The Catecholaminergic Response to Stress and Exercise

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Human beings respond to most stresses by activation of the sympathetic nervous system (SNS). We are all familiar with the tachycardia, piloerection, and pupillary dilatation that this activation engenders, but we are now able to measure norepinephrine (NE) in blood and quantitate this response. This chapter reviews the human response to stresses, ranging from standing quietly for 5 minutes to exposure to seven times the force of gravity, and from a slow walk to exhaustive exercise.

In 1911, Cannon and de la Paz demonstrated that when a cat is frightened by a barking dog, catecholamines (CA) are released from the adrenal gland into the blood [3]. In 1936, Selye [35] described the sequence of pathologic changes that occurred when an animal was exposed to a variety of stresses, and he named this the “general adaptation syndrome.” The stereotyped response to stress leads to adrenocortical and autonomic discharge, and the response may be so violent as to lead to sudden death. When wild rats are subjected in rapid succession to restraint, trimming of the whiskers, and immersion under a jet of water, they may die abruptly [31,32]. Monkeys exposed to a 16-hour stressful avoidance schedule developed electrocardiographic changes characteristic of sympathetic and parasympathetic stimulation and then had ventricular arrest and died [8]. Engel has accumulated 170 examples of sudden death following psychological stress in human beings, including Biblical accounts and current newspaper reports [10]. When there was close medical observation during the stressful event, ventricular fibrillation or myocardial infarction was documented to be the ultimate cause of death.

The studies detailed in this chapter show the impressive magnitude and rapidity of the SNS response to stress. When a person reaches his maximum heart rate through exercise, NE levels are high but only a few minutes more exertion may raise them several-fold higher. It is possible to stress pigs so that sympathetic nervous activity produces gross cardiac lesions. Similar lesions are seen in human beings after fatal head trauma.
AGE AND SYMPATHETIC ACTIVITY

Age increases SNS response and a person’s susceptibility to cardiac damage; age has important effects on both the release of NE from the SNS and the response of tissues to NE. A 60-year-old person has plasma NE levels approximately twice those of a 10-year-old child. Electrical activity in sympathetic nerves and the size of the NE response to stress also increase with age [22]. An old person will secrete twice as much NE in response to standing and isometric exercise [22] or to a cold pressor test [28] as will a young person. Both young and old increase their NE 100% in response to standing, but the old person has a higher resting level of NE and a greater absolute increase in NE in response to stress than the young person. The correlation of plasma NE to age is weak and accounts for approximately 20% of the variance of NE levels; thus it is predictably not seen in small studies and is obscured by diseases that alter NE levels.

Several tissue responses to NE decrease with age. The density of β receptors tends to decrease with age [11], which may mediate the decreased sensitivity of the heart to CA seen in older people [38]. A decrease in the number of receptors does not mediate the decrease in maximum heart rate seen in the elderly: one of our subjects demonstrated that he could secrete three times as much NE as needed to achieve his maximum heart rate (see Figure 2.8). The ability to secrete NE increases with physical fitness, but maximum heart rate does not (see Figure 2.9). Even when the β receptor is bypassed by the drug dibutryl cyclic adenosine 3',5' monophosphate (cAMP), the decrease in cardiac response with age remains [12]. Responses to CA decrease with age, especially β-adrenergic-mediated responses such as those found in cardiac [38] and adipose [18] tissues. α-Adrenergic-mediated responses have not been shown to have a similar decline in sensitivity to NE with age, and this might mediate the rise in blood pressure seen with age.

BLOOD SAMPLING

Blood samples for NE assay are obtained by venipuncture, which some people find acutely painful and stressful. We had 15 subjects lie recumbent and inserted a scalp vein needle in an antecubital vein. Blood samples drawn immediately after venipuncture contained 335 pg/ml NE, and samples taken 20 minutes later contained 262 pg/ml NE. Over the same period of time their pulse rate decreased from 80 to 74 beats per minute. The decrease in both NE levels and heart rate was significant and the change in heart rate correlated with the 22% decrease in NE ($r = 0.58, p < 0.05$). After lying quietly for 3 hours, NE levels were no different than after 20 minutes. Robertson et al [33] found NE levels of 201 pg/ml in subjects resting for 30 minutes with a heparin lock in place. NE levels were 13% higher when subsequently obtained by venipuncture, but the increase was not significant. Because the decrease in NE level correlates with heart rate, tachycardia is a useful guide to anxiety that may artifactually elevate NE levels.
EFFECT OF ACCELERATION ON SYMPATHETIC ACTIVITY

