Xenon protects left ventricular diastolic function during acute ischemia, less than ischemic preconditioning

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Abstract

Anesthetics modify regional left ventricular (LV) dysfunction following ischemia/reperfusion but their effects on global function in this setting are less clear. Aim of this study was to test the hypothesis that xenon would limit global LV dysfunction as caused by acute anterior wall ischemia, comparable to ischemic preconditioning. In an open-chest model under thiopental anesthesia, 30 pigs underwent 60-minute left anterior descending coronary artery occlusion, followed by 120 minutes of reperfusion. A xenon group (constant inhalation from previous to ischemia through end of reperfusion) was compared to control and ischemic preconditioning. Load-independent measures of diastolic function (end-diastolic pressure-volume relation, time constant of relaxation) and systolic function (end-systolic pressure-volume relation, preload-recruitable stroke work) were determined. Heart rate, arterial pressure, cardiac output, and arterial elastance were recorded. Data were compared in 26 pigs. Ischemia impaired global diastolic but not systolic function in control, which recovered during reperfusion. Xenon limited and preconditioning abolished diastolic dysfunction during ischemia. Arterial pressure decreased during reperfusion while arterial elastance increased. Tachycardia and antero-septal wall edema during reperfusion were observed in all groups. In spite of ischemia of 40% of LV mass, global systolic function was preserved. Deterioration in global diastolic function was limited by xenon and prevented by preconditioning.

Key words: myocardial ischemia; myocardial reperfusion; ischemic preconditioning; myocardial protection; inhalation anesthesia; xenon; conductance technique

Funding: This study was supported by a grant from Deutsche Forschungsgemeinschaft, Grant DFG Ro 2000/6-1.

doi: 10.4103/2045-9912.191358
How to cite this article: Baumert JH, Roehl AB, Funcke S, Hein M (2016) Xenon protects left ventricular diastolic function during acute ischemia, less than ischemic preconditioning. Med Gas Res 6(3):130-137.

Introduction

The effect of acute coronary ischemia on global left ventricular (LV) function mainly depends on the extent and localization of the ischemic part of the myocardium. It is generally accepted that myocardial cells lose their function within minutes after the onset of complete ischemia (Turschner et al., 2004). Functional impairment in partially ischemic areas may occur in the diastolic as well as in the systolic part of the cardiac cycle, but not necessarily to the same extent or at the same time. Furthermore, the ability of the non-ischemic (usually called "remote" because of the distance from the ischemic part) myocardium to compensate for or adapt to the ischemic dysfunction may also vary according to pre-existing disease, species, medication, *etc*. It is not well known how such divergent functional changes in these different parts of the acutely ischemic LV affect global LV function. Many drugs, including several anesthetics, are known to modify the extent of myocardial ischemia-reperfusion damage, and the recovery from it. Those drug effects on global LV function however, which are observed already during ischemia and early reperfusion, will largely involve the remote myocardium. Accordingly, only later effects of reperfusion would then reflect recovery of ischemic cells as well. Whereas isoflurane and xenon improve recovery from myocardial stunning (Kersten et al., 1996; Toller et al., 1999b; Preckel et al., 2000; Hartlage et al., 2004), only

isoflurane has been shown to reduce diastolic impairment in the remote and ischemic area of the ventricle during ischemia, without affecting hypercontractility demonstrated in the remote regions (Pagel et al., 1995) .

While it was demonstrated earlier that xenon inhalation and ischemic preconditioning reduced infarct size in this model, observed differences in LV end-diastolic pressure (LVEDP) suggested that these interventions also affected myocardial function, already during ischemia and the beginning of reperfusion (Baumert et al., 2007) .

