# Catecholamines and Exercise

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Both plasma norepinephrine and epinephrine increase during exercise. Briefly, norepinephrine is correlated to hemodynamic parameters and oxygen requirement while plasma epinephrine is dependent on both sympathetic nervous activity and blood glucose concentration.

## NOREPINEPHRINE

Rise in plasma norepinephrine is correlated with an increase in heart rate, provided that the latter is mediated by the sympathetic nervous system. This is the case during exercise, with the exception of the initial rise in heart rate, which is due to withdrawal of vagal tone. Correspondingly, there is no rise in plasma norepinephrine during light work.[1] The increase in heart rate that occurs when one stands up is mediated by sympathetic nerves, and plasma norepinephrine increases.[1] Figure 1 shows the relationship between rise in heart rate and rise in plasma norepinephrine upon standing and during exercise.

When one stands up, a part of the increase in plasma norepinephrine is independent of any change in heart rate, but there is a further rise in norepinephrine that is correlated to the rise in heart rate. During exercise there is no rise in plasma norepinephrine provided the increase in heart rate at steady state is less than approximately 25 beats/min. During an exercise requiring higher increases in heart rate, these increases are paralleled by increases in plasma norepinephrine.

The greater rise in plasma norepinephrine when standing as compared with the rise in norepinephrine during exercise (with a comparable increase in heart rate) is explained, in part, by the different autonomic nervous mechanisms involved in the regulation of heart rate during these procedures but is most probably also due to a more pronounced vasoconstriction when standing up than when performing light exercise. During exercise, plasma norepinephrine is also correlated to splanchnic vascular resistance which is mostly controlled by sympathetic nervous activity.[2,3]

During exercise plasma norepinephrine probably correlates most closely with pulmonary arterial oxygen saturation (Figure 2).[2] The results in Figure 2 were obtained in a group of patients with ischemic heart disease, but results have been found to be basically similar in normal subjects (unpublished results).

Pulmonary arterial oxygen saturation is an integrated measure of the metabolic situation in the tissues and normally reflects the ratio of cardiac output to oxygen consumption. For a given individual it is an index of the demand on the cardiovascular system. Although the correlation between plasma norepinephrine and pulmonary arterial oxygen saturation is remarkably close in individual subjects, it is unlikely that pulmonary arterial oxygen saturation has a direct regulatory effect on sympathetic nervous activity. However, these data support results of other studies indicating a significant role of afferent signals from the tissues, probably neural, in the regulation of sympathetic nervous activity during exercise and in patients with heart failure, probably also in the resting state.[2]

If exercise is prolonged the concentration of norepinephrine in plasma continues to increase.[4] Correspondingly, the exercise-induced changes in heart rate, splanchnic vascular resistance, and pulmonary arterial oxygen saturation increase with duration of exercise.[4,5]

The origin of plasma norepinephrine during exercise in man is the sympathetic axon terminals in the cardiovascular system. Studies of norepinephrine and epinephrine concentrations in the coronary sinus and brachial artery at rest and during exercise have shown that norepinephrine is released from the heart and epinephrine is taken up by the heart.[6] However, calculations show that the heart is not a major source of circulating norepinephrine. The plasma norepinephrine concentrations are approximately similar in

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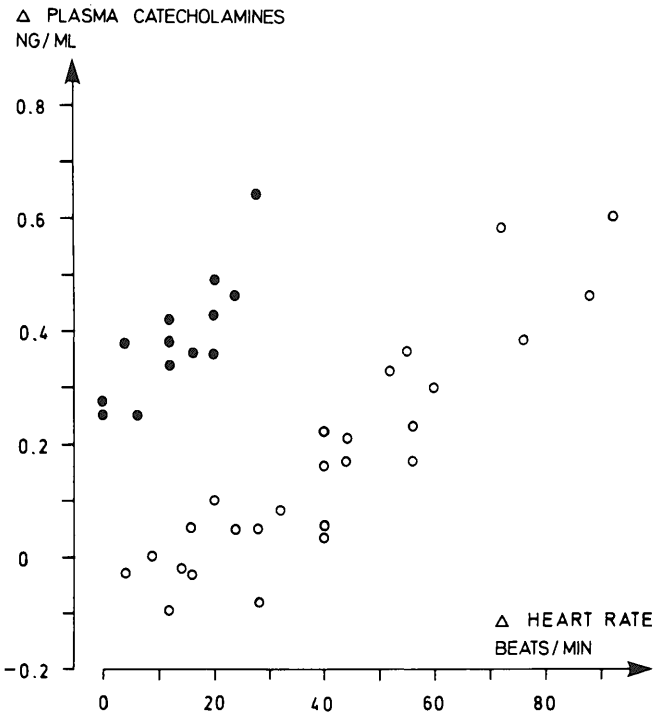



