Renal synthesis of dopamine in asymptomatic post-infarction left ventricular systolic dysfunction

António FERREIRA*, Paulo BETTENCOURT*, Manuel PESTANA†, Nuno OLIVEIRA‡, Paula SERRÃO§, Maria Júlia MACIEL‡, Mário CERQUEIRA-GOMES|| and Patrício SOARES-DA-SILVA§

*Serviços de Medicina 3, Hospital S. João, Alameda Hernani Monteiro, 4200 Porto, Portugal, †Serviços de Cardiologia, Hospital S. João, Alameda Hernani Monteiro, 4200 Porto, Portugal, ‡Serviços de Nefrologia, Hospital S. João, Alameda Hernani Monteiro, 4200 Porto, Portugal, §Institute of Pharmacology and Therapeutics, Porto Faculty of Medicine, Alameda Hernani Monteiro, 4200, Porto, Portugal, and ||Unidade I&D Cardiovascular do Porto, Alameda Hernani Monteiro, 4200, Porto, Portugal

ABSTRACT

Left ventricular systolic dysfunction (LVSD) following acute myocardial infarction (AMI), by decreasing renal blood flow, may interfere with renal L-DOPA availability and, consequently, dopamine synthesis. Dopamine of renal origin exerts local natriuretic effects. We studied 17 post-AMI patients with asymptomatic LVSD (ejection fraction < 40%) and 14 without (ejection fraction > 40%), measuring 24-h urinary excretions of L-DOPA, dopamine and its metabolites, and plasma levels of the amines, amine derivatives and type-B natriuretic peptide (BNP). Baseline characteristics were well balanced between the two groups. No differences were observed in urinary volume and sodium and creatinine excretions. The group with asymptomatic LVSD presented lower urinary excretion of L-DOPA (66.8 ± 10.1 versus 115.3 ± 21.9 nmol·day⁻¹, P = 0.04), whereas plasma levels of L-DOPA were identical in both groups. Urinary dopamine was similar in the two groups (1124.2 ± 172.4 versus 1049.0 ± 146.4 nmol·day⁻¹, P = 0.86), resulting in higher urinary dopamine/L-DOPA ratios in patients with asymptomatic LVSD (20.4 ± 3.0 versus 9.9 ± 0.8, P < 0.001). Plasma levels of BNP were higher in the asymptomatic LVSD group (348.5 ± 47.3 versus 146.8 ± 21.9 pg·ml⁻¹, P = 0.003). Ejection fraction was negatively correlated with both plasma levels of BNP and urinary dopamine/L-DOPA ratios. Renal dopamine production is well preserved in patients with asymptomatic LVSD and increased neurohumoral activation, despite reduced urinary excretion of its precursor. This suggests that renal uptake and/or decarboxylation of L-DOPA is enhanced in this condition, as a compensatory mechanism, contributing to preservation of urinary sodium excretion.

INTRODUCTION

The integrity of the arterial circulation, as determined by cardiac output and peripheral vascular resistance or compliance, is the main determinant of renal sodium and water retention [1,2]. Several mechanoreceptors on the high-pressure side of the circulation can sense underfilling and their decreased activation due to a decrease in systemic arterial pressure, stroke volume, renal perfusion, or peripheral vascular resistance leads to activation of several neurohumoral systems that, finally, results in renal sodium and water retention [3–5].

Epithelial cells of renal proximal tubules are endowed with a high aromatic L-amino acid decarboxylase activity,
AMI remains to be established. Sodium metabolism in asymptomatic LVSD following reduced and, consequently, renal dopamine synthesis.

Dopamine of renal origin, by activating D1-like receptors [12,13], exerts natriuretic and diuretic effects through inhibition of main sodium transport mechanisms at the basolateral and apical membranes of proximal tubular epithelial cells, respectively the Na+/K+ ATPase [6,14] and Na+/H+ exchanger [15]. The regulation of renal dopamine production appears to depend on the renal availability of its precursor, the uptake of L-DOPA by tubular epithelial cells, and its decarboxylation into dopamine [16]. The amount of sodium delivered to the kidney affects the renal synthesis of dopamine and has been suggested to represent a major role in determining its availability [17–19]. Dopamine produced in the kidney is extensively metabolized to 3,4-dihydroxyphenylacetic acid (DOPAC), its deaminated metabolite, and to homovanillic acid (HVA), the deaminated and O-methylated metabolite [16].

Acute myocardial infarction (AMI) can lead to left ventricular systolic dysfunction (LVSD) with decreased cardiac output and renal vasoconstriction, resulting in increased renal sodium reabsorption. It is expected that, in this setting, L-DOPA delivery to the kidney might be reduced and, consequently, renal dopamine synthesis. However, the role of the renal dopaminergic system in sodium metabolism in asymptomatic LVSD following AMI remains to be established.

