Regional Release and Clearance of C-Type Natriuretic Peptides in the Human Circulation and Relation to Cardiac Function

Suetonia C. Palmer, Timothy C.R. Prickett, Eric A. Espiner, Timothy G. Yandle, A. Mark Richards

Abstract—Production and clearance of plasma C-type natriuretic peptide (CNP) and amino terminal (NT)-proCNP immunoreactivity in the human circulation remain poorly characterized. Accordingly, we have measured arterial and venous concentrations of CNP and NT-proCNP across multiple tissue beds during cardiac catheterization in 120 subjects (age: 64.2 ± 9.0 years; 73% men) investigated for cardiovascular disorders. The heart, head and neck, and musculoskeletal tissues made the clearest contributions to both plasma CNP and NT-proCNP (P < 0.05). Net release of NT-proCNP was also observed from hepatic tissue (P < 0.001). Negative arteriovenous gradients for CNP were observed across renal, hepatic, and pulmonary tissue (P < 0.05), indicating net clearance, whereas no tissue-specific site of NT-proCNP clearance was identified. Age, mean pulmonary artery pressure, left ventricular end diastolic pressure, Brandt score of myocardial jeopardy, and troponin I were independent predictors of circulating CNP levels in multivariable analysis. Sex and kidney function were independently predictive of arterial NT-proCNP. The proportional step-up of CNP (+60%) across the heart was less than for brain natriuretic peptide (+123%) but greater than for NT–pro-brain natriuretic peptide (NT-proBNP) (+36%) and NT-proCNP (+42%; P < 0.001 for all). We conclude that cardiac and head and neck tissue are important sources of CNP. Circulating CNP but not NT-proCNP concentrations are related to cardiac hemodynamic load and ischemic burden. Although cardiac release is most evident, multiple additional tissues release NT-proCNP immunoreactivity without evidence for an organ-specific site for NT-proCNP degradation. Taken together, differences in magnitude and direction of transorgan gradients for CNP compared with NT-proCNP suggest net generalized cosecretion with differing mechanisms of clearance. (Hypertension. 2009;54:612-618.)

Key Words: natriuretic peptides ■ circulation ■ plasma ■ glomerular filtration rate ■ human

C-type natriuretic peptide (CNP), a vasoactive and anti-proliferative peptide,1,2 shares sequence homology and biological actions3 with the endocrine cardiac peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). After the isolation of CNP from porcine brain tissue,4 both CNP and CNP mRNA have been identified in vascular endothelium5,6 and cardiac,7,8 renal,9 skeletal,10 and reproductive11,12 tissues. Although ANP and BNP activate the guanylate cyclase–coupled natriuretic peptide receptor (NPR)-A and promote natriuresis and diuresis,3 CNP is the predominant ligand for another NPR, NPR-B,13 which is also widely distributed in tissues including brain,14 vascular endothelium, smooth muscle cells,15 and myocardium.16 Binding to NPR-B, CNP induces in vitro venodilatation,17 cardiac inotropy, and chronotropy18 and inhibits vascular smooth muscle proliferation.15 Recent studies have shown that CNP exhibits antihypertrophic and antifibrotic properties during ventricular modeling after experimental myocardial infarction.19

Distinct from ANP and BNP, circulating plasma CNP concentrations are low and thought to be insufficient to affect end-organ function. Recent work, however, has shown that clinical states of cardiac impairment are associated with increases in circulating and coronary sinus CNP levels,20–22 which suggest that elevated cardiac tissue production of CNP may be associated with increasing myocardial dysfunction. Although individual studies have separately measured transcardiac22–25 and transrenal26 CNP immunoreactivity, little is known about CNP production and clearance across other organs in health or cardiovascular disease. Such studies have been hindered by the largely autocrine/paracrine nature of CNP with rapid local (and systemic) degradation through uptake by the clearance receptor27 and hydrolysis by nepri-

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Methods

Subjects

A total of 120 unselected patients requiring cardiac catheterization for coronary angiography (n=44), percutaneous coronary intervention (n=73), or right and left heart study (n=3) were enrolled for sampling of arterial and venous blood to yield multiple transorgan gradients for CNP and NT-proCNP. BNP forms were also measured for comparison. The study protocol was approved by a regional ethics committee (Ministry of Health, New Zealand); all of the subjects provided written informed consent.

