

Effect of Classic or Delayed Ischemic Conditioning on Left Ventricular Pressure-Volume Relations in Dogs

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Received: 28 Apr 2022; Accepted: 24 May 2022; Published: 30 May 2022

Citation: Kingma JG, Simard D, Rouleau JR. Effect of Classic or Delayed Ischemic Conditioning on Left Ventricular Pressure-Volume Relations in Dogs. *Cardiol Vasc Res.* 2022; 6(3): 1-8.

ABSTRACT

Objective: Non-pharmacologic interventions such as ischemic conditioning (IC) markedly reduce infarct size but it remains unclear whether this protection translates to a significant attenuation of ischemia-mediated LV contractile dysfunction. In this study we evaluated pressure-volume (P-V) data obtained by the load-insensitive conductance catheter method, to examine LV pressure-volume (LVP-V), diastolic function and ventricular-arterial coupling in anesthetized dogs exposed to ischemic conditioning (IC) or delayed IC (dIC; 48h prior to ischemia). The objective was to determine if IC, or dIC pre-treatment could influence post-ischemic recovery of LV contractile function.

Methods: Three groups were studied – nIC, IC and dIC; all dogs underwent 90-min acute coronary occlusion (CO) followed by 180-min reperfusion (REP). IC consisted of 4 cycles of 5-min CO and 5-min REP of the left main coronary artery. LV P-V relations were constructed under steady-state conditions (by transient occlusion of the inferior vena cava) prior to IC treatment and at the end of the experiment; P-V loop data was also acquired at different points during the experiment to evaluate changes in end-systolic and end-diastolic parameters.

Results: During CO dP/dt_{max} and dP/dt_{min} (indicator of rate of LV relaxation) decreased significantly compared to baseline in the IC group; these variables were unchanged in the dIC group. LVEF decreased during CO and REP in the nIC and IC groups but was stable in the dIC group. Tau was increased only in the IC group during CO and REP. ESV and EDV increased significantly in all groups during CO and REP; none of these negative effects was resorbed by the end of the experimental period.

Conclusions: Diminished LV contractile function caused by CO did not improve with IC, or dIC pre-treatment, despite significant reduction in infarct size.

Keywords

Ischemic conditioning, Delayed ischemic conditioning, Ischemia, Reperfusion, Ventricular function, Pressure-volume relations.

Introduction

Myocardial infarction causes left ventricular remodeling that over time produces progressive heart failure, which leads to persistent left ventricle (LV) contractile dysfunction. Mechanisms involved include changes in LV chamber dimensions and

geometry as well as hemodynamic modifications that decrease cardiac performance [1]. Pharmacologic interventions designed to improve post-ischemic cardiac function are currently being investigated and recommendations from international medical associations advocate their use in patients due to proven benefits for reducing mortality [2,3]. Non-pharmacologic interventions such as ischemic conditioning (IC) can also markedly reduce infarct size in humans and almost all animal species studied [4-6]. Whether significant restoration of LV contractile function can

be achieved by IC remains uncertain based on studies performed in globally ischemic isolated rabbit hearts [7] and in *in situ* canine and porcine hearts [8,9]. In the present study, we used LV pressure-volume (LVP-V) measurements to evaluate changes in systolic and diastolic parameters of LV contractile performance. For these studies in anesthetised dogs were subjected to IC (classic or delayed - dIC) prior to a prolonged coronary occlusion (CO) followed by reperfusion (REP). Our findings provide additional information on the efficacy of non-pharmacologic interventions on post-ischemic LV contractile function.

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). Experiments were carried out, and results reported as described in the ARRIVE guidelines [10].