Materials and methods

Animals and modelling

After approval by the Animal Care Committee (Bezirksregierung Köln AZ 50.203.2-AC 38, 19/01, Dr. S. Löer, Cologne, Germany), 30 German land-race pigs (Sus scrofa domestica), 30 to 35 kg, were investigated, following physical examination by a veterinarian. After overnight fasting, animals received general anesthesia. Anesthetic technique and surgical preparation have been previously described in more detail (Baumert et al., 2007). In short, animals in supine position, following intramuscular premedication with azaperone 4 mg/kg and induction with intravenous propofol 3 mg/kg, were kept under thiopental anesthesia. Continuous intravenous infusion of 18 mg/kg/h provided full surgical tolerance in the absence of restraint or muscle paralysis, with no need for other anesthetic medication. The animals were ventilated *via* an endotracheal tube, and underwent median sternotomy and exposure of the anterior descending branch of the left coronary artery (LAD). In several animals, direct epicardial echocardiography was performed using an Omniplane II TEE probe in connection with a Sonos 5500 machine (Philips, Best, Netherlands), in order to prove functional effectiveness of ischemia. The probe was placed in contact to the right ventricle free wall and thereby provided a complete short-axis view of the left ventricle at the level of the mid-papillary muscles. From this view, systolic and diastolic wall thickness and thickening fraction were determined for the anteroseptal (ischemic) and posterior (remote) wall.

Heart function detection and blood gas analysis

Via the right internal carotid artery, a 7-F multi-segment pressure volume catheter with 12 electrodes, 12 mm spacing and a pressure sensor between the fifth and sixth electrode (CA-71123-PN, CD Leycom, Zoetermeer, Netherlands) was advanced into the left ventricle along its long axis, with the tip in the ventricular apex. Correct placement was confirmed *via* synchrony of segmental volume signals. The volume arm of the catheter was connected to a signal processor (Sigma-5 DF, CD Leycom; Zoetermeer, Netherlands) and the pressure sensor to an electronic pressure interface (Sentron pressure interface, CD Leycom; Zoetermeer, Netherlands).

The conductance catheter technique has been described in detail previously. Briefly, through the two most proximal and two most distal electrodes of the catheter, which was positioned along the longitudinal axis of the LV, two 20-kHz currents opposite in polarity are applied, creating a dual electric field in the ventricular cavity. The interposed electrodes are used to measure the conductance of five intraventricular segments. Total time varying volume ($V(t)$) is calculated as the sum of these segmental conductances ($G(t)$) as follows: $V(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot (G(t) - G^P)$, where α is the ratio of the stroke volume calculated from the conductance catheter and from a reference method (in our case, the pulmonary artery catheter), σ the specific conductivity of the blood, L the electrode spacing of the catheter and G^P the parallel conductance, which was calculated from injection of hypertonic saline (Baan et al., 1984; Steendijk and Baan, 2000). The parallel conductance reflects the surrounding structures, like ventricular walls and the other cardiac chamber. Calibrations of the conductance catheter were performed at the beginning of each measurement period as previously described using cardiac output from thermodilution. Left ventricular parallel conductance was determined by injection of 5 mL hypertonic saline (10%) into the internal jugular vein. Together with the intraventricular pressure sensor, pressure volume loops were generated and analysed using custom made software. Conductance catheter derived stroke volume (SV_{cond}) was defined as the difference between volume at maximal (dP/dt_{max}) and minimal (dP/dt_{min}) first derivative of ventricular pressure *versus* time. After calibration, steady state parameters of the conductance catheter were recorded for 10 seconds during apnoea. Then the inferior vena cava was occluded by filling the balloon for 10 seconds and pressure-volume loops were recorded in apnoea (to prevent hypoxia, a positive end-expiratory pressure of 10 cm H_2O was maintained). At each data collection, this procedure was repeated three times, and means from these three measurements were used.

From LV pressure volume loops recorded during the unloading interventions (see above), the end-systolic pressure volume relation (ESPVR, as the slope of the end-systolic points during LV unloading) and the preload-recruitable stroke work (PRSW, as the slope of the change in the area within the pressure-volume lops during unloading) were calculated to characterize systolic LV function. Accordingly, the end-diastolic pressure-volume relation (EDPVR) and the time constant of active diastolic relaxation (tau) were measured to denote diastolic function. Global hemodynamic parameters were heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), and systemic arterial elastance

(Ea). This set of parameters was recorded in the same way at all five data collections. In addition, echocardiography loops were stored on tape and arterial blood samples were drawn at each collection point for blood gas analysis.

