

Experimental paper

Left ventricular diastolic dysfunction during acute myocardial infarction: Effect of mild hypothermia[☆]

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ABSTRACT

Background: Mild hypothermia (MH) decreases infarct size and mortality in experimental reperfused myocardial infarction, but may potentiate ischaemia-induced left ventricular (LV) diastolic dysfunction. **Methods:** In anaesthetized pigs (70 ± 2 kg), polystyrol microspheres (45 μm) were infused repeatedly into the left circumflex artery until cardiac power output decreased >40%. Then, pigs were assigned to normothermia (NT, 38.0 °C, n = 8) or MH (33.0 °C, n = 8, intravascular cooling) and followed for 6 h (CME 6 h). *p < 0.05 vs baseline, †p < 0.05 vs NT.

Results: In NT, cardiac output (CO) decreased from 6.2 ± 0.3 to 3.4 ± 0.2 l/min, and heart rate increased from 89 ± 4 to 101 ± 6 bpm. LV end-diastolic volume fell from 139 ± 8 to 64 ± 4 ml*, while LV ejection fraction remained constant (49 ± 1 vs 53 ± 4%). The corresponding end-diastolic pressure–volume relationship was progressively shifted leftwards, reflecting severe LV diastolic dysfunction. In MH, CO fell to a similar degree. Spontaneous bradycardia compensated for slowed LV relaxation, and the leftward shift of the end-diastolic pressure–volume relationship was less pronounced during MH. MH increased systemic vascular resistance, such that mean aortic pressure remained higher in MH vs NT (69 ± 2† vs 54 ± 4 mmHg). Mixed venous oxygen saturation at CME 6 h was higher in MH than in NT (59 ± 4† vs 42 ± 2%) due to lowered systemic oxygen demand during cooling.

Conclusion: We conclude that (i) an acute loss of end-diastolic LV compliance is a major component of acute cardiac pump failure during experimental myocardial infarction, and that (ii) MH does not potentiate this diastolic LV failure, but stabilizes haemodynamics and improves systemic oxygen supply/demand imbalance by reducing demand.

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1. Introduction

The induction of mild hypothermia (MH, 32–34 °C) after cardiac arrest improves both neurological outcome and survival^{1,2} and has become intensive care guideline therapy.³ There is increasing evidence that better survival may in part be related not only to neurological, but also to direct cardiovascular effects. Myocardial infarct size could be reduced by MH when cooling was initiated

before the onset of reperfusion, both in the experimental setting⁴ and in patients.⁵ MH induces a hypometabolic state, allowing for higher central venous oxygen saturation and better preserved oxygen supply/demand balance at a given reduction of cardiac output in pigs.^{6,7} Finally, MH increased left ventricular (LV) contractility in normal and resuscitated porcine hearts in vivo, which, however, occurred at slowed LV relaxation and reduced LV end-diastolic distensibility.^{7,8}

In a porcine model of reperfused myocardial infarction and subsequent cardiogenic shock, Götzberg et al. reported reduced mortality and improved systemic haemodynamics in hypothermic vs normothermic animals.⁶ However, effects of MH on LV function were not assessed in this study. Such analysis would be of particular interest, as myocardial ischaemia and subsequent infarction per se negatively affect LV diastolic function. In humans, transient ischaemia induced by pacing in the presence of an epicardial stenosis increased LV end-diastolic pressure, resulting

Abbreviations: CME, coronary microembolisation; MH, mild hypothermia; NT, normothermia; LV, left ventricular.

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from both slowed active relaxation and an up- and leftward shift of the LV end-diastolic pressure–volume relationship.^{9,10} In rats, dogs and pigs, permanent coronary artery ligation^{11,12} or coronary microembolisation¹³ induced an acute leftward shift of the LV end-diastolic pressure–volume relationship that lasted up to three days after the onset of myocardial infarction.¹² Similar findings were obtained in patients during acute myocardial infarction.^{14,15}

MH could thus critically potentiate LV diastolic dysfunction during acute myocardial infarction. We aimed to characterize in detail the effect of MH on LV systolic and diastolic function during acute myocardial infarction. We applied coronary microembolisation as a model of no-reflow myocardial infarction, as the no-reflow phenomenon represents the worst outcome of reperfusion therapy. It is a strong predictor of short- and long-term mortality,¹⁶ and was therefore expected to generate pronounced diastolic abnormalities.

2. Methods

The experimental protocol was approved by the local Bioethics Committee of Vienna, Austria (BMWF-66010/0103-II/10b/2009), and conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85-23, revised 1996).

An expanded method section is provided in the [online supplement](#).

2.1. Experimental model

19 anaesthetized pigs (70 ± 2 kg) were instrumented with a Swan-Ganz catheter, a right atrial pacing probe, a LV pressure-conductance catheter, a valvuloplasty catheter (20 ml) in the descending aorta, and an intravascular cooling catheter (Accutrol™ Catheter 14F, InnerCool RTX Endovascular System, Philips Healthcare, Vienna, Austria) in the inferior vena cava. Body temperature was maintained at 38 °C by the intravascular device.

