

M. Toepfer^a
S.M. Lang^a
G. Hartmann^b
T. Sitter^a
H. Schiffli^a

Departments of

^a Nephrology and

^b Clinical Pharmacology, Medizinische
Klinik, Klinikum Innenstadt, Ludwig
Maximilians University, Munich, Germany

Plasma Adrenomedullin Levels, Body Fluid Status, and End-Stage Renal Failure

Dear Sir,

Adrenomedullin (AM), a recently discovered 52-amino-acid peptide hormone, has biological actions on various organs, most of which appear to be involved in the regulation of cardiovascular function (vasodilation, positive inotropism) and body fluid/electrolyte homeostasis (natriuresis and diuresis). Recently, it has been speculated that this peptide may be important both as a paracrine and an autocrine factor and may serve as a classical circulating hormone [1].

The origins of AM in the plasma of healthy subjects, typically in the low picomolar range, are uncertain. However, circulating AM concentrations are increased in chronic renal failure, and they are strongly correlated with the severity of the disease [2]. To date the mechanisms contributing to the 2- to 4-fold increase in AM levels in patients with end-stage renal disease remain undefined. Clearance or metabolism and increased synthesis or secretion have not been elucidated in dialysis patients with coexisting disorders of body fluid volume status.

Forty-four patients with end-stage renal disease receiving regular hemodialysis (3–4 h three times per week, volumetrically controlled ultrafiltration, low-flux membranes) were selected from a large outpatient population. End-stage renal disease was caused by different etiologies, high blood pressure was defined by repeated predialysis recordings (RR > 140/80 mm Hg), and heart failure was classified by clinical symptoms and verified by X-rays of the chest and echocardiography.

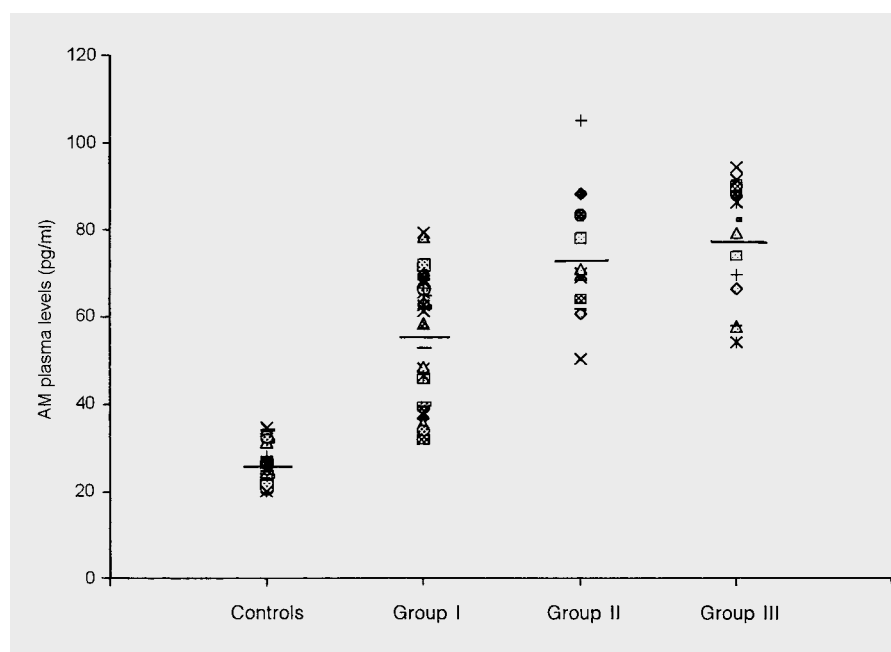


Fig. 1. Plasma concentrations of AM in three subgroups of patients on hemodialysis and in controls: group I were normotensive patients without heart failure; group II hypertensive patients without heart failure, and group III consisted of normotensive patients with heart failure NYHA classes II–IV.

These patients were assigned to three groups: group I (n = 25) were patients with end-stage renal disease only; group II (n = 15) patients with end-stage renal disease complicated by hypervolemic hypertension, and group III (n = 14) consisted of patients

with end-stage renal disease and congestive heart failure according to the New York Heart Association (NYHA) classes III and IV.

Healthy subjects (n = 24) with normal renal function, blood pressure, and heart

function served as controls. The three groups of patients did not differ in age, gender, duration of hemodialysis, and residual renal function. The plasma concentrations of AM were measured with a specific radioimmunoassay for human AM (1–52), as previously described elsewhere [3]. The coefficients of variation were <5% for the intra-assay and 8% for the interassay determinations.

The plasma AM concentrations were significantly increased in each patient with end-stage renal disease as compared with matched control subjects (67.9 ± 15.4 vs. 27.1 ± 4.6 pg/ml; $p < 0.001$). The circulating AM concentrations were significantly higher in hypervolemic hypertensive patients as compared with normotensive dialysis patients (71.4 ± 15.4 vs. 58.0 ± 13.2 pg/ml; $p < 0.01$; fig. 1). Furthermore, the plasma AM levels in patients with end-stage renal failure and heart failure of NYHA classes III or IV were significantly higher as compared with those of patients without signs of heart disease (74.3 ± 14.9 vs. 58.0 ± 13.2 pg/ml; $p < 0.01$).

The major results of our investigation confirm reports of other authors [4, 5] who found an increase in plasma AM levels in patients with end-stage renal disease on hemodialysis. But our data demonstrate for the first time that circulating AM concentrations are affected by the coexistence of cardiovascular disorders. Since other investigators reported that plasma AM levels are positively

correlated with serum creatinine concentrations, one might accept that the elevation of AM in chronic renal failure is associated with a decreased clearance of the peptide in failing kidneys [6]. However, the progressive rise in circulating AM levels in hypervolemic cardiovascular disorders [7], the close correlation between plasma levels of AM and the volume marker atrial natriuretic peptide [8, 9], as well as the fall in plasma AM by isolated ultrafiltration, but not by isovolemic hemodialysis [10], all indicate that plasma AM in end-stage renal disease is elevated by increased synthesis/secretion. There is compelling evidence that AM is secreted by the failing human heart in proportion to the increase in left ventricular filling pressure. In conclusion, we are aware that changes in circulating AM occur in end-stage renal disease, but it is premature to identify a cause-and-effect relationship between increased AM concentrations and pathological states of the cardiovascular system.

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