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Mild Hypothermia Reduces Acute Mortality and Improves Hemodynamic Outcome in a Cardiogenic Shock Pig Model

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Short title: Hypothermia reduces mortality in cardiogenic shock

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Abstract

INTRODUCTION: Cardiogenic shock is the main cause of death in patients hospitalized due to an acute myocardial infarction. Mild hypothermia reduces metabolism and could offer protective effects for this condition. The aim of our study was to investigate if mild therapeutic hypothermia would improve outcome and hemodynamic parameters in an ischemic cardiogenic shock pig model.

METHODS: Twenty five pigs (40-50kg) were anesthetized and a normothermic temperature of 38° C was established utilising an endovascular cooling catheter in a closed chest model. A Swan-Ganz catheter was placed in the pulmonary artery. Hemodynamic parameters were continuously monitored and blood gases were sampled every 30 min. Ischemia was induced by inflation of a PCI balloon in proximal LAD for 40 min. 16 pigs who fulfilled predefined shock criteria were randomized to hypothermia (n=8), or normothermia (n=8). Hypothermia (33° C) was induced after onset of reperfusion by using an endovascular temperature modulating catheter and was maintained until termination of the experiment.

RESULTS The pigs in the hypothermia group were cooled to $<34^{o}$ C in approximately 45 min. 5/8 pigs in the normothermia group died while all pigs in the hypothermia group survived (p<0.01). Stroke volume and blood pressure were significantly higher in the hypothermia group (p<0.05), whereas heart rate was significantly lower in the hypothermia group (p=0.01). Cardiac output did not differ among the groups (p =0.13). Blood gas analysis revealed higher mixed venous oxygen saturation, pH, and base excess in the hypothermia group indicating less development of metabolic acidosis (p<0.05).

CONCLUSIONS: In this pig model, mild therapeutic hypothermia reduces acute mortality in cardiogenic shock, improves hemodynamic parameters and reduces metabolic acidosis. These findings suggest a possible clinical benefit of therapeutic hypothermia for patients with acute cardiogenic shock.

Key words:

Hypothermia, Myocardial infarction, Cardiogenic shock

Abbreviations

LAD   Left anterior descending artery

PCI   Percutaneous coronary intervention

CS   Cardiogenic shock

Introduction

Cardiogenic shock is a major complication to acute myocardial infarction. The condition occurs in 7-10% of patients hospitalized due to myocardial infarction and is the main cause of death among these patients.[1] The mortality rate despite early revascularization and circulatory support still remains around 50 %.[2] The condition is considered to be caused by an inability of the heart to maintain an adequate tissue perfusion. The result is hypotension with metabolic acidosis and often a fatal outcome. Hypothermia has shown to offer tissue protection in myocardial ischemia, and preclinical studies have shown beneficial results in reducing infarct size in experimentally induced myocardial infarction if hypothermia is induced before reperfusion.[3-5] The mechanisms of local tissue protection are not completely understood but are believed to be a combination of slower metabolism, reduced myocardial demand, increased ATP preservation and a reduction in apoptosis.[6] In contrast, hypothermia induced after reperfusion has no effect on infarct size.[3, 7] Mild hypothermia (32-34ºC) has also in experimental studies shown to have a neutral or even positive effect on myocardial contractility[8-10]. Applying hypothermia as an adjunctive treatment in patients with cardiogenic shock could thus be a desirable option since hypothermia theoretically could decrease

peripheral tissue oxygen demand while preserving or increasing cardiac function. The hypothesis of this study was that endovascular hypothermia would improve acute outcome and hemodynamic parameters in cardiogenic shock even when induced after reperfusion. A randomized study in a closed-chest porcine model with experimentally induced cardiogenic shock due to a large myocardial infarction was used in order to test the hypothesis.

Materials and methods

Ethics

The study conforms to the Guide for the Care and Use of Laboratory Animals, US National Institute of Health (NIH Publication No. 85-23, revised 1996) and was approved by the local animal research ethics committee.

Experimental preparation

Twenty-five healthy domestic male and female 40-50 kg pigs were fasted overnight with free access to water and were premedicated with Ketaminol (Ketamine, Intervet, Danderyd, Sweden), 100mg/ml, 1,5ml/10kg, and Rompun (Xylazin, Bayer AG, Leverkusen, Germany), 20mg/ml, 1ml/10kg intramuscularly 30 min before the procedure. After induction of anesthesia with thiopental 12.5 mg/kg (Pentothal, Abbott, Stockholm, Sweden), the animals were orally intubated with cuffed endotracheal tubes. A slow infusion of 1 μl/ml fentanyl (Fentanyl, Pharmalink AB, Stockholm, Sweden) in buffered glucose (25 mg/ml) was started at a rate of 2 ml/min and adjusted as needed. During balanced anaesthesia, thiopental (Pentothal, Abbott, Stockholm, Sweden) was titrated against animal requirements with small bolus doses. Mechanical ventilation was established with a Siemens-Elema 900B ventilator in the volume-controlled mode, adjusted in order to obtain normocapnia (temperature corrected pCO_2: 5.0-6.0 kPa). The animals were ventilated with a mixture of nitrous oxide (70%) and oxygen (30%). Blood gases were analyzed every 30 minutes throughout the experiment in an

automated bench top analyzer (Radiometer Medical ApS, Brønshsøj, Denmark). The blood gas values were corrected for core body temperature at the time the samples were withdrawn from the animals. The pigs were monitored by electrocardiography (ECG) and defibrillations were performed using a Lifepak™ 12 (Medtronic Co., Minneapolis, MN, USA). Heparin (200 IU/kg) was given intravenously at the start of the catheterization. A 12 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left femoral vein. A 0.021-inch guide wire (Safe-T-J Curved™, Cook Medical Inc, Bloomington, IN, USA) was inserted into the inferior vena cava through the introducer. Using the guide wire, a 10.7 F Celsius Control™ catheter (Innercool Therapies Inc, San Diego, CA, USA) was placed into the inferior vena cava with the tip of the catheter at the level of the diaphragm. Body temperature was measured using a temperature probe (TYCO Healthcare Norden AB, Solna, Sweden) placed in the distal part of the esophagus. The catheter and the temperature probe were connected to the Celsius Control and the system was set to maintain a normal pig body temperature of 38.0° C. A 6 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed left carotid artery upon which a 6 F FL4 Wiseguide™ (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the left main coronary artery. The catheter was used to place a 0.014-inch PT Choice™ guide wire (Boston Scientific Scimed, Maple Grove, MN, USA) into the distal LAD. A 3.0-3.5 x 20 mm Maverick monorail™ angioplasty balloon (Boston Scientific Scimed, Maple Grove, MN, USA) was positioned in the proximal LAD. A 9 F introducer sheath (Boston Scientific Scimed, Maple Grove, MN, USA) was inserted into the surgically exposed right jugular vein. A 7.5 F Continuous Cardiac Output Pulmonary Artery Catheter™ (Edwards Lifesciences, Irvine, CA, USA) was inserted into a pulmonary artery. Cardiac Output was continuously recorded using a Vigilance™ monitor (Edwards Lifesciences, Irvine, CA, USA). Arterial blood pressure, pulmonary artery pressure, capillary wedge

pressure and central venous pressure were continuously measured using separate transducers (ADInstruments Inc, Colorado Springs, CO, USA). Hemodynamic parameters were digitally recorded using Chart v4.2 (ADInstruments Inc, Colorado Springs, CO, USA). The procedures were performed in an experimental catheterization laboratory (Shimadzu Corp., Kyoto, Japan).

