Presyncope during progressive hypovolaemia simulated by lower body negative pressure is not prevented by high-dose naloxone

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Abstract

Background. The haemodynamic response to progressive hypovolaemia, whether simulated by lower body negative pressure (LBNP) or head-up tilt, or induced by haemorrhage or haemodilution, has a typical biphasic pattern: a first, sympathoexcitatory, phase of vasoconstriction, tachycardia, and stable blood pressure, and a second, sympathoinhibitory, phase of vasodilatation, bradycardia, and hypotension. The opioid system is involved in this response, since animal studies showed that opioid antagonism by naloxone can attenuate hypovolaemic hypotension. In humans, this finding could not be confirmed. We hypothesized that this could result from inadequate dosing.

Methods. Six healthy subjects underwent LBNP at −45 mmHg until presyncope before and after administration of naloxone 2 mg/kg. During the study, blood pressure, heart rate, vascular resistance, cardiac output, and plasma β-endorphin were measured.

Results. LBNP caused an immediate increase in vasoconstriction and heart rate, resulting in stable blood pressure. After 12±3.5 min, vasodilatory hypotension followed, accompanied by a modest increase in plasma β-endorphin. Naloxone did not alter the first or the second phase of the circulatory response, and tolerance to LBNP even tended to decrease (hypotension after 7.5±2.0 min, NS). Pre-LBNP plasma β-endorphin as well as hypertensive levels were increased after naloxone.

Conclusions. Our results suggest that naloxone, in a sufficient dose to interfere with the opioid system, does not influence the circulatory response to simulated hypovolaemia in humans is not influenced by naloxone. Given the mechanistic resemblance of LBNP hypotension to dialysis-induced hypotension, we propose that high-dose naloxone is not useful to treat the latter form of hypotension.

Key words: β-endorphin; hypotension; lower body negative pressure; naloxone; opioid system; progressive hypovolaemia

Introduction

The physiological haemodynamic response to hypovolaemia has a biphasic pattern. The first phase is characterized by an increase in vascular resistance and heart rate, resulting in a stable blood pressure. After a critical reduction of central blood volume, however, sudden hypotension ensues, characterized by vasodilatation and bradycardia [1,2]. Animal studies [3,4], and more recently studies in humans [5–8] have revealed that sympathoexcitation accompanies the first phase, and sympathoinhibition the second phase.

Several observations in experimental animal and human studies suggest that the central opioid system is involved in the regulation of circulatory control during hypovolaemia. In general, opioids are thought to inhibit central sympathetic outflow during hypovolaemic and other forms of stress. Blockade of opioid receptors with the opioid antagonist naloxone given before or during hypotension results in an increase in blood pressure in several animal species [4,9–13].

Methods to increase haemodynamic stability and to prevent or attenuate hypotension during volume withdrawal are clearly needed in haemodialysis, since still a considerable number of patients experience symptomatic hypotension during the dialysis session [14]. However, naloxone did not have such beneficial effects during simulated hypovolaemia induced by lower body negative pressure (LBNP) or in tilting studies in humans [15–17]. Administration of naloxone before or during haemodialysis [7,18] had no effect on the occurrence of dialysis-induced hypotension, and in one patient even exacerbated vasovagal symptoms [7]. However, these negative results in humans could be due to inadequate dosing. The effective dosages in animals range from 2 to 6 mg/kg, whereas in the human studies the maximum dosage is 0.1 mg/kg [15,16], generally sufficient to antagonize the effects of narcotic overdose. In the present study we assessed the effects of high-dose naloxone on haemodynamic parameters during the first and second phase response to simulated progressive hypovolaemia in healthy humans. We applied −45 mmHg LBNP until presyncope before and after administration of high-dose
Subjects and methods

Six healthy volunteers (one female, age 25 ± 2 years, (range 20–36), mean body weight 80 ± 4 kg, (66–93)) were studied. They were known from previous experiments to show presyncope during −45 mmHg LBNP within 30 min. The subjects had abstained from coffee or smoking for 12 h prior to the experiment, and were allowed a light breakfast. All experiments were performed in the morning, in a comfortable warm room (23 °C). The protocol was approved by the Hospital Ethical Committee for Studies in Humans, and informed consent was obtained.

