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Psychological Stress Does Not Affect Plasma Catecholamines in Subjects With Cardiovascular Disorder

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STANFORD, S. C., G. MIKHAIL, P. SALMON, D. GETTINS, S. ZIELINSKI AND J. PEPPER. *Psychological stress does not affect plasma catecholamines in subjects with cardiovascular disorder.* PHARMACOL BIOCHEM BEHAV **58**(4) 1167–1174, 1997.—Whereas the effects of cardiac transplantation on the catecholamine response to physical exercise have been studied previously, the impact on psychological stress is unknown. Here, the arterial catecholamine response to the Stroop test of patients with an orthotopic heart transplant (OHT) was compared with that in subjects who had received a coronary artery bypass graft (CABG) or who were in heart failure and destined for a heart transplant (HF). Subjects were tested whilst sitting and their usual drug therapy was maintained. The Stroop test increased subjects' subjective tension but did not affect arterial concentrations of adrenaline or noradrenaline in any group of subjects. Also, the concentration of both catecholamines was significantly higher in OHT and CABG subjects than in the HF group, but their relative concentration was unaffected by cardiovascular status or stress. It is concluded that the absolute concentrations of arterial catecholamines, but not their relative concentrations, depend on clinical status. Moreover, under these test conditions, subjects with a history of cardiovascular disorder do not show the normal catecholamine response to psychological stress. © 1997 Elsevier Science Inc.

Cardiac transplant Coronary bypass Heart failure Humans Plasma catecholamines Stress Stroop test

UNDER controlled conditions, changes in the concentration of plasma catecholamines can be used as an index of sympathoadrenal activation (12). This is consistent with the increase in circulating catecholamines induced by physical stress, such as strenuous exercise (30) and psychological challenges, such as the Stroop colour word conflict test (16). The Stroop test causes changes in subjective feelings of anxiety, cardiovascular performance, and forearm EMG activity that are all indicative of a stress response (28). Moreover, the cardiovascular response to this procedure resembles the classical "defense reaction" described by Folkow (13).

Hitherto, most studies of the effects of stress on plasma catecholamines have been carried out on healthy, young adults with no history of cardiovascular disease. Yet, posture, age (5,9), cardiovascular status (17,18,25) and even parental history of cardiovascular disease (14) are all known to modify sympathoadrenal function. Also, experimental conditions are usually stringently controlled so as to ensure low "basal" concentrations of catecholamines: the stress is generally imposed after subjects have experienced a period of supine rest, for instance. Little is known about the extent to which any of these factors influence the peripheral catecholamine response to psychological stress.

The possibility that this response is disrupted in subjects with a transplanted heart is particularly intriguing. This might be predicted because decentralization of the innervation of

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the donor heart is an unavoidable consequence of the surgical procedure. Evidence that this is the case comes from studies of heart-lung transplant subjects experiencing passive "head-up tilt" or strenuous exercise on a bicycle ergometer. The increase in forearm venous noradrenaline in the subjects was appreciably greater than in unoperated, healthy subjects (3,4). It was inferred that the sympathetic response to the haemodynamic demands of exercise is increased after a heart transplant. However, these findings could rest on changes in local sympathetic neuronal activity, unrelated to any changes in other elements of the sympathoadrenal system (20). Also, it remains unclear whether this exaggerated sympathetic response generalizes to other forms of stress with no overt haemodynamic burden.

Other evidence supports the prediction that the sympathetic response to stress is abnormal in heart transplant subjects. Whereas the magnitude of the haemodynamic response to psychological stress in transplant subjects was similar to that in healthy control subjects and subjects with a renal transplant, its latency was increased. It was inferred that the peripheral catecholamine response to psychological stress in heart transplant subjects relies on the increased, albeit delayed, secretion of catecholamines from the adrenal medulla to a greater extent than that in the control subjects (26).