When we stand, approximately 500 ml of blood pools in our legs [36]. Standing for 10 minutes leads to a further loss of intravascular volume as a 10% hemoconcentration occurs while water moves into interstitial spaces and causes swelling of the feet and legs [43]. The SNS responds to this stress by stimulating the heart and blood vessels to maintain blood pressure. This response has been quantitated by measuring NE levels in reaction to the acceleration produced by as little as a 10-degree tilt and as much as seven times the force of gravity. A 10-degree tilt for 10 minutes produced no detectable change in NE levels, although a 30-degree tilt increased them appreciably. Subsequent tilting to 45 degrees further increased NE levels [34] and a 60-degree tilt increased plasma NE from 70\% [22] to 88\% [15] above baseline. NE levels increased rapidly after tilting and were nearly maximal at 3 minutes. This increase is largely in response to loss of blood volume to the legs as application of 60 mm Hg pressure to the legs by an antigravity suit diminished the tilting-induced increase in plasma levels of NE from 88\% to 37\% [15]. Placing subjects on a tilt-table may have psychological as well as gravitational effects. Subjects commonly faint on a tilt-table, particularly if they are young, and Rosenthal et al [34] report one subject who had high NE levels while being tilted and who subsequently fainted. Sitting increases plasma NE by approximately 60\% over baseline levels, and standing approximately doubles plasma NE (Figure 2.1) [22]. Although we do not ordinarily think of standing as a stress, the doubling of plasma NE on standing indicates that the body activates potent homeostatic mechanisms to cope with gravity. People who lack these homeostatic mechanisms

![Graph showing the percent increase over baseline norepinephrine (NE) levels while recumbent in subjects who were tilted from 20 to 60 degrees above horizontal or who sat or stood. Data are from Rosenthal et al [34], Hesse et al [15,16], and Lake et al [22].]
cannot stand and may die if kept upright for several minutes [44]. As a simple and practical test of the body's ability to respond to stress with a sympathetic response, plasma NE levels may be obtained through an indwelling cannula while the subject is recumbent. People who find venipuncture stressful will have an increase in NE levels of approximately 20%, and those accustomed to venipuncture may have no detectable change in NE. Standing is a more potent stimulus to NE secretion than is a tilt-table and has the practical advantage of requiring no special equipment and of eliciting less frequent fainting in young subjects. When people are to have simultaneous tests requiring instrumentation, however, a tilt-table may be necessary. The usual increases in NE levels found on tilting can be seen in Figure 2.1.

**SYMPATHETIC RESPONSE TO ACCELERATION GREATER THAN 1G**

Acceleration that is a fraction of 1G can be simulated on a tilt-table and the sympathetic response to these small forces can be seen in Figure 2.1. Modern life routinely exposes human beings to acceleration slightly higher than 1G in elevators and automobiles. In exceptional circumstances, such as commercial roller coaster rides and fighter airplanes, a person may be subjected to acceleration equivalent to 9G. Acceleration greater than 7G lasting more than a few seconds induces syncope in an untrained person and will induce syncope in less than 1 minute in a pilot who is trained to withstand this sort of acceleration force, who is wearing an antigravity suit in a sitting posture, and who is straining to maintain blood pressure. Tolerance to this increased level of acceleration is enhanced if subjects perform a Valsalva maneuver with intermittent straining respirations. Valsalva maneuver increases intrathoracic pressure and thus increases the pressure of arterial blood supply to the brain. The "weight" of the column of blood from the heart to the brain is increased ninefold at 9G and is so "heavy" that ordinary arterial pressure cannot maintain blood flow to the brain. When acceleration force is so high that calculated arterial pressure at eye level is 0, the subject undergoes a blackout and soon faints. We have been unable to obtain blood samples from humans during high acceleration, in part owing to uncertainty about the added risk of an intravascular cannula when the "weight" of the cannula would increase manyfold. Adult miniature swine are good models for studying the response to high acceleration because the height of the column of blood from their hearts to their eyes is similar to that of human beings, and they spontaneously perform straining maneuvers in response to high G as humans are trained to do. Three adult miniature swine were exposed to high acceleration lasting for 100 seconds with acceleration up to 9G and an average acceleration of 7G. The high G exposure was repeated five times, and blood samples from indwelling cannulas were taken from the animals while they were relaxed, while they were placed in a harness prior to their first exposure, and prior to their fifth high G exposure.