Surgical preparation

Anesthesia protocols are described in earlier studies from our laboratory [11-14]. 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 maintained 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 space; 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 placement of a vascular clamp for regional coronary artery occlusion. Umbilical tape was placed around the inferior vena cava (IVC) cranial to the diaphragm. This allowed for brief IVC occlusion later in the experiment for construction of LVP-V relations. A catheter (7Fr) was advanced into the main pulmonary artery (for determination of parallel conductance using hypertonic saline) [15]. 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, Leycom, Oegstgeest, The Netherlands) was advanced (via femoral artery) to the LV apex along the longitudinal axis of the ventricle as previously described [16]. Steady state LVP-V loops were recorded during normal sinus rhythm and apnea; blood resistivity was measured prior to acquisition of

conductance catheter data using a resistivity cuvette (Leycom, Oegstgeest, The Netherlands). Bolus 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 completion of surgical procedures, a 30-min stabilization period was allowed before initiation of the experimental protocol. For the dIC study, dogs were pre-medicated with diazepam (1 mg/Kg IV) and fentanyl (20 µg/Kg IV) and anesthetized with 1.5-2.0% isoflurane. IC was performed by coronary catheterization [17]; briefly, the right femoral artery was cannulated with a 7F sheath for percutaneous transluminal coronary angioplasty and 1000 IU heparin administered IV. Under angiographic guidance, a 6F guiding catheter was inserted and advanced to the coronary ostium. Left coronary angiography (oblique view) was performed to delineate the left main coronary artery and its branches; a floppy guide wire (0.0014 inch) was advanced into the left main circumflex artery and an inflatable balloon catheter was positioned just distal to the first marginal branch (defined by angiography). Ischemic conditioning (4 cycles of 5-min CO and 5-min REP) was done by balloon inflation (3 bars)/deflation; 1-min after onset of CO or REP contrast medium was injected and an angiogram obtained to verify absence/restoration of blood flow within the infarct-related artery. After completion of IC, catheters were removed and tissue and skin incisions sutured; dogs were weaned from the respirator and extubated after restoration of a regular breathing pattern. Each dog was administered antibiotic (cefazoline sodium, 5.5 mg/Kg, im), analgesic (buprenorphine, 0.05 mg/Kg, im) and heparin (500 IU, sc) before returning to the recovery room. After 48h recovery, dogs underwent the above-described surgical procedure for ischemia-reperfusion.

Experimental Protocol

Dogs (n=24) were randomly assigned to control (nIC), ischemic conditioning (IC), or delayed ischemic conditioning (dIC) groups as shown in Figure 1. In the nIC group, a 40-min wait period was instituted to allow comparisons between treatments. In the IC groups, dogs were subject to 4 cycles of 5-min CO and 5-min coronary REP prior to prolonged CO [6].

For all dogs, LVP-V loops were recorded under steady-state conditions (during apnea) prior to CO and at the end of the experimental period (cf. Figure 1); LVP-V loops were obtained by transient occlusion of the IVC [18,19]. Dogs underwent 90-min regional CO followed by 180-min REP; xylocaine was administered (10 mg IV bolus; Astra Pharma, Inc., Mississauga, ONT, CAN) after 30-min of CO and just prior to REP 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. 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 (Leycom, Oegstgeest, The Netherlands). All data were recorded continuously and stored