2.2. Experimental protocol

Blood samples were drawn at baseline conditions, and steady-state haemodynamics were acquired at spontaneous heart rate and during right atrial pacing at 100, 120, 140, 160, and if possible, at 180 bpm. Loading conditions were varied by short inflation of the aortic balloon catheter at spontaneous heart rate. Myocardial infarction was then induced by coronary microembolisation (CME) into the proximal left circumflex coronary artery: repetitive slow (1 min) injections of 500,000 polystyrene microspheres (45 µm) were administered until cardiac power output (W, mean aortic pressure × cardiac output/451) was reduced by more than 40%. Three animals developed sustained ventricular fibrillation during microsphere injections and were excluded from subsequent analysis. The remaining pigs were assigned sequentially 1:1 to either MH ($n = 8$, 33 °C) or normothermia (NT, $n = 8$, 38 °C). Measurements were repeated immediately (CME 0 h), and at 2 h, 4 h and 6 h after CME (CME 2 h, CME 4 h, CME 6 h, respectively). In MH, cooling was started after the CME 0 h measurement. Animals were sacrificed by an 80 mmol potassium chloride bolus. Blood gas analyses were performed immediately after withdrawal. Troponin T levels were assessed in serum obtained at CME 6 h.

2.3. Data analysis and statistics

Haemodynamic and conductance data were analysed off-line by CircLab software (custom made by P. Steendijk). Beyond standard parameters, we analysed data obtained during varied loading conditions (linear regression) to assess values for τ , dP/dt_{min} and the end-systolic volume at an end-systolic pressure of 100 mmHg,

as well as the end-systolic pressure–volume relationship. The end-diastolic pressure–volume relationship was derived from an exponential fit of corresponding data points.⁷

All data are presented as mean ± SEM. Data were analysed by 1-way or 2-way ANOVA for repeated measurements. Pressure–volume relationships were compared by analysis of covariance (ANCOVA). Post hoc testing was performed by Tukey's test. A p -value < 0.05 indicated significant differences.

3. Results

Three to five (median 4) microsphere injections were necessary to decrease cardiac power output by more than 40% according to the protocol. The total number of injected microspheres was similar between groups (NT: 2.1 ± 0.2 million, MH: 2.1 ± 0.1 million; 2.1 million microspheres correspond to a volume of approximately 0.1 ml). After the final injection, coronary angiography demonstrated reduced left circumflex coronary artery blood flow (TIMI 1 in all animals) that remained unchanged at the end of the protocol. No coronary artery damage was observed. At CME 6 h, levels of troponin T (ng/ml) were 2.2 ± 0.2 in NT and 2.8 ± 0.7 in MH ($p = NS$).

3.1. Systemic haemodynamics

In normothermic pigs heart rate increased, while cardiac output and mean aortic pressure decreased, resulting in a reduced cardiac power output after CME (all $p < 0.05$ vs baseline, Fig. 1A–C). During MH heart rate decreased ($p < 0.05$ vs baseline and vs NT). At a similar cardiac output, an increased systemic vascular resistance during MH resulted in a better preserved mean aortic pressure (both $p < 0.05$ vs NT, Fig. 1A–C, Table 1). Mean pulmonary arterial pressure increased to a small extent in both groups ($p < 0.05$ vs baseline, Table 1).

3.2. Blood samples

Mixed venous oxygen saturation decreased progressively after CME during NT ($p < 0.05$ vs baseline and vs CME 0 h, Fig. 1D). With lower whole body oxygen consumption in MH ($p < 0.05$ vs baseline, Table 1), mixed venous oxygen saturation recovered to near baseline values (Fig. 1D). The haemoglobin concentration slightly decreased during normothermia with no significant difference between groups (Table 1).

3.3. LV dimensions

LV end-diastolic, end-systolic and stroke volume decreased after CME in both groups ($p < 0.05$ vs baseline, Fig. 2A–C). This decrease was progressive at CME 6 h in NT ($p < 0.05$ vs CME 0 h), but not in MH ($p = NS$ vs CME 0 h). LV ejection fraction remained near baseline levels throughout the protocol in both groups (Fig. 2D).

3.4. LV systolic function

LV maximum pressure (LVPmax) as well as maximum dP/dt decreased after CME in both groups ($p < 0.05$ vs baseline, Fig. 3A–F, Table 1); this decrease was progressive in NT ($p < 0.05$ vs CME 0 h). LVPmax remained higher during MH than during NT at CME 6 h ($p < 0.05$, Table 1). Pressure–volume analysis did not reflect a loss of LV contractility after CME. In both groups, the slope of the end-systolic pressure–volume relationship increased, the loops did not shift rightwards, and the LV end-systolic volume at an end-systolic pressure of 100 mmHg remained constant compared to the respective baseline values (Figs. 3G–I and 4A and B, Table 1).