Study design

Subjects were positioned horizontally in an airtight Plexiglas box up to the level of the iliac crests. In this box, controlled negative pressure can be applied by means of a vacuum cleaner. After a 30-min resting period, baseline measurements and blood samples were obtained, followed by application of LBNP at −45 mmHg. LBNP was stopped if presyncopal signs developed, defined as a decline in mean arterial blood pressure of ≥20 mmHg in ≥20 s. Subjects then rested for 30 min in the same position, after which 2 mg/kg naloxone (1 mg/ml) was administered intravenously in 10 min. The pressor effect of naloxone in human septic shock occurs immediately after infusion, and lasts for 50–180 min [19,20]. The half-life of naloxone is 64 min. Therefore, the next −45 mmHg LBNP session, starting after another 20 min rest, was conducted within the period where naloxone was effective.

Measurements

Blood samples for haematocrit and β-endorphins were obtained through an indwelling lower-arm venous cannula before LBNP and immediately after stopping LBNP. Blood pressure and heart rate were recorded continuously by finger photoplethysmography (Finapres) of the middle finger of the left arm, and analysed per 10 s. The Finapres method allows reliable beat-to-beat, non-invasive blood-pressure recording, and is in particular useful for monitoring rapid changes in blood pressure [21,22]. Forearm blood flow was measured by venous occlusion plethysmography of the right arm at 10-s intervals, using a mercury-in-silastic strain gauge. The upper arm cuff was inflated to 40 mmHg. During these measurements, the hand was not excluded from the circulation. Cardiac index was measured once per minute by thoracic impedance plethysmography (Biomed). By this technique, current is passed between electrodes at both sides of the neck and the lower thorax. The electrical impedance of the thorax is measured between a second pair of electrodes adjacent to the first. As blood leaves the chest with each cardiac cycle the impedance of the system changes, and the cardiac output can be calculated. The method is in particular useful for measuring changes in cardiac output, and has recently been proven to be an accurate and reproducible way for assessment of cardiac output [23]. For β-endorphin a RIA kit (Incstar) was used where a Sepharose antigen extraction of plasma is followed by elution and measurement of β-endorphin with a RIA procedure [24].

Calculations and statistical analysis

Beat-to-beat recordings of blood pressure and heart rate were averaged per minute. Cardiac index was calculated once per minute from cardiac output and body surface area, and stroke volume index was derived from cardiac index divided by heart rate. Total peripheral vascular resistance index was calculated using the formula $TPRI=(MAP/CI)\times 80,$ and expressed as dynes/cm$^2$/m$^2$. Forearm vascular resistance was calculated by dividing mean arterial pressure by forearm blood flow, expressed as resistance units and averaged per minute. Data during presyncope were synchronized to the lowest value of systolic blood pressure.

Data are presented as means ± SEM. Data were analysed with repeated measures ANOVA and Student-Newman-Keuls post hoc tests. P values of <0.05 were considered significant.

Results

Sympathoexcitatory phase

LBNP caused an immediate drop in systolic blood pressure, pulse pressure and stroke volume index, and an increase in heart rate, forearm vascular resistance and calculated total peripheral resistance index, whereas MAP did not change. Most of these changes developed within the first 3 min (Figure 1). Therefore baseline (last 3 min before LBNP) and 3rd min data have been listed in Table 1. After naloxone, the haemodynamic response to LBNP was largely identical to the first session, except for a larger decline in pulse pressure in the 3rd minute. This difference, however, disappeared later during the first phase (Figure 2).

Sympathoinhibitory phase

Before naloxone administration, subjects tolerated LBNP for 12.3 ± 3.5 min before presyncopal signs developed. Presyncopal hypotension was characterized by vasodilatation and a lack of further increase in heart rate, while stroke volume remained decreased without further change (Table 1 and Figure 1). The duration of LBNP until presyncope was not extended by naloxone, and in fact tended to be shorter (7.5 ± 2.0 min, NS). After administration of naloxone the haemodynamic events in this phase were unchanged, although heart rate tended to be higher in the naloxone session. Before naloxone, three of six subjects showed a slight decrease in heart rate during presyncope, and after naloxone this was the case in just one subject (Table 1 and Figure 2).

