

SEX DIFFERENCES IN CATECHOLAMINE REACTIONS TO STRESS AND ITS RELEVANCE  
TO CORONARY HEART DISEASE

Lorenz J.P. van Doornen and Dorret I. Boomsma

Vrije Universiteit  
Department of Psychology  
Psychophysiology Division  
De Boelelaan 1115  
1081 HV Amsterdam, The Netherlands

ABSTRACT

The present paper presents an overview of studies dealing with sex differences in catecholamine reactivity. Evidence suggests that under stressful conditions males show a larger catecholamine response than females. The strongest evidence for a sex difference in catecholamine reactivity exists for adrenaline (epinephrine), but sex differences in noradrenaline (norepinephrine) have also been observed. These differences in catecholamine reactivity may be related to the way men and women cope with stress, to differences in personality (for example type A behavior), to sex hormones, or to genetic influences on catecholamine reactivity. In addition, it is possible that a difference between males and females in catecholamine reactivity can explain part of the observed difference in mortality due to coronary heart disease. In the first part of this article evidence for a sex difference in catecholamine reactivity is reviewed. Next, the influences of age, sex hormones, genetic factors and type A behavior are discussed. Finally, arguments are put forward for the relevance of catecholamines to (sex differences in) coronary heart disease.

SEX, STRESS AND CATECHOLAMINES

In a recent experiment conducted in our laboratory (van Doornen, 1984) adrenaline and noradrenaline excretion was measured in 29 male and 23 female students. Measurements were taken on three different days: just before the students were going to take an

exam, before and after they performed a series of laboratory tasks (a reaction time avoidance task, a tracking task and a cold-pressor test) and on a control day. Measurements always took place at ten o'clock in the morning. The results (Figure 1) indicated that there were no sex differences for adrenaline on the control day. On the examination day males had significantly higher adrenaline levels. On the control day female students had significantly higher noradrenaline levels, but this difference tended to disappear on the examination day.

For the laboratory tasks (Figure 2) there was a significant increase in adrenaline in males; the increase in females did not reach statistical significance. At the beginning of the experimental session females again had higher noradrenaline levels. This difference in noradrenaline disappeared because males showed an increase in noradrenaline and females a decrease. Neither the increase nor the decrease was significant. The interaction of sex by periods was significant, however.

Most research concerning sex differences in catecholamine responsivity comes from Sweden. Johansson (1972) studied catecholamine excretion in a group of 99 boys and 78 girls with an average age of 12 years. Measurements were taken after an emotional neutral film of 42 minutes and a subsequent period of mental arithmetic of equal length. Looking at the change from film to arithmetic, the adrenaline excretion in boys increased significantly more than in girls. The sexes did not differ during the passive film period. Girls performed better on the arithmetic tasks and scored significantly lower on a scale measuring "apprehension for schoolwork".

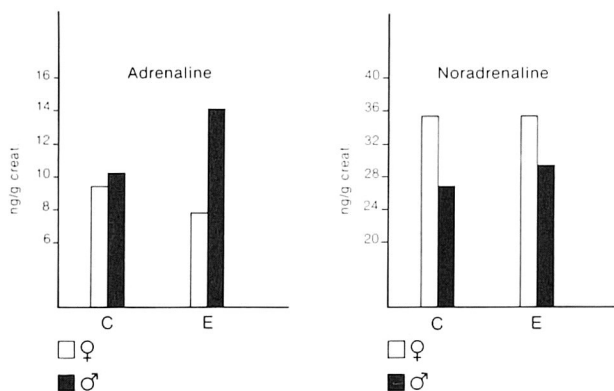


Figure 1. Adrenaline and noradrenaline levels of female and male students on the day of an exam (E) and on a control day (C).

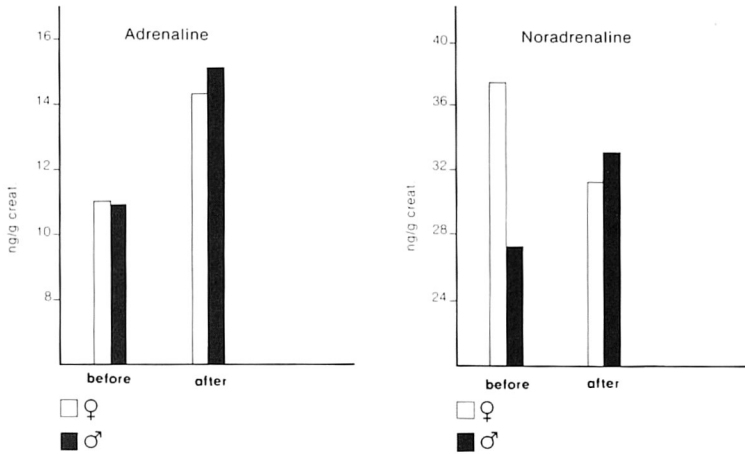


Figure 2. Adrenaline and noradrenaline levels of female and male students, before and after a series of laboratory tasks.

Johansson and Post (1974) obtained reliable data by taking 24-hour urine samples once a month during a year, from 11 females and 13 males, working in the same factory. To induce stress they had their subjects fill out a test battery which contained an intelligence test. There appeared to be no difference in adrenaline excretion during daily work routine, but on the stress day the adrenaline excretion in males was significantly higher than in females. The noradrenaline concentrations in both conditions did not differ.