The main aim of the present experiments was to test the ensuing prediction that the peripheral catecholamine response to psychological stress is abnormal in subjects who have received an orthotopic heart transplant (OHT). To control for the effects of remedial cardiac surgery and decentralization of cardiac innervation, two additional experimental groups were included in the study: subjects with a coronary bypass graft (CABG) and patients suffering heart failure, of miscellaneous aetiology, who were awaiting a donor heart (HF). Because all measurements were carried out under identical conditions, these experiments also enabled direct comparison of resting plasma catecholamine concentrations in these different groups of subjects.

Adrenaline and noradrenaline concentrations were measured in samples taken from arterial blood. This was because catecholamine concentrations in such samples, like those in mixed venous samples, are thought to provide a more reliable index of systemic sympathoadrenal activation than those measured in peripheral venous samples (20,21). Finally, to fulfill wider objectives of the study, it was considered essential to investigate the effects of psychological stress under conditions that mimic as closely as possible subjects' normal routine. For this reason, no attempt was made to artificially reduce the basal concentrations of the amines: subjects were studied while sitting (rather than supine) and their normal drug regimen was maintained.

The present results form part of a larger multidisciplinary study that incorporated psychometric testing and evaluation of subjects' cardiovascular function during the stress. These broader aspects of the study will be the subject of separate reports.

METHOD

Subjects

All experimental procedures were approved by the Hillingdon District Ethics Committee and informed consent was obtained from all subjects. Age matching across the different experimental groups was not feasible because subjects with a coronary bypass were generally older than those who had been given, or were waiting for, a heart transplant. It was also not possible to balance gender across the three groups because of the greater incidence of cardiovascular disease in male subjects.

General criteria for exclusion of any subject from the study were: less than 20 or more than 75 years of age; evidence of previous or concurrent psychiatric illness; insufficient understanding of English to complete the psychometric questionnaires (not reported here); insulin-dependent diabetes; and persistent, clinically defined neurological disorder.

Criteria for excluding transplant subjects were: concurrent treatment for acute rejection; more than one transplanted organ (e.g., kidney or liver); and coronary artery disease. Subjects in the heart failure group, who were recruited from the cardiac transplant waiting list, were excluded if there was evidence of renal or hepatic dysfunction.

Inclusion criteria for heart transplant subjects were those who had undergone an orthotopic heart transplant not less than 6 months previously and who had not experienced an episode of rejection, or serious infection, for at least 3 months before the test. In the bypass group, subjects were included only if they were angina free in their normal daily lives. All HF subjects fulfilled established criteria for the New York Heart Association (NYHA) class III and IV dypsnoea.

Subjects were recruited either during their routine attendance at their respective out-patient clinics or by telephone. Only two subjects in the OHT group had an infection at the time of testing: one with Epstein Barr Virus, and the second with an unidentified viral infection. Recent infections were also reported in two subjects in the heart failure group (influenza and a chest infection within 2 days and 2 weeks of the study, respectively).

Profiles of the subjects and the samples collected are given in Table 1. Cancellation by the subjects was attributed, most commonly, to difficulties with transport to the centre ($n = 45$). Of the subjects who presented for testing, a small number of studies were canceled, or aborted, for technical reasons. These included: failure to implant an arterial line ($n = 38$), computer failure ($n = 8$), or use of the study area for emergency intensive care of other patients ($n = 8$). One subject experienced a vasovagal attack during the test and the study was discontinued. In no other subjects were medical complications experienced during the procedure. The normal schedule for subjects' drug therapy was maintained on the day of the study (summarised in Table 2).

Preparation for the Stroop Test

The experiment was carried out in a side room of the Intensive Care Unit at Harefield Hospital. Subjects were seated in a comfortable chair in front of a video display unit (VDU) and a small electronic control panel was placed on the table in front of them. Every subject was given a full explanation of the task they were about to undertake. They were told that they were about to undergo a period of relaxation followed by a test of mental speed; this was described in a way intended to minimize stress to the subject.

