Neurohormonal activation, the renal dopaminergic system and sodium handling in patients with severe heart failure under vasodilator therapy

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ABSTRACT

The benefits of tailoring therapy with vasodilators in patients with severe heart failure are well documented, but this may lead to neurohormonal activation and sodium retention. Renal dopamine has local natriuretic actions and interacts with other hormones involved in renal sodium handling. The aim of the present work was to determine the effects of arterial underfilling induced by vasodilator therapy on renal sodium handling, neurohormonal activation and the activity of the renal dopaminergic system in patients with severe heart failure. For this purpose we monitored haemodynamic parameters, plasma levels of type B natriuretic peptide (BNP), catecholamines, aldosterone, renin activity (PRA), sodium and creatinine, and urinary excretion of sodium, creatinine, L-DOPA, dopamine and its metabolites, before initiation of sodium nitroprusside therapy and every 6 h thereafter (for 42 h), and again after 5 days of angiotensin-converting enzyme (ACE) inhibition, in 10 male patients with severe heart failure. The results of nitroprusside therapy were a marked increase in cardiac index and a substantial decrease in systemic vascular resistance index. Plasma levels of BNP decreased significantly, while PRA, noradrenaline and aldosterone showed marked increases, resulting in a substantial reduction in urinary sodium excretion. Creatinine clearance was not affected. Urinary dopamine and dopamine metabolites increased in response to nitroprusside therapy. After 5 days of ACE inhibition, urinary sodium returned to baseline values, while urinary dopamine was markedly reduced. These results suggest that the renal dopaminergic system is activated in patients with severe heart failure by stimuli leading to sodium renal reabsorption.

INTRODUCTION

The integrity of the arterial circulation is the main determinant of sodium and water balance. A decrease in either cardiac output, as in low-output heart failure (HF), or peripheral vascular resistance, as in the case of high-output HF or other vasodilatation states, results in arterial underfilling, leading to understimulation of the baroreceptors located in the high-pressure side of the circulation. This results in activation of several systems

Key words: heart failure, neurohormonal activation, renal dopamine, sodium.

Abbreviations: ACE, angiotensin-converting enzyme; BNP, type B natriuretic peptide; DOPAC, 3,4-dihydroxyphenylacetic acid; HF, heart failure; HVA, homovallinic acid; PRA, plasma renin activity.

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with anti-natriuretic, anti-diuretic and vasoconstrictor actions (namely sympathetic and renin/angiotensin/aldosterone systems, and the non-osmotic release of vasopressin), leading to renal sodium and water re-absorption, and consequently to volume overload and the occurrence of oedema. Different counter-regulatory systems, with natriuretic, diuretic and vasodilator properties (as in the case of the natriuretic peptides of cardiac origin), are also activated [1–7]. Type B natriuretic peptide (BNP) is produced mainly in the left ventricle in response to increases in volume and pressure. BNP plasma levels rise early in the setting of ventricular dysfunction, and correlate well with the severity of cardiac dysfunction [8,9]. Dopamine has been included among these counter-regulatory systems [10,11], although the status of endogenous dopamine in HF, and particularly of renal dopamine metabolism in this condition, has not yet been studied [10].

The epithelial cells of the renal proximal convoluted tubules are endowed with high aromatic l-amino acid decarboxylase activity. Filtered t-DOPA (l-3,4-dihydroxyphenylalanine) is taken up by these cells and decarboxylated to form dopamine [12–17]. The amine is then secreted into the tubular lumen and activates dopamine D1 receptors located in cell membrane, thus inhibiting major sodium transport mechanisms at the basolateral and apical membranes of the renal proximal tubules (respectively Na+/K+-ATPase and the Na+/H+-exchanger), which results in increased natriuresis and diuresis [12,18–21]. The metabolism of renal dopamine involves both monoamine oxidase and catechol-O-methyltransferase. Dopamine is extensively degraded to 3,4-dihydroxyphenylacetic acid (DOPAC), the deaminated metabolite, and to homovallinic acid (HVA), the deaminated and O-methylated metabolite [22].