Frankenhaeuser, Dunne and Lundberg (1976) compared two kinds of stressors to a control condition: a passive stressor (a venous blood sample) and an active one (the Stroop test). No sex differences were observed in the control condition. For both kinds of stressors the adrenaline excretion was elevated in boys and did not rise in girls. Boys and girls did not differ in their rating of the aversiveness of the situation. Although the results point in the expected direction, they did not reach statistical significance because of the small number of subjects and the large interindividual variations in catecholamine excretion.

Frankenhaeuser, Rauste-von Wright and Collins (1978) collected urine samples from students, aged 18 and 19 years, during and immediately after a six-hour examination. The control condition was an ordinary school day. For both male and female students adrenaline level was elevated on the stressful day, but significantly more so in the males. Only in males noradrenaline rose signifi-

cantly. The sex difference, however, was not significant. Catecholamine levels on the control day did not differ. Because examination success was the same for males and females the authors concluded that "...females tend to deal with psychological demands in a psychophysiological more economic way."

These results were confirmed by Lundberg and Forsman (1979): no sex differences in a resting condition (reading newspapers), but positively so after a Stroop test. In males adrenaline excretion increased significantly more in reference to the base level than in females. Recently, these results were replicated by this same research group, using a choice reaction time task (Frankenhaeuser, Lundberg and Forsman, 1980): 24 male students responded significantly stronger than 24 females. In this case the difference can also hardly be ascribed to a difference in task attitude. Males and females chose the same work pace and committed an equal amount of errors.

Sanchez et al. (1980) studied plasma catecholamine levels in a group of 6 female and 9 male students during rest and a subsequent 5 minute period of sustained isometric contraction. No sex differences were observed at rest. During exercise catecholamine levels increased in males, but were essentially unaffected in females. The only significant sex difference was observed for adrenaline during the first minute of the test. There were no differences between men and women in the duration of hand grip.

Lundberg (1983) measured catecholamine excretion in 15 boys and 11 girls between 3 and 6 years of age. Urine samples were taken on an ordinary day in a day-care centre and on a day at home. At-home boys showed significantly higher adrenaline and noradrenaline levels than girls, while at the day-care centre they only showed higher noradrenaline levels. In both boys and girls adrenaline excretion at the centre was significantly higher than at home.

In a recent experiment of Forsman and Lindblad (1983) blood samples were taken just before, during and after subjects performed a Stroop Test. Subjects were 6 men and 6 women with an average age of 25 years. The adrenaline level of males during the task period was significantly higher than that of females. In the pre-task period males already had nearly significantly higher adrenaline levels. So it is possible that the sexes did not really differ in reactivity to the test. There was no significant effect for noradrenaline.

Based on these studies, it seems justified to conclude that males are sympathetic adrenergic more reactive to stress than females, especially with respect to adrenaline.

## THE CRITICAL ROLE OF THE KIND OF SITUATION

Because people are on the average more often in "normal" than in stressful circumstances, it seems important to study sex differences in more or less basal conditions. The definition, however, of "basal conditions" differs largely between studies, from "the average value across a year of labor" to "a routine school day". Moreover, the sex differences in resting conditions in the above-mentioned experiments are often not separately statistically tested. After an inspection of the represented means in the tables or the graphs, we preliminary conclude that there is no sex difference under "normal circumstances". However, "normal circumstances" probably should not be equated to real basal conditions. An experiment in which males and females were compared under real basal conditions produced a surprising result. Cuche et al. (1975) measured catecholamines in 10 females and 10 males during three days of strict bed rest. The urine noradrenaline concentration was higher in females. Adrenaline showed no sex difference. Furthermore, the noradrenaline reaction to assuming a sitting position was larger in males, leading to the disappearance of the sex difference. This suggests that females in "real basal conditions" are adrenergically more active. This suggestion seems to be supported by the results of Lundberg et al. (1981). They compared 3-year old boys and girls and their parents on different points of time during the day, on two different days and places: at home and in the hospital. The morning urine samples pointed to higher adrenaline and especially noradrenaline values in girls than in boys. At the other measuring points the sex difference was reversed. The differences were not significant and the groups were small, so replication is desirable. The mothers had higher morning noradrenaline levels than the fathers. This difference was the same in the other observations both at home and in the hospital. Presumably, the reason for this unchanged pattern is that women were relatively more active in the household and were more actively involved in taking care and playing with the children in the hospital. In two conditions we also observed women to have higher noradrenaline morning levels (Figure 1 and 2). Lundberg et al. suggest that these higher values reflect nocturnal adrenergic activity.

It is clear that the situation in which catecholamine activity is measured is crucial for the kind of sex difference observed. Based on the literature presented thus far the following hypotheses may be formulated:

- Under real basal conditions females tend to have a higher adrenergic activity level.
- In daily life conditions this difference disappears because of a higher male reactivity.
- In stressful circumstances males show a higher adrenergic activity level.

Whether a sex difference will appear in adrenaline or noradrenaline

depends on the kind of stress situation. Mental effort mainly has an effect on adrenaline, while physical effort mainly influences noradrenaline (Fibiger, Singer and Miller, 1984). Research is needed in which three factors should be systematically manipulated; i.e. the amount of "real basality" of a resting condition, the amount of physical load (leading predominantly to noradrenaline reactions) and the amount of mental load and emotionality (leading predominantly to adrenaline reactions).

