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Experimental paper

Cerebral perfusion and metabolism with mean arterial pressure 90 vs. 60 mmHg in a porcine post cardiac arrest model with and without targeted temperature management

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Abstract

Aim: To determine whether targeting a mean arterial pressure of 90 mmHg (MAP90) would yield improved cerebral blood flow and less ischaemia compared to MAP 60 mmHg (MAP60) with and without targeted temperature management at 33 °C (TTM33) in a porcine post-cardiac arrest model.

Methods: After 10 min of cardiac arrest, 41 swine of either sex were resuscitated until return of spontaneous circulation (ROSC). They were randomised to TTM33 or no-TTM, and MAP60 or MAP90; yielding four groups. Temperatures were managed with intravasal cooling and blood pressure targets with noradrenaline, vasopressin and nitroprusside, as appropriate. After 30 min of stabilisation, animals were observed for two hours. Cerebral perfusion pressure (CPP), cerebral blood flow (CBF), pressure reactivity index (PRx), brain tissue pCO_2 ($PbtCO_2$) and tissue intermediary metabolites were measured continuously and compared using mixed models.

Results: Animals randomised to MAP90 had higher CPP ($p < 0.001$ for both no-TTM and TTM33) and CBF (no-TTM, $p < 0.03$; TH, $p < 0.001$) compared to MAP60 during the 150 min observational period post-ROSC. We also observed higher lactate and pyruvate in MAP60 irrespective of temperature, but no significant differences in $PbtCO_2$ and lactate/pyruvate-ratio. We found lower PRx (indicating more intact autoregulation) in MAP90 vs. MAP60 (no-TTM, $p = 0.04$; TTM33, $p = 0.03$).

Conclusion: In this porcine cardiac arrest model, targeting MAP90 led to better cerebral perfusion and more intact autoregulation, but without clear differences in ischaemic markers, compared to MAP60.

Institutional protocol number: FOTS, id 8442.

Keywords: Resuscitation, Post-ROSC, Cardiac arrest, MAP, Blood pressure, Experimental study, Target temperature management, TTM, Hypothermia, Microdialysis, Cerebral perfusion pressure, Haemodynamic: post-cardiac arrest care

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Introduction

Cardiac arrest is an important health problem with high mortality.[1] After successful resuscitation, mortality is largely determined by the severity of the global reperfusion injury causing the post cardiac arrest syndrome (PCAS).[2] The brain is most susceptible to this reperfusion injury, attributing to two-thirds of all hospital deaths.[3,4] Optimising haemodynamics after cardiac arrest is believed to be beneficial in order to avoid secondary brain injury. Evidence to guide specific haemodynamic targets or how these are affected by temperature are lacking.[5]

Current guidelines for post-resuscitation care include treatment of the cause of cardiac arrest, maintaining targeted temperature management (TTM) between 32-36 °C for 24 h and avoiding mean arterial pressure (MAP) <65 mmHg.[5] These guidelines are based on a recent evidence update identifying several observational studies and two randomised controlled trials (RCTs).[6] While observational studies generally find lower blood pressures to be associated with poor outcome,[6] two recent, smaller randomised controlled trials (RCTs) did not find any clear benefit from targeting MAP 65−75 mmHg compared to 80−100 mmHg.[7,8] Yet, optimal blood pressure target remains debated.

RCTs in cardiac arrest patients are challenging, due to heterogeneity regarding pre-arrest morbidity, aetiology and severity of the brain injury. Animal models provide important insights into therapeutic interventions by offering standardisation between groups, and invasive monitoring that surpasses anything possible in the clinical setting. In this experimental porcine study, we aimed to explore potential differences in brain perfusion, metabolism, and autoregulation in animals where MAP was targeted to 60 mmHg vs. 90 mmHg after 10 min of untreated cardiac arrest, both with and without TTM.

Methods

Study design

A non-blinded RCT performed at the Institute for Experimental Medical Research, Oslo University Hospital, Ullevål, consisting of two experimental series. In the first series, pigs were randomised to MAP 90 mmHg (MAP90) or 60 mmHg (MAP60) without TTM (no-TTM). In the second series, pigs were randomised to MAP90/MAP60 with TTM 33 °C (TTM33). Only pigs with return of spontaneous circulation (ROSC) were randomised and included with a computer based random order generator. As the study was performed with two separate experimental series, one before the other, comparisons between groups are only made within each series.

Norwegian National Animal Research Authority approved the study, and the involved staff were certified with Federation of Laboratory Animal Sciences Associations category C.[9] The study was performed in compliance with EU Directive 2010/63/EU for animal experiments, with reporting in accordance with ARRIVE guidelines.[10]

Animal preparation

Fifty-three crossbreed Norwegian Landrace pigs of either sex were kept overnight with free access to water and food. They were premedicated with an intramuscular injection of ketamine (30 mg/kg), atropine (1 mg) and morphine (10 mg) followed by intravenous (IV) anaesthesia induction with a bolus of propofol (2 mg/kg) and fentanyl (10 mcg/kg). Anaesthesia was maintained with continuous infusions of propofol (12−20 mg/kg/h) and fentanyl (30−100 mcg/kg/h).

The airway was secured by tracheostomy, and the animals were mechanically ventilated (Datex Capnomac Ultima™, Helsinki, Finland). All animals were initially ventilated with fraction of inspired oxygen (FiO_2) 30%, tidal volume of 15 ml/kg, respiratory rate 16 per minute and received positive end-expiratory pressure of 5 cm H_2O. FiO_2 and minute ventilation were adjusted to target SpO_2 95−100%, pO_2>10 kPa and end-tidal carbon dioxide ($EtCO_2$) 4.5−5.5 kPa. Defibrillation pads were placed on the thorax, connected to a defibrillator and used for electrocardiogram monitoring (LP12 Physio Control, Redmond, Wa., USA).