The right femoral artery and vein were cannulated (6F) under local anesthesia. Femoral arterial samples were obtained at beginning and end of the sampling protocol to assess stability of peptide levels over the time required for sampling (20 minutes). As a multipurpose diagnostic catheter (6F) was advanced, blood samples were drawn sequentially from the femoral, renal, hepatic, and internal jugular veins and, finally, the pulmonary artery. An Amplatz left-1 (6F) catheter was then used to cannulate and draw samples from the coronary sinus (n=86). The position of the catheter tip at the time of blood draw was ±1 to 2 cm within the vessel of interest, as confirmed by a small-volume retrograde contrast injection.

Hemodynamic measurements recorded concurrently with blood sampling included initial femoral, pulmonary, and final (repeated) femoral arterial pressures and cardiac output (determined by the Fick technique). A 6F “pigtail” catheter was used to measure left ventricular end diastolic pressure (LVEDP). Clinical data collected included age, sex, body mass index, estimated glomerular filtration rate (eGFR), 31 hemoglobin, troponin I, and arterial oxygen tension. The ischemic burden of coronary artery disease was adjudicated by a cardiologist (A.M.R., who was blinded to other results) using the Brandt score of myocardial jeopardy. 32

Transtracheal echocardiography was performed in 104 patients (87%) within 3 weeks of sampling. The standardized imaging protocol included apical 4- and 2-chamber views according to the American Society of Echocardiography. 33 Parasternal, short-, and long-axis views (averaged over 4 cycles) were obtained for M-mode measurements of left ventricular dimensions. Biplane diastolic and systolic volumes and ejection fraction were calculated by planimetry according to Simpson’s method.

Assays

Blood samples were collected in prechilled tubes containing EDTA. After centrifugation at 4000 rpm and 4°C for 10 minutes, plasma was stored at −80°C. After extraction with Sep Pak C18 cartridges, NT-proCNP, 29 NT-proBNP level were measured using our established radioimmunoassays. CNP was measured as described previously. 28 BNP immunoreactivity was measured using our BNP radioimmunoassay that currently uses antisera from Bachem (catalog No. T-4021, Bachem).

Cross-reactivities with human ANP and ovine BNP-26 in the CNP assay, using commercial CNP-22 antisera (catalog No. RAB-014-03, Phoenix Pharmaceuticals), were <0.004% and 1.400% respectively. This CNP radioimmunoassay also cross-reacted with human BNP, as has been reported recently by others. 38 We found that the cross-reactivity of human BNP (at 100 pmol/L) in the CNP assay was ~4%. A linear relationship existed between the logarithm of BNP cross-reactivity and log BNP concentration (n=7; r=0.99 for BNP concentration range 100 to 700 pmol/L; P<0.001). We, therefore, derived the following equation to determine the contribution of endogenous BNP in the concentrated plasma extracts to the CNP assay result: BNP cross-reactivity = 10-0.564 × log(BNP) + 1.41. The plasma CNP values, adjusted for concurrent plasma BNP were calculated as follows: Corrected CNP (pmol/L) = CNP (pmol/L) – BNP cross-reactivity (pmol/L).

Using our NT-proCNP assay, cross-reactivities with human NT-proANP(1-30), NT-proBNP(1-21), ANP, BNP, CNP-22, and CNP-53 were all <0.02%. Within- and between-assay coefficients of variation for the CNP assay were 1.3% and 7.0%, respectively, at 4.6 pmol/L after 4-fold concentration during extraction. Within- and between-assay coefficients of variation for the NT-proCNP assay were 6.5% and 7.5%, respectively, at 15 pmol/L. Plasma limits of detection for CNP and NT-proCNP assays were 0.4 pmol/L and 1.2 pmol/L, respectively.

