Effect of Inhaled Xenon on Cardiac Function in Comatose Survivors of Out-of-Hospital Cardiac Arrest—A Substudy of the Xenon in Combination With Hypothermia After Cardiac Arrest Trial

OBJECTIVES: This explorative substudy aimed at determining the effect of inhaled xenon on left ventricular function by echocardiography in comatose survivors of out-of-hospital cardiac arrest.

DESIGN: A randomized two-group single-blinded phase 2 clinical drug trial.

SETTING: A multipurpose ICU in two university hospitals.

PATIENTS: Of the 110 randomized comatose survivors after out-of-hospital cardiac arrest with a shockable rhythm in the xenon in combination with hypothermia after cardiac arrest trial, 38 patients (24–76 yr old) with complete echocardiography were included in this study.

INTERVENTIONS: Patients were randomized to receive either inhaled xenon combined with hypothermia (33°C) for 24 hours or hypothermia treatment alone. Echocardiography was performed at hospital admission and 24 ± 4 hours after hypothermia.

MEASUREMENTS AND MAIN RESULTS: Left ventricular ejection fraction, myocardial longitudinal systolic strain, and diastolic function were analyzed blinded to treatment. There were 17 xenon and 21 control patients in whom echocardiography was completed. Clinical characteristics did not differ significantly between the groups. At admission, ejection fraction was similar in xenon and control patients (39% ± 10% vs 38% ± 11%; $p = 0.711$) but higher in xenon than control patients after hypothermia (50% ± 10% vs 42% ± 10%; $p = 0.014$). Global longitudinal systolic strain was similar in xenon and control patients at admission (−9.0% ± 3.8% vs −8.1% ± 3.6%; $p = 0.555$) but better in xenon than control patients after hypothermia (−14.4.0% ± 4.0% vs −10.5% ± 4.0%; $p = 0.006$). In patients with coronary artery disease, longitudinal strain improved in the nonischemic myocardial segments in xenon patients. There were no changes in diastolic function between the groups.

CONCLUSIONS: Among comatose survivors of a cardiac cause out-of-hospital cardiac arrest, inhaled xenon combined with hypothermia was associated with greater recovery of left ventricular systolic function in comparison with hypothermia alone.

KEY WORDS: cardiac arrest; cardiac function; cardioprotection; echocardiography; ejection fraction; myocardial strain

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Despite restitution of coronary blood flow with successful cardiopulmonary resuscitation with or without percutaneous coronary intervention, out-of-hospital cardiac arrest (OHCA) is followed by prolonged myocardial dysfunction (1–3). 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 (4, 5). In addition, the severity of myocardial injury impacts on both short- and long-term mortality (6–8). Therefore, new strategies to attenuate the myocardial ischemia-reperfusion injury leading to cardiomyocyte death after cardiac arrest are needed.

Inhalation of the noble gas xenon may be cardioprotective by decreasing heart rate without affecting cardiac contractility in patients undergoing noncardiac surgery (9–11). In animal models, xenon has provided cardioprotection against ischemic myocardial injury by pre- and postconditioning mechanisms (12–14). We have previously reported that xenon combined with hypothermia confers neuroprotection by attenuating brain white matter injury more than hypothermia alone in comatose survivors of cardiac arrest (15). Furthermore, inhaled xenon combined with hypothermia reduced the release of cardiac troponin-T compared with hypothermia alone suggesting less severe myocardial injury (16).

The purpose of this explorative study was to evaluate the effect of xenon on left ventricular (LV) systolic and diastolic function in comatose survivors of OHCA from shockable initial rhythm.

