Measurements of Plasma Norepinephrine Concentrations in Human Primary Hypertension

A Word of Caution on Their Applicability for Assessing Neurogenic Contributions

BJÖRN FOLKOW, M.D., GERALD F. DI BONA, M.D., PAUL HJEMDAHL, M.D., PETER H. TORÉN, M.D., and B. GUNNAR WALLIN, M.D.

SUMMARY The relationship between plasma levels of norepinephrine (NE) and sympathetic neural activity is discussed with special reference to human primary hypertension. Since sympathetic discharge is differentiated, neural activity to a given target organ will contribute variably to plasma NE levels in different situations. Hemodynamically, early primary hypertension is often characterized by a mild defense reaction-like pattern with signs of increased sympathetic activity to the heart and vasoconstriction in the renal and splanchnic vascular beds. Although important hemodynamically, these organs seem to be of less importance as contributors to peripheral plasma NE levels. In contrast, muscle sympathetic activity and muscle vascular resistance is unchanged or reduced. Since this organ mass contributes importantly to plasma NE levels, especially in peripheral venous blood, it is not surprising that most patients with primary hypertension have normal NE levels. It is concluded that NE concentrations in forearm or mixed venous blood are unreliable indicators of sympathetic neural contributions to essential hypertension, tending to underestimate this element, and that regional measurements of NE overflow are needed for a reliable analysis. (Hypertension 5: 399-403, 1983)

KEY WORDS: hypertension • sympathetic activity • plasma norepinephrine • norepinephrine overflow • defense reaction

MODERN methods for measurement of catecholamine concentrations in body fluids have reached high sensitivity and accuracy and can for some purposes be a valuable tool, particularly for studies in humans when simple and safe indicators of sympathetic activity are needed. Such measurements have also become widely used for assessing the involvement of neurogenic elements in primary hypertension (recently surveyed by Goldstein1-2). It should be realized, however, that norepinephrine (NE) is a locally released transmitter, rather than a hormone, and that the autonomic nervous system operates quite differently from hormonal systems. Thus, there are good reasons for considerable caution when interpreting plasma NE levels, particularly in hypertension, as will be outlined below.

Sympathetic nerve-fiber discharge often occurs in highly differentiated and distinct patterns; fiber activity can be increased to some target organs at the same time as it is unchanged or even decreased to others. A striking example is the well-known defense reaction,3-4 which is mildly engaged whenever individuals are even slightly aroused.5-6 This limbic-hypothalamic pattern can overrule bulbar reflex control and thereby redirect the cardiovascular system to "anticipate" challenging environmental situations. This results in increased sympathetic nerve activity to the heart and veins, to kidneys, splanchnic region, and skin, while the vasoconstrictor fiber activity to the skeletal muscles is, if anything, reduced. The hemodynamic consequence is a mainly rate-dependent neurogenic increase in cardiac output, which favors the blood supply to the skeletal muscles and the myocardium at the expense of the abdominal organs. As a net balance, total systemic resistance is little changed, and the increased cardiac output is therefore associated with an often substantial increase of mean arterial pressure. The pressure rise in this situation is regularly associated with an increased heart rate.

Obviously, this powerful neurogenic "pressor pattern" can be expected to be associated with increased NE overflow wherever sympathetic adrenergic nerves

From the Department of Physiology, University of Göteborg (Dr. Folkow and Dr. Thorén); Department of Pharmacology, Karolinska Institutet, Stockholm (Dr. Hjemdahl); and the Department of Clinical Neurophysiology, University of Uppsala, Sweden (Dr. Wallin); and the Department of Internal Medicine, University of Iowa, Iowa City, Iowa, (Dr. Di Bona).

Address for reprints: Dr. Björn Folkow, Fysiologiska Institutionen, Göteborgs Universitet, Medicinaregatan 11, 400 33 Göteborg 33, Sweden.

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are activated, but certainly not so in regions where the activity is unaltered or decreased. Thus, increased NE release is to be expected in the heart as well as in the hemodynamically important renal and splanchnic circuits, but it should, if anything, be reduced in skeletal muscle. The important question is what will be the net result with respect to the plasma NE concentration in mixed blood and, in particular, in forearm venous blood which is usually sampled in humans.

