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Inhaled Xenon Attenuates Myocardial Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest

The Xe-Hypotheca Trial

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ABSTRACT

BACKGROUND The authors previously reported that inhaled xenon combined with hypothermia attenuates brain white matter injury in comatose survivors of out-of-hospital cardiac arrest (OHCA).

OBJECTIVES A pre-defined secondary objective was to assess the effect of inhaled xenon on myocardial ischemic damage in the same study population.

METHODS A total of 110 comatose patients who had experienced OHCA from a cardiac cause were randomized to receive either inhaled xenon (40% end-tidal concentration) combined with hypothermia (33°C) for 24 h (n = 55; xenon group) or hypothermia treatment alone (n = 55; control group). Troponin-T levels were measured at hospital admission, and at 24 h, 48 h, and 72 h post-cardiac arrest. All available cases were analyzed for troponin-T release.

RESULTS Troponin-T measurements were available from 54 xenon patients and 54 control patients. The baseline characteristics did not differ significantly between the groups. After adjustments for age, sex, study site, primary coronary percutaneous intervention (PCI), and norepinephrine dose, the mean ± SD post-arrival incremental change of the ln-transformed troponin-T at 72 h was 0.79 ± 1.54 in the xenon group and 1.56 ± 1.38 in the control group (adjusted mean difference −0.66; 95% confidence interval: −1.16 to −0.16; p = 0.01). The effect of xenon on the change in the troponin-T values did not differ in patients with or without PCI or in those with a diagnosis of ST-segment elevation myocardial infarction (group by PCI or ST-segment elevation myocardial infarction interaction effect; p = 0.86 and p = 0.71, respectively).

CONCLUSIONS Among comatose survivors of OHCA, in comparison with hypothermia alone, inhaled xenon combined with hypothermia suggested a less severe myocardial injury as demonstrated by the significantly reduced release of troponin-T. (J Am Coll Cardiol 2017;70:2652-60) © 2017 by the American College of Cardiology Foundation.

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Throughout Europe, the in-hospital mortality of successfully resuscitated out-of-hospital cardiac arrest (OHCA) patients ranges from 41% to 86% (1-3). International guidelines for post-resuscitation care recommend targeted temperature management with target temperatures between 32°C and 36°C (4,5).

Post-cardiac arrest syndrome is a complex combination of ischemic cerebral and myocardial injury combined with a reperfusion response leading to different combinations of multiorgan failure; it is responsible for significant morbidity and mortality as a consequence of whole-body ischemia (4). Although ischemic brain injury is the leading cause for in-hospital deaths after OHCA, myocardial dysfunction and circulatory failure account for most deaths during the first 3 days (6,7). In addition, the severity of myocardial injury affects both short- and long-term mortality (8-10). Therefore, new strategies to attenuate the ischemic reperfusion myocardial injury leading to cardiomyocyte death after cardiac arrest are needed.

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Earlier clinical studies in patients with and without cardiovascular disease have demonstrated that inhalation of the noble gas xenon may be cardioprotective by decreasing heart rate without affecting either cardiac conductance or contractility (11-13). In animal models, xenon has provided cardioprotection by pre- and post-conditioning mechanisms (14,15). We have reported previously that xenon combined with hypothermia confers neuroprotection by attenuating the brain white matter injury more than hypothermia alone in comatose survivors of cardiac arrest (16). Inhaled xenon is feasible, well-tolerated, and safe in OHCA patients (17). The purpose of this study was to evaluate the effect of xenon on myocardial damage in comatose survivors of OHCA.

METHODS

STUDY DESIGN. The Xe-HYPOTHECA trial (Effect of Xenon and Therapeutic Hypothermia, on the Brain and on Neurological Outcome Following Brain Ischemia in Cardiac Arrest Patients; NCT00879892) was a randomized 2-group, single-blinded phase II clinical drug trial at 2 multipurpose intensive care units (ICU) in Finland. The ethics committee of the Hospital District of Southwest Finland and the institutional review boards of the Helsinki University Hospital and the Finnish Medicine Agency approved the study. As described previously, an independent data and safety monitoring committee reviewed data after enrollment of every 4 patients and after each 6-month interval. The study was conducted according to good clinical practice and the current revision of the Declaration of Helsinki. Written informed assent was obtained from the next-of-kin or from the legal representative of the patient within 4 h after hospital admission. The patient's family was informed about the right to withdraw from the study at any point, but the data collected until possible withdrawal could be used in the analyses as predefined in the protocol. Patients were informed accordingly if they regained consciousness (16,17).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