After subjects had given informed consent, they were interviewed about their drug history, general health, mobility, and occupation. They were then given an explanation of the procedure to follow and a radial arterial catheter was implanted into the nondominant arm for blood sampling. ECG electrodes were also attached for continuous monitoring (not reported here). Subjects were then allowed a recovery period of 40 min, during which time they completed psychological questionnaires, including the tension scale of the Profile of Mood States (23). Immediately before the start of the stress

TABLE 1
SUMMARY OF RECRUITED PATIENTS AND INVENTORY OF SAMPLES

	OHT	CABG	HF
Time since cardiac surgery (months) mean ± SEM	42.2 ± 3.9	23.7 ± 1.5	N/A
Gender			
M	45	40	30
F	5	10	5
Mean age at study (years) ± SEM	50 ± 2	59 ± 1	52 ± 1
Number of plasma samples collected	56	67	42
Plasma catecholamines measured	50	50	35
Sample storage time (days): (median and interquartile range)	27 (18–52)	25 (16–41)	35 (26–57)

N/A: not applicable.

test, subjects were given a headphone set, to occlude extraneous noise, through which they heard a buzzer during the Stroop test. The buzzer sounded if the key response was incorrect or if no key was pressed within 1 s (see below). During all phases of the test, the experimenter sat behind a screen so that there was no interaction with the subject, apart from during withdrawal of blood samples. All phases of the Stroop test were fully automated and controlled by microcomputer which also recorded subjects' errors.

The Stroop Test

Following on-screen instructions, which subjects could read at their leisure, there was an initial relaxation phase of 10 min, during which subjects viewed a kaleidoscope colour sequence on the VDU. At the end of this period, subjects again completed a mood questionnaire. This was followed by a further set of instructions on the Stroop colour word conflict task, which was used to induce the psychological stress: colour names were presented, on the VDU, in either the named or a different colour. The onset of the test was governed by the subject who pressed a start button when ready. The task was to press one of two keys on the electronic panel to indicate whether the colour name and the colour in which the name was displayed were the same or different. The pace of the presentation was set at one word/s so that an entirely correct performance was beyond all subjects' capability. Subjects were told that every mistake would be penalized by addition of an extra word to the test. In fact, the test was always of the same duration (10 min). Subjects' self-esteem was threatened further by

TABLE 2
SUMMARY OF PATIENTS' DRUG THERAPY

Drug Therapy	OHT	CABG	HF
Immunosuppressants: azathioprine, cyclosporin, steroids	113 (100)	0 (0)	0 (0)
'Cardiac' drugs: ACE inhibitors, amiodarone, Ca^{2+} channel blockers, β-blocker, digoxin, dipyridamole, hydralazine, indoramin, nitrates, prazosin, diuretics	51 (66)	23 (32)	114 (97)
Antidiabetic agents: glicazide, metformin, glibenclamide	2 (4)	2 (4)	1 (3)
Antidepressants: tricyclics, SSRIs	0 (0)	2 (4)	1 (3)
Anxiolytic/hypnotics: benzodiazepines	1 (2)	1 (2)	5 (14)
NSAIDs: aspirin, coproxamol, ibuprofen, paracetamol, voltarol	34 (66)	46 (92)	14 (40)
Antihypercholesterolaemia and antihyperlipidaemia: simvastatin, bezalip, pravastatin	11 (22)	15 (30)	4 (11)
Others: acyclovir, allupurinol, aminophylline, antacids, antiasthma (steroids, salbutamol), Ca^{2+}, disodium etidronate, Fe^{2+}/Folate, H_2 antagonist, laxatives, mesalazin, metaclopramide, nystatin, prednisolone, quinine, septrin, sucrafalate, thyroxine, warfarin	53 (48)	21 (8)	53 (80)

Total number of drug treatments in group (for each patient, each drug scores as '1'). Numbers in parentheses indicate the percentage of subjects receiving at least one drug treatment from each group.

telling them that their scores would be compared with those of other subjects at the end of the experiment. The Stroop test was followed by a further set of instructions, after which a third mood questionnaire was completed within 2 min. A 10-min recovery period followed, during which the subject watched the kaleidoscope sequence again. Immediately after this, and after reading a further set of instructions, subjects were asked to complete a final mood questionnaire.

