Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2022, 12, 236-249
https://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

Impact of Acute Ischemia-Reperfusion Injury on Left Ventricular Pressure-Volume Relations in Dogs

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How to cite this paper: Kingma, J.G., Simard, D. and Rouleau, J.R. (2022) Impact of Acute Ischemia-Reperfusion Injury on Left Ventricular Pressure-Volume Relations in Dogs. *World Journal of Cardiovascular Diseases*, **12**, 236-249.
https://doi.org/10.4236/wjcd.2022.124024

Received: March 1, 2022
Accepted: April 26, 2022
Published: April 29, 2022

Abstract

Objective: Ischemic conditioning (IC) limits myocyte necrosis after acute myocardial ischemia-reperfusion; however, controversy persists regarding its potential to attenuate LV contractile dysfunction. Pressure-volume (P-V) loop analysis, via the load-insensitive conductance catheter method, was used to evaluate LV contractility, diastolic function, and ventriculo-arterial coupling. The goal of this study was to evaluate the ability of IC to improve post-ischemic recovery of LV contractile function. **Methods:** Twelve anesthetized dogs were randomly distributed to either the IC or the non-IC group; all dogs were subject to 60-min acute coronary occlusion followed by 180-min reperfusion. IC consisted of 4 repeated cycles of 5-min occlusion and 5-min reperfusion of the left main coronary artery. LV P-V relations were constructed under steady-state conditions (by inferior vena cava occlusion) at the beginning and end of the experiments; P-V loops were acquired at different time points before and during ischemia-reperfusion. **Results:** During ischemia and reperfusion, dP/dt_{max} decreased significantly compared to baseline in both groups; dP/dt_{min}, an indicator of the rate of LV relaxation rate was not affected for either group. Significant changes in several parameters of LV function including LVEF, SW, tPFR, ESV, and EDV caused by ischemia were also identified; none of these negative effects were resorbed, even in part, during reperfusion. **Conclusions:** Diminished LV contractile efficiency during systole and diastole produced by ischemia-reperfusion did not improve with IC pre-treatment despite significant endogenous protection against tissue necrosis.

Keywords

Ischemic Conditioning, Ischemia, Reperfusion, Ventricular Function, Pressure-Volume Relations

1. Introduction

Disruptions in blood perfusion produced by coronary artery disease can produce significant injury that results in loss of left ventricular (LV) contractile function [1] [2] [3] [4]. Post-occlusion restoration of blood flow commonly carried out in cardiac clinics with the use of different reperfusion interventions helps to restore oxidative phosphorylation and availability of high-energy phosphates in salvageable myocardium, limit the extent of cellular injury and improve LV contractile performance [5] [6].

Left ventricular pressure-volume (P-V) loops provide information on dynamic ventricular changes that occur during the cardiac cycle independent of loading conditions [7] [8] [9] [10] and in addition, they provide information on global LV function and intrinsic myocardial properties [11] [12]. Myocardial fiber shortening and LV stroke volume are modulated by preload, afterload, and intrinsic myocardial contractility. In our laboratory, we have been using combined pressure and conductance transducers developed initially by Baan and coworkers [12] [13] to assess post-ischemic cardiac function in anesthetized canine models. Infarct size correlates directly with myocardial contractility and LV function [11]. The goal of the present study was to evaluate the effects of acute ischemia-reperfusion injury, in the absence/presence of ischemic conditioning on recovery of LV function.

2. Materials and Methods

Dogs were acquired through the Division of Laboratory Animal Services at Laval University; they were housed in individual cages under conditions of constant temperature and humidity and kept on a strict 12:12 h dark-light cycle. Dogs had free access to food and water. This study was approved (#2007-001-2) by the institutional animal welfare committee at Laval University (A5012-01) and was carried out in compliance with the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health (publication 85-23; revised 1996). The experiments were carried out, and results were reported as described in the ARRIVE guidelines [14].

