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Mild Hypothermia to Limit Myocardial Ischemia-Reperfusion Injury: Importance of Timing

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Abstract

Background—Hypothermia during ischemia has been shown to reduce myocardial reperfusion injury. We sought to establish the cardioprotective effect of very mild total-body hypothermia ($\leq 2.5^{\circ}\text{C}$) and to determine whether the application of hypothermia at different points during the ischemia-reperfusion period influenced the degree of myocardial salvage.

Methods—Rabbits were subjected to 30 minutes of myocardial ischemia followed by 3 hours of reperfusion. Twenty-five animals were maintained at normal temperature (39.5°C) throughout the experiment (W-W-W group). All other animals were cooled to reduce left atrial temperature 2.0°C to 2.5°C . Eleven animals reached goal temperature before coronary occlusion (C-C-C group), in 14 animals cooling was initiated at coronary occlusion (W-C0-C group), in 8 animals cooling was initiated 15 minutes after coronary occlusion (W-C15-C group), in 5 animals cooling was initiated 25 minutes after coronary occlusion (W-C25-C group), and in 13 animals cooling was started concurrently with reperfusion (W-W-C group). Infarct size as a percentage of the risk area (I/AR) was determined by a double staining-planimetry technique.

Results—Goal temperature was achieved before reperfusion in the C-C-C and W-C0-C groups but was not achieved until the reperfusion period in the other treatment groups. Infarct size was $59.0 \pm 1.2\%$ in the W-W-W group and was reduced in all cooling groups (C-C-C = $30.4 \pm 4.9\%$; W-C0-C = $33.4 \pm 5.0\%$; W-C15-C = $42.4 \pm 1.4\%$; W-C25-C = $44.1 \pm 2.3\%$; W-W-C = $50.5 \pm 4.1\%$). The temperature at reperfusion correlated most strongly with infarct size ($r = 0.72$, $p < 1 \times 10^{-12}$).

Conclusions—Very mild hypothermia affords a significant cardioprotective effect. Temperature at the time of reperfusion most strongly correlates with the degree of myocardial salvage.

Early and sustained reperfusion remains the only proven method for salvaging jeopardized myocardium after acute coronary artery occlusion [1]. Even when contemporary reperfusion strategies are employed, many patients still experience suboptimal short-term and long-term outcomes attributable to extensive myocardial damage [2,3]. Because infarct size is an important predictor of early and late survival after acute myocardial infarction (AMI) [4], adjunctive therapies that improve myocardial salvage after reperfusion would likely improve clinical outcomes. While numerous pharmacologic interventions have been proposed and tested clinically, few have been demonstrated to be a significant improvement over reperfusion alone [5,6].

Nearly four decades ago, Angell and colleagues [7] demonstrated the cardioprotective effects of profound hypothermia. Deep myocardial hypothermia is currently a commonly employed strategy for protecting the heart during cardiac surgery [8]. The levels of hypothermia used for intraoperative protection are typically below 15°C and are not possible without circulatory support. However, recent animal studies have demonstrated that much less drastic temperature reduction can improve myocardial salvage rates after ischemia and subsequent reperfusion [9-12]. This work has resulted in the development of intravascular and topical cooling devices that are currently being assessed as adjuncts to reperfusion therapy [13,14].

Most laboratory and clinical studies have utilized a 4°C to 10°C reduction in normal body temperature. However, it has been demonstrated in both small and large animal models that a near linear response between temperature reduction and myocardial salvage is operative with as little as a 1°C reduction in body temperature [9,10]. The exact time point during ischemia and subsequent reperfusion that mild hypothermia is most critical to myocardial salvage has yet to be determined. It is clear that hypothermia initiated before or early after the induction of ischemia reduces myocardial injury; however, the effect of cooling late in the ischemic period or after reperfusion has not been fully elucidated.

The goals of this experiment were to establish that very mild ($\leq 2.5^{\circ}\text{C}$) hypothermia is cardioprotective and, more importantly, to assess the time course over which such subtle levels of hypothermia need to be applied to achieve a salutary effect on myocardial salvage. An understanding of this temporal effect has important clinical implications. If mild hypothermia is required throughout the ischemic period then it is unlikely that such a strategy will be clinically relevant. However, if cooling late in the ischemic interval or early in the reperfusion period has beneficial effects on myocardial salvage, the likelihood of efficacy in patients would be greatly increased.