Plasma Samples

From each subject, a total of eight arterial blood samples were withdrawn at fixed time intervals during the relaxation, stress and recovery periods. Sample 1 was taken immediately before the start of the preparatory relaxation phase of the procedure (not less than 40 min after insertion of the catheter) and after subjects had completed the first mood questionnaire. Further samples were withdrawn, starting at 5 and 9.5 min after the onset of this relaxation phase (samples 2 and 3); 5 min and 9.5 min after the start of the Stroop phase of the test (samples 4 and 5); and, finally, 1.5, 3, and 8 min (samples 6, 7, and 8) during the post-Stroop recovery period. The blood samples were collected into heparinized tubes and stored at 4°C until the end of the test, after which they were centrifuged immediately to separate the plasma. All samples were stored at −80°C before chromatographic analysis. Interfering peaks on the chromatogram prevented measurement of plasma catecholamines in a small number of plasma samples from all groups; all samples from these subjects were discarded (total number of subjects affected: OHT 6; CABG 7; HF 2). Samples from a further 10 subjects from the bypass group and 5 subjects from the heart failure group thawed in transit for neurochemical analysis and were also discarded.

Neurochemical Analysis

Adrenaline and noradrenaline were extracted from the plasma samples by alumina adsorption using dihydroxyphenylbenzylamine as an internal standard. The amine content of the extracts was measured by reverse-phase high-pressure liquid chromatography with electrochemical detection. Separation was achieved on a Hypersil ODS 5 mm column (25 × 4.6 mm; Jones) with a citrate acetate-buffered mobile phase (pH 5.8) containing 10% methanol and 0.6 g/l of the ion pair agent, octanesulphonic acid. The buffer was isocratically pumped through the system at 1.0 ml/min. Eluted catecholamines were detected with an amperometric detector (BAS 4A) set at an oxidizing potential of +450 mV. Chromatograms, calibrated with external standards, were relayed to a chart recorder where peak height was used to quantify the concentration of catecholamines. The amine concentration of the plasma samples was expressed in pmol/ml of plasma (nM) after correction for recovery. The maximum sensitivity of the system was approximately 25 fmol/50 μl plasma extract and the coefficients of variation for the concentrations of adrenaline and noradrenaline across all groups of samples were 0.06 and 0.05, respectively.

Data Analysis and Statistics

The effects of the Stroop test on plasma catecholamines in different groups of subjects were assessed on $\log_{10}$ transformed data using one- or two-way ANOVA (repeated measures) with sample or questionnaire number as the within-subject factor and subject group as the between-subjects factor. The significance of differences in plasma catecholamines, both within and between subject groups, was evaluated by the Newman–Keuls multiple comparison test.

For each plasma sample, the ratio of ($\log_{10}$ transformed) concentration of noradrenaline:adrenaline was calculated. Mean ratios were compared between the three phases of the test (relaxation phase, Stroop test, and recovery period) and between-subject groups, using ANOVA. The Pearson correlation coefficient was used to evaluate the association between $\log_{10}$ transformed concentrations of plasma noradrenaline on adrenaline in each phase of the test, for each group, separately. Because all correlations turned out to be statistically significant, least-squares regression analysis was carried out to estimate the regression coefficient (noradrenaline on adrenaline) for each subject, for each phase of the test. Criterion for statistical significance was $p < 0.05$.

Reagents

The following chemicals were used to prepare the mobile phase for the HPLC: methanol and acetonitrile (Hypersolve chromatography grade: BDH); octane-sulphonic acid (Sigma Chemical Company). Dihydroxyphenylbenzylamine hydrobromide, l-arterenol bitrartrate and l-epinephrine (free base), used for preparing standards, were all purchased from Sigma Chemical Co. (UK). All other reagents (AnalaR grade) were purchased from BDH.