METHODS

Study Design and Interventions

The present explorative study reports a subanalysis of the xenon in combination with hypothermia after cardiac arrest (Xe-HYPOTHECA) trial that was a randomized two-group single-blinded phase 2 clinical drug trial conducted between August 2009 and March 2015 at two multipurpose ICUs in Finland (15–17). In the Xe-HYPOTHECA trial, the primary hypothesis was that xenon would attenuate white matter injury after OHCA (15). The study protocol has been published earlier (15). The ethics committee of the Hospital District of Southwest Finland (§65, February 17, 2009; Dno. 10/2009) and the institutional review boards of the Helsinki University Hospital (§167, August 21, 2012) and the Finnish Medicine Agency (KLnro. 22/2009) approved the study. The study protocol conforms to the 1975 Declaration of Helsinki. Written informed consent was obtained from the next-of-kin or from the legal representative of the patient within 4 hours after hospital admission (15). Authors (A.S., T.L.) had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Consecutive comatose survivors of OHCA 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 minutes (for details, see the **Supplemental Digital Content Table 1**, http://links.lww.com/CCX/A741). As shown in study flow diagram (**Supplemental Digital Content Fig. 1**, http://links.lww.com/CCX/A741), 224 patients were screened for eligibility, and 110 were enrolled. The patients were allocated in a 1:1 ratio with random block sizes of 4, 6, and 8 to openly receive either therapeutic hypothermia treatment alone for 24 hours (designated as the control group) or inhaled xenon (LENOXe; Air Liquide Medical GmbH, Düsseldorf, Germany) in combination with hypothermia for 24 hours (designated as the xenon group). Xenon is not labeled for the use under discussion and is still investigational. The patients were cooled with an invasive intravascular temperature management device to target core temperature of 33°C, which was then maintained for 24 hours. 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. There was adherence to a detailed treatment protocol that included strict blood pressure and ventilator targets during cooling and normothermia as described previously (15, 17).

Assessment of LV Function

Transthoracic echocardiography was performed when feasible at admission to hospital and repeated 24 ± 4 hours after completion of rewarming (after hypothermia) by experienced cardiologists in the study group. Due to logistic reasons or death before follow-up, echocardiography could not be performed on both time points in 33 xenon patients and 31 controls. Apical views required for analysis of LV function could not be obtained in five xenon and three control patients who were excluded from analysis. Thus, the final study population consisted of 17 xenon and 21 control patients.

Patients were examined in supine position with the use of a GE Vivid E9 or Vivid Q device and MS5 transducer (GE Vingmed Ultrasound, Horten, Norway). In order to evaluate LV systolic function, standard 2D grayscale images of the three standard apical views (four-chamber, two-chamber, and long-axis) were

acquired (18). For speckle tracking, frame rate was adjusted to 40–80 frames/s. In order to assess variables of diastolic function, LV inflow velocities were recorded by pulsed-wave Doppler at the level of mitral valve leaflet tips, and the lateral and septal mitral valve annulus velocities were recorded by pulsed-wave tissue Doppler imaging in the apical four-chamber view (19). All images were stored in Digital Imaging and Communications in Medicine format.

LV systolic and diastolic volumes, ejection fraction (EF), peak systolic global longitudinal strain (GLS), regional longitudinal strain (LS), and measures of diastolic function were analyzed off-line by a single investigator blinded to treatment using EchoPAC PC Version 113 software (GE Vingmed Ultrasound) as demonstrated in **Supplemental Digital Content Figure 2** (http://links.lww.com/CCX/A741). LV EF was measured using the biplane method of disks summation technique (modified Simpson's rule) by manually tracing the LV endocardial borders at end-diastolic and end-systolic frames. Strain was analyzed using speckle-tracking technique in 18 myocardial segments including six (anteroseptal, anterior, lateral, posterior, inferior, and inferoseptal) segments at apical, papillary muscle and basal levels as previously described (20, 21). The endocardial borders were traced at the end-systolic frame in three apical views. The software then automatically tracked myocardial motion and rejected poorly tracked segments. In the presence of poor tracking, the analyst readjusted the endocardial trace. Segments rejected both by software and by the analyst were excluded from analyses. Numeric and graphical displays of average deformation variables of each segment were automatically generated. GLS was calculated as an average strain of the 18 segments. GLS values were reported both for all patients and after excluding three control patients and one xenon patient in whom regional tracking was suboptimal in more than two segments in a single view. In addition to GLS, average regional LS in the nonischemic and ischemic segments was calculated in 13 xenon patients and 14 controls who underwent coronary angiography. Segments that received supply from an artery treated by percutaneous coronary intervention (PCI) were considered as ischemic region and other segments as nonischemic region.

