamic status (*i.e., blood pressure (BP), end-tidal carbon dioxide ($ETCO_2$)*) during CPR.[21,22] However, the effect of LV chest compression (LVCC) on cerebral blood flow (CBF) remains unknown. It is difficult and, in many cases, unethical to study how alternative CPR protocols influence CBF in humans. Therefore, the majority of research in this area is completed using porcine models. Importantly, porcine and human cardiovascular and cerebrovascular anatomy and function are similar; thus, preclinical porcine models are considered translationally relevant for human CPR.[23] Accordingly, the work described herein used a porcine model of CA and CPR to investigate the effect of chest compression location on indicators of systemic hemodynamic status and CBF. The overall goal of this thesis is to provide needed insight into the potential effectiveness of LVCC, which could be used to inform future CPR recommendations.

CHAPTER 2

2. REVIEW OF LITERATURE

2.1 Mechanisms of CPR

2.1.1 Cardiovascular System

The cardiovascular system is responsible for pumping and distributing blood throughout the body.[24] To accomplish this, the heart acts as a pump to move blood through this closed-circuit system.[24] Deoxygenated blood from the vena cava enters the right atria (RA) of the heart. The blood then moves inferiorly through the right atrioventricular (RAV, tricuspid) valve to the right ventricle (RV).[24] At rest, approximately two-thirds of ventricular filling is passive during diastole, with the remaining third being forced into the RV during atrial contraction.[24] Blood is propelled from the RV through the semilunar (pulmonic) valve into the pulmonary artery.[24] The pulmonary artery branches and directs blood towards the capillaries of the left and right lung.[24] Once blood arrives in the capillaries of the lungs, gas exchange occurs.[24] Whereas carbon dioxide (CO_2) diffuses from the blood into the lungs, oxygen diffuses from the lungs into the blood.[24] Oxygen-rich blood returns to the left atria (LA) of the heart from the pulmonary veins.[24] Once in the LA, blood travels through the left atrioventricular (LAV, bicuspid) valve into the left ventricle (LV).[24] Contraction propels blood through the LVOT and semilunar (aortic) valve into the ascending aorta.[24] The aorta divides into large muscular arteries that subsequently divide into resistance arterioles and then capillary beds in organs throughout the body.[24] Metabolites are exchanged in the capillaries as oxygen is delivered to systemic organs and CO_2 is removed.[24] Deoxygenated blood then enters the venous system, flowing into venules then veins before ultimately joining the vena cava.[24] Blood travels through the vena cava and into the RA, where the cycle is repeated.[24] It is important to note, this process is continuous as the adult human heart typically contracts rhythmically at ~72 beats per minute under awake resting conditions.

The right side of the heart and vasculature that serves the lungs is called the pulmonary circulation.[24] The left side of the heart and the vasculature that services all systemic organs make up the systemic circulation.[24] The left and right sides of the heart pump an identical volume of blood.[24] All of the blood that travels through the pulmonary circulation travels through the systemic circulation.[24] Cardiac output (CO) is the volume of blood pumped from the heart per minute.[24] This is a measure of cardiac function. A normal CO for an average individual at rest is between five and six litres per minute.[24] During untreated CA, the absence of cardiac activity results in a total absence of CO. By extension, perfusion ceases in the lungs and systemic organs, including the brain.

2.1.2 Cerebral Circulation

At rest, approximately 14% of CO is supplied to the brain.[24] The brachiocephalic trunk, left common carotid artery, and left subclavian artery branch off from the aortic arch.[24] The brachiocephalic trunk splits into the right subclavian artery and right common carotid, matching their left-sided counterparts.[24] The right and left common carotid arteries branch into internal and external carotid arteries.[25] The right and left vertebral arteries branch from the subclavian arteries.[25] The internal carotid and vertebral arteries supply the brain.[25] The vertebral arteries converge to form the basilar artery, which enters the head through the dorsal aspect of the cranium.[25] The internal carotid arteries and basilar artery connect via communicating arteries to form the Circle of Willis.[25] The left and right pairs of the anterior, middle, and posterior cerebral arteries stem from the Circle of Willis to form the main blood supply to the cerebrum.[25] Cerebral arteries divide into smaller arteries before penetrating the brain and becoming parenchymal arteries.[25] Parenchymal arteries divide into parenchymal arterioles and then capillaries.[25] Gas exchange occurs in the capillaries, and blood then enters into the venous system of the brain.[25] The cerebral venous system is an interconnected system of dural sinuses and cerebral veins.[25] Blood travels through the cerebral venous system, draining into the jugular veins to return to the vena cava and ultimately the heart to be circulated through the pulmonary and systemic circulations once again.[25] In clinical scenarios that are associated with low flow states (i.e., cardiogenic shock), vasodilation of the cerebral vasculature occurs simultaneously with vasoconstriction of the systemic vasculature resulting in

an increased proportion of CO directed to the brain.[25] During untreated CA, blood flow to the brain ceases completely. During active CPR, blood flow to the brain is reduced by approximately 70%.

2.1.3 Neurological Deficits Following Cardiac Arrest Recovery

The fundamental objective of CPR is to circulate blood throughout the body to restore perfusion to vital organs until the body can regain self-sufficient circulation, termed a return of spontaneous circulation (ROSC). However, after a CA and ROSC, brain injury and neurological deficits are of great concern. Owing to halted CO, subsequent loss of CBF, and given the lack of metabolic reserve in the brain, neurological impairment is a frequent consequence of CA-induced ischemia.[26] Indeed, estimates indicate between 12-20% of victims that survive CA experience CA-related cognitive impairment,[27] with the severity of symptoms being directly proportional to the duration of CA.[27] Functional deficits following CA include impairments in short-term memory, immediate memory, delayed recall, executive functions, and a greater risk of developing attention deficit disorders.[27] As neurological and cognitive status is foundational to quality of life, the ischemia-related impairments that stem from a prolonged interruption of blood flow to the brain directly impact post-arrest life.[27] Mental health problems are also common in patients who have recovered from CA, which can add further duress to recovery and rehabilitative efforts.[27] Minimizing ischemic hypoxic damage by improving brain blood flow during CPR is paramount to a better quality of life for successfully resuscitated patients.

2.1.4 Thoracic and Cardiac Pump Theory

There are two main theories of how chest compressions generate blood flow during CPR: thoracic pump theory and cardiac pump theory. Thoracic pump theory relies on chest compressions creating a pressure gradient when intrathoracic pulmonary vascular bed pressure exceeds left-sided heart and systemic circulatory pressure, forcing blood to disseminate into the systemic circulation.[28,29] According to this theory, the heart acts as a passive conduit for blood without requiring direct contraction or compression.[28] To act as a conduit in this manner, ventricular size remains constant, and both AV valves remain open throughout CPR.[30] The pulmonary valve must be competent to prevent retrograde flow.[29] During compression, increased intrathoracic pressure

exceeds that of the systemic circulation, and blood travels from the pulmonary circuit through a docile left heart to the systemic circulation.[28,29] In contrast, according to cardiac pump theory, direct compression of the heart between the sternum and spine causes blood to propel from the heart into the pulmonary and systemic circulation.[28] A key differentiator in cardiac pump theory is that the AV valves of the heart must close during compression, preventing backflow into the atria.[28,31] The rationale is that, similar to the normal cardiac cycle, direct compression causes intraventricular pressure to rise, AV valves to close, and semilunar valves to open, thus, propelling blood out of both the RV and LV.[30] During the release of compression, intraventricular pressure falls, AV valves open allowing blood to flow into the ventricles, and semilunar valves close.[30] A substantial change in ventricular size and intraventricular pressure during CPR is needed to mimic the cardiac cycle.[30] Although the theories rely on different mechanisms of action, they are not necessarily competing. The relative contribution from either mechanism of action does not appear to be fixed and may depend on a variety of factors, including patient size, compression depth, compression rate, compression site, underlying anatomy, etc.[27,30-41] The efficacy of chest compression is a fundamental indicator in the success of CPR, regardless of the underlying physiological mechanism of action.[30]

2.1.5 Underlying Anatomy

The anatomical site for external chest compressions is the centre of the chest on the lower half of the sternum.[12] Compression of the underlying anatomy is the primary consideration supporting the investigation into alternative chest compression locations. Assuming compression of the chest cavity also compresses the heart, causing an immediate increase in stroke volume, noting the underlying anatomy, compression in the centre of the chest on the lower half of the sternum may not maximize stroke volume during CPR. Using computed tomography (CT), it has been established that the LVOT, aortic root, aorta, RA, or LA underlie the current chest compression location landmark in ~80% of patients.[14–16,18,19,43] This holds true despite changes in arm position, raised or at sides, which was falsely hypothesized to relocate the overlying structures drastically.[14–16,18,19,43] Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) findings were consistent with findings from CT imaging, further confirming that the LV is not beneath the standard chest compression (SCC) landmark.[44–46] A CT

study conducted in cadavers imaged the chest during external compressions at incremental chest compression depths from 1 cm to the standard depth of 5 cm.[17] This work revealed compression on the lower half of the sternum caused compression of the sternum, ribs, atria, and great vessels, consistent with the *in vivo* human research.[17] The RV and LV were not compressed but shifted laterally and inferiorly into the left chest cavity.[17] In a case series of actual CA victims undergoing CPR, TTE identified no compression of the LV in four out of five patients.[47] In addition to a lack of LV compression, SCC is also associated with a sustained 50% narrowing of the LVOT or aorta during compression.[20] Collectively, the evidence indicates, the LV is not below the SCC location in the vast majority of patients, and therefore, the LV is not being compressed during CPR. Of note, outflow vessels and the atria do not host the largest volume of the heart, nor is compression of these structures conducive to normal flow of blood. The ventricles host a larger volume within the heart, and the LV is the chamber that ejects blood into the systemic circulation. Thus, in an attempt to enhance the cardiac pump effect during CPR, LVCC is emerging as a novel technique to improve CPR effectiveness. LVCC targets the LV of the heart, as opposed to SCC which targets the upper third of the heart. Preliminary findings have shown LVCC to increase some indicators of hemodynamic status and measures of CPR efficacy.[21,22]

2.2 Standard Versus Left Ventricle Chest Compressions

Chest compressions have been delivered in the same general SCC location since the inception of CPR.[13] Owing primarily to the underlying anatomy, the SCC location may not be the optimal location for external chest compressions.[14–19,42–46] Novel LVCC, delivered to the LV, is beginning to be explored as an alternative treatment to SCC that may enhance the incidence of ROSC and increase survival.[21,22] The greatest ventricular and overall heart width underlie the LVCC location.[80-91] The ventricles host the largest structural volume within the heart.[48] Therefore, a larger volume of blood may be impacted by compressing the LV and RV directly (*i.e., LVCC location*) versus the LVOT, aortic root, aorta, RA, or LA (*i.e., SCC location*).[14–19,21,42–50] In addition, by not compressing the LVOT, aortic root or aorta, LVCC may impose less resistance to blood being ejected from the LV. Consistently propelling a larger volume of blood from the heart while facing less resistance would likely cause improvements to hemodynamic performance during

CPR. Such improvements may lead to enhancements in other indicators of CPR quality, such as superior CBF, which serve prognostic value for ROSC as well as post-arrest quality of life.

Occlusion of the aorta during CPR may cause site-specific aortic ballooning and influence blood flow distribution during resuscitation. Ballooning of the aorta at the site of chest compression has been observed during the compression phase of CPR.[33] Mechanistically, aortic ballooning functions by incidental occlusion of the aorta during chest compressions reducing or preventing blood flow at that site.[33] Site-specific aortic ballooning (*i.e., degree of occlusion, site of occlusion, etc.*) may contribute to movement and directionality of blood during CPR. During SCC, aortic ballooning may occur at the level of the aortic arch (*i.e., location of branching arteries that supply the brain*), which could be a cause of reduced CBF during standard CPR. Under LVCC, aortic ballooning would likely occur inferior to the aortic arch (*i.e., the aorta descends behind the heart after the aortic arch*), which would allow non-occluded supply to the brachiocephalic trunk, left subclavian, and left common carotid arteries. The effect of chest compression location on site-specific aortic ballooning in relation to systemic hemodynamic status remains to be fully elucidated. Owing cumulatively to these mechanistic facets of chest compression delivery, LVCC could improve CO and CBF during CPR.

2.2.1 Human and Porcine Models of CPR

Owing to the inherent risk of CA, conducting CPR research is seldom achievable and often unethical in clinical patients. Ergo, reliable preclinical models are fundamental to research aimed at better understanding CA and improving CPR protocols.[23] A major requirement for any experimental model is the translational potential to the human context. Swine are an excellent model of CPR research given that the human and swine vascular and neuroanatomy and function are closely related.[23] Both human and swine brains are gyrencephalic, contain greater than 60% white matter and rely on the internal carotid, vertebral arteries, Circle of Willis and cerebral arteries for perfusion.[23,52] Heart size, heart rate (HR), and serum characteristics are also comparable between the two models.[53–55] The similarities in anatomy are continued through relevant indicators of hemodynamic status and are discussed for each CPR metric below. Porcine models can accommodate extensive instrumentation and similar clinical tools can be applied to both populations.[23] Swine, when compared to other research animals, have large chests that can

accommodate external chest compressions using the same chest compression devices used in humans.[23] To maximize translational relevance of CPR research for pediatric populations, it is recommended to use ~5 kg piglets.[56,57] In contrast, for the results of a study to be more applicable for adult populations, it is recommended to use 20-60 kg swine.[58–61]

Despite the many advantages of using swine for CA and CPR research, as with most preclinical models, there are also limitations. Typically, juvenile disease-free swine are used, which are not representative of the older diseased population who typically succumb to CA.[23] Older swine are more expensive to rear and, owing to their large stature (a full-grown sow can weigh >170 kg), are not anatomically favourable for CPR research. With respect to the latter point, it is critical to use appropriately sized swine to ensure the size of the chest cavity is comparable with humans.

Although chest cavities can be a similar size between species, structural differences do exist. For example, the anterior and posterior walls of the porcine thorax are pointed, whereas the anterior and posterior walls of the human thorax are relatively flat.[48,62,63] Furthermore, the swine thorax will become increasingly elongated with age.[63] In addition to the structural differences of the thorax, the orientation of the heart is also different. In humans, the heart is positioned left of the midline, and the long axis of the heart is angled ~40° to the left.[54,64] In swine, the heart is also left of the midline, but the long axis orientation is approximately vertical.[49] As result of the orientation of the swine heart, the heart is positioned more medially and vertically when compared to the human heart.[54] Despite the vertical orientation of the swine heart, the vast majority of left ventricular area is left of the midline in both humans and swine.[49] The midpoint of the LV, the intersection between the long and short axis of the LV, remains left of the anatomical midline of the body in both humans and swine during standard CPR.[17,49] As the heart is positioned more medially and vertically in swine, surface landmarks in swine may not translate to humans. Thus, for research purposes, TTE must be used to properly landmark compression sites in swine.

In addition to structural considerations, there are also experimental differences between animal and human CPR studies. For humane reasons, porcine research is performed while animals are under anesthesia. However, human out-of-hospital CA (OHCA) victims are not anesthetized like their porcine counterparts, which can influence hemodynamic status as well as ROSC.[23] Use of porcine models must be conducted under these conditions (*i.e., young healthy pigs, under anesthesia, etc.*) for ethical and logistical reasons. Nevertheless, findings from porcine studies are considered translationally relevant and able. Porcine CPR research typically compares

hemodynamic status and ROSC between two similar groups and/or compares each animal to baseline. Using these methods, relative assessment of porcine CPR (*i.e., treatments among swine populations or swine to baseline*) can be used to establish concepts in resuscitation to guide clinical research in human populations. Direct comparisons between humans and swine must be interpreted cautiously and followed up with clinical research. Weighing the advantages and limitations of the porcine model of CA and CPR, it can be used effectively to advance the science of resuscitation beyond what is accomplishable without it. However, the applicability of results must be interpreted cautiously, and porcine research cannot replace the accumulation of clinical observations and epidemiological findings.[23]

2.3 Measures of Cardiopulmonary Resuscitation

2.3.1 Return of Spontaneous Circulation

Attaining ROSC is vital to successful resuscitation during CPR. An electrocardiogram (ECG) uses purposefully placed electrodes to measures the bioelectrical potentials at the interface of the skin and the electrode. Measurement of these potentials provides information specific to the patient about electrical activity of the heart and if ROSC has occurred.[65–67] During CPR, an ECG can be misleading, owing to pulseless electrical activity, and subject to interference during chest compressions.[65–67] Circulations checks involve a momentary pause in CPR to assess for ROSC. During circulation checks, any interference from chest compressions is absent; thus, the ECG can be interpreted more accurately. In OHCA without an ECG, manual pulse palpation of the carotid artery is used to assess for ROSC. Carotid Doppler ultrasound is a more sensitive technique to assess for a pulse than manual palpation; however, it is seldom used. Briefly, as sonography is able to establish a pulse wave under lower pressure conditions than an external pulse check by hand, the presence of a carotid blood flow velocity ($CarBF_v$) wave is the preferred method to assess for ROSC.[68] $CarBF_v$ is not used commonly in OHCA as it is not readily available.[68–70] For this reason, there are currently no clinical targets for $CarBF_v$, just waveform existence. Achieving a ROSC is the clinical target during CPR when no other metrics are available.[12] Achieving a ROSC is a measure of CPR efficacy, not CPR quality.