Calculations

To derive gradients across tissue beds, initial femoral artery peptide values were paired with concentrations in the femoral, renal, hepatic, and internal jugular veins; final femoral artery peptide concentrations were paired with levels in the coronary sinus and pulmonary artery. The transorgan peptide gradient was defined as Cn – Ch, where Cn and Ch were plasma peptide concentrations in the arterial and paired venous sites, respectively. Peptide tissue fractional extraction (FE) was calculated as follows:

\[ FE = \frac{(C_n - C_h)}{C_n} \]

Statistical Analysis

Descriptive variables were calculated as mean±SD for all of the normally distributed variables or median (interquartile range [IQR]). Peptide values were log transformed to normalize variances before analysis. Matched arterial and venous concentrations were compared using paired t-tests. Univariable Pearson’s coefficients were used to determine correlates of femoral artery CNP and NT-proCNP values. Multivariable regression analysis was used to determine independent predictors of arterial CNP and NT-proCNP levels, incorporating variables with univariable association significant at the P<0.10 level. LVEDP and left ventricular end systolic volume were rotated through the model in place of mean pulmonary artery pressure and left ventricular ejection fraction (LVEF), respectively. Data analysis was performed using SPSS version 13 (SPSS Inc). Statistical significance was assumed at P<0.05.

Results

Clinical and cardiovascular characteristics are shown in Tables 1 and 2. Heart rate and mean arterial pressure remained stable over the duration of sampling (P>0.20). Femoral arterial plasma CNP (mean increment: 0.02±0.01 pmol/L), NT-proCNP (0.28±0.20 pmol/L), and BNP (1.50±0.42 pmol/L) levels increased minimally across the time required for multisite sampling (P<0.05 for all). Seventy-seven (7.1%) of the 1080 CNP assay results were below the plasma limit of detection for the assay and were unavailable for analysis.

C-Type Natriuretic Peptide

The median arterial CNP value was 0.65 pmol/L (IQR: 0.36 to 0.91 pmol/L; adult reference range: 0.4 to 1.0 pmol/L). As shown in Figure 1, a significant step-up in CNP immunoreactivity was seen across the heart (0.4±0.03 pmol/L; P<0.001), head and neck (0.06±0.01 pmol/L; P<0.001), and lower limb (0.04±0.02 pmol/L; P<0.05). Negative arteriovenous CNP gradients were observed across renal (~0.10±0.01 pmol/L; P<0.001), hepatic (~0.06±0.01 pmol/L; P<0.01), and pulmonary tissues (~0.01±0.01 pmol/L; P<0.05).

As shown in Figure 2, plasma arterial CNP immunoreactivity strongly correlated with mean pulmonary artery pressure and also correlated positively with age, hypertension, LVEF, left ventricular end systolic volume, LVEDP, Brandt score, and peak troponin I and negatively with eGFR (P<0.05 for all; Table 3). In multivariable analysis, age, mean pulmonary artery pressure, LVEDP, Brandt score, and
troponin I were independent predictors of plasma arterial CNP concentrations (Table 3). Similar correlates of peripheral venous CNP immunoreactivity were observed (data not shown).

The coronary sinus plasma CNP concentration correlated with mean pulmonary artery pressure (n=85; r=0.43; P<0.001) and LVEDP (n=82; r=0.34; P=0.002) but no significant correlations of the net cardiac arteriovenous CNP gradient were identified in univariable analysis. Fractional extractions of CNP across the renal, hepatic, and pulmonary circulations were all correlated with each other (r=0.25 to 0.58; P≤0.01), as were the proportional increments of CNP across the heart and head and neck (n=64; r=0.68; P<0.001), eGFR (range: 41 to 109 mL/min per 1.73 m²) was not correlated with renal CNP fractional extraction (n=104; r=−0.03; P=0.74).