Intervention

The animals were randomly allocated to the following three groups: control group (CON) receiving myocardial ischemia without other interventions, ischemic preconditioning group (IPC), and xenon anesthesia group (XEN). The study design was adopted based on previous studies (Kersten et al., 1996). When surgical preparation was completed (taking about 40 minutes), the inspired fraction of oxygen (FIO_2) was reduced to 0.21 in all animals and "baseline" measurements were performed as described above. In XEN group, inhalation of xenon 70% (equal to 0.55 MAC, with 1 MAC at 120 kPa) was started and thiopental infusion dose was reduced to 12 mg/kg/h with no further changes in anesthesia until the end of the protocol. One hour for equilibration was allowed in CON and XEN groups, and then "pre-ischemia" measurements were performed. In IPC group, ischemic preconditioning was exerted by five 5-minute LAD occlusions, each followed by five minutes of reperfusion. Following these procedures (taking about one hour), the second, "pre-ischemia" set of measurements was carried out.

In all animals ischemia was induced by 1 hour of complete LAD occlusion. Effectiveness of occlusion was verified by the sudden onset of epicardial cyanosis and antero-septal wall akinesis (*i.e.* no change in wall thickness as detected by direct epicardial echography) corresponding to the perfusion area of the LAD. After 1 hour of ischemia, the third, "ischemia" measurement was performed with the LAD still occluded, and immediately thereafter, reperfusion was started. Fourth and fifth data collections were done after 1 and 2 hours of reperfusion, following complete release of the LAD tourniquet. At the end of the study, the animals were killed by intravenous injections of thiopental 1 g and potassium chloride 20 mEq (1.49 g).

Statistical analysis

Data were expressed as the mean ± SD. *Post-hoc* power calculations were based on the assumption that a 20 % post-ischemic difference in at least one of the primary parameters (ESPVR, PRSW, EDPVR and tau) would be a relevant finding (the a priori estimate had been based on the determination of infarction size which was reported earlier) (Baumert et al., 2007). A sample size of 8 animals in each group provides a power of 0.8 at an alpha of 0.05, with a parameter standard deviation of 20%.

A two-way repeated-measures analysis of variance (ANOVA) with the factors "time" and "group" was carried out. Bonferroni's *post-hoc* test was used to compare respective values at each time point between groups (GraphPad Prism 5.01 software, GraphPad Software Inc., La Jolla, CA, USA). A P value < 0.05 was regarded significant. All statistical calculations were performed on raw data but several percentage changes are also reported to facilitate comparison.

Results

There were two incomplete data sets in the CON group and one in each the IPC and XEN groups, because of partial equipment failure. As this is an experimental study, an intention-to-treat approach was not appropriate and those animals were excluded from the analysis. Thus the remaining numbers are $n = 8$ for the CON, and $n = 9$ for the IPC and XEN groups. Myocardial Evans Blue stains (injection of 40 mL Evans Blue solution 0.5% into the left atrial appendage, followed immediately by injection of potassium chloride solution as mentioned above) after completion of the study showed that the extent of ischemia ("area at risk") was around 40% of the total LV mass, identical in all groups. Regional LV function: Because of technical limitations, echocardiography was only available in 9 of the 26 animals (2 in the control, 3 in the xenon, and 4 in the IPC groups). Consequently, between-group comparisons were not carried out for regional function. In all animals investigated, there was complete anteroseptal akinesis during ischemia (decrease of thickening fraction to 0 after one hour of ischemia), with no change after one hour reperfusion and some recovery after two hours. In addition, anteroseptal diastolic wall thickness increased during reperfusion, indicating edema. At the same time, there were no changes in the remote, posterior LV wall (**Figure 1**).

Global LV function: Acute impairment of diastolic function following the onset of ischemia was evidenced in the control group by increases in EDPVR and tau: EDPVR increased by more than 100% ($P < 0.001$, *vs*. IPC group; $P < 0.01$, *vs*. XEN group) and tau increased by about 20% (interaction between time and group effects: $P = 0.007$). In IPC and XEN groups, small increases in EDPVR and no increases in tau were seen. After reperfusion, pre-ischemia values were restored in all groups (**Figure 2**).