As the principal outcome of CPR efficacy, comparison of the occurrence of ROSC between SCC and LVCC is of key importance when considering chance of survival. Beyond ROSC, 60-minute survival is used to measure self-sustained circulation over time.[21,51,71,72] Globally, between 3-10% of patients that undergo CPR survive,[8,73] yet 30% of patients that receive CPR achieve ROSC.[50] Thus, 60-minute survival is a different measure of CPR efficacy, quantifying longevity of treatment instead of ROSC alone. In the clinical realm, patients who receive CPR are typically receiving SCC, making the rate of ROSC during SCC ~30%.[50] To date, no studies in a human population have compared the prevalence of ROSC or 60-minute survival with SCC versus LVCC.

In porcine CPR research, the Anderson group has conducted seminal work in the area of SCC versus LVCC, specifically focusing on ROSC and 60-minute survival as primary outcomes.[21,51,71,72] However, all but one of the Anderson group's SCC versus LVCC studies used a traumatic model of CA. [21,51,71,72] Traumatic CA yields a prognosis worse than non-traumatic CA (non-Traumatic CA ~10% versus Traumatic CA ~2%).[8,51,74] Massive blood loss resulting in severe hypovolemia and subsequent decrease in CO is the commonly accepted reason for traumatic pulseless electrical activity CA.[74,75] Over 90% of CA are of cardiac etiology; thus, traumatic CA is not representative of the greater problem.[8,76] Further, the futility of resuscitative efforts during traumatic CA has advanced a line of thought that CPR should not be performed in these cases.[74,77] CPR research examining hemodynamic status commonly incorporates traumatic CA in the exclusion criteria to avoid this type of arrest from adding a confounding variable to research.[22,31,78] Research utilizing traumatic CA models could mask the effect of chest compression location on ROSC, 60-minute survival, and hemodynamic status. For this reason, the following discussion will include only the Anderson group's work using the non-traumatic SCC versus LVCC OHCA model.

The Anderson group reported a significant increase in the occurrence of ROSC with LVCC versus SCC in their 2017 porcine model of adult OHCA (SCC 0% (0/13) versus LVCC 69% (9/13); $P<0.001$).[21] All animals that achieved ROSC survived to 60 minutes (SCC 0% (0/13) versus LVCC 69% (9/13); $P<0.001$).[21] No animals that received SCC achieved a ROSC or subsequent 60-minute survival. This preliminary animal finding shows that LVCC caused a 70% ROSC rate,[21] more than double the SCC human ROSC rate.[50] Although these findings must be interpreted cautiously, they indicate that under experimental conditions, LVCC may increase the occurrence of ROSC and 60-minute survival versus SCC.

2.3.2 End-Tidal Carbon Dioxide

$ETCO_2$ is the partial pressure of CO_2 at the end of exhalation of each breath.[79] $ETCO_2$ is most commonly measured from a sampling line connected to an intubated respiratory support (*i.e., ventilator, bag-valve-mask*) of a ventilated patient. Waveform capnography is used to track CO_2 partial pressure through each ventilatory cycle, denoting the peak as $ETCO_2$.[80] The metric is an established indicator of CO in CPR owing to the relationship with pulmonary blood flow.[80–84] More specifically, because of the mirror blood volumes pumped through the left and right heart, the amount of exhaled CO_2, which corresponds with the amount of blood pumped by the RV to the lungs, is used as a functional proxy to estimate CO in CPR. Normative $ETCO_2$ values for humans and swine range from 35-40 mmHg.[21,51,59,71,72,85–87] The clinical target for $ETCO_2$ during CPR was previously recommended as ≥20 mmHg.[88] However, recently updated guidelines support a patient-specific $ETCO_2$ guided approach, as the ≥20 mmHg target may not be applicable to all clinical situations.[12,88,89] This longstanding clinical target still holds merit as a clinical outcome and preclinical target, owing to the relationship to CO as well as for experimental research where animal characteristics, CA, and CPR conditions are highly controlled. A sudden rise in $ETCO_2$, ergo CO, ≥10 mmHg is an early indicator of ROSC,[88,90] while failure to achieve >10 mmHg on waveform capnography is associated with death.[91–93] Owing to the ease of instrumentation to measure $ETCO_2$, it is a very common measure used to guide CPR. Owing to the breadth of CPR research using different SCC protocols, $ETCO_2$ values vary grossly. Factors including time to measurement (*i.e., within 5 minutes, within 45 minutes*), arrest location (*i.e., in-hospital CA (IHCA), OHCA*), and time of untreated CA (downtime) influence $ETCO_2$.[86,94] Recent research found a strong positive correlation between the compression of the maximum area of the ventricles and $ETCO_2$.[95] This indicates that the more the ventricles are compressed, the more $ETCO_2$ will increase. In line with that work, Cha and colleague's flagship 2013 SCC-first LVCC-second trial, using human patients, found greater $ETCO_2$ during LVCC versus SCC.[22] Briefly, in this study, after a varying amount of collapse-to-emergency department time (1-35 minutes), patients underwent 30 minutes of in-hospital SCC CPR including Advanced Life Support (ALS) procedures before 2 additional minutes of LVCC.[22] Mean $ETCO_2$ were significantly greater during 2 minutes

of LVCC after >30 minutes of SCC versus the final 2 minutes of in-hospital SCC CPR (SCC=10±7 mmHg versus LVCC=11±7 mmHg; P=0.020).[22] Given ETCO2 values were compared after >30 minutes of CPR, the extended time between CA and time of measurement may be a factor in the overall low $ETCO_2$ values reported in this study. Nevertheless, despite this delay, LVCC elicited an increase in $ETCO_2$, demonstrating promise for the clinical application of this novel technique. In a separate study, where TEE was used to guide compression towards the LVCC location during active CPR, CA patients experienced an increase in $ETCO_2$ after compression location was adjusted to compress the LV.[47] These patients presented with $ETCO_2$ pressures <20 mmHg during ongoing SCC, but all improved to >40 mmHg with compression of the LV.[47]

It is important to note, however, that not all studies report a clinical benefit of LVCC. Qvigstad and collaborators conducted a four chest compression site alternative location study that measured $ETCO_2$ sequentially after initially optimized SCC.[96] CPR was optimized initially with $ETCO_2$ feedback prior to trial of alternative experimental compression positions.[96] Once optimized, altering the chest compression location did not offer any additional benefits. More specifically, mean $ETCO_2$ pressures were greater, but not statistically significant, when delivered 2 cm inferior to the inter-nipple line (Inter-Nipple Line=23 [range 5-65] mmHg versus Left=26 [range 4-77] mmHg, Centre=26 [range 4-80] mmHg, Right=29 [range 3-66] mmHg).[96] Of note, this study did not directly target the LV or monitor LV compression but instead compressed surface landmarks and adjusted the compression location based on achieving the greatest $ETCO_2$. As such, it is unknown if initial CPR optimization involved a shift from the original SCC position towards an LVCC position causing greater ventricular compression. This research did note that, on average, a 7 mmHg $ECTO_2$ difference was observed between the best and worst location for each patient.[96] Thus, although somewhat contrasting to other research, these findings do not detract from the potential clinical benefit of LVCC as they demonstrate that the initial SCC location did not produce the greatest $ETCO_2$ values.

The Anderson group's findings from their SCC versus LVCC porcine OHCA model support the aforementioned clinical findings and revealed greater $ETCO_2$ in the LVCC group versus SCC group (SCC=26±15 mmHg versus LVCC=37±18 mmHg; P<0.001).[21] The LVCC-induced improvements persisted throughout Basic Life Support (BLS), which involved ventilation and chest compressions, and ALS, which involved ventilation, chest compression, defibrillation, and medication administration.[21] Unfortunately, hemodynamic status variables, except Coronary

Perfusion Pressure (CorPP, discussed in later section), were not reported separately for BLS and ALS CPR.[21] Thus, it is impossible to know from these data whether the improvement was owing to LVCC or was secondary to the combined effect of ALS and LVCC. This is the only study to date to examine $ETCO_2$ under SCC versus LVCC conditions. Therefore, the collective evidence from preclinical and clinical trials supports the notion that compared with SCC, LVCC promotes greater $ETCO_2$ and by extension CO values during CPR.

2.3.3 Blood Pressure

Assessing arterial BP is paramount in comparing hemodynamic status during CPR. BP refers to the amount of pressure in the arterial system. Systolic BP (SBP) represents the pressure during cardiac systole. Diastolic BP (DBP) is the minimum pressure maintained between contractions of the heart when no blood is being ejected. Mean BP (MBP) is the average amount of pressure in the system throughout the cardiac cycle. During CPR, SBP refers to the pressure during compression, DBP refers to the pressure during decompression, and MBP refers to pressure throughout the compression-decompression cycle. In normal healthy people, BP is commonly measured externally with a sphygmomanometer and stethoscope; however, during clinically necessary situations, more advanced measurement is required. Invasive BP measurement would typically use an arterial catheter line connected to a pressure transducer. A catheter is inserted into an artery, and beat-by-beat BP registers on the transducer, measuring SBP and DBP, and enabling the calculation of MBP. Humans and swine share comparable SBP (95-145 mmHg), DBP (60-90 mmHg), and MBP (70-110 mmHg), with an average SBP/DBP of 120/80 mmHg.[87,97,98]

DBP is of particular interest because of the relationship to coronary artery perfusion. As the heart is perfused primarily during relaxation (*i.e., decompression*), CorPP is the primary impetus of myocardial blood flow in CPR.[1,88,99–102] If DBP is too low, then coronary arteries will not be perfused adequately and it is unlikely that the heart will regain spontaneous contraction.[21] The clinical target for DBP was recommended as ≥25 mmHg.[88] However, the recently updated guidelines support a patient-specific DBP guided approach, as the ≥25 mmHg target may not be applicable to all clinical situations.[12,88,89] Like $ETCO_2$, the clinical target for DBP remains pertinent as a clinical outcome and preclinical target. Measurement of CorPP is more direct than DBP but requires both aortic and central venous pressures.[88] As the difference between DBP in the aorta and

RA during the decompression phase of chest compressions, supplementary invasive transducer placement is needed to assess CorPP. During CPR, the clinical target for CorPP was recommended to be ≥20 mmHg but has also shifted from a blanket target to a patient- and situation-specific guide.[12,88,89]

A MBP of 40-50 mmHg is the lowest allowable pressure threshold needed to perfuse the brain adequately.[103,104] During CPR, MBP varies depending on factors like CPR quality as well as extra CPR factors such as untreated time to CPR, pharmaceutical treatments (*i.e., epinephrine, vasopressors*), etc., but often falls below 50 mmHg.[105,106] A MBP <50 mmHg indicates CBF is likely compromised.[103,104] Unlike CorPP, cerebral perfusion pressure (CerePP, mean aortic minus intracranial pressure) is not a stand-alone indicator of CBF.[107] Briefly, CBF relies on cerebral autoregulation to ensure steady-state flow to the brain over a wide range of physiologic circumstances.[104] Vasodilation (*i.e., increased cerebral blood volume*) and vasoconstriction (*i.e., decreased cerebral blood volume*) maintain intracranial pressure and CerePP throughout BP changes.[104] However, too much alteration beyond normal CBF ranges (*i.e., during CA*) can lead to brain ischemia.[104] As achieving a MBP ≥50 mmHg is needed to perfuse the brain adequately, BP is of great interest.

Cha and colleagues' SCC-first LVCC-second clinical study reported BP findings consistent with their $ETCO_2$ results.[22] That is, similar to $ETCO_2$, they documented higher SBP and MBP with LVCC versus SCC, even though the LVCC were performed after 30 minutes of SCC (SBP SCC=95±42 mmHg versus LVCC=114±51 mmHg; P<0.001; MBP SCC=50±23 mmHg versus LVCC=56±27 mmHg; P=0.010).[22] Given CO is a primary determinant of MBP, and an increased $ETCO_2$ is thought to reflect an increased CO, it would be anticipated that increased $ETCO_2$ would be associated with increases in MBP. However, DBP differences between groups were not significant (SCC=28±17 mmHg versus LVCC=28±18 mmHg; P=0.883).[22] Of note, DBP is a better reflection of total peripheral resistance than CO, which may have been similar between conditions and unaffected by cardiac compression. SBP showed more robust differences than MBP, indicating that the difference between the two conditions was likely a result of compression stroke volume. Thus, except for DBP, LVCC generated greater SBP and MBP in 2 minutes following >30 minutes of SCC CPR. No other studies in human patients have measured BP during SCC and LVCC.

Similar to the clinical study, the Anderson group's preclinical porcine SCC versus LVCC OHCA study also demonstrated superior BP with LVCC versus SCC.[21] Further, in addition to

simultaneous increases in $ETCO_2$ and SBP (SCC=45±29 mmHg versus LVCC=72±44 mmHg; P=0.005), the study also documented increases in DBP (SCC=18±15 mmHg versus LVCC=27±20 mmHg, P=0.013) in swine receiving LVCC versus SCC.[21] Of clinical relevance, the mean DBP in the SCC group was below the preclinical target of ≥25 mmHg, while the mean DBP in the LVCC group reached the preclinical target of ≥25 mmHg.[21,88] The discrepancy in findings related to the effect of LVCC on DBP in the clinical compared with the preclinical work is unknown but may relate to experimental design. More specifically, in Cha and colleagues' trial in human patients, downtime was variable, and LVCC always followed SCC. In contrast, in the swine study, downtime was controlled, and there were separate experimental groups. With respect to the study in humans, lower and more variable DBP would be expected, as downtime prior to LVCC was both inconsistent and longer.

2.3.4 Coronary Perfusion Pressure

CorPP is a common measure in CPR because myocardial perfusion is paramount to achieving ROSC. The former clinical target for DBP was based on the minimum pressure needed to perfuse the coronary circulation.[88] Thus, when CorPP is available, it provides relevant prognostic information regarding CPR quality and the likelihood of survival. The preclinical target for CorPP ≥20 mmHg remains pertinent to perfusion of the heart. Cha and colleagues measured CorPP in their clinical SCC-first LVCC-second study in human patients.[22] Consistent with the DBP findings; there was not a significant difference in CorPP with LVCC versus SCC (SCC=16±12 mmHg versus LVCC=14±14 mmHg; P=0.398).[22] Additional research with more comparable experimental conditions between compression locations in human populations is needed to understand how LVCC influences hemodynamic status, including CorPP.

With respect to animal research, in contrast to their DBP findings, the Anderson group's SCC versus LVCC OHCA porcine study likewise did not observe a significant difference in CorPP with SCC versus LVCC (SCC=13±18 mmHg versus LVCC=22±24 mmHg; P=0.116).[21] However, it is important to note that mean CorPP was higher in animals that achieved ROSC versus those that did not. All animals that achieved ROSC did so during ALS CPR, but CorPP values were greater in animals that achieved ROSC in both BLS (No ROSC 11±11 mmHg versus ROSC 18±14, P=0.002) and ALS (No ROSC 13±14 mmHg versus ROSC 42±31; P<0.001), and only swine in

the LVCC group achieved ROSC.[21] Whether LVCC improved CorPP resulting in ROSC, or the attainment of ROSC supported an improvement in CorPP is unknown. Thus, based on these data, it is possible that chest compression location has an effect on CorPP; however, more research is needed to determine if LVCC increases CorPP directly.

2.3.5 Clinical Use of CPR Quality and Efficacy Measures

In most instances, CA occurs out of hospital.[3] For OHCA, physiological indicators of CPR effectiveness are limited. Defibrillators can guide rescuers on the delivery of manual chest compression and can be used to perform cardiac rhythm analysis.[108,109] However, the defibrillators cannot guide CPR quality. Some emergency service units can collect $ETCO_2$ during OHCA once the patient has been intubated.[110,111] The majority of patients who experience OHCA will undergo at least some portion of their treatment without a real-time indicator of quality of CPR. During IHCA, $ETCO_2$, DBP, and CorPP may be available. This varies by factors, including patient situation, intended treatment, pre-arrest condition, etc. The key physiological guide during CPR is approached by using the best available metric. CorPP would be the primary directive quality measure. If CorPP is unavailable, the DBP is the next best directive quality measure. If CorPP and DBP are unavailable, $ETCO_2$ is the final quality directive measure. If all quality of CPR directive measures, CorPP, DBP, and $ETCO_2$, are unavailable, then the attainment of ROSC should be used to assess CPR efficacy.

