C-type natriuretic peptide production by the human kidney is blunted in chronic heart failure

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ABSTRACT

CNP (C-type natriuretic peptide) is a vasodilatory peptide produced by vascular endothelium and the human heart with a short half-life. CNP has been identified within the human kidney; however, few results are available on whether the human kidney is a systemic source of CNP. The aim of the present study was to establish whether CNP is secreted by the human kidney and if synthesis is blunted in CHF (chronic heart failure). A total of 20 male subjects (age, 57±2 years; mean ± S.E.M.) undergoing CHF assessment (n = 13) or investigation of paroxysmal supraventricular arrhythmia (normal left ventricular function in sinus rhythm during procedure) (n = 7) were recruited. Renal CNP production was determined from concomitant plasma concentrations in the aorta and renal vein. When considering all subjects, a significant step-up in plasma CNP was found from the aorta to renal vein (3.0±0.3 compared with 8.3±2.4 pg/ml respectively; P = 0.0045). The mean increase in CNP was 5.3±2.4 pg/ml (range, −0.9 to +45.3 pg/ml). In patients with CHF, the aortic concentration was 3.3±0.4 pg/ml compared with a renal vein concentration of 4.3±0.6 pg/ml (P = 0.11). In those with normal left ventricular function, the respective values were 2.5±0.5 and 15.7±6.0 pg/ml (P = 0.01). In conclusion, CNP is synthesized and secreted into the circulation by the normal human kidney, where it may have paracrine actions. Net renal secretion of CNP appears to be blunted in patients with CHF.

INTRODUCTION

The natriuretic peptide family comprises structurally related vasoactive peptides with similar physiological properties. Clinical and research interests have focused on ANP and BNP (atrial and B-type natriuretic peptides respectively) and their role in circulatory homoeostasis [1]. Much less is known about the pathophysiological role of CNP (C-type natriuretic peptide) in humans [2]. CNP exerts its biological effects via an interaction with a specific transmembrane receptor (natriuretic peptide receptor-B). In comparison with ANP and BNP, CNP has a much shorter circulatory half-life [3]. CNP has been detected at a low concentration in the plasma of healthy human subjects, but, unlike ANP and BNP, initial studies found that peripheral venous plasma levels of CNP did not appear to be significantly elevated in patients with CHF (chronic heart failure) [4,5].

CNP has been identified in a number of human tissues. CNP immunoreactivity has been demonstrated in the human kidney [2]. When considering whole kidney tissue, CNP concentrations are an order of magnitude lower compared with plasma [6]. In the present study, we investigated whether CNP is synthesized and secreted by the human kidney and if synthesis is blunted in CHF.

Key words: C-type natriuretic peptide (CNP), heart failure, kidney, natriuretic peptide, urine.

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, ACE inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CHF, chronic heart failure; CNP, C-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left ventricular.

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in cultured human endothelial cells, whereas its receptor is located in high concentrations in adjacent vascular smooth muscle cells [6]. Studies with isolated arteries and veins have confirmed the vasodilator effects of CNP [7]. These findings, together with its short circulatory half-life, have led to the suggestion that CNP exerts effects locally within the vascular wall.

We have shown previously that, in patients with CHF, the heart synthesizes CNP [8]. The presence of CNP in human atrial and ventricular myocardial tissue has been confirmed by immunohistochemistry and RIA; atrial and ventricular myocardial levels of CNP were significantly elevated (100–200 %) in patients with CHF in comparison with controls \( (P < 0.05) \) [4]. mRNA transcripts for the CNP receptor have also been detected in the human heart [9]. Thus CNP may have important local paracrine effects adjacent to its site of production.

In the human kidney, CNP is located in cells of all tubular segments and glomeruli [10]. Studies in humans with CHF have provided conflicting results on whether urine CNP is altered or not [11–13]. To clarify the issue of renal CNP production, we measured CNP simultaneously in both the aorta and the renal vein in subjects with normal ventricular function and in patients with CHF. We hypothesized that renal production would be greater in patients with CHF. Further studies were undertaken to assess urinary CNP excretion in both healthy individuals and those with CHF.