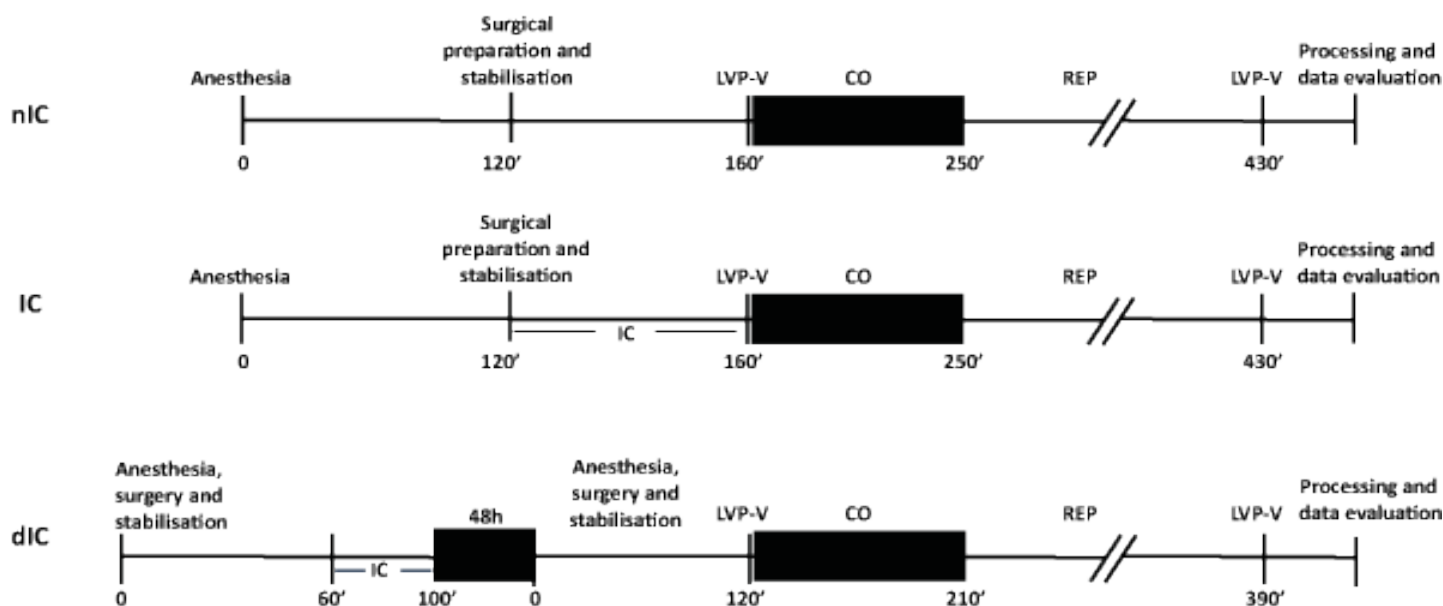


Figure 1: Timeline of the experimental protocol.

on computer hard drive for later analysis.

Statistical analysis

Data are expressed as means \pm 1SD. 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 determination of statistical differences; selection of a covariance structure was based on the Akaike information criterion. We compared data with a Tukey's test when interactions were not 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, and Austria.) and SAS v9.4 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Twenty-four dogs ($n=8$ per group) completed the experimental protocol. The incidence of ventricular arrhythmias during ischemia/reperfusion (2/8 nIC; 1/8 IC; 1/8 dIC) but is not markedly different between groups. Infarct size (necrosis as percent of risk area) was smaller in IC and dIC groups (32 ± 10 nIC; 17 ± 6 IC; 17 ± 6 dIC; $p=0.01$ vs nIC) [11]. A summary of changes in cardiac dynamics is presented in Table 1. Heart rate (HR) was stable during CO and REP in each experimental group. During CO, dP/dt_{max} decreased significantly in the IC (versus baseline) group; however, results were not changed in the nIC and dIC groups, respectively. A similar pattern was observed for dP/dt_{min} for the IC group. LV end-systolic pressure (ESP) decreased markedly during CO in all groups. LV end-diastolic (EDP) pressure increased in the IC group during CO and REP; however, similar changes did not occur in the nIC or dIC groups.

Changes in stroke volume (SV) varied significantly in IC dogs during CO and REP (Table 2). LV ejection fraction (LVEF)

decreased significantly during CO and REP in nIC and IC groups indicating impaired LV systolic performance (also supported by reductions in dP/dt_{max}); however, LVEF remained stable in the dIC group during the experiment. Stroke work (SW) decreased during CO but did not achieve a level of statistical significance; however, at the end of the experimental protocol some recovery to near baseline values was observed in IC and dIC groups. Tau (i.e. time constant of LV relaxation) was significantly higher during CO and REP in the IC group with no change in either nIC or dIC dogs; tPFR (time to peak filling rate) was unchanged for all groups. LV end-systolic volume (ESV) increased significantly during CO and REP in all groups; we observed a similar pattern for LV end-diastolic volume (EDV).

A summary of changes in cardiodynamics and LVP-V data afforded by IC treatment is reported in Table 3. HR was markedly lower than baseline values at the end of REP-4; ESP was not changed (compared to baseline) but EDP increased significantly during each CO cycle and subsequently returned to normal values during REP. dP/dt_{max} and dP/dt_{min} decreased during CO-4 but were otherwise not markedly affected. LVEF (global indicator of LV contractile performance) also decreased significantly during CO-4. No change in SW or tPFR were observed during the IC protocol. ESV and EDV increased significantly beginning with CO-2 and remained higher than baseline values from CO-3 to the end of the IC protocol. These findings suggest a gradual reduction of LV function caused by IC; however, the underlying cause has not been determined since it is generally acknowledged that myocyte injury (i.e. necrosis) produced by IC treatment is limited.