The splanchnic region — some 4 to 5 kg of tissue in an average-sized man — receives up to 25%–30% of resting cardiac output, and all its venous blood passes through the liver. Increased sympathetic activity to this hemodynamically important part of the systemic circulation will certainly lead to a regional increase in NE overflow. This, however, contributes only little to mixed venous plasma NE levels since the liver efficiently clears catecholamines from the blood.7, 8

Both the heart and the kidneys are no doubt richly innervated and together receive a larger fraction of resting cardiac output than the skeletal muscles. Since their sympathetic activities are increased during a defense reaction, overflow of NE is a likely consequence. However, the two kidneys weigh only 0.4 kg vs 30 kg for skeletal muscle. Even if there can be a considerable release of NE from the kidneys to the blood,6-10 the total quantity of innervated vasculature is far larger in the skeletal muscles. Thus, there is no congruency between the sympathetic hemodynamic influences on the mentioned organ circuits (i.e., kidneys vs skeletal muscles) and their respective amounts of adrenergically innervated vessels. Equal degrees of sympathetic nerve-fiber activation to the kidneys and to the total skeletal muscle tissue should therefore release far more NE in the skeletal muscle tissue, simply because it is almost 100 times larger. Yet, the respective neurogenic blood flow restrictions would lead to fairly equal increases of overall systemic resistance.6

Further, the heart apparently does not contribute much to mixed plasma NE concentrations, at least not during the resting steady state, because the NE concentration in coronary sinus blood is often lower than in the coronary arterial blood, suggesting a substantial NE uptake by the heart.6-11

Thus, both at rest and during generalized increases of sympathetic discharge, the biggest single tissue mass in the body, the skeletal muscles, can be expected to contribute much of the NE overflow to the bloodstream. Moreover, in the reclining state, the legs alone, i.e., mainly skeletal muscle, contribute more to mixed plasma NE concentration than the kidneys.8 Furthermore, Wallin et al.12 have recently shown that the directly recorded muscle sympathetic activity (MSA) in humans correlates closely to plasma NE levels.

The hypothesis that the skeletal muscles are the most important contributors to mixed plasma NE concentration is further supported by the relationship between changes in plasma NE concentration, heart rate (HR), mean arterial blood pressure, muscle vascular resistance, and skeletal MSA, as found during different provocations. This is illustrated in figure 1, which is based on data from a considerable number of studies.13-31 In this context, it is important to point out that in humans sustained reflex increases in MSA are induced only by decreases in the activity of the cardio-pulmonary “volume” receptors,19, 20, 31 while selective decreases in carotid baroreceptor activity do not induce prolonged MSA increases.15, 16 Mental “stress” if anything decreases MSA.6, 27, 28 and also muscle vascular resistance.5, 26 The hemodynamically powerful defense reaction can for such reasons, as shown in figure 1, occur with very little net spillover of the adrenergic transmitter NE, despite the often marked neurogenic pressor effects. On the other hand, the concentration of the hormonal component of the sympathoadrenal system, epinephrine, is, as expected, often increased in the blood.2, 22, 23, 29 Further, it has been shown in awake rats, exposed to alerting stimuli, that the neurogenic HR increases are closely paralleled by increases in sympathetic fiber discharge to the splanchnic regions.34 Thus, in defense reaction patterns the neurogenic HR increase is a good marker of increased sympathetic activity to, for example, the hemodynamically important abdominal organs, but not so the NE levels in mixed or forearm venous blood (fig. 1).