Surgical Preparation. Anesthesia protocols are described in earlier studies from our laboratory [15] [16] [17] [18]. Briefly, dogs (both male and female; 20 - 25 Kg) were intubated and anesthesia was maintained with isoflurane (1% - 2%) and oxygen-enriched room air. Fentanyl (0.005 mg/Kg IV bolus followed by constant infusion at 0.005 mg/Kg/h) was administered for analgesia. Normothermia was conserved with a water-jacketed Micro-Temp heating blanket (Zimmer, Dover, OH, USA); saline was given (250 mL/h IV) to replace fluid loss.

Dogs were placed in the supine position and vascular introducer sheaths (8Fr, Terumo Medical Corp. USA) were placed in the left and right femoral arteries; a triple-lumen central venous catheter (7Fr, Arrow-Howes™, Arrow Intl. Inc., Reading, PA, USA) was positioned in the right femoral vein.

A left lateral thoracotomy was performed through the fifth intercostal; the heart was exposed and suspended in a pericardial cradle. A section of the left anterior descending artery branch (distal to the first diagonal branch) was dissected to allow the placement of a vascular clamp for regional coronary artery occlusion. The umbilical tape was placed around the inferior vena cava cranial to the diaphragm. This allowed occlusion of the inferior vena cava later in the experiment to reduce cardiac preload for the construction of LVP-V relations. A catheter (7Fr) was advanced into the main pulmonary artery (for determination of parallel conductance calibration factors using hypertonic saline) [13]. A solid-state pressure transducer (5Fr, MPC500, Millar Instruments Inc., Houston, TX, USA) was placed in the LV cavity via an apical approach. A 12-electrode conductance catheter (7Fr, CD Leycom, Zoetermeer, the Netherlands) was advanced (via femoral artery) to the LV apex along the longitudinal axis of the ventricle as previously described [12]. P-V loops were recorded during apnea; blood resistivity was assumed to be constant (150 Ω·cm). A bolus of heparin sodium (500 IU, IV) was given, followed by hourly (100 IU, IV) administrations to prevent undue blood clotting after all catheters were positioned. After all surgical procedures were completed the preparation was allowed to stabilize for 30-min before initiation of the experimental protocol.

The Millar solid-state pressure transducer was cross-calibrated with both systolic aortic and diastolic left atrial pressure; the conductance catheter was connected to a Sigma 5DF signal conditioning and processing unit. All data were recorded continuously and stored on a computer hard drive for later analysis.

Experimental Protocol. Dogs (n = 12) were randomly assigned to either control (nIC) or ischemic conditioning (IC) groups (**Figure 1**). In the nIC group, a 40-min wait period was instituted to allow comparisons between treatments. In the IC group, dogs were subject to 4 cycles of 5-min coronary occlusion and 5-min coronary reperfusion prior to acute coronary occlusion as previously described [13]. Prior to the onset of ischemia, and at end of reperfusion,