Statistical Analyses

The sample size of 110 patients was based on a power analysis of the fractional anisotropy values from brain MRI, that is, the primary endpoint of the Xe-HYPOTHECA trial (15). A specific sample size estimation was not made for this exploratory substudy, but considering test-retest variability of 7% in quantitative assessment of LV EF by echocardiography, a sample size of 15 patients per group was considered sufficient for the detection of at least 6% difference (22). The Shapiro-Wilk W test was used to evaluate the normality of continuous variables that are reported as means ± SD or medians and interquartile ranges. Two-sample t test or Mann-Whitney U test was used to compare continuous variables and chi-square or Fisher exact to compare categorical variables between groups. Changes in continuous variables during follow-up were tested using paired t test or Wilcoxon signed-rank test. The correlations between the change in EF or GLS during follow-up and doses of norepinephrine and propofol were calculated using Spearman correlation coefficients. A two-sided p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS System for Windows, Version 25 (SAS Institute, Cary, NC).

RESULTS

Patients

The final study population included 17 xenon and 21 control patients with complete echocardiography data (Supplemental Digital Content Fig. 1, http://links.lww.com/CCX/A741). Their characteristics are compared with Xe-HYPOTHECA study patients without echocardiography in **Supplemental Digital Content Table 2** (http://links.lww.com/CCX/A741). Patients with complete echocardiography data had less frequently diabetes but more often coronary angiography at admission than other patients in the main study.

In this substudy, six patients in the control group and three patients in the xenon group died in hospital. Clinical characteristics, medication, resuscitation, cooling, characteristics of coronary artery disease, and the number of patients with an acute ST-elevation myocardial infarction (STEMI) were similar in the xenon and control groups in this analysis (**Table 1**). Of the STEMI patients, all eight in the xenon group and six of seven in the control group were treated with percutaneous coronary intervention on hospital arrival, and one patient in the control group underwent coronary artery bypass surgery. Of the patients with

TABLE 1.
Clinical Characteristics, Medication, Resuscitation, and Cooling Data

Clinical Characteristics	Xenon (N = 17)	Control (N = 21)	p Xenon vs Control
Age (yr), mean (SD)	58 (12)	59 (11)	0.82
Male, n (%)	13 (76)	15 (71)	1.00
Hypertension, n (%)	7 (41)	9 (43)	0.92
Congestive heart failure, n (%)	2 (12)	0	0.19
Diabetes, n (%)	0	1 (5)	1.00
Dyslipidemia, n (%)	4 (24)	6 (29)	1.00
Kidney dysfunction, n (%)	8 (47)	7 (33)	0.29
Smoker, n (%)	8 (47)	10 (48)	1.00
Medication, n (%)			
Beta-blocker	3 (18)	3 (14)	1.00
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	4 (24)	6 (29)	1.00
Calcium-channel blocker	3 (18)	3 (14)	1.00
Diuretics	1 (6)	0	0.45
Antiplatelet/anticoagulation	4 (24)	6 (29)	1.00
Statin	3 (18)	4 (19)	1.00
Resuscitation			
Bystander resuscitation, n (%)	11 (65)	16 (76)	0.49
Emergency medical service response time (min), mean (SD)	9 (4)	10 (3)	0.57
Return of spontaneous circulation (min), mean (SD)	22 (6)	21 (5)	0.32
Time to basic life support initiation (min), median (IQR)	0 (8)	0 (0)	0.43
Cooling			
Core temperature prior start of cooling (°C), mean (SD)	34.9 (0.9)	35.1 (1.5)	0.58
Time from OHCA to target temperature (min), median (IQR)	310 (74)	344 (105)	0.66
Time from OHCA to initiation of xenon (min), median (IQR)	244 (71)		
Coronary artery disease, n (%)			
Previous coronary artery bypass grafting	1 (6)	2 (10)	1.00
ST-elevation myocardial infarction	8 (47)	7 (33)	0.39
Anterior	8 (47)	5 (24)	0.20
Inferior	0	1 (5)	0.47
Lateral	0	1 (5)	0.47
Percutaneous coronary intervention at admission	9 (53)	8 (38)	0.42
Obstructive coronary artery disease[a]	14 (93)	16 (84)	0.71
Left main or left anterior descending coronary artery disease[a]	12 (80)	11 (58)	0.71
One-vessel disease[a]	9 (60)	7 (37)	0.30
Two-vessel disease[a]	4 (27)	5 (26)	0.98
Three-vessel disease[a]	1 (7)	4 (21)	0.49
Troponin-T (ug/L), median (IQR)			
Admission	0.07 (0.14)	0.08 (0.19)	0.73
72 hr after OHCA	0.20 (0.25)	0.26 (1.62)	0.28

IQR = interquartile range, OHCA=out-of-hospital cardiac arrest.