While miniature swine are in the relaxed state, they have NE and epinephrine (E) levels that are roughly comparable to human levels (Table 2.1). The stress of
Table 2.1 Effects of Stress of Preparation for High-Gravity Experiments on Plasma Norepinephrine and Epinephrine

<table>
<thead>
<tr>
<th>State of Animal</th>
<th>Relaxed</th>
<th>Prior to High G (first exposure)</th>
<th>Prior to High G (fifth exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>420 ± 88</td>
<td>1500 ± 420</td>
<td>7400 ± 2700</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/ml)</td>
<td>100 ± 30</td>
<td>800 ± 300</td>
<td>1000 ± 0</td>
</tr>
</tbody>
</table>

G = gravity.

Placing the animals in a harness preparatory to high G exposure led to a large increase in both NE and E. When these animals were exposed to 100 seconds of high G force, plasma NE levels increased to more than 40,000 pg/ml, but 2 minutes later NE levels had decreased to as low as 5000 pg/ml (Figure 2.2). These NE levels are higher than we have ever recorded in humans, but it has not been possible to withdraw blood samples from man during high G. E levels showed a similarly sharp increase in response to the stress of high G (Figure 2.3). Because of this enormous outpouring of CA from the SNS during high G exposure, we wondered if the swine might not deplete their releasable stores of CA. However, both E and NE levels were higher while the animals rested after exposures to high G forces on the same day, and the animals showed greater NE and E responses to the stress of the fifth high G run.

![Figure 2.2](image-url) Levels of plasma norepinephrine (NE) in adult miniature swine exposed to high-gravity forces for 100 seconds. The solid line shows NE levels in response to the first exposure, and the interrupted line shows the response to the fifth exposure on the same day. Data are expressed as mean ± standard error of the mean (SEM) for five animals.
Figure 2.3 Plasma levels of epinephrine (E) in response to a 100-second high-gravity exposure in adult miniature swine. The solid line shows responses to the first and the interrupted line shows responses to the fifth high-gravity experiment of the day. Data are expressed as mean ± standard error of the mean (SEM) for five animals.

The decrease in CA levels immediately following exposure to high G was extremely rapid. For example, plasma NE levels increased to more than 40,000 pg/ml, but by 2 minutes after the high G stress they had decreased to approximately 5,000 pg/ml (see Figure 2.2). This corresponds to a CA half-life of slightly more than one-half minute, although several studies have indicated that the half-life of circulating CA is approximately 2 minutes. The extremely high CA levels attained in these animals might be expected to saturate the high-affinity, low-capacity uptake1, mechanism and thereby prolong half-life rather than shorten it. It may be that a large fraction of the animals’ blood supply was sequestered in venous pools in the lower body and was not accessible to the general circulation during high G forces. After high G force stopped, this sequestered blood would be released back into the general circulation and dilute the blood containing high CA levels, which had been sampled during high G. This blood trapping could then help explain the extremely high CA levels attained and short apparent half-life of CA, which would actually be due to an altered volume of distribution. Both the plasma levels of NE and E attained during high G exposure were sufficient to cause marked vasoconstriction. However, the blood NE levels attained in the legs where vasoconstriction is most needed to maintain blood pressure would be lowest.

Dopamine β-hydroxylase (DBH) has a much longer half-life than CA, so any brief period of sympathetic activity should have a relatively small influence on the large circulating pool of DBH [23]. As shown in Figure 2.4, there is a fairly moderate increase in DBH levels during a single high G exposure, but with a more marked accumulation of plasma DBH by the fifth high G exposure.
Figure 2.4 Dopamine $\beta$-hydroxylase (DBH) levels in response to high-gravity forces in adult miniature swine. The solid line shows a response to the first and the interrupted line shows the response to the fifth high-gravity experiment of the day. Data are expressed as mean ± standard error of the mean (SEM) for five animals.

