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Clinical Characteristics of Patients with Increased Urinary Excretion of Adrenaline in Mild to Moderate Heart Failure

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Summary

Background: We have previously demonstrated that adrenaline (AD) is released into the circulation during acute myocardial infarction and is associated with a more severe clinical course. The role of elevated AD levels in congestive heart failure is not known.

Hypothesis: The study aimed to determine whether increased daily AD excretion is associated with more severe clinical symptoms and a more complicated clinical course in patients with exacerbation of congestive heart failure (CHF).

Methods: Urinary excretion of AD, noradrenaline, magnesium (Mg), and potassium (K), serum levels of aldosterone, K, and Mg, as well as the incidence of arrhythmias (24-h Holter) were assessed in 49 patients with CHF New York Heart Association (NYHA) class II–III. The patients were allocated to two groups, with normal (Group 1) and increased (Group 2) excretion of AD.

Results: Groups 1 and 2 did not differ in respect of age, etiology of CHF, or the medication used. Also, left ventricular ejection fraction was similar in the two groups. However, left ventricular end-diastolic dimension was greater in Group 2 (61 ± 9 vs. 55 ± 11 mm, $p < 0.05$), as was the proportion of patients in NYHA class III (74 vs. 40%). Group 2 was also characterized by increased urinary excretion of Mg (60 ± 24 vs. 43 ± 16 mg/24 h, $p < 0.007$) and the presence of more complex and numerous ventricular arrhythmias (74 vs. 37% and 68 vs. 33% of patients, respectively).

Conclusions: Urinary excretion of AD is increased only in a subgroup of patients with CHF. These patients are characterized by a more advanced NYHA class, increased end-diastolic left ventricular diameter, and increased urinary excretion of magnesium. It is likely that all these factors contribute to the presence of more complex and numerous ventricular arrhythmias in this subgroup of patients.

Key words: heart failure, adrenaline, noradrenaline, clinical features

Introduction

Congestive heart failure (CHF) is a major medical problem that is still increasing in prevalence.[1] The long-term prognosis in patients with CHF is very poor. Congestive heart failure is characterized by reflex augmentation of a number of neuroendocrine systems, including the sympathetic nervous system.[2–4] Of importance is the fact that increased sympathetic activity has been shown to be a strong predictor of clinical outcome in CHF.[5] Although not specific to the heart, plasma noradrenaline (NA) concentration has been widely used as a marker of overall sympathetic nervous system activity in patients with CHF.[6,7] It has been consistently found to be elevated in CHF (due to increased neuronal release and decreased efficiency of reuptake) irrespective of the etiology of heart failure, being an independent prognostic marker of subsequent mortality.[2,3,8–10]

In contrast to NA, the pathophysiologic role of adrenaline (AD) in CHF has been studied much less extensively and its importance as a prognostic marker is unknown. Unlike plasma NA (which is a neurotransmitter), plasma AD is a true hormone, released mainly from the adrenal medulla under normal circumstances, with a more significant contribution of extra-adrenal AD stores in CHF.[11] Compared with NA, the magnitude of an increase in plasma AD concentration in patients with CHF is smaller and usually associated with a more advanced stage of the disease.[12,13]

Our previous experimental and clinical studies have demonstrated that AD is released into the circulation during acute myocardial infarction, and it is AD rather than NA that is asso-

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ciated with a more severe clinical course.[14–17] The aim of the present study was to establish whether elevated AD levels are associated with any characteristic clinical and laboratory findings in patients with exacerbation of CHF. In the present study, 24-h urine excretion rather than plasma levels of catecholamines was evaluated, because plasma catecholamine levels reflect only instantaneous sympathetic system activity and cannot be reliably related to all-day sympathetic activity.

Methods

Study Group

The study group consisted of 49 consecutive patients (26 men, 23 women, aged 41–80 years, mean 69.2 ± 8.3 years), admitted to our Department with CHF in New York Heart Association (NYHA) class II–III. Congestive heart failure was diagnosed on the basis of a medical history (dyspnea on exertion or at rest, nocturnal dyspnea), clinical signs of heart failure (tachycardia, jugular venous distension, hepatojugular reflex, crackles, dependent pitting edema), and a chest x-ray (showing an increased cardiac size and pulmonary congestion). All patients were in sinus rhythm and were not taking any antiarrhythmic medication. The exclusion criteria were unstable angina, acute myocardial infarction, myocardial infarction during the last 12 months, evidence of digitalis toxicity; infection, significant renal insufficiency (serum creatinine > 2 mg/dl), other major concomitant diseases.