Instrumentation and monitoring

Surgical preparation included tracheostomy, urine catheter with thermometer via cystotomy, cranial burr hole/craniectomy and placement of left intraventricular pressure and right intraatrial pressure catheters (7 Fr micro-tip Model SPC 470, Millar Instruments, TX, USA) through the left carotid artery and right internal jugular vein. An ultrasound flowmeter probe (model 3SB880, Transsonic Systems Inc., Ithaca, NY, USA) was placed around the carotid artery, a pulmonary artery catheter (7.5 Fr Swan-Ganz CCO, Edwards Lifesciences, CA, USA) via an 8F introducer in the right femoral vein. A fluid filled polyethylene catheter was inserted into the lower abdominal aorta from the right femoral artery. Both catheters were used for continuous pressure monitoring and blood gas monitoring. In addition, cardiopulmonary bypass (CPB) cannulas were placed through the right external jugular vein and left femoral artery (DLP Jugular 21 Fr, Medtronic Inc., MN, USA) controlled by x-ray and connected to the Ringer's acetate primed CPB circuit (Stöckert S 3Double Head pump, Sorin Group, Milano, Italy). In the second series, a 9.3 Fr cooling catheter (Cool Line®, Zoll Medical Corporation, CA, USA) was inserted in the left femoral vein for invasive temperature management.

Three cranial right side 3 mm burr holes and a small left side 15 × 30 mm craniectomy were used to gain access to cerebral cortex in the first series. Due to frequent complications with the craniectomy procedure, this was changed to three 3 mm burr holes bilaterally for the second series. A laser Doppler flowmetry probe (Model 407, Perimed AB, Stockholm, Sweden) was placed on the surface of left side cerebral cortex to measure cerebral blood flow (CBF), and a pressure catheter (7 Fr micro-tip Model SPC 470, Millar Instruments, TX, USA) was inserted 1−2 cm into cerebral cortex for intracranial pressure (ICP) monitoring. Two miniature sensors (IscAlert™), <1 mm diameter (Sensocure AS, Skoppum, Norway), measuring changes of brain tissue pCO_2 ($PbtCO_2$) from baseline, were placed right and left on the brain. IscAlert sensors rely on a conductometric method to detect changes in tissue pCO_2 ($PtCO_2$).[11] CO_2 is produced in the brain to buffer anaerobic lactic acidosis, and an increase in local CO_2 may reflect ischaemia.[12−16] Finally, two microdialysis catheters (CMA 71, 100 kDa cut-off, 1 cm membrane, 1 μl min^{-1} flow, (MDialysis, Stockholm, Sweden) were placed right and left on the brain.

Experimental protocol

After completion of surgical instrumentation, pigs were placed on their left side with fastened limbs, anticoagulated with Heparin 500 IU/kg IV

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and connected to the CPB circuit (in stand-by) and clamped vascular connections. Baseline blood gas analysis and registration of all variables were performed after stabilisation. Ventricular fibrillation (VF) was induced by trans-thoracic current (90 V AC for 3 s), and cardiac arrest confirmed by electrocardiogram and abrupt drop in blood pressure. VF was left untreated for 10 min without ventilation and propofol infusion. Resuscitation with CPB was initiated with a flow of 100 ml/kg/min, propofol and mechanical ventilation were restarted. In the second series, TTM33 was initiated by lowering the temperature of the CPB heat exchanger to 20 °C and initiating cooling through the endovascular cooling catheter. After two minutes of resuscitation, defibrillation was performed with 360 J. The study protocol allowed for defibrillations every two minutes until ROSC, with a maximum of six shocks. Animals achieving ROSC were weaned off the CPB with 0.5 l/min and residual blood in the circuit returned. After weaning, pigs were randomised to MAP90/MAP60. Thirty minutes stabilisation was followed by 120 min of observations with registration of outcome parameters. Noradrenaline, vasopressin, or nitroprusside were used to maintain blood pressure targets, as appropriate. Finally, all animals were euthanized with intravenous injection of 50 mmol potassium chloride (Fig. 1).

Measurement parameters

All haemodynamic variables were sampled continuously throughout the experiment (1000 Hz) using real time data acquisition hardware (NI SCXI-1000, NI PCI-6036E, National Instruments Company, TX, USA) supported with VI logger (National Instruments Company, TX, USA). Cerebral perfusion pressure (CPP) was calculated as the difference between aortic and intracerebral pressure, and coronary perfusion pressure (CorPP) as the difference between aortic and right atrial pressure. Microdialysis (lactate, pyruvate, lactate/pyruvate-ratio, glutamate, glucose, glycerol), $PbtCO_2$, brain and core body temperatures were recorded continuously, with data presented at 15-min intervals. Cardiac output (CO) and blood gas analyses were measured every 15 min. Pressure reactivity index (PRx), a correlation coefficient between ICP and MAP, was calculated as the moving correlation coefficient between consecutive 5-second averages of ICP and MAP and has been used as a measure of autoregulation.[17,18] Cerebral Flow reactivity index (CFRx) was calculated as the moving correlation coefficient between consecutive 5-second averages of ICP and CBF.

Experimental outcomes

Cardiac parameters

Cardiac parameters heart rate [beats/min], MAP [mmHg], pulmonary artery pressure (PAP) [mmHg], end-diastolic left ventricular pressure (EDLVP) [mmHg], CorPP [mmHg] and CO [litres/min].

In addition to standard haemodynamic monitoring, PAP and EDLVP were added to the experimental set-up to provide information on any additional strain put on the heart by targeting MAP90 vs. MAP60.