ICU = intensive care unit

NSTEMI = non-ST-segment elevation myocardial infarction

OHCA = out-of-hospital cardiac arrest

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

The patients were allocated in a 1:1 ratio with random block sizes of 4, 6, and 8 to receive either therapeutic hypothermia treatment alone for 24 h (designated as the control group) or inhaled xenon (LENOXe, Air Liquide Medical, Düsseldorf, Germany) in combination with hypothermia for 24 h (designated as the xenon group). The clinical investigators enrolled the patients, and after assent was received, randomization was performed with sealed computer-randomized envelopes followed by the assigned intervention. Due to practical and safety considerations, the personnel involved in the patient treatment could not be blinded. A mode of death was classified as neurological, cardiac, or multiorgan as described previously (16). A local neurological prognostication consensus was used in decisions to withdraw life-sustaining treatment (16).

In the Xe-HYPOTHECA trial, the primary hypothesis was that xenon would attenuate white matter injury after OHCA. We have previously published the feasibility and cardiac safety of inhaled xenon after OHCA, and the effect of inhaled xenon on cerebral white matter damage and on the clinical outcome at 6 months in comatose survivors of OHCA (16,17). The latter report also included the protocol of the Xe-HYPOTHECA trial. The effect of xenon on myocardial injury was a pre-defined secondary endpoint.

PATIENT POPULATION. Consecutive comatose survivors of OHCA admitted to Turku and Helsinki University hospitals were screened for eligibility. The main criteria for inclusion were witnessed OHCA from shockable initial rhythm, that is, ventricular fibrillation or pulseless ventricular tachycardia, and restoration of spontaneous circulation within 45 min. Details of inclusion and exclusion criteria are presented in Online Table 1.

TREATMENT PROTOCOL. If indicated, coronary angiography interventions were performed before ICU admission. There was adherence to a detailed

treatment protocol that included hemodynamic and ventilator targets during cooling and normothermia as described previously (17). The sedation depth was assessed with the Richmond Agitation Sedation Scale every 4 h from admission into intensive care to the end of hypothermia treatment. The patients were cooled with an invasive intravascular temperature management device, the Alsius CoolGard 3000 thermal regulation system (Zoll Medical Corporation, Chelmsford, Massachusetts) to target a core temperature of 33°C, which was maintained for 24 h. Inhaled xenon was initiated immediately after randomization through a closed-circuit ventilator (PhysioFlex, Dräger, Lübeck, Germany). The end-tidal xenon concentration was adjusted to at least 40% and delivered until start of rewarming. The pre-defined arterial partial oxygen pressure was maintained during hypothermia treatment and the ventilator was adjusted if indicated as described previously (17).

ASSESSMENTS. Troponin-T was assessed at admission (baseline), and at 24, 48, and 72 h after OHCA. Until March 1, 2012, troponin-T was analyzed with a limit of detection of 0.03 μg/l (Electrochemiluminescence immunoassay, ECLIA Troponin-T Cardiac, Roche Diagnostics, Mannheim, Germany). Thereafter, a high-sensitivity cardiac troponin-T assay was used with a limit of detection of 5 ng/l (Electrochemiluminescence immunoassay, ECLIA Troponin T high-sensitive, Roche Diagnostics). The high-sensitivity troponin-T values were transformed to the corresponding μg/l values. The diagnosis of acute myocardial infarction was based upon the latest recommendations (8), namely, the ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarctions (NSTEMI) were defined by increased blood levels of cardiac troponin-T above the baseline value together with clinical features, including electrocardiographic findings in the field, and on hospital arrival and at 24, 48, and 72 h after cardiac arrest; angiographic findings; and possible autopsy report. The angiographic and electrocardiographic findings were analyzed by experienced cardiologists who were blinded to the intervention group. Acute kidney injury was diagnosed as previously described (16,17).