Although it has not been possible to obtain blood samples from people during exposure to high G, we have obtained samples immediately prior to and 1 minute after high G forces. Two subjects were placed in a sitting posture with an anti-G suit on their legs and exposed to an average force of 4G for 100 seconds. Their plasma NE levels, as shown in Figure 2.5, were markedly increased after exposure to high G, but were still an order of magnitude below the response recorded from the swine. This stress was considerably less than the average 7G force which the swine were exposed to for 100 seconds, so several subjects were tested at a 7G force to their level of voluntary tolerance or for 60 seconds. Their NE levels, shown in Figure 2.6, demonstrate that the shorter exposure to a 7G force was considerably more potent a stimulus than 4G. Their NE levels of 5000 pg/ml in blood samples obtained 1 minute after the cessation of high G exposure were comparable to those seen in swine 2 minutes after their high G exposure. It appears that the human sympathetic nervous response to high G force is similar to that seen in swine, with the exception that the human beings were not as frightened by the procedure and had only mildly elevated CA levels prior to the initiation of high G.

When adult miniature swine are exposed to high G forces, they can develop...
subendocardial hemorrhages and stress cardiomyopathy [2,25]. Connor [7] has noted subendocardial hemorrhage and focal areas of myocardial necrosis in human beings, which are quite similar to those found by Burton and MacKenzie [2] in swine. These cardiac lesions can be reproduced in animals by the administration of CA [30]. Stimulation of the cervicothoracic ganglion to release NE from cardiac nerve endings can also cause these myocardial lesions [19]. Sympathetic stress can lead to myocardial lesions in animals, and human beings appear capable of a level of sympathetic response to stress similar to that seen in adult miniature swine.

We have found markedly elevated NE levels in patients following severe accidental head injury. In reviewing the clinical and autopsy records of 28 fatally head-injured patients treated at the University of Texas Medical Branch in Galveston, nine of the ten patients who had electrocardiograms (ECGs) performed during the course of their hospitalization had abnormal ECGs. Eight of the 28 patients had cardiac lesions demonstrable at autopsy. The anatomically demonstrated lesions uniformly consisted of superficial areas of subendocardial hemorrhage and necrosis. Adjacent myocardial fibrosis was noted in one patient. The lesions were clustered on the left side of the intraventricular septum and occasionally involved the papillary musculature. This type of lesion is similar to that previously described in the adult miniature swine by Burton and MacKenzie in 1969 [2]. We suspect that severe stress can lead to a level of sympathetic nervous activation in human beings sufficient to cause myocardial damage.

**THE NORADRENERGIC RESPONSE TO ISOMETRIC EXERCISE**

Isometric exercise leads to rapid stimulation of the SNS with an increase in heart rate and blood pressure shortly after initiation of exercise. Although isometric exercise is not as simple a test of sympathetic function as standing, it has several
advantages. The response to isometric exercise should not depend on blood volume as alterations in posture do. The test can be as simple as having a patient grip a partially inflated cuff of a sphygmomanometer and can be quickly standardized between subjects by having all subjects maintain a constant fraction of their maximum exertion for a specified length of time. However, different groups have obtained widely varying results with similar isometric exercise protocols. These variations may be due to differences in muscle mass of exercising subjects and differences in the level of voluntary exertion subjects are willing to produce.

Kozlowski et al [20] designed an exercise protocol in which subjects first gripped a dynamometer with one hand to determine the maximum force they were able to exert. They were then asked to continue squeezing the dynamometer to 30% of their maximum force until exhaustion. They found that maximum NE levels were attained at 4 to 5 minutes and that NE levels increased dramatically from 80 pg/ml to 2000 pg/ml in 4 minutes. However, because they measured plasma NE with a fluorometric assay, it is unlikely that their technique was sufficiently sensitive to measure levels as low as 80 pg/ml of NE. Nazar et al [27] used the same isometric exercise protocol and the same assay and found that isometric exercise increased plasma NE from 860 to 1600 pg/ml in hypertensive subjects and to 2400 pg/ml in normotensive subjects. The baseline plasma NE levels they measured were 10 times as high as those Kozlowski measured, and this discrepancy is probably due to the insensitivity of the fluorometric assay technique that both groups used. This change in baseline would, of course, have a dramatic effect on the reported percentage increase of plasma NE over baseline and so this type of data can be more reliably inferred from studies which use radioenzymatic techniques.