Cerebral parameters

Cerebral parameters ICP [mmHg], CPP, carotid flow (CaF) [ml/min], CBF [arbitrary unites –AU] reported relative to baseline ((measurement–baseline value)/baseline value), PRx, CFRx, $PbtCO_2$ [kPa], brain tissue microdialysis (lactate [mM], pyruvate [μM], lactate/pyruvate-ratio, glucose [mM], glutamate [μM], glycerol (μM)).

CaF and CBF were considered important to assess whether increased perfusion pressure would lead to increased flow, whereas $PbtCO_2$ and microdialysis were selected to add information about brain metabolism, ischaemia and inflammation. As post arrest neurological assessments were not possible due to the study design, the reactivity indexes were selected to provide indirect information about brain function.

Statistical analysis

All comparisons between MAP60 and MAP90 were done separately for no-TTM and TTM33. Variables at baseline and after the 150 min

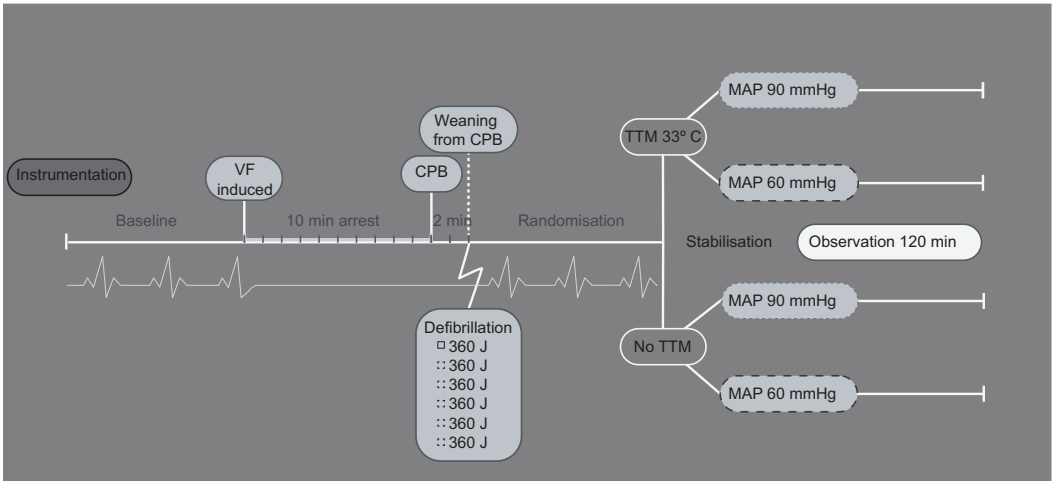

Fig. 1 – Schematic overview of the experiment. Pigs were anaesthetised and instrumented prior to electrical induction of ventricular fibrillation (VF). VF was left untreated for 10 min. Resuscitation with cardiopulmonary bypass (CPB) was initiated with a flow of 100 ml/kg/min for 2 min before defibrillation with 360 J. Maximum 6 shock were allowed to achieve return of spontaneous circulation (ROSC). With ROSC, they were weaned off CPB by 0.5 l/min, and randomised to MAP 90 or 60 mmHg. The study consisted of two experimental series, no temperature target management (No TTM), and TTM 33 °C.

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observation period are reported as medians and compared using 95% confidence intervals (95% CI) for median. Repeated measurements (every 15 min during the 120 min observational period) of MAP, PAP, ICP, CPP, CO, CaF, CBF, PRx, CFRx, mixed venous oxygen saturation (SvO_2), $PbtCO_2$, brain and core body temperature, blood glucose, blood lactate, brain microdialysis (lactate, pyruvate, glucose, glutamate, glycerol, lactate/pyruvate-ratio) for MAP60 and MAP90 were compared using a generalised mixed model with a unstructured covariance matrix. SPSS v22 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant. A new experimental model was designed for this study, and a formal power analysis was not performed.

Results

Fifty-three animals were needed to successfully randomise 41 animals (ROSC could not be achieved in 12 pigs); 21 and 20 in no-TTM and TTM33, respectively. Baseline characteristics are shown in Table 1. Point measurements from the end of the experiment (150 min after successful weaning from cardiopulmonary bypass) are shown in Table 2. After 150 min, there were no differences in EDLVP, but PAP in MAP90 was higher vs. MAP60 with TTM33 (26 (95% CI 15, 39) vs. 17 (95% CI 6, 26)) (Table 2).

Target blood pressures were achieved in no-TTM and TTM33, and led to significantly higher CPPs for MAP90 vs. MAP60 irrespective of temperature ($p < 0.001$ for both no-TTM and TTM33, respectively). CO was significantly higher for MAP90 vs. MAP60 in no- TTM ($p = 0.03$), but without differences in TTM33 ($p = 0.17$) (Fig. 2). Similarly, SvO_2 was significantly higher in MAP90 vs. MAP60 group in no-TTM ($p = 0.001$), but without differences in TTM33 ($p = 0.31$) (Fig. 3).

CBF was significantly higher for MAP90 vs. MAP60, both in no-TTM ($p = 0.03$) and TTM33 ($p < 0.001$) (Fig. 2). There were no differences in $PbtCO_2$ between MAP90 vs. MAP60 ($p = 0.32$ and $p = 0.87$ for no-TTM and TTM33, respectively) (Fig. 3). Both CPP and flow reactivity indexes were significantly lower (indicating more intact autoregulation) for MAP90 vs. MAP60 ($p < 0.001$ for both no-TTM and TTM33, respectively) (Fig. 2).