**MATERIALS AND METHODS**

**Ethics**

The present study conforms to the principles outlined in the Declaration of Helsinki. Ethical approval was granted by the Royal Brompton Hospital local ethics committee. Written informed consent was obtained from all participants.

**Assessment of renal CNP production**

Renal CNP production was assessed by determining the difference in plasma concentration between the aorta and renal vein. The objectives of the study were to establish whether or not the kidney produces CNP and if this is different in patients with CHF compared with healthy subjects. Patients undergoing diagnostic right and left heart catheterization as part of heart failure assessment were recruited. The diagnosis of CHF was based on symptoms, examination and relevant investigations confirming LV (left ventricular) dilation and impairment of systolic function (chest radiograph, echocardiogram and cardiac magnetic resonance imaging) in accordance with published guidelines [14].

It is notoriously difficult to recruit a homogeneous population of healthy control subjects for a catheter-laboratory-based study. Exposure to ionizing radiation and invasive catheterization raises major ethical concerns if there is no clinical mandate to undertake evaluation of any sort. We wanted to make a comparison between patients with CHF and a group with essentially normal cardiac structure and, in particular, normal LV function. Otherwise healthy subjects with paroxysmal supraventricular arrhythmia (in sinus rhythm at the time of study procedure and without symptoms for \( > 24 \) h) undergoing diagnostic or therapeutic electrophysiology study were recruited as the ‘control’ population. Sampling was performed prior to the induction of arrhythmia.

Confirmation of renal vein sampling was made by selective renal angiography. Blood from the renal vein and aorta was collected into chilled EDTA tubes containing aprotinin (trasylo). Samples were centrifuged for 15 min at 500 g and the plasma phase was stored at \(-80^\circ\)C. CNP measurements were performed by an operator blinded to the study subjects using standard competitive RIA kits (Peninsula Laboratories) after solid-phase extraction from plasma proteins, as described previously [5]. The intra-assay coefficient of variation was 11.4 %. There was no demonstrable cross-reactivity of the anti-CNP antibody used with human ANP or BNP. The lower limit of detection for the CNP assays was 0.1 pg/ml. eGFR (estimated glomerular filtration rate) was calculated using the abbreviated MDRD (Modification of Diet in Renal Disease) equation [15].

**Patients with CHF**

At total of 13 patients with CHF were recruited for the study. Baseline characteristics are shown in Table 1 (all male; age, \( 60 \pm 3 \) years). No patient had significant renal failure (mean creatinine, \( 100 \pm 7 \mu \text{mol/l} \)), evidence of active infection, inflammation or diabetes. All were receiving an ACEI [ACE (angiotensin-converting enzyme) inhibitor] \( (n = 12) \) or an ARB (angiotensin receptor blocker) \( (n = 1) \), eight were receiving \( \beta \)-blockers and nine received diuretic therapy (see Table 1 for the doses of furosemide).

**Subjects with paroxysmal supraventricular arrhythmia and normal LV function (control group)**

A total of nine subjects were recruited (Table 2). Of these, two were in arrhythmia at the time of sampling. As such they were excluded from the main analysis, although individual results are presented for interest. The remaining seven subjects were all male (age, \( 53 \pm 4 \) years). Of these, five had history of paroxysmal atrial fibrillation, and two had atrioventricular nodal tachycardia. All had normal resting LV systolic function assessed by echocardiography, and were asymptomatic when not in arrhythmia. One individual (patient 3) had undergone prior angioplasty to his right coronary artery, and was subsequently well without angina and had a
normal exercise test prior to study. Another (patient 7) had history of atrioventricular node ablation and dual chamber pacemaker implant. A further individual (patient 4) was found by transthoracic echocardiography to have a small patent foramen ovale/atrial septal defect, but had normal right heart size and pressures (see Table 2 for details of the respective individuals).