## THE ROLE OF AGE

Both catecholamine level and reactivity seem to be a function of age. Dalmaz and Peyrin (1982) studied developmental changes of catecholamines and their main metabolites in urine of females and males from 1 day to 40 years of age. Here we only report their results for adrenaline and noradrenaline. In the first month of life, girls excreted higher amounts of adrenaline and noradrenaline than boys. No sex differences were observed for these hormones in the age group 1 to 3.5 months or in adolescents. Adult women had lower noradrenaline levels than males. It has been suggested that the noradrenaline reactivity to stress increases with age (Palmer, Ziegler & Lake, 1978). Ziegler, Lake and Kopin (1976), however, found that the absolute increase in noradrenaline plasma after isometric exercise correlates with age, but that noradrenaline increase expressed as a percentage does not. In two groups of male subjects in their fifties and seventies, Fauchoux et al. (1981, 1983) found that adrenaline and noradrenaline baseline levels were lower in the older age group. During stress adrenaline levels increased by the same percentage in both age groups, but came back to pre-stress levels more slowly in the older age group. Noradrenaline excretion rose significantly in the older age group only. Whether these findings apply equally to both sexes is unclear. Aslan et al. (1981) measured catecholamine excretion in males and females of two different age groups, of about 30 and about 60 years old. The Stroop test was used as a stressor. In reaction to this test adrenaline excretion increased in all age-sex subgroups, except in the group of young females. Thus, adrenaline hypo-reactivity might be limited to relatively young females. Noradrenaline levels only increased significantly in both older groups. This is in agreement with the findings of the studies cited above. Sex differences in adrenaline excretion were significant in the younger age group, for noradrenaline they were significant in the older group. In both cases males were more reactive. The groups in this study were small, 5, 7, 9 and 12, subjects and the statistical analyses incomplete. The results need replication in a larger study in which the interaction between sex and age with regard to both adrenaline and noradrenaline is investigated in more detail. These data may be important from the perspective of the decreasing sex difference in coronary heart disease incidence with increasing age.

## PERFORMANCE AND SUBJECTIVE STATE

It is interesting to know whether the larger adrenaline reactions of males to stressful situations merely reflect sex differences in task performance or subjective state. In the studies summarized above no differences between males and females were observed for examination success (Frankenhaeuser, Rauste-von Wright & Collins, 1978), for performance in a reaction time task (Lundberg & Forsman, 1979; Frankenhaeuser, Lundberg & Forsman, 1980), or during isometric exercise (Sanchez et al., 1980). Johansson (1972) even observed a better performance of females on a mental arithmetic task. In the study by Johansson and Post (1974) females obtained higher scores on an intelligence test. Frankenhaeuser, Rauste-von Wright and Collins (1978) measured "discomfort", "effort" and "sense of success". No consistent sex differences were apparent in any of these variables. In our own experiment males and females did not differ with respect to performance in the reaction time task (reaction times and number of errors) and with respect to state-anxiety score on the examination day. It would seem then, that females at lower psychophysiological costs obtain an equal or even better performance than males. Holmes, Solomon and Rump (1982) also furnished support for this assumption measuring heart rate during a challenging IQ test. The female performance was better, their heart rate reaction to this task however was the same as in males.

## TYPE A BEHAVIOR PATTERN

Type A is the most commonly used description of coronary prone behavior. Elements of type A are a high activity level and achievement orientedness. It has often been suggested that type A's are adrenergically more reactive than type B's, their counterparts. It has also been suggested that females are "less A" than males. Are these two suggestions tenable?

Friedman et al. (1960) observed that noradrenaline excretion in middle-aged type A males during working hours was more elevated than in type-B's, in comparison with bed rest. This result was later replicated in a laboratory experiment in which puzzles had to be solved under noisy conditions (Friedman et al., 1975). In both studies the resting levels did not differ for A's and B's. Glass, Krakoff and Contrada (1980) found no significant A-B differences in catecholamine reactions to competitive games. In a study from Lundberg and Forsman (1979) A's reacted as strong as B's to series of tasks. This also applied to the reaction-time tasks in the experiments from Frankenhaeuser, Lundberg and Forsman (1980) and Williams, Lane and Kuhn (1982). In reaction to a mental arithmetic task, however, the last authors observed the expected larger reactions of type A's, both in adrenaline and noradrenaline. In our

own experiment with students as subjects we found no relationship between type A characteristics and any catecholamine parameter.

The question whether type A personalities are more reactive than type-B's is only relevant for the case at issue if there is a reliable sex difference in type A behavior. After a review Waldron (1978) indeed concluded that males are "more A" than females. There are reasons, however, to consider this conclusion as too simple and too general. Shekelle, Schoenberger and Stamler (1976) did not find an A-B sex difference when controlling for social status. Haynes, Feinleib and Kannel (1980) found working females to have higher type A scores than housewives. Within a student population we found no sex difference in type A score. This also applies to the studies of Nix and Lohr (1981) and Manuck, Craft and Gold (1978). Lundberg (1983) found that mean type A score for boys aged 3 to 6 years was higher than in girls of that age. Within each of the sexes, however, type A score did not correlate systematically with catecholamine levels. The sex difference also interacts with age. In a group of working people between 18 and 25 years males were more type A than females regardless of their level of education. In the older age group, however, a difference was absent (Waldron et al., 1977).