The regulation of this non-neuronal renal dopaminergic system depends mainly on the availability of t-DOPA, its decarboxylation into dopamine and cell mechanisms of outward amine transfer [22]. The availability of dopamine to activate its specific receptors is determined by factors that affect the formation (mainly the amounts of t-DOPA and sodium delivered to the kidney) and degradation of the amine [23–25]. As mentioned above, the status of the renal dopaminergic system in HF has not been studied previously. However, a recent study suggested that, in asymptomatic left ventricular systolic dysfunction following acute myocardial infarction, there is activation of the production of cardiac natriuretic peptides and stimulation of the renal dopaminergic system, which might contribute to preserve sodium excretion in this setting [26]. Another study showed that the renal dopaminergic system is activated in patients with chronic HF in a sodium-dependent manner [27].

A particular relationship has been described between natriuretic peptides and renal dopamine synthesis. Background levels of endogenous dopamine are needed for the expression of the full effects of natriuretic peptides. However, these peptides may have an inhibitory action on t-DOPA uptake and dopamine formation [25]. Dopamine also interacts with angiotensin II by inhibiting the angiotensin II-mediated activation of Na+/K+-ATPase and the Na+/H+-exchanger, and angiotensin II-mediated proximal tubule re-absorption [28,29]. It also decreases angiotensin AT1 receptor expression in the proximal tubule [30]. An antagonistic relationship between the renal actions of dopamine and noradrenaline has also been documented [31].

Patients with HF due to severe depression of left ventricular systolic function clearly benefit from an individualized therapeutic approach guided by haemodynamic parameters. This approach includes the utilization of direct-acting vasodilators, such as sodium nitroprusside, after a period of volume depletion induced by furosemide [32]. This therapeutic strategy, by reducing left ventricle filling pressure and volume, contributes to decrease mitral valve regurgitation and to increase the forward stroke volume, and has proved very useful in the management of patients with severe HF [33]. Nevertheless, because of the intense arterial vasodilatation produced by sodium nitroprusside, such therapy may intensify underfilling, leading to greater sodium retention.

The aim of the present work was to evaluate the activity of the sympathetic and renin/angiotensin/aldosterone systems, the production of BNP, the activity of the renal dopaminergic system and their relationship with renal sodium handling, in response to a therapeutic approach designed to reduce afterload in patients with HF and severely depressed left ventricular systolic function. Because inhibitors of angiotensin-converting enzyme (ACE) are usually used to chronically maintain optimum haemodynamic parameters following sodium nitroprusside taping [32], the study was repeated after 5 days of ACE inhibition.

METHODS

Patients

This study included 10 patients with newly diagnosed and previously untreated HF due to severe left ventricular systolic dysfunction (left ventricle ejection fraction < 20%). Patients were recruited in the emergency department, to which they had been admitted because of dyspnoea. Patients with acute cardiac ischaemic events, concomitant pulmonary disease, diabetes mellitus, hepatic or renal failure, or systolic blood pressure below 100 mmHg, and those previously treated with ACE inhibitors, 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.

Methods
All patients were submitted to an echocardiographic evaluation (M mode; two-dimensional) using the same echocardiography unit (HP Sonos 5500). The left ventricular ejection fraction was assessed using the biplane disc summation method (Simpson rule). Eligible patients were admitted to an in-hospital unit and treated with furosemide given intravenously at a fixed dose of 20 mg every 6 h (at 01.00, 07.00, 13.00 and 19.00 hours) over 5 days in order to achieve their optimal dry weight. Simultaneously, a low-sodium diet, containing 70 mmol of sodium per day, was started. On day 6 of the investigation, at 07.00 hours, non-invasive haemodynamic monitoring was started, using thoracic electrical bioimpedance (BioZ.com System; CardioDynamics International Corp., San Diego, CA, U.S.A.). At 13.00 hours on the same day, sodium nitroprusside was started at a dose of 0.5 μg min⁻¹ kg⁻¹. This dose was increased every 6 h during the following 36 h, until systemic vascular resistance index dropped to below 1500 dyne·s·cm⁻⁵·m² or systolic blood pressure fell to <90 mmHg. On day 8 of the study, at 07.00 hours, lisinopril was administered at a dose of 10–20 mg, followed by tapering of sodium nitroprusside in order to maintain the haemodynamic objectives described above. Then lisinopril was administered every 12 h until the end of the study period (13 days). Furosemide was maintained at the same dose throughout the study.