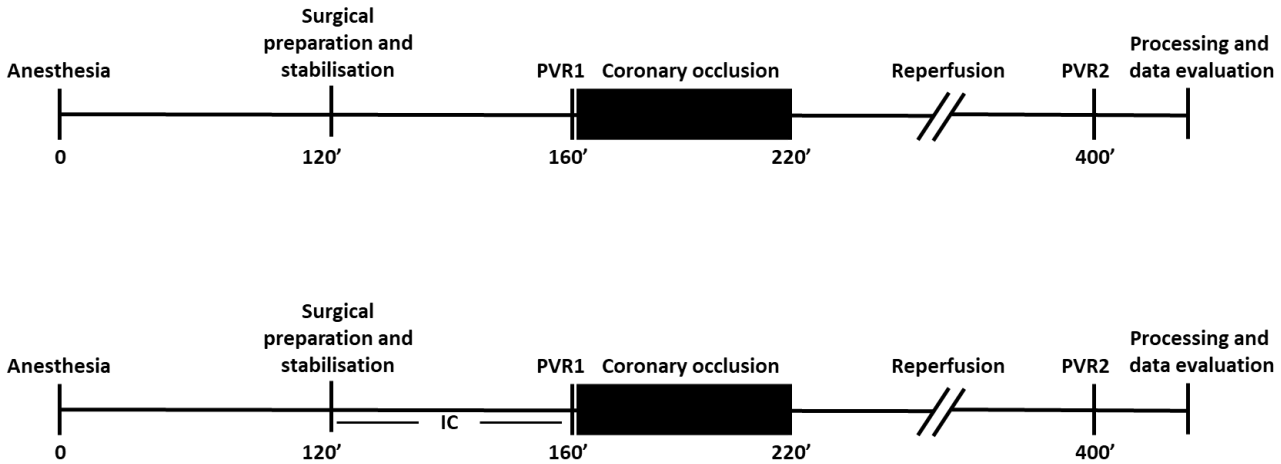

Figure 1. Timeline of the experimental protocol. LVPV relations were recorded prior to acute coronary occlusion and just before the end of reperfusion period. Overall duration of the experiment was 400-min.

P-V loops were recorded under steady-state conditions (during apnea); preload was reduced by temporary occlusion of the inferior vena cava (IVC) [19] [20] to construct LVPV relations (LVPVR). Dogs were then subject to 60-min regional coronary occlusion followed by 180-min reperfusion; xylocaine was administered (10 mg IV bolus; Astra Pharma, Inc., Mississauga, ONT, CAN) after 30-min of coronary occlusion and just prior to reperfusion to limit ischemia- or reperfusion-induced arrhythmias. Hearts that fibrillated were cardioverted (DC shock ≤50 Joules) with a cardiac defibrillator (General Electric); if defibrillation was not successful after two attempts, the animal was euthanized and not entered into the data analysis.

Statistical Analysis. Data are expressed as means ± 1 SD. Data normality was verified by the Shapiro-Wilk test (after Cholesky factorization); a linear mixed-effects model was used to identify changes in cardiac variables. A repeated-measure ANOVA (linear mixed model) allowed the determination of statistical differences; the selection of a covariance structure was based on the Akaike information criterion. We compared data using Tukey's test when no interaction was significant. A p value < 0.05 was considered statistically significant for all analyses. Statistical analyses were performed using the statistical packages R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria.) and SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Twelve dogs (n = 6 per group) completed the experimental protocol. The incidence of ventricular arrhythmias during ischemia/reperfusion (0/8 nIC vs 2/8 IC) was not statistically different. Infarct size (area of necrosis as a percent of risk area) was statistically different between the two groups (25 ± 5 vs 13 ± 3; p = 0.01) [18]. Changes in cardiac dynamics are shown in **Table 1**. Heart rate (HR) was not significantly reduced between groups but in the IC a significant drop in HR was observed during ischemia. During ischemia and reperfusion, dP/dt_{max} decreased significantly compared to baseline in both groups; dP/dt_{min} was not changed in either group suggesting little effect on the rate of relaxation. LV end-systolic (ESP) and end-diastolic (EDP) pressure were not significantly modified.

Stroke volume (SV) was consistent in both experimental groups (**Table 2**). LV ejection fraction (LVEF) was significantly reduced by ischemia. Stroke work (SW) decreased during ischemia in both groups and remained lower than baseline levels during reperfusion. The time constant of LV relaxation (Tau) was stable during the experiment in nIC and IC groups; the time to peak filling rate (tPFR) was lower after reperfusion in the IC group (compared to baseline values). End-systolic (ESV) and end-diastolic volume (EDV) increased substantially in both experimental groups (compared to baseline).