Acute ischemia did not induce any significant change in global systolic function, as measured by ESPVR and PRSW. However, PRSW slightly decreased over time ($P = 0.005$; **Figure 3**).

In global hemodynamics, there was a 25–35% increase in heart rate, predominantly during reperfusion (change over time: $P < 0.0001$) which was not different between groups. Changes in cardiac output were limited, with a trend towards decrease during ischemia and early reperfusion in IPC and XEN groups (interaction between time and group:

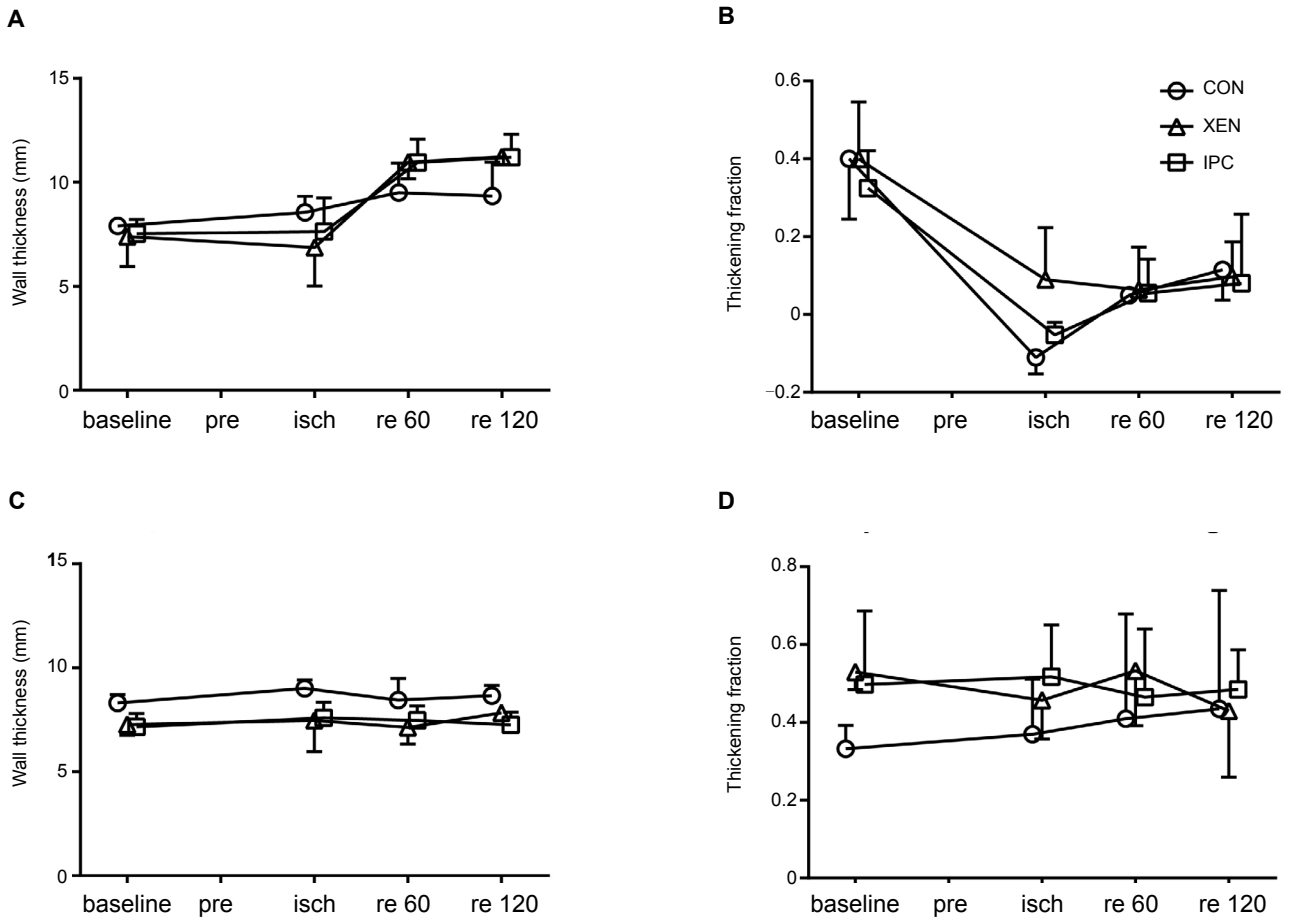

Figure 1: Regional myocardial function.