Three of the seven subjects in sinus rhythm at the time of sampling were receiving anti-arrhythmic medication. Two (subjects 1 and 3; Table 2) were on amiodarone, and one individual (subject 5) was on a combination of flecainide and sotalol.

**Assessment of urinary CNP excretion**

Subsequent to the analysis of the data from the cross-kidney sampling study, we felt it important to undertake a further study to clarify whether urinary CNP excretion was different in patients with CHF and healthy individuals. Prior to recruiting subjects to this additional study, we determined whether urinary CNP was influenced by the methodology relating to collection conditions. A series of studies demonstrated a good agreement of CNP measurements irrespective of whether urine was collected into containers containing aprotinin or surrounded by ice, according to methodology recommended by standard Bland and Altman plots (results not shown). For ease of convenience, we performed standard 24-h urine collections, thereby enabling the study to be performed on an outpatient basis.

A different cohort of patients with stable CHF (n = 16) on standard medication and healthy control subjects (n = 7; asymptomatic, no history of prior cardiovascular disease and normal cardiovascular assessment) were recruited. Patients and healthy control subjects were similar in terms of age (68 ± 2 compared with 67 ± 2 years respectively; P = 0.8) and renal function (eGFR, 68 ± 6 compared with 79 ± 5 ml · min⁻¹ · 1.73 m²⁻² respectively; P = 0.23).

### Table 1 Clinical characteristics of the patients with CHF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>LVEF (%)</th>
<th>NYHA class</th>
<th>Serum creatinine (μmol/l)</th>
<th>( \Delta \text{CNP}_{\text{RV−aorta}} ) (pg/ml)</th>
<th>Furosemide dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>DCM</td>
<td>15</td>
<td>III</td>
<td>133</td>
<td>2.33</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>IHD</td>
<td>32</td>
<td>I</td>
<td>96</td>
<td>0.88</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>IHD</td>
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<td>II</td>
<td>74</td>
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<td>4</td>
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<td>DCM</td>
<td>40</td>
<td>I</td>
<td>86</td>
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<td>20</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>MR</td>
<td>57</td>
<td>II</td>
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<td>−0.37</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>IHD</td>
<td>15</td>
<td>II</td>
<td>118</td>
<td>0.47</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>DCM</td>
<td>38</td>
<td>II</td>
<td>146</td>
<td>2.64</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>DCM</td>
<td>20</td>
<td>III</td>
<td>108</td>
<td>−0.58</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>DCM</td>
<td>17</td>
<td>II</td>
<td>81</td>
<td>−0.50</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
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<td>IHD</td>
<td>28</td>
<td>III</td>
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<tr>
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<tr>
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<td>II</td>
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<td>50</td>
<td>I</td>
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<td>2.82</td>
<td>0</td>
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</tbody>
</table>

### Table 2 Clinical characteristics of control subjects undergoing electrophysiological studies for paroxysmal supraventricular arrhythmia

*The two patients were in tachyarrhythmia at time of study and, as such, were excluded from main study analysis. \( \Delta \text{CNP}_{\text{RV−aorta}} \), difference between renal vein and aortic CNP concentration; AVNRT, atrioventricular node re-entry tachycardia; PAF, paroxysmal atrial fibrillation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Serum creatinine (μmol/l)</th>
<th>Heart rate (beats/min)</th>
<th>( \Delta \text{CNP}_{\text{RV−aorta}} ) (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>54</td>
<td>PAF</td>
<td>94</td>
<td>60</td>
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<tr>
<td>2</td>
<td>Male</td>
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<td>AVNRT</td>
<td>122</td>
<td>67</td>
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<tr>
<td>3</td>
<td>Male</td>
<td>64</td>
<td>PAF</td>
<td>91</td>
<td>65</td>
<td>13.0</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>60</td>
<td>PAF</td>
<td>73</td>
<td>50</td>
<td>10.1</td>
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<tr>
<td>5</td>
<td>Male</td>
<td>61</td>
<td>AVNRT</td>
<td>92</td>
<td>42</td>
<td>−6.6</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>33</td>
<td>PAF</td>
<td>91</td>
<td>80</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>53</td>
<td>PAF</td>
<td>96</td>
<td>64</td>
<td>4.4</td>
</tr>
<tr>
<td>8*</td>
<td>Male</td>
<td>54</td>
<td>PAF</td>
<td>58</td>
<td>180</td>
<td>0.78</td>
</tr>
<tr>
<td>9*</td>
<td>Female</td>
<td>44</td>
<td>PAF</td>
<td>90</td>
<td>150</td>
<td>4.4</td>
</tr>
</tbody>
</table>