STATISTICAL ANALYSES. The sample size of 110 patients was based on a power analysis of the fractional anisotropy values from brain magnetic resonance imaging, that is, the primary endpoint of the Xe-HYPOTHECA trial (16). The Shapiro-Wilk *W* test was used to evaluate the normality of all continuous variables. Two-sample Student's *t*-test and Mann-Whitney *U* test were used to compare continuous characteristic variables between groups. Categorical characteristic variables were analyzed with the chi-square test or Fisher exact test. The correlations between the increment in the level of troponin-T from hospital admission to 72 h and the dose of administered drugs (i.e., norepinephrine, epinephrine, dobutamine, dopamine, levosimendane, furosemide, propofol, midazolam, fentanyl, and insulin), and hemodynamic parameters (mean and systolic arterial pressure, central venous pressure, heart rate in 2-min [Turku] or 5-min [Helsinki] epochs) during the first 24 h and at 72 h after ICU admission were calculated using Spearman correlation coefficients. The differences in changes in troponin-T values between groups were analyzed using repeated measures analysis of covariance adjusted for age, sex, study site, percutaneous coronary intervention (PCI), and cumulative norepinephrine use in the first 24 h after ICU admission. A natural logarithmic (ln) transformation was performed for troponin-T values before analyses due to their positively skewed distribution. Results of troponin-T values at each time point were presented as geometric mean (95% confidence interval [CI]). The geometric means were calculated by back-transforming the means of ln-transformed troponin-T values to the original scale. An unstructured covariance matrix was used in the repeated measures model. An all-available case analysis was applied to the troponin-T. The effect of troponin-T on survival was analyzed with Cox regression adjusted for age, sex, study site, and group. Results are expressed using hazard ratios (HRs) with 95% CIs. A 2-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS. Turku University Hospital recruited patients between August 2009 and September 2014, and Helsinki University Hospital, between October 2012 and September 2014, respectively. The 6-month follow-up was completed by March 2015. Altogether, 224 patients were screened for eligibility, 110 were enrolled, with 55 being randomly assigned to the xenon group and 55 to the control group. At 6 months after OHCA, 15 of the 55 xenon patients and 19 of the 55 control patients had died. Details of the deaths, mode of deaths, and withdrawals are presented in Online Table 2.

The baseline characteristics of the 54 xenon and 54 control patients for whom we had troponin-T data did not differ between the groups (**Table 1**). The reasons

for missing troponin-T data are summarized in Online Table 3. The number of PCIs, diseased coronary vessels, and patients with incident coronary artery disease on hospital arrival were similar in the 2 groups (**Table 2**). A precise status of the coronary arteries could not be determined in 7 xenon patients and in 4 of the control patients because neither coronary angiography nor autopsy was performed on these patients. Of the patients with STEMI (n = 36), 14 of the 17 in the xenon group and 16 of the 19 in the control group were treated with PCI on hospital arrival. In patients with NSTEMI (n = 64), 2 in the control group and 1 in the xenon group were treated with PCI on hospital arrival. Eight patients without an acute myocardial infarction did not have occlusive coronary disease; etiological reasons for cardiac arrest were arrhythmogenic heart disease in 5 xenon patients and in 1 control patient, thyrotoxicosis in 1 control patient, and dilated cardiomyopathy in 1 control patient. As summarized in Online Table 4, baseline and peak values of plasma creatinine and the incidence of acute kidney injury did not differ between the groups.

TABLE 1 Baseline Characteristics, Medication, Resuscitation, and Cooling Data

	Xenon (n = 54)	Control (n = 54)	p Value
Age, yrs	59.8 ± 11.7	59.7 ± 10.6	0.97
Male	40 (74.1)	39 (72.2)	1.00
Coronary artery disease	37 (68.5)	40 (74.1)	0.67
Hypertension	21 (38.9)	26 (48.1)	0.44
Congestive heart failure	6 (11.1)	3 (5.6)	0.49
Diabetes	9 (16.7)	7 (13.0)	0.79
Asthma/COPD	6 (11.1)	8 (14.8)	0.78
Dyslipidemia	15 (27.8)	22 (40.7)	0.22
Cardiomyopathy	1 (1.9)	1 (1.9)	1.00
Chronic kidney insufficiency	1 (1.9)	3 (5.6)	0.62
Smoker	17 (31.5)	21 (38.9)	0.55
Medication			
ß-blocker	13 (24.1)	15 (27.8)	0.83
ACE inhibitor/ARB	15 (27.8)	20 (37.0)	0.41
Calcium-channel blocker	9 (16.7)	10 (18.5)	1.00
Diuretics	5 (9.3)	6 (11.1)	1.00
Antiplatelet/anticoagulant agents	15 (27.8)	19 (35.2)	0.53
Statin	12 (22.2)	16 (29.6)	0.37
Resuscitation			
Bystander resuscitation	37 (68.5)	39 (72.2)	0.83
Emergency medical service delay, min	8.4 (3.3)	8.7 (3.2)	0.64
Return of spontaneous circulation, min	22.7 (8.0)	22.0 (7.0)	0.63
No-flow, min*	0 (0–6)	0 (0–4.5)	0.62
Cooling			
Core temperature prior start of cooling, °C	34.9 (34.3–35.8)	35.4 (34.0–36.3)	0.25
Time from OHCA to target temperature, min	291 (259–339)	340 (259–397)	0.07
Time from OHCA to initiation of xenon, min	250 (209–281)	–	