2.3.6 Experimental Measures of CPR Quality and Efficacy

In the experimental setting, different measures of CPR can be used to characterize hemodynamic status and CPR quality beyond what is clinically feasible. Although experimental research has been performed in the clinical setting, owing to inherent limitations to CPR research, much of the experimental findings in this area have been studied using animal models. With respect to animal research, because of similar cardiovascular anatomy and function compared with humans, the bulk of modern CPR work is performed using swine models. This enables monitoring of clinical indicators (*i.e., BP, $ETCO_2$*) and experimental measures (*i.e., blood flow using Doppler ultrasound, regional microspheres*) to be observed simultaneously.[99,107,112] Synchronized

recordings of clinical and experimental measures create beat-to-beat (compression-to-compression) data to characterize experimental outcomes and increase translational ability to clinical guidance. For example, DBP is clinically relevant because there is a relationship between CorPP and DBP, such that a DBP ≥25 mmHg is needed to perfuse the heart.[88,99–102] As measurement of CorPP is not readily available during CA and CPR, DBP is used because it is a predictive indicator of coronary perfusion. Discoveries that characterize cardiovascular physiology during CPR can better inform resuscitation science towards improving CPR administration and saving more lives. Thus, experimental CPR research is vital to furthering the science of resuscitation and prioritizing outcome variables relevant to vulnerable organs, like the heart and brain.

2.3.7 Cerebral Blood Flow

Owing to the low energetic reserve and potential neurological deficits occurring from ischemic injury in the brain, monitoring CBF is of interest in CPR research.[107,113] Experimental assessment of CBF is essential, as few clinical tools can be applied broadly to observe CBF in clinical CPR settings. Intracranial pressure can be measured invasively with an intracranial catheter connected to a pressure transducer and is subtracted from MBP to determine the net pressure gradient driving blood to the brain, or CerePP. However, it is only a contributor to and not a measure of CBF. Rather, CBF is a measure of the rate of delivery of arterial blood to a capillary bed in the brain tissue, and it can change independently of changes in CerePP or intracranial pressure.[107] Thus, it is necessary to use alternative techniques beyond CerePP to examine CBF.

Various techniques are used to assess CBF indirectly in CA, including transcranial Doppler (TCD) ultrasound and laser Doppler flowmetry (LDF). Doppler uses the relationship between the wavelength, frequency, and velocity of emitted waves that echo back to a transducer to identify structures, motion, blood flow velocity, and blood flow directionality.[114] TCD is a non-invasive Doppler ultrasound technique used primarily to assess CBF velocity (CBF_v) and cerebrovascular function.[115] A probe is placed externally on the transorbital or transtemporal acoustic window, and a Doppler waveform is captured indicating the velocity of blood in that vessel.[113,116] As arterial diameter cannot be resolved, TCD cannot assess CBF directly but instead is used as a proxy measure.[116,117] A measuring concern with TCD during CPR is that, owing to chest compressions

causing total body movement, motion artifact can create ultrasonic noise that overwhelms the spectrum analyzer.[113,118] Such occurrences cause interruptions to continuous waveform recordings.[113,118] To overcome this potential limitation, in research settings, CBF_v values during CPR are often averaged over multiple short time periods, and velocities that exceed normal physiological values (*i.e.*, *artifacts*) are removed from the analyses.[97,118] A calculation (CerePP=MBP·Min CBF_v/Mean CBF_v^{-1}+14) using MBP and CBF_v has been used to accurately estimate CerePP.[119,120] This estimation can provide information related to perfusion of the brain without the need for further invasive measurement required to measure CerePP directly. However, this calculation has not been validated during CPR, and CerePP does not always reflect CBF. TCD CBF_v is a proven technique, validated against gold standard microspheres, in the assessment of CBF during CA and CPR.[118]

TCD CBF_v has accurately reflected CBF at rest, and during CA and CPR.[113,117,118,121–123] Resting TCD CBF_v values in humans are typically between 65-100 cm/s Peak CBF_v, 20-50 cm/s minimum CBF_v, (Min CBF_v), and 40-60 cm/s Mean CBF_v.[87,97] In swine CBF_v values are typically lower, ranging between 25-70 cm/s Peak CBF_v, 10-20 cm/s Min CBF_v, and 15-30 cm/s Mean CBF_v.[116,118] Owing to the lack of widespread accessibility and use, there is currently no clinical or preclinical target for CBF_v during CPR. However, in rare clinical cases, TCD has been used to guide CPR but was only used because of situational convenience during unanticipated CA.[121] A prognostic value of TCD during CA may exist as the presence of CBF_v has denoted a return of cerebral perfusion before peripheral pulses in patients that achieved ROSC. Further, deterioration of cerebral perfusion, declining to a total absence of CBF_v, was observed when ROSC was not achieved.[113,122] Despite different resting CBF_v values among humans and swine,[87,97,116,124] CPR produces ~70% of baseline Peak CBF_v under SCC treatment in both species.[113,118,122] No studies have been conducted comparing CBF_v by TCD in SCC versus LVCC.

LDF uses the same Doppler principle, but instead of emitting soundwaves, LDF emits intersecting visible spectrum laser lights.[123] A photodetector measures the changes in light burst when blood cells travel through the converging point and interprets it into a flux, velocity, and concentration.[123] LDF can be performed invasively or non-invasively, depending on probe type and application.[123] A major benefit of LDF is that the technique can assess microcirculation, whereas conventional Doppler ultrasound cannot.[123] Changes are measured as a net flux of perfusion during microcirculatory provocations, and changes that are equal in magnitude but in

opposite directions are cancelled out.[123] Owing to the measurement of fluctuation, as opposed to directional velocity, LDF of microcirculation is a relative measure of change of the underlying structure(s).[123] These values are commonly presented as a percent of baseline perfusion or arbitrary units.[85,123–125] Furthermore, once the probe is placed, it is not discernable what specific structure or structures are being measured, just the variation within the underlying vasculature. Given the site-specific nature of a relative measure, any alteration in the underlying site can cause unreliable quantification. Cerebral LDF has been reported to measure relative CBF in animal CA and CPR research accurately.[85,124–127] Some research reports LDF values at baseline and during ROSC but not active CPR,[126,127] likely owing to the sensitivity of LDF to record artifactual changes with movement.[128] In research where LDF is reported during CPR, SCC produces ~60% of baseline LDF CBF in both humans and swine.[85,129] Issues with cerebral LDF include any movement of the measured zone (*i.e., risk of change to a relative measure*), movement interference (*i.e., noise invalidating the signal or being mistaken for flow*), and the lack of knowledge as to what is actually being measured.[123] Although cerebral LDF can provide useful information for researchers, owing to the aforementioned limitations, it is not a viable tool in the clinical setting. No studies have been conducted comparing CBF by LDF in SCC versus LVCC.

Quantification of radioactive microspheres is another technique that can be used to measure regional blood flow experimentally. Briefly, labelled microspheres are injected into the bloodstream, and a blood sample is taken to assess the concentration of microspheres.[118,130] Differently labelled microspheres are injected at baseline, prior to and during experimentation (*i.e., CPR*).[118,130] Post mortem, tissue samples are then taken to measure the concentration of each labelled microsphere relative to the concentration in the blood.[118,130–132] Use of microspheres is considered the gold standard technique for regional perfusion, owing to the high sensitivity and specificity of the measure.[118,130–133] However, the use of this approach is technically intricate, unstandardized, costly, and requires expert knowledge.[133] Measuring labelled microspheres in the brain is the premier measure to assess cerebral perfusion. Cerebral perfusion measured by labelled microspheres during CPR with SCC is estimated between 20-30% of baseline.[118,131] No studies have been conducted comparing cerebral perfusion by microspheres in SCC versus LVCC.

Cerebral oximetry is a proxy technique of CBF measurement that does not use the Doppler principle.[134] Cerebral oximetry is conducted by the use of near-infrared spectroscopy (NIRS). NIRS emits light into the tissue and analyzes the intensity of backscattered light waves.[134] This allows

for non-invasive monitoring of regional hemoglobin oxygen saturation (rSO_2) in the brain.[134] This real-time gauge of oxygen delivery to the brain has been utilized to detect cerebral oxygen delivery during CPR and post-arrest recovery.[134] Roughly 70% of blood sampled is venous owing to the sample volume location 2 cm below the skull.[134] Normal resting cerebral rSO_2 values are between 60-80%.[134] rSO_2, opposed to arterial pulse oximetry, can be measured in non-pulsatile or absent flow, making this technique viable during CA research.[134] rSO_2 values recorded during CPR are typically ~30% (40-50% of baseline). Unlike TCD or LDF, NIRS is much less susceptible to movement artifact created by CPR. Limitations of this technique include the risk of contamination by extracerebral circulation (*i.e., skin vasculature*), making rSO_2 likely more indicative of whole-body rSO_2 than site-specific, and the relationship between rSO_2 and CBF not being fully elucidated.[134] The Anderson group measured cerebral rSO_2 in their porcine OHCA SCC versus LVCC model.[21] Despite an increase in $ETCO_2$ and BP, there was no significant differences in cerebral rSO_2 between SCC and LVCC groups (SCC 34±19% versus LVCC 40±21%; P=0.378). Owing to the inherent limitations of cerebral rSO_2 during CA and CPR, further research examining CBF during SCC versus LVCC is warranted.

Despite being of the utmost importance during CA, assessing CBF under different chest compression location conditions remains relatively unexplored. CBF during CPR is estimated as between 20-70% of baseline.[85,113,118,121,122,129,131,134] No research in human subjects examining CBF in SCC versus LVCC exists. The Anderson group has conducted the only SCC versus LVCC OHCA study in a swine population measuring cerebral rSO_2, and despite improvements in hemodynamic status in the LVCC condition, no differences in cerebral rSO_2 were observed.[21] Presently, no other research using animals has compared indices of CBF amongst SCC and LVCC. Additional research examining CBF during SCC versus LVCC is needed to expand the body of knowledge in resuscitation science.

2.4 Objective

The primary objective of this thesis was to investigate the effect of SCC versus LVCC during CPR on indicators of systemic hemodynamic status ($ETCO_2$ and BP) and CBF during CA. Although the use of point-of-care ultrasonography and hemodynamic-directed CPR, which often lead to compression of the LV, are advised in clinical resuscitation,[12] the effects of LVCC on

hemodynamic status are not well established, and it is not abundantly clear whether LVCC promotes superior CPR-related outcomes. Preliminary human research has indicated that specific compression of the LV improves hemodynamic status during CPR.[66] Animal models support and extend on clinical observations, revealing improvements in $ETCO_2$, BP, and, at certain time points, CorPP with the implementation of LVCC.[65,79,81,111] Whether LVCC improves CBF has not been studied.

2.5 Purpose

The primary purpose of this study was to investigate the effect of SCC versus LVCC on indicators of systemic hemodynamic status and CBF in a porcine model of CA and CPR.

2.6 Hypothesis

The overall hypothesis was that compared with SCC, LVCC would elicit a greater estimated CO (measured as $ETCO_2$), BP, and by extension indices of CBF.

CHAPTER 3

3. METHODS

3.1 Ethical Approval

This was a conducted a preclinical systematically assigned comparative investigation. This thesis research was approved by the University Animal Care Committee (UACC) at the University of Saskatchewan, Saskatoon, SK, under ethics number 20200042. This research complied with all the regulations and guidelines established to protect animals from undue harm. The Crisis Operations Team at the University of Saskatchewan approved this research for operation under COVID-19 Exceptional Status Protocol US-2605.

3.2 Study Design

This study was a prospective interventional preclinical trial conducted at the Western College of Veterinary Medicine at the University of Saskatchewan, Saskatoon, SK. All animals received the same preparation and instrumentation (described below). Animal group assignment into SCC or LVCC was systematically assigned to achieve the necessary sample size (Figure 3.1). Based on a power calculation using SigmaPlot 14.0 and blood flow data averaged from previous studies,[21,22,51,71,72] it was estimated a final sample size of n=14 per group would be needed to achieve statistical significance (α=0.05, β=0.80) for CBF_V. Group selection was rotated systematically 1:1 (SCC:LVCC) for the first 20 animals. Following separate incidences of ROSC or equipment failure in the LVCC condition, group assignment was adjusted to 1:2 (SCC:LVCC) for the final 12 animals to ensure adequate sample size in the experimental LVCC condition.

3.3 Animal Preparation

To avoid sex as a confounder, female landrace swine (N=32) were selected for this study. Swine were transported to the Animal Care Unit (ACU) at the University of Saskatchewan, Saskatoon, SK. Animals were acclimatized for a minimum of 7-days prior to experimentation. Animals were reported to be viral, bacteria, and parasitic pathogen-free, as per the vendor. Upon initial arrival, animals were assessed to be in good physical health by ACU Staff. Additional daily assessment occurred for the duration of the animal housing. Animals were housed in a temperature (21 °C) and humidity (<65%)-controlled room with textured rubber floor matting. The housing units were automated on a 12-hour light/dark cycle. Animals had free access to water and food (Whole Earth Swine Pig Starter, CO-OP AGRO, Saskatoon, SK, CAN). Each swine was assessed visually for injury or illness 24 hours prior and then again immediately before each experiment. Prior to each final wellness check, animals were systematically assigned to receive either SCC or LVCC. At the time of experimentation, swine weighed 35±2 kg (to best mimic human thorax size with minimal swine chest barreling).

Animals had free access to water but were fasted for 12 hours prior to initial sedation. Animals were sedated with an intramuscular injection of 20-30 mg/kg of ketamine (Narketan, Vetoquinol, Lavaltrie, QC, CAN) and anesthesia depth was maintained with inhaled isoflurane (1-5%) (^{Pr}AErrane, Baxter, Mississauga, ON, CAN). Animals' body temperature was maintained with heating pads and blankets at ~38 °C (rectal thermometer). An intravenous catheter was inserted into an auricular vein for fluid maintenance and medication delivery. Once secured, a hanging bag of normal saline was connected to the catheter via intravenous drip set. The drip rate was set to 10 ml/kg/hr. Swine were intubated with an endotracheal tube. Proper tracheal placement of the endotracheal tube was confirmed with bilateral auscultation of the inferior, middle and superior lobes of the lungs and visible bilateral chest wall expansion. The tube was secured, and mechanical ventilation (Excel 210 SE, 7900 SmartVent, Datex Ohmeda, Helsinki, SF, FIN) initiated with maintenance anesthesia of 1-3% isoflurane, and a tidal volume of 10 ml/kg. A gas analyzer (ADI, Colorado Springs, CO, USA) was calibrated using a two-point calibration for oxygen and CO_2. Then a sampling line was connected to the ventilatory circuit. The ventilation rate was adjusted to maintain an $ETCO_2$ range of 35-40 mmHg.[135,136]

While in the prone position, a right-sided portion of the skull was exposed through a 2x2 cm window, and a burr hole was drilled 1 cm anterior to the coronal suture and 1 cm lateral to the sagittal suture.[124–126] The animal was then placed supine in a V-shaped holder with limbs secured to prevent displacement of the chest during CPR.[21,49,51,71,72,136] Now in CPR position, a needle was inserted into the burr hole to create a ~1 mm pilot hole through the dura above the right frontal cortex.[85,124,125] A micro LDF probe was inserted into brain tissue to a depth of ~10 mm[137,138] (Fine Needle Probe MNP110XP, ADI, Colorado Springs, CO, USA). The probe was then secured to the skull with a mouldable adhesive, and the head was fixed in position to minimize movement.[137,138] The probe was connected to a blood flow meter (ADI, Colorado Springs, CO, USA) to measure cerebral perfusion flux.[85,124–126] The needle probe and blood flowmeter were calibrated to manufacturer specifications with a standardized solution.[139] Although LDF CBF monitoring has been conducted in CPR,[124,125] the use of a micro LDF probe to examine microvascular perfusion in the brain during CPR is a novel technique.

Continuous HR and cardiac activity were monitored by ECG using a 3-lead limb system (ADI, Colorado Springs, CO, USA).[21,51,71,72] An area on each of the right forelimb, left forelimb, and left hind limb were shaved and then cleaned with alcohol swabs. Sticker electrodes were placed on the prepared areas and the corresponding leads, white to right forelimb, black to left forelimb, and red to left hind limb, were attached, and fed into a BioAmp (ADI, Colorado Springs, CO, USA).