LV elastance at end-systole (E_{es} ; mm Hg/mL) of the LVP-V relation did not change but the LV volume intercept (V_0 ; mL) was shifted to the right in all groups after ischemia-reperfusion principally due to higher ESV and EDV as shown in Figure 2. No improvement in this relation (i.e. leftward shift) was observed for the IC or dIC

Table 1: Summary of cardiac hemodynamics.

	nIC			IC			dIC			ANOVA		
	Base	CO	REP	Base	CO	REP	Base	CO	REP	Grp	Int	Grp*Int
HR	110 ± 32	107 ± 20	119 ± 29	103 ± 18	94 ± 15	102 ± 33	116 ± 27	113 ± 21	116 ± 23	0.47	0.45	0.78
dPdt _{max}	1990 ± 604	1786 ± 797	1496 ± 450	1427 ± 175	980 ± 150	1405 ± 514	1856 ± 635	2009 ± 1230	1734 ± 825	0.23	0.56	0.02
dPdt _{min}	1825 ± 507	1744 ± 799	1517 ± 659	1251 ± 100	873 ± 132	1053 ± 325	2535 ± 1368	2398 ± 1484	2105 ± 1120	0.04	0.05	0.16
ESP	105 ± 8	98 ± 6	95 ± 13	96 ± 1	88 ± 3	94 ± 16	115 ± 20	103 ± 6	105 ± 17	0.21	0.001	0.04
EDP	9 ± 4	12 ± 6	9 ± 8	5 ± 2	11 ± 4	12 ± 6	6 ± 4	4 ± 5	4 ± 5	0.07	0.001	0.04

Data are means ± 1SD. nIC, IC, dIC: no ischemic conditioning, ischemic conditioning and delayed 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, EDP: end-systolic and end-diastolic pressure (mmHg), Grp, Int, Grp*Int; group, intervention, group*intervention statistical analyses.

Table 2: Summary of LV P-V data.

	nIC			IC			dIC			ANOVA		
	Base	CO	REP	Base	CO	REP	Base	CO	REP	Grp	Int	Grp*Int
SV	15 ± 4	13 ± 4	12 ± 4	16 ± 6	12 ± 3	18 ± 7	14 ± 2	14 ± 4	15 ± 7	0.51	0.001	0.015
LVEF	37 ± 14	26 ± 7	26 ± 10	34 ± 13	14 ± 3	19 ± 5	30 ± 6	28 ± 11	26 ± 11	0.19	0.02	0.13
SW	1240 ± 516	1054 ± 512	840 ± 256	1193 ± 589	634 ± 114	1191 ± 565	1351 ± 475	1127 ± 482	1344 ± 723	0.71	0.32	0.51
Tau	32 ± 9	34 ± 11	35 ± 9	36 ± 3	49 ± 6	42 ± 7	35 ± 8	34 ± 8	34 ± 8	0.10	0.02	0.004
tPFR	401 ± 53	449 ± 69	389 ± 72	442 ± 35	501 ± 73	445 ± 64	474 ± 102	398 ± 91	407 ± 61	0.48	0.22	0.10
ESV	20 ± 6	27 ± 5	27 ± 6	23 ± 4	47 ± 7	52 ± 13	25 ± 4	29 ± 8	36 ± 7	0.001	0.001	0.001
EDV	32 ± 8	38 ± 6	37 ± 3	37 ± 7	57 ± 9	66 ± 22	37 ± 6	41 ± 9	47 ± 12	0.005	0.001	0.001

Data are means ± 1SD. nIC, IC, dIC: no ischemic conditioning, ischemic conditioning, delayed ischemic conditioning; SV: stroke volume (mL); LVEF: LV ejection fraction (%); SW: stroke work (mmHg/mL); Tau: LV isovolumetric relaxation time constant (ms); tPFR: time to peak filling rate (ms); ESV, EDV: end-systolic and end-diastolic volume (mL). Grp, Int, Grp*Int; group, intervention, group*intervention statistical analyses.