Values are mean ± SD, n (%), or median (interquartile range). A diagnosis of coronary artery disease was based on patient history and angiographic findings. *No-flow is defined as the time from cardiac arrest to start of any chest compression by bystander or medical emergency personnel.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; OHCA = out-of-hospital cardiac arrest.

TROPONIN-T RELEASE. The absolute values of troponin-T at hospital arrival, and at 24, 48, and 72 h in both groups are presented in the **Central Illustration**. The baseline values at hospital arrival did not differ between the xenon and control groups (geometric mean [95% CI] 0.100 μg/l [0.070 to 0.141 μg/l] vs. 0.098 μg/l [0.071 to 0.135 μg/l], respectively). At 72 h after OHCA, the geometric mean troponin-T was 111% higher in the control group than in the xenon group (geometric mean [95% CI] 0.464 μg/l [0.300 to 0.716 μg/l] vs. 0.220 μg/l [0.128 to 0.380 μg/l], respectively) as illustrated in the **Central Illustration** and in Online Table 5.

Adjusted geometric means of troponin-T peaked at 24 h in both groups with a significant increase from the baseline values ($p < 0.0001$). A decline of troponin-T from the peak to 72 h differed significantly between the groups ($p = 0.0008$) with a significant decline of 44.8% ($p < 0.0001$) in the xenon group and a nonsignificant decline of 11.3% ($p = 0.56$) in the control group (**Central Illustration,** Online Table 5). In NSTEMI patients, the decline from peak to 72 h was significantly different between the groups ($p = 0.0004$): a significant decline of 48.6% within the xenon group ($p < 0.0001$), but a nonsignificant increase of 0.9% within the control group ($p = 0.93$). In STEMI patients, the difference of troponin-T decline between the groups was nonsignificant ($p = 0.61$); the decline from peak to 72 h was significant within the xenon group ($p = 0.01$), but nonsignificant within the control group ($p = 0.053$) (Online Table 6). Geometric mean (95% CI) of troponin-T was significantly higher in STEMI than in NSTEMI at each time point after baseline (Online Table 7).

The change over time of the levels of troponin-T differed between the xenon and the control groups (time by group interaction $p = 0.003$); after adjustment for age, sex, study site, PCI, and norepinephrine, the increase of troponin-T values from hospital admission to 72 h was significantly less in the xenon group than in the control group (adjusted mean difference of ln-transformed values: −0.66; 95% CI: −1.16 to −0.16; ratio of adjusted geometric means: 0.52; 95% CI: 0.31 to 0.85; $p = 0.01$) (**Table 3**).

The effect of xenon on the change in the troponin-T values did not differ in patients with or without PCI or in those with a diagnosis of STEMI (PCI or STEMI by group by time interaction effect; $p = 0.72$ and $p = 0.29$, respectively).