Beat-to-beat BP was obtained from an arterial catheter line. Briefly, the right femoral artery was exposed, cleaned of fascia and connective tissue, and cannulated with a peripheral Teflon catheter (Nexiva, Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Once the catheter was secured, animals were given an initial intravenous bolus of heparin of 300 IU/kg (Fresenius Kabi Canada Ltd., Toronto, ON, CAN) with an additional 75 IU/kg bolus each subsequent hour to prevent clotting.[21,51,60,112] The femoral catheter was connected to a pressure transducer[26,116,136] (DELTRAN II, Utah Medical Products, Midvale, UT, USA) using a fluid line of heparinized saline. The transducer was calibrated using a two-point sphygmomanometer calibration.

After instrumentation was complete, TTE (GE Vivid I, GE 3Sc-Rs Probe; CCE Medical, Mississauga, ON, CAN) was used to locate and externally mark the location for SCC or LVCC.[21,51,71,72] The SCC location was defined as the sternal midline at the level of the aortic root (Appendix A).[21,51,71,72] The LVCC location was defined as the intersection of the parasternal long

axis and parasternal short axis of the LV (Appendix A).[21,51,71,72] Echocardiography was performed by trained personnel and agreed upon by another trained sonographer. Each location was marked externally with an "+" to indicate the exact site (Appendix B).[21,51,71,72]

TCD (Multigon Industrial Inc., Elmsford, NY, USA; 2 MHz probe) signal was then obtained to assess indices of CBF (Appendix C).[118,140,141] A pencil probe was positioned superficially over the right transorbital window to obtain CBF_v from the middle cerebral artery.[113,116,118,122,142,143] Time-aligned indices of systemic hemodynamic status ($ETCO_2$, ECG, BP) and CBF (LDF, CBF_v) were recorded continuously throughout baseline, CA, and CPR in LabChart 8 (ADI, Colorado Springs, CO, USA).

Carotid artery Doppler ultrasound (GE Vivid I; GE 9L-D Probe; CCE Medical, Mississauga, ON, CAN) signal was also obtained to conduct circulation checks. Briefly, a cross sectional view was used to locate the common carotid artery. The probe was then rotated, maintaining the artery in the field of view until a clear longitudinal image was established. Pulse wave mode was enabled, and calipers were positioned in the middle of the artery, with the caliper borders positioned just inside the luminal wall. A Doppler Audio Translator (DAT)[144] was used to convert the real-time audio signal into an analogue signal to obtain $CarBF_v$.[144] $CarBF_v$ is more sensitive than manual palpation of an arterial pulse to identify ROSC.[68,145] The presence or absence of a $CarBF_v$ signal was used to discern a ROSC during circulation checks in the absence of chest compressions.

3.4 Experimental Protocol

3.4.1 Baseline and Cardiac Arrest

Following animal instrumentation, animals were allowed 60 minutes to stabilize.[146] After stabilization, the mechanical chest compression device (LUCAS 3, Stryker, Stockholm, UP, SWE) was positioned and secured over the previously assigned SCC or LVCC landmark.[21,51,71,72] With all equipment in place (Appendix D), baseline data was collected for 2 minutes. To induce CA, swine were then asphyxiated. Briefly, the endotracheal tube was clamped, and the ventilator was turned off. To prevent gasping, animals were given a bolus 5-20 mg/kg of propofol (^{Pr}Propofol, Baxter, Mississauga, ON, CAN) followed by a 10 ml saline flush.[147,148] CA was confirmed by loss

of cardiac motion, observed via subxiphoid TTE, and total absence of a carotid Doppler pulse. Prior to beginning the CPR protocol, animals underwent 2 minutes of untreated CA (Figure 3.1).

3.4.2 Basic Life Support Cardiopulmonary Resuscitation Protocol

BLS CPR consists of ventilation and compressions only and was administered to animals. During BLS CPR, mechanical ventilation was resumed on 100% oxygen.[21,51,71,72] In accordance with the American Heart Association 2020 CPR guidelines, the chest compression rate was 100/min, the depth was 5 cm, and full recoil was allowed.[12] BLS CPR was performed for three 2-minute rounds separated by 10-second circulation checks (Figure 3.1).[12]

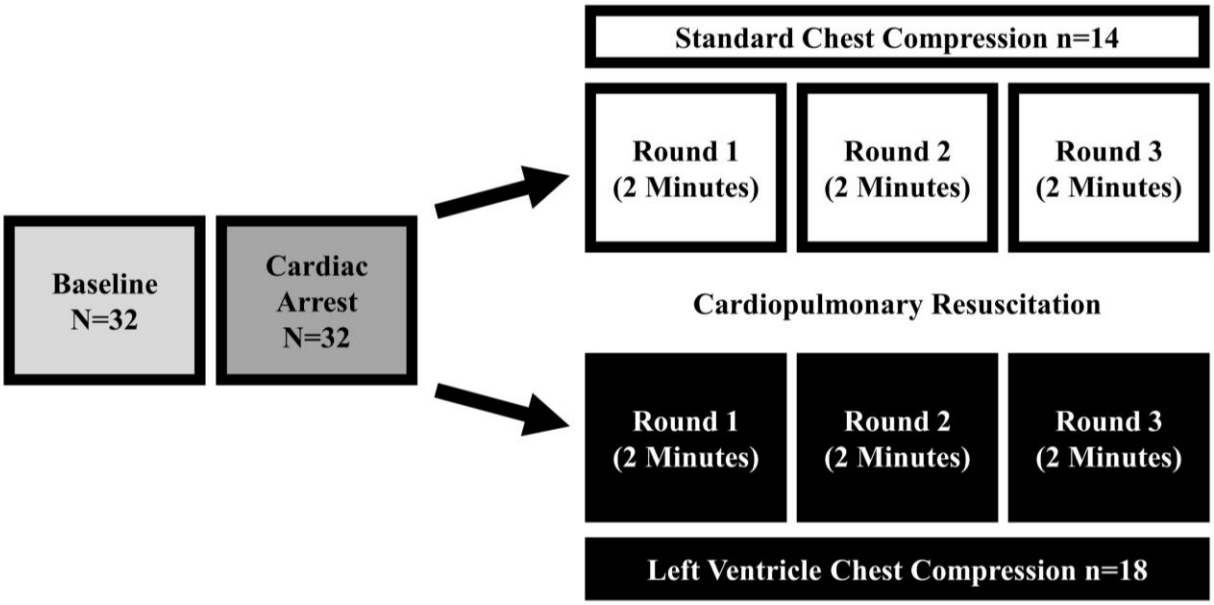

Figure 3.1. Female swine (N=32; 35±2 kg) were systematically assigned to either Standard Chest Compression (SCC, n=14) or Left Ventricle Chest Compression (LVCC, n=18) groups. Thereafter, swine underwent 2 minutes of untreated asphyxiated cardiac arrest followed by either SCC or LVCC treatment. End-tidal carbon dioxide ($ETCO_2$), blood pressure (BP), and cerebral blood flow velocity (CBF_V) were measured at baseline, during cardiac arrest, and through three rounds of basic life support (BLS) cardiopulmonary resuscitation (CPR).

3.4.3 Return of Spontaneous Circulation

Early termination of the protocol occurred if a ROSC was achieved. ROSC was defined as independently sustained regular cardiac activity producing a SBP ≥60 mmHg without intervention for at least 1 minute.[21,51,71,72] If an animal did not achieve ROSC for a full minute, then the protocol was resumed at the point at which it was paused.[21,51,71,72]

3.4.4 Termination Procedure

Animals that achieved ROSC were monitored during mechanical ventilation for up to 10 minutes prior to being euthanized.[21,51,71,72] Animals that did not achieve a SBP ≥60 mmHg after the completion of the BLS CPR protocol were considered expired. All animals were euthanized by exsanguination.

3.5 Data Analyses and Statistics

3.5.1 Swine Characteristics Data Comparisons

In total, 32 swine (SCC n=14, LVCC n=18) were included in the analysis of the primary objectives of this study. Average animal weights between SCC and LVCC groups were compared using an independent two-tailed t-test. Average doses of ketamine and propofol between SCC and LVCC groups were compared using an independent two-tailed t-test. Average elapsed time between initial intramuscular ketamine injection and pre-arrest propofol, initial intramuscular ketamine injection and CA, and initial intramuscular ketamine injection to the end of CPR were compared between SCC and LVCC groups using independent two-tailed t-tests. Initial and final temperatures were compared between SCC and LVCC groups using independent two-tailed t-tests. The above comparisons were repeated for animals that achieved ROSC versus those that did not. Group data comparisons were completed using SigmaPlot 14.0 (SysStat, San Jose, CA, USA). Significance was considered at $P \leq 0.05$. Data are presented as mean ± standard deviation.

3.5.2 Basic Life Support Cardiopulmonary Resuscitation Data Analyses and Statistics

In total, 32 swine (SCC n=14, LVCC n=18) were included in the analysis of the primary objectives of this study. $ETCO_2$ data were analyzed by extracting the average from three consecutive breaths for a maximum of 15 data points (~45 breaths) for each 2-minute round (baseline, CA, CPR Round 1, CPR Round 2, & CPR Round 3). Owing to equipment failure (SCC=3, LVCC=6) and ROSC (LVCC=3), group size for $ETCO_2$ varies (SCC n=11, LVCC n=9-12). Similarly, CBF_v was analyzed by extracting the peak, minimum, and mean over two or three consecutive waveforms for a maximum of 15 data points (~45 waveforms) for each 2-minute round (baseline, CA, CPR Round 1, CPR Round 2, & CPR Round 3). Owing to equipment failure (SCC=2, LVCC=3) and ROSC (LVCC=3), group size for CBF_v varies (SCC n=12-13, LVCC n=12-16). Useable LDF CBF signals were attained in 2 animals (SCC n=1, LVCC n=1). Owing to the widespread failure of this measure (likely as a result of micromovements at the sampling site), it was excluded from data analysis. BP data were analyzed by extracting the peak, minimum, and mean over ten consecutive waveforms for a maximum of 15 data points (~150 waveforms) for each 2-minute round (baseline, CA, CPR Round 1, CPR Round 2, & CPR Round 3). Owing to equipment failure (SCC=1, LVCC=0) and ROSC (LVCC=3), group size for BP varies (SCC n=13-14, LVCC n=15-18).

BLS CPR data analyses were completed using SigmaPlot 14.0 (SysStat, San Jose, CA, USA). Indices of systemic and cerebral hemodynamic status between the SCC and LVCC groups were compared at baseline, during CA and BLS CPR using a mixed model repeated measures analysis of variation (ANOVA) with a *priori* comparisons for BLS CPR Round 1, 2, and 3. Post hoc Tukey's tests were used to determine the location of significance.

3.5.3 Preclinical Targets and Return of Spontaneous Circulation Analyses and Statistics

Fischer's exact tests were used to assess for the association between chest compression location and the number of animals that reached preclinical targets for $ETCO_2$ and DBP in each BLS round and overall BLS CPR. Preclinical target data are presented as percent achieved (achieved/total). Fischer's exact tests were also used to assess for the association between chest compression location and the number of animals that achieved ROSC. Preclinical target and ROSC

analysis were completed using SigmaPlot 14.0 (SysStat, San Jose, CA, USA). ROSC data are presented as percent achieved (achieved/total). Significance was considered at $P \leq 0.05$. Data are presented as mean ± standard deviation.

CHAPTER 4

4. RESULTS

4.1 Swine Characteristics

Body mass was similar between SCC and LVCC groups (SCC=35±2 kg versus LVCC=35±1 kg; P=0.373). Ketamine and propofol doses were both similar between SCC and LVCC groups (Table 4.1). Average elapsed time between initial intramuscular ketamine injection and pre-arrest propofol, initial intramuscular ketamine injection and CA, and initial intramuscular ketamine injection to the end of CPR were similar between SCC and LVCC groups (Table 4.1). Initial temperatures (SCC=38±1 °C versus LVCC=38±1 °C) and final pre-arrest temperatures (SCC=38±1 °C versus LVCC=38±1 °C) were similar between SCC and LVCC groups (P≥0.382).

Table 4.1. Between group ketamine and propofol doses and timing.

	Standard Chest Compression	Left Ventricle Chest Compression	P Value
Ketamine Dose (ml)	8±1	8±1	0.355
Propofol Dose (ml)	25±18	25±14	0.991
Time Between Administration of Ketamine to Propofol (minutes)	182±26	186±25	0.599
Time Between Administration of Ketamine to Cardiac Arrest (minutes)	188±26	197±24	0.342
Time Between Administration of Ketamine to the End of CPR (minutes)	197±26	206±24	0.342

Body mass was similar between animals that achieved ROSC (35±2 kg; n=3) and animals that did not (No ROSC=36±1 kg; n=29; P=0.261). Ketamine (ROSC=8±0 ml versus No

ROSC=8±0 ml) and propofol (ROSC=20±12 ml versus No ROSC=16±9 ml) doses were both similar between animals that achieved ROSC and animals that did not (P≥0.336). Average elapsed time between initial intramuscular ketamine injection and pre-arrest propofol (ROSC=204±17 minutes versus No ROSC=183±25 minutes), initial intramuscular ketamine injection and CA (ROSC=216±12 minutes versus No ROSC=191±25 minutes), and initial intramuscular ketamine injection to the end of CPR (ROSC=225±12 minutes versus No ROSC=200±25 minutes) were similar between animals that achieved ROSC and animals that did not (P≥0.105). Initial temperatures (ROSC=39±0 °C versus No ROSC=38±1 °C) and final pre-arrest temperatures (ROSC=38±1 °C versus No ROSC=38±1 °C) were similar between animals that achieved ROSC and animals that did not (P≥0.147).

4.2 End-Tidal CO_2

$ETCO_2$ values were similar at baseline and during CA (P≥0.226) but greater in the LVCC versus SCC group in all three rounds of CPR (P≤0.003; Figure 4.1).

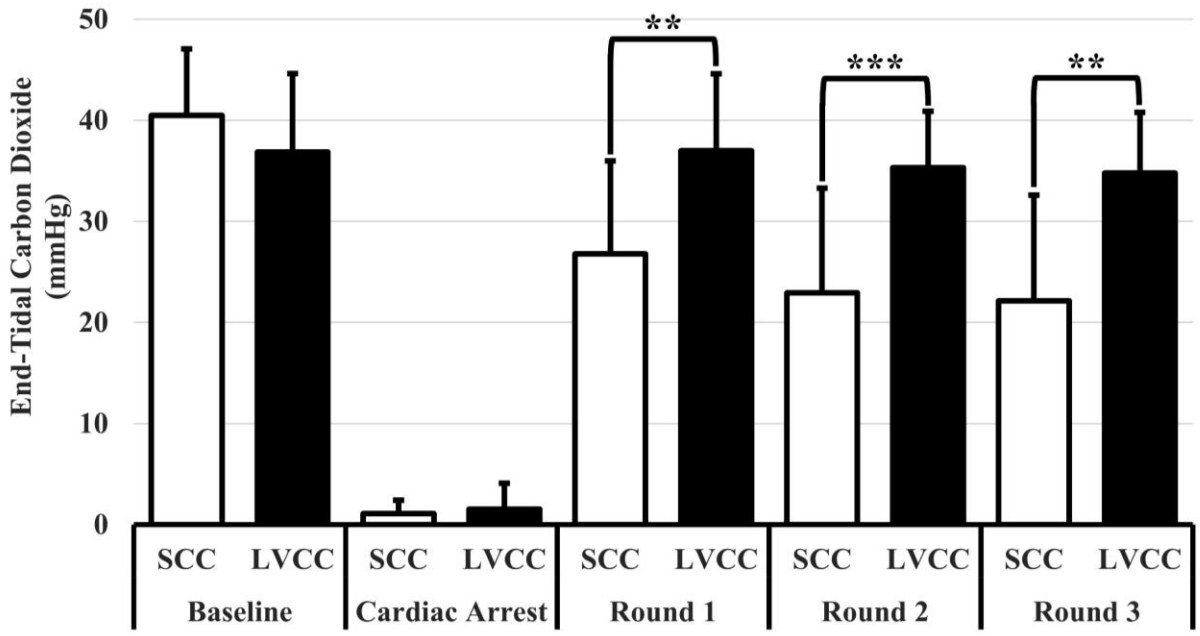

Figure 4.1. Average End-tidal Carbon Dioxide ($ETCO_2$) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=11, LVCC n=12), CPR Round 2 (SCC n=11, LVCC n=11), and CPR Round 3 (SCC n=11, LVCC n=9). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC *****($P<0.05$), ******($P<0.01$), *******($P<0.001$). Bars represent mean, and whiskers represent standard deviation.

