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Cardiovascular and metabolic responses to noradrenaline in men acclimatized to cold baths

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Summary. The purpose of this study was to see whether artificial acclimatization to cold would reduce the pressor response to noradrenaline (NA) as natural acclimatization has been shown to do, and whether it would induce nonshivering thermogenesis. Three white men were infused with NA at four dosage levels between 0.038 and 0.300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (2–23 $\mu g \cdot min^{-1}$), before and after artificial acclimatization to cold and again 4 months later when acclimatization had decayed. Acclimatization was induced by ten daily cold (15° C) baths of 30–60 min followed by rapid rewarming in hot (38–42° C) water, and was confirmed by tests of the subjects' responses to whole-body cooling in air. Three control subjects also underwent the first and third tests. Acclimatization substantially reduced the pressor response to NA at 0.150 and 0.300 $\mu g \cdot kg^{-1} \cdot min^{-1}$, confirming earlier findings by the same technique in naturally acclimatized men, and its decay increased this response to beyond its initial levels ($P < 0.05$ for both changes). Acclimatization did not change the response to NA of heart rate, subjective impressions, skin temperature of finger and toe, pulmonary ventilation, or plasma free fatty acids and ketone bodies. At no time did NA increase oxygen consumption, or increase skin temperature or heat flow over reported sites of brown fat. These findings would seem to show that acclimatization to cold reduces sensitivity to the pressor effect of NA but does not induce nonshivering thermogenesis, and that the reduced sensitivity is replaced by a hypersensitivity to NA when acclimatization decays.

Key words: Blood pressure – Heart rate – Fat mobilization – Nonshivering thermogenesis – human acclimatization to cold

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Introduction

The important role of noradrenaline (NA) in the temperature regulation of cold-acclimatized small animals has long been established (Hsieh and Carlson 1957), but knowledge of its role in human acclimatization to cold is still rudimentary. In the only previous study in which the subjects were independently shown, by concurrent tests of their responses to whole-body cooling, to be acclimatized (Budd and Warhaft 1966a,b), acclimatization was accompanied by a striking reduction in the pressor and subjective effects of infused NA, and by the apparent development of a small calorigenic response which increased resting heat production by about 10%.

By contrast, men conditioned in cold rooms (Joy et al. 1963), and Korean women divers (Ama) in winter (Kang et al. 1970), have shown no change in their pressor response to infused NA, although a small calorigenic response (7%–14% of resting heat production) has been detected. A 17% increase in heat production has also been observed (Itoh and Kuroshima 1972) in the Ainu inhabitants of the cold northern islands of Japan following subcutaneous injection of NA; it was accompanied by a greater mobilization of plasma free fatty acids (FFA) and ketones, and more marked subjective reactions, than the same dose had evoked in a control group.

Whether these small increases in heat production constitute a realistic parallel to nonshivering thermogenesis (NST) in the acclimatized rat has been questioned (Kang et al. 1970) and it is not yet clear whether adult humans possess thermogenically active brown fat – the tissue which has been found to contribute much of the nonshivering heat production in acclimatized rodents (Alexander 1979). However, some anatomical studies (Heaton 1972; Huttunen et al. 1981) have reported the presence of brown fat at certain sites in the adult human, and local warming at those sites has been observed in response to infused NA (James and Trayhurn 1981) and oral ephedrine (Rothwell and Stock 1979).

We here report the effects of artificial acclimatization to cold and its subsequent decay (Budd et al. 1993) on responses to infused NA. The study was part of the scientific programme of the International Biomedical Expedition to the Antarctic (IBEA)[1] (Lugg and Rivolier 1982) and was carried out in accordance with the Declaration of Helsinki. Its main aim was to see whether artificial acclimatization would result in:

1. A reduced sensitivity to the pressor and subjective effects of NA, and/or
2. The development of a capacity for NST, as shown by an increase in oxygen consumption ($\dot{V}O_2$) or fat mobilization, or by local warming at reported sites of brown fat.

An additional aim was to compare the results with observations previously made by the same techniques (Budd and Warhaft 1966a, b) in naturally acclimatized men wintering in Antarctica.

