Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans

Steven M. FRANK*, Patricia SATITPUNWAYCHA*, Simon R. BRUCE†, Peter HERSCOVITCH‡ and David S. GOLDSTEIN†

*Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, MD 21287, U.S.A., †Clinical Neurocardiology Section, National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, U.S.A., and ‡PET Imaging Section, National Institutes of Health, Bethesda, MD 20892, U.S.A.

ABSTRACT

Potential mechanisms of cold-induced myocardial ischaemia are sympathetically mediated coronary vasoconstriction and/or catecholamine-induced increases in cardiac work. To examine these parameters, 11 human volunteers were each studied on one day with, and on another day without, β-adrenoceptor blockade. On each day, warm (37 °C) saline (control) and cold (4 °C) saline (hypothermia) were given intravenously. Myocardial perfusion was assessed by positron emission tomography using H215O, and coronary vascular resistance was calculated. Plasma catecholamines were measured to assess sympathoadrenal activation. The core temperature decreased by 1.0 ± 0.2 °C with cold saline, and was unchanged with warm saline. Myocardial perfusion increased by 20 % (P = 0.01) and the rate–pressure product by 33 % (P = 0.0004) with cold saline compared with warm saline. β-Blockade eliminated these increases. Coronary vascular resistance was similar with warm and cold saline, and was unaffected by β-blockade. Plasma adrenaline increased by 120 % and noradrenaline by 251% during cold saline, but were unchanged during warm saline. In conclusion, core hypothermia triggers β-adrenoceptor-mediated increased cardiac work, sympathoadrenal activation and increased myocardial perfusion. There is no evidence for hypothermia-induced coronary vasoconstriction.

INTRODUCTION

Cold stress can trigger myocardial ischaemia in patients with coronary artery disease. The incidence of death from myocardial infarction increases during the winter, even in moderately temperate climates [1–3]. Immersion of the forearm or hand in cold water – the cold pressor test – can trigger coronary vasoconstriction and decreased coronary perfusion [4,5], although this test poses more of a painful than a thermoregulatory challenge. Mild core hypothermia (≈ 1.5 °C) is associated with a 2–3-fold greater incidence of myocardial ischaemia [6] and major morbidity cardiac events [7] in awake postoperative surgical patients with coronary disease. This is related to and may be caused by activation of the sympathetic nervous system [8].

Two mechanisms, which are not mutually exclusive, could explain cold-induced myocardial ischaemia. One is adrenergically mediated coronary vasoconstriction, from agonist occupation of α-adrenoceptors in coronary arteries [9]. This would decrease the myocardial oxygen supply for a given level of demand. The other is increased myocardial oxygen demand relative to supply. This increased demand could arise from the local myocardial or peripheral vascular effects of sympathetic nervous and adrenomedullary hormonal stimulation. Consistent
with the latter mechanism, cooling the core temperature by as little as 1 °C increases values for the heart rate-systolic pressure product – an index of cardiac work – and is associated with large increases in plasma levels of noradrenaline (norepinephrine), the sympathetic neurotransmitter [10], and smaller increases in levels of adrenaline, the main adrenomedullary hormone [11].

The present study was designed to test the hypothesis that mild core hypothermia elicits coronary vasoconstriction, thereby decreasing myocardial perfusion. To unmask α-adrenoceptor-mediated coronary vasoconstriction, which might be balanced by β-adrenoceptor-mediated coronary vasodilation, perfusion was assessed with and without β-adrenoceptor blockade. Myocardial perfusion was assessed by positron emission tomography (PET) after intravenous injection of the perfusion imaging agent, H$_2^{15}$O [12].

**METHODS**

**Study protocol**

The subjects were 11 healthy men (mean age 29 ± 2 years) who gave written, informed consent to participate in the protocol, which was approved by the Intramural Research Board of the National Institute of Neurological Disorders and Stroke and by the Radiation Safety Committee of the National Institutes of Health. All subjects had normal medical histories and physical examinations, and were taking no medications at the time of the study. All subjects were non-smokers who refrained from ingesting caffeinated or decaffeinated coffee or caffeine-containing foodstuffs, and from drinking alcohol, for at least 18 h prior to the study.

Each subject was studied on two separate testing days: one day with, and one day without, β-adrenoceptor blockade. On each day, the subjects received two treatments: (1) intravenous warm saline (30 ml·kg$^{-1}$) as a normothermic control treatment, and (2) the same volume of intravenous chilled saline, to lower the core temperature by ≈ 1 °C. A 30 min rest period was given between treatments. To avoid discomfort, a condom catheter was used and the subjects were allowed to urinate at any time during the study.