4.3 Blood Pressure

SBP values were similar at baseline and during CA (P≥0.277) but greater in the LVCC versus SCC group in all three rounds of CPR (P≤0.001; Figure 4.2). DBP values were similar at baseline and during CA (P≥0.188) but greater in the LVCC versus SCC group in all three rounds of CPR (P≤0.040; Figure 4.3). MBP values were similar at baseline and during CA (P≥0.190) but greater in the LVCC than SCC group in all three rounds of CPR (P≤0.007; Figure 4.4).

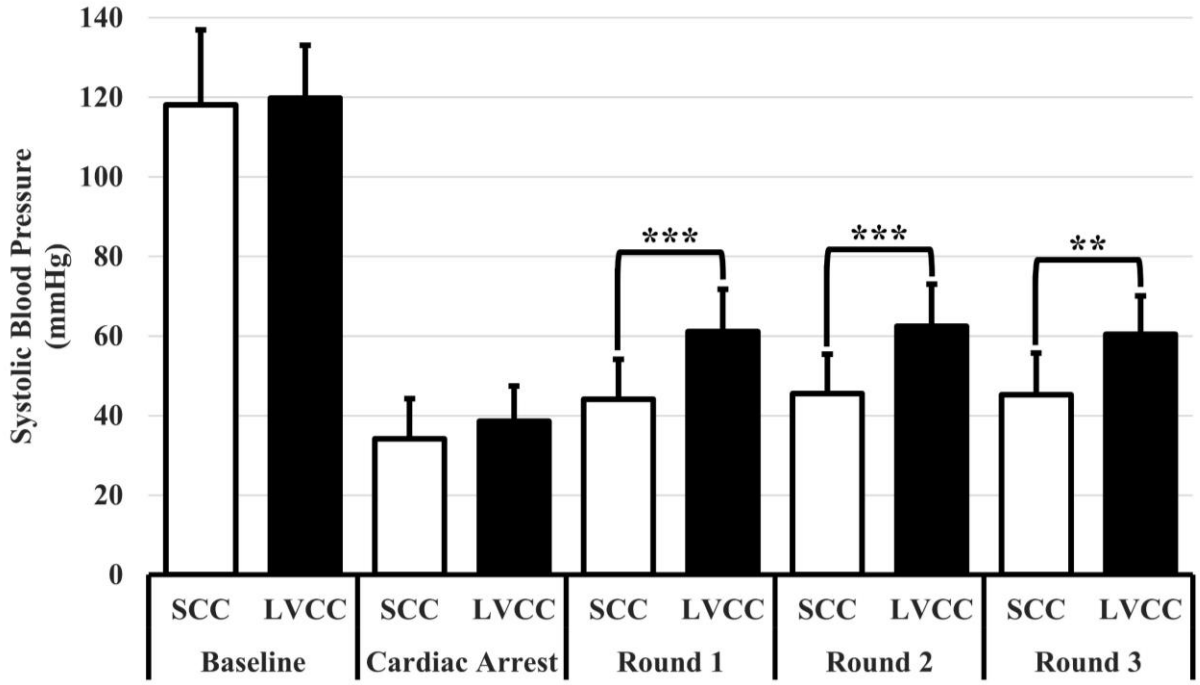

Figure 4.2. Average Systolic Blood Pressure (SBP) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=14, LVCC n=18), CPR Round 2 (SCC n=13, LVCC n=16), and CPR Round 3 (SCC n=13, LVCC n=15). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC *****(P<0.05), ******(P<0.01), *******(P<0.001). Bars represent mean, and whiskers represent standard deviation.

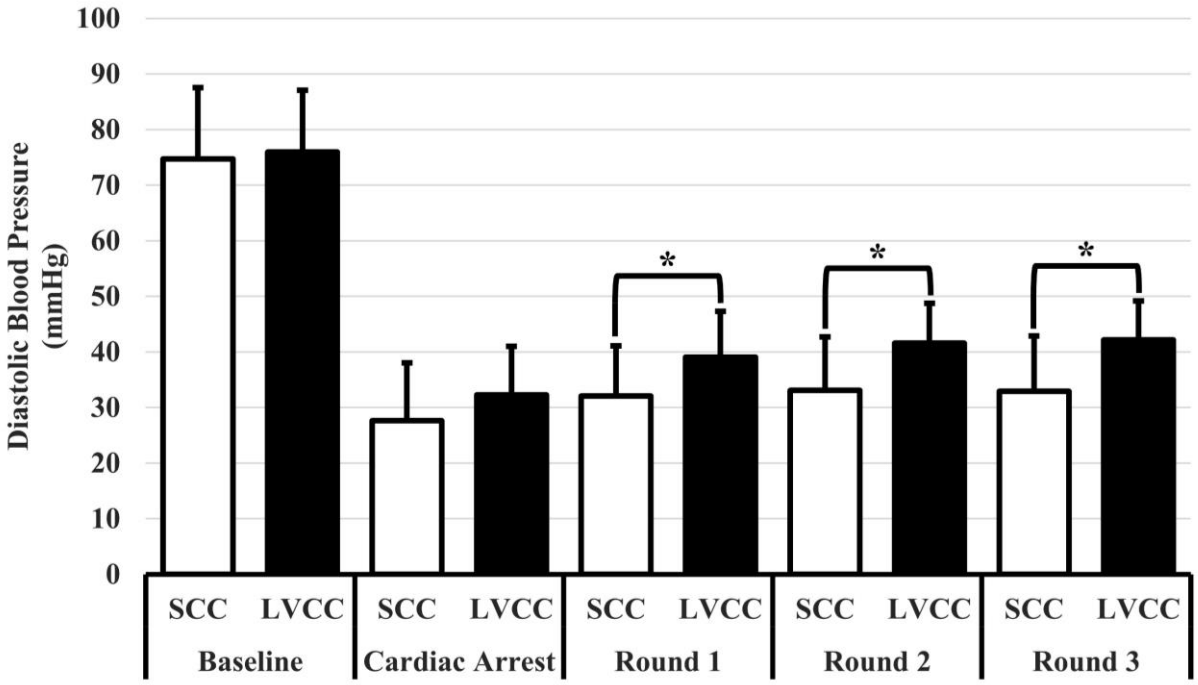

Figure 4.3. Average Diastolic Blood Pressure (DBP) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=14, LVCC n=18), CPR Round 2 (SCC n=13, LVCC n=16), and CPR Round 3 (SCC n=13, LVCC n=15). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC *****($P<0.05$), ******($P<0.01$), *******($P<0.001$). Bars represent mean, and whiskers represent standard deviation.

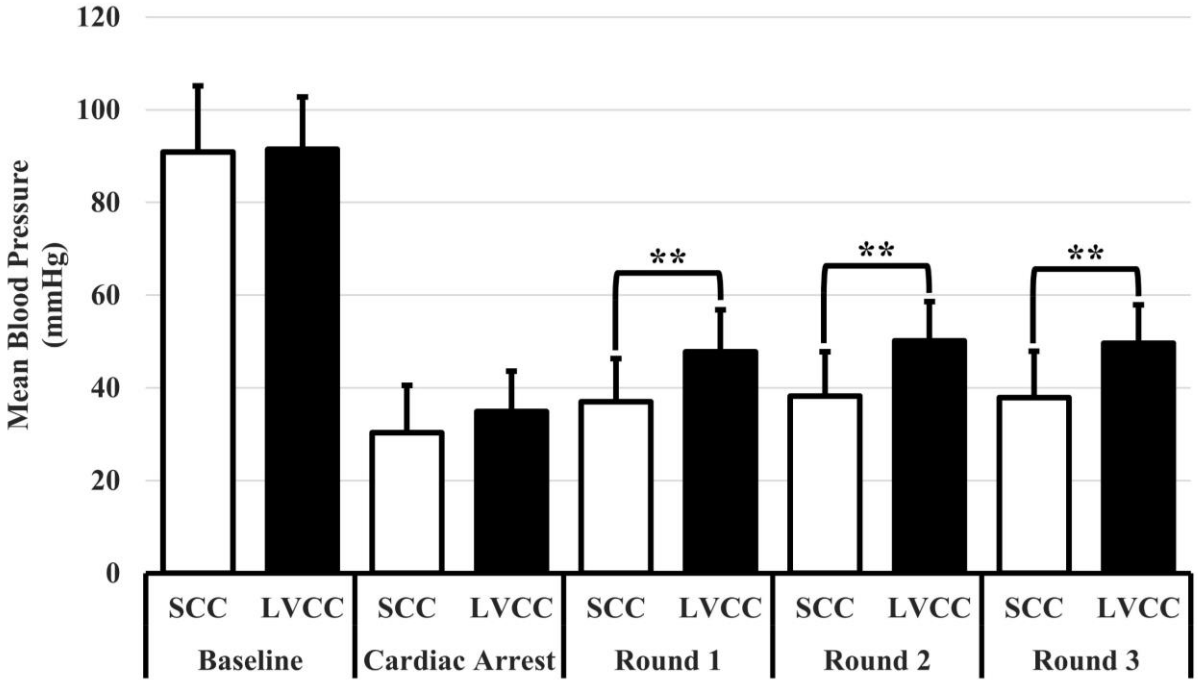

Figure 4.4. Average Mean Blood Pressure (MBP) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=14, LVCC n=18), CPR Round 2 (SCC n=13, LVCC n=16), and CPR Round 3 (SCC n=13, LVCC n=15). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC ***** ($P<0.05$), ****** ($P<0.01$), ******* ($P<0.001$). Bars represent mean, and whiskers represent standard deviation.

4.4 Cerebral Blood Flow Velocity

Peak CBF_v values were similar at baseline and during CA ($P\geq0.506$) but greater in the LVCC versus SCC group in all three rounds of CPR ($P<0.001$; Figure 4.5). There was no difference in Min CBF_v values between groups ($P\geq0.249$; Figure 4.6). Mean CBF_v values were similar at baseline and during CA ($P\geq0.512$) but greater in the LVCC than SCC group in all three rounds of CPR ($P\leq0.006$; Figure 4.7).

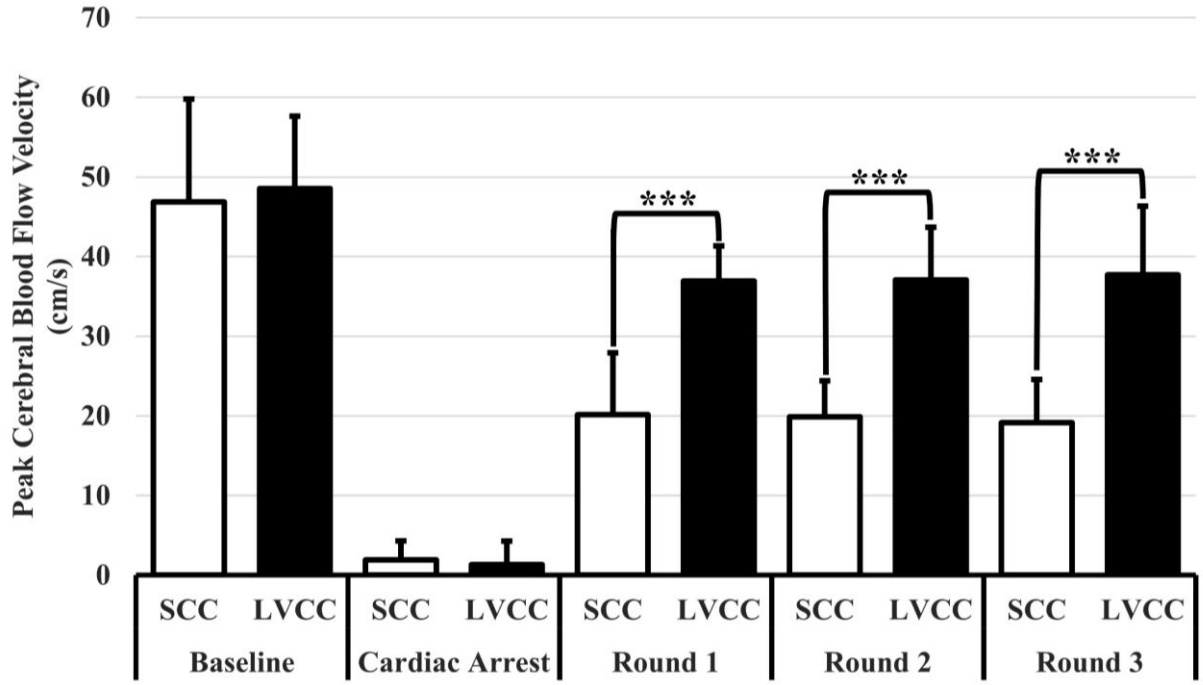

Figure 4.5. Average Peak Cerebral Blood Flow Velocity (Peak CBF_V) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=12, LVCC n=16), CPR Round 2 (SCC n=13, LVCC n=12), and CPR Round 3 (SCC n=13, LVCC n=13). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC *****($P<0.05$), ******($P<0.01$), *******($P<0.001$). Bars represent mean, and whiskers represent standard deviation.

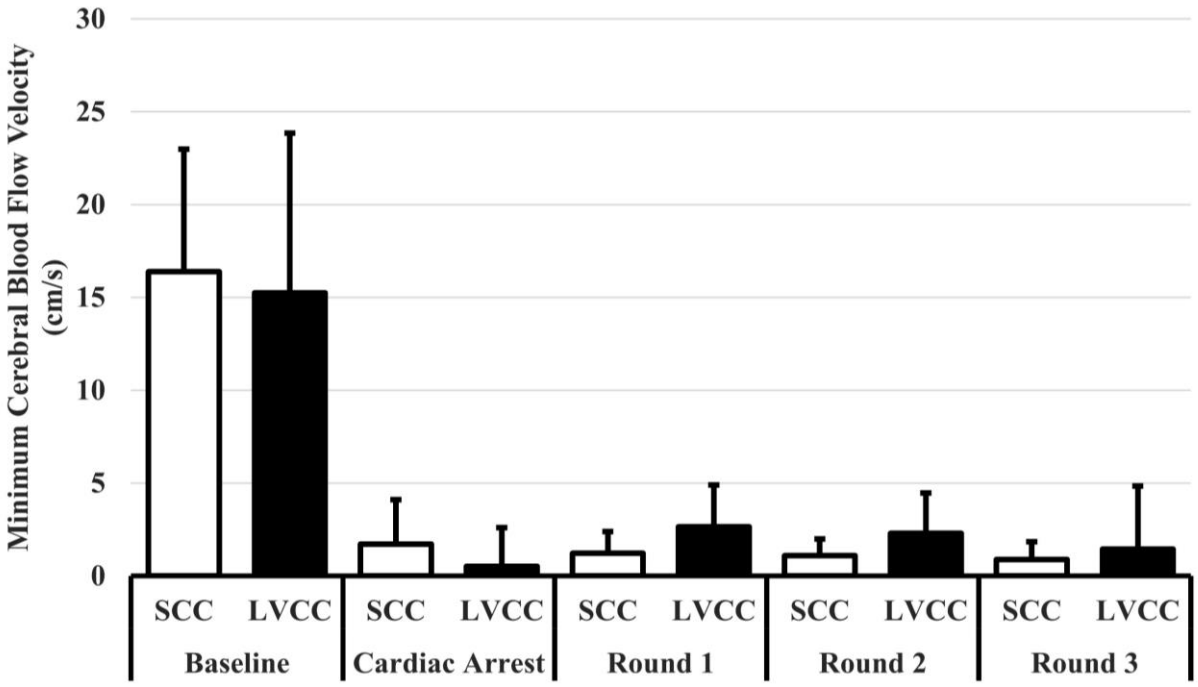

Figure 4.6. Average Minimum Cerebral Blood Flow Velocity (Min CBF_v) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=12, LVCC n=16), CPR Round 2 (SCC n=13, LVCC n=12), and CPR Round 3 (SCC n=13, LVCC n=13). Data were analyzed using a mixed model ANOVA. Bars represent mean, and whiskers represent standard deviation.