Material and Methods

Animal Model

New Zealand white rabbits (3 to 4 kg) were sedated with intramuscular ketamine (100 to 120 mg/kg) and bu-prenorphine (0.05 mg/kg). After oral intubation, the animals were ventilated with a mechanical ventilator (Model AWS; Hallowell EMC, Pittsfield, MA) using room air enriched with 0.6 L/minute of oxygen. Anesthesia was maintained with continuous ketamine infusion (10 to 20 mg/hour). A high fidelity pressure transducer (Millar Instruments Inc, Houston, TX) was placed in the left ventricle through the carotid artery for continuous pressure measurement. Heart rate (HR), arterial blood pressure (ABP), left ventricular pressure (LVP), and surface electrocardiogram (ECG) were continuously monitored (HP 78534C; Hewlett Packard, Palo Alto, CA) and recorded (Sonometrics Inc, London, Ontario, Canada). A left thoracotomy was performed, and the heart was exposed. A ligature was passed around the proximal segment of a large branch of the circumflex coronary artery at approximately 50% of the distance from base to apex of the heart. Myocardial ischemia was achieved by tightening the snare and confirmed by ST elevation on ECG and a distinct myocardial color change. After 30 minutes of ischemia, the snare was released and the myocardium was allowed to reperfuse for 180 minutes. At the end of reperfusion, the coronary artery snare was reapplied, and Evans blue dye (Sigma, St. Louis, MO) was injected into the left atrium to delineate the ischemic risk area. The animal was then euthanized with a potassium overdose and the heart was excised.

Temperature Control and Measurement

Left atrial (LA) and rectal temperature were measured with a digital thermometer (Thermalert TH-8; Physitemp Instrument, Clifton, NJ). After sedation and upon arrival in the operating room, rectal temperature was measured immediately and recorded as the “initial” temperature. After thoracotomy, but prior to coronary occlusion, temperature was immediately recorded in the LA and recorded as the “baseline” temperature. The LA and rectal temperatures were measured every 5 minutes during ischemia and every 15 minutes during reperfusion. Goal temperatures were achieved by surface cooling with a water blanket (Medi Therm III; Gaymar Industries Inc, Orchard Park, NY).

Experimental Protocol

Seventy-six rabbits were used in the study and were treated in compliance the Guide for the Care and Use of Laboratory Animals (National Institute of Health Publication No. 85-23 as revised in 1996). Animals were divided into 6 groups in which different temperature management strategies were employed (Fig 1). Normal rabbit body temperature is between 39°C and 40°C (39.7 ± 0.4 , $n = 165$ animals in our facility). When hypothermia was induced in this experiment the goal temperature was 2°C to 2.5°C below the recorded initial temperature. Twenty-five animals were maintained at their initial temperature throughout the course of the experiments (W-W-W group). Hypothermia was induced in 11 animals immediately after induction of anesthesia and measurement of the initial temperature (C-C-C group). These animals reached goal temperature prior to coronary occlusion. In 14 animals cooling was initiated as the coronary artery was occluded (W-C0-C group). In 8 and 5 animals cooling was initiated at 15 minutes (W-C15-C group) and 25 minutes (W-C25-C group) after the start of myocardial ischemia, respectively. Finally, in 13 animals cooling was begun as the coronary snare was removed and the myocardium was reperfused (W-W-C). In all cases when the target temperature was achieved it was maintained until the conclusion of the experiment.

Analysis of Area at Risk and Infarct Size

At the completion of the protocol, the coronary snares were retightened and vascular clamps were used to occlude the aorta, pulmonary artery, and inferior vena cava, and the right atrium was incised. Evans blue dye (1 mg/kg;) was injected into the left atrium to delineate the ischemic myocardial area at risk (AR). All animals were then euthanized by an injection of potassium chloride into the left atrium and the heart was excised. The left ventricle was sectioned perpendicular to its long axis into 6 to 8 slices. The thickness of each slice was measured with a digital micrometer and all slices were photographed. The infarct area was delineated by photographing and measuring the slices after 20 minutes of incubation in 2% triphenyltetrazolium chloride (TTC) at 37°C. All photographs were imported into an image analysis program (Image Pro Plus; MediaCybernetics, Silver Spring, MD) and computer-assisted planimetry was performed. The AR is expressed as a percentage of the LV, and the infarct size is expressed as a percentage of the AR.

