Reduction in postsystolic wall thickening during late preconditioning

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METHODS

The animal instrumentation and the ensuing experiments were conducted in accordance with the official regulations of the French Ministry of Agriculture.

Surgical preparation. As previously described (19), a left thoracotomy was performed in 11 dogs under anesthesia (pentobarbital sodium, 30 mg/kg iv). Filled fluid catheters were implanted in the descending thoracic aorta and the left atria. A solid-state micromanometer (Konigsberg Instruments) was introduced into the LV through the apex. A Transonic flow probe and a pneumatic occluder were implanted around the circumflex coronary artery. Two pairs of ultrasonic crystals were placed within the distribution of the circumflex coronary artery (ischemic zone) and of the left anterior descending coronary artery (nonischemic zone) for LV wall thickening measurement. One crystal was implanted in the endocardium, and the other was sutured to the epicardium, independently from the muscle fiber’s orientation. Finally, in four dogs, bipolar electrodes were sewn on the epicardial surface of the right ventricle for subsequent electrical pacing. All catheters and wires were exteriorized between the scapulae. Cefazolin (1 g iv) and gentamycin (40 mg iv) were administered before and during the first week after surgery. Peri- and postoperative analgesia were provided with morphine.

Experimental protocol. Three weeks after instrumentation (day 0), seven dogs were installed to lie quietly on a table in the conscious state. After baseline measurements, a 10-min occlusion of the left coronary artery (CAO) and reperfusion induce myocardial stunning and late preconditioning. Postsystolic wall thickening (PSWT) also develops with CAO and reperfusion. However, the time course of PSWT during stunning and the regional function pattern of the preconditioned myocardium remain unknown. The goal of this study was to investigate the evolution of PSWT during myocardial stunning and its modifications during late preconditioning. Dogs were chronically instrumented to measure (sonomicrometry) systolic wall thickening (SWT), PSWT, total wall thickening (TWT = SWT + PSWT), and maximal rate of thickening (dWT/dtmax). Two 10-min CAO (circumflex artery) were performed 24 h apart (day 0 and day 1, n = 7). At day 0, CAO decreased SWT and increased PSWT. During the first hours of the subsequent stunning, evolution of PSWT was symmetrical to that of SWT. At day 1, baseline SWT was similar to day 0, but PSWT was reduced (–66%), while dWT/dtmax and SWT/TWT ratio increased (+48 and +14%, respectively). After CAO at day 1, stunning was reduced, indicating late preconditioning. Simultaneously vs. day 0, PSWT was significantly reduced, and dWT/dtmax as well as SWT/TWT ratio were increased, i.e., a greater part of TWT was devoted to ejection. Similar decrease in PSWT was observed with a nonschismic preconditioning stimulus (rapid ventricular pacing, n = 4). In conclusion, a major contractile adaptation occurs during late preconditioning, i.e., the rate of wall thickening is enhanced and PWST is almost abolished. These phenotype adaptations represent potential approaches for characterizing stunning and late preconditioning with repetitive ischemia in humans.

postsystolic thickening is the part of myocardial contraction that occurs beyond the closure of the aortic valve (5, 16, 29) and is a marker of left ventricular (LV) asynchrony (10), which has been extensively described during experimental and clinical myocardial ischemia (5, 29). However, the mechanisms involved in this phenomenon remain presently unclear and depend on the level of wall thickening (26) and ischemic substrate (28, 32, 33). Whether it is a passive and/or an active mechanism (5) and whether it is a marker of myocardial viability (5, 12, 29) are still debated. Postsystolic thickening has also been reported during myocardial stunning (6, 9, 11, 23) and has been shown to result from both a reduced contractile velocity and an inhomogeneity in the LV contraction (11). However, the overall time course of postsystolic thickening during myocardial stunning has never been fully described. In addition, it is interesting to consider that the time course of postsystolic thickening can also be modified with repetitive ischemia, i.e., the reduction in the duration and severity of myocardial stunning that occurs 24 h after a first brief ischemic episode during late preconditioning (7, 25, 27). Despite intensive investigations, the regional function pattern and phenotype of the preconditioned myocardium have not been described yet, especially regarding postsystolic wall thickening.

Accordingly, the purposes of this study were 1) to investigate the respective time course of systolic (SWT) and postsystolic wall thickenings (PSWT) that occurs after a brief ischemia and 2) to determine whether the relative contribution of these two parameters to total wall thickening in the stunned myocardium is altered by late preconditioning. For these purposes, we used a model of chronically instrumented conscious dogs that enables us to perform two brief episodes of coronary artery occlusion (CAO) 24 h apart (7). Both SWT and PSWT were measured by sonomicrometry.

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Poststolic Thickening and Stunning

Total wall thickening was calculated as the sum of SWT and PSWT. Twenty-four hours later (day 1), the 10-min CAO was repeated. All hemodynamic and wall thickness parameters were recorded and calculated during CAO and during the 6 h of the subsequent reperfusion period.

