Cardiovascular effects of epinephrine during rewarming from hypothermia in an intact animal model

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Kondratiev, T. V., E. S. P. Myhre, Ø. Simonsen, T.-B. Nymark, and T. Tveita. Cardiovascular effects of epinephrine during rewarming from hypothermia in an intact animal model. J Appl Physiol 100: 457–464, 2006. First published October 6, 2005; doi:10.1152/japplphysiol.00356.2005.—Rewarming from accidental hypothermia is often complicated by “rewarming shock,” characterized by low cardiac output (CO) and a sudden fall in peripheral arterial pressure. In this study, we tested whether epinephrine (Epi) is able to prevent rewarming shock when given intravenously during rewarming from experimental hypothermia in doses tested to elevate CO and induce vasodilation, or lack of vasodilation, during normothermia. A rat model designed for circulatory studies during experimental hypothermia and rewarming was used. A total of six groups of animals were used: normothermic groups 1, 2, and 3 for dose-finding studies, and hypothermic groups 4, 5, and 6. At 20 and 24°C during rewarming, group 4 (low-dose Epi) and group 5 (high-dose Epi) received bolus injections of 0.1 and 1.0 μg Epi, respectively. At 28°C, Epi infusion was started in groups 4 and 5 with 0.125 and 1.25 μg/min, respectively. Group 6 served as saline control. After rewarming, both CO and stroke volume were restored in group 4, in contrast to groups 5 and 6, in which both CO and stroke volume remained significantly reduced (30%). Total peripheral resistance was significantly higher in group 5 during rewarming from 24 to 34°C, compared with groups 4 and 6. This study shows that, in contrast to normothermic conditions, Epi infused during hypothermia induces vasoconstriction rather than vasodilation combined with lack of CO elevation. The apparent dissociation between myocardial and vascular responses to Epi at low temperatures may be related to hypothermia-induced myocardial failure and changes in temperature-dependent adrenoreceptor affinity.

resuscitation; epinephrine; cardiovascular function; rat; cold; temperature

DESPITE CONTINUED IMPROVEMENTS in medical therapy, the success rate when rewarming patients from accidental hypothermia has not been improved in the last five decades. Mortality from profound hypothermia reported by McLean and Emshlie-Smith (18) was between 52 and 80%, depending on methods of rewarming. This is similar to data from Murray and Hall (20), who described mortality as high as 70% after profound hypothermia in some studies. “Rewarming shock” is a clinically descriptive term that refers to a pathophysiological state of cardiovascular collapse during or after rewarming and recognized as a progressive reduction of cardiac output (CO) and a sudden fall in arterial blood pressure. In an attempt to treat or prevent rewarming shock, the initiation of cardioactive drug therapy to treat the low CO appears advisable, but pharmacological effects of cardiovascular drugs used during accidental hypothermia are not well characterized. This fact is reflected in the lack of consensus-based guidelines for use of such drugs during hypothermia (3). The last guidelines from the American Heart Association, discussing resuscitation after hypothermia, date back to 1992 (4).

The prevailing knowledge about using cardioactive agents during hypothermia is governed by two conflicting opinions. The one is that some authors conclude that the hypothermic heart is unresponsive (16) or little responsive (20, 26, 28) to cardioactive drugs, and its use is even dangerous due to accumulation of toxic doses. Kornberger et al. (13) tested the use of epinephrine (Epi) during hypothermic cardiopulmonary resuscitation (CPR) in pigs. They concluded that repeated Epi administration during CPR should be avoided, as beneficial effects of Epi seemed to be outweighed by exaggerated β-receptor stimulation and increased oxygen demand. However, it must be emphasized that Epi used in these experiments was given as repeated injections after hypothermic cardiac arrest in doses as high as 45–200 μg/kg (13), which are two to eight times the dose recommended for clinical use during normothermic conditions. The other view is based on findings by Chernow et al. (9), assuming that, <30°C, hypotensive patients may benefit from infusions of exogenous catecholamines because the sympathetic nervous system is “switched off” at these temperatures. In addition, a pharmacologically induced elevation of CO has been proposed to make rewarming more efficient (21). Rubinstein (28) tested Epi, both as injections (1–2 μg) and in continuous infusion (1.2–1.4 μg·kg⁻¹·min⁻¹), which is in much lower doses than used by Kornberger et al. (13). Compared with normothermia, he showed that, during hypothermia, single injections of Epi had a diminished vasopressor effect, whereas a greater vasopressor effect occurred if given as continuous infusion (28). In recent experiments (14, 30), using the same porcine model of hypothermic CPR as Kornberger et al. (13), vasopressin was tested as an alternative to high doses of Epi (45 and 200 μg/kg). These studies advocate for using vasopressors during hypothermic CPR, but they warn against continuous administration of these drugs (14, 30).