Protocol

After a stable core body temperature of 38.0° C was achieved, ischemia was induced by inflation of the angioplasty balloon in the proximal LAD for 40 min. An angiogram was performed after inflation of the balloon and before deflation of the balloon in order to verify total occlusion of the LAD and correct balloon positioning. After deflation of the balloon a subsequent angiogram was performed to verify restoration of blood flow in the previously occluded artery. The animals were included in the study if they fulfilled our prespecified criterion of a high risk of developing sustained cardiogenic shock (<90 mm Hg for at least 15 min) immediately before reperfusion. If the animal fulfilled this criteria, it was randomized to hypothermia (n=8) or to normothermia (n=8), by drawing folded notes which read "cool" or "warm" out of a box (Figure 1a). Hypothermia was then induced after reperfusion and maintained by using the Celsius Control^{TM} endovascular cooling system. After reaching the target temperature of 33° C, hypothermia was maintained throughout the experiment. In the normothermia group, the endovascular catheter was used to maintain a normal pig body temperature of 38° C. After 4 hours the experiment ended and surviving pigs were sacrificed. Pigs that died during ischemia or did not meet the criterion for cardiogenic shock (< 90 mm Hg during at least 15 minutes) before randomization were excluded from the study. In order to exclude any positive effects on volume-loading, cold fluids during the experiment were excluded from the hypothermia protocol. No additional fluids in either group were permitted except for administration of anaesthetic drugs.

Calculation and statistics

Calculations and statistics were performed using the GraphPad Prism 4.0 software (GraphPad Software Inc., La Jolla, CA, USA). Significance for survival was tested using the Fischer's exact test. In order to test significance for hemodynamic and blood gas variables in a conservative manner, the mean value of the tested variable was calculated from the time of randomization (at 40 min) until the end of experiment (4h) in the respective groups. Mann-Whitney's test was then performed to test for any difference in mean values. Statistical significance was accepted when $p < 0.05$.

Results

A total of 25 pigs were studied. Five pigs died during ischemia before randomization due to intractable ventricular fibrillation or pulseless electrical activity despite repeated resuscitation attempts and where excluded from the study. Four pigs were excluded due to failure to meet the criterion for cardiogenic shock. Hemodynamic values before randomization are shown in table 1. There was no difference between the groups at the time of randomization.

Arrhythmias

The occurrence of ventricular tachycardia/fibrillation during ischemia and at the onset of reperfusion was recorded. VT/VF occurred in 4/8 pigs in the hypothermia group and in 5/8 pigs in the normothermia group, and were defibrillated during manual compressions. No pigs died from intractable arrhythmias after randomization. Mean time to spontaneous circulation was 123 ± 99 seconds (hypothermia) vs. 76 ± 41 seconds (normothermia), p=0.70.

Temperature measurements

Measurements of core body temperature during the experiment are shown in figure 1b. At the time of initiation of ischemia and at reperfusion there was no difference in temperature among the groups. At the time of reperfusion, hypothermia was induced by the endovascular catheter.

45 minutes after initiation of hypothermia, the mean temperature in the hypothermia group was $33.6 \pm 0.7°$ C. The mean cooling rate in the study was $5.9°$ C/hr.

Survival

From the time of reperfusion until the end of experiment, 5/8 pigs in the normothermia group died due to circulatory failure while none of the pigs in the hypothermic group died (p=0.025). (Figure 2) The pigs in the normothermia group died due to circulatory failure at a mean time of 1h 53 ± 38 minutes after onset of reperfusion. No pigs included in the study died due to arrhythmias.

Hemodynamic and blood gas measurements

Outcome of hemodynamic and blood gas variables are shown in table 2. Heart rate and mean arterial pressure were continuously recorded. Furthermore, using a Swan-Ganz-catheter, recordings of hemodynamic parameters were performed. Hypothermia resulted in an increase in mean arterial pressure and stroke volume in the hypothermia group compared to normothermia (Figure 3a-b). Heart rate in the hypothermia group was lower and with less variability compared to normothermia (Figure 3c). Cardiac output did not differ among the groups (Figure 3d). Furthermore, central venous pressure and pulmonary capillary wedge pressure did not differ among the groups (Figure 3e-f). Systemic vascular resistance was higher in the hypothermia group, whereas mean pulmonary artery pressure and pulmonary vascular resistance did not differ among the groups (Figure 3g-i).

Arterial blood-gas samples and mixed venous saturation were recorded every 30 minutes. Mixed venous saturation was higher in the hypothermia group indicating lower peripheral oxygen consumption (Figure 4a). Arterial pH was significantly higher in the hypothermia groug (Figure 4b). PO_2 did not differ among the groups (Figure 4c). Furthermore, pCO_2 was lower in the hypothermia group (Figure 4d). PCO_2 often became deranged in the

normothermic pigs prior to death due to circulatory failure affecting gas exchange in the lungs. This is reflected in the large variations in pCO_2 seen. Finally, base excess was negative and significantly lower in the normothermia group indicating less development of metabolic acidosis in the hypothermia group (Figure 4e).

Discussion

This study demonstrates that mild therapeutic hypothermia in cardiogenic shock reduces acute mortality in a porcine model. Hypothermia also improved blood pressure and increased myocardial contractility. Furthermore, a decrease in peripheral oxygen consumption with an increase in mixed venous saturation and an improved metabolic balance was seen.

Hypothermia protocol

Previous studies have demonstrated that endovascular cooling alone achieves a significant reduction in core body temperature in approximately 45 min.[4, 11-13] In a previous experimental study, utilising a combination of an infusion of cold saline together with an endovascular catheter caused a reduction in core body temperature to <35° C in five minutes.[3] A quicker reduction in core body temperature could thus have been achieved and could potentially have been more beneficial, though for the purpose of avoiding a volume loading effect bias with an infusion of cold saline, endovascular cooling alone was used for the current study.

Infarct size

The ability of hypothermia to reduce infarct size during ischemia has been demonstrated in several experimental studies.[3, 4, 7, 14-17] Furthermore, previous experimental studies demonstrate that induction of hypothermia after onset of reperfusion does not reduce infarct size.[3, 7] It is however unclear whether a significant reduction in infarct size would have any positive hemodynamic effects immediately after the onset of reperfusion. In order to exclude any possible bias from a reduction in infarct size in this study, hypothermia was induced after onset of reperfusion.

Hemodynamic effects of hypothermia

Previous experimental studies have demonstrated that mild hypothermia increases myocardial contractility in excised heart preparations as well as in the in situ heart. [8-10] The increase in contractility is considered to be mediated by an increased myofilament sensitivity to existing Ca^{2+}.[8] The positive inotropic effects however do not seem to be associated with a corresponding increase in myocardial oxygen consumption.[9, 10] In the *in vivo* heart, Weisser et al also found an increase in stroke volume and cardiac output when applying mild hypothermia to healthy anesthetized pigs. [8] In another experimental porcine study, Dae et al found an increase in stroke volume but with unchanged cardiac output when inducing mild hypothermia during myocardial ischemia.[4]

In the current study, a significant decrease in heart rate with a concomitant increase in stroke volume but with an unchanged cardiac output was seen. Hypothermia also caused an increase in systemic vascular resistance. This is a known phenomenon caused by increased peripheral vasoconstriction. Nishimura and co-workers observed that this effect in an experimental model could reduce cardiac output.[10] However, the reduction in cardiac output was diminished when vasodilators were administered together with hypothermia.[10] In our study, an unaltered cardiac output was seen despite higher systemic vascular resistance. Note that the Vigilance monitor could not accurately calculate a cardiac output <1L/min. In the normothermia group prior to death due to circulatory failure, CO was <1L/min. During statistical analysis, CO was set to 1L/min. A possible overestimation of cardiac output in the normothermia group could thus explain the lack of difference in cardiac output between the groups. The increase in vascular resistance may explain the observed increase in mean arterial pressure in the hypothermia group. Increasing afterload may have negative effect on the failing heart but it may also be beneficial since it also increases the arterial pressure and thus perfusion to the heart and peripheral tissues. Furthermore, the reduced heart rate combined

with increased stroke volume observed could be beneficial in cardiogenic shock since the effect is mediated through a prolonged contraction and relaxation time without an increase in oxygen consumption. In the ischemic heart, a lower heart rate could result in improved tissue perfusion in the heart.