Most experiments in which male adrenergic overreactivity was observed used students as subjects. This group is very homogeneous with respect to social class and age and this might be the reason that there are no indications of sex differences in A-B score. The statement that types A react to stress with a larger adrenergic response than B's is, in its general, unspecified form, too simple. The conditions under which it applies depend on age, sex, kind of type A measurement and kind of stress-situation. The explanation that males are more type A and by that adrenergically more reactive is implausible. This certainly applies to the most investigated group, namely students. In this group sexes do not differ in type A score and most often types A are not found to be adrenergically overreactive. It remains possible, however, that the explanation holds for the general population.

## SEX HORMONES

Assuming that males are more reactive than females, the question arises whether sex hormones play a significant role in catecholamine reactivity. Both within-sex analyses of the association of sex hormones and catecholamines and between-sex comparisons are relevant. Patkai, Johansson and Post (1974) studied 6 women during daily work routines for a period covering two menstrual cycles. Four periods of the menstrual cycle were compared with



respect to urinary catecholamines. No significant differences between periods were observed in adrenaline and noradrenaline. Zagur et al. (1978) took blood samples throughout the menstrual cycle of 6 women. No systematic pattern of noradrenaline variations was observed (adrenaline was not measured). That the adrenaline excretion is relatively constant during the menstrual cycle is an argument against the importance of oestrogen and/or progesterone in explaining sex differences in adrenaline reactivity. Recently, Rosen et al. (1984) compared females in luteal and follicular phases of the menstrual cycle with males. Both sex hormones and catecholamines were measured. Plasma adrenaline concentration was slightly but significantly higher in luteal phase women than in follicular phase women or in men. No differences in noradrenaline were observed. The authors conclude that "these data provide no support for a role of physiological variations of testosterone, estradiol or progesterone in the regulation of catecholamine actions in humans".

#### GENETIC INFLUENCES ON CATECHOLAMINES

A discussion on sex differences would not be complete if the issue of the relative roles of heredity and environment is ignored. However, looking for possible genetic influences on sex differences is useful only when hereditary factors play an important role on catecholamines. One strategy that has been used to study the genetics of catecholamine systems is the measurement in nonneural tissue of activities of enzymes important in catecholamine biosynthesis and metabolism. Blood is often used in such experiments. The underlying assumption is, of course, that enzyme activity in red blood cells and platelets reflects enzyme activity in the nervous system. There is substantial evidence, both from human and animal studies, that genetic influences play an important role in the enzymatic pathways responsible for catecholamine synthesis. The enzyme that has been studied most is dopamine-beta-hydroxylase (DBH). DBH is a key enzyme in catecholamine synthesis because it converts dopamine to noradrenaline in noradrenergic and adrenergic cells of both the central and the peripheral nervous system. Plasma DBH is biochemically and immunologically similar to the enzyme in the sympathetic nerves and adrenal medulla (Weinshilboum, 1979). There is evidence that DBH in rats increases in response to stressors which also release catecholamines from the adrenal gland and increase catecholamine excretion. These findings suggest that DBH activity may be an index of activity of the sympathetic nervous system (Weinshilboum et al., 1971). Planz and Palm (1973) observed in a group of 34 males a 25% rise in DBH activity in serum after a maximum workload test. There is a wide interindividual variability in plasma DBH levels and only a slight variation in activities in the same person at different times (Planz & Palm,

1973). This suggests a genetic basis for the enzyme variability, that is supported by twin and sibling studies. Ross, Wetterberg and Myrhed (1973) found correlation coefficients of 0.96 in male monozygotic twin pairs and 0.75 in dizygotic twins for plasma DBH activity. Winter et al. (1978) reported intraclass correlations of 0.92 and 0.35 for male monozygotic and dizygotic twins, respectively. In a group of 94 sibling pairs Weinshilboum et al. (1973) observed a highly significant correlation of 0.57 for DBH activity. No difference in the degree of correlation was found for brother-brother, brother-sister or sister-sister pairings. Mendlewicz, Levitt and Fleiss (1975) found intraclass correlations of 0.99 for male and female monozygotic twins and a correlation of 0.33 in sets of siblings. The correlation in 10 pairs of brothers was 0.73 and 0.98 in 5 pairs of sisters. These results indicate that plasma DBH activity in humans is under genetic control and that environmental factors seem of less importance. If DBH activity reflects the activity of the peripheral sympathetic nervous system, it could be concluded that sympathetic nerve activity is to a large extent genetically controlled.

Monoamine oxydase (MAO) and catechol-O-methyltransferase (COMT) are the two major catecholamine metabolic enzymes. MAO activity in humans has been measured almost exclusively in platelets. Platelet MAO activity in an individual is fairly stable over time and varies over 20-fold among normal individuals. Females tend to have somewhat higher activity levels than males (Murphy, 1976).