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Peripheral venous plasma samples were also taken for N-terminal pro-BNP in this cohort of subjects. These were analysed in the biochemistry laboratory at the Royal Brompton Hospital, London, U.K. using the Roche Diagnostics NT-pro-BNP kit on a Roche 1010 immunoassay analyser. Cross-reactivity with ANP, BNP and CNP was < 0.001 %. The within-assay co-efficient of variation was approx. 2.2 %.

The 24-hour urine collection started with the first urine specimen in the morning of day 1 of the study and included all samples up to, but not including, the first morning specimen on day 2. At the end of the collection the total urine volume was recorded, and samples were aliquoted from each container, frozen and stored at −80 °C until analysis.

**Statistics**

Data were analysed with StatView 4.5 (Abacus Concepts) and are expressed as means ± S.E.M. Because of the skewness of CNP concentrations, logarithmic transformation was used. Differences between sample sites were assessed using a paired Student’s t test. An unpaired Student’s t test was used to assess the differences between groups. In view of the fact that comparisons were made between a number of Student t tests, analysis with repeated-measures ANOVA was also performed. A probability value of < 0.05 was considered statistically significant.

**RESULTS**

When considering all individuals (n = 20; all male), a significant step up in the CNP concentration from the aorta to renal vein was observed (from 3.0 ± 0.3 to 8.3 ± 2.4 pg/ml respectively; P = 0.0045). The mean increase in CNP was 5.3 ± 2.4 pg/ml (range, −0.9 to +45.3 pg/ml).

Patients with CHF were similar to the control group in terms of age (P > 0.15) and renal function (creatinine, 100 ± 7 compared with 94 ± 6 μmol/l; eGFR, 75 ± 5 compared with 79 ± 5 ml · min⁻¹ · 1.73 m²⁻¹ respectively; both P = 0.5). In patients with CHF, there was no significant difference in CNP concentration between the aorta and renal vein (3.3 ± 0.4 and 4.3 ± 0.6 pg/ml respectively; P = 0.11) (Table 1 and Figure 1). In contrast individuals with normal LV function in sinus rhythm demonstrated a significant step up from the aorta to renal vein (2.5 ± 0.5 to 15.7 ± 6.0 pg/ml; P = 0.01) (Table 2 and Figure 2).

The concentration of CNP in the aorta was similar in patients with CHF and individuals with normal LV function (P = 0.28). In contrast, the CNP concentration was significantly higher in the renal vein in those with normal LV function when compared with patients with CHF (P = 0.025).

An additional analysis with repeated-measures ANOVA was performed. The difference between renal vein and aortic CNP concentration [ΔCNP(renal vein–aorta)] in pg/ml] was the dependent variable, the absence/presence of CHF as a factor and eGFR as a covariate. This confirmed a significantly higher step up in plasma CNP from the aorta to the renal vein in the subjects without CHF (i.e. controls) compared with the patients with CHF (mean difference, 12.3 pg/ml; between groups, P = 0.017).