Metabolic effects of hypothermia

Hypothermia decreases metabolic rate by approximately 8 % per $1°$ C drop in core body temperature. A small study has previously described a significant reduction in oxygen consumption when applying therapeutic hypothermia to critically ill febrile patients. [18] A low mixed venous saturation is also a heavy predictor for mortality in patients who experienced acute heart failure after myocardial infarction.[19] In our study, hypothermia treatment resulted in a significantly higher mixed venous saturation. The finding also correlates with the lower pH and base excess seen in the normothermia group. The pigs in the hypothermia group did not develop progressive metabolic acidosis despite similar cardiac output. One explanation to the observed results could be that hypothermia lowered the peripheral oxygen demand which resulted in less tissue hypoxia and no development of metabolic acidosis. This may explain the significant difference in acute mortality between the two groups. There was also a trend towards increased pO_2, and pCO_2 was significantly lower in the hypothermia group. When hypothermia was induced, in order to keep pCO_2 within normal levels, ventilation had to be systematically reduced by approximately 30-40% reflecting the decrease in metabolism and oxygen demand.

There is an unbalance between cardiac work and metabolic requirements in cardiogenic shock. Our results indicate that hypothermia improves survival via restoration of this balance by reducing metabolic requirements and at the same time maintaining cardiac output. Increased blood pressure and prolonged diastolic phase due to a reduction in heart rate probably contributes to survival by improving coronary perfusion.

Clinical application

In two retrospective studies with patients presenting with cardiogenic shock after resuscitation due to cardiac arrest, hypothermia did not adversely affect the expected outcome.[20, 21] Furthermore, two small observational studies in which hypothermia was applied to patients with severe circulatory failure after cardiac surgery resulted in stabilization of circulation with an unchanged or increased cardiac output, an increase in mixed venous O_2 saturation and urine output.[22, 23] Additionally, a significant decrease in tissue oxygen consumption was seen. Thus, some promising clinical experience of hypothermia in cardiogenic shock does exist. The current experimental study provides further evidence of the beneficial effects of hypothermia in stabilizing the circulation and improving outcome. Hypothermia could potentially offer an adjunctive therapy in this group of patients with high mortality rates.

Limitations

To counteract hypothermia, the body starts to shiver. The process of shivering causes an increase in metabolic rate, heart rate and myocardial oxygen consumption.[24] It is therefore likely that shivering would attenuate the beneficial effects of hypothermia and it must be managed properly in order not to worsen the condition. In order to prevent hemodynamic effects from volume loading, the use of intravenous fluids were restricted in both groups. In the clinical setting in cardiogenic shock, fluid restriction may have negative effects on renal function. In an interpretation of the results of this study to the clinic setting, the limitation with regards to fluid restriction needs to be considered. Furthermore, the study was terminated after four hours and it is not known if the beneficial effects of hypothermia extend beyond this short time span.

Conclusions

Mild therapeutic hypothermia improves survival, stabilizes circulation and improves metabolic balance in cardiogenic shock. The possibility of utilising hypothermia as an adjunctive treatment in cardiogenic shock needs to be explored further.

Acknowledgements

Conflicts of interest

The authors do not have any conflicts of interest.

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Figures

Figure 1

a) Hypothermia was induced by using an endovascular cooling catheter after 40 min of ischemia, and after onset of reperfusion in order to exclude any beneficial effects of hypothermia in reduction of infarct size. Target temperature was 33.0° C and the temperature was maintained throughout the duration of the experiment. The normothermia group was maintained at a temperature of 38.0° C.

b) Core body temperature in the two groups. The dotted line illustrates the time of randomization and initiation of hypothermia. 45 minutes after initiation of hypothermia, the average temperature in the hypothermia group was 33.6° C.

Figure 2

Kaplan-Meier curve displaying the outcome among the groups. Approximately 150 min after onset of reperfusion, 5/8 pigs in the normothermia group had died due to circulatory failure while none of the pigs in the hypothermia group died during the experiment (p=0.025)

Figure 3

The dotted line illustrates the time of randomization. Data are expressed as mean ± S.E.M. Please note that in the normothermia group, only three pigs survived beyond 190 min. Mean values in the normothermia group beyond this time point should be interpreted with caution.

a) Mean arterial pressure was significantly higher in the hypothermia group (p<0.01).

b) Stroke volume was significantly higher in the hypothermia group (p<0.001).

c) Heart rate was significantly lower with less variability in the hypothermia group (p=0.01).

d) Cardiac output did not differ among the groups (p=0.13).

e) Central venous pressure did not differ among the groups (p=0.19).

f) Pulmonary capillary wedge pressure did not differ among the groups (p=0.10).

g) Mean pulmonary artery pressure did not differ among the groups (p=0.29).

h) Systemic vascular resistance was significantly higher in the hypothermia group (p<0.05).

i) Pulmonary vascular resistance did not differ among the groups (p=0.50).

Figure 4

The dotted line illustrates the time of randomization. Data are expressed as mean ± S.E.M. Please note that in the normothermia group, only three pigs survived beyond 190 min. Mean values in the normothermia group beyond this time point should be interpreted with caution.

a) Mixed venous saturation was significantly higher in the hypothermia group indicating lower metabolic demand in peripheral tissue (p<0.01).

b) Arterial pH was significantly lower, indicating no development of metabolic acidosis in the hypothermia group (p<0.001).

c) PO_2 did not differ among the groups (p=0.06)

d) PCO_2 was significantly lower in the hypothermia group indicating less oxygen demand (p=0.04).

e) Base excess was significantly lower in the normothermia group indicating development of metabolic acidosis due to the cardiogenic shock (p<0.01).

Table 1

Mean hemodynamic values before randomization are displayed.