Immediately after cardiac arrest, $PbtCO_2$ rapidly increased due to brain ischaemia. After ROSC $PbtCO_2$ declined and approached values close to pre-cardiac arrest values indicating close to normal brain blood supply (Fig. 3). Brain lactate and lactate/pyruvate-ratio increased, and brain pyruvate and glucose decreased during cardiac arrest. After ROSC, lactate and pyruvate increased and lactate/pyruvate-ratio decreased up to 60 min post-ROSC. Lactate and pyruvate were significantly higher for MAP60 vs. MAP90, leaving similar lactate/pyruvate-ratios between the groups. Similarly, there were no differences in glycerol (indicating similar degree of neuronal membrane damage) between groups (Fig. 4).

Table 1 – Baseline characteristics.

	No temperature management		Temperature management 33 °C	
	MAP 90 mmHg (n = 11)	MAP 60 mmHg (n = 10)	MAP 90 mmHg (n = 10)	MAP 60 mmHg (n = 10)
Weight (kg)	35 (32, 37)	35 (33, 37)	34 (33, 36)	35 (33, 36)
Pressure measurements				
Heart rate (beats/min)	90 (70, 120)	95 (90, 120)	90 (80, 110)	70 (70, 130)
Mean arterial pressure (mmHg)	92 (84, 110)	94 (82,120)	98 (83, 130)	105 (87, 129)
Pulmonary artery pressure (mmHg)	19 (16, 27)	18 (11, 21)	19 (10, 29)	17 (10, 23)
End-diastolic left ventricular pressure (mmHg)	10 (8, 12)	10 (7, 13)	9 (8, 11)	10 (8, 12)
Intracranial pressure (mmHg)	6 (2, 9)	6 (2, 11)	9 (6, 13)	8 (5, 12)
Cerebral perfusion pressure (mmHg)	91 (70, 113)	87 (73, 103)	92 (73, 120)	99 (78, 127)
Coronary perfusion pressure (mmHg)	85 (76, 119)	87 (65, 100)	94 (74, 115)	100 (76, 118)
Flow and reactivity measurements				
Cardiac output (litres/min)	4.5 (3.5, 6.4)	4.5 (3.5, 5.5)	3.9 (3.5, 5.1)	4.2 (3.8, 5.8)
Carotid flow (ml/min)	256 (192, 289)	236 (174, 277)	240 (157, 402)	258 (235, 325)
Pressure reactivity index (PRx)	0.12 (0.08, 0.13)	0.07 (0.01, 0.07)	0.09 (0.05, 0.34)	0.03 (0.02, 0.05)
Laser Doppler cerebral flow reactivity index (CFRx)	0.09 (0.02, 0.19)	0.11 (0.01, 0.16)	0.07 (0.00, 0.13)	0.05 (0.01, 0.14)
Metabolism				
SvO_2 (%)	57 (48, 67)	53 (45, 61)	62 (46, 66)	62 (56, 72)
Brain tissue pCO_2 (kPa)	7.5 (6.5, 8.5)	9.6 (6.6, 10.4)	7.2 (6.6, 9.1)	7.7 (6.3, 9.7)
Brain lactate (mM)	0.9 (0.6, 1.0)	0.9 (0.8, 1.4)	0.8 (0.7, 1.0)	0.7 (0.5, 0.9)
Brain pyruvate (μM)	41 (23, 62)	25 (18, 55)	28 (18, 43)	44 (29, 98)
Brain glucose (mM)	1.1 (0.8, 1.5)	0.7 (0.6, 3.0)	1.3 (0.7, 1.6)	1.1 (0.7, 2.0)
Brain glutamate (μM)	32 (23, 93)	40 (23, 131)	38 (15, 47)	44 (20, 54)
Brain glycerol (μM)	71 (50, 84)	68 (66, 89)	72 (57, 79)	69 (52, 79)
Brain lactate/pyruvate Ratio	20 (15, 39)	31 (25, 52)	31 (15, 41)	15 (9, 27)
Brain temperature (^{0}C)	38.2 (37.8, 39.1)	38.6 (37.5, 39.8)	37.8 (37.3, 38.1)	38.4 (37.6, 38.9)
Core body temperature (^{0}C)	39.3 (38.2, 40.0)	39.3 (38.5, 40.3)	37.2 (36.9, 37.6)	37.4 (37.0, 38.6)
Blood lactate (mM/l)	0.6 (0.4, 1.0)	0.5 (0.5, 0.6)	0.7 (0.5, 1.2)	0.6 (0.4, 0.8)
Blood glucose (mM/l)	5.0 (3.2, 6.0)	5.4 (4.4, 6.1)	4.7 (1.8, 5.2)	5.2 (2.9, 5.3)

MAP; middle arterial pressure, SvO_2; mixed venous oxygen saturation. Continuous variables reported as median with 95% confidence intervals for median.

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Table 2 – Haemodynamic, reactivity, metabolism and total doses of vasoactive drugs at 150 min after cardiac arrest.