Few experimental works have focused on effects of cardioactive drugs during rewarming from hypothermia. Nicodemus et al. (21) compared negative inotropic and positive inotropic agents during hypothermia and rewarming and concluded that using dopamine alone or in addition to lidocaine reversed the...
cardiovascular depression associated with rewarming from hypothermia and provided almost complete recovery. Data from Weiss et al. (35, 36) indicated that hypothermia caused a change in the physiological response to norepinephrine, which rewarming did not reverse. In the American Heart Association guidelines, the use of Epi is recommended also in hypothermic patients with core temperature >30°C (3). However, there are no prospective clinical studies or experimental reports supporting the recommendation to avoid Epi when body temperature is <30°C (13). Thus the purposes of this study were as follows: 1) to test whether Epi is able to increase CO and prevent rewarming shock during rewarming from experimental hypothermia; and 2) to explore in further detail, by infusing Epi in different doses and at different temperatures, whether hypothermia causes relative changes in myocardial compared with vascular effects of this drug. To achieve this, we utilized an intact animal model designed for hemodynamic studies during experimental hypothermia and rewarming. This model has already demonstrated reduced myocardial inotropy and low CO during rewarming (32–34). We determined to infuse Epi at two different concentrations during rewarming, which both increased CO by ~25–30% when tested during normothermia, but caused different effects on vascular resistance (vasodilation vs. lack of vasodilation).

MATERIALS AND METHODS

Wistar rats (males, 250–350 g), age ~60 days, were used in the experiments. The rats had a microbiological status, according to the recommendation of the Federation of European Laboratory Animal Science Associations, and were provided by Harlan UK. On arrival, animals were quarantined for 1 wk. Housing during experiments was provided in accordance with guidelines for accommodation and care of animals (article 5 of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, Strasbourg, 18.III.1986). Free food and water access were permitted. Experimental protocol was approved by the Norwegian Animal Research Authority and conducted accordingly.

Anesthesia

Anesthesia was induced by 50 mg/kg body wt ip of pentobarbital sodium, followed by a continuous infusion of 7.5 mg·kg⁻¹·h⁻¹ through an intravenous line in the right jugular vein extended to the right auricle. The normothermic groups were given anesthesia during experiments. In the hypothermic groups, the infusion was terminated when cooling was started due to hypothermia-created anesthesia and reduced drug metabolism.

Respiratory Support

The rat was placed on the operating table in a supine position. The trachea was opened, and a tracheal tube inserted. All animals had spontaneous and sufficient ventilation at core temperatures >20°C. At core temperatures <20°C, normoventilation had been achieved by a volume-controlled small-animal respirator (New England rodent ventilator, model 141, New England Instruments, Medway, MA) using room air.

Core Cooling and Rewarming

The animals in the hypothermia groups were cooled and rewarmed by circulation of cold or warm water (Thermo stated water bath type RTE-110, Neslab Instruments, Newington, NH) through U-shaped polyethylene tubes placed in the esophagus and the lower bowel. In addition, the double-layered operating table made of hollow aluminum was circulated by temperature-adjusted water. Core temperature was continuously monitored using thermocouple wires positioned in the aortic arch via the right femoral artery, connected to a thermocouple controller (Thermoalert TH-5, Columbus Instruments, Columbus, OH). Cooling lasted 1.5 h.

