Left ventricular dysfunction following rewarming from experimental hypothermia

TORKJEL TVEITA,1,2 KIRSTI YTREHUS,1 EIVIND S. P. MYHRE,1 AND OLAV HEVRØY2 Left ventricular dysfunction following rewarming from experimental hypothermia. J. Appl. Physiol. 85(6): 2135–2139, 1998.—This study was aimed at elucidating whether ventricular hypothermia-induced dysfunction persisting after rewarming the unsupported in situ dog heart could be characterized as a systolic, diastolic, or combined disturbance. Core temperature of 8 mongrel dogs was gradually lowered to 25°C and returned to 37°C over a period of 328 min. Systolic function was described by maximum rate of increase in left ventricular (LV) pressure (dP/dtmax), relative segment shortening (SS%), stroke volume (SV), and the load-independent contractility index, preload recruitable stroke work (PRSW). Diastolic function was described by the isovolumic relaxation constant (τ) and the LV wall stiffness constant (Kp). Compared with prehypothermic control, a significant decrease in LV functional variables was measured at 25°C: dP/dtmax 2.180 ± 158 vs. 760 ± 78 mmHg/s, SS% 20.1 ± 1.2 vs. 13.3 ± 1.0%, SV 11.7 ± 0.7 vs. 8.5 ± 0.7 ml, PRSW 90.5 ± 7.7 vs. 29.1 ± 5.9 j/m–1, Kp 0.78 ± 0.10 vs. 0.28 ± 0.03 mm–1, and τ 78.5 ± 3.7 vs. 25.8 ± 1.6 ms. After rewarming, the significant depression of LV systolic variables observed at 25°C persisted: dP/dtmax 1.241 ± 108 mmHg/s, SS% 10.2 ± 0.8 j, SV 7.3 ± 0.4 ml, and PRSW 52.1 ± 3.6 j/m–1, whereas the diastolic values of Kp and τ returned to control. Thus hypothermia induced a significant depression of both systolic and diastolic LV variables. After rewarming, diastolic LV function was restored, in contrast to the persistently depressed LV systolic function. These observations indicate that cooling induces more long-lasting effects on the excitation-contraction coupling and the actin-myosin interaction than on sarcoplasmic reticulum Ca2+ trapping dysfunction or interstitial fluid content, making posthypothermic LV dysfunction a systolic perturbation.

Rewarming in victims of accidental hypothermia may be complicated by inadequate cardiac output and hypotension (20–22, 29, 31). This clinical situation has often been termed “the rewarming shock” (22). Despite it being a well-recognized concept, its underlying pathophysiology is still obscure. Thus the issue of optimal management of accidental hypothermia has not been settled, and further experimental studies elucidating how hypothermia and rewarming influence the cardiovascular system are mandatory.

Hypothermia has been reported to enhance myocardial contractility (2). Cooling has been shown to augment both the strength and duration of contractions as well as the load-independent measure of cardiac contractility (35). However, most of these observations were performed in isolated in vitro preparations subjected to moderate hypothermia (4, 30). In more intact animal preparations, marked depressed left ventricular (LV) function has been reported even at mild (34°C) levels of hypothermia (15). In a report using excised cross-circulated dog hearts, the efficiency of myocardial LV contractile function could not be shown as improving during a temperature decrease of 7°C from normothermia (35).

In clinical practice, a part of rewarming therapy has been liberal infusion of intravenous fluid to prevent cardiovascular collapse (19). This strategy has been based on the assumption that hypothermia is associated with intravascular hypovolemia caused by plasma loss (8, 10, 32). However, experimental studies have shown that rewarming causes spontaneous return of this fluid. Thus the plasma volume levels are restored and may even become greater than before cooling (10, 18). As a consequence, some reports advocate restriction of intraventricular fluids (12, 20, 21, 24) during and after rewarming to avoid volume overload. Thus it appears more rational to focus on myocardial function to elucidate rewarming shock mechanisms.

We have reported earlier a deterioration of myocardial function and cardiac output in an in vivo dog model after rewarming from hypothermia (25°C) (36). In this model, systolic and diastolic LV function were recorded. To avoid confounding effects due to changes in circulating plasma volume and ventricular load alterations, we used a load-independent index, preload recruitable stroke work (PRSW) (14), to describe changes in LV systolic function during cooling and rewarming. To describe diastolic function, we calculated the isovolumic relaxation index (τ) and ventricular segmental stiffness constant (Kp) (33).