E_{es} (elastance at end-systole; mm Hg/mL) of the LVPVR was unchanged but LV volume intercept (V_0; mL) moved rightward after ischemia-reperfusion principally due to the increased ESV and EDV (**Figure 2**) in both groups; no

Table 1. Summary of cardiac hemodynamics.

	nIC			IC			Group	Intervention
	Base	Isc	Rep	Base	Isc	Rep		
HR	147 ± 20	142 ± 14	146 ± 9	148 ± 22	136 ± 21	149 ± 25	0.81	0.05
$dPdt_{max}$	1809 ± 404	1316 ± 358	1294 ± 113	1952 ± 653	1401 ± 223	1393 ± 197	0.45	0.002
$dPdt_{min}$	1404 ± 169	1196 ± 168	1278 ± 125	1332 ± 186	1291 ± 198	1353 ± 238	0.57	0.11
ESP	94 ± 12	84 ± 11	88 ± 12	91 ± 10	85 ± 9	83 ± 10	0.97	0.12
EDP	4 ± 2	6 ± 3	5 ± 4	5 ± 3	5 ± 3	4 ± 2	0.68	0.17

Data are means ± 1 SD. nIC: no ischemic conditioning; IC: ischemic conditioning; HR: heart rate (beats per minute); $dPdt_{max}$: rate of pressure change over time during systole (mmHg/sec); $dPdt_{min}$: rate of pressure change over time during diastole (mmHg/sec); ESP: end-systolic pressure (mm Hg); EDP: end-diastolic pressure (mm Hg).

Table 2. Summary of LV pressure-volume loop data.

	nIC			IC			Group	Intervention
	Base	Isc	Rep	Base	Isc	Rep		
SV	15 ± 5	16 ± 4	15 ± 4	17 ± 7	14 ± 7	13 ± 5	0.73	0.56
LVEF	36 ± 7	27 ± 5	22 ± 7	41 ± 11	23 ± 10	20 ± 5	0.82	0.001
SW	1052 ± 339	941 ± 378	822 ± 349	1086 ± 338	759 ± 406	660 ± 309	0.60	0.03
Tau	30 ± 4	32 ± 4	31 ± 3	32 ± 4	33 ± 5	29 ± 2	0.99	0.13
tPFR	368 ± 65	382 ± 75	344 ± 35	374 ± 89	369 ± 54	314 ± 35	0.67	0.04
ESV	20 ± 5	28 ± 8	37 ± 15	17 ± 5	29 ± 5	33 ± 6	0.75	0.001
EDV	32 ± 9	42 ± 12	51 ± 18	32 ± 6	41 ± 7	43 ± 8	0.63	0.001

Data are means ± 1 SD. nIC, IC: no ischemic conditioning, ischemic conditioning; SV: stroke volume (mL); LVEF: LV ejection fraction (%); SW: stroke work (mm Hg/mL); Tau: LV isovolumetric relaxation time constant (ms); tPFR: time to peak filling rate (ms); ESV: end-systolic volume (mL); EDV: end-diastolic volume (mL).