Holter Recordings

Holter monitoring was performed using a Medilog II recording device (Oxford Instruments, Inc., Largo, Fla., USA) and analyzed automatically by using an appropriate computer algorithm, with manual overread performed by an investigator blinded to the patients' diagnosis and treatment. Description and quantification of ventricular rhythm disturbances was performed by using both automatic and manual analysis (Medilog II). Sections containing recording artifacts were removed and excluded from analysis. Nonsustained ventricular tachycardia (VT) was defined as a sequence of three or more consecutive ventricular extra beats at a heart rate of > 110 beats/min, lasting for < 30 s.

Echocardiography

For echocardiographic examination, an Ultramark 8 apparatus (ATL, Bothell, Wash., USA) was used. Standard M-mode, two-dimensional (2-D) and pulsed-wave Doppler recordings were performed in the parasternal (long- and short-axis planes) and apical (two-, four- and five-chamber views) positions. The following parameters were assessed: dimensions of the heart chambers, left ventricular wall thickness, ventricular contractility, valve function. End-diastolic left ventricular and maximal transverse left atrial dimensions were measured in the four-chamber view, with respective upper normal values of 56 and 40 mm. Left ventricular ejection fraction was calculated in the apical two- and four-chamber views, using a Cardio 200 computer (Kontron, Germany).

Biochemical Measurements

Twenty-four hour urine excretion of NA and AD were measured using a radioimmunoassay (kits from Bio-Rad Laboratories, Munich, Germany). The normal upper values with this method are 39 mg/24 h for NA and 7.5 mg/24 h for AD. Serum aldosterone (ALD) levels were measured using a radioimmunoassay (Aldosterone Ria-Kit 125-J, Insititute for Research, Production, and Applications of Radioisotopes, Prague, Czech Republic). The normal range with this method is 25–310 pg/ml (mean 122 ± 72 pg/ml).

Serum and urine potassium (K) levels were measured with a Beckman Photometer (Beckman Instruments GmbH, Munich, Germany) using flame photometry. The normal serum and urine K levels measured with this method are 3.5–5.5 and 42.8–85.6 mEq/l, respectively. Serum magnesium (Mg) levels and its urine content were determined with an atomic absorption spectrophotometer (OPTON, type FL 6, Oberkochen, Germany). The normal serum and urine Mg levels obtained with this method are 1.7–2.6 mg% and ≤ 40 mg/24 h, respectively.

Study Protocol

Once clinical stabilization had been achieved and the patients had been put on optimal drug therapy (angiotensin-converting enzyme inhibitors, diuretics, digoxin, nitrates), 24-h Holter monitoring was performed. Two categories of Holter-based parameters were considered: (1) the presence or absence of complex arrhythmias (multiform ventricular beats, couplets, or episodes of nonsustained VT);[18–20] (2) the presence or absence of > 10 ventricular extrasystolic beats (VEBs) per hour (i.e., ≤ 10 vs. > 10 VEBs/h).[21]

Echocardiographic examination was performed 1 to 2 days prior to Holter monitoring. For biochemical measurements, fasting venous blood samples were collected between 8 and 9 A.M. after a 2-h rest, 12–18 h after the latest drug administration, immediately before putting on a Holter apparatus. Once the Holter apparatus had been put on, 24-h urine catecholamine collection was started. Magnesium and potassium urine excretion were measured during the following 24 h.

The patients were divided into two groups according to the absence (Group 1) or presence (Group 2) of elevated 24-h urine excretion of AD (i.e., > 7.5 mg/24 h).

Statistical Analysis

The baseline characteristics of the two study groups were compared using an unpaired two-tailed Student's *t*-test and a chi-square test. The Spearman coefficient of correlation was used to evaluate relationships between different parameters measured. A p value of ≤ 0.05 was considered statistically significant. All data are expressed as mean ± standard deviation (SD).

TABLE I Clinical characteristics of patients in Group 1 and Group 2

	Group 1 n = 30	Group 2 n = 19	p < Value
Age (years)	69.0 ± 9.5	69.7 ± 6.3	NS
Sex			
Male	14	12	NS
Female	16	7	
Medical history			
Coronary artery disease	25	16	NS
Myocardial infarction	12	7	NS
Hypertension	14	13	NS
Medication			
Digoxin	17	11	NS
Diuretics	30	19	NS
Nitrates	26	16	NS
ACE inhibitors	7	7	NS
NYHA class			
II	18	5	0.04
III	12	14	

Abbreviations: ACE = angiotensin-converting enzyme, NYHA = New York Heart Association, NS = not significant.

