Published in final edited form as:

Resuscitation. 2009 May ; 80(5): 561–566. doi:10.1016/j.resuscitation.2009.01.016.

Intra-arrest Hypothermia: Both Cold Liquid Ventilation with Perfluorocarbons and Cold Intravenous Saline Rapidly Achieve Hypothermia, but Only Cold Liquid Ventilation Improves Resumption of Spontaneous Circulation

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Abstract

Background—Rapid intra-arrest induction of hypothermia using total liquid ventilation (TLV) with cold perfluorocarbons improves resuscitation outcome from ventricular fibrillation (VF). Cold saline intravenous infusion during cardiopulmonary resuscitation (CPR) is a simpler method of inducing hypothermia. We compared these 2 methods of rapid hypothermia induction for cardiac resuscitation.

Methods—Three groups of swine were studied: cold preoxygenated TLV (TLV, n=8), cold intravenous saline infusion (S, n=8), and control (C, n=8). VF was electrically induced. Beginning at 8 minutes of VF, TLV and S animals received 3 minutes of cold TLV or rapid cold saline infusion. After 11 minutes of VF, all groups received standard air ventilation and closed chest massage. Defibrillation was attempted after 3 minutes of CPR (14 minutes of VF). The end point was resumption of spontaneous circulation (ROSC).

Results—Pulmonary arterial (PA) temperature decreased after 1 minute of CPR from 37.2°C to 32.2°C in S and from 37.1°C to 34.8°C in TLV (S or TLV vs. C $p < 0.0001$). Coronary perfusion pressure (CPP) was higher in TLV than S animals during the initial 3 minutes of CPR. Arterial pO_2 was higher in the preoxygenated TLV animals. ROSC was achieved in 7 of 8 TLV, 2 of 8 S, and 1 of 8 C (TLV vs. C, $p = 0.03$).

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest regarding this manuscript.

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Conclusions—Moderate hypothermia was achieved rapidly during VF and CPR using both cold saline infusion and cold TLV, but ROSC was higher than control only in cold TLV animals, probably due to better CPP and pO₂. The method by which hypothermia is achieved influences ROSC.

Keywords

Hypothermia; cardiopulmonary resuscitation; ventricular fibrillation; perfluorocarbons

INTRODUCTION

The International Liaison Committee on Resuscitation (ILCOR) Guidelines for Cardiopulmonary Resuscitation currently recommend the induction of hypothermia to 32°C – 34°C in all unconscious adult patients with spontaneous circulation after resuscitation from out-of-hospital cardiac arrest.^{1–2} This recommendation is supported by two large prospective clinical studies from Australia and Europe, which demonstrated better neurologic outcomes if such patients underwent induced hypothermia.^{3–4}

Externally induced hypothermia is slow, requiring hours to reach moderate hypothermia.^{3–4} Various intra-arrest cooling techniques have been investigated to determine the feasibility of rapid hypothermia induction during VF cardiac arrest. Total liquid ventilation (TLV) with cold perfluorocarbons (PFCs) has been shown to rapidly decrease pulmonary arterial temperature to 33.8°C after only 4 minutes of liquid ventilation in an animal model of ventricular fibrillation arrest and resuscitation, and cold TLV animals had improved resumption of spontaneous circulation (ROSC) after CPR compared with a control group.⁵ In addition to rapid induction of hypothermia, TLV with PFCs may provide additional protective benefits in the setting of ischemia and production of reactive oxygen species. These include improved gas exchange, decreased ventilatory inflation pressures, matching the ventilation/perfusion ratio in the lungs, improving pulmonary blood flow, and decreasing the number of pulmonary inflammatory cells present which release inflammatory mediators during cellular injury.^{6–11}

Cold intravenous fluid is a simpler method used to rapidly induce hypothermia.^{12–15} When mild hypothermia was initiated early during CPR with cold saline, ROSC was more frequent and neurological outcomes improved.¹⁶ Kim et al.¹⁷ determined that hypothermia induction in patients just resuscitated from cardiac arrest could be initiated in the field even before arrival in an emergency department.

The aim of the current study was to compare two methods of rapid hypothermia induction – cold PFC TLV versus cold intravenous saline – during resuscitation in a large animal model of ventricular fibrillation cardiac arrest.