Blood samples were obtained before initiation of sodium nitroprusside therapy and every 6 h thereafter for 42 h, and at the end of the study. Blood was collected from an antecubital vein into a plastic tube with heparin (for measurement of l-DOPA, dopamine, DOPAC and noradrenaline), a plastic tube with K₂EDTA [for measurement of plasma renin activity (PRA) and aldosterone], a plastic tube with K₂EDTA and aprotinin (for measurement of BNP) and a plastic tube with heparin/lithium (for creatinine and electrolytes). Tubes for PRA, aldosterone, BNP and catechol derivatives were previously refrigerated. Blood for PRA, aldosterone, BNP and amines was centrifuged immediately at 0 °C for 15 min at 2000 g and stored at −80 °C until assay. Starting at 07.00 hours on day 6 and ending 6 h after the last increment in sodium nitroprusside dose, and again on the last day of the study, 6 h urine samples were collected into plastic bags containing 5 ml of 6 M HCl for determination of dopamine, its precursor (l-DOPA) and metabolites, and of creatinine and sodium. For this purpose, a Foley catheter was passed through patient’s urethra into the bladder, and connected to a valve device, leading finally to the plastic bag.

The assay of catecholamines and their metabolites in urine (l-DOPA, dopamine, noradrenaline, DOPAC and HVA) and in plasma (l-DOPA, dopamine, noradrenaline and DOPAC) was performed by HPLC with electrochemical detection, as described previously [34,35]. Dihydroxybenzylamine was used as internal standard, and the inter-assay coefficient of variation was <5%. The quantification of HVA was performed separately by HPLC with electrochemical detection, using 50 μl aliquots of filtered samples injected directly 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 (Shianogi Co Ltd., Osaka, Japan), and PRA and aldosterone were measured by RIA (alderctk-2 and renctk; DiaSorin s.r.l., Saluggia, Italy). The inter-assay coefficient of variation was <8%, and the lower limit of detection was 2 pg ml⁻¹ for BNP, 0.20 ng ml⁻¹ for PRA and 20 pg ml⁻¹ for aldosterone.

Statistical analysis
The Wilcoxon signed ranks test was used to test for differences between sequential measurements. Data are expressed as means ±S.E.M. P values of <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
All patients were male, with a mean age of 70.2 ± 2.9 years. The baseline ejection fraction was 15.2 ± 1.1%. The maximum sodium nitroprusside dose was 3.6 ± 0.7 μg min⁻¹ kg⁻¹ and the lisinopril dose was 30.0 ± 3.0 mg day⁻¹.

Effects of sodium nitroprusside administration
As shown in Figure 1, sodium nitroprusside therapy resulted in a marked reduction in the systemic vascular resistance index and an increase in the cardiac index. These haemodynamic alterations were accompanied by a marked decrease in urinary sodium excretion and a moderate decrease in urinary volume. Urinary creatinine was increased by sodium nitroprusside therapy, but creatinine clearance remained unaltered.

Plasma BNP levels were significantly lowered by sodium nitroprusside (Figure 2). PRA, plasma aldosterone and plasma noradrenaline increased substantially in response to sodium nitroprusside therapy. Plasma levels of l-DOPA underwent a less pronounced increase. The renal delivery of l-DOPA, which takes into account the plasma levels of l-DOPA and creatinine clearance, was increased slightly by sodium nitroprusside therapy. Plasma dopamine and DOPAC levels remained un-
altered. Serum sodium decreased as a consequence of sodium nitroprusside therapy (Table 1).

Urinary levels of dopamine and its metabolites (DOPAC and HVA) were increased significantly in response to sodium nitroprusside therapy (Figure 3). In contrast, no statistically significant variations were observed in urinary L-DOPA. Urinary noradrenaline was not altered. However, the urinary dopamine/noradrenaline ratio was increased significantly during nitroprusside therapy.

**Effects of ACE inhibition**

As shown in Table 1, plasma levels of L-DOPA and DOPAC were significantly reduced as a result of lisinopril therapy. As a consequence of the decrease in plasma levels of L-DOPA, the renal delivery of L-DOPA was significantly decreased after ACE inhibition (from 3991.2 ± 426.5 to 1944.2 ± 269.6 pmol·min⁻¹·1.73 m⁻²; P = 0.005). Plasma dopamine remained unaltered. ACE inhibition resulted in an increase in the plasma levels of BNP and sodium. However, BNP plasma levels remained significantly lower than baseline values (before nitroprusside therapy). Plasma noradrenaline and aldosterone returned to baseline values after ACE inhibition. As expected, PRA was markedly increased as a result of ACE inhibition.

