Editorial Comment

Atrial Natriuretic Factor: Its Role in Hypertension*

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The story of the atrial natriuretic factor is a fascinating one. Over an extremely short time, a putative hormone was suggested, its biochemical characteristics were identified, the amino acid sequence was determined, the peptide was cloned and the pure hormone was made available through recombinant technology. Thus, thanks to modern day high technology, a new hormone, one originating in the heart, was identified and commercially synthesized. Yet industry became frustrated because the commercial potential of atrial natriuretic factor made available through "high tech" developments outpaced the physiologic knowledge about its role in health and disease. The latter requires the luxury of time to permit acquisition of biologic (e.g., physiologic, biochemical) information, scientific interchange at meetings and in publications and, of course, confirmation of the data. It is inevitable that this experience will recur in the future.

Pathophysiology of atrial natriuretic factor. In this issue of the Journal (1) we are presented with new physiologic information concerning the role of atrial natriuretic factor in health and disease. Before commenting on this article, I will examine briefly the teleology of the pathophysiology of atrial natriuretic factor. Consider the circumstances of a volume-overloaded circulation. Here we find a situation of an increased venous return to the heart and an expanded cardiopulmonary volume. Ideally, if the heart could "sense" this overload in its low pressure chamber and then initiate a response to induce natriuresis and diuresis, this would provide the negative feedback that we expect from finely tuned circulatory homeostasis. Indeed, we now know that atrial stretch associated with volume overload serves to release atrial natriuretic factor from the atrium; this, in turn, stimulates the renal excretion of sodium (and water), which restores a normal cardiopulmonary volume and circulation (2).

However, the foregoing events are only partially true and certain data are, at present, conflicting. As a result, the teleology is not totally supported. On the one hand, early studies demonstrated that, in vitro, atrial natriuretic factor reduced vascular smooth muscle tone in vessel strip preparations and produced a potent natriuresis and diuresis with minimal kaliuresis in vivo (3). On the other hand, in the total body situation, atrial natriuretic factor has been shown to reduce arterial and venous pressures associated with a reduced cardiac output and an increased total peripheral resistance (4). These findings, of course, suggest a questionable role for atrial natriuretic factor in cardiac failure and a less than ideal action for a new antihypertensive agent. Commercial interests were soon diverted to providing the hormone for investigative and radioimmunoassay purposes rather than for therapeutic goals. However, more recently, long-term infusion of atrial natriuretic factor was shown to decrease total peripheral resistance (5) and to increase cardiac output in patients with cardiac failure (6). These responses have been difficult to utilize clinically because of the short half-life of the native peptide, although current studies reported in abstract form (7-9) using endopeptidase inhibitors that interfere with the degradative metabolism of atrial natriuretic factor support a potential role for this peptide in the treatment of hypertension.

Present study. Data are now becoming available on the role of atrial natriuretic factor in health and disease (1). In their study, Gnanou et al. (1) were concerned with the relation of atrial natriuretic factor to systemic hemodynamics and cardiac structure in patients with systemic arterial hypertension. Well established essential hypertension is characterized by an elevated arterial pressure secondary to an increased total peripheral resistance that is associated with a contracted intravascular (plasma) volume and with adaptive structural changes characterized by left ventricular hypertrophy and vessel wall thickening (10). Even before these changes are found in patients with established essential hypertension, the elevated arterial pressure may be related to an increased cardiac pulmonary volume. This increased volume elevates cardiac output in association with an "inappropriately normal" total peripheral resistance that would actually be reduced in normal subjects with that degree of elevation in cardiac output (11). The incremental increase in cardiopulmonary volume (and cardiac output) results from peripheral vasoconstriction that redistributes the (normal) circulating intravascular volume centrally. In this regard, alterations in atrial natriuretic factor levels have been shown with related physiologic interventions and in disease. Thus, with cardiopulmonary volume expansion or peripheral vasoconstriction (e.g., water immersion), or both, atrial natriuretic factor levels increase. In certain diseases associated with expanded cardiopulmonary volume, such as congestive heart failure, atrial natriuretic factor levels are elevated (3). Therefore, in patients with congestive heart failure, it may be possible to reduce left atrial pressure by stimulating the release of atrial natriuretic factor.