METHODS

Animal Preparation

The University of Iowa Animal Care and Use Committee reviewed and approved the animal preparation and experimental protocol for the investigation. Twenty-four female swine (22.7 ± 1.7 kg) were randomized into one of three groups: cold TLV (TLV), cold intravenous saline (S), or control (C). Both ketamine 20 mg/kg and acepromazine 0.2 mg/kg were used for induction of general anesthesia followed by inhalational 4% isoflurane via face mask. Animals were intubated with placement of a Sheridan/HVT[®] 7.0 French endotracheal tube (Hudson RCI[®], Temecula, CA USA) and mechanically ventilated (15 breaths/minute, tidal volume 10–15 cc/kg) with supplemental isoflurane (0.5–4.0%) and oxygen to maintain adequate anesthesia. Anesthesia was further augmented in all animals with pentobarbital 100 mg I.V. Additional intravenous pentobarbital (50 mg/hour) was used as needed. Animals were placed

over a warming blanket to maintain baseline temperature (36.5–38.0°C) during preparation for the experiment. A pulmonary artery (PA) catheter (Swan-Ganz thermodilution) was advanced to the PA through a venous access sheath. Arterial blood gas sampling was used to maintain physiologic partial pressure of oxygen (≥ 100 mmHg), carbon dioxide (35–45 mmHg), pH (7.35–7.45); mechanical ventilation was adjusted as necessary. Baseline and experimental temperatures (esophageal, pulmonary artery, and inferior vena cava thermistor catheters), arterial blood gas, heart rate, and right heart hemodynamics were recorded.

Initiation of VF and Resuscitation

Figure 1 provides a diagram of the study protocol. VF was induced by delivering 60 Hz alternating current, 4 ms pulse width, using a pacing catheter positioned in the right ventricle. VF was allowed to persist without support (no ventilation or CPR) for eleven minutes. After the 11 minutes of arrest, CPR was begun including chest compressions (100/minute), ventilation and oxygenation (10 breaths/minute, 5 L/minute supplemental 100% oxygen). At the beginning of CPR, intra-abdominal pressure was increased by an abdominal cuff, inflated to 20 mmHg. This technique has been shown in prior studies to improve CPP.¹⁸ Animals were defibrillated after 3 minutes of uninterrupted CPR using a commercially available truncated exponential biphasic waveform defibrillator (Philips Medical Systems, Andover, MA USA) and self adhesive pads positioned in the anterior/posterior location. An initial defibrillation shock of 100J was administered with an additional single 200J impulse delivered immediately if the initial shock failed to terminate VF. CPR was resumed, interrupted briefly each minute for less than 5 seconds to assess rhythm and pulse and deliver an additional 200J shock if a pulseless ventricular arrhythmia was present. The resuscitation protocol continued until resumption of spontaneous circulation (ROSC) (systolic arterial pressure ≥ 60 mmHg without pharmacologic support or chest compressions) or for a total attempt at resuscitation of 11 minutes. Intravenous epinephrine (1 mg) was administered at minutes 4, 7, and 10 for persistent ventricular arrhythmia or bradycardia. Atropine (0.4 mg) was given for bradycardia (HR < 60 bpm). During CPR the RA pressure was measured during the relaxation segment of chest compressions. Arterial blood gases were obtained at 2.5 and 6.5 minutes of CPR and NaHCO₃ was infused for pH < 7.20. Coronary perfusion pressure (CPP), arterial diastolic blood pressure minus RA pressure, was monitored continuously. Animals achieving ROSC were monitored for 60 minutes with previously described baseline parameters repeated at 10, 30, and 60 minutes of ROSC.

Cold Total Liquid Ventilation (TLV)

Animals in this group underwent the same protocol as described in the “Initiation of VF and Resuscitation” section. At 8 minutes of unsupported VF a ventilator system containing the PFC (Fluorinert™ FC-77, 3M, Saint Paul, MN USA) was connected to the endotracheal tube and TLV with cold PFCs was initiated at 6 breaths/minute with a tidal volume of 200–220 cc and maintained for 3 minutes. Prior to installation the cold PFCs were pre-cooled to –15°C. The liquid ventilation system consisted of a Harvard large animal respirator connected to a PFC reservoir submerged in an ice water bath. The system was a closed circuit in which PFC fluid was continuously circulated through the lungs and reservoir container. Suction could be applied to the reservoir to increase recovery of PFC from the lungs during exhalation in order to control ventilation pressure by modifying the amount of PFC circulating through the lungs. The lungs were not allowed to fill with PFC above the filling volume of 40 mL/kg. To minimize barotrauma during liquid ventilation, average maximum intra-tracheal pressure was kept close to normal air ventilation pressures by controlling intrapulmonary PFC volume via changes in ventilation rate and suction during exhalation. At 11 minutes of arrest (after 3 minutes of liquid ventilation) the TLV ventilator was stopped in the exhalation phase, the ET tube was unplugged and the liquid PFC allowed to drain using suction. The ET tube was reconnected to the standard air ventilator with the expiratory circuit connected to a reservoir to collect residual PFC