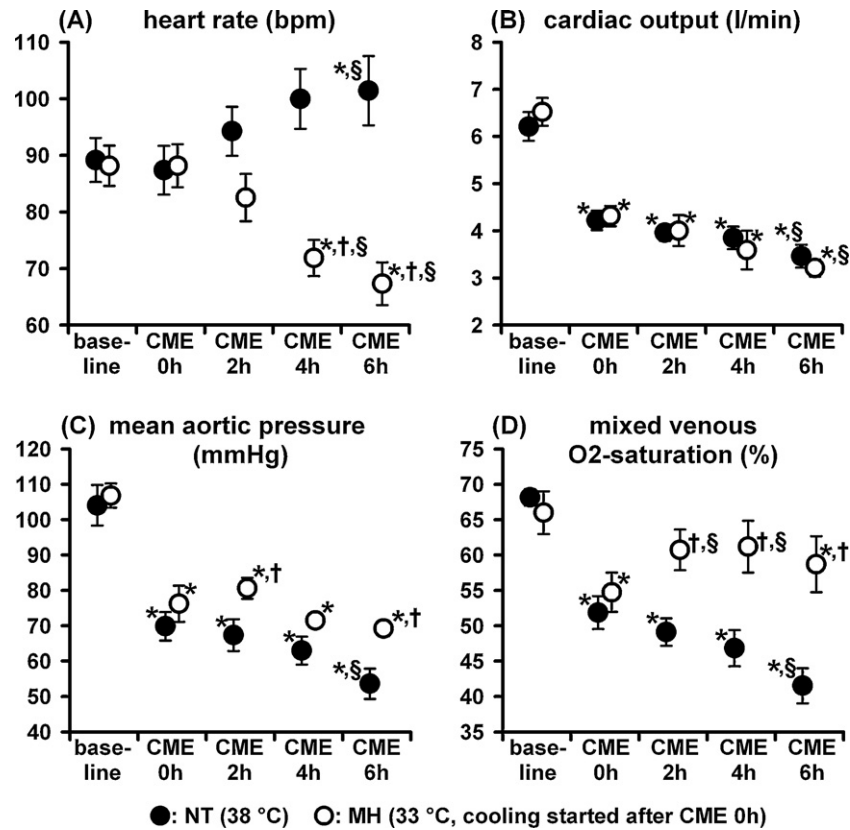
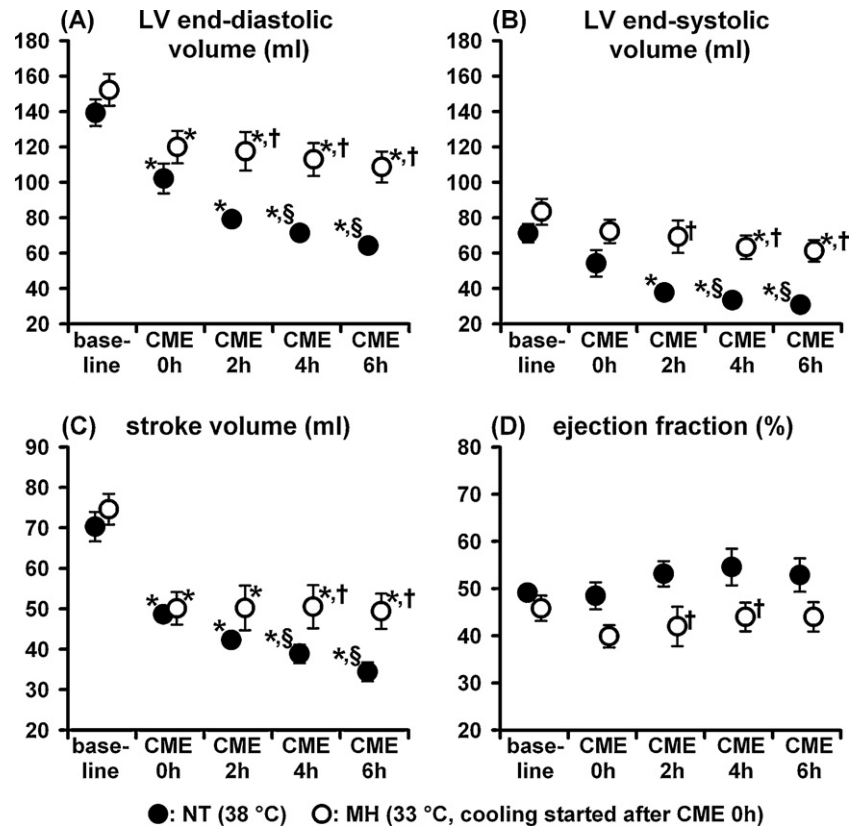
Fig. 1. * $p < 0.05$ vs baseline, † $p < 0.05$ vs NT, § $p < 0.05$ vs CME 0 h.Fig. 2. * $p < 0.05$ vs baseline, † $p < 0.05$ vs NT, § $p < 0.05$ vs CME 0 h.