[a]Nineteen controls and 15 xenon patients who had coronary angiography or autopsy.

non–ST-elevation myocardial infarction, one in the xenon group and two in the control group were treated with percutaneous coronary intervention on hospital arrival. Baseline troponin values were similar in the xenon and control patients.

Significantly less propofol was administered in the xenon group compared with the control group during the first 72 hours (**Table 2**). The amount of administered norepinephrine or the use of other inotropic medications did not differ between the xenon and control groups. The amount of administered furosemide was comparable in the xenon and control groups. During hypothermia, heart rate was significantly lower in the xenon group, whereas there was no difference in systolic blood pressure (**Supplemental Digital Content Table 3**, http://links.lww.com/CCX/A741).

Echocardiography

Time from OHCA to the first echocardiography at admission was similar between the xenon and control groups (4.0; SD, 1.3 hr; range, 1.9–6.8 hr vs 4.8; SD 2.2 hr; range, 1.8–8.3 hr; $p = 0.24$). Likewise, time from OHCA to second echocardiography at 24 ± 4 hours after completing hypothermia was similar (64; SD 10 hr vs 63; SD, 9 hr; $p = 0.68$). At the time of echocardiography, heart rate and arterial blood pressure were similar in the xenon and control groups, whereas there was a trend toward lower central venous pressure in the xenon group at 24 ± 4 hours after completing hypothermia (Supplemental Digital Content Table 3, http://links.lww.com/CCX/A741).

There was a tendency toward lower LV end-diastolic and end-systolic volumes in the xenon group than control group at admission and at 24 ± 4 hours after hypothermia (**Table 3**). At admission, EF and GLS were similar in the xenon and control groups. Both EF and GLS improved in both groups during follow-up, but the change between the first echocardiogram at admission and second at 24 ± 4 hours after hypothermia was significantly higher in the xenon group than in the control group (mean difference for EF 7.3% [95% CI, 1.3–13.3; $p = 0.02$] and for GLS 3.0% [95% CI, 0.5–5.5; $p = 0.020$] (**Fig. 1** and Table 3). EF improved by greater than or equal to 5% in 11 xenon (65%) and five controls (24%) ($p = 0.04$). GLS improved by greater than 1 SD in 12 xenon patients (71%) and seven control patients (33%) ($p = 0.02$) during follow-up. The change in GLS was similar after excluding patients with suboptimal tracking in greater than two segments in a single view (one xenon and three control patients). In patients with coronary artery disease, the improvement of regional LS from admission to 24 ± 4 hours after hypothermia was significantly higher in the xenon than control group in the nonischemic regions but did not reach statistical significance in the ischemic regions (Table 3).

Xenon inhalation did not have effect on the variables of LV diastolic function (Table 3). Early diastolic velocity of the mitral annulus was higher in xenon patients than controls, but its change during follow-up was similar in the xenon and control groups.

There were no correlations between the change in the EF or GLS from hospital admission to 24 ± 4 hours after hypothermia and administered dose of norepinephrine in the xenon ($r = 0.386$; $p = 0.126$ and -0.002; $p = 0.993$, respectively) or control ($r = 0.006$; $p = 0.980$ and -0.114; $p = 0.622$, respectively) groups.

TABLE 2.
Medications at Hospital

Medications	First 24 hr After ICU Admission			First 72 hr After ICU Admission		
	Control	Xenon	p	Control	Xenon	p
Propofol (mg), median (25–75th percentile)	6,236 (5,022–7,463)	2,183 (1,414–2,486)	< 0.001	16,400 (13,340–23,292)	11,647 (9,908–14,652)	0.001
Norepinephrine (mg)[a], median (25–75th percentile)	6 (1–11)	3 (1–9)	0.43	14 (6–31)	9 (5–23)	0.44
Furosemide (mg), median (25–75th percentile)	5 (0–15)	5 (0–15)	0.95	30 (10–65)	30 (15–60)	0.87

[a]One patient in each group received levosimendan, and one patient in each group received dobutamine.