expelled during closed chest compression. The majority of the PFC fluid was expelled by the end of the first minute of CPR. As in the previous section, air ventilation was resumed at 11 minutes at the beginning of resuscitation.

Cold Intravenous Saline (S)

The animals in this group underwent the same protocol as described in the “Initiation of VF and Resuscitation” section. Eight animals were randomized to receive cold intravenous normal saline (0.9%, 30 mL/kg). A fluid pump (Cole-Palmer Instrument Company, Barrington, IL USA) was used to rapidly infuse cold saline into the central venous catheter within 3 minutes. The infusion was initiated at 8 minutes of VF and completed before onset of CPR in all animals.

Statistics

Baseline comparative measures were assessed using one-way analysis of variance (ANOVA) with the exception of weight and heart rate. A Kruskal-Wallis test was used for these values. Linear mixed model analysis for repeated measurements was used for arterial blood pH, pCO₂, CPP, and temperatures. We found that pO₂ was not normally distributed and therefore used a non-parametric Kruskal-Wallis test for arterial blood oxygen partial pressure measurements. Fischer’s exact test with Bonferroni adjustment was used to compare overall ROSC and a log-rank test for time to ROSC assessment. Total number of defibrillator shocks and shocks to termination of ventricular fibrillation were assessed by Kruskal-Wallis testing with Bonferroni adjustment. Linear mixed model analysis for repeated measures was used to test for differences in mean pressures (RA, intratracheal, and aortic diastolic) among the 3 groups over the 11 minutes of CPR. To compare group means between the groups at each time point, test of mean contrast based on the fitted model was performed with Bonferroni adjustment to account for the number of tests performed. Values are expressed as a mean $\pm$ standard deviation unless otherwise specified.

RESULTS

Baseline

A total of 24 swine were studied and randomized into 3 groups: control (C, n=8), cold intravenous saline (S, n=8), and cold total liquid ventilation (TLV, n=8). Compared to C animals, there were no differences in baseline heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), coronary perfusion pressure (CPP), pH, partial pressure of arterial oxygen (pO₂), and temperature (esophageal, pulmonary arterial, inferior vena caval). C weighed slightly more than TLV animals (23.7 ± 1.5 kg vs. 21.9 ± 1.4 kg, $p=0.03$). RA was lower in S compared to TLV (6 ± 2 mmHg vs. 9 ± 2 mmHg, $p=0.04$) but this difference did not translate into a difference in baseline CPP. Partial pressure of arterial carbon dioxide (pCO₂) was lower at baseline in C group vs. S (40 ± 3 mmHg vs. 43 ± 1 mmHg, $p<0.05$). Baseline characteristics are presented in Table 1.

Resumption of Spontaneous Circulation (Fig. 2)

Seven of 8 (88%) animals in the TLV arm achieved ROSC while 2 of 8 S (25%) and 1 of 8 (12%) C animals resumed spontaneous circulation ($p=0.03$ TLV vs. C, $p=0.12$ TLV vs. S, $p=1.0$ S vs. C). There were significant differences in the duration of CPR and defibrillation required to achieve ROSC between the groups: after 5 minutes CPR, 1 of 8 (25%) of TLV animals versus 0% of C and S animals achieved ROSC. After 8 minutes, 4 of 8 (50%) of TLV achieved ROSC versus only 1 of 8 (12%) in C and S groups. The intergroup differences are significant at both time points (TLV vs. C $p=0.02$, TLV vs. S $p=0.04$, C vs. S $p=NS$). Thus, cold TLV yielded higher and earlier ROSC during CPR than cold IV saline.