ACE inhibition was accompanied by an intense natriuretic response (Table 2). Urine volume also increased, but not significantly. Urinary creatinine and creatinine clearance (from 75.1 ± 8.7 to 68.0 ± 8.7 ml·min⁻¹·1.73 m⁻²; P = 0.11) showed non-statistically significant reductions. Urinary dopamine metabolites were lowered by ACE inhibition, returning to baseline values. Urinary noradrenaline presented a non-significant trend to decrease after ACE inhibition.

We found an inverse relationship between the changes in urinary sodium and dopamine (Figure 4). Urinary sodium decreased as a consequence of sodium nitroprusside therapy, whereas urinary dopamine increased. In contrast, the effects of ACE inhibition were a marked
Figure 2  Plasma levels of BNP, PRA, aldosterone, noradrenaline, L-DOPA, dopamine and DOPAC, and renal delivery of L-DOPA, in 10 patients with severe HF treated with increasing doses of sodium nitroprusside
Significance of differences: *P < 0.05 compared with values at 0 h.

Table 1  Plasma sodium, L-DOPA, dopamine, DOPAC, noradrenaline, PRA, aldosterone and BNP at baseline, after 42 h of sodium nitroprusside therapy and after 5 days of ACE inhibition
Significance of differences: *P < 0.05 compared with baseline; †P < 0.05 compared with after 42 h of nitroprusside.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 42 h of nitroprusside</th>
<th>After 5 days of ACE inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol·l⁻¹)</td>
<td>138.0 ± 0.9</td>
<td>134.1 ± 1.5 *</td>
<td>137.6 ± 1.1†</td>
</tr>
<tr>
<td>L-DOPA (pmol·ml⁻¹)</td>
<td>43.6 ± 3.1</td>
<td>55.9 ± 5.7</td>
<td>28.7 ± 1.2†</td>
</tr>
<tr>
<td>Dopamine (pmol·ml⁻¹)</td>
<td>59.5 ± 11.5</td>
<td>66.1 ± 9.5</td>
<td>55.0 ± 10.7</td>
</tr>
<tr>
<td>DOPAC (pmol·ml⁻¹)</td>
<td>69.3 ± 11.1</td>
<td>100.8 ± 27.6</td>
<td>50.9 ± 3.1†</td>
</tr>
<tr>
<td>Noradrenaline (pmol·ml⁻¹)</td>
<td>6.83 ± 1.39</td>
<td>14.08 ± 1.44 *</td>
<td>6.61 ± 1.09†</td>
</tr>
<tr>
<td>PRA (ng·h⁻¹·ml⁻¹)</td>
<td>1.88 ± 0.69</td>
<td>8.70 ± 3.19 *</td>
<td>17.88 ± 4.17†</td>
</tr>
<tr>
<td>Aldosterone (pg·ml⁻¹)</td>
<td>161.1 ± 32.5</td>
<td>320.7 ± 74.8 *</td>
<td>164.0 ± 46.4</td>
</tr>
<tr>
<td>BNP (pg·ml⁻¹)</td>
<td>739.9 ± 181.2</td>
<td>397.8 ± 125.1 *</td>
<td>548.5 ± 189.7*</td>
</tr>
</tbody>
</table>
Figure 3  Urinary l-DOPA, dopamine, DOPAC, HVA and noradrenaline levels in 10 patients with severe HF treated with increasing doses of sodium nitroprusside

Significance of differences: *P < 0.05 compared with values at 0 h.

Table 2  Values for 6 h urine volume, urinary sodium, creatinine, l-DOPA, dopamine, DOPAC, HVA and noradrenaline, and natriuretic index (dopamine/noradrenaline ratios), before sodium nitroprusside initiation, during the highest sodium nitroprusside dose and after 5 days of ACE inhibition