TABLE 2 Heart Disease Characteristics

	Xenon (n = 54)	Control (n = 54)	p Value
STEMI	17 (31.5)	19 (35.2)	0.68
Anterior	17 (31.5)	11 (20.4)	0.19
Inferior	0 (0.0)	5 (9.3)	0.06
Lateral	0 (0.0)	3 (5.6)	0.24
Right side	0 (0.0)	0 (0.0)	1.00
NSTEMI	32 (59.3)	32 (59.3)	1.00
Primary PCI on admission	15 (27.8)	18 (33.3)	0.53
Coronary angiography during hospital stay	44 (81.5)	47 (87.0)	0.43
Angiographic findings*			0.61
Nonocclusive coronary artery disease	12 (27.3)	11 (23.4)	
Left main disease	3 (6.8)	8 (17.0)	
1-vessel disease	15 (34.1)	14 (29.8)	
2-vessel disease	10 (22.7)	9 (19.1)	
3-vessel disease	7 (15.9)	13 (27.7)	

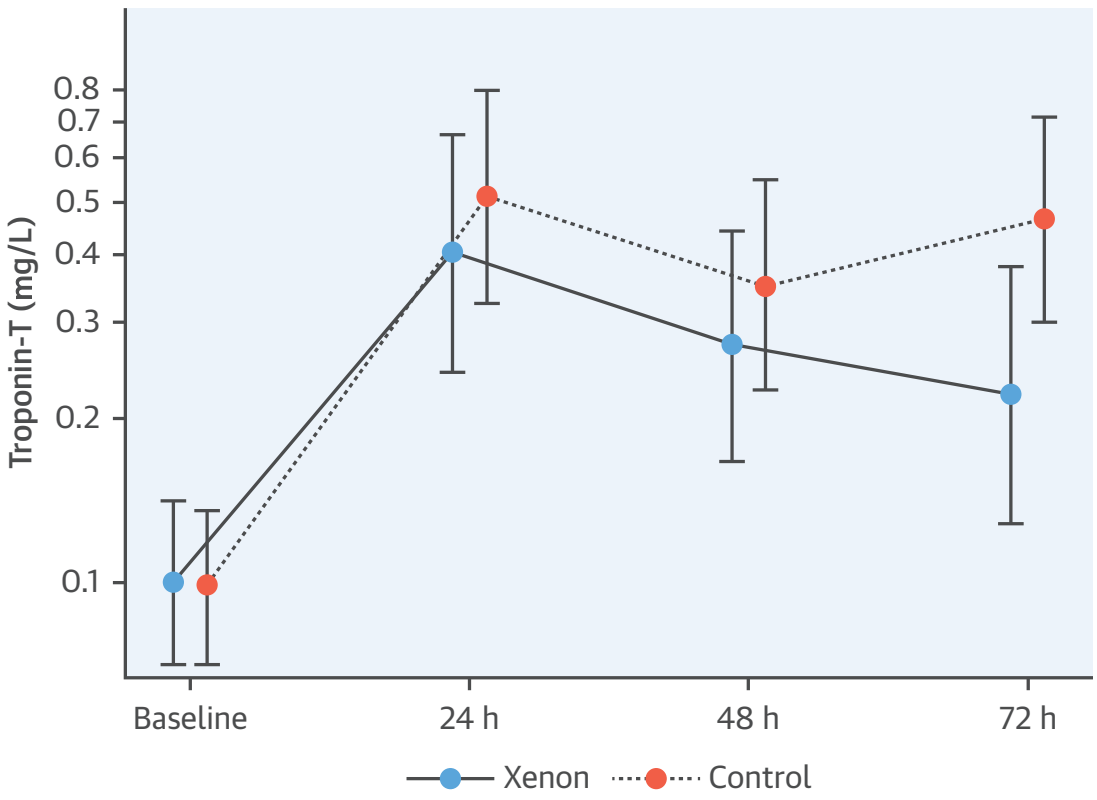
Values are n (%). A diagnosis of acute myocardial infarction was based on the latest recommendations (8). *Data are for 44 patients in the xenon group and for 47 patients in the control group due to missing data.

NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

PREDICTIVE VALUE OF TROPONIN-T FOR MORTALITY AT 6 MONTHS. The adjusted absolute value of each time point after baseline and the incremental change from baseline to each of time point of troponin-T release had a significant predictive value for mortality at 6 months after the index event within the groups and in the whole population (Online Table 8). The association of troponin-T release on survival did not differ between the groups (for all time points in the group by troponin-T interaction $p > 0.10$).