Temperature (Fig. 3)

As expected, the rapid infusion of cold IV saline between minutes 8 and 11 of VF resulted in a pronounced but transient fall in PA temperature to $19 \pm 3.9^\circ\text{C}$ at the 11 minute measurement. After one minute of CPR PA temperature was $32.2 \pm 0.6^\circ\text{C}$ in S animals, $34.8 \pm 0.5^\circ\text{C}$ in TLV animals, and remained normothermic at $37.2 \pm 0.2^\circ\text{C}$ in C animals (S or TLV vs. C $p < 0.0001$, S vs. TLV $p < 0.0001$). Temperatures during the entire 11 minutes of resuscitation remained lowest in S animals and highest in C (S vs. TLV or C $p < 0.05$, TLV vs. C $p < 0.05$). The smallest temperature difference was observed at 11 minutes of CPR with C $37.0 \pm 0.2^\circ\text{C}$, TLV $35.8 \pm 0.4^\circ\text{C}$, and S $34.9 \pm 0.4^\circ\text{C}$ ($p < 0.05$ for all comparisons). In summary, PA temperature rapidly reached a significant difference between both hypothermia groups and control after only minute of CPR and this difference was maintained throughout the entire CPR period. Esophageal temperature decreased rapidly after 1 minute of CPR from 36.9°C to 28.6°C in TLV, from 37.1°C to 32.0°C in S, and remained unchanged in C. At 11 minutes of CPR esophageal temperature was TLV 35.6°C , S 36.1°C , and C 36.8°C (TLV or S vs. C $p < 0.05$). IVC temperatures were similar to PA temperature (data not shown).

Arterial Blood Gas

Arterial pO_2 at 2.5 minutes was higher in the TLV group compared with S ($71 \pm \text{SEM } 5 \text{ mmHg}$ vs. $47 \pm 3 \text{ mmHg}$, $p = 0.01$) without a difference between TLV and C ($p = 0.36$) or C and S ($p > 0.99$). By 6.5 minutes of CPR the differences between TLV and S were no longer significant ($84 \pm \text{SEM } 15 \text{ mmHg}$ vs. $55 \pm 5 \text{ mmHg}$, $p = 0.26$). pH was not different between groups at any time interval during resuscitation.

Defibrillation

There were no differences in the number of defibrillation shocks required to terminate VF in TLV animals compared to S and C (median shocks for termination of VF TLV=1, S=2, C=2, $p = \text{NS}$). No difference was seen in the number of shocks required to terminate re-fibrillation after initial termination (median number of additional shocks TLV=0.5, S=0, C=1.5, $p = \text{NS}$).

Coronary Perfusion Pressure (Fig. 4)

Linear mixed model analysis for repeated measures showed that the difference in mean coronary perfusion pressure (CPP) within the groups did not significantly vary over time (group time interaction $p = 0.81$). Across all time points there was a trend ($p = 0.06$) for the mean CPP to be higher by 5.5 mmHg in the TLV group compared to the S group. The mean coronary perfusion pressure in the C group did not significantly differ from either the TLV ($p = 0.13$) or the S groups ($p = 0.88$). There was a significant difference in CPP when data from the first 3 minutes of CPR are isolated from the remainder of the resuscitation period. This reflects the time before which defibrillation had been attempted. During these first 3 minutes the mean CPP was higher in TLV compared to S ($14 \pm \text{SEM } 1 \text{ mmHg}$ vs. $8 \pm 1 \text{ mmHg}$, $p < 0.01$).

There were no differences between the 3 groups in aortic diastolic pressure during the CPR period to account for the changes observed in coronary perfusion. However, right atrial pressure was lower at 1 minute of CPR in the TLV group compared to S animals (TLV $10 \pm \text{SEM } 1 \text{ mmHg}$, S $16 \pm 1 \text{ mmHg}$, C $15 \pm 1 \text{ mmHg}$, $p = 0.02$ TLV vs. S) (Figure 5).

Intratracheal pressure

There was a significant difference in inspiratory intratracheal pressure after 3 minutes of CPR between TLV and S animals with an inspiratory pressure of $16 \pm \text{SEM } 1 \text{ mmHg}$ in TLV and $22 \pm 1 \text{ mmHg}$ in S ($p < 0.05$). TLV intratracheal pressures were significantly lower than both C and S at 6, 8, and 11 minutes and significantly lower than S at 11 minutes of CPR.

Post resuscitation

No animals initially resuscitated died during the post resuscitation period (60 minutes). There were no differences in hemodynamic and arterial blood gas parameters between the 3 groups, but there were only 2 survivors in the S group and 1 survivor in the C group.