METHODS

Patients
This study included 31 consecutive patients with AMI admitted to a single cardiac unit in a university hospital, located in the North of Portugal. AMI was defined by the presence of two of three of the following criteria: typical cardiac ischaemic symptoms, presence of ischaemic changes on the ECG in two or more leads, or peak elevation of plasma creatine kinase to at least twice the normal level. Patients with concomitant pulmonary diseases, hepatic or renal failure, diabetes mellitus, symptomatic heart failure or clinical evidence of volume overload (elevated jugular venous pressure, peripheral oedema or pulmonary rales) or cardiac valve diseases were excluded from the study.

The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The local Ethics Committee approved the study protocol and participants gave informed consent.

Protocol
Patients were on controlled sodium intake (70 mmol·day−1), for seven days before the investigation was carried out. At the ninth day after AMI, an echocardiography examination (M mode, 2D) was performed. One experienced cardiologist, with the use of the same echocardiography unit (Sonos 2500), performed all echocardiograms. Left ventricular systolic function was assessed by measurement of the left ventricular ejection fraction (EF) using the biplane disc summation method (Simpson rule). In two patients, because of technical reasons, we used the Bullet single and biplane ellipse method. LVSD was considered to be when a patient had an EF less than 40%.

Within 1 h preceding echo examination, between 8.00 and 9.00 am, after overnight fasting, venous blood samples for the determination of sodium, creatinine, L-DOPA, dopamine, noradrenaline, DOPAC and type-B natriuretic peptide (BNP) were collected from an antecubital vein after 20 min of rest in the supine position. Blood was immediately chilled in a plastic tube with heparin (for measurements of amines) and a K2-EDTA tube with aprotinin (for measurement of BNP), centrifuged at 2000 g (4500 rev./min) for 15 min at 0°C, and the plasma stored at −80°C until it was assayed.

Between the eighth and the ninth day, 24-h urine collections were made, using a plastic container with 15 ml 6 M chloridric acid, for the determination of sodium, creatinine, L-DOPA, dopamine and its metabolites. Urine samples for the measurement of amines were stored in plastic tubes at −80°C until required.

The assay of catecholamines and their metabolites in urine (L-DOPA, dopamine, noradrenaline, DOPAC and HVA) and in plasma samples (L-DOPA, dopamine, noradrenaline and DOPAC) were performed by HPLC with electrochemical detection, as described previously [20,21]. Dihydroxybenzylamine was used as internal standard and the inter-assay coefficient of variation was less than 5%. The quantification of HVA was performed separately by HPLC with electrochemical detection, using 50 μl aliquots of filtered samples directly injected into the chromatograph. The lower limit of detection of L-DOPA, dopamine, noradrenaline, DOPAC and HVA ranged from 350 to 1000 fmol.

BNP was measured by immunoradiometric assay (IRMA; Shianogi Co Ltd., Osaka). The inter-assay coefficient of variation was less than 8% and the lower limit of detection was 2 pg·ml−1.

Statistical analysis
We used the Mann–Whitney U test to test for differences in numeric variables. For comparisons of categorical variables, we used the likelihood ratio χ2 or the Fisher’s exact test when appropriate. For bivariate correlation, we used the Spearman ρ.

In order to adjust for subtle differences in glomerular filtration rate, urinary excretions of dopamine, L-DOPA, and metabolites were analysed not only as 24-h total excretion but also after adjustment for creatinine urinary excretion.

Data are expressed as means ± S.E.M. P values less than
Renal dopamine in left ventricular dysfunction

0.05 were considered statistically significant. Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) software from SPSS Inc. (Chicago, IL, U.S.A.).

RESULTS

No differences in baseline characteristics were observed between patients with an EF $< 40\%$ ($32.5 \pm 1.4\%, n = 17$) and patients with an EF $\geq 40\%$ ($47.1 \pm 1.7\%, n = 14$) with respect to age, body surface area, sex, heart rate, blood pressure, creatinine clearance and medications (Table 1). None of the patients was on diuretic therapy. All patients received 100 mg of aspirin per day, starting on admission day. No other non-steroid anti-inflammatory drugs or other drugs known to affect sodium handling were used.