Table 3: Summary of cardiodynamics and LVP-V data during IC.

	Base	CO-1	REP-1	CO-2	REP-2	CO-3	REP-3	CO-4	REP-4
HR	103 ± 18	104 ± 17	99 ± 16	98 ± 19	99 ± 15	100 ± 17	98 ± 15	97 ± 18	95 ± 16*
ESP	96 ± 1	84 ± 9	96 ± 7	86 ± 8	102 ± 7	91 ± 10	102 ± 6	88 ± 10	100 ± 11
EDP	5 ± 2	8 ± 2	7 ± 4	11 ± 7*	7 ± 2	11 ± 4*	7 ± 2	12 ± 4*	8 ± 3
dPdt _{max}	1427 ± 175	1249 ± 194	1282 ± 256	1232 ± 191	1377 ± 131	1293 ± 166	1301 ± 195	1183 ± 195*	1233 ± 197
dPdt _{min}	1251 ± 100	1018 ± 176	1160 ± 187	1029 ± 163	1237 ± 120	1081 ± 161	1184 ± 82	999 ± 178*	1137 ± 154
LVEF	34 ± 13	25 ± 14	30 ± 7	25 ± 13	30 ± 10	25 ± 13	28 ± 8	23 ± 10*	26 ± 7
SW	1193 ± 589	886 ± 491	1216 ± 309	976 ± 524	1339 ± 491	1030 ± 529	1198 ± 289	905 ± 401	1248 ± 378
tPFR	442 ± 35	478 ± 55	469 ± 32	484 ± 58	453 ± 45	442 ± 38	469 ± 22	449 ± 36	490 ± 80
ESV	23 ± 4	32 ± 8	31 ± 6	35 ± 8*	30 ± 7	36 ± 10*	33 ± 7*	38 ± 10*	38 ± 13*
EDV	37 ± 7	43 ± 5	45 ± 9	48 ± 9*	46 ± 9	50 ± 9*	48 ± 8*	52 ± 10*	53 ± 15*

Data are means ± 1SD; * = $p \leq 0.05$ vs. Base (ANOVA). HR: heart rate (beats per minute); ESP, EDP: end-systolic, end-diastolic pressure (mmHg), dPdt_{max}: rate of pressure change over time during systole (mmHg/sec); dPdt_{min}: rate of pressure change over time during diastole (mmHg/sec); LVEF: LV ejection fraction (%); SW: stroke work (mmHg/mL); tPFR: time to peak filling rate (ms); ESV, EDV: end-systolic, end-diastolic volume (mL).

groups. Rightward shift of LVP-V loops at different time periods during the experiment, with attendant reduction of LV contractility caused by CO, are illustrated in Figure 3; LV contractile function in dogs pretreated with either IC or dIC was not restored to baseline levels.

Discussion

Pharmacologic or non-pharmacologic interventions that afford protection against ischemia-induced myocardial injury should hypothetically allow for more rapid restoration of post-ischemic cardiac contractile function. In this study, in dogs subject to prolonged CO, IC or dIC did not markedly improve post-ischemic LV contractile function even though infarct size is significantly reduced.

Normal LV function depends on intricate interactions between contractility, heart rate, pre- and after-load [20]. Since blood

pressure is highly regulated minor deviations from the norm can result in serious complications. Both systolic and diastolic ventricular properties depend on muscle mass, LV chamber architecture and geometry [21]. Abnormal LVEF demonstrates incapacity of the cardiovascular system to modulate contractile and loading conditions that are essential for normal homeostasis. However, LVEF is an unreliable marker of LV intrinsic contractility as it is strongly influenced by LV loading conditions [22]. Consequently, LVEF is a ventriculo-arterial coupling index principally related to LV mechanical efficiency [23]. In the present study, ischemia causes marked reduction of LVEF that does not improve by IC pre-treatment; reperfusion did not restore LVEF to baseline, or near-baseline values. Interestingly, post-ischemic LV contractile dysfunction appears to be less affected in dogs exposed to dIC.