MATERIALS AND METHODS

Eight overnight-fasted mongrel dogs of either sex, average weight 20.3 kg, were used. Anesthesia was induced by an injection of 30 mg/kg iv of pentobarbital sodium, followed by a continuous infusion of 3.5 mg·kg–1·h–1. The dogs were placed in the right supine position and ventilated with a volume-controlled ventilator (Servo 900C, Siemens Elema, Stockholm, Sweden). Ventilator volumes were adjusted to achieve normocapnia, reported to be 5.06 ± 0.73 (SD) kPa in normothermic dogs (16). Arterial blood gases and pH were determined by a Radiometer ABL1 Acid-Base Laboratory (Radiometer, Copenhagen, Denmark). In accordance with Ashwood et al. (1), pH and blood-gas values from hypothermic dogs were not temperature corrected. The respirator adjustment was left unchanged throughout the experimental period, and

REWARMING IN VICTIMS OF ACCIDENTAL HYPOTHERMIA may be complicated by inadequate cardiac output and hypotension (20–22, 29, 31). This clinical situation has often been termed “the rewarming shock” (22). Despite it being a well-recognized concept, its underlying pathophysiology is still obscure. Thus the issue of optimal management of accidental hypothermia has not been settled, and further experimental studies elucidating how hypothermia and rewarming influence the cardiovascular system are mandatory.

Hypothermia has been reported to enhance myocardial contractility (2). Cooling has been shown to augment both the strength and duration of contractions as well as the load-independent measure of cardiac contractility (35). However, most of these observations were performed in isolated in vitro preparations subjected to moderate hypothermia (4, 30). In more intact animal preparations, marked depressed left ventricular (LV) function has been reported even at mild (34°C) levels of hypothermia (15). In a report using excised cross-circulated dog hearts, the efficiency of myocardial LV contractile function could not be shown as improving during a temperature decrease of 7°C from normothermia (35).

In clinical practice, a part of rewarming therapy has been liberal infusion of intravenous fluid to prevent cardiovascular collapse (19). This strategy has been based on the assumption that hypothermia is associated with intravascular hypovolemia caused by plasma loss (8, 10, 32). However, experimental studies have shown that rewarming causes spontaneous return of this fluid. Thus the plasma volume levels are restored and may even become greater than before cooling (10, 18). As a consequence, some reports advocate restriction of intraventricular fluids (12, 20, 21, 24) during and after rewarming to avoid volume overload. Thus it appears more rational to focus on myocardial function to elucidate rewarming shock mechanisms.

We have reported earlier a deterioration of myocardial function and cardiac output in an in vivo dog model after rewarming from hypothermia (25°C) (36). In this model, systolic and diastolic LV functions were recorded. To avoid confounding effects due to changes in circulating plasma volume and ventricular load alterations, we used a load-independent index, preload recruitable stroke work (PRSW) (14), to describe changes in LV systolic function during cooling and rewarming. To describe diastolic function, we calculated the isovolumic relaxation index (τ) and ventricular segmental stiffness constant (Kp) (33).

MATERIALS AND METHODS

Eight overnight-fasted mongrel dogs of either sex, average weight 20.3 kg, were used. Anesthesia was induced by an injection of 30 mg/kg iv of pentobarbital sodium, followed by a continuous infusion of 3.5 mg·kg–1·h–1. The dogs were placed in the right supine position and ventilated with a volume-controlled ventilator (Servo 900C, Siemens Elema, Stockholm, Sweden). Ventilator volumes were adjusted to achieve normocapnia, reported to be 5.06 ± 0.73 (SD) kPa in normothermic dogs (16). Arterial blood gases and pH were determined by a Radiometer ABL1 Acid-Base Laboratory (Radiometer, Copenhagen, Denmark). In accordance with Ashwood et al. (1), pH and blood-gas values from hypothermic dogs were not temperature corrected. The respirator adjustment was left unchanged throughout the experimental period, and
normocapnia was maintained. Saline (0.15 ml · kg⁻¹ · min⁻¹) was administered continuously. The heart was exposed through a left-sided thoracotomy and the pericardium was opened by a longitudinal incision, reflected to form a cradle for suspending the heart. Approval for the experiments was obtained from the National Animal Research Committee, and the experiments conformed with the recommendations of the European Council for Laboratory Animal Science. Especially

Hemodynamic measurements. An electromagnetic probe was positioned around the ascending aorta to measure stroke volume (SV) flow (Scalar Instruments, Delft, The Netherlands). Left ventricular pressure was obtained by a microtransducer catheter (Dräger Medical Electronics, The Netherlands) inserted via the left carotid artery. Aortic pressure was measured through a fluid-filled polyvinyl catheter positioned in the thoracic part of descending aorta via the left femoral artery and connected to a Statham P23 ID transducer (Spectramed).

To measure instantaneous segmental dimensions, a pair of 5-MHz piezoelectric ultrasonic crystals (diameter 2–3 mm) was positioned through stab wounds in the anterior part of the LV wall and connected to an ultrasound dimension meter (Schleusseler). The crystals were placed 1–10 mm apart and oriented in parallel to the diagonal branches of the left descending coronary artery.