Results

Characterization of the Study Groups

Biochemical measurements revealed normal and increased excretion of AD in 30 (Group 1) and 19 (Group 2) patients, respectively. On average, AD excretion was 4.3 ± 1.6 mg/24 h in Group 1 and 11.8 ± 5.0 mg/24 h in Group 2 ($p < 10^{-10}$). The clinical characteristics of the two subgroups are shown in Table I. The subgroups did not differ with respect to age, etiology of CHF, or the medication used. However, the proportion of patients in NYHA class III was greater in Group 2.

Echocardiographic Measurements

As shown in Table II, the two groups did not differ with respect to left ventricular ejection fraction or left atrial diameter. In contrast, left ventricular end-diastolic diameter was significantly greater in Group 2.

TABLE II Echocardiographic characteristics of patients in Group 1 and Group 2 (mean ± standard deviation)

	Group 1 n = 30	Group 2 n = 19	p < Value
Ejection fraction (%)	37.1 ± 9.1	37.1 ± 10.5	NS
Left atrial diameter (mm)	44.0 ± 6.6	47.3 ± 6.5	NS
Left ventricular diameter (mm)	55.3 ± 10.6	61.3 ± 8.7	0.05

Abbreviation as in Table I.

TABLE III Endocrine and electrolyte measurements in patients in Group 1 and Group 2 (mean ± standard deviation)

	Group 1 n = 30	Group 2 n = 19	p < Value
NA excretion (mg/24 h)	36.2 ± 35	49.2 ± 27.7	NS
Serum aldosterone (pg/ml)	99.7 ± 46.4	124.4 ± 69.3	NS
Serum K (mEq/l)	4.6 ± 0.4	4.7 ± 0.5	NS
K excretion (mEq/l)	36.9 ± 22.4	39.4. ± 19.5	NS
Serum Mg (mEq/l)	1.7 ± 0.3	1.7 ± 0.3	NS
Mg excretion (mg/24 h)	43.0 ± 16.4	59.7 ± 24.5	0.007
Serum Na (mEq/l)	140.9 ± 2.4	141.9 ± 2.3	NS
Na excretion (mEq/l)	163.8 ± 47.2	163.9 ± 68.2	NS

Abbreviations: NA = noradrenaline, K = potassium, Mg = magnesium, Na = sodium, NS = not significant.

Endocrine and Electrolyte Measurements

The results of these biochemical measurements are summarized in Table III. There was no significant difference between Groups 1 and 2 with regard to 24-h excretion of NA or serum aldosterone levels. Serum ion concentrations were also similar in the two groups. However, Group 2 was characterized by a markedly increased urinary magnesium excretion.

Incidence of Ambient Arrhythmias

Holter monitoring revealed that the proportion of subjects with complex arrhythmias was significantly greater among patients with increased AD excretion. Similarly, the proportion of patients with > 10 VEBs/h was greater in Group 2 (Table IV).

Correlations between the Parameters Measured

There was no correlation between various parameters measured, except a significant association between AD and

TABLE IV Holter-based characterization of patients in Group 1 and Group 2 according to the presence or absence of complex arrhythmias (multiform ventricular beats, couplets or episodes of non-sustained VT) or > 10 ventricular extrasystolic beats per hour

	Group 1 n = 30	Group 2 n = 19	p < Value
Complex arrhythmias			
Absent	19	5	0.02
Present	11	14	
>10 VEBs/h			
Absent	20	6	0.02
Present	10	13	

Abbreviations: VT = ventricular tachycardia, VEBs = ventricular extrasystolic beats.

NA levels ($r = 0.4$, $p < 0.005$). A significant correlation was found between the number of VEBs and AD levels ($r = 0.41$, $p < 0.004$), NA levels ($r = 0.4$, $p < 0.005$), and left ventricular end-diastolic dimension ($r = 0.37$, $p < 0.02$).

Discussion

The main finding of the present study is that of an increase in urine AD excretion in a subgroup of patients with CHF. This increase is associated with a more advanced NYHA class, increased end-diastolic left ventricular diameter, increased urinary excretion of magnesium, and the presence of more complex and numerous ventricular arrhythmias. The lack of any difference between the groups with normal and increased AD excretion with respect to the aldosterone and sodium levels suggests that the activation of the renin-angiotensin system was similar in the two groups studied.