Lake et al [22] measured plasma NE levels with a phenylethanolamine-N-methyltransferase (PNMT)-based radioenzymatic technique and had subjects perform isometric exercise by maintaining 30% of their maximum gripping force for 5 minutes while they were standing. NE levels increased from 538 pg/ml to 778 pg/ml, an increase considerably smaller than that reported by Kozlowski. Watson et al [40] used a similar protocol except that subjects were sitting and performed isometric gripping exercise for only 3 minutes. They studied both normotensive and hypertensive subjects but found no difference in NE levels between the groups. They reported that, in the exercising arm, NE levels increased from 398 to 438 pg/ml, and in the nonexercising arm NE levels went from 498 to 585 pg/ml. They also measured E and found a greater increase in the exercising arm, even though NE levels had increased less in the exercising arm. They attributed this change to an increased blood flow in the exercising arm, which diluted released NE but allowed less opportunity for clearance of E owing to its more rapid blood flow. Vlachakis [39] had subjects exert two-thirds of their maximum gripping effort for 3 minutes while standing and found that subjects with labile hypertension increased their plasma NE by 315 pg/ml in response to isometric exercise. This increase was appreciably greater than that seen in normotensive subjects. Isometric exercise increased plasma NE markedly in all groups of subjects and also induced a notable increase in plasma E. Robertson et al [33] reported that isometric exercise
at 30% of maximum handgrip capacity for 3 minutes increased NE levels only 27%.

There appears to be a wide disparity between the amount of NE increase found after isometric exercise, but the greatest discrepancies are attributable to differences in assay techniques. All of these studies found that NE increased markedly after handgrip, while isometric exercise increased plasma NE in hypertensive subjects more [39], the same [40], or less [27] than in normotensive subjects. Handgrip at 30% maximum effort for 3 minutes is not a potent stimulus to NE release [33,40], but handgrip for two-thirds of maximum effort for 3 minutes [39] or one-third or 30% of maximum effort for 5 minutes [22] leads to an appreciable increase in plasma NE levels over those obtained by standing alone.

Vlachakis [39] measured a large increase in plasma NE from handgrip at two-thirds of maximum effort for 3 minutes. It thus appears that a more intense isometric exercise will lead to a more rapid rise in plasma NE, but there is a limit to the intensity of effort obtainable with one arm. Because there is a much larger muscle mass in the legs and abdomen, we studied NE levels in eight subjects who maintained fixed, static leg efforts at 35%, 55%, and 75% of maximum effort against a force plate while performing repetitive Valsalva maneuvers until fatigued. This effort led to heart rates of 101, 124, and 120 respectively at these percentages of maximum effort. The peak levels of plasma NE attained at the termination of exercise were higher for the more intense exercise, even though subjects were able to continue the more intense exercise for a shorter length of time (Figure 2.7). Because higher NE levels were attained over a shorter period

![Figure 2.7](image_url)

**Figure 2.7** Norepinephrine (NE) levels and the rate of increase in NE levels per minute in subjects performing isometric exercise with both legs against a pressure plate at 35%, 55%, and 75% of their maximal effort.
of time, we calculate that the increase in NE levels per minute of exercise is more than three times as great at 75% maximum effort as at 35% of maximum effort (Figure 2.7).

Isometric exercise leads to a sympathetic nervous response characterized by an increase in heart rate, blood pressure, and plasma NE levels. Isometrics can increase NE levels over those obtained by upright posture alone and can be done by procedures as simple as handgripping. It appears that intense isometric exercise over a brief period of time produces both a higher final level of circulating plasma NE and a more rapid rise in NE levels. The degree of sympathetic nervous activation elicited by isometric exercise can be quite large, and this is probably adequate to explain the tachycardia and the increase in blood pressure that occurs with this type of exertion.

ISOTONIC EXERCISE

Running and bicycling are isotonic exercises in which a constant force is applied to move an object and accomplish work. When exercise begins, heart rate increases markedly, initially by withdrawal of parasympathetic tone [5] and then by sympathetic stimulation. The maximum heart rate attained with exercise varies with age and can be predicted fairly accurately in the absence of heart disease [9,37]. After any increase in the level of work, 3 to 4 minutes are needed for the heart rate to reach a new plateau level [29]. During isotonic exercise, cardiac output increases rapidly owing to tachycardia and increased filling pressure from venoconstriction. Deep inspiration causes negative intrathoracic pressure, which helps maintain the increased cardiac filling. In young, healthy adults, cardiac output may increase fivefold over resting levels [9,37].