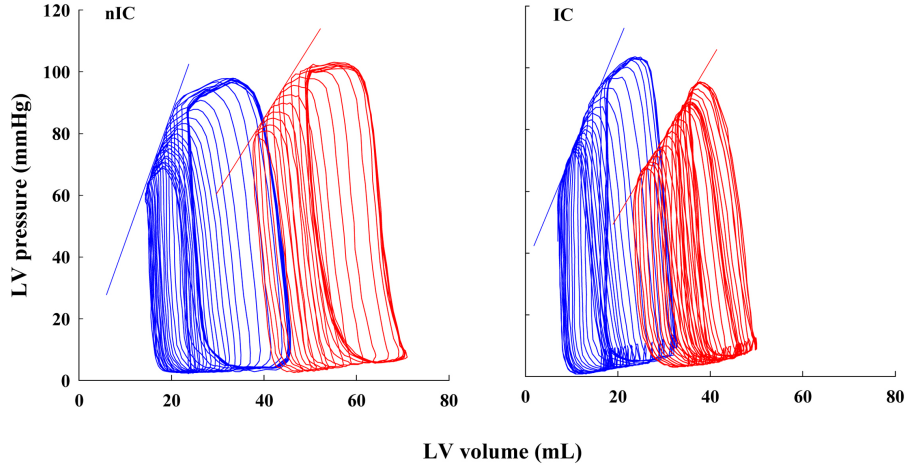

Figure 2. Representative steady-state LV ESPV relations obtained by transient IVC occlusion for nIC (left panel) and IC (right panel) dogsat baseline (blue line) and after 180-min reperfusion (red line). In nIC dogs, E_{es} was 3.14 mm Hg/mL (r^2 = 0.96) before and 2.61 mm Hg/mL (r^2 = 0.93) post-ischemia (p = NS); in IC dogs, E_{es} was 3.53 mm Hg/mL (r^2 = 0.097) before and 3.26 mm Hg/mL (r^2 = 0.90) post-ischemia (p = NS). The P-V relation shifted rightward after ischemia in both groups due to an increase in LV volume and suggests a reduction of reduced LV contractility. IC did not mitigate the effect of acute ischemia in the short term.

improvement in this relation (confirmed by a leftward shift of the relation) was observed for the IC group. Figure 3 shows the progressive rightward shift of P-V loops with attendant reduction of LV contractility caused by ischemia for each experimental group. Preload recruitable SW plotted against EDV shifted downward and leftward in IC dogs (versus controls) as shown in Figure 4. These results indicate that LV work for a given LV volume is diminished by IC; this could potentially influence the recovery of LV contractile function over time.

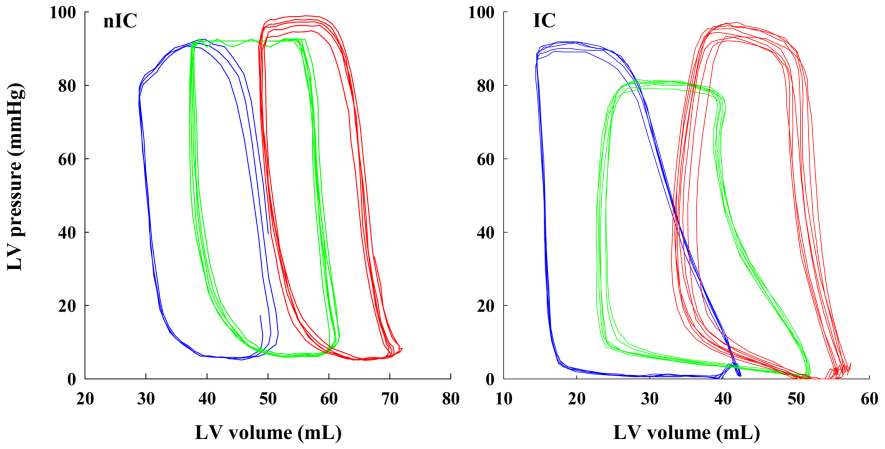

Figure 3. Representative P-V loops obtained at baseline (blue line), 60-min ischemia (green line) and 180-min reperfusion (red line) in nIC (left panel) and IC (right panel) groups. Note that the rightward shift of the P-V loops produced by ischemia was not modulated by reperfusion; no difference between groups was afforded by IC.