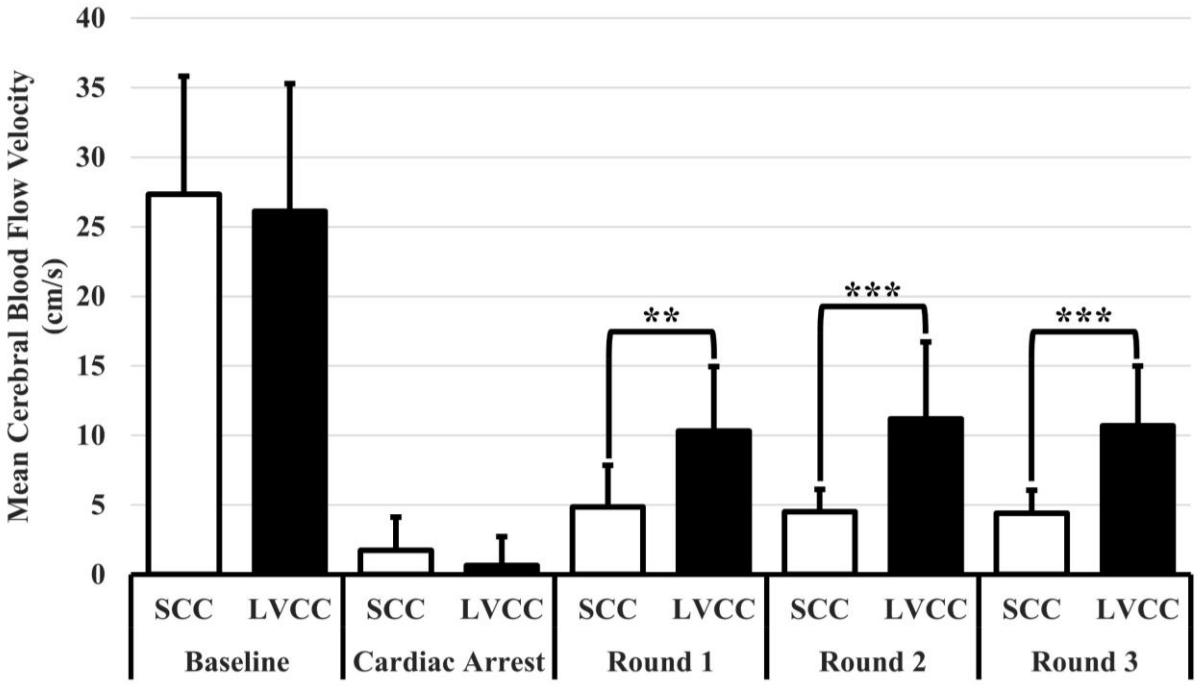

Figure 4.7. Average Mean Cerebral Blood Flow Velocity (Mean CBF_V) values for Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) groups during baseline, cardiac arrest (CA), cardiopulmonary resuscitation (CPR) Round 1 (SCC n=12, LVCC n=16), CPR Round 2 (SCC n=13, LVCC n=12), and CPR Round 3 (SCC n=13, LVCC n=13). Data were analyzed using a mixed model ANOVA. Significantly greater than SCC *****($P<0.05$), ******($P<0.01$), *******($P<0.001$). Bars represent mean, and whiskers represent standard deviation.

4.5 Preclinical Targets and Return of Spontaneous Circulation

There was an association between achieving the preclinical target for $ETCO_2$ and LVCC in all rounds of BLS CPR (Table 4.2). There was also an association between the total number of rounds in BLS CPR that animals achieved the preclinical target and LVCC (Table 4.2).

Table 4.2. Preclinical end-tidal CO_2 targets.

	Standard Chest Compression	Left Ventricle Chest Compression	P Value
Basic Life Support CPR Round 1	64% (7/11)	100% (12/12)	0.037*
Basic Life Support CPR Round 2	46% (5/11)	100% (11/11)	0.012*
Basic Life Support CPR Round 3	46% (5/11)	100% (9/9)	0.014*
Basic Life Support CPR Cumulative	52% (17/33)	100% (34/34)	<0.001***

There was no association between achieving the preclinical target for DBP and chest compression location in each BLS CPR round independently (Table 4.3). There was, however, an association between the total number of rounds in BLS CPR that animals achieved the preclinical target and LVCC (Table 4.3). There was no association between ROSC and chest compression location (SCC 0% (0/14) versus LVCC 17% (3/18); P=0.238).

Table 4.3. Preclinical diastolic blood pressure targets.

	Standard Chest Compression	Left Ventricle Chest Compression	P Value
Basic Life Support CPR Round 1	79% (11/14)	94% (17/18)	0.295
Basic Life Support CPR Round 2	85% (11/13)	100% (17/17)	0.179
Basic Life Support CPR Round 3	85% (11/13)	100% (15/15)	0.206
Basic Life Support CPR Cumulative	82% (17/33)	98% (49/50)	0.020*

CHAPTER 5

5. DISCUSSION

The prevalence of CA and low survival rate justify the ongoing effort to improve CPR quality. In the present study, $ETCO_2$, indicative of CO, and BP were greater with LVCC versus SCC. Corresponding with increased CO and BP, CBF_v was likewise greater with LVCC versus SCC. Furthermore, a greater portion of animals achieved the preclinical targets for $ETCO_2$ and DBP with LVCC versus SCC. The external chest compression location has remained unchanged since the inception of closed-chest cardiac massage in 1960.[13,149] Validation of the present results in clinical settings is required to determine the utility of LVCC for improving ROSC and neurological outcomes following CPR. The results herein provide a rationale for future investigations in clinical populations and provide evidence for LVCC emerging as the next great advancement in life-saving CPR.

5.1 Hemodynamic Status

In the present study, LVCC increased $ETCO_2$, indicative of increased CO during CPR. In prior research, improvements in $ETCO_2$ have been found with targeted compression of the LV.[21,22] A change in $ETCO_2$, and by extension CO, in this study could not derive from a change in HR, as the mechanical compression rate was standardized to 100 compressions per minute for all animals. Thus, a change in stroke volume must be responsible for the corresponding increase in CO. Targeted LV compression, in theory, should result in an increased stroke volume compared with SCC because the latter is associated with compression of the upper third of the heart, which includes the atria, and outflow structures. Indeed, previous studies reported vast narrowing of cardiac outflow vessels during SCC.[33] LVCC likely does not cause the same narrowing of the LVOT and therefore would reduce cardiac afterload, supporting a larger volume of blood to be ejected with each compression. In the present study, the $ETCO_2$ findings were comparable to the

work by the Anderson group despite their longer untreated CA time (2-minute versus 10-minute).[21] Increasing $ETCO_2$ towards achieving the preclinical target supports the implementation of LVCC versus SCC to increase CO. With respect to clinical human data, Cha and coworkers documented an increase in $ETCO_2$ values with 2 minutes of LVCC after 30 minutes of SCC, but all values were below the preclinical target.[22] Taken together, it appears LVCC is better for increasing $ETCO_2$.

Consistent with elevated CO during LVCC was a corresponding elevated BP. Thus, SBP, DBP and MBP were greater with LVCC versus SCC during CPR. CO is a primary determinant of BP; therefore, it follows that with increased predicted CO, there would be a simultaneous increase in BP. Of note, BP was measured in the femoral artery, indicating the rise in pressure was observable beyond the aorta. This is important, as ballooning of the ascending aorta is sometimes observed during CPR, owing to the compression of the descending aorta behind the heart in compression systole.[33] Although this may increase ascending aortic pressure, it may decrease peripheral arterial pressure measured below the heart. Indeed, in research by the Anderson group focused on traumatic CA, the effects of LVCC on BP were nullified by aortic ballooning.[51,71,72] Importantly, the aforementioned research was designed to test the effects of aortic ballooning, and the present results complement other studies that demonstrate that it is unlikely LVCC unequivocally causes complete compression of the aorta and decreases BP. Alternatively, if LVCC did cause slight aortic ballooning, and if blood flow was impeded in the descending aorta, and directed cranially owing to compression, then differences in SBP and MBP may be even greater than what was observed herein.

With increased estimated CO and BP, it follows that CBF_v values were greater with LVCC versus SCC CPR. LVCC produced 77% of baseline CBF_v values during compression systole, almost double that generated by SCC during the same phase. Increases in CBF_v may be the result of increased stroke volumes associated with LVCC as well as potential redistribution of blood flow cranially secondary to aortic ballooning. That is, as discussed above, LVCC may occlude the descending aorta and redirect blood flow cranially during the compression phase of CPR. Of note, this effect would be compounded if stroke volume were also greater (*i.e., a greater proportion of total flow would be directed cranially*). Thus, increases in CBF may extend beyond what would be predicted by the measured increase in BP. In contrast, SCC may not only exaggerate impedance by compression of the LVOT, but it may also favour a more normalized, systemic distribution of blood flow as it likely does not cause the same occlusion of the descending aorta. Given blood flow

to the lower extremities may come at the expense of blood flow to the heart and brain during CPR, future studies should explore how aortic occlusion created by compression alters the distribution of blood flow cranially versus caudally during SCC and LVCC.

An inherent limitation to TCD is that it quantifies CBF_v and not volumetric flow. Thus, it cannot be concluded that LVCC enhanced CBF in the current study. Nevertheless, given predicted CO and BP were also greater in the LVCC group, this supports the notion that an increase in Peak and Mean CBF_v in the LVCC group was reflective of an increase in cerebral perfusion during active CPR. Although this study demonstrated a clear benefit with respect to LVCC and CBF_v, it is important to note the work by Anderson did not discover enhancements in regional cerebral oxygenation.[21] The discrepancy between divergent results may be secondary to differences in experimental design including, length of downtime between CA and CPR (2-minute versus 10-minute), method of CA (asphyxia versus electric shock), the mechanical device used for chest compressions (LUCAS versus Thumper), and differences between measurement techniques (TCD versus cerebral rSO_2). Briefly, while TCD was used to quantify flow velocity in a major intracranial supply artery of the brain, cerebral oximetry measures the regional oxygen saturation of hemoglobin. Beyond being fundamentally different measures, the former provides an index of arterial perfusion to an entire hemisphere of the brain, and the latter is more localized to immediately beneath the site of measurement and is derived ~70% from venous blood. Perhaps the use of radiolabelled microspheres, a gold standard in terms of measuring regional blood flow within the brain, in future trials is justified in order to determine how different types of CPR influence total and regional brain blood flow. However, it is important to note, owing to factors such as low BP, compromised local and systemic circulation, and coagulation, microsphere mixing and capture in the brain may be limited during CPR, which can undermine the accuracy of this technique.

5.2 Return of Spontaneous Circulation

Achieving ROSC is crucial to survival. In contrast to work from Anderson's group, the present study did not find an association between chest compression location and ROSC. Importantly, there are a number of differences between these studies that can help explain the divergent results. First, Anderson's group only observed ROSC during the ALS protocol of their study.[21] That is, not during compressions alone, but during compressions preceded by

administration of epinephrine and amiodarone, and in conjunction with defibrillation. In the present study, three ROSC during BLS CPR were observed; however, an ALS protocol was not performed. Defibrillation was omitted from the current study because sensitive ultrasound equipment and sonographers themselves would have been at risk of electrocution if they remained in contact with the animal during shock delivery. Additionally, as the primary outcome measures were indicators of hemodynamic status and not ROSC, the risk of not being able to re-obtain a good signal once probes were removed from the animal was a concern. In the present work, ROSC was achieved during BLS CPR in the LVCC group only. This finding was contrary to the Anderson group's study, where ROSC was only achieved during their ALS CPR protocol and in both SCC and LVCC groups. ROSC differences between the two studies during BLS CPR were likely owing to the shorter 2-minute downtime in the present study versus the longer 10-minute downtime in the Anderson group's study. Further, the Anderson group observed ROSC during ALS CPR, which supports the use of ALS treatments even during suboptimal CPR. The effect of SCC versus LVCC on ROSC during BLS CPR only in the OHCA (*i.e., settings in which epinephrine and defibrillation are often delayed or not delivered*) setting warrants further study. Based on a power calculation (ClinCalc, Chicago, IL, USA) using data from the present study, an estimated sample size of 41 animals per group would be needed to detect a significant difference in the occurrence of ROSC between SCC and LVCC groups. All animals that achieved ROSC in the present study survived to 10 minutes (as per protocol) without additional intervention beyond inhaled anesthetic and mechanical ventilation. Swine in the Anderson group's study were survived to 60 minutes with standard post-resuscitative intervention. Given that the swine in the present study survived 10 minutes without restorative intervention, it appears likely that adequate cardiovascular function to sustain life was attained and could have been sustained. However, as 60-minute survival was not an outcome in the current study, the latter prospect cannot be concluded. It is possible the best chance of survival, or at least ROSC, during BLS CPR is early initiated LVCC.

5.3 Clinical Considerations

Clinical translational ability is crucial in preclinical models. This study examined the fraction of animals that reached the preclinical targets during CPR by round and cumulatively during BLS. All LVCC animals met or exceeded the preclinical target for $ETCO_2$ (≥20

mmHg).[47,50,51] Increased $ETCO_2$ means not only was estimated CO greater in the LVCC group, but more swine achieved a CO that is predictive of better outcomes following CA. Coupled with increased CBF_v, it is possible LVCC would improve post-arrest quality of life. Only half of the SCC animals were able to achieve the preclinical target for $ETCO_2$. Similarly, while both groups reached the preclinical target for DBP (≥25 mmHg),[88] that LVCC achieved the preclinical target more often indicates coronary perfusion may have also been more consistently elevated during this treatment. Superior coronary perfusion during CPR would likely decrease coronary microvascular dysfunction, reperfusion impairment, and ischemic injury during CA recovery. Further, all animals that met or exceeded the preclinical target for $ETCO_2$ also achieved the preclinical target for DBP, meaning that it is likely LVCC imparts benefits to systemic hemodynamic status versus SCC. Superior whole-body perfusion as a result of LVCC could allow patients the best opportunity to regain life and recover with minimal lingering deficits in post-arrest function. Validation of these results in clinical settings is needed to determine if LVCC enhances survival and post-arrest life.

5.4 Limitations and Future Considerations

Inherent limitations exist with the use of porcine models of CA and CPR. For example, although the intention of this study was to translate to adult human CPR physiology, young healthy swine were used, which is not representative of the typical demographic that succumbs to CA. Further, the method of CA induction involved asphyxiation, which is also not common in adult CA cases. While the age and induction of CA are more relevant to pediatric CPR, the size of swine used was selected because their chest cavity and cardiovascular anatomy closely resemble that of the adult human. Thus, although a young healthy porcine model of asphyxiated CA is more representative of pediatric CA because of the size of the swine used, the results of this study may be generalized to adult cardiovascular physiology. Older cardiovascular compromised swine are not commonly used in CPR models owing to the cost of rearing swine, swine size, and advancement of the barrelled shape of the swine chest to interfere with compression mechanics.

The anatomical and physiological differences between swine and humans, namely heart orientation, an extra lobe of the lung in the left porcine hemithorax, and the size and shape of the thoracic wall structure, create a disparity between the two models.[23,48,54,63] These factors can alter compression mechanics, making it difficult to generalize results to human CPR. In the average

human, LVCC would be delivered even more laterally than their porcine counterparts.[45] These anatomical differences do not negate the importance of this work or other preclinical studies. More specifically, preclinical studies provide the physiological basis for interpreting CPR studies conducted in humans, guiding future studies in human CPR and are necessary to inform CPR guidelines. Measuring time aligned $ETCO_2$, BP, and CBF_v would not occur under normal clinical conditions. Further, as LVCC is not a widely accepted practice, it would not be used clinically as a first-choice treatment. Using swine allows us to overcome these limitations. The current work complements a growing body of clinical and preclinical literature that indicates an alternate chest compression location could improve indicators of hemodynamic status during CPR, promote ROSC and minimize post-arrest deficits including attenuation of neurological impairment.

The inherent need for anesthesia in swine models of CA and CPR can be considered a limitation, as the specific anesthetics used in this experiment may have influenced the cardiovascular system. Along with the anesthetic effect of ketamine, the drug may also act as a cardiovascular stimulant and increase HR and BP.[150] With an expected half-life between 2-4 hours,[150] it is possible the presence of ketamine may have influenced hemodynamic status. These potential effects would have likely been greater in pre-CA versus post-CA settings in the current study, as swine in the latter setting were considered dead and did not have a HR or pulsatile BP. Owing to the parity of ketamine dose and time to experimentation from ketamine delivery as well as the similarity in baseline hemodynamics between SCC and LVCC groups, possible group-specific effects were likely negligible.

Propofol, although primarily selected for its general anesthetic properties to ensure animal well-being and prevent gasping, does have marked effects on the cardiovascular and respiratory systems. Cardiorespiratory depression, decreased CBF, and reduced cerebral metabolism are common with the use of propofol.[151] Although the half-life of propofol can extend for up to 60 minutes, the duration of action from an intravenous bolus lasts typically between 3-10 minutes and the time to peak effect is approximately 5 minutes.[151] Thus, it is possible residual effects of propofol may have affected hemodynamic status or ROSC in this study, particularly during Round 1 of BLS CPR. However, because the dose of propofol and time to experimentation from the propofol dose was similar between groups, it is unlikely the propofol differentially affected the SCC and LVCC groups.