Table 1
Haemodynamic and metabolic data.

| | | Baseline | CME 0 h | CME 2 h | CME 4 h | CME 6 h |
|--------------------------|----|-------------|--------------------------|-----------------------------|-----------------------------|-----------------------------|
| Temp (°C) | NT | 38.0 ± 0.0 | 38.2 ± 0.1 | 38.1 ± 0.1 | 38.1 ± 0.0 | 38.0 ± 0.0 |
| | MH | 38.0 ± 0.1 | 38.0 ± 0.2 | 35.0 ± 0.3 ^{*,†,§} | 33.2 ± 0.2 ^{*,†,§} | 32.9 ± 0.1 ^{*,†,§} |
| LVPmax (mmHg) | NT | 119 ± 6 | 83 ± 3 [*] | 79 ± 4 [*] | 75 ± 3 [*] | 66 ± 4 ^{*,§} |
| | MH | 121 ± 5 | 88 ± 5 [*] | 91 ± 3 [*] | 80 ± 2 [*] | 79 ± 3 ^{*,†} |
| LVPed (mmHg) | NT | 9.0 ± 0.9 | 14.7 ± 1.3 [*] | 15.5 ± 1.2 [*] | 13.5 ± 1.3 [*] | 11.4 ± 1.7 |
| | MH | 7.7 ± 0.6 | 15.9 ± 1.7 [*] | 16.4 ± 1.4 [*] | 14.9 ± 1.1 [*] | 14.2 ± 0.9 [*] |
| dP/dtmax (mmHg/s) | NT | 1819 ± 84 | 1216 ± 53 [*] | 1235 ± 52 [*] | 1095 ± 51 [*] | 974 ± 67 ^{*,§} |
| | MH | 1777 ± 79 | 1310 ± 137 [*] | 1462 ± 110 [*] | 1232 ± 88 [*] | 1174 ± 73 [*] |
| dP/dtmin (mmHg/s) | NT | −2293 ± 107 | −1308 ± 82 [*] | −1213 ± 102 [*] | −1132 ± 79 [*] | −957 ± 84 ^{*,§} |
| | MH | −2317 ± 100 | −1348 ± 118 [*] | −1005 ± 66 ^{*,§} | −705 ± 54 ^{*,†,§} | −672 ± 72 ^{*,†,§} |
| dP/dtmin–Pes100 (mmHg/s) | NT | −2136 ± 76 | −1563 ± 50 [*] | −1584 ± 63 [*] | −1547 ± 47 [*] | −1446 ± 42 [*] |
| | MH | −2199 ± 94 | −1554 ± 81 [*] | −1204 ± 54 ^{*,†,§} | −978 ± 55 ^{*,†,§} | −889 ± 69 ^{*,†,§} |
| τ (ms) | NT | 39 ± 1 | 43 ± 1 | 43 ± 2 | 43 ± 1 | 43 ± 1 |
| | MH | 39 ± 1 | 48 ± 2 | 74 ± 4 ^{*,†,§} | 103 ± 13 ^{*,†,§} | 101 ± 8 ^{*,†,§} |
| τ–Pes100 (ms) | NT | 34 ± 2 | 50 ± 2 | 48 ± 3 | 50 ± 2 | 57 ± 2 [*] |
| | MH | 30 ± 2 | 56 ± 4 [*] | 74 ± 3 ^{*,†,§} | 104 ± 7 ^{*,†,§} | 118 ± 12 ^{*,†,§} |
| Slope ESPVR (mmHg/ml) | NT | 1.6 ± 0.2 | 2.2 ± 0.3 | 2.6 ± 0.3 [*] | 2.6 ± 0.3 [*] | 2.6 ± 0.4 [*] |
| | MH | 1.3 ± 0.2 | 2.1 ± 0.2 | 2.5 ± 0.4 [*] | 2.4 ± 0.3 [*] | 2.9 ± 0.4 [*] |
| Ves–Pes100 (ml) | NT | 62 ± 7 | 63 ± 8 | 50 ± 4 | 42 ± 5 | 47 ± 4 |
| | MH | 76 ± 8 | 83 ± 8 [†] | 77 ± 9 [†] | 75 ± 7 [†] | 68 ± 7 [†] |
| SVR (mmHg/l/min) | NT | 16.2 ± 1.4 | 15.1 ± 1.0 | 15.3 ± 0.9 | 14.7 ± 0.9 | 13.6 ± 1.1 |
| | MH | 15.8 ± 0.6 | 16.6 ± 1.6 | 19.8 ± 1.6 ^{*,†} | 19.9 ± 1.7 ^{*,†} | 20.2 ± 1.0 ^{*,†,§} |
| CPO (W) | NT | 1.43 ± 0.10 | 0.66 ± 0.06 [*] | 0.60 ± 0.06 [*] | 0.55 ± 0.06 [*] | 0.42 ± 0.06 ^{*,§} |
| | MH | 1.55 ± 0.10 | 0.73 ± 0.06 [*] | 0.71 ± 0.05 [*] | 0.57 ± 0.06 [*] | 0.50 ± 0.03 ^{*,§} |
| Mean PAP (mmHg) | NT | 21 ± 1 | 23 ± 1 | 27 ± 1 [*] | 26 ± 1 [*] | 26 ± 2 [*] |
| | MH | 18 ± 1 | 23 ± 3 | 25 ± 2 [*] | 28 ± 3 [*] | 28 ± 2 [*] |
| Hb (g/dl) | NT | 10.4 ± 0.2 | 10.2 ± 0.2 | 9.8 ± 0.2 [*] | 9.8 ± 0.2 [*] | 9.6 ± 0.2 ^{*,§} |
| | MH | 10.3 ± 0.3 | 10.1 ± 0.2 | 10.2 ± 0.1 | 10.1 ± 0.2 | 10.1 ± 0.3 |
| WB–VO2 (ml/min) | NT | 308 ± 12 | 298 ± 6 | 283 ± 7 | 283 ± 7 | 272 ± 12 |
| | MH | 315 ± 15 | 291 ± 13 | 233 ± 12 ^{*,†,§} | 197 ± 8 ^{*,†,§} | 191 ± 8 ^{*,†,§} |