To investigate whether changes in regional function observed at day 1 were independent from residual myocardial stunning, late preconditioning was induced in four additional dogs with a nonschematic stimulus, i.e., rapid ventricular pacing (240 beats/min during 40 min) (17). Dogs underwent 2 days of experiments: on day 0, the animals underwent the late preconditioning stimulus, i.e., rapid ventricular pacing, and, on day 1, i.e., 24 h later, a 10-min CAO was performed. The time course of myocardial stunning was compared with another sequence performed 1 wk apart when dogs were only subjected to a 10-min CAO without preliminary rapid ventricular pacing.

**Hemodynamic measurements.** Data were recorded and analyzed using the data-acquisition software Notocord-HEM 3.3. Aortic and left atrial pressures were measured with Statham P23ID strain-gauge transducers and were used to cross-calibrate the Konigsberg gauge. LV pressure was measured using the Konigsberg gauge, and LV pressure first derivative (LV dP/dt) was computed from the LV pressure signal. Circumflex coronary artery blood flow was measured with a Transonic transit-time flowmeter to assess proper CAO.

**Measurements of regional systolic function.** End-diastolic and end-systolic wall thicknesses were measured with an ultrasonic trans-time dimension gauge. End-diastolic time was defined at the initiation of the upstroke of LV pressure tracing and end-systolic time 20 ms before the negative peak of LV dP/dt (Fig. 1) (29).

Rate of wall thickening (dWT/dt) was computed from the wall thickness signal, and the maximal value of dWT/dt was measured during systole (dWT/dt max).

**Measurements of regional myocardial blood flows.** Regional myocardial blood flows were measured by the fluorescent microspheres technique, as previously reported (20). Microspheres labeled with fluorescent dyes (FluoSpheres, Triton System, San Diego, CA) were injected via the left atrial catheter. Arterial blood reference samples were withdrawn (7.5 ml/min during 2 min). At termination of the study, the heart was excised, and LV was cut into three to four slices and further divided into subendocardium, midmyocardium, and subepicardium layers. Samples were then processed to extract the fluorescence, and blood flows (expressed as milliliter per minute per gram of myocardium) were calculated. Mean transmural flow was calculated as the combined flow of all three layers.

**Regional work index.** The regional myocardial work index was computed on three consecutive beats as the area of the LV pressure-wall thickness loop.

**RESULTS**

**Hemodynamics.** As shown in Table 1, heart rate, mean arterial pressure, LV pressure, and LV dP/dt max were not significantly different at baseline and during CAO and reperfusion between day 0 and day 1. Regional myocardial blood flows measured similar during CAO between day 0 and day 1 (0.11 ± 0.06 and 0.09 ± 0.05 ml/min·g−1, respectively) (n = 4).

**Statistical analysis.** Data are reported as means ± SE. Analysis was performed using a two-way ANOVA for repeated measures and by checking for interactions. The F-test was used to test the significance of analysis of variance. When needed, pairwise comparisons between day 0 and day 1 were performed using a paired two-sided Student’s t-test with Bonferroni correction. Significance was accepted at P < 0.05.

**Fig. 1.** Left: typical waveform representing the evolution of myocardial wall thickness during a single beat recorded from a stunned posterior wall: systolic wall thickening (SWT) was defined as the difference between end-diastolic and end-systolic wall thicknesses; maximal wall thickness was defined as the maximal distance between crystals measured after end systole; left ventricular (LV) postsystolic wall thickening (PSWT) was defined as the maximal minus end-systolic wall thicknesses. Right: representative recordings of aortic and LV pressures, LV pressure first derivative (LV dP/dt), and LV posterior wall thickness measured at baseline and during myocardial stunning. dWT/dt max, maximal systolic rate of wall thickening.

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reperfusion, ischemic SWT remained initially depressed and progressively returned to its corresponding baseline value, indicating myocardial stunning. As illustrated in Fig. 2, values of SWT measured during the first 6 h of reperfusion at day 1 were significantly greater compared with day 0. The deficit of wall thickening over the 6 h of recovery was reduced at day 1 compared with day 0 (60 ± 20 vs. 136 ± 27 units, respectively, P < 0.05), demonstrating late preconditioning.

In the nonischemic zone (Table 2) at day 0, SWT increased up to 3.0 ± 0.3 mm during CAO but returned to its baseline value (2.7 ± 0.3 mm) immediately after relief of the occlusion and remained unchanged throughout reperfusion. There were no significant differences in nonischemic SWT between days 0 and 1 (Table 2).