Isoflurane, the anesthetic used during instrumentation, stabilization and baseline in the current study, is an inhaled general anesthetic that has been reported to cause respiratory depression and decrease BP as a result of peripheral vasodilation.[152] As the minimum alveolar concentration of isoflurane, the concentration of anesthetic needed to prevent a movement response to surgical incision, would not be maintained beyond the cessation of mechanical ventilation and animal asphyxiation (*i.e., induction of CA*),[152] it is unlikely the cardiorespiratory effects of the drug would have a profound impact on hemodynamic status throughout CPR. Further, the use and titration of isoflurane was consistent between groups. Importantly, although the impacts of anesthetic agents were unavoidable in the present (*i.e., limiting the interpretation of absolute values*), the effects of anesthesia were likely similar among groups and therefore do not detract from the major conclusions of this work.

Exclusion of data must also be considered a limitation in the present study. As a result of equipment failure and the occurrence of ROSC, group size varied throughout experimentation. Although ROSC was to be expected, the failure of recording equipment further bolstered the removal of data from this experiment. Unfortunately, equipment failure is sometimes unavoidable in physiology research. Although reducing sample size can decrease statistical power and may contribute to an enhanced probability of a type 2 error, perhaps owing to the homogeneity of animal characteristics, this was the not case for the major outcomes (*i.e., $ETCO_2$, BP and CBF_v*) in the present study.

TTE was used to assess chest compression location prior to CA. This relies on the heart not shifting shape or position as CA occurs. Furthermore, direct compression of each location was not confirmed during CPR. Cha and coworkers selected an external landmark in their human LVCC study, making the same assumptions as this work.[22] The Anderson group also used TTE to mark externally and did not monitor the exact compression site with TTE or TEE during CPR.[21] Briefly, this means if the heart changed in shape or location within the thoracic cavity during CA, the exact location denoted when the heart was beating normally may not have been compressed. An alternative approach is to use echocardiography guided CPR and observe real-time feedback of $ETCO_2$ *(i.e., making subtle changes in compression location based on echocardiography*). Although the latter is emerging as an effective resuscitation tool,[47] this technique addresses a fundamentally different experimental question and is also not feasible in most OHCA cases.

Nevertheless, the current results lend support to this alternative approach as they reveal altering the location of compression can improve CPR quality.

There are many future considerations spanning from this study, including work focused on both the quality and efficacy of LVCC CPR. Regarding CPR quality, future studies assessing BP cranially and caudally to the site of compression are needed to determine whether compression location influences site-specific aortic ballooning and blood flow distribution during CPR. With respect to CPR efficacy, repetition of this model with the implementation of a full ALS protocol should be considered. This would better establish if LVCC increases the likelihood of ROSC. In animals that achieve ROSC, measuring 60-minute survival and eventually, cognitive function would allow researchers to determine if increased CBF_v is associated with ROSC and attenuates neurological deficits following ROSC.

Based on the body of evidence in experimental preclinical models and clinical populations, there is currently an unmet and growing need for a clinical trial focused on the efficacy of SCC versus LVCC CPR in humans.[17,21,22,45–47,51,96] However, preceding such a trial, a repeatable method to locate or landmark the LV in humans must be proven. Ultimately, the goal of this research would be to establish a new external chest compression location landmark for common CPR without the need of echocardiography. The centre of the chest or inter-nipple line are easy for laypeople to identify. It may be more onerous to locate alternative landmarks necessary to perform LVCC properly. There are more OHCA than IHCA; thus, equipment and personnel will not be close by at all times to facilitate landmarking. A novel facile landmark must be established to implement LVCC on a mass scale. When a human LVCC location landmark is achieved, a randomized control trial with SCC versus LVCC measuring ROSC, 60-minute survival, hospital admission, hospital discharge, cognitive deficits, and hemodynamic status is warranted. Although the location of compressions has not changed since the inception of cardiac massage in 1960,[149] a new SCC location over the LV could be the future of resuscitation science.

5.5 Conclusion

The present study provides novel insight into the benefits of LVCC versus SCC on hemodynamic performance in a preclinical model of porcine CPR. First, this study confirms previous observations regarding the merit of LVCC to improve indicators of systemic

hemodynamic status versus SCC, namely ETCO2 and BP. Secondly, it extends on previous work by demonstrating LVCC produces greater CBF_v. Given this is the first study to examine indices of cerebral perfusion in SCC versus LVCC, the finding that LVCC elicits greater estimated CO, BP and CBF_v may be considered a foundational discovery in resuscitation science. Validating these results in different models of porcine CA and in human populations holds extraordinary promise in refining longstanding CPR recommendations. Focusing on the brain during CPR is essential, as superior perfusion to the brain may increase ROSC and attenuate neurological deficits in post-CA victims. Owing to the prevalence of CA in Canada and around the World, even small enhancements to treatment can have enormous implications for saving lives. As resuscitation science continues to evolve, optimizing CPR quality to maximize systemic hemodynamic performance and cerebral perfusion must remain at the forefront of thought in the fight against time.

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APPENDICES

APPENDIX A

Echocardiographic images of the heart distinguishing Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) locations.

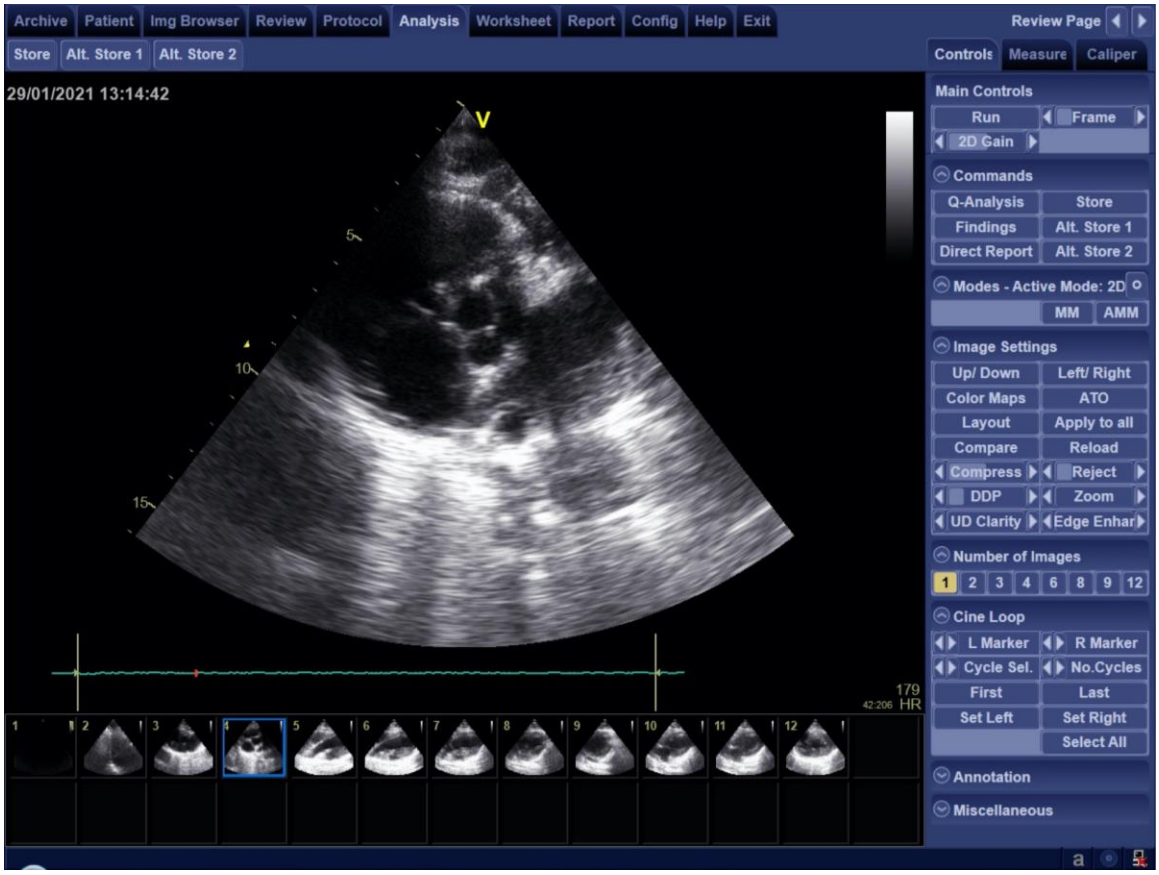

Figure A.1. Parasternal short axis (PSAX) of the aortic root, representative of the superior-inferior site of Standard Chest Compression (SCC).

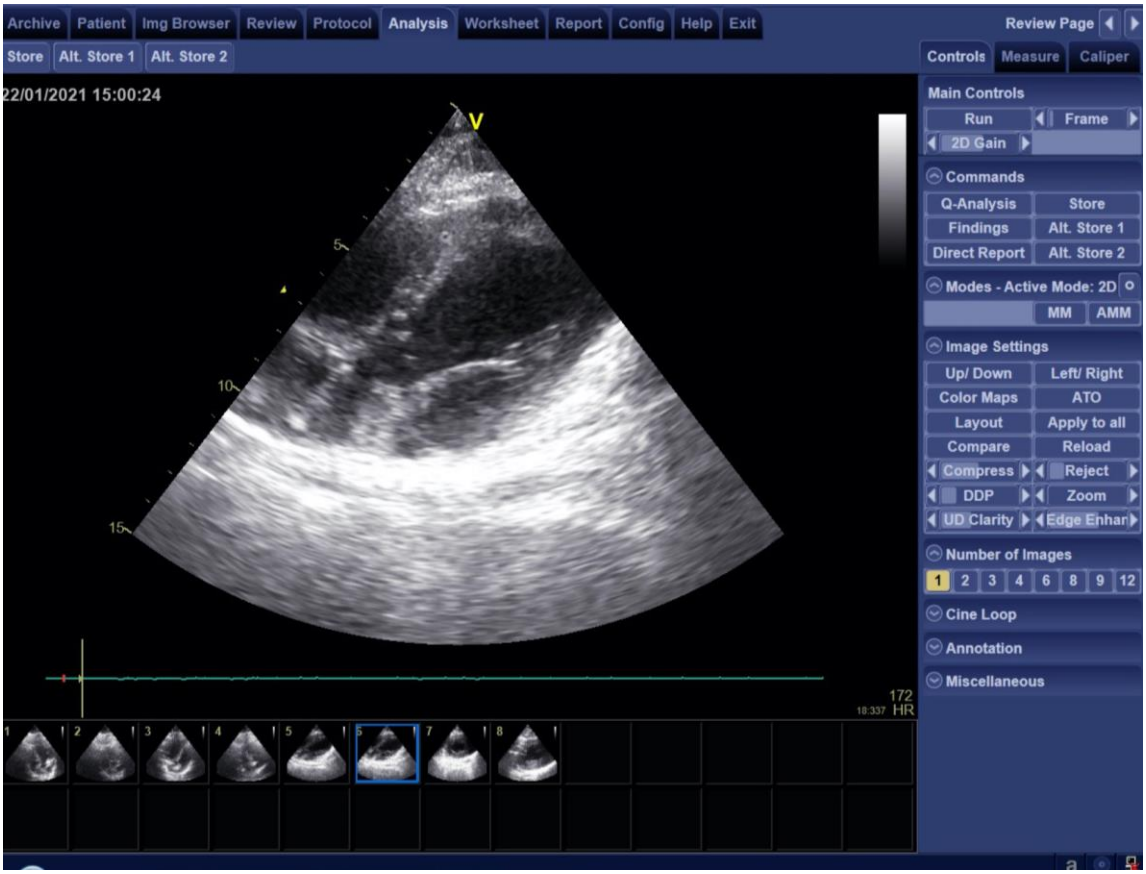

Figure A.2. Parasternal long axis (PLAX) of the Left Ventricle (LV) and aortic valve, representative of the superior-inferior site of Standard Chest Compression (SCC).

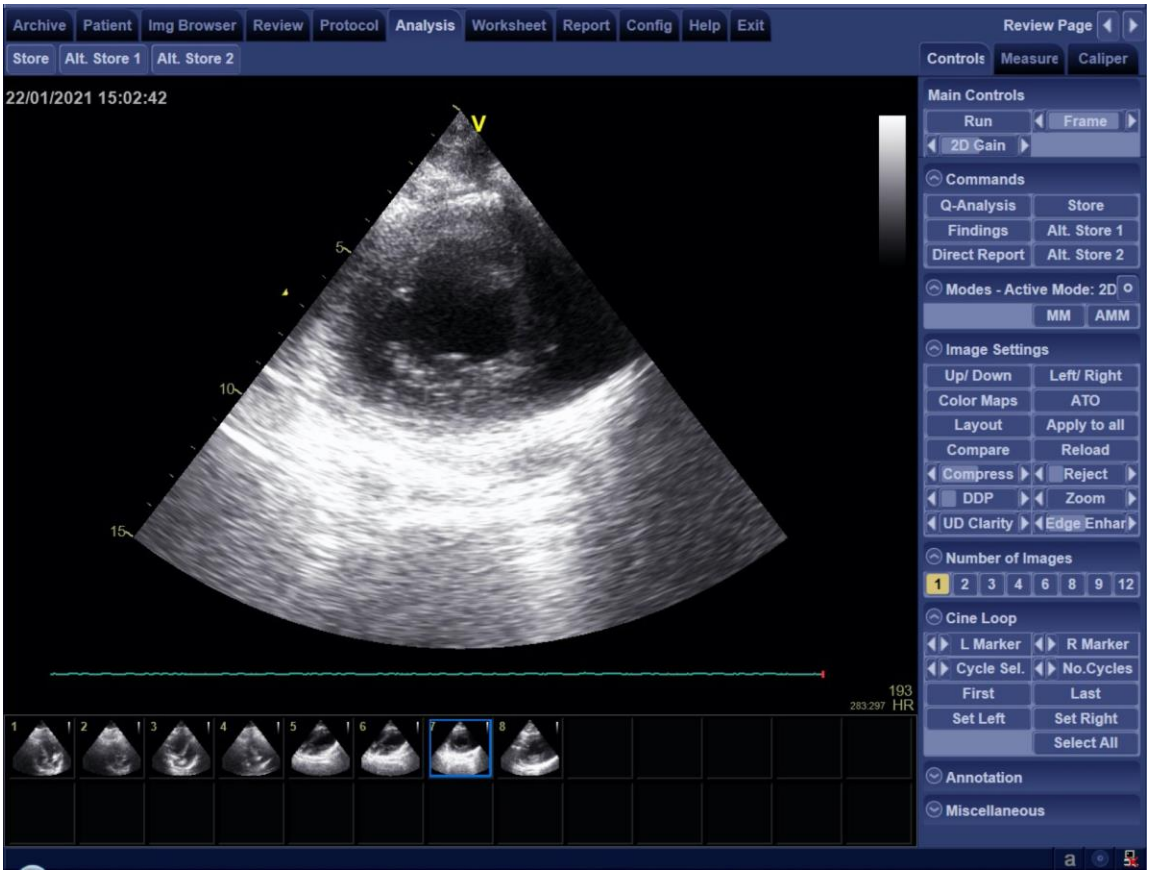

Figure A.3. Parasternal short axis (PSAX) of the Left Ventricle (LV), representative of the medial-lateral site of Left Ventricle Chest Compression (LVCC).