Methods

Three expedition members (the bath group) were infused with NA at several dosage levels before (series 1, abbreviated as S1) and after (series 2, S2) they had undergone ten daily baths in water at 15° C, as described elsewhere (Budd et al. 1993). They were retested in the same way 4 months later (series 3, S3), 3 weeks after they had completed a 10-week motor-toboggan traverse on the Antarctic plateau. Three other expedition members (the control group), who shared in the traverse but underwent only two baths (which were required as assessment tests in another study), were also tested in S1 and S3; unfortunately the demanding timetable of the expedition did not permit the control group to be tested in S2.

In a concurrent study the same six subjects, together with the six remaining members of the expedition (three bath and three control), underwent tests of their responses to whole-body cooling in air (Budd et al. 1993). These tests showed that the immersions had acclimatized the six-man bath group, as shown by significantly lower heat production and heat loss in the cold, and that this acclimatization, together with any natural acclimatization that may have developed in either group during the Antarctic traverse, had completely decayed by the time of S3.

Subjects. The subjects were white, male, self-selected biomedical scientists and technicians, mainly of sedentary habits, who had spent the previous 6 months or more in temperate climates. All were in good health. Average values for bath and control group were age 41 and 43 years, height 185 and 175 cm, body mass 72 and 79 kg, mean skinfold thickness 9 and 12 mm, body fat content 21% and 26%, and aerobic capacity 53 and 52 $ml \cdot O_2 \cdot min^{-1} \cdot kg^{-1}$ fat-free mass, respectively. Individual characteristics for the bath group (subjects 4, 5, and 6), and the control group (subjects 1, 9, and 11) are reported elsewhere (Brotherhood et al. 1986).

Procedures. Procedures were the same as in the earlier study in Antarctica (Budd and Warhaft 1966b). The tests for each subject were carried out at the same time of day; he was not fasting but had not eaten in the 2 h before the test. During the test and for at least 1 h before it the subject, wearing only nylon briefs, lay supine in a warm (28–30° C) air-conditional room, under a cotton sheet which was adjusted as necessary to keep him comfortably warm without sweating. The right cubital or brachial vein was cannulated, and an indwelling needle for blood samples was placed in a forearm vein of the same arm; both veins were kept open by a slow drip of 4.3% dextrose in 0.18% saline ('dextrose saline'). Levophed NA solution from a single recent batch was used in all tests; it was purchased from the manufacturers (Winthrop Laboratories, Sydney) 1 month before S1 and was stored in the dark at 5° C. Immediately before each subject was tested a stock solution of NA in dextrose saline was prepared which at the highest rate of infusion would deliver a dose of 0.300 $\mu g \cdot min^{-1} \cdot kg^{-1}$ body mass.

Dextrose saline alone, and the NA stock solution, were alternately infused (control and NA periods respectively) by a Thorp-Palmer continuous-injection machine for 10-min periods at successive rates, within the voluntary acceptance of the subject and the judgement of the supervising physician, of 0.038, 0.075, 0.150, and 0.300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (2–23 $\mu g \cdot min^{-1}$) – designated here for convenience as multiples of the lowest dose, namely D1, D2, D4 and D8. After the highest dose the entire sequence was repeated, to obtain duplicate measurements at each dose. The subject, who did not know what was being infused at any given time, reported his subjective responses at the end of each 10-min infusion. All responses except those of plasma FFA and ketone bodies disappeared within 1–2 min after each NA infusion ceased, and measurements during successive control periods did not show any increase with time that would suggest an accumulation of NA.

Blood pressure and heart rate. Blood pressure (BP) was measured at the left brachial artery with a mercury sphygmomanometer, and heart rate (f_c) was counted by palpation, every minute by the same experienced observer in every test on a given subject; diastolic pressure (BP_d) was taken as the first muffling of sound (Korotkow IV). Electrocardiograph and f_c were continuously monitored by an oscilloscope and cardiotachometer.

Rectal, tympanic, and skin temperatures. These were measured every 2 min with copper-constantan thermocouples and an automatic data acquisition system of sensitivity 100 nV. Rectal temperature (T_{re}) was measured at a depth of 12 cm. Tympanic temperature (T_{ty}) was measured with a 36 G thermocouple placed close to the tympanic membrane and insulated with a large pad of cotton wool under a wool balaclava. Mean skin temperature ($\bar{T}_{sk}$) was calculated from six sites (lateral thigh, medial thigh, back, chest, arm, cheek) by the formula of Teichner (1958). Skin temperature was also measured at the finger (T_{fi}) and toe (T_{to}), and at the sternum and nape of neck – which have been reported to be sites of brown fat (Heaton 1972; Rothwell and Stock 1979; Huttunen et al. 1981) – as described in the accompanying paper (Budd et al. 1993). A factory-calibrated heat flow disc (Hatfield type) was attached to the nape beside the thermocouple.