At day 1 (Fig. 3, Table 2), PSWT increased up to 1.58 ± 0.15 mm during CAO. This value was significantly greater than corresponding PSWT at day 0. During reperfusion, the time course of PSWT paralleled that observed at day 0, but its values remained significantly lower throughout the whole recovery period (average of -49%) compared with day 0. The area under the curve for PSWT was significantly reduced at day 1 compared with day 0 (4.7 ± 1.1 vs. 10.2 ± 1.8 mm/h).

In the nonischemic zone, PSWT values were not altered during CAO and/or reperfusion, with no differences being observed between days 0 and 1 (Table 2).

Table 2. Regional function

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Values are means ± SE; n = 7. *P < 0.05 vs. day 0.
a pattern similar to the evolution of SWT (Fig. 5, Table 2). At day 1, baseline dWT/dₜ_max was significantly increased by 30 ± 10% compared with its corresponding value at day 0. During reperfusion, the pattern of recovery was also similar to day 0, but all values were significantly higher (averaging 48 ± 5%). Interestingly, this effect was not related to differences in SWT, as the ratio of dWT/dₜ_max to SWT was significantly greater at baseline and during the whole recovery at day 1 vs. day 0.

Regional work index. As illustrated in Fig. 6, the regional work index was significantly reduced at day 1 compared with day 0.

Rapid ventricular pacing. In the four additional dogs submitted to rapid ventricular pacing, PSWT was significantly reduced at day 1 (0.38 ± 0.08 mm) compared with day 0 (0.77 ± 0.02 mm), although SWT was similar at baseline (day 0 vs. day 1: 3.0 ± 0.3 and 3.1 ± 0.4 mm, respectively).

Fig. 2. Percent change from baseline of SWT measured during coronary artery occlusion (CAO) and reperfusion at days 0 and 1. Inset: deficit of wall thickening calculated at days 0 and 1. The duration and severity of myocardial stunning were reduced at day 1 vs. day 0, indicating late preconditioning. *P < 0.05 vs. day 0.

Fig. 3. Time course of PSWT (expressed in mm) measured at baseline and during CAO and reperfusion at days 0 and 1. The pattern was symmetrical to that observed with SWT. At day 1, PSWT was reduced at baseline and throughout reperfusion vs. day 0. *P < 0.05 vs. day 0.

Fig. 4. Time course of the SWT-to-total wall thickening ratio measured at baseline and during CAO and reperfusion at days 0 and 1. At day 1, a greater part of total wall thickening was devoted to ejection, as demonstrated by increased ratio values at baseline and during reperfusion vs. day 0. *P < 0.05 vs. day 0.

Fig. 5. Evolution of dWT/dₜ_max in relation to SWT measured at baseline and during CAO and reperfusion at day 0 and 24 h later (day 1). At day 1, dWT/dₜ_max was significantly increased at baseline and throughout recovery. Inset: evolution of the ratio between dWt/dₜ_max and SWT. This ratio was significantly increased at day 1 vs. day 0, demonstrating that the increases in this ratio observed at day 1 were not related to differences in SWT values between day 1 and day 0. *P < 0.05 vs. day 0.

DISCUSSION

Brief ischemia is well known to induce myocardial stunning and the development of an endogenous protective mechanism that confers resistance to posts ischemic dysfunction 24 h later, i.e., late preconditioning (7, 25, 27). To date, few if any data are yet available about the regional function and phenotype of the preconditioned myocardium, especially regarding PSWT, although numerous studies have been devoted to the investigation of the intracellular mechanisms of late preconditioning, particularly those involving the nitric oxide hypothesis (3). Indeed, a postsystolic phenomenon develops during reperfusion, but its overall time course during myocardial stunning and late preconditioning had never been fully described. In this
context, the present study demonstrates that the recovery in SWT of the stunned myocardium is accompanied by a progressive and symmetrical decrease in PSWT. More importantly and for the first time to our knowledge, our results demonstrate that the PSWT almost vanishes 24 h after a brief ischemia, although SWT returns to baseline. In other words, in the late preconditioned heart, a greater part of total wall thickening is devoted to the ejection. Interestingly, a significant increase in dWT/dt, although SWT returns to baseline. In other words, in the late preconditioned heart, a greater part of total wall thickening is devoted to the ejection. Interestingly, a significant increase in dWT/dt, although SWT returns to baseline. In other words, in the late preconditioned heart, a greater part of total wall thickening is devoted to the ejection. Interestingly, a significant increase in dWT/dt, although SWT returns to baseline.