Table 2

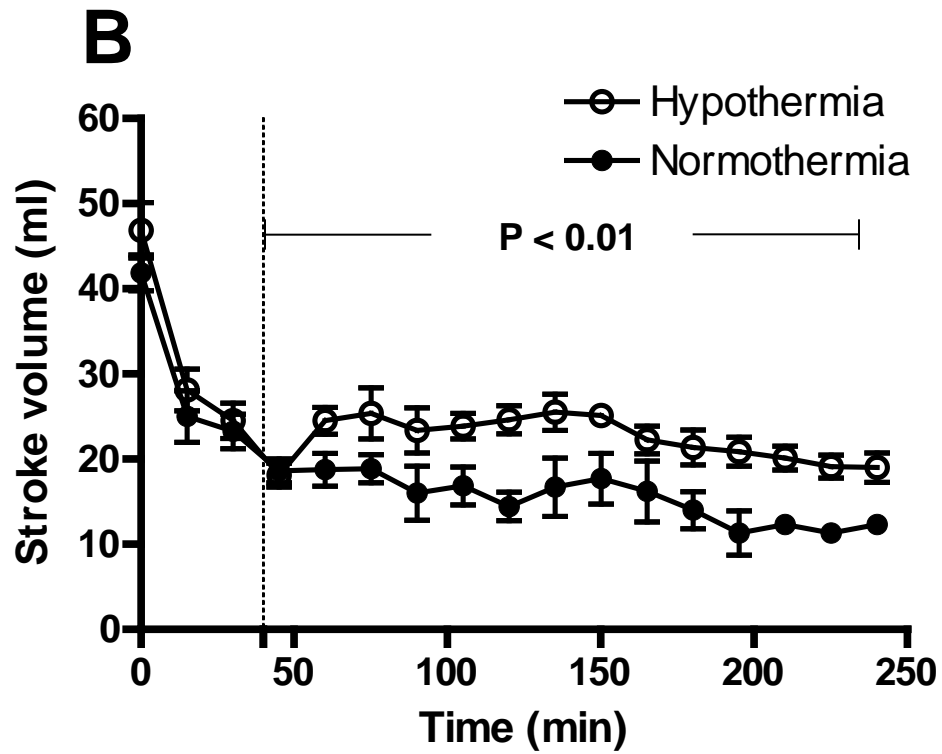The calculated mean value of the variables from the time of randomization until the end of experiment are displayed.
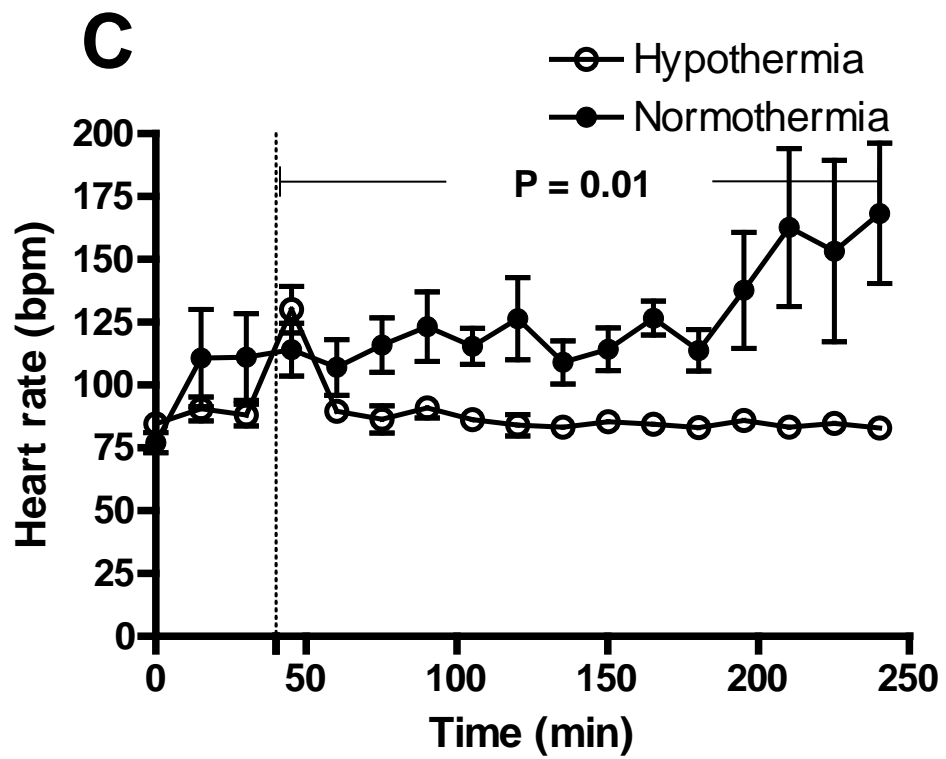
A

Normothermia

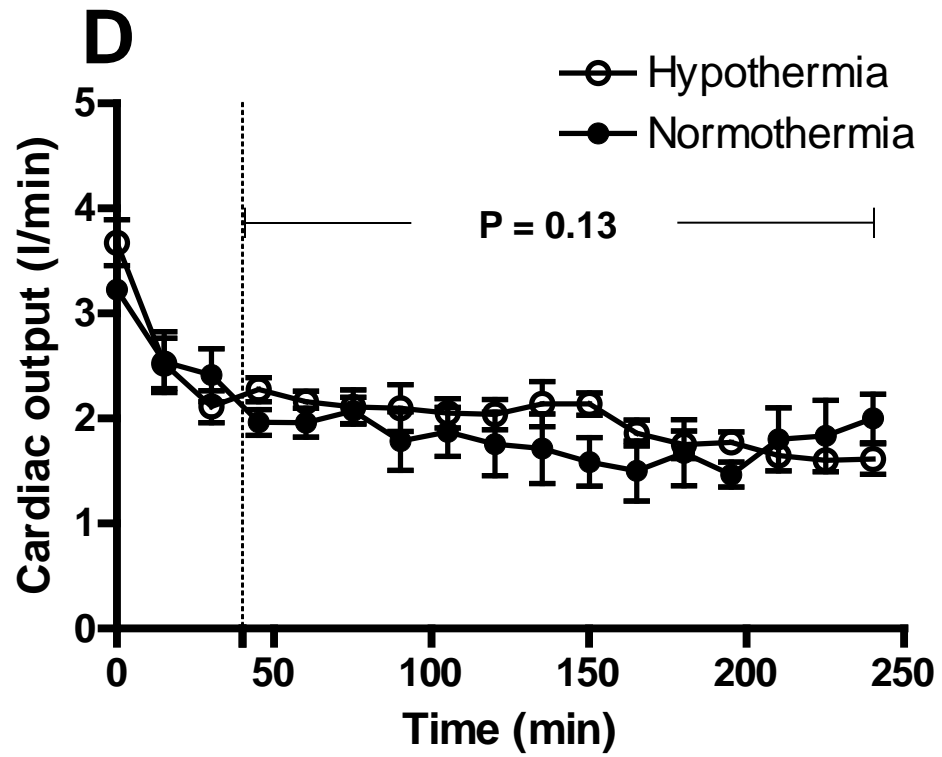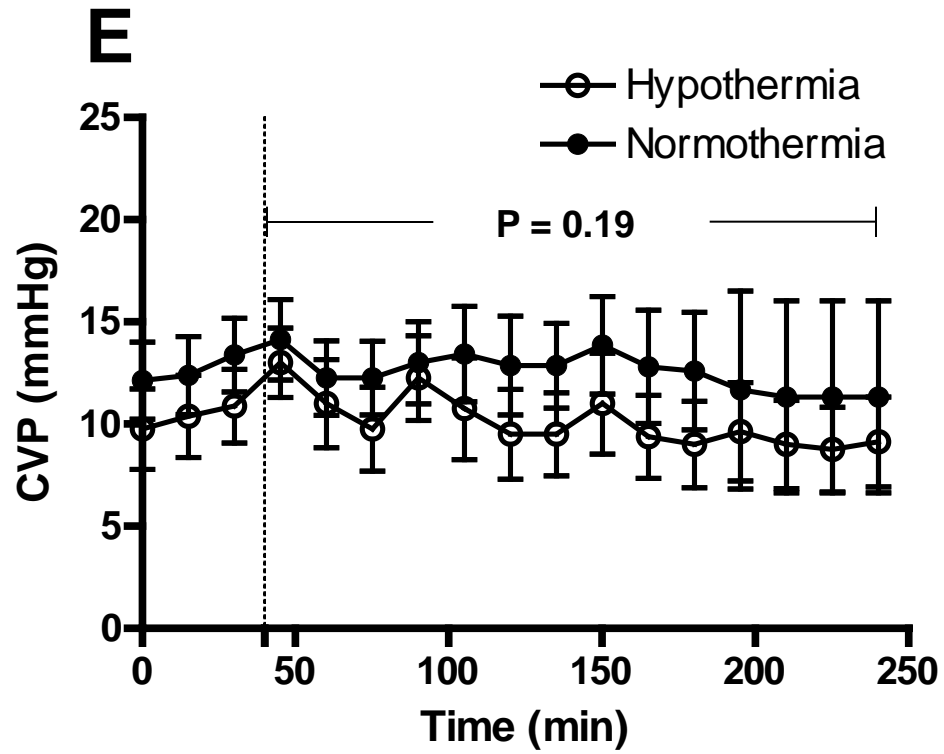Ischemia
(40 min)

Normothermia (38°C)

$\longleftarrow$ 4 h $\longrightarrow$

Hypothermia

Ischemia
(40 min)

Normothermia (38°C)   Hypothermia (33°C)