Urinary volume ($1.32 \pm 0.09$ versus $1.81 \pm 0.25$ litres · day$^{-1}$, $P = 0.32$), urinary sodium excretion ($65.5 \pm 8.1$ versus $70.5 \pm 10.1$ mmol · day$^{-1}$, $P = 0.77$) and creatinine ($1.12 \pm 0.08$ versus $1.17 \pm 0.09$ g · day$^{-1}$, $P = 0.44$) and the fractional excretion of sodium ($0.46 \pm 0.07$ versus $0.39 \pm 0.04\%$, $P = 0.52$) were also similar in the two groups.

Urinary l-DOPA was found to be significantly lower in patients with asymptomatic LVSD than in patients with and EF $\geq 40\%$, whereas dopamine excretion was similar in both groups (Table 2). Urinary dopamine/l-DOPA ratios (a rough measure of renal l-DOPA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EF $&lt; 40%$ ($n = 17$)</th>
<th>EF $\geq 40%$ ($n = 14$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.1 $\pm$ 2.8</td>
<td>60.0 $\pm$ 2.7</td>
<td>0.98</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>76.5</td>
<td>85.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Body surface area (m$^2$)</td>
<td>1.77 $\pm$ 0.04</td>
<td>1.79 $\pm$ 0.05</td>
<td>0.57</td>
</tr>
<tr>
<td>Heart rate (beats · min$^{-1}$)</td>
<td>64.2 $\pm$ 2.4</td>
<td>61.4 $\pm$ 2.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>78.1 $\pm$ 2.6</td>
<td>80.1 $\pm$ 3.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Creatinine clearance (ml · min$^{-1}$ · 1.73 m$^{-2}$)</td>
<td>72.1 $\pm$ 6.3</td>
<td>83.2 $\pm$ 6.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Urinary sodium (mmol · day$^{-1}$)</td>
<td>65.5 $\pm$ 8.1</td>
<td>70.5 $\pm$ 10.1</td>
<td>0.77</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.46 $\pm$ 0.07</td>
<td>0.39 $\pm$ 0.04</td>
<td>0.52</td>
</tr>
<tr>
<td>ACE-inhibitors (%)</td>
<td>76.5</td>
<td>64.3</td>
<td>0.69</td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>64.7</td>
<td>71.4</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Table 2 Differences in urinary l-DOPA, dopamine and its metabolites, and in urinary dopamine/l-DOPA ratios between patients with an EF $< 40\%$ and those with an EF $\geq 40\%$, and their statistical significance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EF $&lt; 40%$ ($n = 17$)</th>
<th>EF $\geq 40%$ ($n = 14$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-DOPA (nmol · day$^{-1}$)</td>
<td>66.8 $\pm$ 10.1</td>
<td>115.3 $\pm$ 21.9</td>
<td>0.04</td>
</tr>
<tr>
<td>(nmol · g$^{-1}$ of urinary creatinine)</td>
<td>59.7 $\pm$ 7.4</td>
<td>94.7 $\pm$ 13.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Dopamine (nmol · day$^{-1}$)</td>
<td>1124.2 $\pm$ 172.4</td>
<td>1049.0 $\pm$ 146.4</td>
<td>0.86</td>
</tr>
<tr>
<td>(nmol · g$^{-1}$ of urinary creatinine)</td>
<td>999.2 $\pm$ 122.8</td>
<td>881.6 $\pm$ 88.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Noradrenaline (nmol · day$^{-1}$)</td>
<td>133.8 $\pm$ 20.4</td>
<td>133.1 $\pm$ 20.0</td>
<td>0.98</td>
</tr>
<tr>
<td>(nmol · g$^{-1}$ of urinary creatinine)</td>
<td>125.5 $\pm$ 20.5</td>
<td>118.1 $\pm$ 16.2</td>
<td>0.95</td>
</tr>
<tr>
<td>DOPAC (nmol · day$^{-1}$)</td>
<td>3798.0 $\pm$ 760.1</td>
<td>3803.5 $\pm$ 644.1</td>
<td>0.74</td>
</tr>
<tr>
<td>(nmol · g$^{-1}$ of urinary creatinine)</td>
<td>3361.3 $\pm$ 572.1</td>
<td>3247.1 $\pm$ 471.1</td>
<td>0.89</td>
</tr>
<tr>
<td>HVA (nmol · day$^{-1}$)</td>
<td>8367.4 $\pm$ 1476.6</td>
<td>8854.5 $\pm$ 1499.7</td>
<td>0.83</td>
</tr>
<tr>
<td>(nmol · g$^{-1}$ of urinary creatinine)</td>
<td>7841.2 $\pm$ 1301.1</td>
<td>7528.0 $\pm$ 1146.0</td>
<td>0.65</td>
</tr>
<tr>
<td>Urinary dopamine/l-DOPA ratios</td>
<td>20.4 $\pm$ 3.0</td>
<td>9.9 $\pm$ 0.8</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Left ventricular dysfunction leads to activation of several neurohumoral systems. Some of these systems have vasoconstrictor, anti-natriuretic and anti-diuretic properties, while others act as vasodilators, and increase natriuresis and diuresis. The balance between these systems modulates renal sodium metabolism. In advanced phases of ventricular dysfunction, the vasodilators and natriuretics are clearly overwhelmed by the vasoconstrictors and anti-natriuretics, but in the earlier phases, activation of natriuretic systems, namely natriuretic peptides, is able to maintain sodium excretion [22,23]. In our study sample, the group of patients with asymptomatic LVSD presented higher levels of plasma BNP (revealing more intense activation of the compensatory natriuretic peptides system) and higher urinary dopamine/L-DOPA ratios than the other group. EF was shown to be negatively correlated with both plasma BNP levels and urinary dopamine/L-DOPA ratios. These data suggest that the worsening of ventricular dysfunction is associated with increasing activity of both the natriuretic peptide system and renal dopaminergic system. Furthermore, urinary sodium excretion and fractional excretion of sodium were similar in both groups, suggesting that, not only BNP, but also the contemporary activation of the renal dopaminergic system may act as an early compensatory response to stimuli leading to sodium and water retention.