Note: Diastolic wall thickness (A and C) and thickening fraction (systolic wall thickness minus diastolic wall thickness divided by diastolic thickness; B and D) in the ischemic anteroseptal and the remote posterior left ventricular walls; echocardiographic measurements from 9 animals (2 in CON, 3 in XEN, 4 in IPC groups; mean and SD). pre: Before left coronary artery occlusion; isch: at the end of 60 minutes left coronary artery occlusion; re 60 and re 120: after 60 minutes and 120 minutes of reperfusion; CON: control group; XEN: xenon anesthesia group; IPC: ischemic preconditioning group.

$P = 0.054$). Mean arterial pressure decreased, again mainly during reperfusion (change over time: $P < 0.0001$), without significant differences between groups. Arterial elastance increased during ischemia and reperfusion (change over time: $P < 0.0001$; **Table 1**).

Discussion

One hour of acute LAD ischemia, resulting in complete akinesis of the antero-septal wall, produced significant impairment in global diastolic but not in global systolic LV function, in the control group. Ischemic preconditioning and xenon inhalation limited global diastolic dysfunction, without affecting systolic function. Cardiac output moderately decreased during ischemia, and heart rate increased.

During reperfusion, increasing tachycardia occurred in all groups, stabilizing cardiac output and arterial pressure-with a trend towards hypotension, however, found in the control group. At the same time, global diastolic function recovered in this group. After two hours of reperfusion, there were no more significant differences between groups.

Since the discovery of anesthetic preconditioning, protection of myocardial structure and function from ischemic damage by anesthetics has been an important target of investigation. While most studies aimed at the reduction of myocardial infarct size (Toller et al., 1999a; Kehl et al., 2002) , effects of anaesthetics on myocardial function may also be relevant (Pagel et al., 1995; Preckel et al., 2000). Moreover, most of the available data are focused on reperfusion and recovery but the effects of anesthetics, especially xenon, on acute ischemia itself have not been described yet.

While regional systolic function within the respective area is disabled completely during ischemia and early reperfusion, the interpretation of global systolic function is complicated because contractile force, speed of contraction