Two 5-ml Fogarty balloon-occlusion catheters (23-Fr) were placed proximally in both caval veins via the left jugular and femoral veins. Rapid alterations of ventricular preload were achieved by inflating the balloons simultaneously. Position of catheters was controlled by fluoroscopy. Balloon inflation created a transient venous occlusion resulting in a progressive fall in LV pressure and segment length. During an expiratory pause, caval occlusion was performed over a 10- to 15-s period, resulting in a reduction in LV systolic pressure by 25–30 mmHg over 10–15 cardiac cycles. Recordings during bicalval occlusion were rejected if heart rate increased above 10% or if arrhythmia occurred. In this case, LV pressure and segment length recordings during caval occlusion were repeated after a short stabilization period.

Stability of the model with respect to hemodynamics was confirmed, as no alterations were observed during 5 h at normothermia in two sham-operated animals. Especially cardiac output, peak LV systolic pressure, and maximum rate of increase in LV pressure (LV dP/dt max) remained unchanged.

Core cooling and rewarming. The method of core cooling and rewarming has been previously described (36). Briefly, the animals were cooled and rewarmed by circulating water of different temperatures through heat-exchanging tubes placed in the esophagus and lower bowel. The desired temperature was easy to achieve and to maintain stable (±0.2°C) during measurements by using this method. Core temperature was continuously recorded by a thermocouple wire positioned in the thoracic aorta and monitored on a thermocouple controller (Bailey Instruments). The animals were cooled gradually to 25°C and subsequently rewarmed to 37°C. The cooling and rewarming procedure lasted 328 ± 9 min, with the time equally divided between cooling and rewarming stages.

Experimental protocol. Electrocardiogram, aortic pressure and flow, LV pressure, and segment length were continuously recorded on a Gould ES 200 recorder (Gould, Cleveland, OH). At different core temperatures, after a short stabilization period with stable temperature, baseline recordings of all parameters were made over a 10-s period. In addition, measurements of LV pressure and segment length were acquired during bicalval occlusion at the different core temperatures. All recordings were digitized at 200 Hz to an online computer using a commercially available program (Asyntast, Macmillan Software, New York, NY) and stored for further processing.

Calculations. LV dP/dt max and maximum rate of decrease in LV pressure (LV dP/dt min) were obtained by differentiating the LV pressure signal. The systolic part of the aortic flowmeter signal was integrated to obtain LV SV. Mean aortic pressure (AoP) was obtained by electronic averaging of the aortic pressure signal. Peak LV systolic pressure was measured as maximum LV pressure during systole. LV end-diastolic pressure and segment length (LVED-SL) were measured at the instant of maximum R wave in the electrocardiographic signal. LV end-systolic segment length (LVES-SL) was determined at the instant of maximum negative LV dP/dt.

Relative segment shortening in percent (SS%) was calculated as

$$SS\% = \left( \frac{LVED-SL - LVES-SL}{LVED-SL} \right) \times 100$$

where k is the x-axis intercept at zero pressure.

The time constant of isovolumic relaxation (τ) was calculated assuming a nonzero asymptote of LV pressure decay by using the method of Raff and Glantz (27). LV negative dP/dt was plotted against ventricular pressure, as measured every 5 ms between peak negative dP/dt and 5 mmHg above end-diastolic pressure of the next beat (corresponding to the opening of the mitral valve) to yield τ as the negative inverse of the slope.

Segmental ventricular stiffness was determined by fitting the series of end-diastolic pressure-segment length data obtained by caval occlusion to an exponential relationship according to the formula

$$Ped = a \cdot e^{-k \cdot (LVED-SL)} + b$$

where Ped is end-diastolic pressure, k, is segmental stiffness, and b is the extrapolated Ped intercept at zero length. This analysis was done by using a commercially available program package (Asyntast, Macmillan Software).

Statistics. Data, presented as means ± SE, were analyzed by analysis of variance for repeated measurements. When significant differences were observed, values were compared by using Tukey’s test. P < 0.05 was considered significant.

RESULTS

All animals survived cooling and rewarming. Except for single ectopic beats, there were no episodes of other arrhythmias during cooling and rewarming.

Hemodynamic variables are given in Table 1.

Cooling. Cooling to 25°C resulted in depression of LV function, demonstrated as a significant depression of all variables measured, except LVED-SL and LV end-diastolic pressure. The latter remained unchanged throughout the experiment.
Hemodynamic effects of hypothermia and rewarming

During cooling, an increase in heart rate was measured, whereas AoP, LV pressure, SV, dP/dt_{max}, dP/dt_{min}, and SS% were all still lowered at 31°C compared with the corresponding values at 31°C during cooling (Table 1). Values for τ and K_{p} shown during cooling (31°C) returned to within the same level at 31°Crewarming, whereas PRSW index M_{w} at 31°C rewarming was 40% less than during cooling (Fig. 1). LVSW was 73% of what was observed at 31°C during cooling (Table 1).