	No temperature management		Temperature management 33 °C	
	MAP 90 mmHg (n = 11)	MAP 60 mmHg (n = 10)	MAP 90 mmHg (n = 10)	MAP 60 mmHg (n = 10)
Pressure measurements				
Heart rate (beats/min)	120 (100, 230)	120 (120, 160)	110 (95, 125)	114 (85, 143)
Mean arterial pressure (mmHg)	90 (86, 107)	61 (54, 67)	89 (69, 109)	61 (57, 66)
Pulmonary artery pressure (mmHg)	16 (11, 26)	16 (15, 21)	26 (15, 39)	17 (6, 26)
End-diastolic left ventricular pressure (mmHg)	9 (6, 13)	10 (7, 11)	10 (7, 13)	8 (6, 9)
Intracranial pressure (mmHg)	14 (8, 27)	15 (9, 25)	18 (15, 20)	13 (11, 16)
Cerebral perfusion pressure (mmHg)	78 (55, 88)	45 (40, 52)	69 (53, 97)	46 (43, 53)
Coronary perfusion pressure (mmHg)	81 (73, 94)	48 (33, 67)	80 (67, 93)	53 (47, 59)
Flow and reactivity measurements				
Cardiac output (litres/min)	4.0 (3.0, 5.0)	4 (3.0, 4.0)	3.9 (2.5, 4.2)	3.7 (2.7, 4.9)
Carotid flow (ml/min)	192 (170, 270)	198 (166, 248)	370 (296, 445)	298 (254, 342)
Laser Doppler cerebral flow (%)	17 (-4, 37)	−53 (-81, 12)	−13 (-44, 30)	−41 (-67, -19)
Pressure reactivity index (PRx)	−0.08 (-0.29, 0.24)	0.21 (-0.04, 0.46)	0.01 (-0.23, 0.32)	0.22 (0.03, 0.54)
Laser Doppler cerebral flow reactivity index (CFRx)	0.26 (0.11, 0.72)	0.76 (0.47, 0.94)	0.01 (-0.22, 0.50)	0.58 (0.22, 0.74)
Metabolism				
SvO_2 (%)	54 (42, 70)	45 (39, 60)	68 (58, 73)	68 (61, 79)
Brain tissue pCO_2 (kPa)	8.4 (7.5, 12.0)	10.8 (6.9, 14.0)	8.3 (6.2, 10.9)	8.6 (6.1, 11.1)
Brain lactate (mM)[a]	2.0 (0.8, 3.6)	1.9 (1.3, 4.1)	1.4 (0.9, 1.5)	1.9 (1.3, 3.4)
Brain pyruvate (μM)[a]	44 (23, 60)	33 (22, 73)	46 (39, 68)	43 (19, 287)
Brain glucose (mM)[a]	1.2 (0.7, 1.5)	0.8 (0.6, 4.5)	1.1 (1.0, 1.3)	1.2 (0.9, 1.3)
Brain glutamate (μM)[a]	22 (4, 47)	28 (4, 36)	7 (4, 16)	11 (5, 76)
Brain glycerol (μM)[a]	164 (120, 263)	176 (134, 222)	162 (134, 175)	146 (111, 237)
Brain lactate/pyruvate Ratio[a]	28 (8, 62)	46 (21, 48)	26 (16, 32)	30 (6, 95)
Brain temperature (^{0}C)	37.6 (35.7, 38.2)	37.3 (36.5, 38.6)	33.1 (30.8, 33.8)	33.4 (31.0, 34.0)
Core body temperature (^{0}C)	38.0 (37.0, 39.0)	38.0 (37.0, 39.0)	32.3 (32.0, 32.7)	32.7 (31.9, 32.9)
Blood lactate (mM/l)	1.0 (0.5, 2.3)	0.8 (0.5, 1.8)	1.3 (0.8, 3.3)	1.5 (1.2, 2.0)
Blood glucose (mM/l)	5.6 (3.5, 7.1)	4.2 (2.2, 5.0)	4.2 (3.2, 4.9)	4.6 (3.8, 5.4)
Vasoactive drugs, total dose				
Noradrenaline (mg)	0.7 (0.4, 1.3)[b]	0.4 (0.2, 1.1)	0.5 (0.4, 0.7)	0.04 (0, 0.25)
Vasopressin (U)	2.2 (0.2, 4.6)[b]	1.2 (0, 2.6)	2.2 (1.4, 3.4)	0 (0, 0)
Nitroprusside (mg)	0 (0, 0)	18.5 (14.5, 22.5)	0 (0, 0)	7.75 (0, 23)
Number of animals treated with:				
Noradrenaline	11 (100%)	9 (80%)	10 (100%)	7 (70%)
Vasopressin	11 (100%)	7 (70%)	10 (100%)	0 (0%)
Nitroprusside	0 (0%)	6 (60%)	0 (0%)	8 (80%)

MAP; middle arterial pressure, SvO_2; mixed venous oxygen saturation. Laser Doppler Cerebral Flow is measured in arbitrary unites (AU) and reported relative to baseline ((measurement at 150 min −baseline value)/baseline value). Continuous variables reported as median with 95% confidence intervals for median.
[a] Results from 10 animals with no temperature management and 4 animals with temperature management to 33 °C had to be excluded due technical problems with collection and/or analysis of dialysate.
[b] The exact amount of vasoactive drugs are missing in 5 animals.

Discussion

In the present experimental pig study, we compared haemodynamic and metabolic effects of MAP90 vs MAP60 with or without TTM33 during the first hours after cardiac arrest. MAP90 significantly increased CO and thereby oxygen delivery. It further improved the balance between oxygen supply and demand (higher SvO_2) in animals with no-TTM, but these differences were not observed in animals with TTM33. Despite the lack of increase in global perfusion with no-TTM, MAP90 animals had better CBF and more intact autoregulation (suggested by cerebral reactivity indexes), irrespective of the temperature.

Previous laboratory studies have illustrated how transient hypertension and cerebral hyperaemia immediately following resuscitation from cardiac arrest can be followed by a prolonged period of impaired autoregulation and hypoperfusion.[19–24] Similar observations have been suggested in clinical studies, using less invasive methods such as Near-infrared spectroscopy (NIRS) or transcranial Doppler.[25–27] These experimental and clinical observations underlines the importance to ensuring adequate brain perfusion during the critical initial post arrest phase.