Significance of differences: *P < 0.05 compared with before nitroprusside; †P < 0.05 compared with highest nitroprusside dose.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before nitroprusside</th>
<th>During highest nitroprusside dose</th>
<th>After 5 days of ACE inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml·6 h⁻¹)</td>
<td>558.0 ± 64.5</td>
<td>348.0 ± 63.1*</td>
<td>662.0 ± 153.2</td>
</tr>
<tr>
<td>Sodium (mmol·6 h⁻¹)</td>
<td>54.9 ± 11.5</td>
<td>15.7 ± 4.6*</td>
<td>57.4 ± 19.5†</td>
</tr>
<tr>
<td>Creatinine (mg·6 h⁻¹)</td>
<td>287.3 ± 28.6</td>
<td>380.8 ± 55.4*</td>
<td>293.9 ± 26.8</td>
</tr>
<tr>
<td>l-DOPA (nmol·6 h⁻¹)</td>
<td>14.9 ± 2.0</td>
<td>22.3 ± 3.7</td>
<td>13.3 ± 3.1</td>
</tr>
<tr>
<td>Dopamine (nmol·6 h⁻¹)</td>
<td>281.9 ± 39.9</td>
<td>421.9 ± 70.6*</td>
<td>270.6 ± 39.2‡</td>
</tr>
<tr>
<td>DOPAC (nmol·6 h⁻¹)</td>
<td>1053.9 ± 160.6</td>
<td>2041.1 ± 420.5*</td>
<td>984.9 ± 141.9†</td>
</tr>
<tr>
<td>HVA (nmol·6 h⁻¹)</td>
<td>3929.5 ± 498.3</td>
<td>5666.0 ± 1067.5*</td>
<td>4035.3 ± 528.9</td>
</tr>
<tr>
<td>Noradrenaline (nmol·6 h⁻¹)</td>
<td>211.8 ± 59.0</td>
<td>202.3 ± 46.2</td>
<td>160.8 ± 38.7</td>
</tr>
<tr>
<td>Urinary dopamine/noradrenaline</td>
<td>3.26 ± 0.61</td>
<td>20.8 ± 8.47*</td>
<td>3.61 ± 0.61†</td>
</tr>
</tbody>
</table>
DISCUSSION

Sodium nitroprusside therapy produced intense arterial vasodilatation. The subsequent arterial underfilling resulted in activation of the renin/angiotensin/aldosterone and sympathetic systems, as shown by the increased levels of PRA, aldosterone and noradrenaline, thus leading to increased renal sodium re-absorption. The decrease in BNP plasma levels induced by sodium nitroprusside may be explained by a decrease in left ventricular volume and pressure, and contributed additionally to lower sodium excretion.

The reduction in sodium excretion that resulted from sodium nitroprusside therapy was accompanied by a substantial increase in the urinary excretion of dopamine and its metabolites DOPAC and HVA, indicating that renal dopamine tonus increased. This suggests that the renal dopaminergic system acts as a compensatory mechanism that is activated by stimuli leading to sodium retention. Interestingly, renal sympathetic activity was not affected by nitroprusside therapy, as indicated by the absence of variations in the urinary excretion of noradrenaline. This resulted in an increase in the so-called natriuretic index (urinary dopamine/noradrenaline ratio), favouring dopamine and thus the stimulation of sodium excretion, as noradrenaline and dopamine have antagonistic actions on renal sodium handling [31].

Dopamine of renal origin plays a central role in the interactive network that regulates renal sodium handling. This network involves an intricate interaction between signals from extrarenal and intrarenal sources, and between anti-natriuretic and natriuretic factors [31,36]. Angiotensin II exerts direct effects on proximal tubule transport, the major site of salt and water re-absorption, independent of alterations in renal haemodynamics [37,38]. It stimulates sodium re-absorption via activation of apical Na⁺−H⁺ exchanger and basolateral Na⁺/K⁺-ATPase [29]. Dopamine exerts natriuretic effects by inhibiting the activity of these two transporters [12,18–21]. Furthermore, dopamine inhibits the angiotensin II-mediated activation of these transporters and re-absorption in the proximal tubule [28,29]. It also decreases the expression of angiotensin II type-1 receptors [30]. Noradrenaline exerts anti-natriuretic effects by acting at α-adrenoreceptors [31], and aldosterone acts primarily in the distal nephron to increase the re-absorption of sodium [39]. Natriuretic peptides also act in the distal nephron, increasing sodium excretion [40,41]. They inhibit L-DOPA uptake, thus reducing renal dopamine production [25]. The present study reveals that underfilling caused by sodium nitroprusside activates anti-natriuretic systems, such as the renin/angiotensin/aldosterone and sympathetic systems, and suppresses the production of natriuretic peptides. Renal dopamine synthesis was increased, probably as a compensatory process. Various mechanisms have been implicated in the increase in renal dopamine production. On the one hand, the increase in the plasma levels of L-DOPA contributed...
to an improvement in the renal availability of the dopamine precursor, and might explain the increment in the production of renal dopamine. On the other hand, it can be speculated that the decrease in plasma BNP levels following sodium nitroprusside therapy facilitated the uptake of L-DOPA into the tubular cells and its conversion into dopamine.