The haematocrit increased from $40.3 ± 0.8$ to $41.8 ± 0.9$% ($P<0.05$) during the first LBNP session, and from $40.0 ± 0.9$% to $40.8 ± 0.8$% ($P<0.05$) during the second session. The values before both experiments were not different from each other, indicating complete return to the baseline situation before restarting LBNP. In the experiment without naloxone, LBNP raised
plasma $\beta$-endorphin from 3.9 $\pm$ 0.4 to 5.6 $\pm$ 0.6 pmol/l ($P<0.05$). Pre-LBNP levels after naloxone were significantly higher than baseline levels before naloxone (8.1 $\pm$ 0.9 pmol/l, $P<0.05$). The hypotension after naloxone was accompanied by a large further increase in $\beta$-endorphin levels, to 23.2 $\pm$ 4.2 pmol/l, $P<0.001$ (Figure 3). The subjects did not experience any side-effects of naloxone, although some reported drowsiness in the hour after the experiment.

**Discussion**

In the present study we show that lower-body negative pressure, a model to simulate progressive hypovolaemia, causes a typical biphasic haemodynamic response: a phase of vasoconstriction, tachycardia, and stable mean arterial pressure, followed by vasodilatory hypotension. In contrast to studies in animals, high-dose naloxone given in healthy humans before LBNP
Fig. 2. Haemodynamic data after naloxone administration. The first 3 min of LBNP and the 2 min of LBNP preceding syncope are shown. Presyncope (P) occurred at 7.5 ± 2.0 min. Values are means ± SEM.

Fig. 3. Plasma β-endorphin levels before and after naloxone (NAL). Open bars are values before LBNP, speckled bars are values during hypotension. *P < 0.05, ***P < 0.005. Values are means ± SEM.

does not alter this pattern, and cannot prevent or delay hypotension.

Hypovolaemia, whether simulated by LBNP or head-up tilting, or induced by haemorrhage, causes a decrease in cardiac output and pulse pressure. The resultant deactivation of cardiopulmonary receptors, which occurs already at low levels of LBNP [25], and of arterial baroreceptors, which occurs only with stronger LBNP as presently applied [26], leads to loss of tonic inhibition of the sympathetic outflow from the brain-stem vasomotor centre [27]. The resultant sympathoexcitation maintains a stable mean arterial pressure, through vasoconstriction and acceleration of heart rate. However, if hypovolaemia is prolonged and progressive, this sympathoexcitatory phase can be followed by a sudden decrease in blood pressure, accompanied by vasodilatation, and a decrease in heart rate [1,2]. Animal and human studies [3–6,8] have shown by direct measurement of muscle sympathetic nerve activity (MSNA), that this phase is characterized by sudden cessation of sympathetic activity. It is unknown why this sympathoinhibition develops. It has been hypothesized that forceful contractions of a progressively emptying ventricle trigger excitation of vagal afferents. This causes inhibition of the central vasomotor centre, resulting in inhibition of sympathetic activity and overriding the sympathoexcitatory stimulus of the baroreflex [28]. However, other mechanisms may play a role as well, since sympathoinhibition has also been demonstrated during sodium nitroprusside infusion in a heart-transplant patient [29].

The high concentration of opioid-containing nerves and opioid receptors in the cardiovascular centre in the brain stem has led to the hypothesis that opioid peptides are involved in the physiological control of the circulation. Exogenous opiates cause hypotension and bradycardia [30]. During hypotensive shock, β-
endochoose opioid levels are increased [31]. A pathophysiolog-
ical role for endogenous opioids in vasodepressor syncope is further supported in two recent studies, showing that at the presyncopal stage during head-up tilt [32] or LBNP [33], plasma β-endorphin levels are elevated. Subjects without syncope lacked an increase in β-endorphin. We also observed an increase in β-
endorphin in blood collected immediately after col-
apse. This increase, however, was modest, and by
its own course provides no direct argument for a
causative role in the genesis of hypotension.