Two patients in the ‘control’ group went into tachyarrhythmia (heart rate of 180 beats/min for patient 8...
and 150 beats/min for patient 9) at the time of the study, prior to sampling. Although they were excluded from the main analysis, relevant results are presented in Table 2 and Figure 2. A step up in plasma CNP concentration from aorta to renal vein was observed in both individuals.

No relationship was observed between the step up in CNP from the aorta to the renal vein and renal function (as estimated by serum creatinine or eGFR; \( P > 0.9 \)). There was no relationship between resting heart rate and the concentration of CNP in renal vein \( (P > 0.2) \).

**Urinary CNP**

In patients with CHF and control subjects, 24-h urine volumes (1756 ± 148 and 2219 ± 259 ml respectively; \( P = 0.11 \)) and the urine CNP concentration (28.6 ± 2.0 and 23.9 ± 1.7 pg/ml respectively; \( P = 0.17 \)) were similar. The rate of urinary CNP excretion was similar in patients with CHF and healthy control subjects (32.4 ± 1.9 and 35.3 ± 2.4 pg·ml\(^{-1}·min^{-1} \) respectively; \( P = 0.3 \)). Plasma concentrations of CNP were not significantly different between the groups, although values on the whole were low (results not shown). In contrast, patients with CHF had higher concentrations of circulating N-terminal pro-BNP when compared with the control group (281.1 ± 123.8 compared with 39.1 ± 24.5 pmol/l; \( P < 0.05 \)). There was no relationship between the rate of urinary CNP excretion and eGFR \( (R^2 = 0.005, P = 0.7) \).

**DISCUSSION**

The results of the present study have shown that CNP is synthesized and secreted by the human kidney. In the normal kidney, the excess CNP produced exits the kidney through the renal vein more than through the urine. In CHF, CNP production by the kidneys and release into the venous system appears blunted when compared with individuals with normal LV function.

As expected, there was inter-subject heterogeneity within both groups of subjects. The pattern was much more consistent in the healthy controls. Although we found in patients with CHF a step up in CNP concentration from the aorta to renal vein of similar magnitude to that from the aorta to coronary sinus observed in our previous study [8], this did not reach statistical significance. This may relate, in part, to the small number of patients included in the present study. However, the fairly consistent finding of a greater magnitude of step up in plasma CNP concentration from the aorta to renal vein in the subjects with normal LV function suggests that renal production does genuinely appear blunted in patients with CHF.

Our findings share similarities with those observed in a sheep model of heart failure. Charles et al. [16] demonstrated a significant step up in plasma CNP across the heart, kidney and liver in healthy sheep (suggesting net production). This was in contrast with ANP and BNP, where the heart was the key source of circulating peptide and net extraction of these peptides was observed across the other organ beds. After the induction of heart failure (rapid pacing), a significant step up in CNP remained across the heart. Although arterial levels were still higher than respective venous levels across the kidney and liver, these no longer reached statistical significance.

Extensive research has helped to elucidate the central role for ANP and BNP in the pathophysiology of CHF [17]. In contrast, the role of CNP in health and diseased states remains less certain. Initial studies of patients with CHF demonstrated that the plasma CNP concentration was similar to that in control subjects [4,5]. More recently, Del Ry et al. [18] found that CNP levels were increased in patients with CHF as a function of clinical severity.

In terms of urinary excretion of CNP, there are conflicting results, with some studies finding elevated urine CNP in CHF and others finding little difference [11–13]. Mattingly et al. [11] assessed urinary CNP in a timed collection (4 h) with urine collected on ice, Bentzen et al. [12] used a standard 24-h collection, and Ng et al. [13] evaluated urinary CNP on a spot sample. We performed a series of studies and demonstrated a good agreement of CNP measurements, irrespective of whether urine was collected into containers containing aprotinin or surrounded by ice. Our findings showed a similar urinary CNP excretion rate in patients with CHF and control subjects.