Induction of
hypothermia

B

A
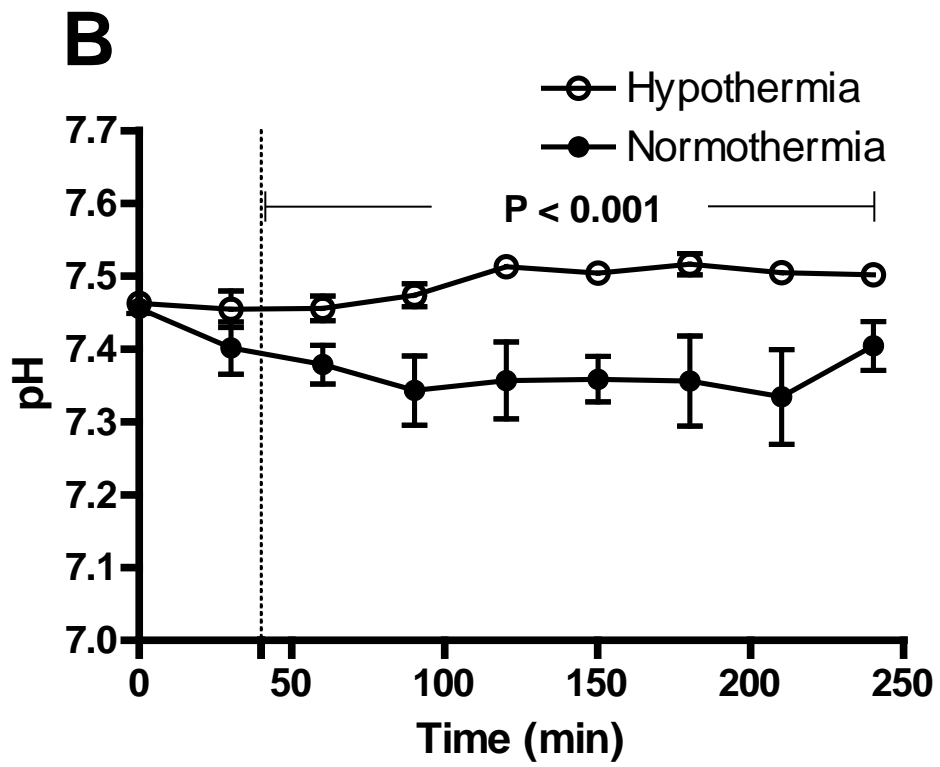
B

C

D

F

H

A

B
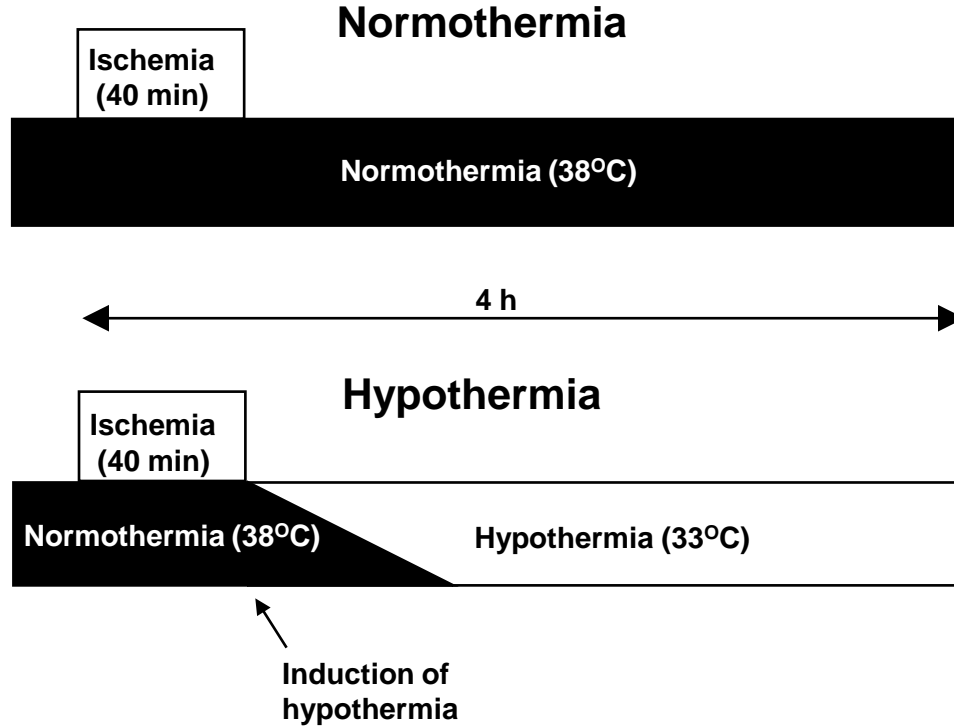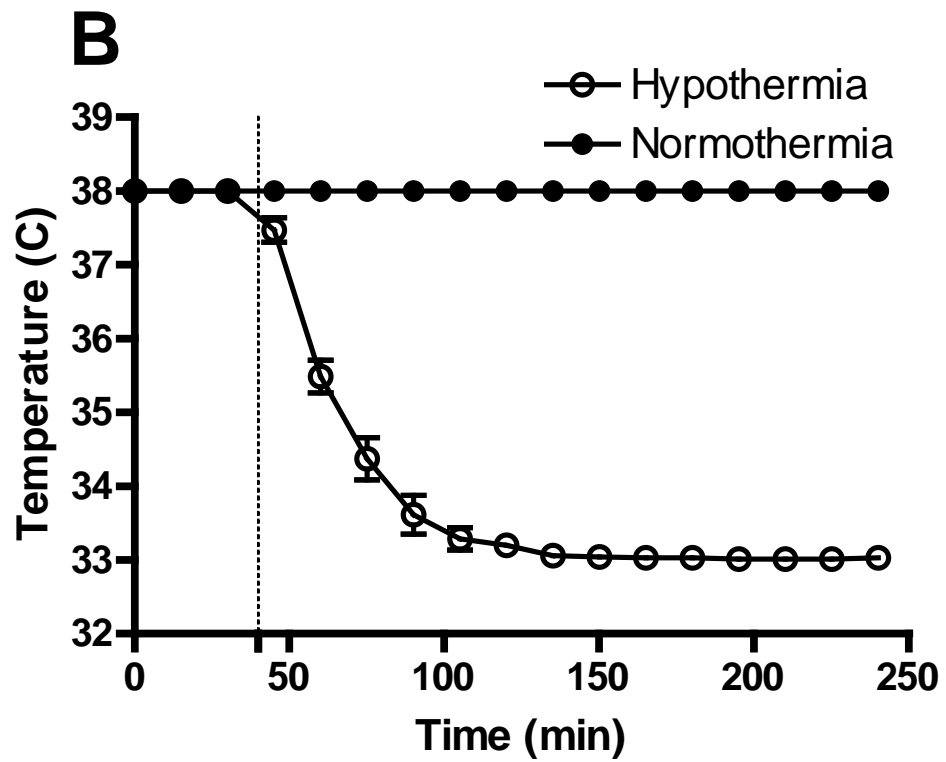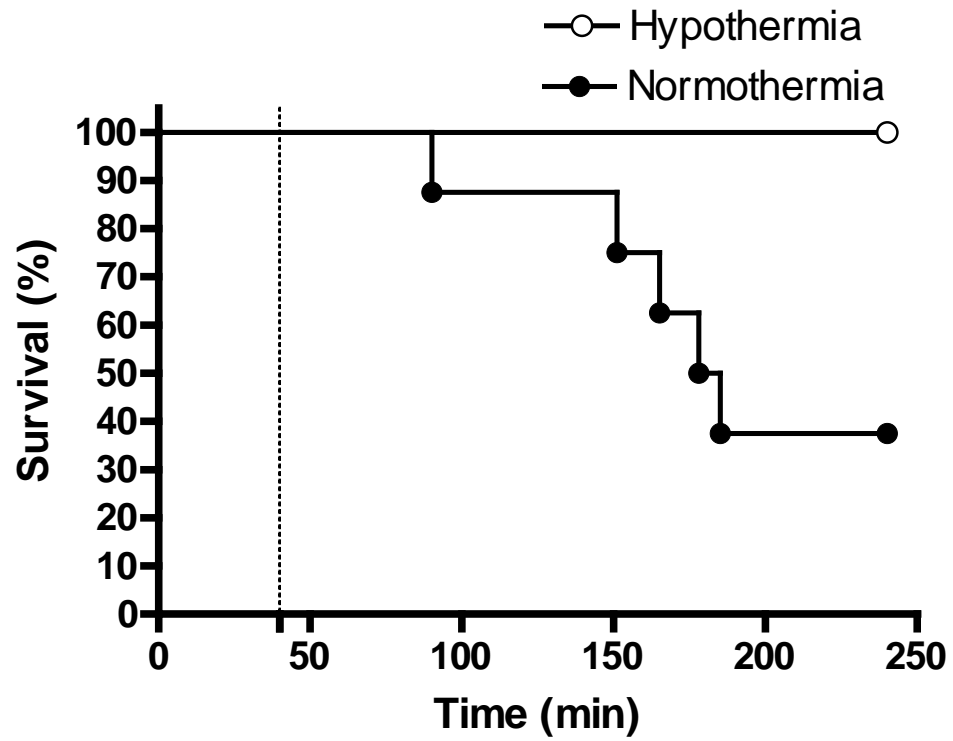