RESULTS

Psychological Response to the Stroop Test

All groups responded to the Stroop test with an increase in subjective tension (Table 3). There was a significant effect of questionnaire number, $F(3, 486) = 65.33$, $p < 0.001$, but no group × questionnaire interaction, $F(6, 486) = 0.57$, $p = 0.752$.

Effects of Subject Group and the Stroop Test on Arterial Concentrations of Catecholamines

During the initial relaxation phase, the mean plasma concentrations for adrenaline were (nM): OHT, 2.54 ± 0.17; CABG, 3.04 ± 0.32; HF, 1.38 ± 0.2. Equivalent noradrenaline concentrations were: OHT, 5.86 ± 0.41; CABG, 4.92 ± 0.38; HF, 2.57 ± 0.24. Across the sequence of eight samples taken during the test procedure, there was a main effect of subject group for both adrenaline, $F(2, 131) = 3.79$, $p < 0.001$, and noradrenaline, $F(2, 132) = 13.49$, $p < 0.001$ (Fig. 1). At every point in the time course, the arterial concentrations of noradrenaline and adrenaline in OHT and CABG subjects were significantly greater than in the HF group. However, there was

TABLE 3

SUMMARY OF TENSION SCORES IN THE PROFILE OF MOOD STATES ADJECTIVE CHECKLIST

Questionnaire	OHT	CABG	HF
Baseline	3.57	3.78	4.6
Prestress	2.3	2.85	3.57
Poststress	5.39	3.57	7.5
Recovery	2.41	2.97	4.14

Values show mean tension scores for the three groups of subjects: orthotopic heart transplant (OHT); coronary bypass graft (CABG); heart failure (HF). The pooled S.E.D. for comparisons of questionnaires was 0.285.

no effect of sample number, indicating that the Stroop test did not affect the plasma concentrations of either adrenaline or noradrenaline in any of the three groups of subjects (Fig. 1).

Relationship Between Concentrations of Arterial Plasma Noradrenaline and Adrenaline

There were no significant differences between the three groups of subjects in the ratio of noradrenaline: adrenaline concentration during the relaxation phase. These were: OHT, 4.16 ± 0.47; CABG, 3.02 ± 0.32; HF, 3.43 ± 0.37. Also, the ratios did not differ, either between subject groups or between the three phases of the procedure (Fig. 2). This close association between the concentrations of arterial noradrenaline and adrenaline is underlined by the statistically significant correlation between the plasma concentrations of the two catecholamines in all phases of the test (Table 4). There was no effect of subject group, or phase of the test procedure, on the regression coefficient, and there was no interaction between these two factors. Scatterplots pooled over all three phases of the test are shown in Fig. 3 for each subject group.