$\dot{V}O_2$ and pulmonary ventilation. These were measured by 7-min Douglas bag collections of expired air, using a mouthpiece and nose clip, from the 4th min of each NA and control period; volume and composition were measured as described in the accompanying paper (Budd et al. 1993).

Fat mobilization. Venous blood for the determination of plasma FFA and the ketone bodies aceto-acetate (AA) and beta-hydroxy butyrate (BHB) was sampled without stasis during the 7th and 8th min of the first control infusion and the two highest doses of NA, in each half of the test. Because of technical difficulties no blood was obtained from subject 1. The blood was immediately mixed with lithium heparin for assay of FFA, and with fluoride-oxalate for assay of AA and BHB, and was centrifuged at 4° C; the decanted plasma was stored at −20° C until it was analysed. The FFA were estimated by Dole extraction and radiochemical assay (Ho and Meng 1969), AA by enzymic assay (Price et al.

[1] The IBEA was a scientific project organised by the Scientific Committee on Antarctic Research (SCAR) Working Group on Human Biology and Medicine: SCAR is a committee of the International Council of Scientific Unions

1977), and BHB by enzymic assay using immobilized enzyme (Williamson and Mellanby 1974).

Analysis of results. Except for blood constituents, which are presented as the observed values, the response to each dose of NA was calculated as change from the preceding control period, using the average values (4th through 9th min) of BP and f_c, the observed values of $\dot{V}O_2$ and ventilation volume ($\dot{V}_E$), and the maximal change observed for other variables. A Δ is used to distinguish these computed response variables (ΔBP, Δf_c, etc.) from the observed variables (BP, f_c, etc.). The response of pulse pressure (ΔPP) was calculated by subtracting ΔBP_d from Δ systolic blood pressure ΔBP_s.

Within each group of subjects (bath and control), responses to the three lowest doses of NA – which most subjects could tolerate – were analysed by 2-factor (series and dose) analyses of variance, using a repeated-measures model in the GENSTAT statistical program (Alvey et al. 1977). Statistical analysis was impractical for biochemical measurements (FFA, AA, and BHB) because of the limited number of samples drawn and their uneven distribution among dose levels (Fig. 4), and for variables (e.g. T_{ty}, $\bar{T}_{sk}$) in which NA caused little or no measurable change.

Results

Cardiovascular responses

Figure 1 shows that within each series NA caused dose-related increases in BP_s, BP_d, and PP, and a slowing of f_c ($P<0.01$ for all changes). Between series, substantial and significant changes occurred in the ΔBP_s, ΔBP_d, and ΔPP (although not in their Δf_c) of the bath group, whereas the responses of the control group did not change.

In S2 the pressor response of the bath group (i.e. the extent to which NA increased BP_s and BP_d) was substantially reduced at D4 and D8. Thus, at D4 the average ΔBP_s and ΔBP_d were 13.3 and 6.1 mmHg (0.81 kPa) less than in S1, equivalent to reductions of 45% and 33% ($P<0.05$ for both changes). Similarly, at D8 all three bath subjects could safely tolerate the infusion in S2, whereas in S1 and S3 the blood pressure of two of them had risen so much in response to D4 that D8 was not given; consequently responses to D8 could not be included in the analyses of variance or the average values presented in Figs. 1–3. In the remaining bath subject (subject 6) ΔBP_s and ΔBP_d at D8 were 2.3 and 7.4 mmHg (0.31 and 0.99 kPa) less in S2 than in S1, equivalent to reductions of 7% and 35%.