Hemodynamic Measurements

A fluid-filled catheter (22 gauge) was implanted in the left femoral artery for continuous recording of arterial pressure. The signals from the pressure transducer were amplified to 0–10 V and passed to a 12-bit analog-to-digital converter (BNC 2090, National Instruments, Austin, TX). Signal processing and analysis were performed with the help of a special computer program developed at our department using a software package (LabVIEW version 6.0, National Instruments, Austin, TX). CO was measured by the thermodilution technique (19), by injecting saline (0.1–0.15 ml) precooled in ice water through the intravenous line positioned in the right auricle. The change in temperature was recorded from the thermocouple positioned in the aortic arch through the right femoral artery. Thermodilution curves were recorded on a Linearrecorder (type Mark II, WR3101, Watanabe Instruments). These curves were digitalized with Calcomp digitizing table (model 23180, Calcomp Digitizer Products Division, Anaheim, CA), and CO was calculated with a program designed with the LabView package. CO was calculated as the mean of three measurements.

Blood-Gas Measurement

Blood gases, oxygen saturation, pH, and base excess were measured in 0.15-ml arterial blood samples taken from the femoral artery after surgery, at 13°C, and after rewarming to 37°C. Samples were analyzed by a RapidLab 800 blood-gas analyzer (Chiron Diagnostics).

Experimental Protocol

After surgery, the animals were allowed to rest for 40 min before the start of the experiment.

Normothermic groups. To relate effects of low and high Epi concentrations during hypothermia as well as to determine if different Epi doses could cause various effects on vasculature (vasodilatation vs. vasoconstriction), a dose-finding study had to be performed in normothermic animals.

In group 1 (n = 5), two different series of Epi infusions (Adrenalin: 1 mg/ml, Nycomed Pharma, Asker, Norway) were performed: 0.125, 0.25, 0.375, and 0.5 μg/min (low doses of Epi), and 1.25, 2.5, 3.75, and 5 μg/min (high doses of Epi). Each separate Epi infusion lasted ~5 min. Between each step, care was taken that hemodynamics returned to baseline before the next infusion was started.

Groups 2 and 3 (n = 5) underwent a sham protocol without hypothermia; i.e., the animals were kept for 4 h, with body temperature at 37°C, and then given a continuous infusion of Epi in 60 min, with a constant dose of 0.125 μg/min (group 2) and 0.625 μg/min in 30 min followed by 1.25 μg/min in the next 30 min (group 3). This was done in an attempt to mimic drug administration in hypothermia/rewarmed animals (below) in which a lower dose Epi was given <28°C and infusions were started at 28°C and continued for the last 30 min of rewarming.

Hypothermic groups. In groups 4–6, all animals were cooled to 15°C and kept at this temperature for 2 h. Then temperature was lowered and maintained at 13°C for another 2 h. Finally, all animals were rewarmed to normothermia. The rewarming period lasted 2.5 h.

During rewarming, animals were given bolus injections and infusions of Epi or saline as follows: at 20 and 24°C, group 4 (low-dose Epi, n = 7) and group 5 (high-dose Epi, n = 7) received, respectively, a bolus injection of 0.1 and 1.0 μg Epi. Bolus injections rather than infusion of Epi were given at temperatures <28°C due to the following. First, pilot experiments showed that, after injections at 20 and 24°C, pharmacological effects lasted up to 5 min compared with only
a few seconds after injection at 37°C. Therefore, to avoid toxic drug accumulation, infusions were not used at less than 2°C. Second, the prolonged half-life (several minutes) for Epi gave sufficient time to record hemodynamic variables following injections at 20 and 24°C. This enabled us to investigate possible differences in pharmacological effects of injections vs. infusion already reported for Epi (28) at lower core temperatures. Due to fast normothermic Epi metabolism, it was technically impossible to estimate the hemodynamic response to the same bolus injections in normothermic controls. At 28°C, Epi infusion was started in groups 4 and 5 with 0.125 and 1.25 μg/min, respectively. In group 6 (hypothermia control group, n = 8), saline was given during rewarming from 20°C in volumes equivalent to Epi given in groups 4 and 5 (hypothermia intervention groups).

Statistics

Results are presented as means and SD. For between-group comparisons, one-way ANOVA was used. When significant differences were found, P values were obtained by using Scheffé’s test in hypothermic groups. Analysis of between-group variation in normothermic controls was done by using a Student's t-test. For within-group comparisons, one-way repeated-measures ANOVA was used. When significant differences were found, Dunnett’s method was used to compare values within group vs. baseline. Differences were considered to be significant at P < 0.05.