During isotonic exercise, systolic blood pressure increases in proportion to the workload and mean blood pressure remains unchanged [37] or increases moderately [17]. There is a marked increase in coronary and skeletal blood flow at the expense of the renal and mesenteric vascular beds. At the beginning of exercise, blood flow to the skin increases to facilitate heat loss, but at heavy workloads, the skin may vasoconstrict and redistribute blood to the exercising muscles. Cerebral blood flow remains unchanged at all levels of exercise [9,17].

The maximal rate of exercise can be monitored by the rate of oxygen consumption. Heart rate, cardiac output, and oxygen consumption increase linearly as workload increases [1]. The maximum heart rate is attained at the maximum rate of oxygen consumption and, in the absence of intrinsic cardiac disease, reliably reflects oxygen consumption [29].

Although there are an endless variety of isotonic exercises, two are especially suited to laboratory investigation. Exercise on a bicycle ergometer is easily quantitated and allows the subject to place his arms in a fixed and resting position so that blood pressure and blood samples can be easily obtained. However, bicycle exercise uses only a fraction of the body's total musculature so fatigue usually occurs before maximum rates of oxygen consumption or maximum heart rate
are attained. As bicycle testing allows subjects to easily attain 85% of their maximal rate of exertion, it is ideally suited to submaximal exercise protocols. As discussed later in the chapter, the last 15% of a subject’s exercise potential may be considerably more stressful than the previous 85%, and testing the last fraction of a subject’s capacity for exercise usually requires treadmill testing.

**Bicycle Exercise**

Claus Weideking (personal communication) measured plasma norepinephrine NE in eight healthy subjects while at rest and after bicycle exercise for 5 minutes at 100, 150, and 200 watts (W). He found no major change in NE levels at the lower exercise level, but a progressive increase in NE levels was observed as exercise increased. The NE levels attained at 150 W were remarkably similar to those recorded in a separate experiment performed by Henquet et al [13] (Figure 2.8). Manhem et al [26] measured NE levels after 6 minutes of exercise at 50 W and 150 W in supine subjects. They sampled blood from numerous sites, including artery, coronary sinus, and renal vein, and calculated that the heart produced NE at the rate of 389 pg/min and the kidney produced NE at the rate of 62 pg/min during exercise at 150 W. At the same time, coronary blood flow increased fourfold and renal blood flow decreased to one fourth of resting levels [24]. NE levels at 150 W exercise recorded in these three studies using healthy, young subjects were quite similar (see Figure 2.8).

**Treadmill Exercise**

It is more difficult to study people exercising on a treadmill than on a bicycle ergometer, but the treadmill has the advantage of allowing most normal subjects to reach their maximal level of voluntary exertion. Robertson et al [33] found

![Figure 2.8](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAAofCAYAAAA4zY6AAAABgca...</image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAAofCAYAAAA4zY6AAAABgca...)}
that treadmill exercise at only 4 mph for 3 minutes was the most effective of six stimuli tested for increasing plasma NE levels. We exercised nine normal subjects on a treadmill and sampled their blood every 3 minutes. We found that the logarithm of plasma NE correlated linearly with the percent maximum heart rate over a wide range (Figure 2.9). Over the range of 40 to 80% of maximum heart rate, NE levels increased exponentially with increasing heart rate, but from 80 to 100% of maximum heart rate, NE levels increased even more rapidly. This was dramatically illustrated by one subject who decided that he wanted to set a new record for endurance running on the treadmill. He attained 100% of his predicted maximum heart rate and at that time had a plasma NE level of 5000 pg/ml. He continued to run for another 3 minutes and increased his plasma NE to 14,500 pg/ml with, of course, no further change in heart rate.

Using percent maximum of heart rate as an index of the rate of exercise has several advantages. It corrects for the slowing of maximum heart rate with age and is closely proportional to rate of oxygen consumption. Heart rate can be displayed continuously by electrocardiographic monitoring for the subject to view while exercising and serves as an immediate stimulus for the subject to meet his exercise goals. Although rate of oxygen consumption might be a better guide to the level of exercise, it needs to be monitored through a face mask, which prevents many subjects from reaching their maximum level of exertion because of discomfort, increased dead space (which raises CO₂ levels), and increased resistance to the work of respiration, which is perceived by many subjects as a limiting factor to exercise.