Wyatt et al. (1973) reported a correlation of 0.94 for platelet MAO activity in a sample of 9 normal monozygotic twins. Nies et al. (1974) measured platelet MAO and found that the intraclass correlations were higher in monozygotic than dizygotic twins and that the dizygotic correlations were also greater than the correlations in a group of controls. Winter et al. (1978) obtained median intraclass correlations for platelet MAO of 0.88 for monozygotic and 0.52 for dizygotic twin pairs. Pandey et al. (1979) got a heritability estimate of 0.54 for platelet MAO from pedigree analysis. For COMT, which can be measured in red blood cells, Weinshilboum et al. (1974) reported a sibling-sibling correlation of 0.49. Winter et al. (1978) observed intraclass correlations of 0.95 and 0.65 for male monozygotic and dizygotic twins, respectively.

These data demonstrate that enzyme activity important in catecholamine biosynthesis and metabolism is partly under genetic control. The question whether sex differences in catecholamine reactivity are to some extent genetically influenced has to remain unanswered, although in rats there is evidence that the mode of inheritance of serum DBH activity may be sex specific (Stolk et al., 1979). A clear answer to this question could be provided in a twin study in which catecholamine reactivity is studied in monozygotic and dizygotic twins of both sexes as well as in dizygotic twins of opposite sex.

An alternative approach to the question what the relative roles of genetic and environmental influences on sex differences in catecholamine reactivity are is provided by Frankenhaeuser (1983, p100). This approach is to study differences between women who have adopted different social roles, the hypothesis being that those who have taken on a male role in, for example their professional life, would tend to exhibit the neuroendocrine stress response typical of men. This hypothesis seems to apply to female students on technical schools (Collins & Frankenhaeuser, 1978) and to female bus drivers and lawyers. However, these observations do not permit a straightforward conclusion, because of the possibility that more masculine women choose certain kinds of educations and professions.

### SEX DIFFERENCES IN CARDIOVASCULAR REACTIONS

Both adrenaline and noradrenaline are cardiovascular agents. Adrenaline induces a rise in heart rate, cardiac output and systolic blood pressure. Adrenaline may cause a decrement in total peripheral resistance which can create a fall in diastolic blood pressure. Adrenaline also increases peripheral blood flow in most organs. The effect of noradrenaline is an increase in peripheral resistance that leads to an increase in systolic and diastolic blood pressure and mean arterial pressure due to vasoconstriction. Despite a direct effect on beta-2 receptors, heart rate may decrease, as may cardiac output and peripheral blood flow. These findings raise the question to what extent sex differences in adrenergic reactivity parallel sex differences in cardiovascular reactivity.

In our own experiment mentioned above (Van Doornen, 1984) heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. On the exam and control days subjects were sitting in a soundproof cabin for 10 minutes while measurements were taken. On another day measurements were taken while the subjects performed the laboratory tasks.

As can be seen in Figure 3, male students had a higher SBP and also a lower HR. A sex difference in reactivity in these variables did not exist. The DBP did not react to the anticipation of the examination and also did not show any sex difference with respect to level or change. For the laboratory tasks no sex difference in reactivity in any of the cardiovascular measures was observed. Remember that in these same groups a difference in adrenaline was demonstrated.

In the two studies of Frankenhaeuser et al. (1976, 1980) in which larger male adrenaline reactivity was observed the sexes also did not differ in HR reaction. Sanchez et al. (1980) obtained similar results: the rise in HR, SBP and DBP was the same in men

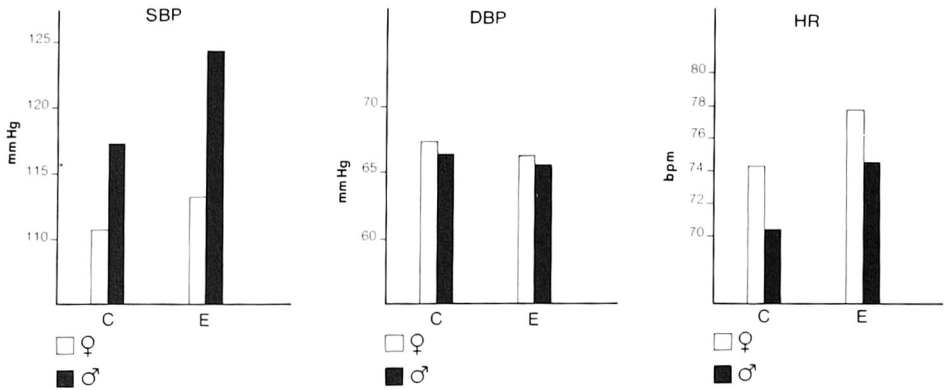


Figure 3. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) of female and male students on the day of an exam (E) and on a control day (C).

and women. In the study of Forsman and Lindblad (1983) the SBP reaction to the Stroop Test was significantly higher in men (18 mm Hg) than in women (6 mm Hg). The sexes did not differ in HR reactivity. Studies in which only cardiovascular variables were measured further complicate the picture: results with regard to sex differences are inconsistent. Jorgenson and Houston (1981), Manuck, Craft and Gold (1978), and Holmes, Solomon and Rump (1982) measured cardiovascular variables in reaction to a variety of laboratory stressors and found no sex differences in reactivity. Schmidt et al. (this volume) report a higher SBP level and reactivity to a video game in young boys as compared to girls of the same age. In the reaction-time task that followed the game this finding was not replicated. The sex effect on DBP reactions was marginal and was absent for HR reactivity. Von Eiff and Piekarski (1977) found larger SBP reactions to mental arithmetic in males than that in females. Public speaking, however, raises HR significantly more in females than in males (Baldwin & Clevenger, 1982). In a mixed-motive game with a competitive strategy von Egeren (1979) observed larger HR reactions in women. The sex difference was reversed when a cooperative strategy was employed. These results suggest the possibility of a differential task attitude of males and females. This argument however also applies to the studies measuring catecholamines. That results are more consistent in that area could imply that sex differences in catecholamine reactivity are indeed more robust.