In S3 these changes in the bath group were reversed and accentuated by increases in ΔBP_s and ΔBP_d at all doses. The average of D1, D2 and D4 showed that BP increased above its S2 level by 11.1 mmHg (1.48 kPa) or 125% ($P<0.025$) for ΔBP_s, and by 6.7 mmHg (0.89 kPa) or 78% ($P<0.001$) for ΔBP_d. The increase even exceeded the original S1 level, by 5.7 mmHg (0.76 kPa) or 40% (not significant, $P=0.15$) for ΔBP_s and by 5.0 mmHg (0.67 kPa) or 49% ($P<0.001$) for ΔBP_d. At D8, the ΔBP_s and ΔBP_d of subject 6 were 19.7 and 7.9 mmHg (2.63 and 1.05 kPa, 62% and 37%) greater than his S1 values.

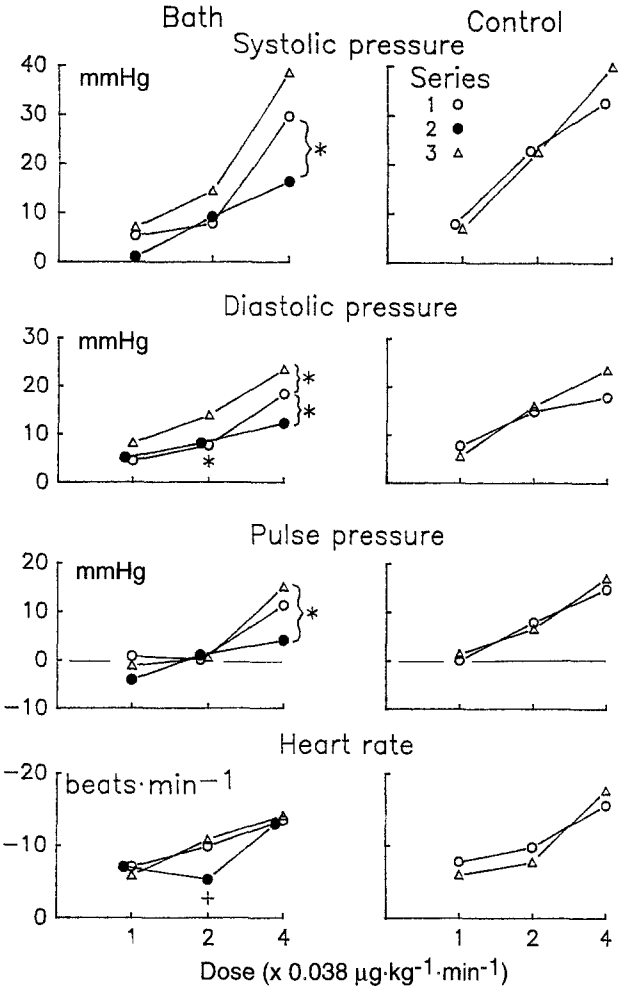

Fig. 1. Changes from control values in blood pressure and heart rate in response to various doses (plotted on log. scale) of noradrenaline. Note inversion of curve for heart rate. Each point is the average of two duplicate measurements on each of three subjects. Significance of differences between series at each dose level: + $P<10$; * $P<0.05$

Changes in ΔPP were in parallel with the changes in ΔBP_s and ΔBP_d of the bath group at D4 but not at D8 (in subject 6), and ΔPP did not change at D1 and D2.

Thermal responses

Cutaneous vasoconstriction caused by NA was evident in a dose-related reduction in T_{fi} and T_{to} (Fig. 2). The dose-response curve changed between series in an apparently random manner that was not significantly correlated with the accompanying changes in pressor response. Vasoconstriction increased T_{ty} (Budd 1989) only in two control subjects; the increases did not exceed 0.10° C and did not change between series. The T_{re} and $\bar{T}_{sk}$ did not change at any time, presumably because of the small skin-to-air temperature gradient and the thermal inertia of the rectum and proximal skin sites.