temp: temperature, LVPmax: maximum LV pressure, LVPed: end-diastolic LV pressure, dP/dtmin–Pes100: dP/dtmin at an end-systolic pressure of 100 mmHg, τ–Pes100: tau at an end-systolic pressure of 100 mmHg, slope ESPVR: slope of the end-systolic pressure–volume relationship (linear regression), Ves–Pes100: LV end-systolic volume at an end-systolic pressure of 100 mmHg, SVR: systemic vascular resistance, CPO: cardiac power output, mean PAP: mean pulmonary arterial pressure, Hb: haemoglobin-concentration, WB–VO2: whole body oxygen consumption.

^{*} $p < 0.05$ vs baseline.

[†] $p < 0.05$ vs NT.

[§] $p < 0.05$ vs CME 0 h.

3.5. LV diastolic function

A decreased dP/dtmin and increased τ demonstrated impaired active relaxation after CME, both at spontaneous pressures and when referred to a LV end-systolic pressure of 100 mmHg (all $p < 0.05$ vs baseline, Table 1). MH potentiated these changes ($p < 0.05$ vs NT).

The end-diastolic pressure–volume relationship was immediately shifted left- and upwards after CME in both groups ($p < 0.05$ vs baseline, Figs. 3G–I and 4A and B). This shift was progressive at CME 6 h in NT ($p < 0.05$ vs CME 0 h), but not in MH.

3.6. Effects of atrial pacing

With higher heart rates, LV end-diastolic volume decreased. At up to 140 bpm, this was associated with a proportionate decrease of LV end-diastolic pressure, such that the data point fell on the corresponding baseline end-diastolic pressure–volume relationship (Fig. 5A and B). At maximum heart rates (pacing at 160 or 180 bpm), however, LV end-diastolic pressure increased in spite of smaller end-diastolic volumes, suggesting that the diastolic time interval was too short to allow for complete relaxation (see also online supplement). This was true also at CME 0 h and 6 h in NT (Fig. 5C and E), while during MH, this increase occurred at substantially lower heart rates (Fig. 5F).

Right atrial pacing increased cardiac output at baseline by a maximum of 2.5 ± 0.3 l/min in NT. This increase was smaller at CME 6 h (0.8 ± 0.3 l/min, $p < 0.05$ vs baseline). A similar change was seen in MH (baseline 2.4 ± 0.6 , CME 6 h: 1.3 ± 0.4 l/min, $p = 0.10$ vs baseline, $p = 0.41$ vs NT), see also online supplement.

4. Discussion

4.1. Acute heart failure after coronary microembolisation during normothermia

Coronary microembolisation (CME) in the normothermic group caused severe heart failure, as illustrated by reduced cardiac output, mean aortic pressure, and a fall of mixed venous oxygen saturation – a net parameter of systemic oxygen supply/demand balance – below 45% at 6 h after CME (Fig. 1B–D). In contrast to long-term LV remodelling after myocardial infarction, this was not associated with LV dilatation and reduced LV ejection fraction, but with a progressive and massive fall of LV volumes with no change in LV ejection fraction (Fig. 2A–D). LV pressure–volume analysis revealed a rapid leftward shift of the underlying end-diastolic pressure–volume relationship after CME that further continued to the end of the protocol at 6 h after CME, leading to a mean reduction of LV end-diastolic volume by more than 50% (Figs. 2A, 3G–I and 4A).

Such compromised LV filling could in principal result from right ventricular dilatation, delayed LV relaxation, increased passive LV stiffness, or all of them. At only moderately increased mean pulmonary artery pressures, it is unlikely that LV filling was restricted by right ventricular chamber enlargement. To challenge LV relaxation, we performed right atrial pacing to shorten the diastolic time interval (detailed data are provided in the online supplement). We suggested that if prolonged active relaxation would limit LV filling, then any increase of heart rate would result in an upward and/or leftward shift of corresponding LV end-diastolic pressure–volume data points compared to the end-diastolic pressure–volume relationship at baseline heart rate. As shown in Fig. 5A, C and E, this was