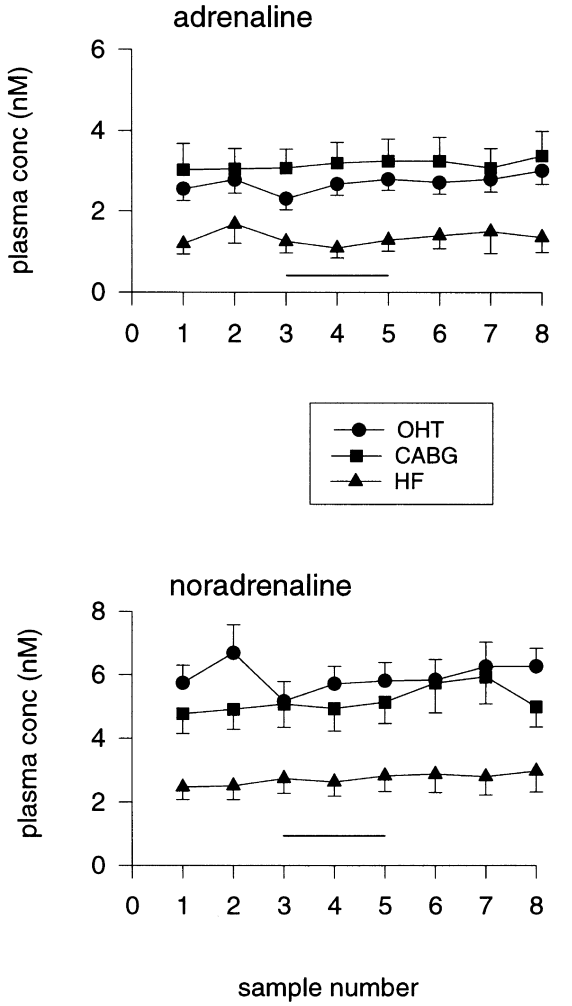

FIG. 1. Points and error bars show mean ± SEM plasma catecholamine concentrations (nM). Collection of three samples during the preparatory, relaxation phase were started at times 0, 5, and 9.5 min, i.e., before subjects were exposed to the Stroop test. Further samples were taken during the stress period (indicated by horizontal bar), starting at 5 min and 9.5 min after the start of the Stroop test. Collection of the final three samples started at 1.5, 3, and 8 min after the onset of the 'post Stroop' recovery phase. Number of subjects = 50 (OHT and CABG) or 35 (HF).

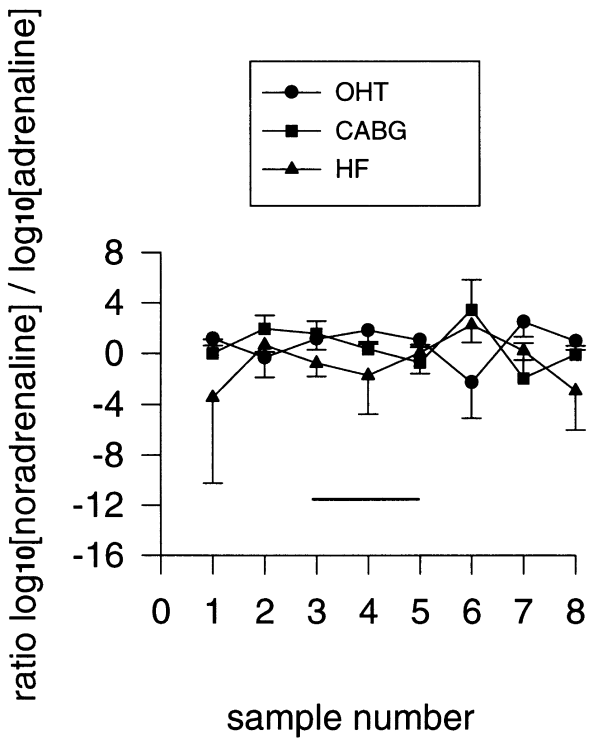

FIG. 2. Ratios of arterial plasma noradrenaline: adrenaline in different groups of subjects during the Stroop Test. Values show mean ± SEM for ratios of $\log_{10}$ transformed data. The stress phase of the Stroop test is indicated by the horizontal bar.

TABLE 4

ASSOCIATION BETWEEN CONCENTRATIONS OF ARTERIAL PLASMA NORADRENALINE AND ADRENALINE

Phase of Test	Sample Cluster	Group	Correlation (r)	Mean Regression Coefficient ± SEM
Relaxation	1–3	OHT	0.366	0.324 ± 0.067
		CABG	0.716	0.603 ± 0.048
		HF	0.564	0.501 ± 0.073
Stress	4–5	OHT	0.369	0.288 ± 0.074
		CABG	0.588	0.588 ± 0.060
		HF	0.553	0.562 ± 0.102
Recovery	6–8	OHT	0.304	0.261 ± 0.067
		CABG	0.736	0.667 ± 0.050
		HF	0.611	0.616 ± 0.078

Correlation coefficients, for noradrenaline on adrenaline, were calculated from $\log_{10}$ transformed data for samples taken: before the Stroop test (samples 1–3); during the Stroop test (samples 4 and 5); and during the recovery period (samples 6–8). In all cases the correlation coefficient was significant at $p < 0.001$. Regression coefficients were calculated, for each subject, for each phase of the test. Values show mean ± SEM for all the subjects within each group.