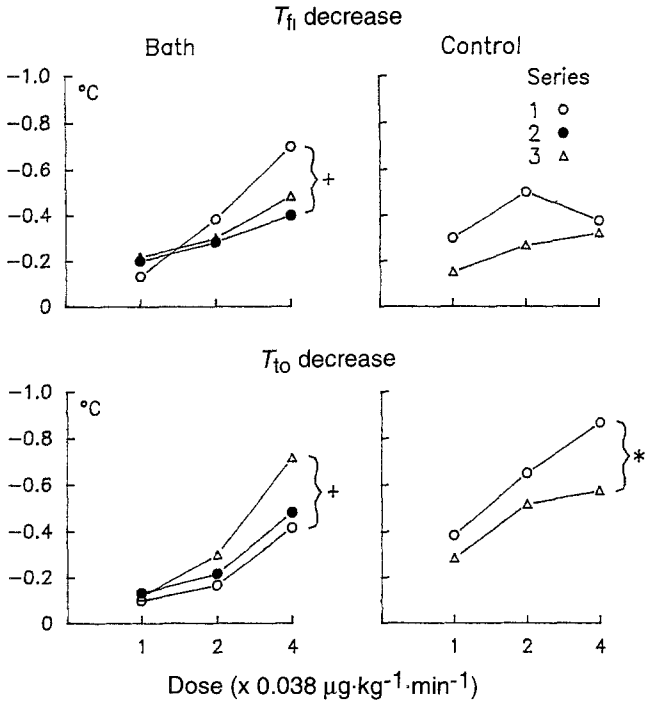

Fig. 2. Changes from control values of finger (T_{fl}) and toe temperature (T_{to}) in response to various doses (plotted on log. scale) of noradrenaline. Note inversion of curves. Other details as in Fig. 1

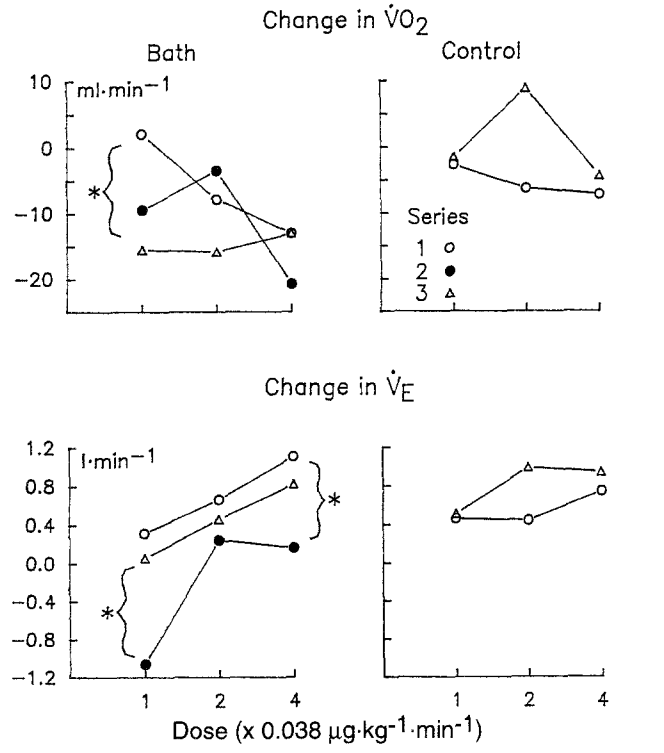

Fig. 3. Changes from control values in oxygen consumption ($\dot{V}O_2$) and pulmonary ventilation ($\dot{V}_E$) in response to various doses (plotted on log. scale) of noradrenaline. Details as in Fig. 1