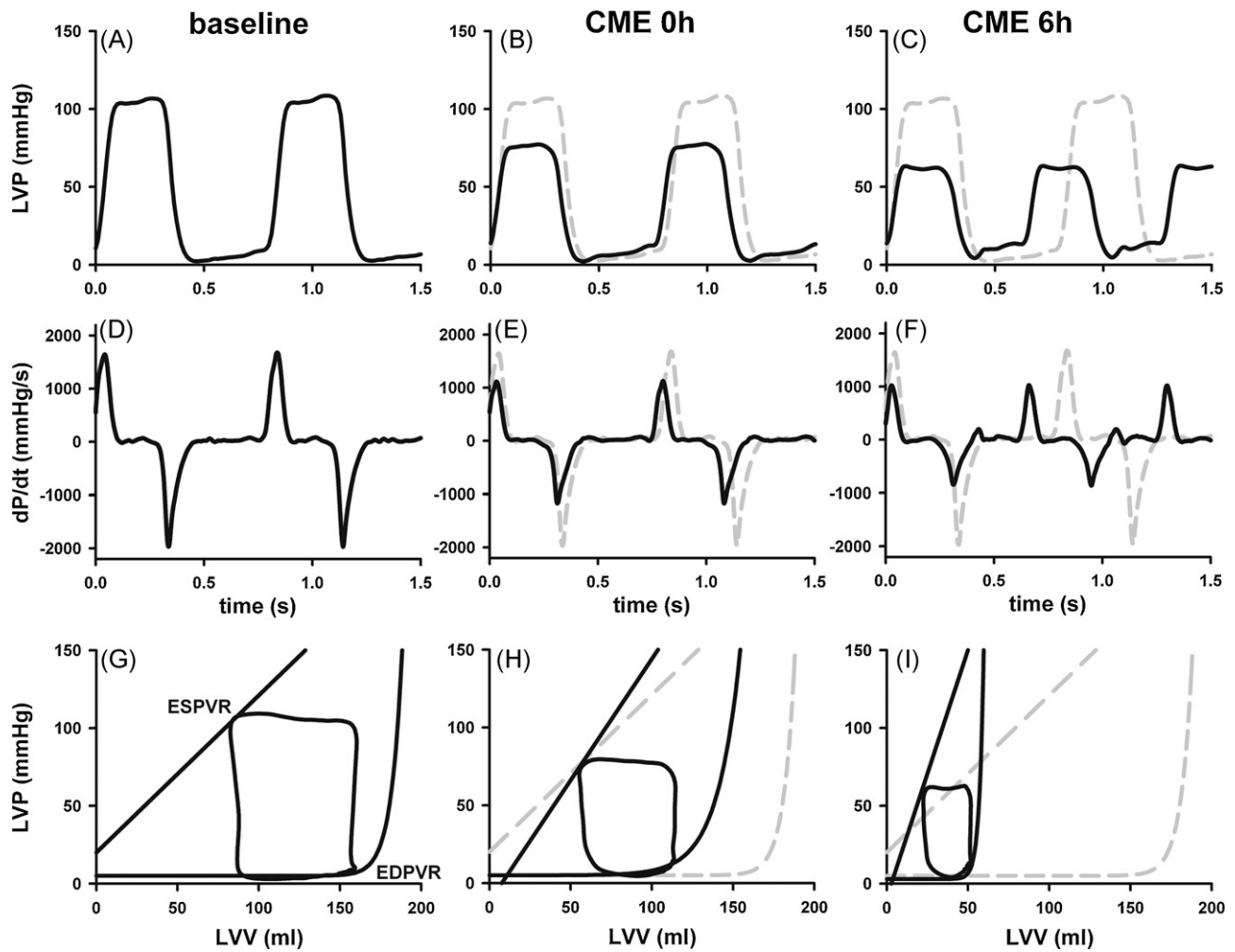


Fig. 3. Original registration of left ventricular pressure (LVP) vs time, dP/dt vs time, and LV pressure vs LV volume (LVV) in an animal of the NT group. CME induced a progressive decrease of maximum LVP and maximum/minimum dP/dt . The LV end-diastolic pressure–volume relationship was progressively shifted leftwards, resulting in substantially lower LV end-diastolic volumes at given end-diastolic pressures.

true only at maximum heart rates both before and at 6 h after CME, but not at moderately increased heart rates of, for example, 120 and 140 bpm. We therefore rule out that active relaxation, although impaired after CME (Table 1), is the limiting factor for LV filling after CME, but conclude that the LV after CME demonstrates an acute and massive loss of compliance. In line with that, the embolized perfusion territory in the present study was clearly recognized by its hard

and stiff consistency during autopsy, in considerable contrast to the non-embolized LV regions. Corresponding findings were obtained in rat hearts isolated at up to three days after left anterior coronary artery ligation; a loss of LV compliance led to an approximately 50% decrease of LV end-diastolic volume at a given end-diastolic pressure and was associated with myocardial swelling, congestion, haemorrhage and contraction band necrosis in the infarct zone.¹²