Although managing MAP is just one small piece of the puzzle in treating comatose cardiac arrest patients, observational studies have clearly shown that this single parameter has a strong association with outcome.[28–31] The two RCTs are underpowered to determine

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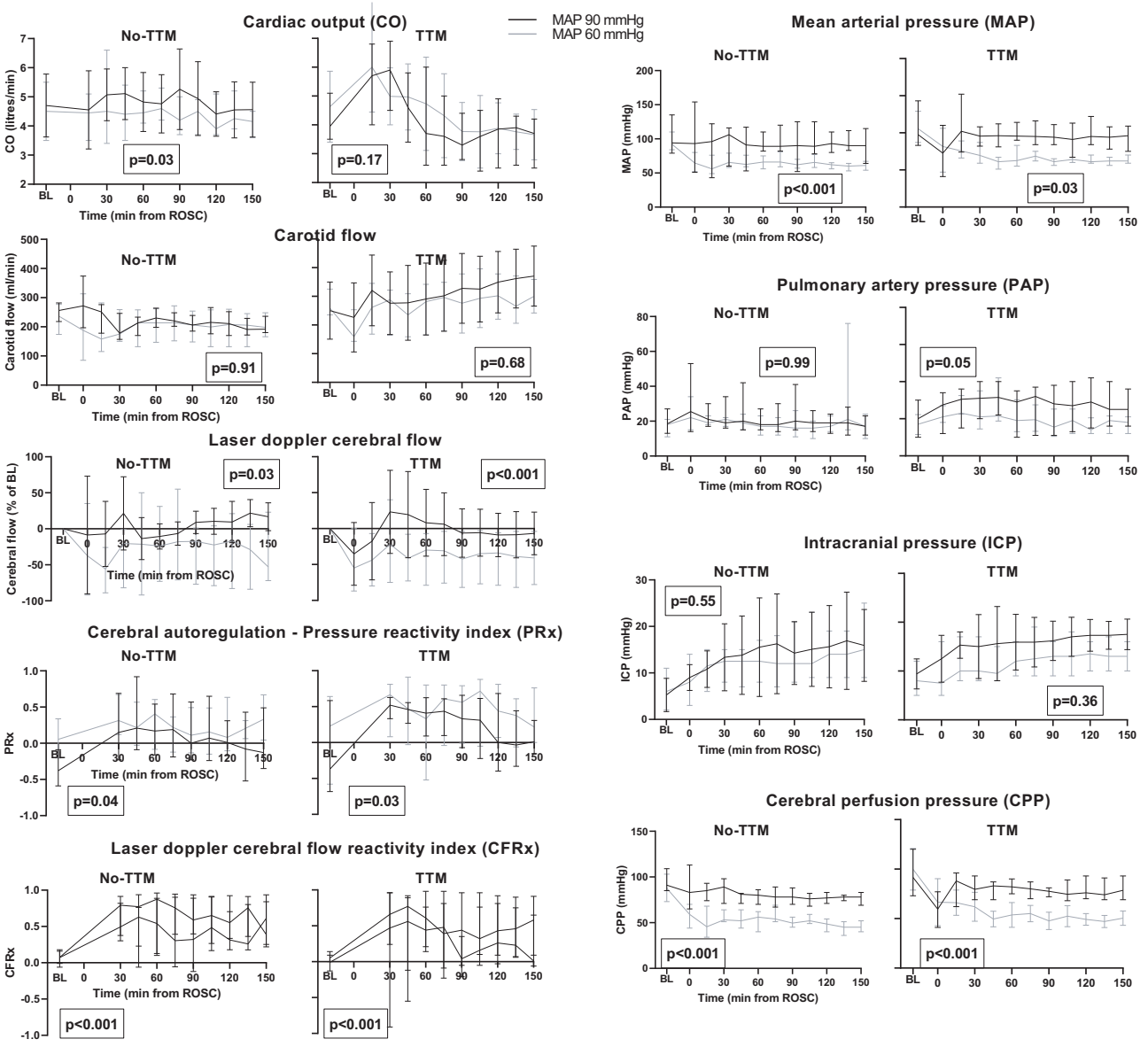

Fig. 2 – Pressure, flow and reactivity measurements.
A thirty minute stabilisation period after successful weaning from cardiopulmonary bypass (0 min) was followed by 120 min of observations with registration of outcome parameters. Repeated measurements every 15 min during the 120 min observational period for MAP60 and MAP90 groups were compared using a generalised mixed model with an unstructured covariance matrix. A p-value of less than 0.05 was considered statistically significant. TTM = Temperature Target Management.

whether we can expect an increase in favourable outcome by simply increasing MAP, but the present data suggest it is unlikely to be that simple.[7,8] Providing optimal individualised care for every patient remains a somewhat unachievable goal, but exploring how measures commonly available and manipulated in the clinical setting correlates with measures such as CBF, reactivity and ischaemia under various conditions might provide clinicians with important insights for individualising care.