DISCUSSION

It is widely agreed that the Stroop test increases the concentration of venous and arterial catecholamines (2,15,21, 22,28). One exception is a report that noradrenaline is not increased significantly until after cessation of the test (1). However, most studies of this type have been carried out on healthy, young subjects after a period of supine rest (16,21). There are few reports of the effects of psychological stress, including the Stroop test, on plasma catecholamines in subjects with a cardiovascular disorder.

In the present study, psychometric testing confirmed that all groups of subjects responded to the Stroop test with an increase in subjective feelings of tension. Yet, in none of the three groups of subjects was there any significant change in the concentration of arterial adrenaline or noradrenaline during either the Stroop test or the recovery period. One previous study of subjects with coronary artery disease (such subjects were excluded from the present study) also failed to find any arterial adrenaline response during a mental arithmetic test and only a small (28%) increase in arterial noradrenaline (31). Another attempt to measure changes in plasma catecholamines, resulting from the Stroop test, in subjects with a cardiac transplant was unsuccessful (26). It seems that, although there is overwhelming evidence for an effect of the Stroop test in healthy, supine subjects, there is no convincing evidence that psychological stress has any impact on circulating catecholamines in subjects with a history of cardiovascular disorder.

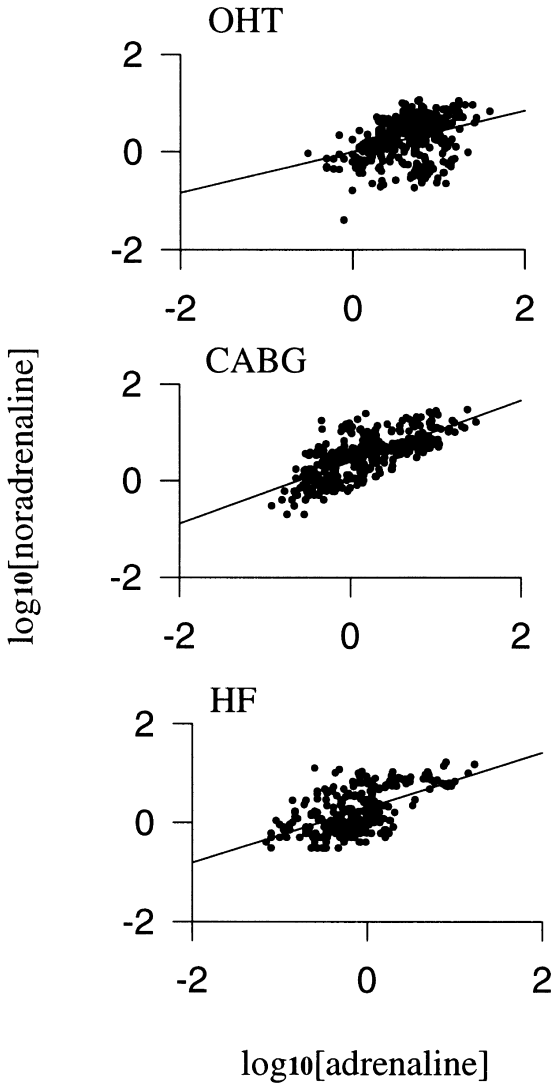

FIG. 3. Scatterplots showing the relationship between the $\log_{10}$ transformed concentrations of arterial plasma noradrenaline and adrenaline. Each plot comprises all samples collected from every subject within the group.