Another point that needs to be considered when looking for a

correspondence in catecholamine and cardiovascular reactivity are the different characteristics of the two kinds of variables. There are large differences in latency and recovery rates. This also applies to the different catecholamine measurement techniques: in plasma or in urine. In the Forsman and Lindblad experiment adrenaline level went down in the rest period after the Stroop Test, while noradrenaline increased in this same period to starting levels. At that time HR already had returned to base level. SBP remained at the same level as during the task. This indicates that period of measurement is important when comparing response amplitudes in different response systems. Before we decide whether sex differences in catecholamine reactivity are or are not reflected in cardiovascular reactivity, we must await studies with more elaborate measurement of both variables.

#### CATECHOLAMINES AND CORONARY HEART DISEASE

In general, the adrenergic response to stress is smaller in females than in males. This is an interesting finding, because of the higher coronary heart disease (CHD) risk in males. In the age group 40-45 men -relative to women- have a sixfold risk of mortality due to CHD. Although no longitudinal studies have been carried out to investigate directly the connection between catecholamine level and CHD incidence, there is evidence for an indirect relationship:

- Hypertension is the most potent risk factor for CHD. Theories about stress-induced hypertension point to catecholamines, and especially noradrenaline as a crucial factor in the early stage of the development (Goldstein, 1981).

- Serum cholesterol is another important CHD risk factor. Recently Dimsdale, Herd and Hartley (1983) carried out a study in which adrenaline was injected in monkeys. They concluded that persistent elevation in adrenaline levels similar to that encountered under emotional stress leads to a significant increase in plasma cholesterol levels.

- Catecholamines raise the plasma content of free fatty acids (FFA). The liver takes up FFA that is not used for energy production. This FFA is then secreted as the CHD risk enhancing very-low-density lipoproteins. FFA also increases the intensity of platelet aggregation, and increases oxygen need of the heart.

- Catecholamines also directly increase the myocardial oxygen consumption. In combination with severe arteriosclerosis this might induce an ischemic state leading to anginal pain, rhythm disturbances or even myocardial infarction.

- Especially adrenaline is a potent agent of platelet aggregation (this, again, is partly mediated by FFA). This is an important factor in the pathogenesis of arteriosclerosis and thrombus formation in the coronary arteries.

- Catecholamines decrease the threshold of cardiac rhythm dis-

turbances: the most important cause of acute cardiac death. So sex differences in catecholamine production are of potential relevance for the understanding of sex differences in CHD-incidence, -mortality and -symptoms.

## CONCLUSIONS

In general, the adrenaline response to stress is smaller in females than in males. A similar difference in noradrenaline is seldom observed. This probably should be ascribed to the fact that most experiments do not use stressors that especially trigger the noradrenaline system. Sex differences in catecholamine levels are possibly dependent on the situation: under real basal conditions females have relatively higher adrenaline and especially noradrenaline levels. Under normal conditions this sex difference tends to disappear and under stress conditions males can be characterized by higher levels.

Sex differences in catecholamine reactivity cannot merely be ascribed to differences between males and females in task performance, type A behavior or sex hormones. The lack of a sex difference in task performance could point to a more economic coping style of females. The A-pattern is not a satisfactory explanatory concept, because in the most frequently investigated population, i.e. the student population, the sexes do not differ in type A score. Moreover, there is no convincing evidence for the often supposed larger adrenergic reactivity of type A's. The few studies that investigated the relationship between sex hormones and catecholamines do not show an important influence of sex hormones on catecholamine household. These studies, however, have not looked at the relationship between catecholamine reactivity and sex hormones. The importance of genetic factors for catecholamine synthesis and metabolism suggests that more research is also needed in which the relative roles of genetic and environmental factors on sex differences in catecholamine reactivity are studied.

Sex differences in catecholamine reactivity do not parallel differences in cardiovascular reactivity. Before any conclusions can be drawn, however, it has to be decided whether this is a result of different measurement techniques of adrenergic and cardiovascular variables.

It seems possible that a difference between males and females in catecholamine reactivity can explain part of the sex difference in CHD risk. It seems appropriate to pay attention to catecholamines when looking for mediating factors between stress and CHD. Assuming the relevance of catecholamines the combination of male adrenergic hyper-responsiveness and the higher male CHD risk needs closer attention.