**FIGURE 1. Relationship between rise in plasma catecholamines (mainly norepinephrine) and rise in pulse rate upon standing up (●) and during exercise (○). Exercise was performed in the supine or in the sitting position, and values at rest were subtracted from exercise values.**

the internal jugular vein and brachial artery during exercise while hepatic veins contain very little norepinephrine. However, only a small fraction of total circulating norepinephrine is taken up by the liver (J. Trap-Jensen and N. J. Christensen, unpublished results).

It is now well-established that basal plasma norepinephrine increases with age, a fact that probably reflects an increased firing rate in sympathetic nerve fibers in elderly subjects.[7,8] It is most likely that the maximum rise in plasma norepinephrine is reduced in elderly subjects.[9]

Plasma norepinephrine concentration during exercise in man is not influenced by blood glucose concentration.[10]

## EPINEPHRINE

The secretion of epinephrine from the adrenal gland is dependent on both the general level of sympathetic nervous activity, as reflected by plasma norepinephrine, and the blood glucose concentration. A rise in plasma norepinephrine is accompanied by a rise in plasma epinephrine provided the increase in plasma norepinephrine is of a certain magnitude. During graded short-term exercise, both plasma norepinephrine and epinephrine increase in parallel with changes in oxygen uptake while blood glucose concentration remains unchanged.[11] During prolonged exercise the blood glucose concentration tends to decrease. If the fall in blood glucose concentration is slightly exaggerated by pharmacologic inhibition of lipolysis or by a preceding depletion of carbohydrate stores, then also the increase in plasma epinephrine is exaggerated[4,12] and the concentration of epinephrine may increase to very high values comparable to those observed during insulin-induced hypoglycemia.[13] That epinephrine secretion during prolonged exercise is partly controlled by the plasma glucose concentration is further supported by the finding that the exercise-induced epinephrine response is considerably reduced, although not abolished, when euglycemia is obtained by glucose infusion (Figure 3).[10,12]

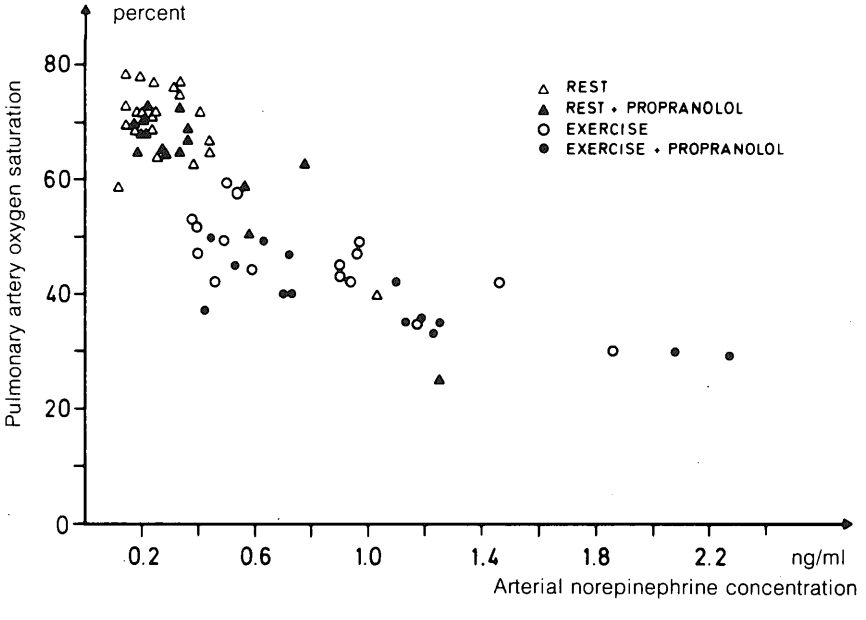
It should be emphasized that the fall in blood glucose concentration during exercise that influenced epinephrine secretion was fairly small and such a small decrease in blood glucose concentration would not provoke epinephrine secretion during resting conditions, e.g. after injection of insulin.[13]

## ALPHA- AND BETA-ADRENERGIC RECEPTOR BLOCKADE

To further elucidate the role of catecholamines in cardiovascular, metabolic, and hormonal homeostasis we have examined effects of alpha- and beta-adrenergic receptor blockade during exercise in man.[2–4,10,14] Both propranolol (a beta-adrenergic receptor blocking agent) and phentolamine (an alpha-adrenergic receptor blocking agent) reduced work capacity.