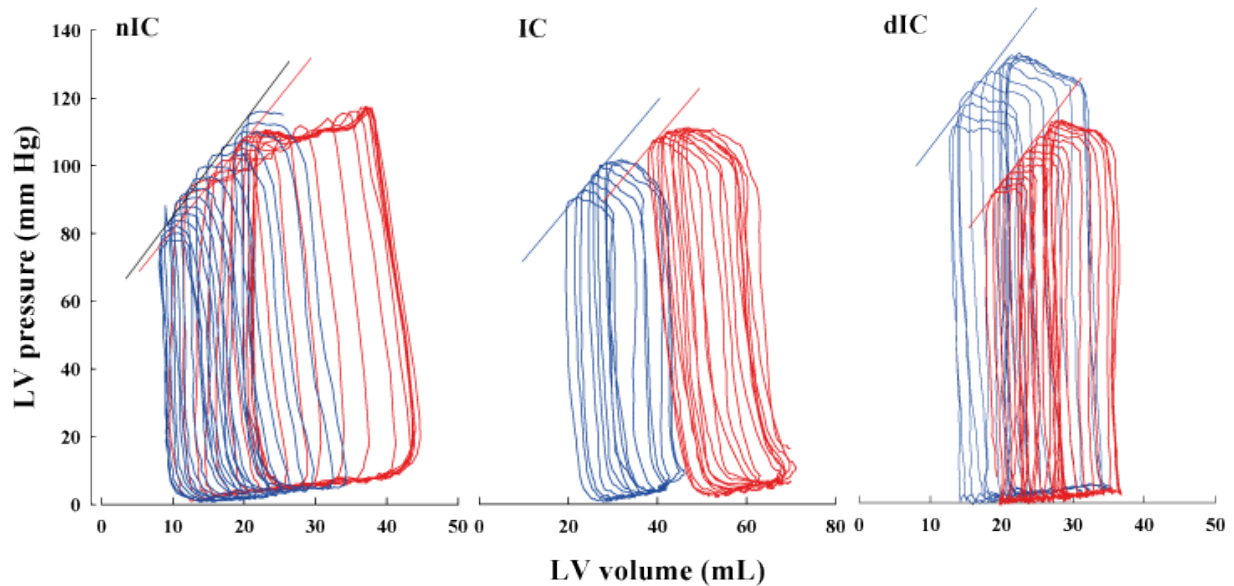


Figure 2: Representative steady-state LVP-V loops generated by transient IVC occlusion in nIC (left panel), IC (middle panel) and dIC (right panel) dogs at baseline (blue line) and after 180-min REP (red line); slopes of end-systolic LVP-V points are shown. In nIC dogs, E_{es} was 2.09 mm Hg/mL ($r^2 = 0.99$) before and 2.64 mm Hg/mL ($r^2 = 0.96$) post-ischemia ($p=NS$). In IC dogs, E_{es} was 1.73 mm Hg/mL ($r^2 = 0.98$) before and 0.99 mm Hg/mL ($r^2 = 0.94$) post-ischemia ($p=NS$). In dIC dogs, E_{es} was 3.80 mm Hg/mL ($r^2 = 0.95$) before and 2.95 mm Hg/mL ($r^2 = 0.98$) post-ischemia ($p=NS$). The LVP-V relation is shifted rightward after CO in all groups consistent with increased ESV and EDV.