RESULTS

Normothermic Controls

Tests for dose-dependent hemodynamic effects of Epi (group 1). See Fig. 1. A stepwise moderate increase in heart rate (HR) (not presented in Fig. 1), mean arterial pressure (MAP), CO, and stroke volume (SV) was observed in response to low doses of Epi tested (0.125, 0.25, 0.375, and 0.5 μg/min). A significant reduction in total peripheral resistance (TPR) was observed during infusion of the two first doses of Epi (0.125 and 0.25 μg/min) and a return to the pretreated baseline level of TPR following infusions of 0.375 and 0.5 μg/min (Fig. 1D).

In response to high doses of Epi tested (1.25, 2.5, 3.75, and 5 μg/min), HR (not presented in Fig. 1) and MAP increased significantly compared with pretreatment baseline values, but the increases were more pronounced than in response to low Epi doses. TPR also increased stepwise (Fig. 1D) and was significantly increased compared with baseline, following infusion of 3.75 and 5 μg/min. In contrast, CO and SV were significantly higher than baseline after the first three and two infusions correspondingly, but they returned to baseline following infusion of 5 μg/min (CO) and 3.75–5 μg/min (SV) (Fig. 1, B and C).

Fig. 1. Mean arterial pressure (MAP; A), cardiac output (CO; B), stroke volume (SV; C), and total peripheral resistance (TPR; D) in group 1 (dose-finding studies). Epi, epinephrine. Values are mean and SD. All comparisons are vs. baseline (0 Epi). *Level of significance: P < 0.05.
Time-matched control animals (groups 2 and 3). See Fig. 2, A and C, and 3, A, C, and E. In groups 2 and 3, HR during Epi infusion was significantly higher than baseline values (Fig. 2A). MAP, however, remained unchanged in both groups compared with baseline (Fig. 2C). Comparing group 3 vs. group 2, both HR and MAP in group 3 appeared significantly higher during the last 60 min. Significant (26–33%) increases in CO in response to 60-min Epi infusions were measured in both groups compared with baseline, but no significant differences between groups were found (Fig. 3A). In group 2, which received 0.125 μg/min Epi, SV was significantly higher than baseline during the whole infusion time (Fig. 3C). In group 3, SV was significantly higher than baseline only during infusion of 0.625 μg/min Epi and returned to near baseline level during infusion of 1.25 μg/min Epi. Changes in SV did not reach statistical significance between groups 2 and 3 during Epi infusions.

Cooling and Stable Hypothermia

Hemodynamics during cooling, stable hypothermia, and rewarming are presented in Figs. 2, B and D, and 3, B, D, and F. All animals survived cooling and stable hypothermia. Compared with prehypothermia, hypothermia led to marked reduction (55–92%) in most hemodynamic variables. However, during cooling, SV remained unchanged down to 32°C, but thereafter increased, and at 20°C it was raised by ~100%. During hypothermia, TPR did not change significantly in any group. No arrhythmias were observed during cooling and stable hypothermia.

Rewarming

Three animals died during rewarming in group 5, and data from these animals are not included. All animals in the other groups survived. Effects of Epi bolus injections (0.1 or 1.0 μg) at 20 and 24°C. See Figs. 2, B and D, and 3, B, D, and F. Neither in group 4 nor in group 5 was HR changed after the first Epi bolus injection.
Fig. 3. CO (A and B), SV (C and D), and TPR (E and F) in normothermia controls (A, C, and E) and hypothermia groups (B, D, and F). At 20 and 24°C, a bolus of 0.1 µg Epi was administrated in group 4 and a bolus of 1.0 µg in group 5. At 28°C, infusion of 0.125 µg/min Epi was started in group 4 and infusion of 1.25 µg/min in group 5. Symbols are as defined in Fig. 2 legend. Values are means and SD. A, C, and E: significance compared with baseline values and *when groups 2 and 3 are compared. B, D, and F: significance compared with prehypothermic values, *when groups 4 and 5 are compared with group 6, and **when groups 4 and 5 are compared. Level of significance: P < 0.05.
injection compared with the saline group (Fig. 2B). MAP was significantly higher in both Epi groups compared with the saline group, but a significantly more pronounced increase was observed in group 5 than in group 4 (Fig. 2D). At 20°C, bolus injection of 0.1 µg in group 4, as well as 1.0 µg Epi in group 5, increased CO significantly compared with group 6, which received saline, but the increase in CO was similar when groups 4 and 5 were compared (Fig. 3B). In all groups, TPR was statistically unchanged (Fig. 3F).