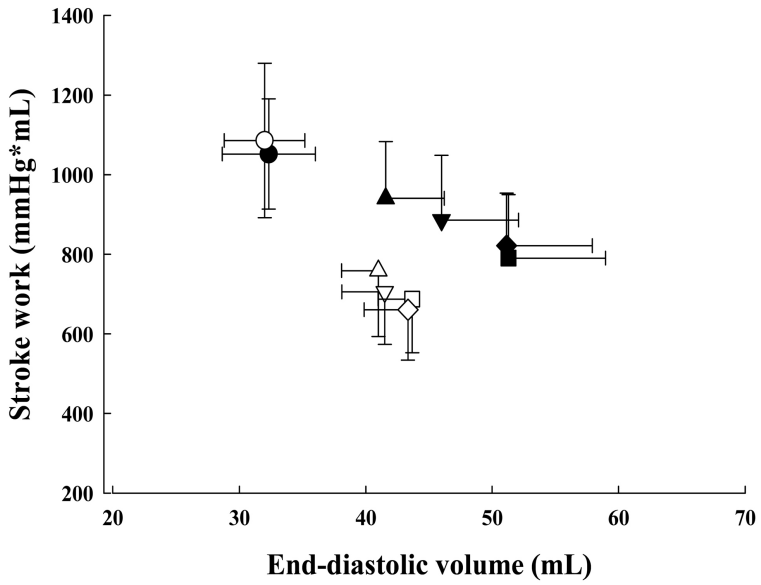

Figure 4. Cardiac function curves showing changes in SW and EDV at baseline (circles), 60-min ischemia (upward triangles), 60 (downward triangles), 120 (squares) and 180-min (diamonds) reperfusion in nIC (filled symbols) and IC (open symbols) groups. Data show a progressive decrease in LV contractile function caused by ischemia-reperfusion injury; IC does not improve LV contractile function.

4. Discussion

The present findings, in a canine model of acute ischemia-reperfusion subject to ischemic conditioning, show that LV contractile function is equally impaired regardless of intervention. Herein, we document that while IC markedly reduces infarct size, significant improvement of LV contractile function, in the short term, reported in several earlier studies, was not observed. Interventions (*i.e.* pharmacologic or non-pharmacologic) that limit ischemic injury should proportionately impact overall post-ischemic cardiac function. To date, reports from a host of studies in various experimental models of ischemic conditioning document either robust improvement, no change or worse contractile function post-ischemia [21]-[26].

The benefits of IC on infarct size are well known [27] [28]; however, it remains unclear whether rapid restoration of LV contractile function is a consequence of smaller ischemic injury, reduced stunning, or both can be achieved. In globally ischemic isolated rabbit hearts [29] and *in situ* canine [30] and porcine [31] hearts, no real beneficial effect of IC on post-ischemic ventricular dysfunction independent of reduction in infarct size has been demonstrated. In animal studies LV contractile function has mostly been assessed using regional wall motion (wall thickening, systolic segment shortening) methods; the accuracy of these methods is principally determinant of crystal placement within the ischemic or under the perfused region. It remains unclear whether improved post-ischemic LV function provided by IC is due to an attenuation of myocardial stunning or infarction; however, at least one study (using sonomicrometry) has reported beneficial effects of IC on regional contractile function in pigs [23]. To date, no significant relation between infarct size and contractile function has been reported.

Preservation of high-energy phosphates and stable myocardial oxygen consumption within ischemic myocardium may explain ischemic conditioning mediated protection [32]. More than 30 years ago, Reimer and colleagues documented that brief, repeated ischemia slowed the rate of high-energy phosphate consumption [33]; washout of ischemic catabolites during each reperfusion period could potentially reduce myocyte injury since high-energy phosphate pools are more readily recharged and capacity for anaerobic glycolysis during subsequent coronary occlusion is restored [34] [35]. During ischemia, myocardial energy demand is reduced due to the downregulation of LV contractile function. As such, metabolic integrity (*i.e.* high-energy phosphate levels) of the ischemic myocardium is prolonged such that myocardium should potentially regain contractile function [36]. Reduced basal myocardial metabolism produced by IC could lead to conservation of myocardial energy reserves to presumably preserve LV contractility, diastolic function, and ventriculo-arterial coupling. However, the ability to resist irreversible ischemic injury also depends on various factors such as duration and severity of ischemia. Tolerance to ischemia-induced myocardial necrosis has been documented with both pharmacologic

and non-pharmacologic treatments; cardioprotection by ischemic conditioning also limits severe post-ischemic ventricular dysrhythmias [37] [38] and endothelial dysfunction [39].