INTRAVENOUS DRUGS AND SEDATION DEPTH. Significantly less propofol was administered in the xenon group compared with the control group during the first 72 h (Table 4), but the propofol dose of the second and the third day after hospital arrival did not differ between the groups ($p = 0.20$ and $p = 0.13$, respectively). None of the other intravenous medications administered during the first 72 h differed significantly between the groups (Table 4, Online Table 9). The mean sedation depth according to the

CENTRAL ILLUSTRATION Troponin-T in the Xenon and Control Groups



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Troponin-T levels in the xenon and control groups after out-of-hospital cardiac arrest at hospital arrival (baseline) and 24, 48, and 72 h post-cardiac arrest are shown. Values are presented in geometric means (95% confidence intervals) on a logarithmic scale.

TABLE 3 Troponin-T Change From Baseline to 72 h After OHCA

	Xenon Group (n = 54)	Control Group (n = 54)	Mean Difference (95% CI)		p Value	
			Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
Absolute values, μg/l						
Baseline (hospital admission)	0.09 (0.03–0.30)	0.08 (0.04–0.23)				
24 h after OHCA	0.38 (0.15–1.27)	0.47 (0.12–1.74)				
48 h after OHCA	0.25 (0.09–0.85)	0.41 (0.10–1.48)				
72 h after OHCA	0.22 (0.05–0.69)*	0.40 (0.14–1.87)†				
ln-transformed change from baseline						
ln ΔTnT 24 h	1.40 ± 1.39	1.65 ± 1.38	−0.26 (−0.79 to 0.27)	−0.16 (−0.62 to 0.30)	0.33	0.49
ln ΔTnT 48 h	1.00 ± 1.37	1.28 ± 1.38	−0.28 (−0.80 to 0.25)	−0.18 (−0.63 to 0.27)	0.29	0.43
ln ΔTnT 72 h	0.79 ± 1.54*	1.56 ± 1.38†	−0.76 (−1.33 to −0.20)	−0.66 (−1.16 to −0.16)	0.009	0.01

Values are median (interquartile range) or mean ± SD, unless otherwise indicated. Natural logarithmic transformation for troponin-T values was used in the statistical analysis due to skewness of the data. *Data are for 52 patients due to missing data of 2 patients at 72 h. †Data are for 53 patients due to missing data of 1 patient at 72 h. ‡Data are adjusted for age, sex, study site, percutaneous coronary intervention, and dose of noradrenalin during the first 24 h after intensive care admission.

Δ = change from the baseline; CI = confidence interval; ln = natural logarithm; OHCA = out-of-hospital cardiac arrest; TnT = troponin-T.

Richmond Agitation Sedation Scale until the end of hypothermia treatment was 4.3 ± 0.6 in the control group and 4.4 ± 0.6 in the xenon group (p = 0.17).

HEMODYNAMIC PARAMETERS. The median (interquartile range) heart rate was significantly lower in the xenon group than in the control group during the first 72 h. The other pre-defined hemodynamic parameters did not differ between the groups during the first 24 or 72 h (Table 4).

CORRELATIONS BETWEEN TROPONIN-T, INTRAVENOUS DRUGS, AND HEMODYNAMIC PARAMETERS. In the xenon group, the incremental change in the troponin-T values from hospital admission to 72 h displayed a significant correlation with norepinephrine (r = 0.51; p = 0.0001) and dobutamine (r = 0.27; p = 0.049) doses during the first 72 h after ICU admission. There were no other significant correlations between the incremental change of troponin-T from hospital admission up to 72 h and the administered drugs or hemodynamic parameters, or between propofol and any of the vasoactive drugs (as listed in Table 4 and Online Table 9) in the 2 groups or within the whole population (correlation data not shown).

DISCUSSION

The main finding of this study was that among comatose survivors of OHCA, inhaled xenon combined with mild therapeutic hypothermia resulted in a reduced myocardial injury when compared with that achieved by hypothermia alone as demonstrated by the significantly lower release of troponin-T from baseline to 72 h after OHCA in the xenon group. The incremental change of troponin-T was also associated with higher mortality at 6 months.

Current results revealed significantly lower troponin-T release in the xenon group than in the control group at 72 h, but not at 24 and 48 h, explaining why the area under the curve remained nonsignificant.