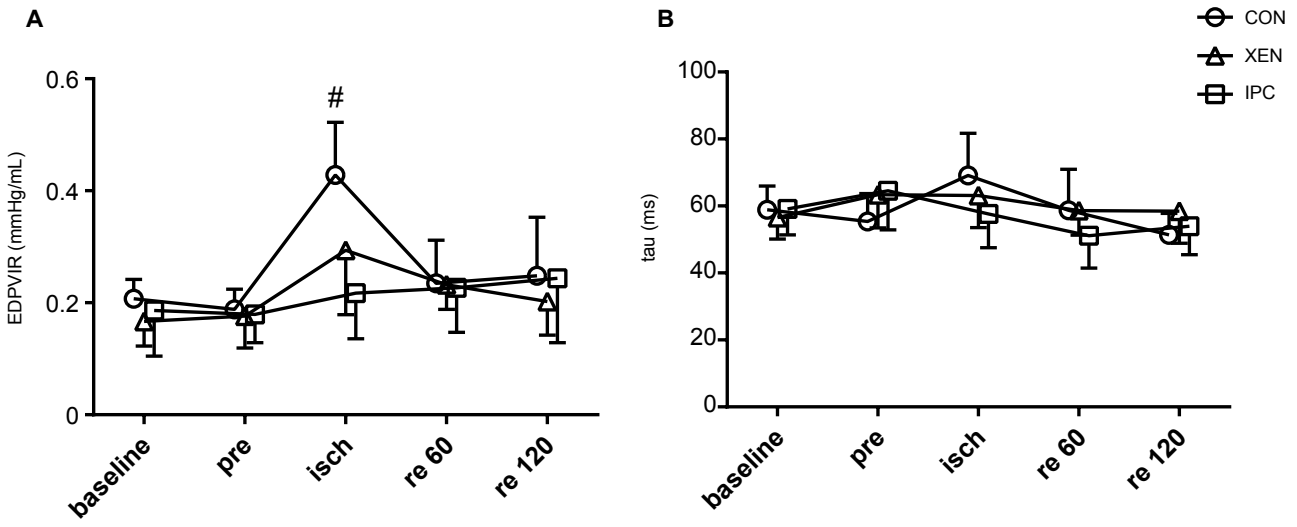

Figure 2: Diastolic function as measured by end-diastolic pressure-volume relation (EDPVR) (A) and time constant of relaxation (tau) (B).
Note: Data were expressed as the mean ± SD from n = 8 (CON group) and n = 9 (XEN, IPC groups); data recorded at baseline, before left coronary artery (LAD) occlusion (pre), at the end of 60 minutes LAD occlusion (isch), and after 60 minutes and 120 minutes of reperfusion (re 60 and re 120, respectively). Changes over time and interaction between time and group are significant (P < 0.01) for both parameters; # P < 0.01, *vs*. IPC and XEN groups; two-way analysis of variance with Bonferroni's t-test. CON: Control group; XEN: xenon anesthesia group; IPC: ischemic preconditioning group.

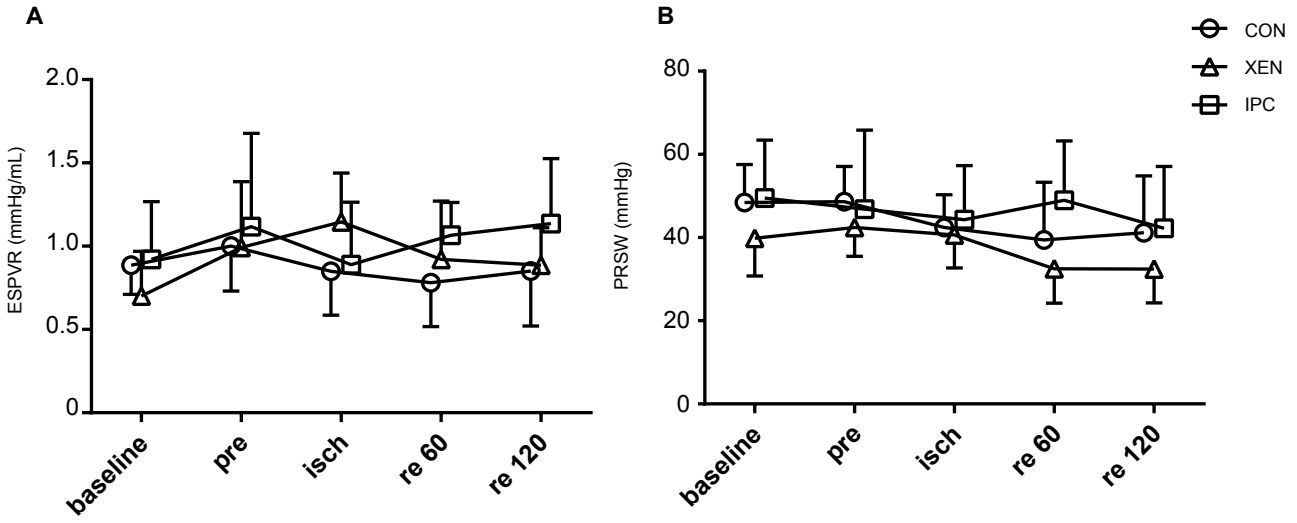

Figure 3: Systolic function as measured by end-systolic pressure-volume relation (ESPVR) (A) and preload-recruitable stroke work (PRSW) (B).
Note: Data were expressed as the mean ± SD from n = 8 (CON) and n = 9 (XEN, IPC groups); data recorded at baseline, before left coronary artery (LAD) occlusion (pre), at the end of 60 minutes LAD occlusion (isch), and after 60 minutes and 120 minutes of reperfusion (re 60 and re 120, respectively); decrease over time in PRSW significant (P < 0.01; two-way analysis of variance), no between-group differences. CON: Control group; XEN: xenon anesthesia group; IPC: ischemic preconditioning group.