The main purpose of our study was to assess whether
high-dose naloxone could prolong the phase I response,
and delay or prevent the phase II vasodilatory hypo-
tensive response to LBNP. Interestingly, naloxone increased both basal β-endorphin concentration and the stimulated levels after LBNP-induced collapse. Naloxone (0.1 mg/kg) has been reported to increase the secretion of ACTH, cortisol, and β-endorphin in normotensive young adults [34], suggesting tonic opioidergic inhibition of anterior-pituitary function. Others demonstrated that naloxone (4 mg) enhanced the increase in β-endorphin during exercise in humans [35]. Conceivably, naloxone displaces opioids from effector receptors as well as clearance receptors, and therefore exaggerates the increased β-endorphin levels found after mental or circulatory stress and exercise [32–35].

The finding of stimulated plasma β-endorphin levels following the administration of naloxone is particularly relevant since it provides the most direct evidence that naloxone, in the dosage used, interacted with the endogenous opioid system. Despite this observation, we found no effect of naloxone on either stage of the haemodynamic response to LBNP, in particular no post postponement of the vasodilatory hypotensive response. This is remarkable, given the consistent observation that proportionately similar dosages of naloxone delay or attenuate the sudden vasodilatory hypotensive response following haemorrhage in rats [12], rabbits [3,4,9,36,37], dogs [38], pigs [39], and primates [11]. In most studies, animals were unanesthet-
ized, since most narcotics attenuate the circulatory response to haemorrhage. The general idea is that naloxone interacts with the brain vasomotor centre and, specifically during reduced cardiac output, enhances the sympathetic outflow to peripheral resistance vessels [13,40], and the kidney [4,37]. It remains unclear why naloxone should not have such an effect in humans.

Our results differ from older data showing that naloxone (0.5 mg/kg) may increase blood pressure in patients with septic shock [19,20], and may attenuate the physiological fall in blood pressure during sleep [41]. Naloxone was recently shown to potentiate in humans the cardiopulmonary reflex during non-hy-
tensive LBNP [42], and the arterial baroreflex tested with nitroprusside infusion [43]. However, this gain in baroreflex activity could be demonstrated only in an increase in muscle sympathetic activity, not in the vasoconstrictive or heart rate response [42,43]. Few studies addressed the effects of naloxone (0.1–0.5 mg/kg) on the phase two circulatory response to progressive hypovolaemia simulated by LBNP [15,16] or head-up tilt [17], however, hypotension was not delayed or prevented. Further studies concern mainly naloxone’s effect on non-baroreceptor-
mediated sympathoexcitation, such as exercise or cold exposure. In general, an effect on blood pressure or heart rate could not be found [44–49], although in some studies naloxone caused an increase in MSNA and plasma catecholamines [44,46,48]. Naloxone may have some, not very convincing, effect on postexercise hypotension [50,51]. Collectively, these data suggest that the difference in the impact of opioids on circulat-
ory control between humans and other species may be
quantitative rather than absolute.

Limitations of the study concern the small number of subjects, and the non-randomized order of the experiments. We selected subjects who had in a pilot study been shown to have limited tolerance to −45 mmHg LBNP. For a doubling of the duration of tolerance to LBNP to be significant with 80% power, we had to study at least six subjects. In fact, however, we found some tendency for decreased tolerance to LBNP after naloxone. This makes it highly unlikely that inclusion of a larger number of subjects would have shown the pursued beneficial effect of naloxone. We did not randomize the order of the experiments, since the long half-life of naloxone would have pre-
cluded performance of the experiments without and with naloxone administration within one study session. In this respect it is important that the response to presyncopal LBNP has been reported to be highly reproducible within subjects [52], as was also the case in previous experiments from our laboratory [5].

In conclusion, we found that high-dose naloxone did not postpone or attenuate LBNP-induced hypoten-
sion. The scarce data currently available did not show a beneficial effect of low-dose naloxone on dialysis hypotension [7,18]. Given the mechanistic resemblance of LBNP hypotension to dialysis-associated hypoten-
sion [8], we surmise that high-dose naloxone is not
useful to treat the latter form of hypotension.

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