An important aspect of providing optimal care for critically ill cardiac arrest patients is balancing oxygen delivery and demand to avoid further ischaemic injury. The brain is particularly susceptible, and brain injury is the most common cause of death among cardiac arrest patients surviving to hospital.[3,4] We found CBF to be more dependent on blood pressure than CO, and observed that autoregulation was more commonly intact at higher blood pressure levels. Disturbed cerebral autoregulation is associated with unfavourable functional outcome in brain injured patients.[32,33] Most studies have been done in patients with traumatic brain injury,[34] but higher mortality has also been reported in patients with non-traumatic brain injury such as post cardiac arrest patients.[27,35,36]

At the end of the 150 min observation period, EDLVP pressure was low and within normal range for all groups, while several of the animals in MAP90 with TTM33 had developed pulmonary hypertension. Our interpretation of these findings are that adequate cerebral perfusion

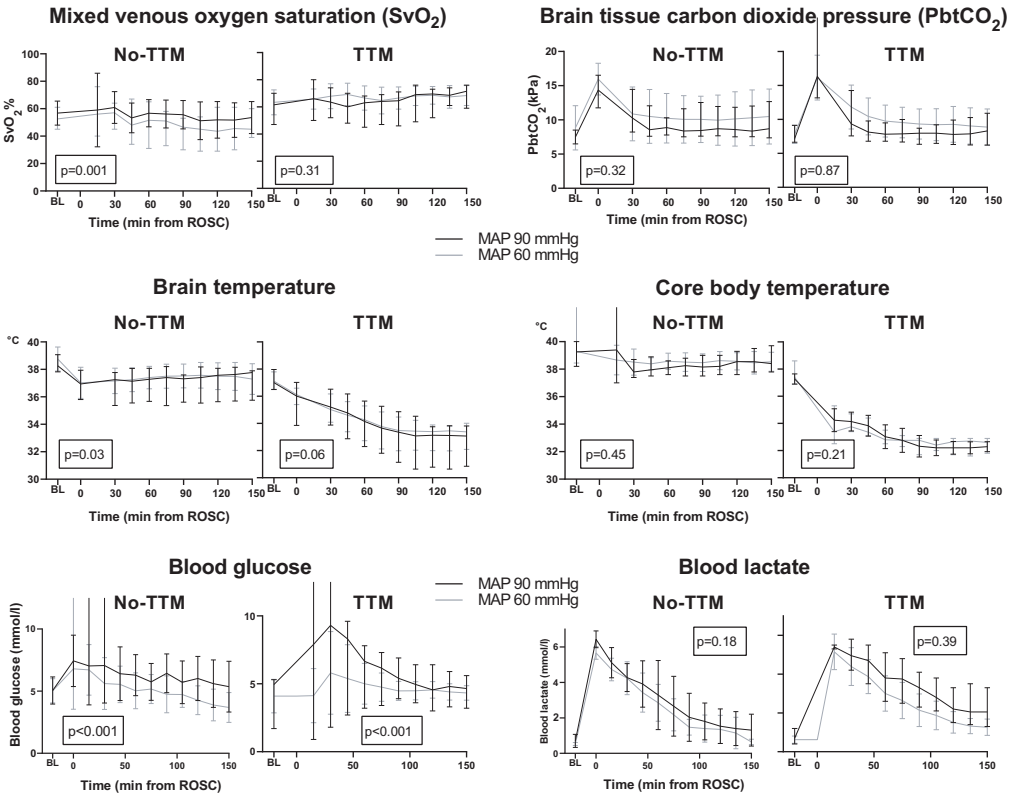

Fig. 3 – Metabolism.

A thirty minute stabilisation period after successful weaning from cardiopulmonary bypass (0 min) was followed by 120 min of observations with registration of outcome parameters. Repeated measurements every 15 min during the 120 min observational period for MAP60 and MAP90 groups were compared using a generalised mixed model with an unstructured covariance matrix. A p-value of less than 0.05 was considered statistically significant. TTM = Temperature Target Management.

pressure is important for post-arrest patients as they are at risk of impaired cerebral autoregulation, but must be balanced against increased work load for the heart. In a pooled analysis of the two RCTs, a higher MAP target led to decreased levels of troponin over time in patients with cardiac arrest and acute myocardial infarction.[37] In addition, a higher MAP target decreased levels of Neurofilament light chain (NfL), a new outcome predictor after cardiac arrest.[38]

$PtCO_2$ is a marker of tissue perfusion. With decreasing blood flow, $PtCO_2$ will increase even under aerobic conditions since the production of pCO_2 is unaltered, but less blood is available for transportation to the lungs. Under anaerobic conditions lactic acid rapidly increases making it acidotic. The acidosis is buffered by bicarbonate producing increasing amounts of pCO_2. Accordingly $PtCO_2$ will rise rapidly.[12–16] Immediately after cardiac arrest $PbtCO_2$ more than doubled. After ROSC, $PbtCO_2$ declined rapidly and reached pre-ROSC levels 45 min after ROSC and continued to be low for the rest of the experiment signifying adequate blood supply.[12–16]

Microdialysis offers the ability to measure tissue lactate, pyruvate, glucose, glutamate and glycerol, and disturbances in these metabolic factors correlates with functional outcome in patients.[39–44] Under anaerobic conditions a pattern of increased lactate, decreased pyruvate and glucose and increased lactate/pyruvate-ratio is formed,[15,45] and this was also confirmed in the present study. After ROSC both lactate and pyruvate increased and lactate/pyruvate-ratio decreased, which previously has been described to be caused by inflammatory conditions and tissue oedema.[46,47] Although targeting higher MAP improved cardiac output and CBF, markers for cerebral ischemia were similar between the two groups. A possible explanation could be an insufficient ischemic insult related to the 10-minute cardiac arrest.