and diastolic fibre distension, which are affected differently by ischemia, are all involved. Consequently, there is not only one single measure of contractility or inotropy. In this study we looked at the end-systolic elastance (the slope of the end-systolic pressure-volume relationship ESPVR) and preload recruitable stroke work (the slope of the relation between stroke work and end-diastolic volume). Both indices are generally regarded as relatively load-independent measures of intrinsic LV function (Glower et al., 1985; Baicu et al., 2005; Burkhoff et al., 2005). We were surprised by the observation that both parameters did not change significantly during ischemia (**Figure 2**). While several investigators reported that global systolic function was impaired by acute ischemia (Labovitz et al., 1987; Yotti et al., 2005),

Table 1: Global hemodynamics detection

	CON	IPC	XEN
HR**			
baseline	62.4±15.5	59.2±8.7	65.8±8.4
pre	60.0±9.0	61.3±10.1	69.3±8.5
isch	75.6±11.3	83.3±26.2	82.2±13.6
re 60	91.2±15.5	100.7±17.7	85.4±14.4
re 120	94.4±15.4	96.7±18.4	90.7±17.8
MAP**			
baseline	91.9±18.3	89.7±12.4	98.2±15.1
pre	97.8±15.6	94.4±9.9	99.7±15.8
isch	97.9±16.9	93.6±9.6	93.8±22.8
re 60	77.6±18.7	87.4±8.4	90.7±23.1
re 120	79.0±17.2	82.8±8.0	83.0±23.9
CO			
baseline	2.62±0.14	2.75±0.51	2.94±0.70
pre	3.02±0.21	2.63±0.63	2.71±0.48
isch	2.77±0.21	2.61±0.43	2.56±0.49
re 60	2.67±0.23	3.06±0.63	2.74±0.57
re 120	2.90±0.22	2.78±0.87	2.83±0.55
Ea**			
baseline	2.27±0.47	2.27±0.71	2.34±0.52
pre	2.16±0.36	2.52±0.61	2.76±0.67
isch	2.91±0.62	2.95±0.71	3.03±0.85
re 60	2.86±0.47	2.75±0.51	3.18±0.99
re 120	2.73±0.62	3.14±0.89	2.94±0.88

Note: Data were expressed as the mean ± SD from $n = 8$ (CON) and $n = 9$ (XEN, IPC groups). **Increases over time in HR and Ea as well as decreases over time in MAP are significant ($P < 0.0001$; two-way analysis of variance), no significant between-group differences. HR: Heart rate (beats/min); CO: cardiac output (L/min); MAP: mean arterial pressure (mmHg); Ea: arterial elastance (mmHg/mL); pre: before left coronary artery (LAD) occlusion; isch: at the end of 60 minutes LAD occlusion; re 60: after 60 minutes of reperfusion; re 120: after 120 minutes of reperfusion.

there are more recent papers from rabbit (Andrews et al., 2009) and pig studies (Angeli et al., 2009) which support our finding that global LV systolic function is not necessarily deteriorated during total ischemia of the mid- or distal LAD area, although it must be noted that both cited reports used only 15 minutes of ischemia. In a model similar to the one reported here, acute right ventricular (RV) ischemia did also not impair global RV systolic function (Hein et al., 2010). In our view, unchanged global systolic function along with regional akinesis suggests an increase in systolic function in the non-ischemic (remote) myocardium. Our echocardiography measurements which were only intended to prove dysfunction in the ischemic area could, however, not detect increased contractility in remote myocardium.