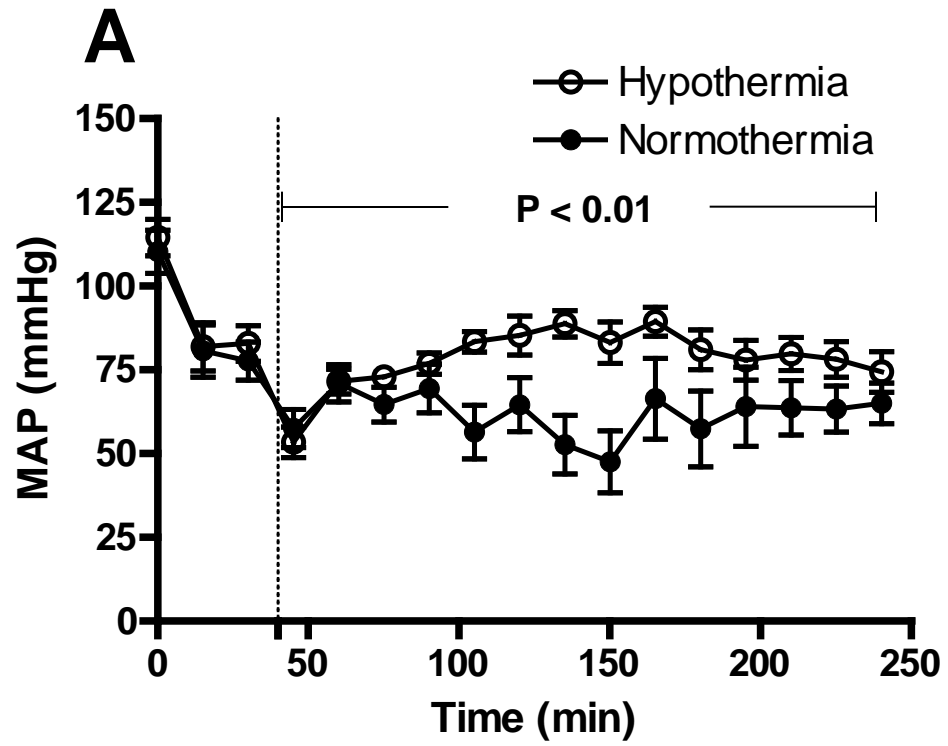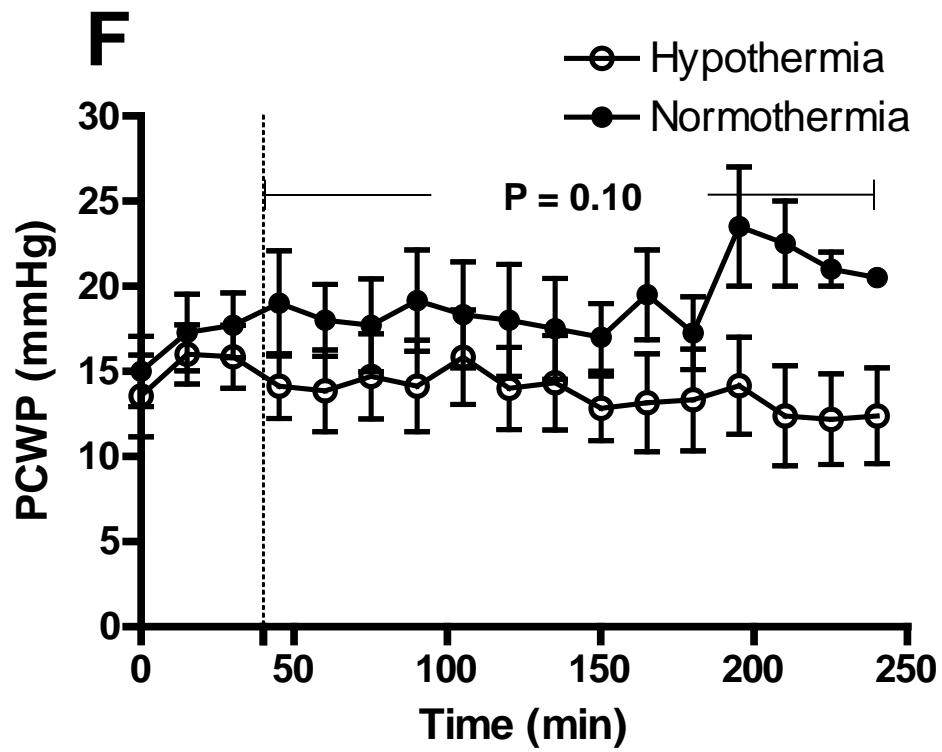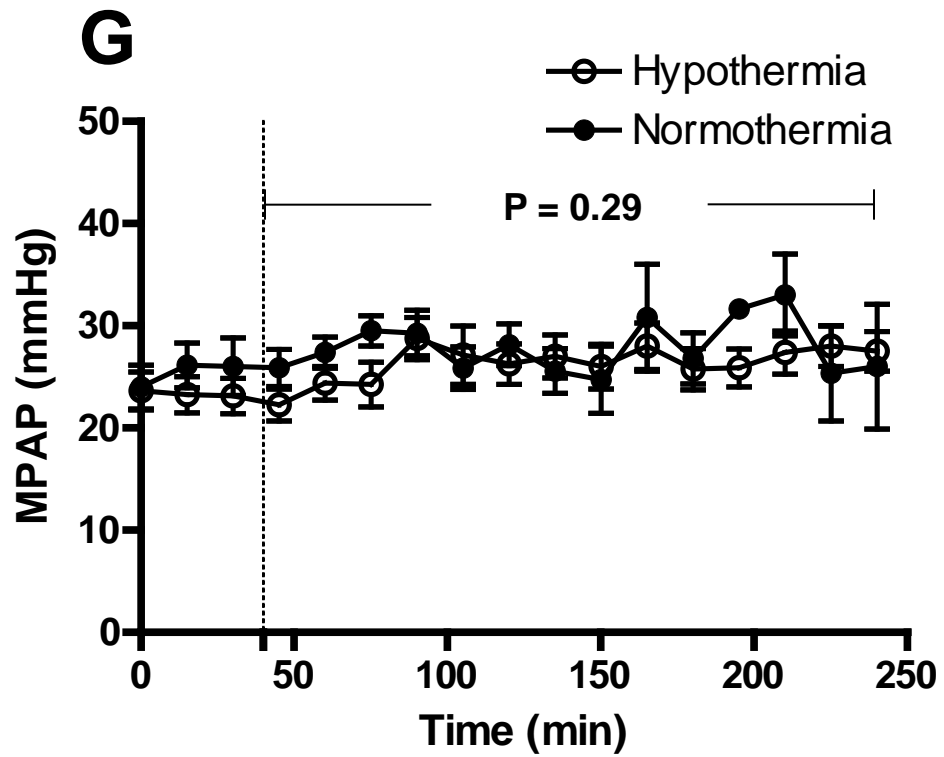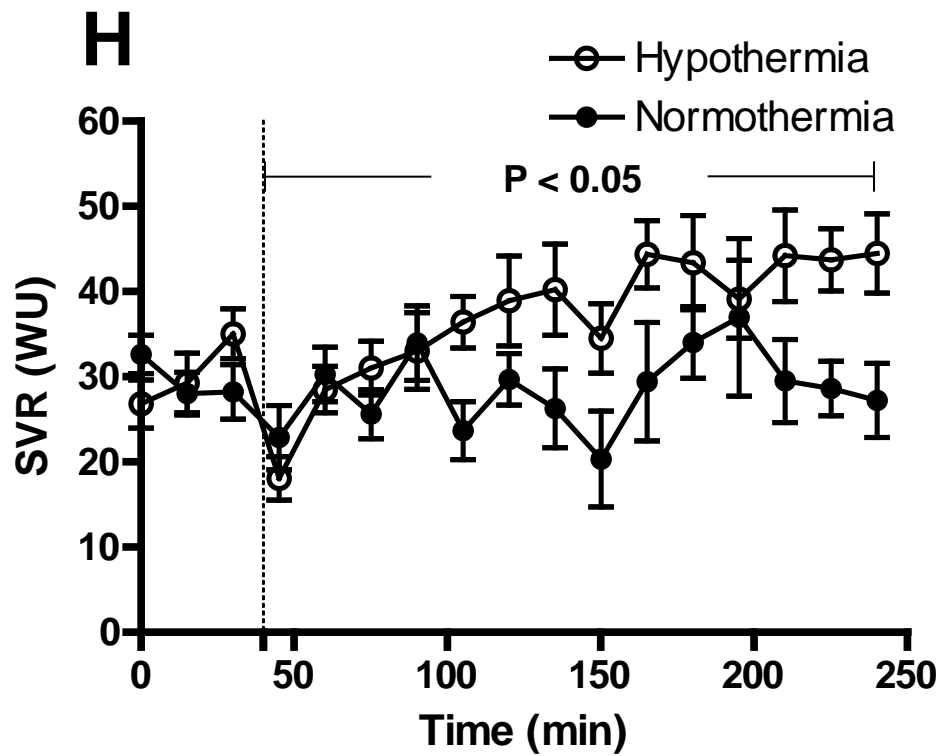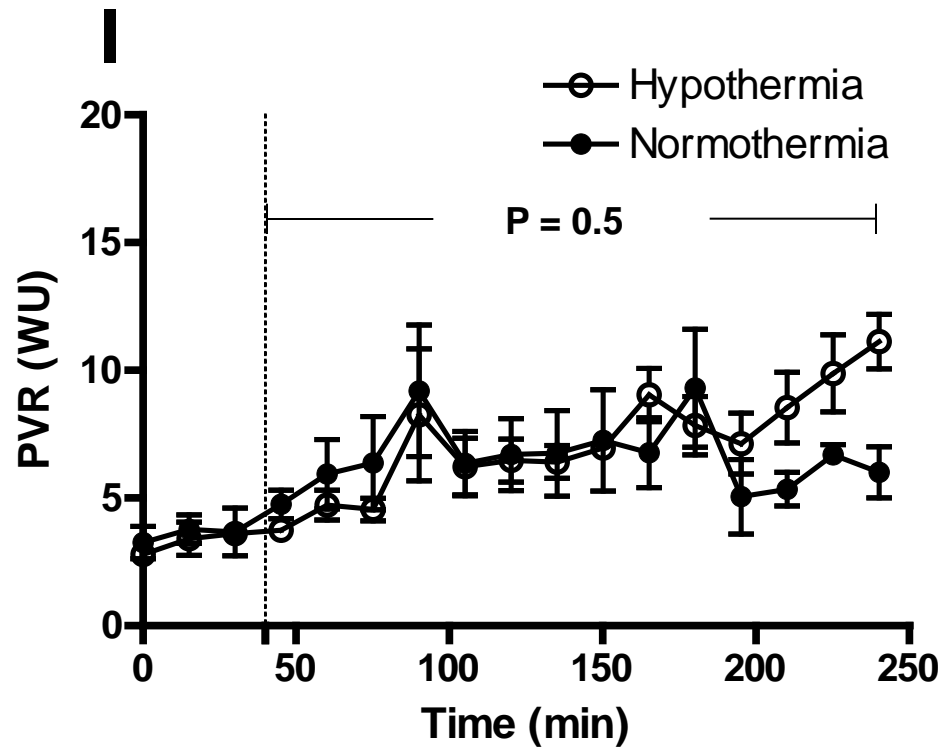