An elevation of plasma AD in CHF has been reported in several studies[3, 11, 12, 22–25] in contrast to some earlier reports.[26–29] These discrepancies may be partly related to a different severity of heart failure in various studies. It is also possible that increased plasma levels of AD characterize certain subgroups of patients and are not always evident when all patients with CHF are pooled together. Indeed, our results suggest that AD levels are elevated in patients with CHF with certain discrete clinical characteristics (see above). Methodological factors can also be important, because in all other studies catecholamine levels were measured only in plasma, reflecting only instantaneous sympathetic system activity (which depends on the moment of blood sampling). In contrast, in the present study urinary excretion of catecholamines rather than their plasma levels was evaluated, which gave us a much better measure of overall 24-h sympathetic system activity.

Our finding of the association between increased AD excretion and the incidence of arrhythmias is not surprising, since an extensive body of evidence has shown that activation of the sympathetic nervous system, mediated by both α- and β-adrenergic receptors, may enhance arrhythmogenesis through various arrhythmic mechanisms, such as reentry, afterdepolarizations, or enhanced automaticity.[30] It is not clear from our study whether the observed increased proarrhythmic potential is causally related to elevated levels of AD. However, it is interesting to note that in the study by Van Veldhuisen *et al.*, in patients with CHF treated with ibopamine, plasma NA decreased while plasma AD was unaffected; and no antiarrhythmic effect was observed.[23] We have previously found that, in the course of acute myocardial infarction, AD is released into the circulation, and it is AD rather than NA that is associated with the occurrence of ventricular arrhythmias.[14–17] Specifically, removal of the adrenal gland (the main source of AD) resulted in the abolition of VEBs, whereas administration of AD (in the amount similar to that released spontaneously during acute myocardial infarction) triggered VEBs. These results, although not univocal, suggest that increased levels of AD can be arrhythmogenic in CHF in their own right.

Another interesting finding of our study is that left ventricular ejection fraction was similar in patients with normal and increased AD excretion. This observation, however, does not necessarily indicate that AD excretion is not related to the degree of CHF. In our study, most patients with increased AD excretion were in NYHA class III and had a significantly increased left ventricular diameter. It is likely, therefore, that in this group of patients increased neuroendocrine activation (related to a greater degree of left ventricular dysfunction) compensated for the impairment of systolic function, preventing a decrease in ejection fraction. Consequently, the increased incidence of ventricular arrhythmias in these patients may be due to a combination of direct AD effects and increased wall stress in the dilated ventricle.[31] The latter is further confirmed by a correlation between the end-diastolic left ventricular diameter and the number of VEBs, as seen in the present study.

Another factor, with a potential contribution to the increased incidence of complex ventricular arrhythmias in our study, is increased magnesium loss. This is not a drug-related effect (for example, due to diuretics or digoxin), because the drugs used did not differ between the two groups studied (see Table I). It is likely that increased magnesium loss, most probably related to increased catecholamine levels, is yet another arrhythmogenic mechanism in patients with CHF.[32]

Limitations of the Study

It must be emphasized that, due to the accepted inclusion criteria (NYHA class II–III, sinus rhythm, no antiarrhythmic medication, no history of recent myocardial infarction, clinical stabilization) only a subgroup of patients with CHF entered the study and, consequently, our results cannot be extrapolated to the general CHF population.

It can also be argued that, due to day-to-day variability of ventricular arrhythmias, 24-h Holter recordings were not sensitive enough for reliable assessment of the true occurrence of these arrhythmias. However, the same argument can be applied to both subgroups studied and, therefore, the increased incidence of ventricular arrhythmias in patients with greater AD excretion suggests that our findings were not incidental.

Finally, although AD is likely to exert a direct proarrhythmic effect, our study does not resolve this issue.

Conclusions

Urinary excretion of AD is increased only in a subgroup of patients with CHF. These patients are characterized by a more advanced NYHA class, increased end-diastolic left ventricular diameter, and increased urinary excretion of magnesium. It is likely that all these factors contribute to the presence of more complex and numerous ventricular arrhythmias in this subgroup of patients. The results of the present study suggest an arrhythmogenic effect of both neural and adrenal sympathetic activation in CHF and may provide a rationale for the use of beta blockers and, perhaps, magnesium supplementation in this group of patients.

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