The subjects rested in the supine position throughout the study. Ambient temperature was between 21 and 23 °C. The intravascular catheters were placed after local anaesthesia using 1% lidocaine. A 16-gauge, 30-cm central venous catheter was inserted into a large antecubital vein for the infusion of the warmed and chilled saline, and for injection of H$_2^{15}$O. This catheter also allowed the measurement of central venous pressure. A 20-gauge catheter was placed in a brachial artery for continuous monitoring of systemic arterial blood pressure and for timed sampling of arterial blood. An antecubital venous 18- or 20-gauge intravenous catheter was also placed for sampling blood. The ECG and the arterial blood pressure waveform were recorded continuously during the studies. Core temperature was measured by a tympanic membrane thermocouple probe (Mallinckrodt Medical Inc., St. Louis, MO, U.S.A.). The probes were inserted into the auditory canal until the subject could detect an audible sound when the thermocouple was touched. All temperature data were recorded continuously using an Isothermex™ electronic thermometer (Columbus Instruments, Columbus, OH, U.S.A.) linked to a laptop computer.

**PET imaging**

Subjects were placed in the PET scanner (GE Advance; General Electric, Milwaukee, WI, U.S.A.), with the heart in the field of view. The scanner provides 35 contiguous slices, with a slice separation of 4.25 mm and a transverse and axial resolution of ≈ 6 mm. Transmission scanning was done, to confirm appropriate positioning in the scanner and to correct for attenuation. Myocardial perfusion was measured three times during the study: (1) before saline infusion (baseline), (2) upon completion of the warm saline infusion, and (3) upon completion of the cold saline infusion. For each measurement, 48 mCi of H$_2^{15}$O, dissolved in 10 ml of physiological saline, was injected intravenously over 30 s. The tracer was prepared just prior to use. PET scans of the thorax were obtained over 5 min after tracer injection, during which time 32 sequential images (20 × 3 s, 6 × 10 s and 6 × 30 s frames) were obtained.

After the baseline PET scan, warm saline (37 °C) was infused intravenously at a rate of 1.0 ml·min$^{-1}$·kg$^{-1}$ over a 20 min period. After a 45 min rest period, an infusion of cold intravenous saline (4 °C) was given at the same administration rate and volume as for the warm saline. On the testing day involving β-blockade, propranolol (0.07–0.1 mg·kg$^{-1}$) was given intravenously as a bolus dose over 5 min before the warm intravenous saline, and again before the cold intravenous saline. The dose was titrated to achieve a 10–15% decrease in resting heart rate.

**Measurement of myocardial perfusion**

Short-axis views of the left ventricle were used to assess myocardial tissue perfusion. First, the summed early images (from the initial 30 s after H$_2^{15}$O injection) were subtracted from the summed late images. This eliminated the high concentration of radioactivity in the ventricular chambers, facilitating visualization of the myocardial tissue. Then 20 slices of left ventricular images were summed into six equal thicker slices. Nine regions of interest were drawn over the anterior, lateral and septal portions of the left ventricle at the level of the apex, mid-level and base. From these regions, time–activity...
curves were derived for myocardial tissue radioactivity. The input function for H215O concentration in the blood pool was obtained from a time–activity curve derived from a region of interest drawn in the centre of the left ventricular cavity. Myocardial perfusion was calculated from the input function and the myocardial time–activity curve using a software program developed at the NIH. The program implements the standard one-compartment model for a freely diffusible tracer, calculating flow from the efflux phase of the dynamic scan data [13]. It incorporates a partial volume factor [12] and a spillover term to account for contamination of the myocardial time–activity curve by activity in the left ventricular chamber, and fixes the myocardial distribution volume (Vd) for water at 0.91 ml/g. Perfusion values were obtained in units of ml·min⁻¹·100 g⁻¹ tissue, and the average perfusion for all nine myocardial regions was used for analysis.

Coronary vascular resistance was calculated from the coronary perfusion pressure (mean systemic arterial blood pressure minus central venous pressure) divided by myocardial blood flow. Since coronary sinus venous pressure was not measured, the central venous pressure was substituted as the 'downstream' pressure for the coronary circulation.

**Catecholamine measurements**

At the time of each myocardial perfusion measurement, brachial arterial and antecubital venous blood samples were taken for noradrenaline and adrenaline assays. The blood samples were cold centrifuged and the plasma was separated and stored at -80° C. Plasma concentrations of noradrenaline and adrenaline were measured by liquid chromatography with electrochemical detection, after barth alumina extraction as described previously [14].

**Data analysis**

Repeated-measures ANOVA was used to assess differences for the physiological and neurochemical dependent measures. Differences were analysed between and within groups; the between-groups factor was treatment (β-adrenoceptor blockade), and the within-groups factor was thermal condition (baseline, warm saline or cold saline). Individual means were compared by dependent-means two-tailed paired t tests. All data are reported as means ± S.E.M., and P < 0.05 defined significance.

**RESULTS**

The subjects were young men of normal body habitus: body mass, 74 ± 3 kg; height, 177 ± 2 cm; age, 29 ± 2 years.

**Core temperature**

Core temperature remained unchanged during the warm saline infusion, and decreased by 1.0 ± 0.2 °C (P = 0.001) during the cold saline infusion, in both the β-blockade and the no-blockade conditions (Figure 1).