Hemodynamic Measurements

As stated above, ABP, LVP, HR, and surface ECG were continuously monitored and recorded throughout the procedure. From these data the maximal rate of LVP increase over time (dP/dt max), rate-pressure product (RPP), and LV end-diastolic pressure (LVEDP) were determined.

Statistics

Measurements are reported as means $\pm$ standard error of the mean. A one-way analysis of variance (ANOVA) was used for all comparisons among groups. Repeated measures

ANOVA was used for all comparisons within groups. Individual post hoc comparisons were performed using the Tukey “Honestly Significantly Different” test. Temperature at each time point was correlated with ischemic area as a percentage of area at risk and the Pearson correlation coefficient calculated. All analyses were completed using SPSS Version 11.0 (SPSS, Inc, Chicago, IL). Statistically significant differences were established at p less than 0.05.

Results

Temperature

Temperature measured simultaneously in the rectum and LA were virtually identical ($r = 0.963$, $p = 3 \times 10^{-38}$) at baseline and during cooling. The initial temperatures in all groups were very similar and averaged $39.8 \pm 0.1^\circ\text{C}$. The degree of maximal cooling was similar in all groups in which hypothermia was induced and averaged $2.4 \pm 0.1^\circ\text{C}$. Because of the different cooling patterns temperature varied significantly between groups during the ischemia and early reperfusion time periods (Table 1 and Fig 2). In the two groups in which cooling was initiated before (C-C-C) and simultaneously with coronary occlusion (W-C0-C) the temperature was $37.4 \pm 0.1^\circ\text{C}$ and $37.5 \pm 0.1^\circ\text{C}$, respectively, at the end of the ischemic period. In the two groups in which hypothermia was initiated at 15 (W-C15-C) and 25 (W-C25-C) minutes after coronary occlusion, the temperatures at the time of reperfusion were $38.0 \pm 0.1^\circ\text{C}$ and $38.2 \pm 0.1^\circ\text{C}$, respectively. Both of these temperatures were significantly higher than the temperatures in the C-C-C and W-C0-W groups. The temperature at reperfusion in the W-W-W and the W-W-C groups was $39.6 \pm 0.1^\circ\text{C}$ and $39.3 \pm 0.1^\circ\text{C}$, respectively, which was significantly higher than the other four groups. Temperature data are presented in Table 1 and Figure 2.

Risk Area and Infarct Size

The AR was similar in all groups (Fig 3A). Infarct size as a percentage of the AR is presented in Figure 3(B). By ANOVA, there was a significant difference ($p < 0.001$) among the six experimental groups, with a large effect size ($\eta^2 = 0.42$). Infarct size (I/AR) was $59.0 \pm 1.2\%$ in the W-W-W group. Cooling at the time of reperfusion (W-W-C) had the smallest effect on infarct size ($50.5 \pm 4.1\%$, $p = 0.09$ vs W-W-W). Cooling before (C-C-C) or simultaneously with (W-C0-C) coronary occlusion had the greatest effect on infarct size ($30.4 \pm 4.9\%$, $p < 0.05$ vs W-W-W and $33.4 \pm 5.0\%$, $p < 0.05$ vs W-W-W). Infarct size in the W-C15-C ($42.4 \pm 1.4\%$) and W-C25-C ($44.1 \pm 2.3\%$) groups were also significantly smaller than the W-W-W group ($p < 0.05$). The C-C-C and W-C0-C groups were also significantly different from W-W-C at the p less than 0.05 level.

Timing of Hypothermia

Although the ultimate degree of cooling was very similar in all animals rendered hypothermic, the time course over which the goal temperature was achieved varied widely. The correlation coefficient between infarct size and temperature is plotted at each experimental time point in Figure 4 and demonstrates that temperature late in the ischemic period and early in the reperfusion period correlates best with infarct size. A plot of infarct size versus temperature at 30 minutes of ischemia (the peak of the curve in Fig 4) for all animals in all groups is presented in Figure 5 ($r = 0.73$, $p = 10^{-12}$).

Hemodynamics

Hypothermia resulted in a 15% to 25% decrease in heart rate from baseline. The LVP and mean ABP were unaffected by temperature. Hypothermia significantly decreased RPP

compared with control. However, at 180 minutes of reperfusion, RPP was not significantly different among all groups (Table 2).