Experimental setting. The model of conscious and chronically instrumented dog used in this study is particularly suitable to investigate late preconditioning against myocardial stunning (7). First, it allows measurement of regional systolic function using a “gold standard method,” i.e., sonomicrometry, without interference of anesthesia or recent surgical intervention (30). Second, the overall hemodynamic parameters are extensively investigated. Third, it allows the repetition of CAOs performed 24 h apart. Fourth, the evaluation of regional systolic function is accurate, repetitive, and reproducible. With this technique, measurements of wall thickening are always made on the same area of the LV wall, independently from the investigator, as determined by the implanted ultrasonic crystals. It should also be stressed that these results cannot be extended to other ischemic substrates, i.e., acute vs. chronic ischemia and CAO vs. stenosis (14). One potential pitfall needs, however, to be addressed. One could argue that postsystolic wall thickening might result from translation motion between the crystals. This is unlikely, as PSWT has also been described using echocardiographic measurements, either in animal models (8, 14, 18) or humans (31). Moreover, using tissue Doppler imaging, we also observed PSWT in our animal preparation, either at baseline or during stunning, thus confirming our sonomicrometric measurements (data not shown).

PSWT during ischemia. PSWT has been described to occur in the normal heart (26, 29, 31). Strain rate imaging has been emphasized that postsystolic contraction should not be confused with PSWT (26). PSWT has been described to occur in the normal heart (26, 29, 31). Strain rate imaging has been extensively investigated. However, it has been attributed to the posterior wall at baseline. This heterogeneity has already been described using MRI in humans. It has been attributed to segmental prestretch (34), or it could result from ventricular electrical asynchrony (22).

In the present study, PSWT increased during ischemia (2, 13), but, 24 h later, the amount of PSWT during CAO was greater in the preconditioned state, although the dramatic decrease in SWT was similar to that observed at day 0. Interestingly, in this context, the positive predictive value of postsystolic contraction during ischemia for subsequent recovery has been described in many studies performed both in experimental (5, 29) and clinical settings (12). However, it has been emphasized that postsystolic contraction should not be considered an irreversible marker of segment viability (28).

Contractile adaptations of the late preconditioned heart. During myocardial stunning at day 0, the impairment in contractile function was characterized not only by the well-known depression of SWT but also by a concomitant increase in PSWT throughout the reperfusion period. Interestingly at day 1, PSWT was dramatically reduced vs. day 0 at baseline but also during stunning. This was associated with a significant increase in the dWT/dt at day 1 (Fig. 6), independently from the SWT value or changes in the ejection time. To ensure that
these changes in regional systolic function were independent from residual myocardial stunning, late preconditioning was induced in additional animals by a nonischemic stimulus, i.e., rapid ventricular pacing (17). The results of the present study might also be biased by denervation during CAO or a greater sympathetic stimulation at day 1. This is, however, unlikely, as no change was observed in the nonischemic anterior zone, and reduction in PSWT was also observed following rapid ventricular pacing. Regional myocardial blood flows were similarly reduced during the 2 days of the protocol. In addition, absence of changes in the nonischemic anterior wall exclude a global effect of late preconditioning. Finally, the lack of simultaneous increase in ischemic SWT and PSWT in the remote anterior zone excludes any interaction between both regions.

The present study demonstrates that, in the preconditioned heart, a greater course of thickening occurred during the ejection period, i.e., more thickening was devoted to ejection. This result suggests that the wasted oxygen due to PSWT is spared in the late preconditioned heart and, therefore, could participate in the anti-ischemic effect of late preconditioning. Interestingly, our laboratory recently reported that late preconditioning induced changes in the metabolic phenotype, i.e., myocardial oxygen consumption of the late preconditioned myocardium was reduced (21). Although not directly assessed here, all of these results suggest a major contractile adaptation associated with an improved cardiac efficiency that could contribute to the protection against myocardial ischemia and stunning. Late preconditioning not only reduces the severity and duration of myocardial stunning but also alters the overall course of myocardial wall thickening, i.e., a smaller part of contraction is wasted after the ejection. This might be the consequence of a positive inotropic-like effect, as reflected by the increase in the \( \frac{dW}{dt} \). It is unlikely related to changes in loading conditions and ventricular stretch, as we did not observe any significant changes in LV end-diastolic wall thicknesses. Although investigation of the cellular mechanisms of these contractile and metabolic adaptations was beyond the scope of our study, it is interesting to speculate that changes in calcium handling (1), e.g., modulation of the ryanodine receptor or \( L \)-type calcium channels, or due to enhanced nitric oxide production with late preconditioning might occur (3). Further studies are needed to investigate these issues.

In conclusion, our study demonstrates major changes in the course of myocardial wall thickening during repetitive stunning with late preconditioning, i.e., the \( \frac{dW}{dt} \) is enhanced and PSWT is almost abolished, involving the almost entire total wall thickening to ejection. This study may have important clinical implications, particularly with the use of Doppler tissue imaging. These results suggest that both the amplitude and the temporal patterns of regional myocardial thickening have to be assessed during myocardial stunning and also during adaptation of the heart to transient ischemia. This would precisely evaluate not only the regional function of the myocardium but also the progressive changes in its contractile phenotype that could appear in the setting of chronic and repetitive ischemia (15).

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