As expected, propranolol diminished the increase in heart rate and cardiac output during exercise. The de-

**FIGURE 2. Correlation between plasma norepinephrine and pulmonary arterial oxygen saturation in a group of patients with ischemic heart disease.**



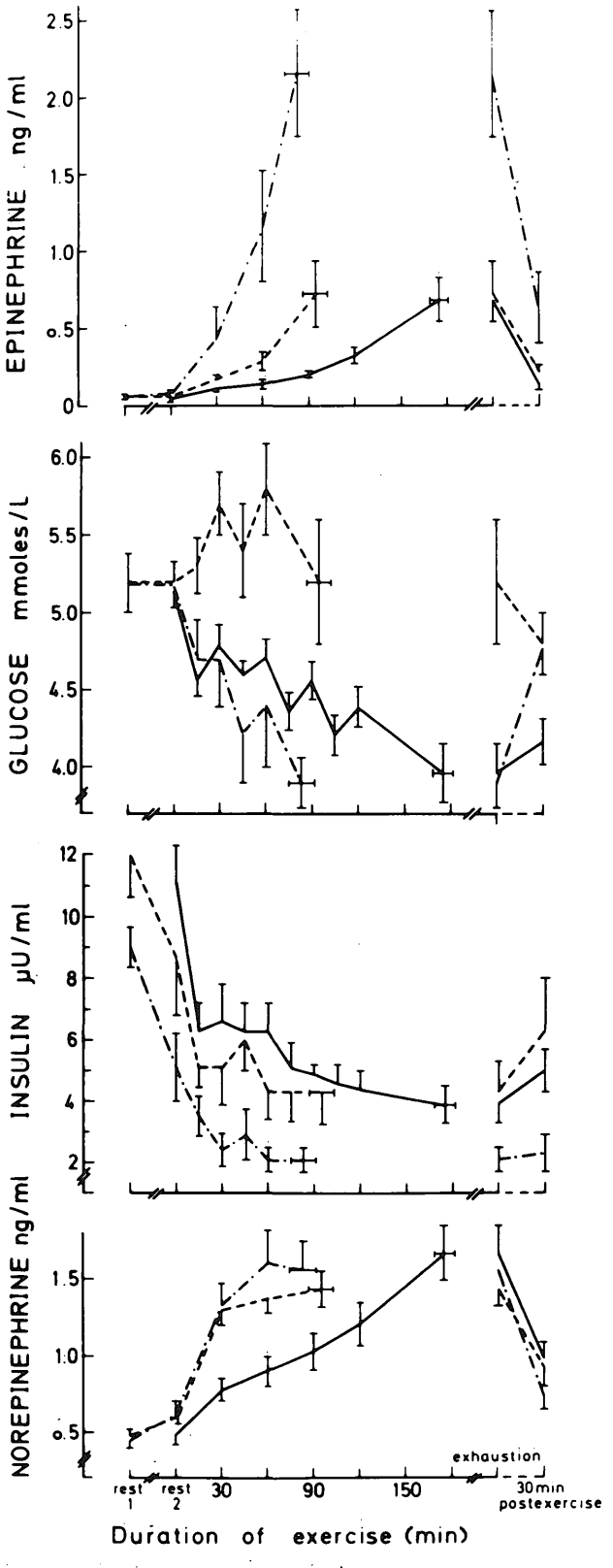



**FIGURE 3. Mean concentrations ± SEM in plasma during rest and exercise of epinephrine, glucose, insulin, and norepinephrine. (———) designates control experiments and (–·–·–) as well as (– – –) designate experiments in which propranolol was administered when rest, samples had been obtained. Furthermore, in (– – –) experiments glucose was infused continuously during exercise.**

crease during exercise in pulmonary arterial oxygen saturation as well as the increases in splanchnic vascular resistance and plasma norepinephrine concentration were further augmented when beta-adrenergic receptors were blocked by propranolol.[2–4]

Plasma concentrations of free fatty acid and glycerol were reduced during exercise after propranolol administration. Since compared to control experiments the overall rate of fat combustion simultaneously was decreased, these findings indicate that beta-adrenergic stimulation promotes lipolysis during exercise.[4]