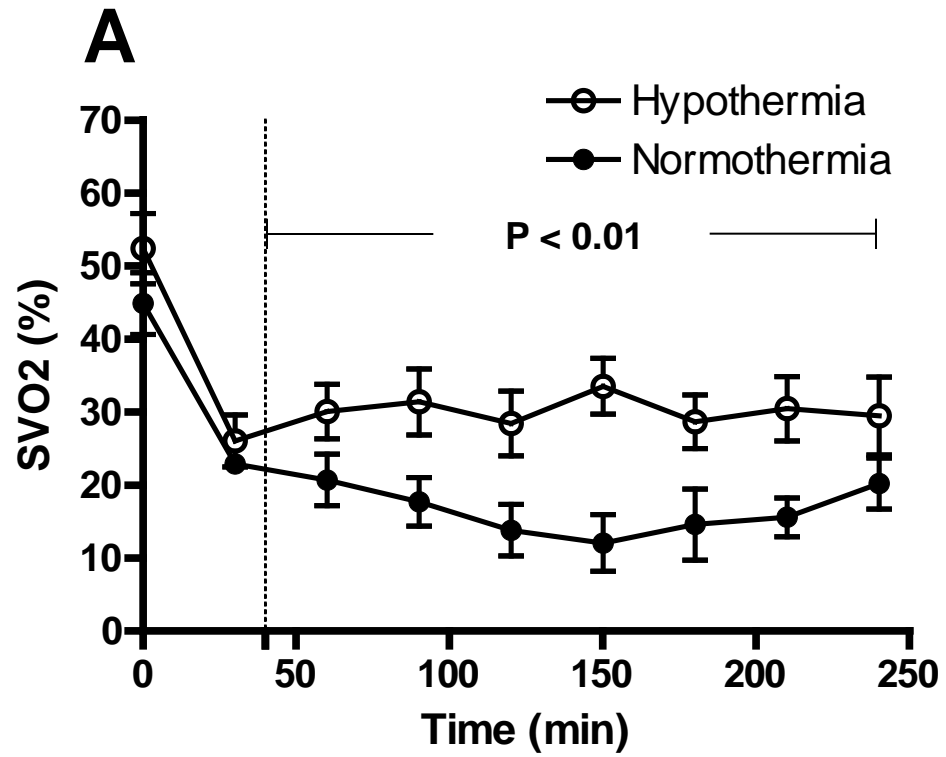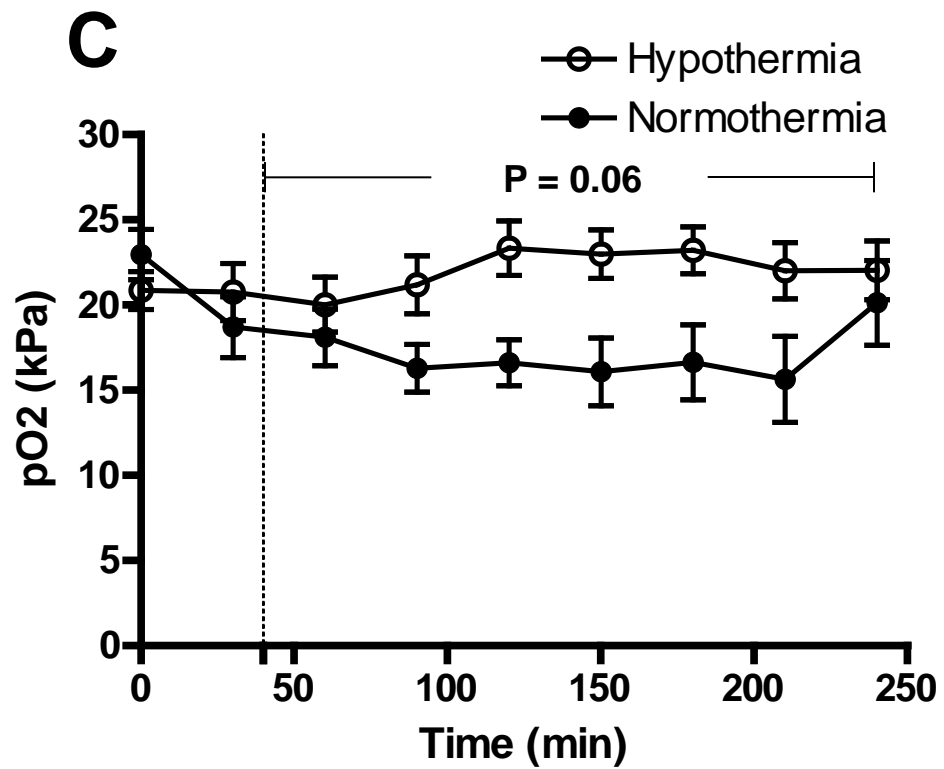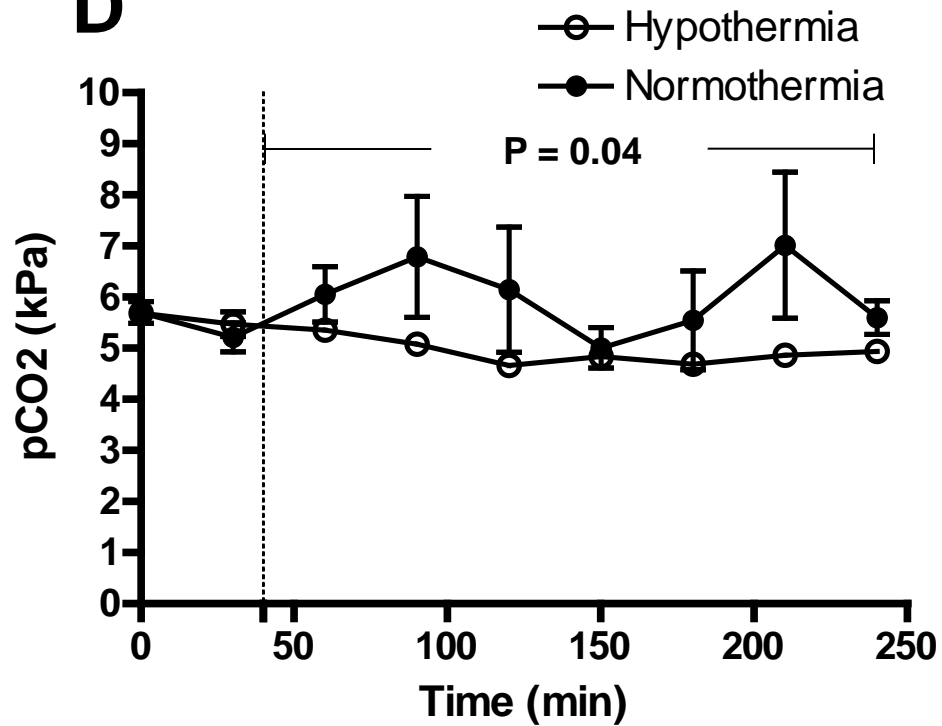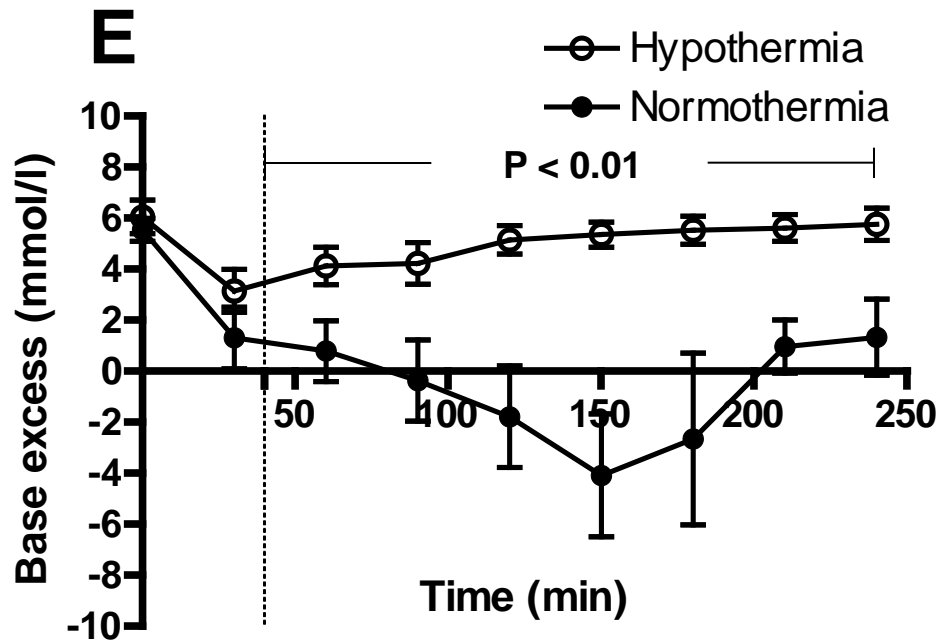
Table 1. Hemodynamic variables before randomization