TABLE 3.
Echocardiography Data at Admission and 24 ± 4 Hours After Hypothermia

Echocardiographic Measure	Xenon (n = 17)	Control (n = 21)	p Xenon vs Control	pᵃ Xenon	pᵃ Control	pᵇ
Admission						
ESV (mL), mean (sᴅ)	58 (29)	73 (31)	0.09			
EDV (mL), mean (sᴅ)	95 (27)	118 (47)	0.09			
EF (%), mean (sᴅ)	39 (10)	38 (11)	0.71			
GLS (%), mean (sᴅ)	−9.0 (3.8)	−8.1 (3.6)	0.48			
LS ischemic region (%), mean (sᴅ)	−8.4 (5.4)	−5.9 (4.1)	0.19			
LS nonischemic region (%), mean (sᴅ)	−8.6 (4.6)	−8.8 (3.2)	0.87			
E velocity (m/s), mean (sᴅ)	0.52 (0.16)	0.53 (0.18)	0.79			
A velocity (m/s), mean (sᴅ)	0.47 (0.26)	0.54 (0.21)	0.38			
E/A ratio, median (IQR)	1.3 (0.9)	0.9 (0.5)	0.13			
e′ velocity (cm/s), mean (sᴅ)	6.5 (2.2)	4.7 (1.2)	0.005			
E/e′ ratio, median (IQR)	13.8 (12.0)	13.9 (12.8)	0.97			
24 ± 4 hr after hypothermia						
ESV (mL), mean (sᴅ)	54 (21)	66 (26)	0.15	0.41	0.10	0.49
EDV (mL), mean (sᴅ)	113 (33)	113 (39)	0.98	0.01	0.48	0.02
EF (%), mean (sᴅ)	50 (10)	42 (10)	0.01	< 0.001	0.02	0.02
GLS (%), mean (sᴅ)	−14.4 (4.0)	−10.5 (4.0)	0.006	< 0.001	0.01	0.02
LS ischemic region (%), mean (sᴅ)	−12.2 (5.2)	−8.5 (5.6)	0.09	0.04	0.16	0.61
LS nonischemic region (%), mean (sᴅ)	−14.4 (4.3)	−11.3 (3.9)	0.06	< 0.001	0.02	0.009
E velocity (m/s), mean (sᴅ)	0.76 (0.21)	0.69 (0.17)	0.26	0.001	0.004	0.22
A velocity (m/s), mean (sᴅ)	0.62 (0.30)	0.61 (0.20)	0.83	0.02	0.05	0.40
E/A ratio, median (IQR)	1.1 (0.6)	1.1 (0.5)	0.89	0.83	0.04	0.24
e′ velocity (cm/s), mean (sᴅ)	9.6 (1.5)	6.4 (2.3)	< 0.001	< 0.001	0.002	0.16
E/e′ ratio, median (IQR)	8.1 (3.1)	10.6 (5.1)	0.13	0.01	0.68	0.31

A = late diastolic mitral inflow velocity, E = early diastolic mitral inflow velocity, e′ = early diastolic mital annular velocity, EDV = end diastolic volume, EF = ejection fraction, ESV = end systolic volume, GLS = global longitudinal strain, IQR = interquartile range, LS = longitudinal stain.
ᵃAdmission vs 24 ± 4 hr after hypothermia within groups.
ᵇThe difference in the change between groups.

Similarly, the change of EF or GLS did not correlate to administered dose of propofol in the xenon ($r = 0.045$; $p = 0.863$ and 0.067; $p = 0.801$, respectively) or control ($r = 0.282$; $p = 0.215$ and 0.097; $p = 0.675$, respectively) groups.

DISCUSSION

The main finding of this explorative study was that among comatose survivors of OHCA with shockable primary rhythm, inhaled xenon in combination with hypothermia resulted in a significantly larger improvement of LV systolic function when compared with that achieved by hypothermia alone as was demonstrated by higher EF and myocardial strain.