Physically trained subjects have smaller physical responses to a given amount of work than untrained subjects. It is a common observation that a physically fit person may walk up several flights of stairs without feeling stressed and an untrained person becomes dyspneic, diaphoretic, and tachycardic. Training alters the noradrenergic response to exercise quite rapidly [42]. Subjects on an exercise program of bicycling and running decreased their NE response to a given level of work after 3 weeks and had no further decrease during 6 more weeks of training.

We studied subjects with a wide range of physical fitness and classified them by how long they were able to run on a standard treadmill test before exhaustion.

![Figure 2.9 Plasma norepinephrine (NE) levels (note logarithmic scale) versus percent maximum heart rate in nine subjects who exercised on a treadmill. Blood samples were drawn every 3 minutes during exercise.](image-url)
When divided into four groups by the level of treadmill exercise that they were able to attain, groups 1 to 4 reached mean maximum heart rates of 182, 184, 183, and 189 respectively. All groups reached 98% of their predicted maximum heart rate, but group 4 had a higher heart rate because the subjects were slightly younger. They attained their maximum level of exertion because they were told what their predicted maximum heart rate was and their heart rate during exercise was continuously displayed before them.

After 9 minutes of exercise, the most fit group had plasma NE levels of less than half those of their less fit counterparts (Figure 2.10). Although this result was expected, it was surprising that at the greatest level of exercise, fit subjects attained NE levels twice as great as those of the least fit group. Thus, physically fit subjects are able to attain a much greater degree of SNS activation during maximum exercise than are sedentary individuals. This observation is in accord with that of Carr et al [4]; following 4 months of exercise training, women secreted higher levels of β-endorphin and β-lipotropin in response to the same fraction of their maximum exercise level. These substances are secreted from CA neurons along with NE, so physical training increases the secretory capacity of the SNS in response to exercise. Stress can increase the level of CA and their synthetic enzymes in sympathetic tissues [21]. Exercise training also decreases vascular sensitivity to NE [41], so repeated stress can increase the capacity of the SNS to synthesize NE and decrease tissue response to NE. Training also increases the subjective

![Figure 2.10](image.png)

**Figure 2.10** Plasma norepinephrine (NE) levels following 9 minutes of exercise and at the point of exhaustion in subjects running on a treadmill. Group 1 was able to exercise for less than 12 minutes on the treadmill, group 2 for 12 to 15 minutes, group 3 for 15 to 18 minutes, and group 4 for longer than 18 minutes.
tolerance of a subject for exertion, and all of these factors may help produce the enhanced NE levels seen in trained subjects during maximal exertion.

When subjects approach their maximum heart rate they are near the limits of cardiac reserve and the ability of the heart to deliver oxygen to exercising muscle. Tissue hypoxia then provides a potent stimulus to NE release. Subjects with chronic hypoxia from obstructive lung disease have elevated plasma NE levels [14], and NE levels in normal subjects during exercise increase more while breathing 14% oxygen than while breathing air [6]. Breathing 100% oxygen decreases the normal NE response to exercise [16]. Under normal circumstances, sympathetic stimulation in response to tissue hypoxia is beneficial as it stimulates cardiac output, increasing oxygen delivery. In some pathologic circumstances, such as lung disease, the sympathetic stimulation may be harmful as it increases metabolic rate and oxygen consumption.

CONCLUSIONS

Most, and perhaps all, stress increases NE release. The rate of NE release is greater with increasing age, but some tissues in older subjects respond less well to NE. Undergoing venipuncture or a change in posture can increase NE release, so the circumstances of blood sampling are important. Standing doubles the NE levels found in recumbent subjects. Acceleration greater than 1 G can increase plasma NE levels 100-fold in 1 minute in experimental animals and probably has a similar effect in human beings. This increase in animals leads to heart damage of a type seen in humans after fatal head trauma.

Exercise is a potent stimulus to NE release, even isometric exercise with one arm. Isometric exercise near the limits of a subject’s strength is more potent than prolonged moderate exercise in raising NE levels. Isotonic exercise on a bicycle ergometer gives a fairly uniform sympathetic response in normal subjects at submaximal exertion, but exercise to maximal exertion requires running. Predictably, physically fit subjects release less NE in response to a given workload than poorly trained subjects. Surprisingly, fit subjects are not only capable of more work, but can attain much higher NE levels than sedentary subjects during maximal exercise.

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