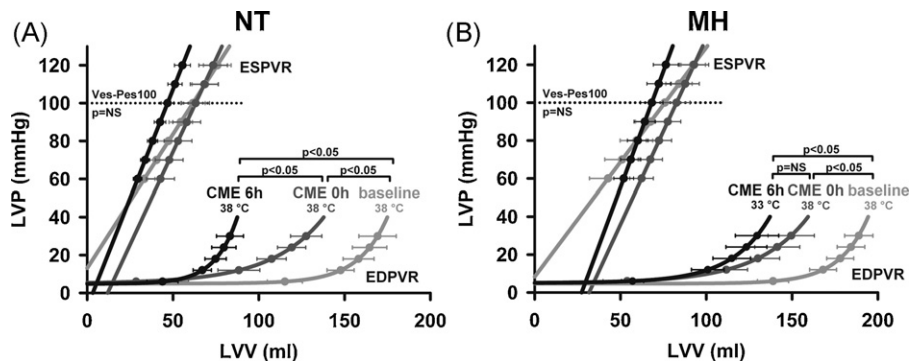


Fig. 4. The end-systolic pressure–volume relationship (ESPVR) was steeper after CME in both groups, but LV end-systolic volume at an end-systolic pressure of 100 mmHg (Ves-Pes100) was not different between time points. The end-diastolic pressure–volume relationship (EDPVR) was shifted leftwards immediately after coronary microembolisation (CME 0h). This shift was further pronounced at CME 6h in NT, but not in MH.

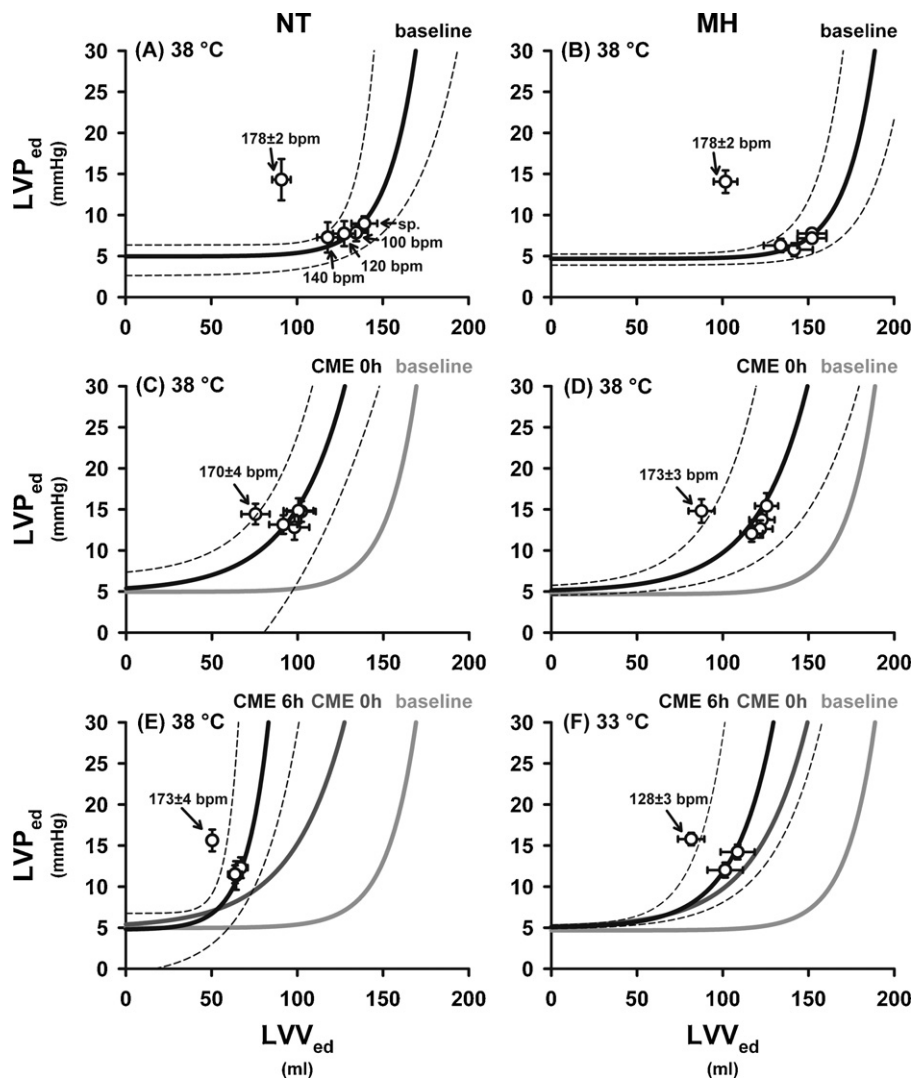


Fig. 5. Only pacing at maximum heart rates caused the corresponding end-diastolic LV pressure–volume points to fall outside of the 95% confidence interval (dashed lines) of the end-diastolic pressure–volume relationship (EDPVR) obtained at spontaneous heart rate. Maximum heart rate during MH was lower than during NT.

4.2. Effects of mild hypothermia

As previously reported by Götzberg et al.,⁶ MH in the present study did not increase cardiac output, yet MH increased mean aortic pressure by an increase of systemic vascular resistance and substantially decreased systemic oxygen demand. This hypometabolic state during MH allowed for a re-increase of mixed venous oxygen saturation to near baseline values, indicating a substantial improvement of systemic oxygen supply/demand imbalance at improved aortic pressure.