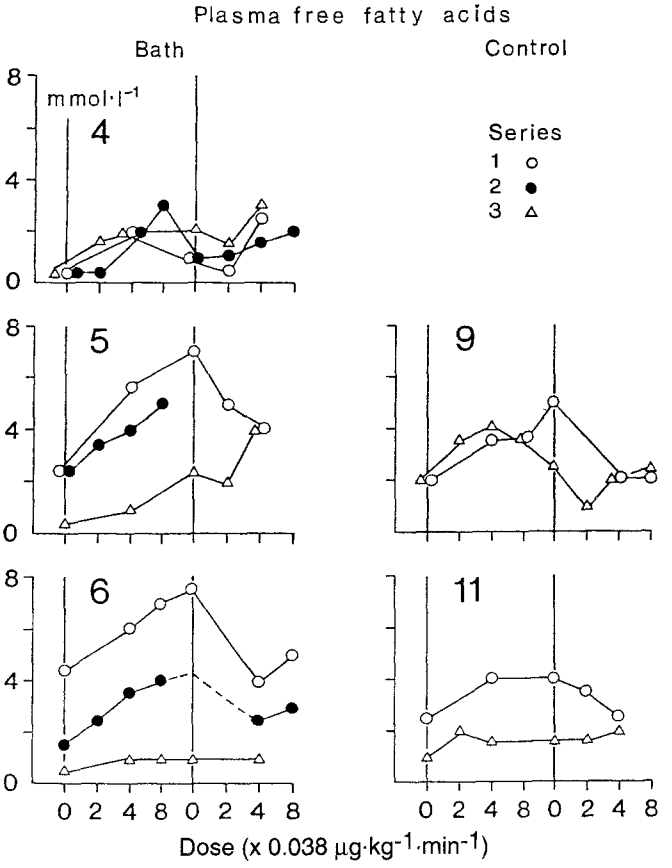

Fig. 4. Response of plasma free fatty acids to successive doses (plotted on log. scale) of noradrenaline. *Numbers* identify the subjects. *Each point* represents one observation

Metabolic responses

$\dot{V}O_2$ and $\dot{V}_E$. The NA caused a dose-related increase in $\dot{V}_E$ but not in $\dot{V}O_2$ (Fig. 3). There were no clear changes between series: inspection of primary data for $\dot{V}_E$ and $\dot{V}O_2$ showed that significant differences between series were due to a few unusually high or low values in the preceding control periods.

Fat mobilization. Figure 4 shows that increasing doses of NA were accompanied by a progressive increase in FFA that usually doubled or trebled their plasma concentrations in the first half of each test. The highest values mostly occurred in the control period immediately after the highest dose of NA, presumably because of a lag in the clearance of FFA (Steinberg 1966) – to which we also attribute the more variable response in the second half of the test. The AA and BHB responded in a similar manner, but the response of AA was small and in two subjects it was negligible. There were no consistent differences between series in the initial concentrations or the response to NA of either FFA, AA, or BHB.

Brown fat activation? The NA did not change skin temperature or heat flow at the nape of the neck, or skin temperature at the sternum, in any series.

Subjective responses

These were typical of NA (e.g. deep breathing, feelings of weight upon chest and abdomen) and they did not change between series.

Discussion

The main findings of this study were that in the bath group:
1. The pressor effect of NA decreased in S2 and subsequently increased in S3 to beyond its initial level
2. No comparable changes occurred in the responses of finger and toe temperature
3. The FFA were mobilised without any accompanying increase in $\dot{V}O_2$ and
4. No local warming that might have suggested activation of brown fat occurred at nape or sternum.

Cardiovascular responses

Reduced pressor response in S2. It must first be asked whether this change was simply the return to normal of a response that had been exaggerated in S1 by apprehension and nonspecific stresses – i.e. by "first-time effects" (Budd et al. 1993). The evidence would suggest this was not the case: the pressor response of the bath group did not remain low but subsequently increased in S3, and no comparable reduction occurred in the pressor response of the control group between their first and second tests (S1 and S3). On the other hand, the reduction and subsequent increase in the pressor response of the bath group to NA were accompanied by similar changes in their heat production and heat loss during whole-body cooling (Budd et al. 1993) and, like those changes, may reasonably be attributed to the development and decay of acclimatization.

The reduced pressor response in S2 confirms our previous observations (Budd and Warhaft 1966b) but differs from the unchanged pressor response which has been reported by Joy et al. (1963) and Kang et al. (1970). The differences might be due to differing levels of acclimatization, since acclimatization was not independently demonstrated by test cold exposures in either of those studies.

Increased pressor response in S3. The exaggerated pressor response in S3 of the bath group was not shared by the control group, and thus could not have been due to any experience common to both groups such as the Antarctic traverse or the seasonal change from summer to autum. It may have been related to the decay of the acclimatization induced by the bath treatment, for a comparable exaggeration in the decrease in T_{re} during cold exposure has been observed (Budd 1962, 1964) after the decay of natural acclimatization – even though the responses to cold in S3 of the present subjects (Budd et al. 1993) did not show this phenomenon.

Physiological mechanisms. The pressor effect of NA has been attributed to peripheral vasoconstriction in the presence of an unchanged or slightly reduced cardiac output (Eckstein and Abboud 1962). Within each series the dose-response curves of ΔBP_s, ΔBP_d, ΔT_{fi}, and ΔT_{to} thus reflect the intensity of peripheral vasoconstriction, that of Δf_c reflects the reflex bradycardia caused by the elevated BP, and that of ΔPP reflects the increased stroke volume which (assuming constant cardiac output) results from the bradycardia.