## REFERENCES

- Aslan, S., Nelson, L., Carruthers, M., and Lader, M., 1981, Stress and age effects on catecholamines in normal subjects, J. Psychosom. Res., 25:33.
- Baldwin, S.F., and Clevenger, T.C., 1980, Effect of speakers sex and size of audience on heart rate changes during short impromptu speeches, Psychol. Rep., 46:123.
- Collins, A., and Frankenhaeuser, M., 1978, Stress responses in male and female engineering students, J. Hum. Stress, 4:43.
- Cuche, J.L., Kuchel, O., Barbeau, A., and Genest, J., 1975, Sex differences in the urinary catecholamines, Endocr. Res. Commun., 2:549.
- Dalmaz, Y, and Peyrin, L., 1982, Sex differences in catecholamine metabolites in human urine during development and at adulthood, J. Neural Transmission, 54:193.
- Dimsdale, J.E., Herd, J.A., and Hartley, L.H., 1983, Epinephrine mediated increases in plasma cholesterol, Psychosom. Med., 45:227.
- Doornen, L.J.P. van, Physiological reactivity to real life stress as a function of sex and the coronary risk personality, (submitted).
- Egeren, L.F. van, 1979, Cardiovascular changes during social competition in mixed-motive game, J. of Pers. & Soc. Psychol., 37:858.
- Eiff, A.W. von, and Piekarski, C., 1977, Stress reactions of normotensives and hypertensives and the influence of female sex hormones on blood pressure regulation, in: "Hypertension and Brain mechanisms. Progress in brain research", vol. 47, W. de Jong et al., eds., Elsevier.
- Faucheux, B.A., Bourlière, F., Baulon, A., and Dupuis, C., 1981, The effects of psychosocial stress on urinary excretion of adrenaline and noradrenaline in 51 to 55- and 71 to 74 years old men, Gerontol., 27:313.
- Faucheux, B.A., Dupuis, C., and Baulon, A., 1983, Heart rate reactivity during minor mental stress in men in their 50s and 70s, Gerontol., 29:149.
- Fibiger, W., Singer, G., and Miller, A.J., 1984, Relationships between catecholamines in urine and physical and mental effort, Int. J. of Psychophysiol., 1:325.
- Frankenhaeuser, M., 1983, The psycho-endocrine response to challenge, in: "Biobehavioral bases of coronary heart disease", T.M. Dembroski, T.H. Schmidt, and G. Blümchen, eds., Karger, Basel.
- Frankenhaeuser, M., Dunne, E., and Lundberg, U., 1976, Sex differences in sympathetic adrenal medullary reactions induced by different stressors, Psychopharm., 47:1.
- Frankenhaeuser, M., Lundberg, U., and Forsman, L., 1980, Dissociation between sympathetic adrenal and pituitary adrenal responses to an achievement situation characterized by high

- controllability : Comparison between type A and type B males and females, Biol. Psychol., 10:79.
- Frankenhaeuser, M., Rauste-von Wright, M., and Collins, A., 1978, Sex differences in psycho-endocrine reactions to examination stress, Psychosom. Med., 40:334.
- Friedman, M., Byers, S.D., Diamant, J., and Rosenman, R.H., 1975, Plasma catecholamine response of coronary prone subjects (type A) to a specific challenge, Metabolism, 24:205.
- Friedman, M., St. George, S., Byers, S.O., and Rosenman, R.H., 1960, Excretion of catecholamines, 17 ketosteroids, 17 hydroxy-corticoids, and 5-hydroxyindole in men exhibiting a particular behavior pattern (IX) associated with high incidence of clinical coronary artery disease, J. Clin. Invest., 39:758.
- Forsman, L., and Lindblad, L.E., 1983, Effect of mental stress on baroreceptor mediated changes in blood pressure and heart rate and on plasma catecholamines and subjective responses in healthy men and women, Psychosom. Med., 45:435.
- Glass, D.C., Krakoff, M.L.R., and Contrada, R., 1980, Effect of harassment and plasma catecholamine responses in type A and type B individuals, Psychophysiol., 17:453.
- Goldstein, D.S., 1981, Plasma norepinephrine in hypertension. A study of the studies, Hypertension, 3:48.
- Haynes, S.G., Feinleib, M., and Kannel, W.B., 1980, The relationship of psychological factors to coronary heart disease in the Framingham study, Am. J. Epidemiol., 41:37.
- Holmes, D.S., Solomon, S., and Rump, B.S., 1982, Cardiac and subjective response to cognitive challenge and the controlled physiological exercise by male and female coronary prone (type A) and noncoronary prone persons, J. Psychosom. Res., 26:309.
- Johansson, G., 1972, Sex differences in the catecholamine output of children, Acta Physiol. Scand., 85:569.
- Johansson, G., and Post, B., 1974, Catecholamine output of males and females over a one year period, Acta Physiol. Scand., 92:557.
- Jorgensen, R.S., and Houston, B.K., 1981, The type A behavior pattern, sex differences and cardiovascular response to and recovery from stress, Motiv. and Emot., 5:201.
- Lundberg, U., 1983, Note on type A behavior and cardiovascular responses to challenge in 3-6 year old children, J. Psychosom. Res., 27:39.
- Lundberg, U., de Chateau, P., Winberg, J., and Frankenhaeuser, M., 1981, Catecholamine and cortisol excretion patterns in three year old children and their parents, J. Hum. Stress, 3:3.
- Lundberg, U., and Forsman, L., 1979, Adrenal-medullary and adrenal-cortical responses to understimulation and overstimulation: Comparison between type A and type B persons, Biol. Psychol., 9:79.
- Manuck, S.B., Craft, S., and Gold, K.J., 1978, Coronary-prone behavior pattern and cardiovascular response, Psychophysiol.,



15:403.