TABLE 4 Selected Intravenous Medication and Hemodynamic Parameters During the First 72 h After ICU Admission

	First 24 h After ICU Admission			First 72 h After ICU Admission		
	Xenon (n = 54)	Control (n = 54)	p Value	Xenon (n = 54)	Control (n = 54)	p Value
Medication						
Propofol, mg	2,325 (1,700–2,980)	6,605 (5,071–7,880)	<0.0001	11,019 (6,585–14,599)	16,010 (12,060–20,846)	<0.0001
Norepinephrine, mg*	5.0 (1.1–14.4)	8.3 (3.9–12.7)	0.10	12.1 (5.6–34.2)	22.3 (10.8–41.0)	0.07
Hemodynamic parameters						
Heart rate, beats/min	46.0 (40.5–54.9)	52.9 (43.6–58.5)	0.02	61.6 (56.8–69.4)	68.8 (59.8–75.9)	0.03
MAP, mm Hg	79.3 ± 6.3	78.8 ± 6.7	0.68	80.3 ± 7.9	78.7 ± 6.3	0.27
SAP, mm Hg	110.6 (103.2–116.3)	109.0 (105.2–117.0)	0.91	119.3 (109.5–127.0)	115.3 (1,108.2–123.8)	0.29
CVP, mm Hg	10.0 (8.3–13.0)	10.8 (8.7–12.9)	0.67	10.5 (8.6–13.5)	11.6 (9.6–13.1)	0.20

Values are median (interquartile range) or mean ± SD. The hemodynamic parameters were recorded in 2-min epochs in Turku and in 5-min epochs in Helsinki. *In the xenon group, 53 patients received norepinephrine during ICU stay.

CVP = central venous pressure; ICU = intensive care unit; MAP = mean arterial pressure; SAP = systolic arterial pressure.

However, release profiles of troponin-T from baseline to 72 h differed significantly between the groups, with a significant decline of 44.8% in the xenon group and a nonsignificant decline of 11.3% in the control group from the peak at 24 h to 72 h. The decline was even more pronounced between the groups in patients with NSTEMI, with a significant decline in the xenon group as compared with a nonsignificant increase in the control group from the peak to 72 h. Although the decline was significant only in the xenon group, the release profile of the control group was very similar to a recently published population of 699 OHCA patients, with a decline of 10.8% (10). Furthermore, current patients with STEMI had a significantly higher troponin-T release than those with NSTEMI, which is in line with earlier studies revealing a similar difference in troponin-T and higher infarct mass in STEMI patients (18). According to earlier firm evidence, all single-point measures of troponin-T at 24, 48, and 72 h (and also at 96 h) correlate significantly well with the final extent of infarct mass (18). Consequently, our interpretation of the current result is that the single-point values of troponin-T, rather than the area under the curve, were likely to be reliable estimates of the ongoing process of ischemia/reperfusion injury, and the difference between the groups reflects a significant treatment effect of xenon observed over the span of 72 h.

The positive effect of xenon was independent of age, sex, study site, dose of norepinephrine, and performed PCI. The effect of xenon on the troponin-T release was similar in patients with or without PCI or with a diagnosis of STEMI, as well as in either survivors or nonsurvivors. Furthermore, the severity of coronary artery disease, as evaluated by patient history, coronary angiography, and autopsy report (when available), was comparable in the study groups, suggesting that the effect of xenon was not likely to be modified by the different causes of myocardial injury after OHCA. As discussed later in more detail, none of the other major confounding variables included in the model either differed between the groups or exhibited any correlation with the release of troponin-T. Therefore, xenon was a significant independent factor attenuating the severity of the myocardial injury after OHCA.

Several animal experiments with models of ischemic myocardial injury with and without hypothermia have demonstrated that xenon's pre- and post-conditioning effects lead to a reduction in the myocardial infarct size (14,15,19–22). In this study, the effect on the troponin-T release was likely due to a post-conditioning effect, because xenon inhalation was initiated with a mean delay of 4 h after OHCA. Multiple molecular targets have been identified as being implicated in xenon's cardioprotective conditioning effect. These include prosurvival signaling kinases, such as protein kinase c_ε (PKC_ε), protein kinase B (Akt), and glycogen synthase kinase 3 β (GSK-3 β), p38 mitogen-activated protein kinase (MAPK), MAPK-activated kinase-2, heat-shock protein 27, and extracellular signal-regulated kinases 1/2 (23–26). Moreover, phosphorylation of PKC_ε, Akt, and GSK-3 β by xenon has been reported to inhibit Ca2+-induced mitochondrial permeability transition pore opening, which is known to preserve mitochondrial function and prevent ischemic reperfusion injury and cell death (27).