DISCUSSION

Boddicker et al.¹⁹ demonstrated that animals rendered hypothermic by external cooling before cardiac arrest was induced showed a higher ROSC rate than normothermic animals, but external cooling is very slow. In the current study, hypothermia was rapidly achieved with cold IV saline or cold total liquid ventilation with perfluorocarbons during resuscitation from VF arrest. Although IV saline achieved a lower pulmonary artery temperature, only TLV improved resuscitation outcome compared to a control group. To our knowledge this is the first study comparing these 2 techniques for rapid hypothermia induction during resuscitation. The study indicates that the *method* by which hypothermia is accomplished may have effects on ROSC.

The higher ROSC of the TLV group may be due in part to differences in CPP (aortic diastolic blood pressure – right atrial pressure during the relaxation phase of closed chest compression) in TLV compared to S in our study of CPR. During the entire CPR period there was a trend towards higher CPP in the TLV group compared to S with a near-significant p value of 0.06. In the first 3 minutes of uninterrupted CPR there was a statistically significant difference in CPP, $14 \pm \text{SEM } 1 \text{ mmHg}$ in TLV versus $8 \pm 1 \text{ mmHg}$ in control animals. The CPP differences in TLV vs. S animals are a result of the expected effect of rapid IV saline infusion to raise RA pressure and thereby decrease CPP in saline animals; the aortic diastolic pressures during chest compressions were similar in the TLV and S groups.

Staffey et al.⁵ also studied intrapulmonary instillation of cold perfluorocarbons to induce hypothermia during cardiac arrest and resuscitation in a swine model. In contrast to our method of total liquid ventilation, they used static intrapulmonary instillation of the PFC's without active ventilation; the PFC's were expelled when chest compressions were initiated. They found a ROSC rate of 82% in the hypothermic animals, similar to our 88% ROSC rate. Arterial oxygenation was also higher in animals receiving cold PFCs than in a control group not receiving intrapulmonary PFCs.

Ditchey et al.²⁰ investigated the effects of volume loading on perfusion during closed-chest resuscitation after electrically induced VF. Coronary blood flow during CPR decreased after volume loading with 1 liter of intravenous 0.9% saline despite an increase in total forward blood flow.¹⁹ In addition, RA pressure increased after the saline infusion (peak RA pressure $41 \pm 4 \text{ mmHg}$ in control versus $50 \pm 4 \text{ mmHg}$ with saline, $p < 0.05$). This study demonstrated dissociation between total forward blood flow and coronary perfusion during CPR; the deleterious effect of volume loading on RA pressure and CPR that we found is consistent with the observations of Ditchey et al.²⁰ Nordmark and Rubertsson¹⁴ also noted a substantial rise in RA pressure with volume loading during CPR. More recently, Yannopoulos et al.²¹ reported decreased coronary perfusion pressure in an animal model of ischemic cardiac arrest, coronary artery occlusion, CPR and rapid saline infusion.

Intratracheal pressures in our study were lower in TLV. TLV, which has been shown to prevent atelectasis, may improve pulmonary compliance, and when open, compliant airways are ventilated the pressure is lower. The lower intratracheal and RA pressures in TLV animals improve right heart venous return and may improve cardiac output. Furthermore, in our study TLV animals had higher arterial blood pO_2 after 2.5 minutes of CPR compared to S, due to the preoxygenation of the PFCs. Higher arterial blood oxygenation in addition to the PFC-induced hypothermia and improved CPP may contribute to an increase in ROSC.

Hypothermia induced during coronary occlusion to produce myocardial infarction has been recently evaluated by other investigators. Tissier et al.²² used cold TLV during coronary artery occlusion in an open-chest rabbit model. Animals that received cold TLV had a pronounced decrease in mean myocardial infarct size compared to air ventilated and warm TLV ventilated animals. Otake et al.²³ investigated catheter based transcatheter myocardial hypothermia and the effects on myocyte necrosis in pigs during experimental myocardial infarction. After 15 minutes of left anterior descending (LAD) artery balloon occlusion, animals were given intracoronary saline at either 4°C or 36.5°C for 60 minutes. After 60 minutes of ischemia balloons were deflated with reperfusion of the ischemic myocardium for 180 additional minutes. Myocardial temperature decreased by 3.2°C in hypothermic animals. Myocardial necrosis and oxidative stress was most pronounced in the normothermic group: Troponin T increased by 2.83 ng/mL, while hypothermic animals had an increase in troponin T of only 0.84 ng/mL ($p=0.037$ vs. control). Thus, hypothermia appears to ameliorate some of the deleterious effects of tissue ischemia.