Comment

This study confirms that a very small reduction in temperature induced by surface cooling can significantly reduce infarct size within the myocardial risk area. The novel aspects of the current study are twofold: (1) temperature reductions as small as 1.5°C are cardioprotective; and (2) the temperature at the time of reperfusion correlates most strongly with the degree of myocardial salvage. Our data strongly suggest that it is the core temperature of the body (or possibly the blood reperfusing the risk area) that determines the infarct size. The core temperature history or time course of temperature change prior to reperfusion is less important. The relative importance of the temperature of the blood reperfusing the risk area and the temperature of the risk area itself at the moment of reperfusion is a subtle but possibly important issue. We cannot definitively address this question because we did not measure temperature in the myocardial risk area. However, work by other groups helps to confirm our suspicion that it is the temperature of the reperfusing blood that has the most influence on the degree of myocardial salvage. Hale and colleagues [15] conducted an experiment using rabbits, in which they used topical ice packs to cool the risk area approximately 6°C at 25 minutes into a 30-minute ischemic interval. These investigators could not demonstrate a reduction in infarct size associated with this cooling strategy. The results of the current study may differ because of the different methods employed to achieve myocardial cooling. We induced global core body hypothermia, resulting in the delivery of hypothermic blood to the risk area early in the reperfusion period. Hale and colleagues employed rapid local topical cooling of the myocardium, which likely resulted in hypothermic ischemic myocardium being initially reperfused by warm blood. The results of these two studies considered together suggest that the temperature of the initial reperfusate is an important variable in determining the degree of myocardial salvage. This hypothesis is further supported by a recent study in human-sized pigs by Otake and colleagues [16] in which saline at 4°C was injected directly down the freshly opened coronary artery at 8 mL/minute until the myocardial temperature was reduced by 3.5°C. This reduced the infarct size by 27% compared with unmodified reperfusion.

The mechanism by which mild hypothermia of the reperfusate limits myocardial injury is probably multifactorial; however, preservation of microvascular integrity is likely an important factor. The pigs in the Otake and colleagues [16] paper treated with hypothermia showed a greater coronary flow reserve (CFR) in the infarct-related coronary artery than normothermia-treated pigs after reperfusion. Because CFR can be used as an indirect parameter for evaluating the function of the coronary circulation [17], preservation of CFR in the hypothermia-treated pigs reflects better coronary microcirculation. Dae and colleagues [18] used sestamibi autoradiography to demonstrate that hypothermia preserves microvasculature function in pigs, whereas Hale and colleagues [19] showed that hypothermia significantly improves coronary reflow and reduces the no-reflow area in a rabbit MI model similar to the one employed in this study.

In addition to preserving microvascular integrity, hypothermia has also been associated with a wide range of additional protective mechanisms, which may ameliorate ischemia-reperfusion injury. These include the induction of heat shock proteins [20], reduced apoptosis [21], decreased complement activation, and a reduction in neutrophil degranulation [22,23]. Although the broad spectrum of hypothermia-induced effects makes it difficult to pinpoint the exact mechanism of protection, it may be advantageous since pharmacologic therapies targeting a single mechanistic pathway have been ineffective adjuncts to reperfusion in clinical trials [24]. The ability to simultaneously suppress multiple

pathologic pathways without significant adverse consequences makes mild late hypothermia a very attractive and a potentially ideal adjunct to reperfusion therapy for acute MI.

The induction of mild hypothermia consistently reduced heart rate 15% to 25% in this study but did not otherwise adversely affect cardiac function. Previous investigators [9] have demonstrated conclusively that the myocardial protective effects of hypothermia are independent of its effect on heart rate.

The results of this study have important clinical implications. Although the effectiveness of profound myocardial hypothermia during cardiac surgery indicate that colder temperatures induced very early after the start of ischemia are likely most cardioprotective, such a strategy is not clinically feasible because of the inherent delay associated with seeking medical attention as well as the potential complications and time required to reach such low temperatures. This study suggests that very limited hypothermia, especially of the reperfusate, could be an effective adjunct to reperfusion therapy for acute MI. Such levels of hypothermia of the reperfused blood could readily be achieved by surface cooling [14] or intravascular [13] cooling devices as the patient is prepared for emergent reperfusion therapy or, more optimally, by the direct administration of a hypothermic reperfusate at the time of reperfusion similar to that described by Otake and colleagues [16].