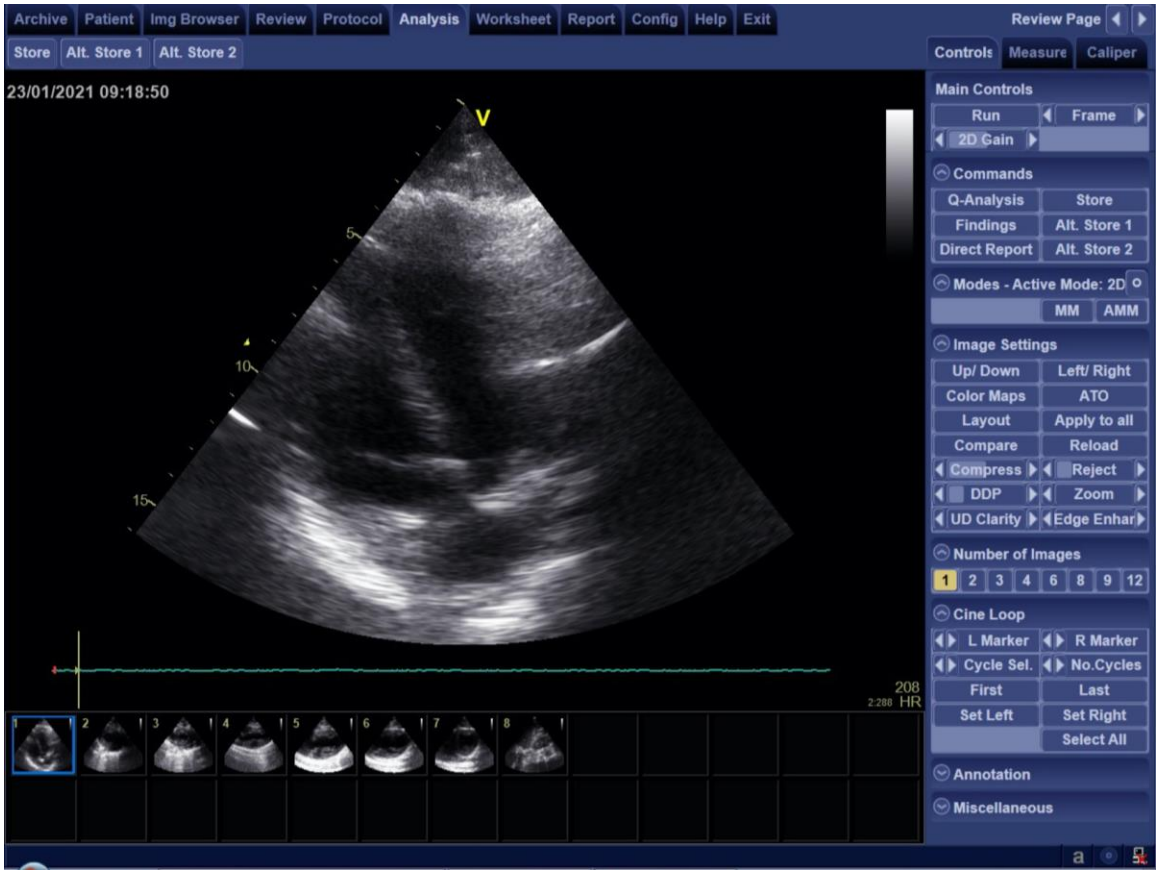

Figure A.4. Subxiphoid four-chamber view of the heart, highlighting the aortic root and Left Ventricle (LV) to confirm the Standard Chest Compression (SCC) or Left Ventricle Chest Compression (LVCC) site.

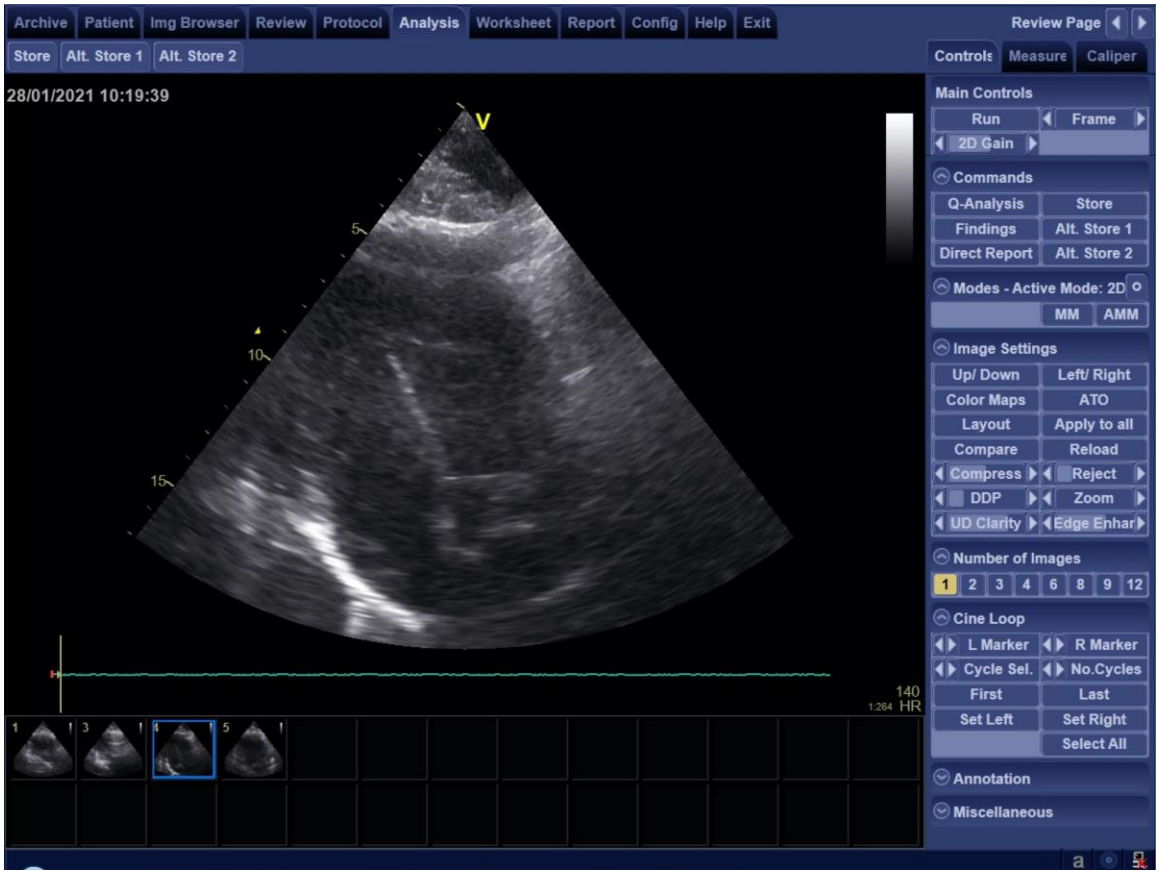

Figure A.5. Subxiphoid four-chamber view of the heart, highlighting the aortic root and Left Ventricle (LV) to confirm the Standard Chest Compression (SCC) or Left Ventricle Chest Compression (LVCC) site.

APPENDIX B

Externally markings denoting Standard Chest Compression (SCC) and Left Ventricle Chest Compression (LVCC) locations.

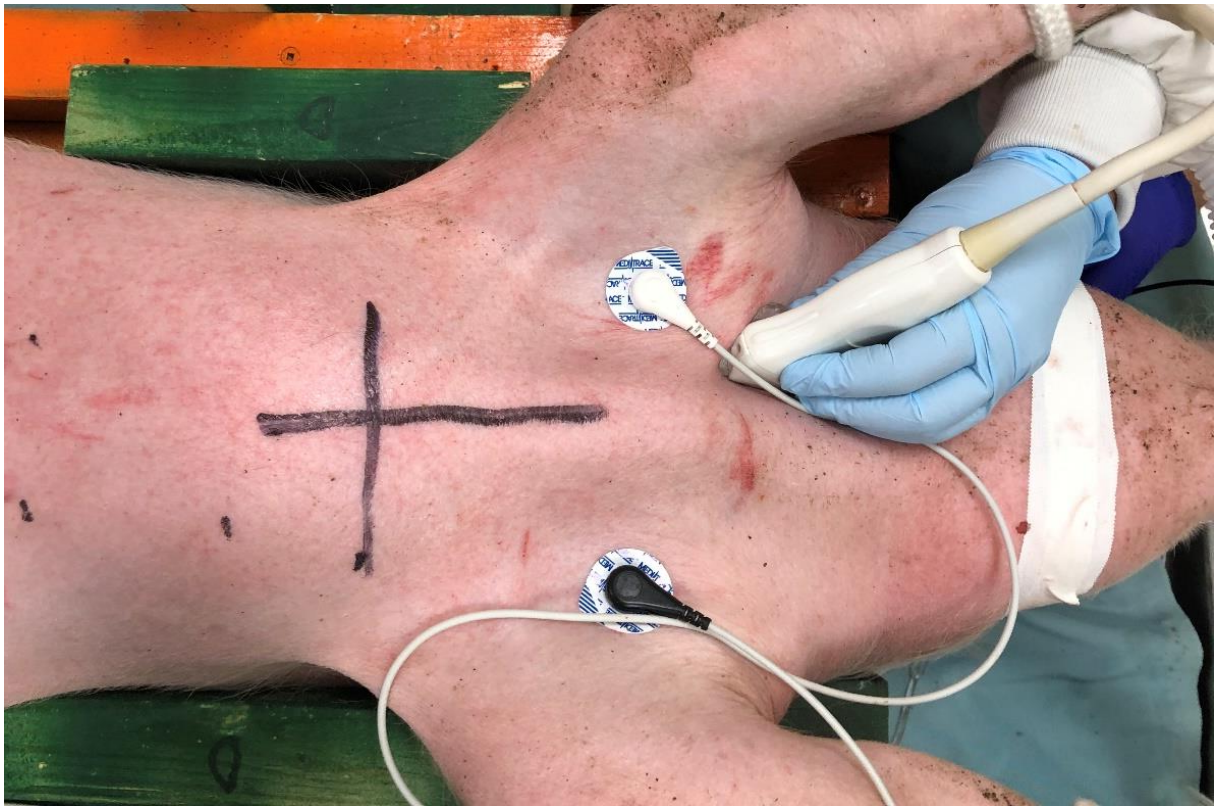

Figure B.1. An example of the external Standard Chest Compression (SCC) “+” marking, located on the midline at the level of the aortic root.

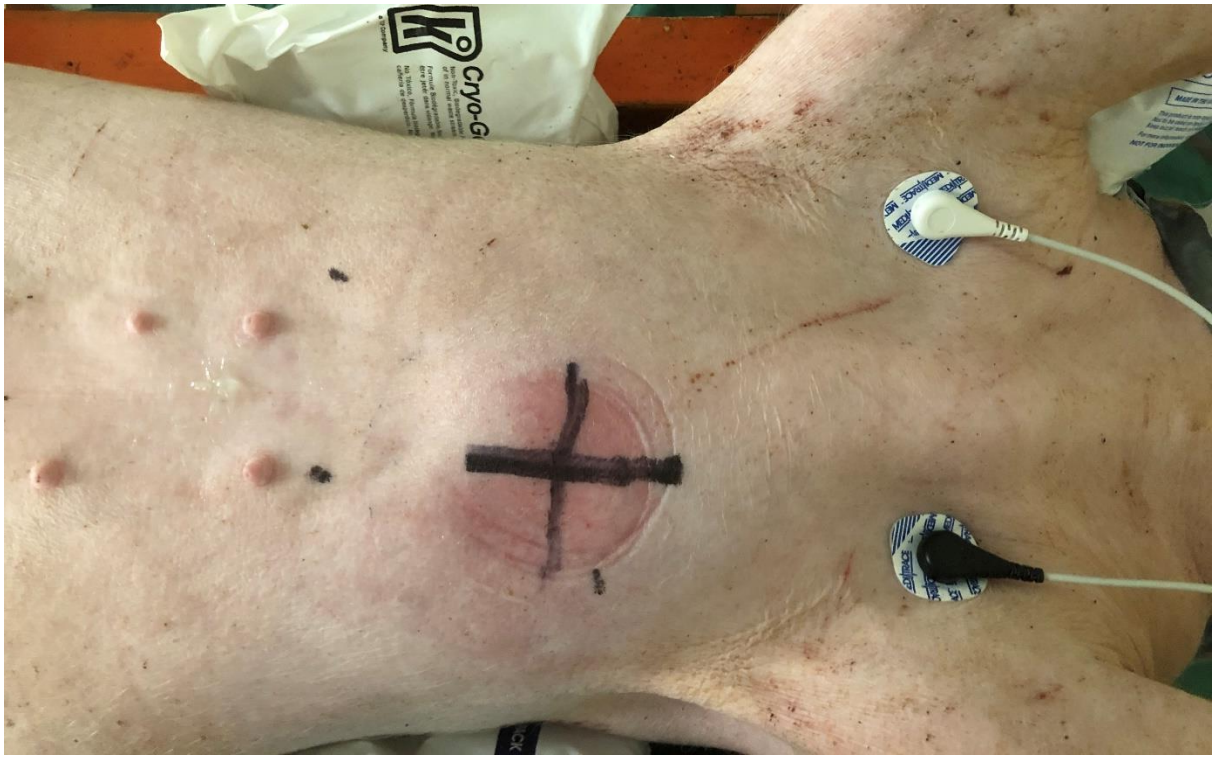

Figure B.2. An example of the external Left Ventricle Chest Compression (LVCC) "+" marking for swine, located on the midline at the intersection of the parasternal short and long axis of the Left Ventricle (LV).

APPENDIX C

A sample image of a Doppler pulse wave tracing of cerebral blood flow velocity (CBF_v) through the middle cerebral artery.

Figure C.1. An image of the screen of the Multigon Doppler pulse wave tracing of the middle cerebral artery capturing cerebral blood flow velocity (CBF_V).

APPENDIX D

Images of fully instrumented swine in the operating room prior to experimentation.

Figure D.1. A tableside view of a fully instrumented animal in the operating room prior to CPR.

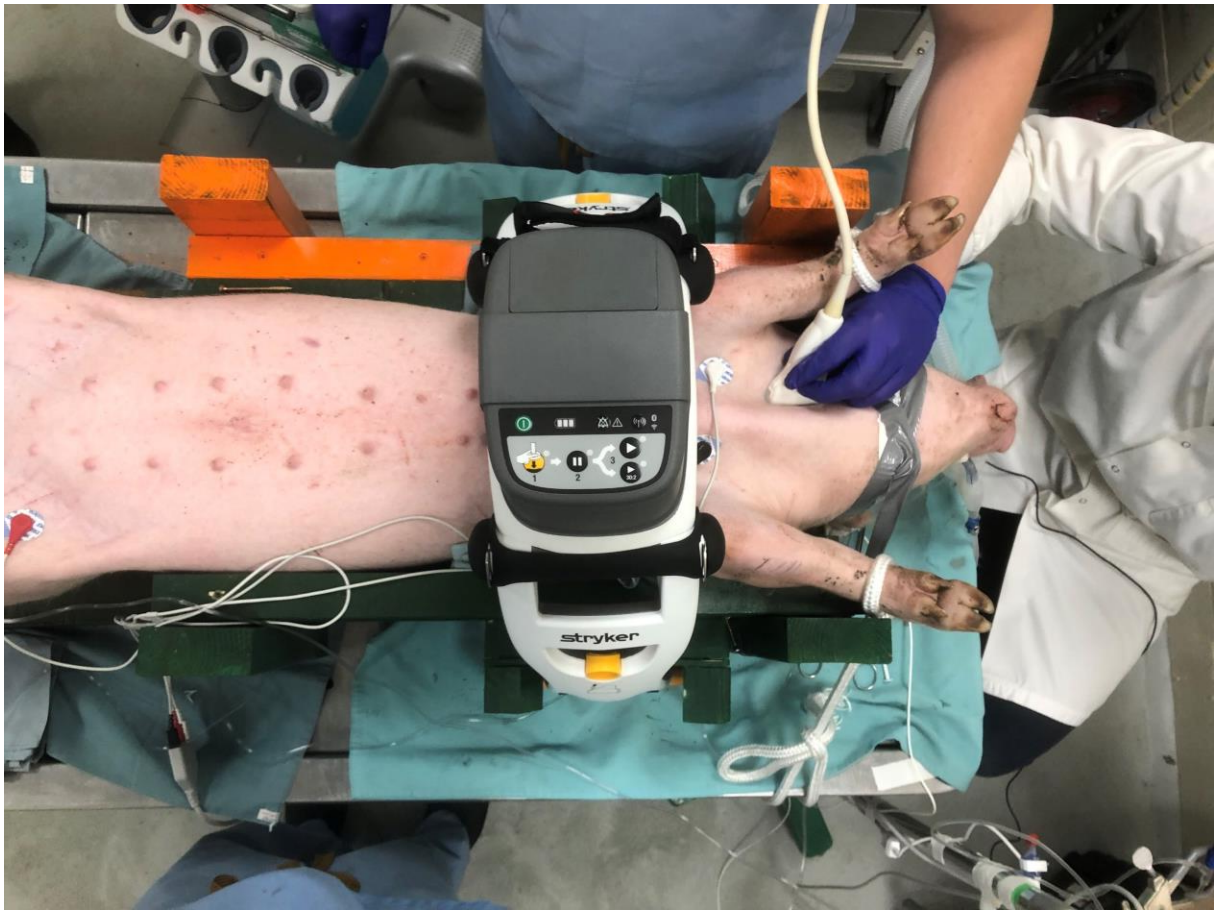

Figure D.2. A bird's eye view of a fully instrumented animal in the operating room prior to CPR.