Posthypothermic depression. Posthypothermic depression of LV function was demonstrated as a 40% reduction in PRSW index M_{w} (Fig. 1), and a 54% reduction in LVSW, compared with prehypothermic baseline values (Table 1). However, heart rate, LVED-SL, τ, and K_{p} returned to within control values. Posthypothermic TPR was not significantly changed from control values.

**DISCUSSION**

This study was aimed at elucidating whether ventricular hypothermia-induced dysfunction persisting after rewarming could be characterized as a systolic, diastolic, or combined disturbance. Systolic function was significantly depressed after rewarming, as indicated by a reduced LV dp/dt_{max}, reduced SS%, reduced SV, and a reduced contractility index M_{w}. These findings indicate depressed isovolumic pressure generation and ventricular wall shortening, i.e., the excitation-contraction coupling and the actin-myosin interaction may be persistently depressed despite normalized body temperature. Because heart rate returned to baseline after rewarming, this factor does not confound these observations.

AoP was still depressed after rewarming. TPR was nonsignificantly increased despite a depressed SV. During such conditions, a significant increase in peripheral arterial tonus should be expected and reflected in a significantly increased TPR. The reported insignificant increase of TPR indicates a persisting cooling-induced paralysis of peripheral arteriolar tonus, which may contribute to the depressed AoP. However, if this was a dominant factor and contractility was normal, SV should have increased or, at least, been unchanged compared with baseline. Thus the depressed AoP must partly be caused by persisting reduced cardiac contractility causing a decreased cardiac output. Our findings of posthypothermic reduction in SV and AoP are in accordance with those of other investigators (5, 11, 25, 25).
26, 28) as well as with findings in previous reports using this model (34, 36).

A reduced cardiac output could be due to a reduced ability for ventricular diastolic filling. Among the potential mechanisms could be increased stiffness due to cooling-induced decreased sarcoplasmic Ca \(^{2+}\) trapping or increased interstitial fluid accumulation secondary to capillary damage. However, posthypothermic isovolumic ventricular relaxation rate was normalized to baseline and so was end-diastolic stiffness. Thus none of these observations indicates that ventricular diastolic dysfunction persisted after rewarming. Because neither end-diastolic pressure nor segment length differed from baseline after rewarming, end-diastolic preloading must be considered similar to baseline, excluding a preload decrease as a possible explanation for the reduced SV. These observations are also in harmony with the observations indicating that plasma volume is decreased during cooling but restitutes during rewarming (10, 18).

Previous studies (34, 36) have demonstrated that the posthypothermic LV dysfunction is not associated with metabolic signs of myocardial ischemia but seems more to be a low-pressure flow situation comparable with postischemic stunning. Stunning is defined as lack of mechanical recovery following recovery from brief episodes of myocardial ischemia, without evidence of structural damage or reduced oxygen supply (7). The mechanisms behind this dysfunction include the overproduction of oxygen-derived free radicals (6, 17), disruption of myocardial repertusion flow by neutrophils (3, 37), transient cellular Ca \(^{2+}\) overload, or reduced availability of activator Ca \(^{2+}\) or a reduced myofilament responsiveness to Ca \(^{2+}\) (23). Engelmann (9) reported that myocardial stunning is a temperature-dependent phenomenon. He showed that the level of postischemic stunning is associated with intracellular Ca \(^{2+}\) accumulation, impaired sarcoplasmatic reticulum Ca \(^{2+}\) uptake, and reduced Ca \(^{2+}\) ATPase activity of hearts rendered ischemic at 4 or 20°C. At 28 and 37°C, however, this relationship could not be demonstrated. However, if the basic mechanics of ischemia-induced stunning is part of the persisting cooling-induced systolic depression, the normalization of \(T\) and \(K_{sp}\), i.e., lacking signs of diastolic dysfunction, must be brought into consideration, making this hypothesis not immediately acceptable.

In conclusion, direct effects on myocardial excitation-contraction coupling and actin-myosin interaction, induced by the cooling and rewarming process, most likely explain the alterations in LV function measured after rewarming in the present model. Posthypothermic depression of myocardial contractile function is probably the main reason for the reduction of cardiac output and systemic arterial pressure, occasionally observed after rewarming.

The skilled technical assistance of Fredrik Bergheim is gratefully acknowledged.

This study was supported by grants from the Norwegian Research Council for Science and the Humanities, the Norwegian Council on Cardiovascular Diseases, and the Laerdal Foundation for Acute Medicine.

Address for reprint requests: T. Tveita, Institute of Medical Biology, Univ of Tromsø, N-9037 Tromsø, Norway.

Received 21 April 1998; accepted in final form 21 August 1998.

REFERENCES