Between series, the simplest explanation of the changes in pressor response of the bath group would seem to be a reduced sensitivity of the peripheral blood vessels to NA at D4 and D8 in S2, and an increased sensitivity at all dose levels in S3. The parallel changes in ΔPP at D4 raise the possibility that changes in cardiac output, resulting from changes in stroke volume with an unchanged Δf_c, may also have been involved, but the different response patterns of ΔPP and Δf_c at D1, D2 and D8 make this unlikely.

Conditions under which responses to NA may be reduced or enhanced have been reviewed by Eckstein and Abboud (1962); in the present study the reduced sensitivity to NA in S2 of the acclimatized subjects may have been an adaptation to the elevated plasma concentrations of NA that would have accompanied each cold bath and were continuously present after acclimatization (Regnard et al. 1984).

Contrary to our previous finding (Budd and Warhaft 1966b), the reduced pressor response of the acclimatized subject was not accompanied by a lesser reflex bradycardia – possibly because it was balanced by a lesser chronotropic effect of NA on the myocardium (Eckstein and Abboud 1962). The lack of correlation between the changes in pressor response and those of ΔT_{fi} and ΔT_{to} confirms an earlier finding (Budd and Warhaft 1966b) and would suggest that the changing sensitivity to NA was confined to blood vessels in sites other than the skin, such as the skeletal muscles or viscera.

Metabolic responses

Oxygen consumption. The finding that the bath group did not develop a calorigenic response to NA differs from our previous observation of a small increase in naturally acclimatized men (Budd and Warhaft 1966b), but it is consistent with the response to whole-body cooling of the bath group (Budd et al. 1993) which provided no evidence of NST. Moreover, as Kang et al. (1970) have pointed out, the calorigenic responses to NA that have been reported (Joy et al. 1963; Budd and Warhaft 1966b; Kang et al. 1970; Itoh and Kuroshima 1972) in acclimatized or cold-conditioned humans have been so small (7%–17% of resting heat production), in comparison to the 100% increases that can occur in cold-acclimatized small mammals (Jansky 1973), that it is doubtful whether they indicate any significant development of NST. This conclusion is in keeping with the findings of eight studies in the Antarctic (summarised

in Budd 1989), which showed that natural acclimatization was insulative rather than metabolic and which found no evidence of NST.

Fat mobilization. Our finding that acclimatization did not change either the baseline values or the response to NA of plasma FFA and ketones (Fig. 4) would suggest that the contrary finding of Itoh and Kuroshima (1972) – lower baseline values and a greater mobilization of FFA and ketones in the Ainu than in controls from warmer regions – may have been due to a different pattern of acclimatization, or perhaps to associated factors unrelated to acclimatization. The finding that NA more than doubled our subjects' plasma concentrations of FFA and ketones without increasing $\dot{V}O_2$ is contrary to the suggestion of Itoh and Kuroshima (1972) that NA accelerates the oxidation of FFA in man, and it supports the conclusion of Steinberg (1966) that fat mobilization is not in itself the cause of a thermogenic response to NA.

Brown fat activation. Local warming in response to sympathomimetic agents has been attributed to NST in brown fat (Rothwell and Stock 1979; James and Trayhurn 1981), although Astrup et al. (1984) have concluded that it was due to increased blood flow. By contrast, in our subjects infused NA caused no increase in skin temperature or heat flow at nape or sternum, either before or after acclimatization. These findings are consistent with the responses to whole-body cooling of the bath group (Budd et al. 1993): nape and sternum cooled no less after acclimatization and changes in $\dot{V}O_2$ were adequately explained by the accompanying changes in shivering and muscle tenseness. The two present studies thus provide no support for the view that the adult human possesses functional brown fat and can develop NST.

In conclusion, this study has confirmed our previous report of a reduced sensitivity to the pressor effects of infused NA in cold-acclimatized men, and has in addition shown that

1. The reduced sensitivity is not a seasonal or first-time effect
2. It occurs in artificial as well as in natural acclimatization and
3. It is replaced by a hypersensitivity to NA when acclimatization has decayed.

The study has provided no evidence of NST: the effect of NA on plasma FFA and ketone bodies did not change with acclimatization, and at no time did NA increase $\dot{V}O_2$, or increase skin temperature or heat flow over reported sites of brown fat.

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