Limitations

There are several limitations worth mentioning. First, the pigs were young and otherwise healthy prior to our experiments whereas human cardiac arrest patients are often older and frequently have co-morbidities such as chronic hypertension that may be associated with disturbance in cerebral autoregulation.[48] Additionally, CPB resuscitation is different from manual or mechanical CPR, and while providing consistent and standardised blood flow, the extracorporeal circulation may contribute to the severity of the sepsis-like syndrome commonly observed after cardiac arrest.[49] We used vasoactive agents to reach and maintain the targeted MAP, and these drugs may have effects that could influence the results. The use of noradrenaline to maintain target MAP is recommended in current post-resuscitation guidelines, whereas titrating nitroprusside to MAP60 is not common practice - and may have had unintentional and clinically relevant effects on CBF.[50] The research team still felt that regulating MAP using nitroprusside was preferable to using increased sedation that could potentially have a greater influence on CBF and metabolism. The use of pre-arrest heparin may also have reduced formation of micro

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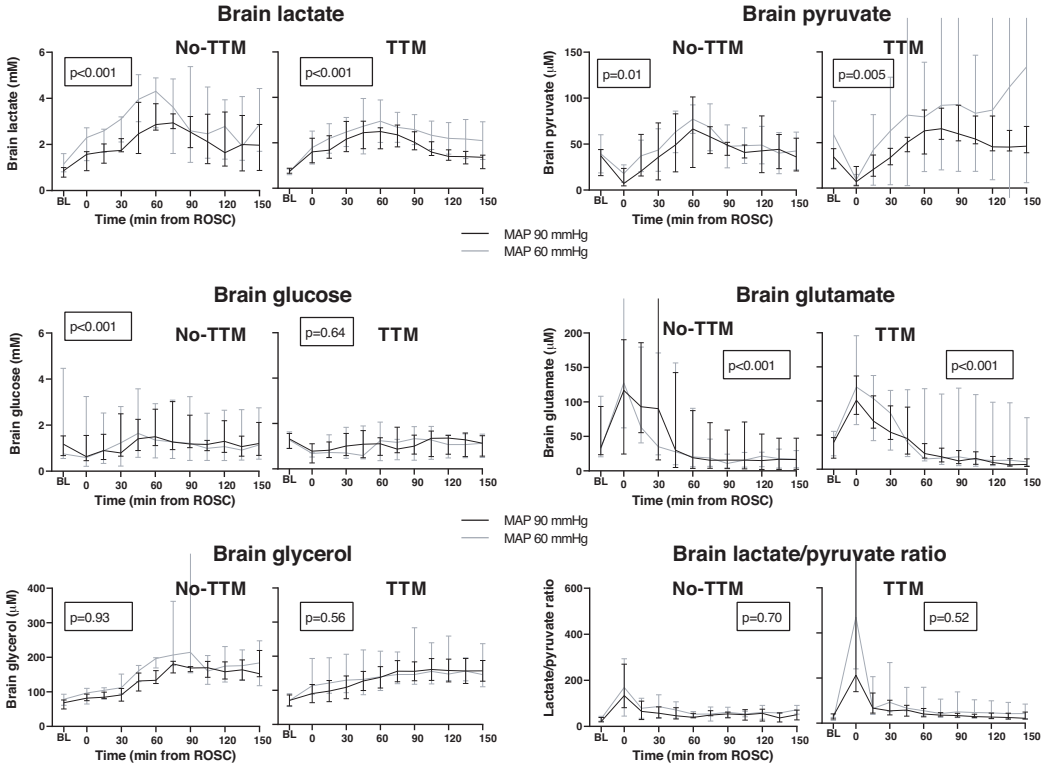

Fig. 4 – Cerebral microdialysis.
A thirty minutes stabilisation period after successful weaning from cardiopulmonary bypass (0 min) was followed by 120 min of observations with registration of outcome parameters. Repeated measurements every 15 min during the 120 min observational period for MAP60 and MAP90 groups were compared using a generalised mixed model with an unstructured covariance matrix. A p-value of less than 0.05 was considered statistically significant. TTM = Temperature Target Management.

thrombi and no-reflow areas, but this effect would be the same in all four groups.

The experimental model was developed for this study and introduced several modalities new to our laboratory. Introduction of microdialysis and $PbtCO_2$ necessitated additional access to the cerebral cortex. In the first series, access on one sides was gained through a craniectomy. Added exposure of the brain led to tissue swelling in several animals, rendering some of our microdialysis and $PbtCO_2$ data useless. Despite causing an important difference in methodology between the two series, we felt the complication rates associated with the craniectomy demanded the change to less invasive burr holes. Despite using two microdialysis catheters and less invasive access, results were still lost for four animals in series 2. The high proportion of missing data severely limited the certainty of the microdialysis data. Brain tissue oxygen monitoring ($PbtO_2$) could also have provided additional information, and could be considered in future experiments.

Conclusions

In this porcine cardiac arrest model, targeting MAP90 vs MAP60 led to better cerebral perfusion and more intact autoregulation, irrespective of the temperature, but without clear differences in ischaemic markers.

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Conflicts of interest

C. Skåre: Research grant from Zoll Foundation, receieved May 2019. H. Karlsen: None R.J Strand-Amundsen: Employed by Sensocure AS. M. Eriksen: None. V.M Skulberg: None. K. Sunde: Received 2019–20 travel grants and/or speakers fee from Bard Medical, a company manufacturing equipment for targeted temperature management. T.I. Tønnessen: Shareholder, board member and medical advisor for Sensocure AS. T.M. Olasveengen: Research grant from Laerdal Foundation.

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CRediT authorship contribution statement

Christiane Skåre: Investigation, Writing - original draft. **Hilde Karlsen:** Investigation, Writing - original draft. **Runar J. Strand-Amundsen:** Investigation, Writing - review & editing, Resources. **Morten Eriksen:** Investigation, Writing - review & editing, Resources. **Vidar M. Skulberg:** Investigation, Writing - review & editing, Resources. **Kjetil Sunde:** Conceptualization, Methodology, Funding acquisition, Supervision. **Tor Inge Tønnessen:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition, Resources. **Theresa M. Olasveengen:** Conceptualization, Methodology, Investigation, Writing - original draft, Funding acquisition, Resources, Supervision.

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