Variable	Hypothermia (n=8)	Normothermia (n=8)	P-value
MAP (mmHg)	65 ± 5	67 ± 9	p = 0.67
Stroke volume (ml)	24 ± 6	27 ± 13	p = 0.87
Heart rate (bpm)	88 ± 12	96 ± 22	p = 0.52
Cardiac output (l/min)	2.1 ± 0.4	2.4 ± 0.7	p = 0.70
CVP (mmHg)	11 ± 5	13 ± 5	p = 0.40
PCWP (mmHg)	16 ± 5	18 ± 5	p = 0.56

Data are presented as means ± SD.

Table 2. Hemodynamic and blood gas variables

Variable	Hypothermia (n=8)	Normothermia (n=8)	P-value
MAP (mmHg)	78 ± 9	61 ± 4	p < 0.01
Stroke volume (ml)	23 ± 4	17 ± 4 ml	p < 0.01
Heart rate (bpm)	89 ± 9	119 ± 28	p = 0.01
Cardiac output (l/min)	2.0 ± 0.2	1.8 ± 0.4 l/min	p = 0.13
CVP (mmHg)	10 ± 6	12 ± 5	p = 0.19
PCWP (mmHg)	13 ± 6	18 ± 6	p = 0.10
MPAP (mmHg)	26 ± 5	28 ± 4	p = 0.29
SVR (WU)	37 ± 9	28 ± 8	p = 0.03
PVR (WU)	6.9 ± 1.4	6.9 ± 2.2	p = 0.50
SvO_2 (%)	30 ± 10	16 ± 9	p < 0.01
Arterial pH	7.49 ± 0.04	7.36 ± 0.09	p < 0.001
Arterial pO_2 (kPa)	22.0 ± 4.1	18.1 ± 5.1	p = 0.07
Arterial pCO_2 (kPa)	4.9 ± 0.3	6.1 ± 1.9	p = 0.04
Arterial BE (mmol/l)	5.1 ± 1.6	-1.0 ± 4.9	p = 0.002

Data are presented as means ± SD.