With respect to human primary hypertension, many studies of the early, “hyperkinetic” phase have revealed a hemodynamic pattern that in detail mimics a mild defense reaction. Starting with Brod’s classic studies in the 1950s and 1960s,26, 30 this has been increasingly well documented.6, 32 Thus, an increased neurogenic involvement in the form of a mild defense reaction is evidently important, both in common variants of early human primary hypertension and in spontaneously hypertensive rat (SHR) hypertension.5, 32 Furthermore, as in young SHR,6 adolescents with a genetic predisposition to primary hypertension commonly show a central nervous system “hyperreactivity” to alerting stimuli, with modestly accentuated and prolonged defense reactions, as expressed by heart rate and arterial pressure elevations.31, 33

It follows that the differentiated pattern of increased sympathetic discharge, which seems to prevail in common variants of early human primary hypertension (and in SHR), will often be reflected only poorly, if at all, as increased concentrations of the adrenergic neurotransmitter NE in mixed blood. Thus, the method is likely to miss many cases where increased sympathetic activity is, indeed, of importance for the high-pressure state and will in others underestimate the relative involvement of neurogenic factors. In fact, plasma epinephrine levels might reflect an increased sympathetic nervous engagement in primary hypertension better than the plasma levels of the adrenergic nerve transmitter,35 as seems to be the case in defense reactions. For these reasons, it is high time to make detailed regional analyses of NE overflow into the renal, gastrointestinal, myocardial, and muscle circuits.8, 10, 36, 37 The complexity is increased by the fact that the NE release per stimulus can also vary considerably, as may the spillover fraction to the bloodstream perhaps both between
PLASMA NE IN PRIMARY HYPERTENSION/Folkow 401

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<th>B. Lower Body Negative Pressure (= decreased cardio-pulmonary receptor activity)</th>
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FIGURE 1. Response patterns concerning heart rate (HR), mean arterial blood pressure (MAP), muscle vascular resistance (MVR), muscle sympathetic activity (MSA), and plasma norepinephrine (NE) in humans. References to papers with relevant data (13-30) are given as numbers within brackets. Mild (‘’), modest ′, considerable ′ increase; decrease ↓. marginal ± change, up or down.

References

organisms and with changes in tissue activity. Particularly, in long-term alterations of sympathetic activity, as in hypertension, such local adaptations of NE kinetics may well have relevant influences on plasma NE levels, and they are not necessarily congruent with the neurogenic impact on pressure and hemodynamics.

These considerations make it evident that the NE concentration in mixed plasma is an unreliable indicator with respect to the hemodynamic importance of increased sympathetic activity in primary hypertension. Therefore, if used uncritically, it may lead to erroneous views not only concerning etiological elements in this disorder but also orient therapeutic principles in wrong directions. One may argue, somewhat provocatively, that to measure NE in mixed blood in primary hypertension is to use a sensitive and, for many other purposes, valuable method "for wrong reasons and in the wrong place."

Commentary

DAVID GOLDSTEIN, M.D.

This manuscript forces a reconsideration of commonly held views about how sympathetic neural activity is related to circulating levels of norepinephrine (NE) and epinephrine (E). One must be careful, though, in judging whether the evidence presented leads necessarily to the conclusions drawn.

At the risk of oversimplification, the following are the authors’ main points:

1. Sympathetic nerve-fiber discharge quite often occurs in differentiated, distinct patterns, and NE concentrations in forearm venous or mixed venous blood ignore this patterning.

2. The skeletal muscles are the most important contributor to NE circulating in mixed venous blood, so that, given Point 1, circulating NE correlates well with muscle sympathetic activity but not necessarily with sympathetic activity elsewhere.

3. Early human hypertension is characterized by a mild “defense reaction,” which is associated with a differentiated pattern of increased sympathetic discharge, but, because of Points 1 and 2, not necessarily associated with increased plasma NE in mixed venous or antecubital venous blood.

Regarding the first point, there is little doubt that sympathetic neural responses to various environmental circumstances are not monolithic and that therefore mixed venous or antecubital venous NE may not reflect patterned changes in sympathetic outflow in individual vascular beds. This does not necessarily mean, however, that NE in mixed blood has no relation to overall sympathetic tone at rest. One can argue that the concept of “overall” or “averaged” sympathetic tone at rest has no physiologic meaning, precisely because of the above-described heterogeneity of sympathetic responses. In my view, though, the concept is worthwhile, just as total peripheral resistance, representing as it does the contributions of resistances to blood flow.
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