Epi injections were repeated at 24°C. As after the first injection, HR was not affected in both Epi groups compared with the saline group. In group 5, injection of 1.0 µg Epi led to a significant increase in both MAP and TPR compared with groups 4 and 6. However, compared with the saline group, CO was not significantly changed after high-dose (1.0 µg) Epi injection, but, in group 4, injection of 0.1 µg Epi increased CO and SV significantly compared with group 5 as well as group 6.

**Effects of Epi infusions during rewarming from 28°C.** See Figs. 2, B and D, and 3, B, D, and F. In both Epi groups, HR increased in a similar manner and returned completely to within control values (Fig. 2B). MAP returned to prehypothermic baseline after rewarming was completed in group 4 as well as in group 5 (Fig. 2D). In group 5, compared with groups 4 and 6, MAP was clearly higher during rewarming to 32°C, with gradual decrease during the remaining rewarming procedure. Infusion of Epi in group 4 provided stable growth and complete restoration of CO back to prehypothermic control values, and CO was significantly higher than corresponding values in groups 5 and 6 (Fig. 3B). Epi infused in group 5 was not able to increase CO compared with group 6. After rewarming was accomplished, CO in group 5 was found to be similar to corresponding value in group 6 and significantly lower than prehypothermic baseline. Group 4 showed complete restoration of posthypothermic SV, which was significantly higher than corresponding values in the two other groups. At the same time, SV in group 5 was significantly lower than baseline at the end of rewarming (Fig. 3D). TPR remained significantly elevated in group 5 compared with groups 4 and 6 during rewarming to 28–34°C (Fig. 3F). In contrast to group 5, TPR in group 4 was low during rewarming and comparable to prehypothermic baseline.

**Effects of saline infusion during rewarming from 28°C.** See Figs. 2, B and D, and 3, B, D, and F. Although rewarming initially increased HR, MAP, and CO in group 6, after rewarming was completed, these variables remained significantly lowered compared with prehypothermia and is typical of rewarming shock condition. After rewarming, TPR remained within prehypothermic control values, and SV was not significantly different from prehypothermic baseline.

**DISCUSSION**

This study shows that rewarming intact animals from profound hypothermia is complicated by low CO, a finding reported by others (6, 21, 22, 24, 25, 27), as well as in previous reports using the present experimental model (32–34). In an attempt to elevate hypothermia-induced low CO, Epi, a relevant pharmacological agent used for CPR and severe cardiovascular depression during normothermic, as well as hypothermic conditions in general, was utilized. Our main findings were that the low Epi dose (0.125 µg/min), which created both elevation of CO and vasodilation during rewarming from profound hypothermia, seems preferable. Following increasing doses of Epi (1.25 µg/min), vasoconstriction was induced, and the preferable effect on CO was not achieved. This is in contrast to our findings during normothermic conditions, where similar doses of Epi elevate CO by ~30% (Fig. 3A), seemingly independent of changes in afterload (Fig. 3E). Thus, comparing equivalent Epi doses during normothermia and rewarming from hypothermia, an apparent hypothermia-induced change in the dose-dependent mode of action emerged. Additionally, Epi is unable to elevate CO above prehypothermic control values at any temperature during rewarming, as well as after normothermia is reestablished.

The well-known dose-dependent hemodynamic effects of Epi, when used in human medicine (12), are also demonstrated during dose-finding studies in the present work on rats. Low doses of Epi (0.125–0.25 µg/min) act predominantly on β1- and β2-adrenoreceptors, resulting in CO elevation and reducing TPR, whereas higher Epi concentrations (1.25–2.5 µg/min) elevate CO, but also activate α1-adrenoreceptors, causing vasoconstriction counteracting vasodilation. Strong vasoconstriction may hamper CO elevation, as shown with the highest Epi dose (5 µg/min) tested in the present experiments.