Acute intravascular overload in healthy dogs resulted in an elevation in pulmonary capillary wedge pressure and plasma ANP, without a change in plasma BNP and CNP concentrations [19]. In contrast, a significant increase in urinary CNP, but not ANP or BNP, was observed after acute intravascular loading. This raises the possibility that the discrepant results of urinary CNP in CHF may be because the patients with CHF in each study were in a different state of fluid retention at the time of investigation. In our present studies, the patients with CHF appeared normovolaemic clinically. It is therefore unlikely that current volume expansion had a significantly impact upon the urinary CNP results.

The appearance of CNP in urine will depend upon the relative contributions of renal filtration, secretion across tubular cells from post-glomerular blood and local production within the kidney with direct secretion into the tubules. Counteracting this are the two pathways involved in the metabolism of CNP: removal by the clearance receptor (natriuretic peptide receptor-C) [20] and hydrolysis by neutral endopeptidase [21]. Neutral endopeptidase has a wide tissue distribution and, in particular, is located in the vascular endothelium and at high levels in the kidney brush border [20]. *In vitro*, CNP appears to be more rapidly hydrolysed by neutral endopeptidase than the other natriuretic peptides [22]. The lack of an increase in renal vein CNP observed in CHF in our present study could, in theory, be due
to the kidneys in patients with CHF having higher levels of neutral endopeptidase than normal kidneys. This has been shown previously in rat models of heart failure [23].

Renal blood flow is reduced in CHF [24]. As such, the lower renal arteriovenous difference found in patients with CHF cannot be explained by an increased renal blood flow and unchanged renal production. Lower flow could predispose to enhanced renal clearance, thereby contributing to reduced CNP concentrations within the venous effluent in patients with CHF. We found no relationship between renal function and step up in plasma CNP from the aorta to renal vein.

It is plausible that medication, such as diuretics and inhibitors of the renin–angiotensin–aldosterone system, might have an impact upon renal CNP production and release in CHF. In the present study, all patients with CHF were receiving either ACEIs or ARBs, which do alter intra-renal haemodynamics. However, it appears intuitively unlikely, but not impossible, that the large differences we observed in renal vein CNP between patients with CHF and controls were due to ACEIs. There was no relationship between diuretic dose and the difference in CNP between the aorta and renal vein in patients with CHF.

We have demonstrated previously that, in patients with CHF, the heart produces CNP, and that the CNP concentration in the coronary sinus is related to the pulmonary capillary wedge pressure [8]. Davidson et al. [25] have shown that CNP is a local endogenous inhibitor of vascular ACE. The present finding adds support to the concept that the primary effects of CNP may be paracrine.

There are limitations with the present study. The control group of individuals had experienced paroxysmal atrial arrhythmia (although in sinus rhythm during the study). It is hard to justify recruitment of an asymptomatic healthy individual for a catheter-laboratory-based study, as all of the procedures carry a small risk of significant complications. As the novel aim of the present study was to see what renal arteriovenous differences were in CNP, we needed to recruit individuals who had a clinical reason for catheterization. Accepting this inevitable limitation, the group of subjects with normal LV function were all asymptomatic when not having paroxysmal arrhythmias, and none had symptoms of heart failure.

Although we assessed CNP levels within the aorta and renal vein, we did not have concomitant data on urinary CNP concentrations in these individuals nor did we measure blood flow so as to calculate total excretion. However, in a subsequent study described here, urinary CNP was much the same in CHF as in control subjects, in agreement with Bentzen et al. [12].

Conclusions

We have demonstrated that the kidney is a site of CNP production and release in humans and that the extra CNP produced spills mainly into the renal vein in healthy humans. The renal production of CNP is blunted in CHF. This blunted production of intra-renal CNP in CHF may contribute to the renal sodium retention that is so characteristic of CHF.

FUNDING

This work was supported by the British Heart Foundation (to P. R. K. and the Department of Clinical Cardiology). P. R. K. was supported previously by Wessex Heartbeat; and the Waring Trust.

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