Several conditions, other than cardiac dysfunction, may affect renal dopamine production. Because the renal tubules are the main source of renal dopamine, renal parenchymal diseases, namely chronic renal failure, are associated with decreased urinary excretion of dopamine [24–26]. On the other hand, some medications, namely angiotensin-converting enzyme inhibitors and frusemide, are also known to influence renal dopamine production [27,28]. There is also some evidence that age correlates negatively with plasma levels of L-DOPA and urinary dopamine [29,30].

We studied a well-balanced population on controlled low sodium intake, finding no significant differences between the two groups, with respect to demographic characteristics, medications, renal function, and levels of L-DOPA and dopamine in plasma. Thus, it is likely that the increased renal ability to synthesize dopamine, despite the reduced availability of L-DOPA, might be the mechanism for the preservation of the amine formation in patients with asymptomatic LVSD.

The non-significant trend to a reduction in glomerular filtration rate among patients with asymptomatic LVSD following AMI may suggest that renal delivery of L-DOPA is reduced in this condition. Further studies are needed, namely determining the renal blood flow and glomerular filtration rate (using para-aminohippurate and inulin clearance respectively), in order to clarify the relationship between ventricular function and renal delivery of L-DOPA in this condition. Studies from
several laboratories have shown that the natriuretic and diuretic response elicited by D1-like receptor agonists involves changes in intrarenal haemodynamics and direct tubular action. At lower doses, it is the direct action on the renal tubules that accounts for the natriuresis and diuresis induced by selective D1-like receptor agonists [12,13]. It is unlikely that dopamine of renal origin may have access to receptors located in renal vasculature to produce changes in renal haemodynamics. In fact, administration of the selective D1-like receptor antagonist Sch 23390 was found to have no effect on renal haemodynamics, but markedly decreased urinary sodium [31]. On the other hand, renal tubular epithelial cells are endowed with high monoamine oxidase and catechol-O-methyltransferase activities, leading to rapid degradation of newly-formed dopamine [32–34]. Interestingly, the urinary excretion of dopamine metabolites and the metabolites/dopamine ratios showed no differences between the two groups, indicating that the renal catabolism of dopamine is not affected in patients with asymptomatic LVSD after AMI.

AMI is followed by an early sharp rise in sympathetic drive followed by a gradual fall in catecholamines plasma levels [35,36]. Because our study was performed on the ninth day post-infarction, it is believed that the results were not influenced by that earlier rise in sympathetic activity. The similarity in urinary noradrenaline excretion and in the natriuretic index (urinary noradrenaline/dopamine ratio) found in the two study groups suggests that their renal sympathetic activity was identical.

In conclusion, patients with asymptomatic LVSD after AMI have a reduced urinary excretion of L-DOPA when compared with patients without ventricular dysfunction. Nevertheless, their renal dopamine production is preserved, as a result of a compensatory increase in the renal ability to take up and/or decarboxylate filtered or circulating L-DOPA, without simultaneous increments in dopamine metabolism, contributing to the preservation of urinary sodium excretion. Whether this is a transient process or a permanent compensatory mechanism is a question that merits further investigation, namely by studying patients with chronic heart failure or chronic asymptomatic LVSD.

ACKNOWLEDGMENT

We gratefully acknowledge the Cardiac Unit and Nephrology laboratory staff for their technical assistance.

REFERENCES


© 2000 The Biochemical Society and the Medical Research Society