Few other experimental studies on the effects of Epi during hypothermia and/or rewarming using intact animal models have been published. Rubinstein (28) studied hemodynamic effects of Epi in dogs at normo- and hypothermic conditions using doses similar to those in the present study. In harmony with our findings, he reported that hypothermia modified the vascular response to Epi; i.e., the Epi doses that induced vasodilation during normothermic conditions increased TPR at 25°C. There is no evidence that the vascular response falls with temperature; in contrast, it may even be enhanced during hypothermia. Dundee and Clarke (11) showed that Epi and norepinephrine increase peripheral vascular resistance, even at temperatures down to 6°C. The impression of an increased vasomotor response due to lowering of temperature is strongly supported by our findings, showing a significant increase in MAP and TPR in the high-Epi group (1.25 µg/min) compared with the low-Epi group (0.125 µg/min). In addition, we also observed that this drug was able to raise CO, but with a seemingly more narrow “therapeutic window” than during normothermic conditions. Furthermore, the present work indicates that the inability to increase CO following exposure to profound hypothermia is not simply caused by a potential temperature-dependent reduction in myocardial β-receptor activity, but it may also be due to the existence of hypothermia-induced myocardial failure. Our study demonstrates that the presence of a low afterload is a prerequisite for achieving pharmacological elevation of CO. This finding supports the idea of a hypothermia-induced myocardial failure.

Conflicting results have been reported concerning to what extent cardiovascular function can be reestablished after rewarming from hypothermia. After rewarming from acute experimental hypothermia using in vivo animal models, substantial depression of left ventricular myocardial function has been reported in earlier as well as recent studies, and also in studies using the present animal model (6, 21, 22, 24, 25, 27, 32–34). The pathophysiological mechanisms explaining lack of restitution of cardiovascular function following rewarming remain
unsolved. In the present study, our finding that the lack of inotropic effect of Epi remains even after normothermia is reestablished weakens the thought that this is exclusively due to reduced adrenoreceptor affinity at low temperatures. From in vitro studies, the hypothesis of hypothermia-induced calcium overload has been favored when explaining posthypothermic myocardial dysfunction (5, 15, 21, 29). In a recent study (37) using the present model, we were able to demonstrate that the increase of myocardial tissue calcium content was significantly dependent on the duration of hypothermic exposure. Total myocardial tissue calcium increased with a factor of 6.6 following 4 h at 15°C, and calcium levels are comparable with those reported following intermittent global myocardial ischemia (1, 2, 31). The lack of effects of Epi to increase CO during hypothermia could, therefore, be due to calcium overload. The results of Schiffrmann et al. (29), using an in vitro working rat heart model, support this assumption. They showed a reduction of CO and SV by inducing varying levels of hypercalcemia during hypothermia (28°C). Following infusion of Epi during these experimental conditions, CO and SV were even more depressed (29). These findings share similarities with findings in the present experiments using an intact animal model. Infusion of high-dose Epi, which induces opening of Ca2+ channels, increases calcium influx and elevates intracellular calcium even further.

Our experimental setting comparing effects of Epi at different temperature levels is complicated by factors like differences in temperature-dependent metabolic drug elimination and changes in drug distribution volume. The first is taken care of by injecting rather than infusing standard doses of Epi at low temperatures (20 and 24°C). Furthermore, intravascular distribution volume is reduced at low temperatures. From different studies using intact animal models, it has been reported that intravascular volume during hypothermia is reduced by 10–35% (7, 8, 10, 17, 23). In our experiments, low and high Epi doses differed by a factor of 10, and we, therefore, think that concentration differences are comparable also at low temperatures, despite possible changes in distribution volume.

We also have to be cautious in extrapolating results obtained from experiments using rodents to human medicine. However, the present results showing temperature-induced alteration of hemodynamic responses to Epi are new information, which may be important for future studies in clinical medicine.

This study, using an intact animal model designed for hemodynamic studies during experimental hypothermia and rewarming, shows that dose-dependent pharmacological effects of Epi on cardiovascular function are essentially changed by warming, shows that dose-dependent pharmacological effects of Epi on cardiovascular function are essentially changed by warming. We thank Dr. Tom Wilsgaard for review of the statistical methods, Fredrik Bergheim and Knut Steinnes for technical support in sampling and analysis of hemodynamic data, and Elisabeth Børde for assistance in analysis of the plasma samples.

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