As demonstrated in previous studies,^{7,8,17} MH substantially slowed active relaxation, and atrial pacing demonstrated a reduced maximum heart rate in MH. However, the end-diastolic pressure–volume data points during right atrial pacing at 100 bpm fell on the end-diastolic pressure–volume relationship obtained at the spontaneous heart rate of less than 70 bpm (Fig. 5F). Slowed LV relaxation during MH did thus not limit LV diastolic filling at spontaneous heart rates. Accordingly, atrial pacing at CME 6 h in MH recruited an increase of cardiac output that was not lower than in NT at the same time point.

MH per se decreased LV compliance in normal porcine hearts,^{7,8} which can be explained by altered LV visco-elastic properties.¹⁸ Surprisingly, the leftward shift of the end-diastolic

pressure–volume relationship from CME 0 h to CME 6 h in MH was less than in NT (Fig. 4B); LV end-diastolic and stroke volume were better preserved during MH. The loss of LV compliance after CME in the present study resembles the “stone heart” after untreated cardiac arrest, which results from ATP loss and subsequent cardiomyocyte contracture.^{19,20} Cooling in isolated rat hearts (28°C)¹⁹ and pigs in vivo (33°C)²¹ delayed the onset of a stone heart, and a similar effect within the embolized LV territory and the hypoperfused but viable infarction border zones may underlie better preserved LV compliance during MH in the present study.

MH is known to exert a positive inotropic effect in a variety of preparations and species (reviewed in Ref.⁸), however, such evidence is missing in the present study. Instead, the slope of the end-systolic pressure–volume relationship increased (rather than decreased) after myocardial infarction per se but was not different in MH vs NT. Also, end-systolic volumes were higher in MH vs NT (Fig. 2B). These findings reflect that acute cardiac pump failure in the present study results not only from acute systolic dysfunction due to loss of contractile myocardium, but also from an acute and progressive increase of passive LV stiffness throughout the cardiac cycle with increased end-systolic and, in particular, end-diastolic stiffness. The end-systolic pressure–volume relationship alone is therefore unable to detect the state of heart failure per se, pointing

to the pivotal role of diastolic LV function in the present study. Of note, the relative measure of LV ejection fraction was transiently lower in MH in spite of higher stroke volumes, illustrating its insufficiency to detect diastolic abnormalities of LV function.

4.3. Clinical implications

In the clinical setting, the LV contractile phenotype at CME 6 h represents a therapeutic dilemma. With the massive leftward shift of the LV end-diastolic pressure–volume relationship, the LV is unable to hold an adequate preload, and volume administration would rapidly induce pulmonary oedema. Catecholamines could only have a limited effect, as the end-systolic volume is already only a small fraction of baseline values thus preventing increases of stroke volume. Even intraaortic balloon counterpulsation (IABP) might be rather ineffective, as coronary perfusion cannot be improved in the presence of massive no-reflow, and the small LV would not be able to increase its stroke volume when afterload has been decreased by preceding inflation/deflation of the IABP balloon. Given the disappointing clinical results on the effect of IABP on mortality in cardiogenic shock,²² it is a tempting hypothesis that failure of IABP may relate to no-reflow and the presence of acute diastolic LV failure as demonstrated in this study. The induction of MH in turn represents a promising intervention, as it improves systemic oxygen supply/demand imbalance not by increasing supply, but by reducing demand. As a method of cooling during acute cardiac failure, an intravascular device seems particularly appropriate, as it is effective also during hypocirculatory states associated with body surface hypoperfusion, and does not require volume loading.

4.4. Limitations

We did not obtain data on mortality and on the effect of rewarming. Boyer et al. reported a survival time of 6.8 ± 0.8 h in normothermic dogs after massive coronary embolization which was extended more than 3-fold by surface cooling (32°C),²³ and similar findings were obtained by Götberg et al. in reperfused myocardial infarction.⁶

Cooling healthy pigs to 25°C and subsequent rewarming induced troponin release and systolic dysfunction.²⁴ At milder degrees of hypothermia, however, such adverse effects seemed to be smaller: dogs cooled to $28\text{--}30^\circ\text{C}$ after massive myocardial infarction and rewarmed after 5 h even demonstrated a better preserved cardiac output and mean aortic pressure compared to normothermic animals.²⁵

Finally, in patients with a culprit lesion in the left circumflex artery, the median time from the onset of symptoms to the onset of cardiogenic shock was only 3.9 h.²⁶ Thus, protective effects of MH within the first hours after myocardial infarction as demonstrated here are likely to be clinically relevant.

5. Conclusion

We demonstrate that a major mechanism of global LV pump failure in our model of no-reflow myocardial infarction relates to acute diastolic heart failure, as the LV is progressively unable to hold an adequate preload. MH attenuates this loss of compliance. In addition, MH improves systemic oxygen supply/demand imbalance at better preserved aortic pressures and may thus be a treatment option for cardiogenic shock.

Conflict of interest

H.P. received an unrestricted grant from Philips Healthcare, Vienna, Austria, which also supplied the cooling devices. The other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2012.05.011>.

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