We also analyzed the predictive value of troponin-T for all-cause mortality at 6 months after OHCA to estimate further whether a clinical benefit would accrue from the significantly lower troponin-T values in the xenon group. We found that all the time points of troponin-T after the baseline value within the groups and in the whole population had a predictive value for all-cause mortality at 6 months after OHCA. This finding is in agreement with the latest consensus statement of the Joint Task Force and recent trials declaring that troponin-T release has an independent predictive value for both short- and long-term morbidity and mortality in cardiac arrest patients, as well as in all intensive care patients, regardless of the underlying disease (8–10).

In earlier clinical trials with cardiovascular surgical patients, xenon anesthesia has been characterized as conferring cardiovascular stability by maintaining systolic blood pressure, myocardial contractility, and stroke volume, as well as preload, accompanied by an inotrope-sparing effect (11–13,28–30). In the current trial with long-term xenon inhalation, the doses of vasoactive medication did not differ significantly between the groups. Most importantly, doses of both norepinephrine and dobutamine showed a significant positive correlation with troponin-T release in the xenon group only. Consequently, vasoactive medication was unlikely to have been responsible for the more severe myocardial injury in the control group.

The xenon group required significantly less propofol to achieve the predefined deep level of sedation, as determined by a Richmond Agitation Sedation Score of at least 4. However, the difference was not sustained during the following days after discontinuation of xenon inhalation. Animal and clinical studies have demonstrated that propofol mitigates oxidative stress and potentially protects the

heart against a post-ischemic reperfusion injury by decreasing troponin-T release after coronary artery bypass surgery (31-35). Despite the possible cardioprotective properties of propofol, there was no correlation between the administered dose and the troponin-T release within the groups in this study. Therefore, it is unlikely that the administration of propofol use had any significant impact on the current results.

Xenon's heart rate-decreasing properties have been well documented (11,13,17,28,29). In our study, the combination of xenon and hypothermia resulted in a significantly lower heart rate when compared with hypothermia alone, with this effect lasting at least up to 72 h after OHCA. Interestingly, a recent trial demonstrated that pronounced sinus bradycardia during hypothermia was associated with improved outcome, and it was proposed to represent an independent marker of favorable neurocognitive outcome (36). Therefore, one could argue that xenon's ability to reduce the heart rate may have some beneficial clinical value in cardiac arrest patients. However, this was not supported by the current results because no correlation could be detected between heart rate and troponin-T release.

STUDY LIMITATIONS. First, neither coronary angiography nor autopsy was performed in 7 xenon and in 4 control patients, and therefore, the severity of coronary disease could not be evaluated in these patients; the diagnosis of acute myocardial infarction was based on clinical data, troponin-T release, and serial electrocardiograms. Second, it was not possible to reliably distinguish between a cardiac and a noncardiac cause of death because all patients with severe ischemic cerebral injury had also myocardial damage due to a global, as well as an occlusive, ischemia (16). Of the nonsurvivors, 85% did not regain consciousness due to a severe ischemic encephalopathy, and the deaths were eventually classified as neurological mode of death (16). Only 2 deaths from both groups were classified into a category of cardiovascular mode of death. Therefore, this study was not sufficiently powered to address xenon's long-term effect on either cardiac or all-cause mortality. A large phase III trial is needed to establish whether these observations actually translate into a clinical benefit.

CONCLUSIONS

Among comatose survivors of OHCA, inhaled xenon combined with mild therapeutic hypothermia results in less severe myocardial injury than hypothermia alone as determined by the lower release of troponin-T from baseline to 72 h after OHCA in the xenon group. Although these observations do not provide a mechanistic explanation for the present findings, we speculate that xenon may provide a protective postconditioning effect against ongoing myocardial injury. These findings will need further evaluation in an adequately powered trial to address the clinical effect of xenon inhalation on long-term outcome among survivors of OHCA.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Inhaled xenon combined with mild therapeutic hypothermia attenuates myocardial injury among survivors of OHCA.

TRANSLATIONAL OUTLOOK: Randomized trials of larger scope will be needed to determine whether the reduction in troponin-T release achieved with combined xenon and hypothermia translates into long-term clinical benefit compared with hypothermia alone.

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APPENDIX For supplemental tables, please see the online version of this article.