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Fig 1. Protocol schematic demonstrating when cooling was initiated in each group. Initial temperature was recorded rectally at the induction of anesthesia. Baseline and all other temperatures were recorded in the left atrium after the chest was opened. (— = normothermia; = hypothermia; C = cooling.)

Fig 2.

Time course of the core temperature change for each experimental group. Initial temperature was recorded rectally at the induction of anesthesia. Baseline and all other temperatures were recorded in the left atrium after the chest was opened. (—●— = W-W-W; —○— = C-C-C; —▼— = W-C0-C; —▽— = W-C15-C; —■— = W-C25-C; —□— = W-W-C.)

Fig 3. (A) Area at risk as a percentage of the left ventricular (LV) mass for all experimental groups (mean $\pm$ SEM). (B) Infarct size as a percentage of the area at risk (AR) for all experimental groups (mean $\pm$ SEM). (^a $p < 0.05$ vs W-W-W; ^b $p < 0.05$ vs W-W-C.)

Fig 4. Plot of the correlation between left atrial (LA) temperature and infarct size during ischemia and reperfusion. Temperature during late ischemia and early reperfusion correlate most strongly with infarct size. (AR = area at risk; I = infarct.)

Fig 5.
Plot of infarct size versus temperature at the time of reperfusion for all animals in all groups.
(AR = area at risk.)

Table 1

Temperature Data: Mean Temperatures (°C) ± Standard Error of the Mean Throughout the Study Period

Group	Initial	Base	Isc (0 min)	Isc (15 min)	Isc (30 min)	Rep (30 min)	Rep (60 min)	Rep (120 min)	Rep (180 min)	Max Drop
W-W-W	39.9 ± 0.1	39.7 ± 0.1	39.6 ± 0.1	39.5 ± 0.1	39.6 ± 0.1	39.6 ± 0.1	39.7 ± 0.1	39.7 ± 0.1	39.7 ± 0.1	0.4 ± 0.1
W-W-C	39.8 ± 0.1	39.5 ± 0.1	39.4 ± 0.1	39.4 ± 0.1	39.3 ± 0.1	37.4 ± 0.1	37.4 ± 0.1	37.4 ± 0.1	37.5 ± 0.1	2.4 ± 0.1
W-C25-C	39.8 ± 0.0	39.7 ± 0.1	39.8 ± 0.1	39.7 ± 0.1	38.2 ± 0.1	37.3 ± 0.1	37.5 ± 0.0	37.6 ± 0.1	37.6 ± 0.1	2.5 ± 0.1
W-C15-C	39.8 ± 0.1	39.8 ± 0.1	39.8 ± 0.1	39.8 ± 0.1	38.0 ± 0.1	37.4 ± 0.0	37.6 ± 0.0	37.5 ± 0.0	37.5 ± 0.0	2.4 ± 0.1
W-C0-C	39.8 ± 0.1	39.6 ± 0.1	39.4 ± 0.1	38.0 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	37.4 ± 0.1	2.4 ± 0.1
C-C-C	39.8 ± 0.1	37.5 ± 0.2	37.4 ± 0.1	37.4 ± 0.1	37.4 ± 0.1	37.5 ± 0.1	37.4 ± 0.1	37.5 ± 0.1	37.5 ± 0.1	2.4 ± 0.1

Base = left atrial temperature recorded immediately before coronary occlusion; Initial = rectal temperature recorded at the induction of anesthesia; Isc = ischemia; Max drop = maximum drop in temperature from initial temperature to lowest temperature; Rep = reperfusion.