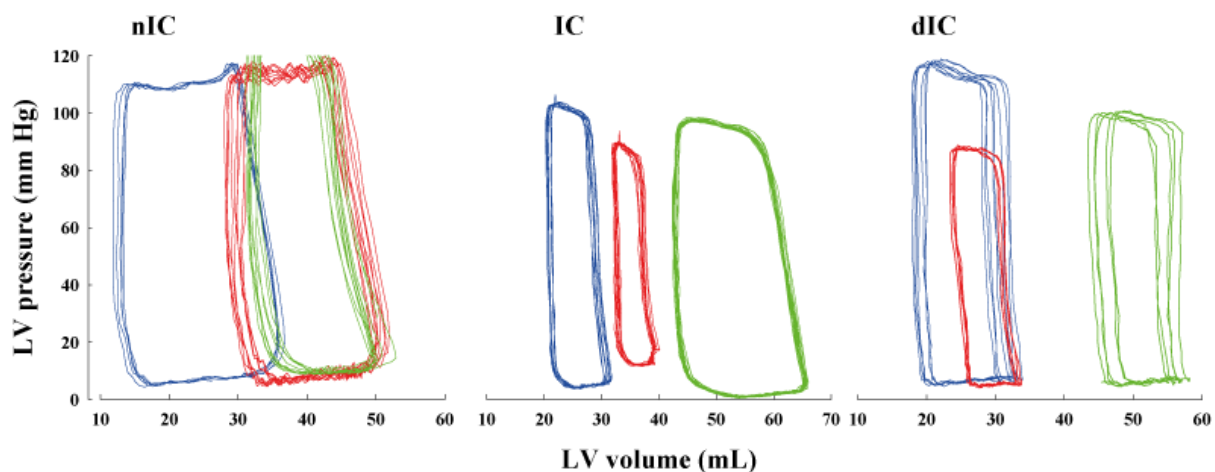


Figure 3: Representative LVP-V loops at baseline (blue line), 90-min CO (green line) and 180-min REP (red line) in nIC (left panel), IC (middle panel) and dIC (right panel) groups. During CO narrowing of LVP-V loops is due to a reduction in SW and shifts to the right are due to increased ventricular volume; IC or dIC did not significantly improve LV contractile status.

Post-ischemic myocardial contractile dysfunction, more commonly referred to as ‘myocardial stunning’ is a persistent mechanical dysfunction that occurs despite absence of irreversible myocyte damage. By definition, stunning denotes a fully reversible abnormality. Repetitive CO used in IC reported decreases LV contractile function (without irreversible cellular damage) beginning with the first ischemic insult [24]. Our findings indicate a restoration to near normal values of LV contractile function after IC and dIC with the exception of LVEF; the global derangement of LV function involves

both systolic and diastolic function. The cumulative effects of repetitive ischemia on recovery of post-ischemic function are not thoroughly investigated. That being stated, IC does 1- afford robust improvement, 2- not change or 3- exacerbate LV contractile dysfunction post-ischemia [25-30].

Many of the positive studies used ultrasonic crystal micrometric methods (segment shortening, wall thickening, etc.) to measure regional myocardial function in small animal models. Various studies compared *in situ* LV contractile

function using sonomicrometry or conductance catheter methods [31-33]; overall consensus is that different techniques for measurement of LV contractile function provide valid data and differences between methods are relatively insignificant. 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 contractile function [21,34]. This method enables continuous LVP-V loop analysis to describe intrinsic ventricular pump properties that are independent of preload, afterload [35-37] and within limits of heart rate, in the normal LV volume range [35,38-40]; however, corrections based on differences in infarct size may also be necessary [41,42]. End-systolic P-V relations provide information that includes end-systolic elastance and volume at zero pressure [43].

This study has some limitations; we used dogs with a health profile distinctly different from humans with heart disease and other comorbidities. Dogs are comparable to humans with respect to heart size and coronary physiology; existence of a large and diverse data bank using canine experimental models also favors comparisons between studies. Sample size, in the present study, is small (determined on basis of protection against ischemic injury) and the post-ischemic follow-up period much shorter than necessary to provide an adequate evaluation of potential recovery of LV function. Second, we used an open-chest preparation in anesthetized dogs; anesthetic agents are documented to protect against ischemic injury [44-46] and might potentially improve post-ischemic LV contractile function [47,48].

Conclusions

In the present study using the conductance catheter method we did not show marked improvement of global LV contractile function by either IC or dIC in dog hearts subject to a relatively prolonged period of CO. However, significant protection against myocardial necrosis occurs, as expected with IC and dIC. Whether pharmacologic or non-pharmacologic interventions can influence post-ischemic LV contractile function remains inconclusive; however, since ischemic durations of variable length cumulatively affect global LV contractile function further studies are encouraged.

Acknowledgements

The authors acknowledge Serge Simard for providing the statistical analyses of the experimental data used in this report. This study was supported by an operating grant from the Heart and Stroke Foundation of Québec.

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