Also, the breakdown of glycogen in working human skeletal muscle seems to be enhanced by catecholamines. When treadmill exercise was performed after either the administration of nicotinic acid or propranolol, lipolysis was similarly inhibited and the overall rates of carbohydrate combustion were identical. However, as judged from biopsies of the vastus lateralis muscle, the glycogen depletion rate was lower during beta-adrenergic blockade than during nicotinic acid administration.[4] It is also of interest that infusion of glucose during exercise plus the addition of propranolol did not significantly prolong work capacity.[10]

It is well established that serum insulin concentration decreases during exercise. We found this response to be uninfluenced by propranolol in our experiments. Furthermore, when euglycemia was maintained by glucose infusion in propranolol experiments, insulin concentrations during exercise were not higher than in propranolol experiments, in which plasma glucose concentrations were allowed to decline (Figure 3).[4,10]

We have also studied the metabolic consequences of alpha-adrenergic receptor blockade.[14] We must emphasize that alpha-adrenergic receptor blocking agents, as for instance phentolamine, block not only postsynaptic alpha-adrenergic receptors but also presynaptic alpha-adrenergic receptors that inhibit release of norepinephrine from the axon terminals. Alpha-adrenergic receptor blockade, both at rest and exercise, leads to a rather massive increase in circulating norepinephrine. This increase is partly a compensatory phenomenon owing to the decrease in blood pressure that is induced by postsynaptic blockade, but the blockade of the presynaptic alpha-adrenergic receptors also adds to the plasma norepinephrine level.

It is well known that catecholamines inhibit insulin secretion.[15] This phenomenon is observed not only during pathophysiologic conditions, such as acute myocardial infarction,[16] but also during physical exercise. Perhaps the most important hormonal consequence of alpha-adrenergic receptor blockade, apart from the rise in circulating catecholamines, is that catecholamine-induced inhibition of insulin release is impeded.[14] The possible consequences of elevated serum insulin concentration during exercise are discussed at greater length below.

## EXPERIMENTAL SYMPATHETIC NEUROPATHY

Although use of alpha- and beta-adrenergic receptor antagonists has led to a considerable understanding of the role of catecholamines in cardiovascular, hormonal, and metabolic homeostasis during exercise, the obtained experimental situation is not strictly comparable to the situation found in a variety of disease states, e.g. in diabetic neuropathy. We have also examined the hormonal and metabolic response in rats after chemical sympathectomy combined with surgical adrenomedullectomy.[17]

Both tissue catecholamines and circulating catechol-

amines at rest and during exercise were considerably reduced in the combined sympathectomized and adrenomedullectomized rats (Table 1). Norepinephrine concentrations in pancreas, liver, and deep vastus muscle averaged 12, 5, and 27% of control values. In these rats, insulin concentrations during exercise were higher and blood glucose concentrations lower. Furthermore, the exercise-induced decrease in liver and muscle glycogen was abolished in the adrenodemedullated and sympathectomized rats (Table 2). It is not completely clear to what extent these findings are related to decreased circulating catecholamine levels during exercise or to increased serum insulin concentrations.

Further studies have shown that the lack of decrease in muscle and liver glycogen in chemically sympathectomized and adrenodemedullated rats is due to abolition of epinephrine secretion, whereas peripheral sympathetic nerves play only a minor role in glycogen breakdown and insulin secretion during exercise.[18] These studies have also shown that a major part of circulating norepinephrine in rats is derived from the adrenal medulla.[18]

## TRAINING

Glucose availability is likely to be a major regulatory factor for various hormonal responses to exercise.[19] In trained rats the blood glucose concentration is higher during exercise while the hormonal response is blunted.[20] The plasma norepinephrine response to exercise in man is also reduced after a period of training.[21]

## DIABETES MELLITUS

Plasma catecholamines' response to exercise in diabetic patients may be influenced by a number of factors. In ketotic diabetic patients, resting plasma catecholamines are elevated, and the response to exercise is about eight times higher than it is in controls (Figure 4).[22,23] Correspondingly, heart rate was also higher at rest and during exercise in untreated diabetic patients. After insulin treatment, catecholamine values at rest and during exercise were similar to those observed in controls. In poorly controlled diabetics, other hormonal responses (viz. growth hormone, glucagon, and cortisol) and the rise in ketone body concentration are greatly exaggerated during exercise, and blood glucose concentration tends to increase.[24,25]

In insulin-treated diabetics, hormonal and metabolic responses to exercise are greatly influenced by insulin mobilization from subcutaneously injected depots. The increased amounts of insulin available, mobilized by the increased subcutaneous blood flow during exercise, de-