Table 2Hemodynamic Data: Mean Values $\pm$ Standard Error of the Mean

Hemodynamic Parameter	Baseline	Ischemia (15 min)	Reperfusion (10 min)	Reperfusion (180 min)
HR (beats/min):				
W-W-W	268 $\pm$ 4	264 $\pm$ 5	260 $\pm$ 5	247 $\pm$ 3 ^b
W-W-C	253 $\pm$ 7	255 $\pm$ 7	250 $\pm$ 6	219 $\pm$ 6 ^{a,b}
W-C25-C	267 $\pm$ 12	264 $\pm$ 9	252 $\pm$ 8	234 $\pm$ 9
W-C15-C	270 $\pm$ 6	261 $\pm$ 7	229 $\pm$ 5 ^{ab}	230 $\pm$ 8 ^b
W-C0-C	250 $\pm$ 7	231 $\pm$ 5 ^{a,b}	219 $\pm$ 5 ^{ab}	210 $\pm$ 5 ^{a,b}
C-C-C	218 $\pm$ 11 ^a	221 $\pm$ 11 ^a	225 $\pm$ 12 ^a	207 $\pm$ 8 ^a
MAP (mm Hg):				
W-W-W	64 $\pm$ 3	52 $\pm$ 2 ^b	52 $\pm$ 2 ^b	47 $\pm$ 2 ^b
W-W-C	63 $\pm$ 5	53 $\pm$ 4 ^b	53 $\pm$ 5 ^b	57 $\pm$ 7
W-C25-C	60 $\pm$ 7	57 $\pm$ 6	58 $\pm$ 5	57 $\pm$ 5
W-C15-C	59 $\pm$ 3	50 $\pm$ 4	53 $\pm$ 4	60 $\pm$ 2
W-C0-C	64 $\pm$ 5	55 $\pm$ 4	52 $\pm$ 3 ^b	53 $\pm$ 5
C-C-C	57 $\pm$ 3	48 $\pm$ 3 ^b	49 $\pm$ 4	51 $\pm$ 1
LVEDP (mm Hg):				
W-W-W	1.7 $\pm$ 0.6	3.4 $\pm$ 0.8	2.5 $\pm$ 0.6	2.5 $\pm$ 0.5
W-W-C	1.7 $\pm$ 0.4	2.7 $\pm$ 0.6	2.6 $\pm$ 0.8	2.8 $\pm$ 1.1
W-C25-C	1.6 $\pm$ 1.6	2.0 $\pm$ 1.8	1.8 $\pm$ 2.4	3.4 $\pm$ 1.7
W-C15-C	2.0 $\pm$ 0.9	3.0 $\pm$ 1.1	2.1 $\pm$ 0.7	3.5 $\pm$ 1.3
W-C0-C	1.1 $\pm$ 0.7	2.6 $\pm$ 0.9	1.8 $\pm$ 0.7	2.1 $\pm$ 0.6
C-C-C	0.4 $\pm$ 0.6	0.4 $\pm$ 0.7	3.1 $\pm$ 2.2	1.1 $\pm$ 0.6
+ dP/dt _{max} (mm Hg/s):				
W-W-W	1967 $\pm$ 74	1591 $\pm$ 78 ^b	1523 $\pm$ 104 ^b	1349 $\pm$ 73 ^b
W-W-C	1884 $\pm$ 65	1781 $\pm$ 84	1799 $\pm$ 141	1665 $\pm$ 167
W-C25-C	2025 $\pm$ 102	1639 $\pm$ 134	1685 $\pm$ 212	1390 $\pm$ 149
W-C15-C	1969 $\pm$ 102	1746 $\pm$ 90	1655 $\pm$ 176	1445 $\pm$ 167
W-C0-C	1727 $\pm$ 146	1616 $\pm$ 127	1468 $\pm$ 145	1446 $\pm$ 128
C-C-C	1736 $\pm$ 102	1686 $\pm$ 81	1619 $\pm$ 71	1657 $\pm$ 67
RPP/1,000 (mm Hg/min):				
W-W-W	20.5 $\pm$ 0.7	16.2 $\pm$ 0.5 ^b	16.5 $\pm$ 0.7 ^b	15.0 $\pm$ 0.5 ^b
W-W-C	18.9 $\pm$ 1.2	16.7 $\pm$ 0.8	16.8 $\pm$ 1.1	16.4 $\pm$ 1.3
W-C25-C	18.3 $\pm$ 2.2	17.4 $\pm$ 1.8	16.6 $\pm$ 1.7	16.5 $\pm$ 1.5
W-C15-C	18.6 $\pm$ 1.2	16.9 $\pm$ 1.8	14.8 $\pm$ 1.5	16.6 $\pm$ 1.0
W-C0-C	18.5 $\pm$ 1.2	15.7 $\pm$ 0.7 ^b	14.5 $\pm$ 0.7 ^b	14.6 $\pm$ 1.1
C-C-C	15.3 $\pm$ 1.1 ^a	14.2 $\pm$ 1.5	14.1 $\pm$ 1.4	13.7 $\pm$ 0.8

+dP/dt_{max} = maximal rate of left ventricular pressure increase over time; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure; MAP = mean arterial pressure; RPP = rate pressure product.

^a
 $p < 0.05$ vs W-W-W group

^b
 $p < 0.05$ vs baseline.