A further finding was that, insofar as estimates can be compared across different studies [see (19)], the concentrations of both adrenaline (approximately 1–3 nM) and noradrenaline (approximately 2–6 nM) in all three groups of subjects recruited into the present study were higher than those reported for healthy young subjects. For adrenaline, typical venous concentrations in supine, healthy subjects are within the range of 0.05–0.44 nM (6,16). The concentration of arterial adrenaline, including the brachial artery, also falls within this range [0.39–0.43 nM: (18,22)]. Estimates of venous noradrenaline concentrations normally range from 0.6 nM (8) to 3.9 nM (3), while arterial noradrenaline levels are usually in the range of 1.2–1.7 nM (7,11).

An obvious factor that could explain why catecholamine levels in this study seem higher than are normally reported rests on the clinical status of the subjects. It is well known that heart failure increases the concentration of plasma catecholamines in both arterial and venous samples. In subjects from whom drug treatment had been withdrawn, adrenaline concentrations of about 1.0 nM have been reported (18,25); this falls within the range of values reported here. For noradrenaline, arterial concentrations of approximately 3 nM have been reported in subjects with therapeutic support withheld (16). Again, this is similar to the values found in the present subjects. In one report where drugs were not withdrawn, an even higher venous concentration was found [8.9 nM: (27)]. It is likely that the high concentrations of plasma catecholamines found in the present study can be attributed to a combination of factors such as the age of the subjects (5), their pharmacotherapy, and the fact that they were not supine during the procedure.

It remains to be explained why no stress response was evident in any of these groups of subjects. A ceiling effect could account for the lack of an increase in the concentration of adrenaline during stress: the resting concentrations found in the present study were similar to those seen after a bout of treadmill exercise in healthy subjects [3.6 nM: (17)]. However, this cannot explain why no changes in noradrenaline levels were observed. There are many reports that venous noradrenaline concentrations can attain levels as high as 14–22 nM [e.g., (6,17,30)]. Such concentrations have even been found in transplant subjects during physical exercise on a bicycle ergometer (24).

Collectively, these findings suggest that the catecholamine response to psychological stress is evident only under rigorous experimental conditions (rested, drug-free, young, healthy subjects), which ensure a low basal secretion of these neuroendocrine factors. Consequently, the catecholamine response to psychological stress could be regarded as an artefact, in that it is normally masked by higher concentrations of basal plasma catecholamines. It follows that the widely reported catecholamine response to psychological stress might not be of appreciable biological importance in normal daily life.

An additional finding was a significant correlation between the concentrations of adrenaline and noradrenaline in all three groups of subjects. Moreover, this relationship was constant throughout the procedure and across groups. It is remarkable that the relative amounts of these two amines in the plasma is so constant, especially in view of the striking differences in their concentration in the different groups of subjects. Previous reports have also noted a significant correlation between the plasma concentrations of these two catecholamines in both healthy subjects (17) and in subjects with heart failure (25). A previous estimate of the correlation coefficient [0.393: (25)] is remarkably similar to that reported here. The present results extend these findings in two ways. First, they show that similar correlations are found in subjects with heart failure and after remedial surgery for cardiac disease (coronary bypass or transplant), as well as in healthy subjects. Second, they suggest that, even in subjects with a decentralised cardiac innervation, this relationship is not significantly altered by psychological stress. This supports evidence that only a small proportion of arterial noradrenaline (approximately 3%) is derived from the heart (10) and further undermines early theories that an adrenaline response predominates in psychological stress [see also (29)].

In conclusion, the peripheral catecholamine response to the psychological stress of the Stroop test is not expressed in any of the three groups of subjects studied here. For noradrenaline, at least, this is unlikely to be due to a ceiling effect. Finally, it seems that the concentrations of arterial adrenaline and noradrenaline are closely related and this relationship is not disrupted by either psychological stress, a history of cardiovascular disorder, or decentralisation of the innervation of the heart.

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