Limitations

Since the saline and TLV groups were not cooled exactly to the same extent, it is conceivable that the different survival rates in the two groups may be in part related to the differences in the degree of cooling achieved. It is possible that the saline group was “over-cooled” which might have deleterious effects on ROSC.

In previous studies using pulmonary instillation of perfluorocarbons in swine, we noted that pulmonary inflammation and edema developed beginning about 1–2 hours after ROSC. This has been discussed in detail by Staffey et al.⁵ Briefly, it appears that this is a species-specific response. Swine have extensive pulmonary intravascular macrophages, which results in high pulmonary localization of circulating particles due to phagocytosis by the macrophages, with release of inflammatory mediators.^{24,25} In other species, such as rabbits, the concentration of pulmonary intravascular macrophages is less and the animals tolerate perfluorocarbon instillation well, as demonstrated by Tissier et al.²¹ In fact, Yang et al.²⁶ showed that cold perfluorochemical-induced hypothermia protects lung integrity in rabbits.

In conclusion, in this animal model hypothermia induced using total liquid ventilation with cold perfluorocarbons improved resuscitation outcomes compared to control, whereas cold IV saline did not. TLV changed hemodynamics and pulmonary function and probably improved coronary perfusion to the arrested, hypoxic myocardium. Finally, the high O₂ carrying capacity of perfluorocarbons is reflected in higher pO₂. Thus, although induced hypothermia may be beneficial during resuscitation from cardiac arrest, the means by which hypothermia is accomplished may affect ROSC.

Acknowledgments

Supported in part by NHLBI grant #5 R01 HL71676-04. No assistance was used in the writing of this manuscript.

Abbreviations

TLV	total liquid ventilation
PFC	perfluorocarbons
VF	ventricular fibrillation

CPR	cardiopulmonary resuscitation
ROSC	resumption of spontaneous circulation
PA	pulmonary artery
CPP	coronary perfusion pressure
HR	heart rate
MAP	mean arterial pressure
CO	cardiac output
MPAP	mean pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
CPP	coronary perfusion pressure

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Figure 1.

Experimental design. VF = ventricular fibrillation. CPR = cardiopulmonary resuscitation. TLV = total liquid ventilation. S = saline. ROSC = resumption of spontaneous circulation.

Figure 2.
Animals achieving resumption of spontaneous circulation (ROSC).

Figure 3.
Mean pulmonary arterial temperatures during CPR. PA = pulmonary artery.

Figure 4.
Coronary perfusion pressures during CPR (mean $\pm$ SEM).

Figure 5. Right atrial pressures during CPR (mean $\pm$ SEM). Values are measured during the relaxation phase of external chest compression.

Table 1

Baseline animal, hemodynamic, and temperature data

	Saline (S) N = 8	TLV N = 8	Control (C) N = 8	
Weight (kg)	22.3±1.7	21.9±1.4	23.7±1.5*	*p<0.05 TLV vs. C
MAP (mmHg)	61±2	65±2	60±1	
HR (bpm)	128±12	108±4	111±4	
RA (mmHg)	6±2	9±2*	7±1	*p<0.05 S vs. TLV
CO (L/min)	3.8±0.2	3.8±0.2	4.1±0.2	
CPP (mmHg)	44±3	44±2	41±2	
MPAP (mmHg)	16±1	16±1	15±1	
PCWP (mmHg)	8±3	7±3	7±1	
PA Temp (°C)	37.2±0.1	37.1±0.1	37.1±0.1	
pH	7.42±0.04	7.43±0.01	7.41±0.04	
pO ₂ (mmHg)	142±28	160±24	141±19	
pCO ₂ (mmHg)	43±1	42±2	40±3*	*p<0.05 C vs. S

Abbreviations: MAP = mean arterial pressure. HR = heart rate. RA = right atrial pressure. CO = cardiac output. CPP = coronary perfusion pressure. MPAP = mean pulmonary artery pressure. PCWP = pulmonary capillary wedge pressure. PA = pulmonary artery.