Global EF and myocardial strain improved during follow-up of 63 hours in both the xenon and control groups with or without PCI for an acute coronary syndrome at admission. Myocardial strain improved both in the myocardial segments that were supplied by an
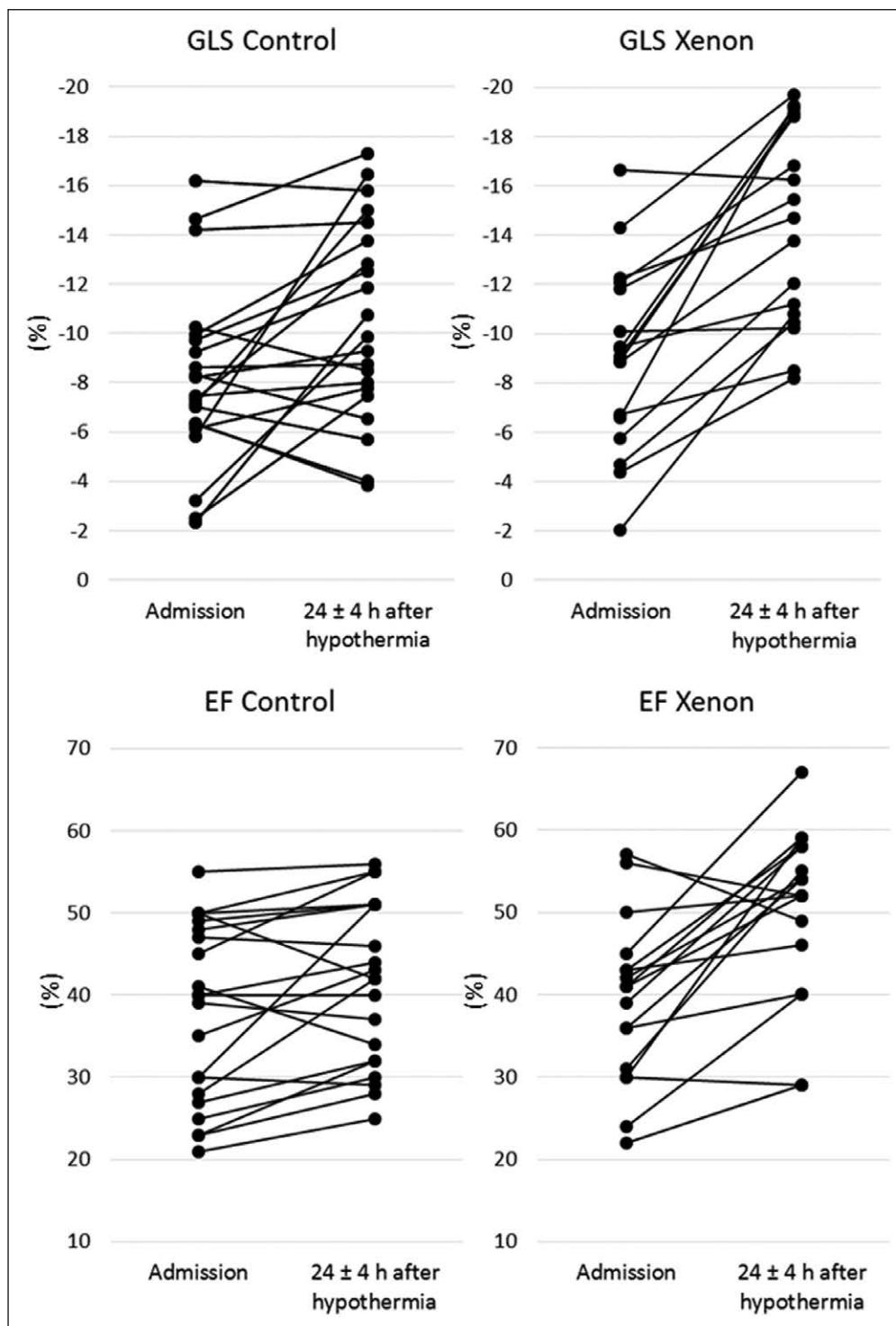
Figure 1. Changes in left ventricular ejection fraction (EF) and systolic global longitudinal strain (GLS) at admission and at 24 ± 4 hr after hypothermia in the control and xenon patients. The change between the first echocardiogram at admission and second at 24 ± 4 hr after hypothermia was significantly higher in the xenon group than in the control group (mean difference for EF 7.3% [95% CI, 1.3–13.3; $p = 0.02$] and for GLS 3.0% [95% CI, 0.5–5.5; $p = 0.020$].

observations of a global and prolonged reversible myocardial dysfunction associated with postcardiac arrest syndrome irrespective of the underlying coronary artery disease (1, 23–25). The observed time course of systolic function improvement is in line with previous studies demonstrating normalization of cardiac function by 72 hours after OHCA (1).