**Catecholamine responses**

Arterial plasma adrenaline concentrations were unchanged during the warm saline infusion. During the cold saline infusion, adrenaline concentrations increased significantly (by 120 %; P = 0.003) in the no-β-blockade condition, but the increase above baseline was not significant (P = 0.09) in the setting of β-blockade (Figure 1). Arterial plasma noradrenaline concentrations decreased slightly during the warm saline infusion, in both the β-blockade and no-blockade conditions. During the cold saline infusion, noradrenaline concentrations increased significantly in both the no-blockade condition (by 251%; P = 0.0001) and during β-blockade (by 79%; P = 0.001) (Figure 1). The cold-induced noradrenaline increase was lower in the presence of β-blockade (P = 0.01).

**Systemic haemodynamic response**

The rate–pressure product, heart rate and systolic arterial blood pressure increased during the cold compared with the warm saline infusion (Figure 2). β-Blockade prevented the increases in rate–pressure product and
heart rate, and attenuated the increase in systolic blood pressure. Compared with baseline, the warm saline infusion increased the heart rate and rate–pressure product slightly. Central venous pressure was increased by 5 ± 1 mmHg during the warm infusion, and by a similar amount during the cold infusion (5 ± 1 mmHg). Before the cold infusion was started, central venous pressure had returned to within 1 or 2 mmHg of the baseline value, indicating that intravascular volume had returned to near normal. These changes were significant within groups (P < 0.05), but not between groups (β-blockade compared with no blockade).

Coronary haemodynamic response

Compared with the warm saline infusion, the cold saline infusion increased myocardial tissue perfusion (by 20 %; P = 0.01) (Figure 3). β-Blockade prevented this increase. Myocardial perfusion increased after the warm saline infusion compared with baseline. Coronary vascular resistance decreased significantly from baseline values during warm saline infusion, but it was unchanged from baseline during the cold saline infusion (Figure 3). Myocardial perfusion divided by the rate–pressure product provided an index of the myocardial oxygen supply/demand ratio. This index increased slightly during warm saline infusion (P = 0.004 with β-blockade; P = 0.05 without β-blockade), but was unchanged during cold saline infusion compared with values at baseline or during warm saline infusion (Figure 4).

DISCUSSION

Our results indicate that mild core hypothermia does not evoke coronary vasoconstriction in healthy human subjects, and actually increases myocardial tissue perfusion, in a manner that matches the increase in the heart rate-systolic pressure product, an index of myocardial oxygen consumption. The increase in rate–pressure product was associated with, and probably resulted from, increased occupation of β-adrenoceptors by endogenous noradrenaline and adrenaline. Large increases in the arterial plasma concentration of noradrenaline indicated a substantial sympatheural response. Smaller but statistically and clinically significant increases in the arterial plasma concentration of adrenaline indicated concomitant adrenomedullary activation.
Since $\beta$-adrenoceptor blockade completely prevented both the increase in coronary perfusion and the increase in rate–pressure product during core cooling, increased myocardial perfusion was effectively linked to $\beta$-adrenoceptor-mediated increases in myocardial work in these normal volunteers. Although future studies are needed in patients with coronary artery disease, these findings suggest that cold-induced myocardial ischaemia may arise from increased myocardial oxygen demand that is not matched by a concomitant increase in myocardial blood flow.

Cold stimuli are known triggers of myocardial ischaemia [6] and ischaemic cardiac morbidity [1,2,7,15,16]. Previous studies using the cold pressor test suggested that the mechanism for ischaemia is a decrease in myocardial oxygen supply due to adrenergically mediated coronary vasoconstriction [4,17]. Accordingly, $\beta$-adrenoceptor blockade maintains coronary perfusion during cold pressor testing [5] and reduces anginal symptoms in patients with Prinzmetal's angina [18]. However, coronary vasoconstriction during cold pressor testing seems to occur in patients with atherosclerotic coronary artery disease, while healthy subjects respond with increased coronary perfusion [17].

In summary, mild core hypothermia (1°C) in healthy humans does not elicit coronary vasoconstriction.
holds true even in the setting of β-adrenoceptor blockade, given to unmask possible α-adrenoceptor-mediated coronary vasoconstriction. The hypothermia causes β-adrenoceptor-mediated increases in the rate-pressure product, an index of myocardial oxygen consumption, which is usually matched by an increase in myocardial perfusion, so that coronary vascular resistance remains unchanged. Core hypothermia is associated with substantial sympathetic nervous system activation and a lesser degree of adrenomedullary hormonal system activation, and these effects probably account for the increased cardiac work. Since patients with coronary artery disease may not be able to increase myocardial perfusion sufficiently during cold challenge to balance the increased cardiac work, myocardial ischaemia might result. The results also help to explain the beneficial effects of β-adrenoceptor blockade [20–22], which prevents adverse haemodynamic changes and attenuates sympathetically mediated noradrenaline release.

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