Ventricular properties (systolic and diastolic) depend on muscle mass, LV chamber architecture, and geometry [40]. Because blood pressure is a highly regulated process even marginal deviations from the norm can produce some manifestation of pathology. Normal LV function depends on intricate interactions between contractility, heart rate, pre- and after-load [41]. In the clinical setting, LV systolic function estimates of LVEF can be obtained by direct assessment of ventricular volumes [42] using echocardiography or radionuclide ventriculography [43] [44] [45]; abnormal LVEF illustrates the inability of the cardiovascular system to modulate contractile and loading conditions to support normal homeostasis. However, LVEF is considered a poor marker of LV intrinsic contractility because it is strongly influenced by LV loading conditions [46]. As such, LVEF is more of a global index of cardiovascular performance and should be considered as a ventriculo-arterial coupling index that is related to LV mechanical efficiency [47]. In the present study, ischemia caused a significant reduction of LVEF that was not ameliorated by IC pre-treatment; reperfusion of the ischemic vascular bed was unable to provide immediate improvement of LVEF. The conductance catheter method (*i.e.* gold standard for *in vivo* determination of systolic contractile performance in the intact heart) provides a comprehensive evaluation of LV function [40] [48]. This method (an overview of LV analysis) has been published by Kerkhof and coworkers [49]) enables continuous P-V loop analysis to describe intrinsic ventricular pump properties that are independent of preload, afterload [50] [51] [52] and within limits heart rate, in the normal LV volume range [50] [53] [54] [55]. End-systolic P-V relations provide information that includes end-systolic elastance and volume at zero pressure [56]; the latter is a result of a linearized approach to the determination of E_{es}.

This study has some limitations; we used dogs with a health profile distinctly different from humans with heart disease and other comorbidities. However, dogs are comparable to humans with respect to heart size and coronary physiology; a large and diverse data bank exists for diverse cardiovascular studies using canine models, which favors comparisons with the present study. The sample size was small and the post-ischemic follow-up period was much shorter than necessary to provide a better evaluation of the potential recovery of LV function. Second, an open-chest, anesthetised dog model was used; anesthesia may, in and of itself, afford a level of protection against ischemic injury [57] [58] [59] that could result in improved post-ischemic recovery of LV contractile function [60] [61]. Potential protective mechanisms include activation of intracellular signalling pathways; however, the same is true for IC protocols so we may simply be looking at a question of timing. Finally, future studies with prolonged reperfusion or recovery periods after ischemia could potentially provide data that would

be more clinically relevant.

5. Conclusion

The influence of IC on post-ischemic LV contractile function in different animal models remains inconclusive. In the present study, we used the conductance catheter method which uses after-load insensitive measures to evaluate LV contractile function. While IC is known to conserve cardiac energy reserves during the relatively brief cycles of hypoperfusion and reperfusion and also significantly reduces myocardial injury, we were unable to demonstrate an expected positive effect on overall LV contractile function after exposure to a prolonged period of ischemia.

Acknowledgements

The authors would like to acknowledge Serge Simard for providing the statistical analyses of the experimental data used in this report. These studies were funded by an operating grant from the Quebec Heart and Stroke Foundation.

Conflicts of Interest

The authors have no conflict of interest to disclose for this work.

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List of Abbreviations

LV: left ventricular
P-V: pressure-volume
IC: ischemic conditioning
nIC: no ischemic conditioning
LVEF: LV ejection fraction
SV: stroke volume
SW: stroke work
ESV: end-systolic volume
EDV: end-diastolic volume
ESP: end-systolic pressure
EDP: end-diastolic pressure
IVC: inferior vena cava
tPFR: time to peak filling rate
E_{es}: LV elastance at end-systole
V_0: LV volume at zero pressure