Xenon anesthesia has been characterized as conferring cardiovascular stability by maintaining systolic blood pressure, myocardial contractility, stroke volume as well as preload, accompanied by an inotrope-sparing effect (9–11, 26–28). Furthermore, xenon had no effect on resting myocardial blood flow (29). However, there is no earlier information on the effect of xenon on compromised myocardial function after cardiac arrest. Current results revealed improved LV systolic function from admission to 24 ± 4 hours after completion of hypothermia treatment in patients treated with xenon. There were no differences in characteristics of patients in terms of age, sex, underlying coronary artery disease, duration of cardiac arrest, or blood pressure between groups. Treatment was similar in both groups, except that patients in the xenon group required significantly less propofol to achieve

acutely obstructed epicardial coronary artery as well as in segments supplied by nonobstructed arteries. Therefore, our findings are consistent with previous

the predefined deep level of sedation. However, it is unlikely that the difference in propofol use between groups had any significant impact on our results, since hemodynamic conditions were comparable at the time of echocardiography examinations, and propofol may even have cardioprotective effects against myocardial ischemia-reperfusion injury (30). Furthermore, there was no correlation between the dose of propofol or vasoactive medication (norepinephrine) and change in EF or systolic strain. Therefore, our interpretation of the current result is that xenon inhalation was independently associated with improvement of systolic function 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$_\varepsilon$), 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 ½ (14, 31–33). Furthermore, phosphorylation of PKC$_\varepsilon$, Akt, and GSK-3 β by xenon has been reported to inhibit Ca^{2+}-induced mitochondrial permeability transition pore opening, which is known to preserve mitochondrial function and prevent ischemic reperfusion injury and cell death (34). Xenon's cardioprotective effect was further demonstrated by our recent study, in which inhaled xenon reduced myocardial injury as demonstrated by the significantly lower release of troponin-T from baseline to 72 hours after cardiac arrest in the xenon group than in the control group (16). However, in this subcohort, the release of troponin was similar in the xenon and control groups.

We found that systolic strain improved both in the ischemic area subtended by an obstructed epicardial coronary artery as well as myocardial regions subtended by unobstructed coronary artery. This indicates that the positive effect of xenon was not limited to recovery of myocardial dysfunction caused by acute coronary occlusion but had a global effect on postcardiac arrest myocardial dysfunction. In contrast to an experimental study, we did not find evidence of positive effects on LV diastolic function by xenon possibly due to small number of patients (35). Nevertheless, current results support earlier suggestions that xenon is a potential cardiostable sedative for intensive care patients with a compromised myocardial function and can provide beneficial recovery effect for the myocardium after OHCA (16, 17, 27). Therefore, further studies are needed in larger population with both nonshockable and shockable primary rhythm.

There are few limitations to be considered. First, although limited by small sample size and large variation in the extent of myocardial injury, our study suggests that in addition to attenuation of irreversible myocyte necrosis, xenon improves recovery of cardiac dysfunction caused by global ischemia during cardiac arrest. Second, due to logistic reasons, only a small group of the Xe-HYPOTHECA study patients could be included in this substudy. However, characteristics of patients were well balanced between groups in this analysis. Furthermore, there were no significant differences between patients with and without echocardiographic studies as demonstrated in the Supplemental Material (http://links.lww.com/CCX/A741). Comparisons were not possible during hypothermia treatment or later than 24 ± 4 hours after completion of rewarming due to small number of patients with complete echocardiography at these time points. Third, neither coronary angiography nor autopsy was performed in two patients in the xenon and control groups, and therefore, the severity of coronary artery disease could not be evaluated in these patients.

CONCLUSIONS

Our results of this explorative analysis in a subgroup of patients included in a trial evaluating neuroprotective properties of xenon provide evidence that inhaled xenon combined with hypothermia improves systolic LV function in comparison with hypothermia among comatose survivors of OHCA. Although exact mechanisms of this effect are unknown, current results suggest that xenon protects against myocardial dysfunction after cardiac arrest. Larger studies on significance of these findings on clinical outcomes after OHCA are warranted in the future.

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