ACE inhibition produced a marked neurohumoral modulator effect, reducing sympathetic activation and aldosterone production, and originating a marked natriuretic response and a more modest diuretic response. This was accompanied by a global decrease in the activity of the renal dopaminergic system, due to a marked decrease in the renal delivery of L-DOPA and probably also to an increased inhibitory effect of natriuretic peptides on L-DOPA uptake. This decrease in renal dopamine tonus also corroborates the antagonistic relationship between the renal dopaminergic system and the renin/angiotensin/aldosterone and sympathetic systems. The inverse relationship between changes in urinary sodium and urinary dopamine also suggests that the paracrine renal dopaminergic system might be activated by stimuli that lead to sodium retention. The preservation of renal function, glomerular filtration rate and urinary creatinine excretion suggests that the renal haemodynamics were not affected significantly by sodium nitroprusside or lisinopril therapy, and were not a major determinant of the variations in renal sodium handling.

**Study limitations**

This was not a placebo-controlled study. Thus its results must be interpreted with caution. However, it seems unlikely that the increase in renal dopamine production was related to haemo-concentration in the setting of a reduced glomerular filtration rate produced by nitroprusside. Firstly, nitroprusside therapy was not accompanied by any alterations in creatinine clearance, an index of the glomerular filtration rate. Secondly, haemo-concentration should lead to a decrease in renal plasma flow and thus in the renal delivery of L-DOPA. This would result in a decrease in the urinary excretion of dopamine, and not to an increase. Furthermore, as stated above, we measured the total urinary excretion of dopamine and not the urinary concentration of the amine in a single urine sample. Thus, even in the presence of a reduction in the glomerular filtration rate, our urinary dopamine results may not have been affected by the urine concentration. 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 the decreased urinary excretion of dopamine [42–44]. For this reason, patients with diseases known to affect renal dopamine production were excluded from the present study.

Intravenous furosemide raises urinary dopamine excretion acutely by increasing the tubular chloride concentration [45], but there is no evidence that stable and prolonged administration of diuretics may influence renal dopamine production. With respect to sodium handling, there is also evidence that acutely administered diuretics alter its fractional excretion. However, the use of diuretics does not interfere with sodium fractional excretion as long as drug dose and dietary sodium intake are relatively constant [46], as was the case in the present study.

**Clinical implications**

Direct-acting vasodilators such as sodium nitroprusside may have beneficial haemodynamic effects in HF. However, by inducing underfilling, they activate the anti-natriuretic neurohormonal systems and reduce the production of natriuretic peptides, thus leading to renal sodium re-absorption. The renal production of dopamine is increased in this setting. Thus the renal dopaminergic system may act as a compensatory natriuretic mechanism that is activated by stimuli leading to sodium retention.

Supplementation with small doses of L-DOPA [47] or administration of inhibitors of cathecol-O-methyltransferase, by increasing renal dopamine, may contribute to increase the distal delivery of sodium and overcome the resistance to natriuretic peptides that occurs in HF. The increased delivery of sodium to distal segments of the nephron may contribute to negate the actions of aldosterone and improve renal sodium handling. Simultaneously, increased levels of dopamine may effectively antagonize the tubular actions of angiotensin II.

It has been shown that high-dose L-DOPA treatment (1.5–2.0 g·day\(^{-1}\)) induces haemodynamic improvement in patients with HF [48,49]. However, much lower doses (300 mg·day\(^{-1}\)) significantly (5-fold) increased urinary dopamine, producing increased natriuresis and diuresis [47]. We suggest that low-dose L-DOPA supplementation may increase natriuresis and diuresis via a predominant renal tubular effect, without significantly affecting haemodynamics. Fenoldopam, a type 1 dopamine receptor agonist, improves haemodynamics in HF patients, but fails to increase natriuresis [50]. This apparent discrepancy may be related to the well known activation of counter-regulatory mechanisms initiated by increases in renin secretion during dopamine-induced renal vasodilatation [51,52]. In contrast, renal dopamine (originating in tubular cells) fails to directly affect the vasculature, and is expected only to produce natriuresis. Recent studies of low-dose L-DOPA in HF patients support this hypothesis [47].

Therefore low-dose L-DOPA supplementation or inhibition of cathecol-O-methyltransferase may be very
helpful in managing the sodium and water overload that afflicts patients with severe HF. Further studies using supplementation with L-DOPA or Glu-DOPA (an analogue of L-DOPA with relative renal specificity) are required in order to test this hypothesis.

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