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heart failure or mitral stenosis, and after paroxysmal atrial tachycardia, atrial natriuretic factor levels also are increased. Each of these conditions is associated with atrial distension and a ready stimulus for atrial natriuretic factor release (12).

Ganau and associates (1) evaluated the various physiologic and clinical determinants of atrial natriuretic factor in normal subjects and patients with essential hypertension. They demonstrated that immunoreactive plasma atrial natriuretic factor levels were directly related to age, systolic pressure and echocardiographically measured left atrial and ventricular chamber sizes in normal subjects, but that only age and ventricular size were independent predictors of the hormonal levels. In patients with essential hypertension, the atrial natriuretic factor levels were independently related to age, systolic pressure, atrial size, total peripheral resistance and ventricular systolic performance, although age, atrial size and vascular resistance were independent predictors. Ganau et al. therefore suggest that, in normal subjects, impaired ventricular relaxation with age may contribute to atrial natriuretic factor secretion. They state that correlation with left ventricular size may relate to fluctuations in plasma volume; the latter was not measured. and plasma and cardiopulmonary volumes do not expand with aging. Ganau et al. suggest that in the patients with uncomplicated hypertension, left atrial enlargement contributes to atrial natriuretic factor release, and they show that there was no relation with left ventricular hypertrophy or systolic function. Furthermore, it is of particular interest that the atrial natriuretic factor levels and plasma renin activity were inversely related in patients with essential hypertension, and Ganau et al. suggest an inhibitory effect of atrial natriuretic factor on renin release from the kidney.

Role of intravascular (plasma) volume expansion. In this respect these speculations relating changes with intravascular (plasma) volume with atrial natriuretic factor levels would appear to merit further consideration. It is unfortunate that plasma volume was not determined because this variable is a major determinant of both atrial natriuretic factor secretion and plasma renin activity. Thus, with volume expansion and increased venous return and cardiopulmonary volume, atrial natriuretic factor should increase (3,12). Similarly, with volume expansion, the release of renin from the kidney should be suppressed in normal individuals as well as in patients with essential hypertension (13). The findings of Ganau et al. (1) are perfectly compatible physiologically with previous reports. In normal individuals, vascular and ventricular stiffening, as suggested by these authors, should favor a less distensible vasculature and heart for the circulating volume. Moreover, in their patients with mild hypertension, the elevated atrial natriuretic factor levels might reflect the previously reported increase in cardiopulmonary volume of such patients with mild hypertension, hence the higher cardiac output in these patients (14,15).

Furthermore, patients with milder hypertension may also have a higher total peripheral resistance, which would suggest some degree not only of precapillary constriction but also of postcapillary constriction that increases the vascular resistance. These changes serve to reduce plasma volume (16) and are also probable in the patients of Ganau et al. (1) because of their higher hematocrit levels. The changes are consistent with the plasma renin activity levels the investigators found; they should be reduced, particularly in normotensive subjects.

Conclusions. Thus, the findings of this study (1) demonstrate several important concepts. First, immunoreactive atrial natriuretic factor is elevated in patients with mild to moderately severe essential hypertension. This elevation may relate to an increased central distribution of circulating volume that reflects peripheral arteriolar and venular constriction. Supporting this thesis are the findings of higher cardiac output, total peripheral resistance and hematocrit in these patients that were associated with the increased levels of atrial natriuretic factor. The findings of a direct relation with age and systolic pressure are also consistent with stiffer cardiac chambers and peripheral vessels in patients with hypertension and in normal subjects with aging. With more severe degrees of hypertension, arterial pressure increases in proportion to the increase in total peripheral resistance; in association with these changes, the left ventricle undergoes hypertrophy. Because cardiac output was maintained in these patients, venous return was normal. However, because of the less compliant cardiac chamber, atrial natriuretic factor remained stimulated.

In the final analysis, we are now learning more of the role of atrial natriuretic factor in health and disease and can relate changes in its circulating levels and release mechanisms to pathophysiologic alterations. As we learn of its relation to hemodynamic and cardiac functions, we shall know more of its therapeutic potential. Until then, new data such as these from Ganau et al. (1) are welcome.

References