- Mendlewicz, J., Levitt, M., and Fleiss, J.L., 1975, A genetic study of plasma dopamine beta hydroxylase activity in man, Acta Genet. Med. Gemellol., 24:105.
- Murphy, D.L., 1976, Clinical, genetic, hormonal and drug influences on the activity of human platelet monoamine oxidase, in: "Monoamine oxidase and its inhibition", Ciba Foundation Symposium 39, Elsevier/North-Holland, Amsterdam, 341.
- Nies, A., Robinson, D.S., Harris, L.S., and Lamborn, K.L., 1974, Comparison of monoamine oxydase substrate activities in twins, schizophrenics, depressives and controls, in: "Neuropsychopharmacology of monoamines and their regulatory enzymes", E. Usdin, ed., Raven Press, New York, 59.
- Nix, J., and Lohr, J.M., 1981, Relationship between sex, sex-role characteristics and coronary-prone behavior in college students, Psychol. Rep., 48:439.
- Palmer, G.J., Ziegler, M.G., and Lake, C.R., 1978, Response of norepinephrine and blood pressure to stress increases with age, J. of Gerontol., 33:483.
- Pandy, G.N., Dows, E., Shaughnessy, R., and Davis, J.M., 1979, Genetic control of platelet monoamine oxidase activity: Studies on normal families, Life Sci., 25:1173.
- Patkai, P., Johannson, G., and Post, B., 1974, Mood, alertness and sympathetic adrenal medullary activity during menstrual cycle, Psychosom. Med., 36:503.
- Planz, G., and Palm, D., 1973, Acute enhancement of dopamine-beta-hydroxylase activity in human plasma after maximum workload, Europ. J. Clin. Pharmacol., 5:255.
- Rosen, S.G., Berk, M.A., Popp, D.A., Serusclat, P., Smith, E.B., Shah, S.D., Ginsberg, A.M., Clutter, W.E., and Cryer, P.E., 1984, Beta-2 and alpha-2-adrenergic receptors coupling to adenylate cyclase in human mononuclear leukocytes and platelets in relation to physiological variations of sex steroids, J. Clin. Endocrinol. Metab., 58:1068.
- Ross, S.B., Wetterberg, L., and Myrhed, M., 1973, Genetic control of plasma dopamine-beta-hydroxylase, Life Sci., 12:529.
- Sanchez, J., Pequignot, J.M., Peyrin, L., and Monod, H., 1980, Sex differences in the sympatho-adrenal response to isometric exercise, Eur. J. Appl. Physiol., 45:147.
- Shekelle, R.B., Schoenberger, J.A., and Stamler, J., 1976, Correlates of the JAS type A behavior pattern score, J. Chron. Dis., 29:381.
- Stolk, J.M., Hurst, J.H., Riper, D.A. van, and Hanes, P.Q., 1979, Genetic analysis of serum dopamine-beta-hydroxylase in rats., Mol. Pharmacol., 16:922.
- Waldron, I., 1978, Type A behavior pattern and CHD in men and women, Soc. Sci. Med., 12B:167.
- Waldron, I., Zyzanski, S., Shekelle, R.B., and Jenkins, 1977, The coronary prone behavior pattern in employed men and women, J. Human Stress, 2-18.

- Weinshilboum, R.M., 1979, Catecholamine biochemical genetics in human populations, in: "Neurogenetics: Genetic approaches to the nervous system", X.O. Breakefield, ed., pp 257-277, Elsevier, New York.
- Weinshilboum, R.M., Koetnansky, R., Axelrod, J., and Kopin, I.J., 1971, Elevation in serum dopamine-beta-hydroxylase after forced immobilization, Nature (New Biol.), 230:287.
- Weinshilboum, R.M., Raymond, F.A., Elveback, L.R., and Weidman, W.M., 1973, Serum dopamine-beta-hydroxylase activity: Sibling-sibling correlation, Science, 181:943.
- Weinshilboum, R.M., Raymond, F.A., Elveback, L.R., and Weidman, W.H., 1974, Correlation of erythrocyte catechol-O-methyltransferase activity between siblings, Nature, 252:490.
- Williams, R.B., Lane, J.D., and Kuhn, C.M., 1982, Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks, Science, 218:483.
- Winter, H., Herschel, M., Propping, P., Friedl, W., and Vogel, F., 1978, A twin study on three enzymes (DBH, COMT, MAO) of catecholamine metabolism, Psychopharmacol., 57:63.
- Wyatt, R.J., Murphy, D.L., Belmaker, R., Cohen, S., Donnelly, C.H., and Pollin, W., 1973, Reduced monoamine oxydase activity in platelets: A possible genetic marker for vulnerability to schizophrenia, Science, 179:916.
- Zagur, H.A., Tyson, J.E., Ziegler, M.G., and Lake, C.R., 1978, Plasma dopamine-beta-hydroxylase activity and norepinephrine levels during the human menstrual cycle, Am. J. Obstet. Gynecol., 130:148.
- Ziegler, M.G., Lake, C.R., and Kopin, I.J., 1976, Plasma noradrenaline increases with age, Nature, 261:333.