To date, the effects of regional ischemia on remote myocardium have not been investigated thoroughly. There is evidence of activation of several enzymatic processes which may lead to hyperkinesis or hypercontractility of remote myocardium (Budaj et al., 2003). Occurrence of such remote hyperkinesis may have positive prognostic significance in patients (Jaarsma et al., 1986) but experimental studies have shown conflicting results (Sakai et al., 1985; Marsch et al., 1993). It is also reported that reperfusion increases global contractility earlier than post-ischemic myocardium could recover and regain its function. This was shown in the border zone (Sakai et al., 1985) and in remote myocardium (Sakamoto et al., 2007). Hypercontractility varies among different regions, especially between apical and basal segments (Marsch et al., 1999) which might possibly be explained by a different density of sympathetic innervations (Kawada et al., 2007). In contrast, recovery of ischemic myocardium after reperfusion would be expected to take longer than the two hours of observation in this experiment. Accordingly, in our echocardiographic findings we only see minimal recovery of anterior wall function after two hours of reperfusion. In our view, it is unlikely that recovery of ischemic myocardium contributed to any of the observed changes in global LV function.

It is generally accepted that diastolic function is more sensitive to ischemia than systolic function and that diastolic dysfunction may occur earlier in the course of myocardial damage (Labovitz et al., 1987), and even without systolic dysfunction (Barletta et al., 1996; Azevedo et al., 2004). In contrast, the existence of systolic without diastolic dysfunction is unlikely if not impossible (Baicu et al., 2005). Therefore we specifically looked at diastolic function using two important measures derived from conductance catheter data: the time constant of relaxation, tau, which is a measure of the active diastolic process (Kasner et al., 2007), and the end-diastolic pressure-volume relationship (EDPVR) which more reflects the passive, compliant properties of the LV (Steendijk et al., 2008). If these are combined, a comprehensive analysis of LV diastolic function can be obtained. It is known that volatile anesthetics can improve these parameters of diastolic function during acute ischemia: Pagel and colleagues described some preservation of diastolic function within the ischemic area, as well as enhancement of systolic function of the remote myocardium, by desflurane in a dog model-but these were regional wall function analyses without the use of a conductance catheter (Pagel et al., 1995). Contrastingly, in normal conditions volatile anesthetics may exert negative effects on both systolic and diastolic function (Humphrey et al., 1990; Harkin et al., 1994). In our experiments, only ischemic preconditioning fully prevented the impairment of diastolic function. Xenon partly protected active relaxation (no increase in tau) and limited the increase

in chamber "stiffness" (EDPVR). To our knowledge, this is the first report that xenon can protect LV diastolic function to some extent (**Figure 1**). Recovery in the control group must then be interpreted primarily as an improvement in remote diastolic function, according to our line of argument.

The global hemodynamic effects of ischemia and reperfusion, such as tachycardia and increased arterial elastance, are not significantly different between groups. Thus they are obviously uniform and not specifically modified by preconditioning or xenon inhalation.

The following limitations of the present study must be addressed: First, the anesthetic effects reported here include the effect of thiopental in all groups. It was chosen because it has the least effect on ischemia/reperfusion and infarct size, of the available anesthetics (Smith et al., 1982). Second, our incomplete analogue echocardiography records only allowed for the very basic analysis of wall thickness and systolic thickening fraction. Accordingly, we cannot comment on regional diastolic function which might have been interesting in the remote area. Third, we cannot provide any data on the cellular mechanisms of the effects of xenon in this setting, and so far, only common pathways of anti-ischemic protection have been identified (Weber et al., 2005a, b). Thus there is lack of evidence for a specific mechanism of the xenon effect. Fourth, the effects shown here are short-term in nature, and we can only speculate if they would translate into a sustained benefit for LV recovery from acute ischemia. The present results do not support such a speculation because after two hours of reperfusion, there was no more difference between groups, as a result of marked recovery in the control group. On the other hand, a limitation of infarction size itself by xenon has been shown in this model (Baumert et al., 2007; Hein et al., 2008) and it seems reasonable to expect a long-term functional advantage, with smaller infarction size as well.

In conclusion, we were able to show that in this large animal model of LV anterior wall ischemia, xenon inhalation but more so ischemic preconditioning could diminish acute global diastolic dysfunction. Moreover, an extent of ischemia sufficient to produce substantial infarction surprisingly did not impair global systolic LV function.

Author contributions

JHB and MH were responsible for study concept and statistical analysis. JHB wrote the paper. All authors were involved in experimental work and data acquisition, literature search and revision, and approved the final version of the paper.

Conflicts of interest

The authors declare no conflicts of interest.

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