TABLE 1
Plasma concentrations of norepinephrine and epinephrine (ng/ml$^{-1}$) in rats after 75 min of swimming

| | Adrenodemedullated and sympathectomized rats | Control rats |
|---|---|---|
| Norepinephrine | 0.92† | 3.14 |
| SEM | 0.09 | 0.59 |
| Epinephrine | 0.36† | 1.40 |
| SEM | 0.12 | 0.32 |

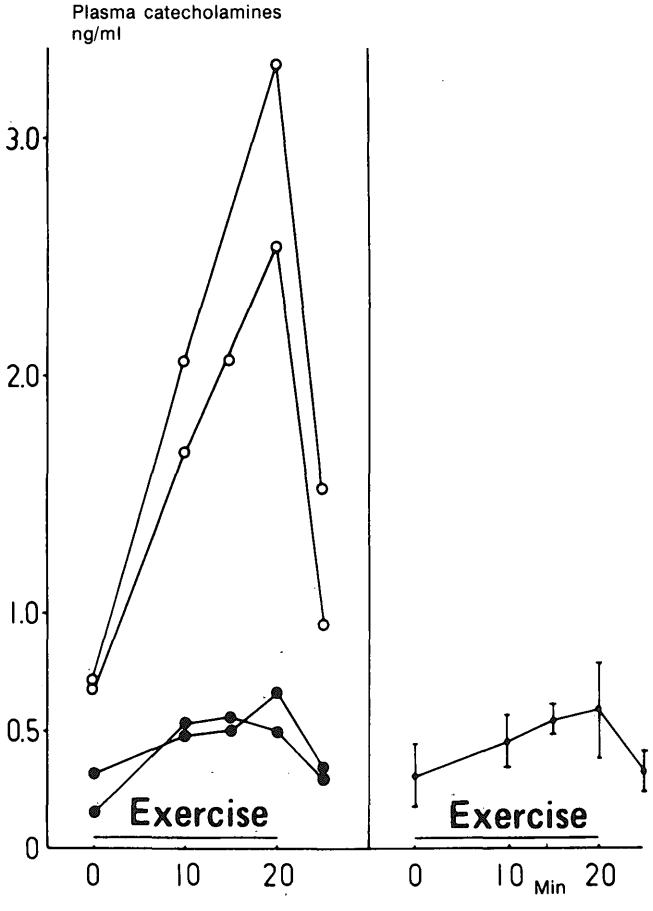
* Results are mean values ± SEM and were obtained in groups of seven rats.
† 2 P is less than 0.02 versus control rats.

TABLE 2
Blood glucose (mg/100 ml), serum insulin (pmol/L$^{-1}$), and glycogen (mmol/glucose/kg wet weight$^{-1}$) at rest and after exercise in control rats and in adrenodemedullated and chemically sympathectomized rats*

| | Control rats | | Adrenodemedullated and sympathectomized rats | |
|---|---|---|---|---|
| | Rest | After exercise | Rest | After exercise |
| Blood glucose | 118 | 173† | 111 | 111‡ |
| SEM | 3 | 6 | 3 | 6 |
| Serum insulin | 59 | 52 | 73 | 86‡ |
| SEM | 3 | 4 | 13 | 9 |
| Liver glycogen | 317 | 197† | 274 | 278 |
| SEM | 12 | 31 | 23 | 12 |
| Soleus muscle glycogen | 25 | 15† | 30 | 35 |
| SEM | 2 | 1 | 1 | 2 |
| Superficial vastus muscle glycogen | 33 | 24† | 39 | 37 |
| SEM | 2 | 1 | 3 | 2 |

* Results are mean values ± SEM and were obtained in groups of eight to ten rats.
† 2 P is less than 0.05 versus rest.
‡ 2 P is less than 0.05 versus control rats.

**FIGURE 4. Plasma catecholamines in subjects at rest, during, and after exercise in the supine position. Left: two diabetics, (○ – ○ – ○) untreated; (● – ● – ●) treated. Right: average values of five controls ± SD.**



crease glucose production and may result in hypoglycemia.[26]

Most likely the catecholamine response to exercise in diabetes depends upon the degree of autonomic neuropathy. This, however, remains to be studied. The concentrations of catecholamines in blood and tissues are considerably reduced in long-term diabetics.[27,28] As we can conclude from our previous investigations showing that catecholamines are of major importance for cardiovascular, metabolic, and hormonal homeostasis during exercise, work capacity is undoubtedly reduced in diabetic patients with neuropathy. Future studies, however, will elucidate to what extent a lack of catecholamines will impede various physiologic functions (viz. cardiovascular adaptation, temperature regulation, fat mobilization, and so forth) during exercise in these patients.

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