**NT-proCNP**

The median arterial plasma NT-proCNP value was 17.2 pmol/L (IQR: 14.3 to 20.5 pmol/L; adult reference range: 13 to 29 pmol/L). As was found for CNP, NT-proCNP immunoreactivity increased significantly across the heart (6.9±0.5 pmol/L; P<0.001) and head and neck (3.3±0.3 pmol/L; P<0.001; Figure 1). A step-up in NT-proCNP levels was also seen across the liver (2.2±0.04 pmol/L; P<0.001) and lower limb (0.6±0.03 pmol/L; P<0.001). No arteriovenous gradient of NT-proCNP was seen across renal or pulmonary tissue (P>0.6). The arteriovenous gradient for NT-proCNP was markedly greater than for CNP across the heart (6.9±0.5 pmol/L; IQR: 12.8 to 19.9 pmol/L; P<0.001). Arterial NT-proCNP levels were significantly higher in men (median: 17.2 pmol/L; IQR: 14.7 to 21.1 pmol/L) than in women (15.1 pmol/L; IQR: 12.8 to 19.9 pmol/L; P<0.05). As noted for CNP, NT-proCNP levels were also significantly inversely correlated with eGFR (n=117; r=−0.24; P<0.01). Sex and eGFR were independent predictors of circulating NT-proCNP levels in multivariable analysis (P<0.001). In contrast to the situation for CNP, however, NT-proCNP immunoreactivity was not correlated to any other measured covariable, including mean pulmonary artery pressure (Figure 2). No correlates with the net cardiac NT-proCNP arteriovenous gradient were identified in univariable analysis.

**Comparisons With BNP**

Median arterial BNP and NT-proBNP levels were 12.9 pmol/L (IQR: 7.2 to 25.3 pmol/L) and 36.7 pmol/L (IQR: 18.9 to 90.0 pmol/L), respectively. BNP levels were, on average, 20 times corresponding CNP concentrations. Arterial CNP and NT-proCNP values were correlated with each other (n=107; r=0.26; P=0.006) but less tightly than BNP with NT-proBNP levels (n=116; r=0.83; P<0.001). Arterial
CNP levels positively correlated with BNP (n=109; r=0.72; P<0.001) and NT-proBNP (n=109; r=0.87; P<0.001). By contrast, arterial NT-proCNP levels were not correlated with either corresponding BNP (n=113; r=0.09; P=0.36) or NT-proBNP (n=117; r=0.12; P=0.20) values.

The proportional step-up of CNP (+60%) across the heart was less than for BNP (+123%; P<0.001) but greater than for NT-proBNP: +36%; P<0.001) and NT-proCNP (+42%; P<0.001). Although arteriovenous gradients across the heart were positively correlated for BNP with NT-proBNP (n=89; r=0.60; P<0.001), no significant relationship between transcardiac arteriovenous gradients of CNP and NT-proCNP was observed (n=81; r=0.08; P=0.46). Arterial BNP concentrations were better correlated with mean pulmonary artery pressure (n=109; r=0.72; P<0.001) than arterial CNP immunoreactivity (n=109; r=0.43; P<0.001).

**Discussion**

This is the first report of regional plasma CNP and NT-proCNP immunoreactivity across the heart and other tissues in humans. In addition to supporting previous (and smaller) studies showing net cardiac release of CNP,22,24,25 the present study relates these findings to cardiac function and reports new findings of CNP release by head and neck and lower limb tissues and extraction of CNP across hepatic, renal, and pulmonary tissues in adult humans.

In contrast to the natriuretic peptides ANP and BNP, which are sourced primarily from cardiac myocytes,3 CNP is secreted by various tissues, including endothelial cells5,6 and cardiac fibroblasts.3 Of note, in the adult rat ventricle, the CNP receptor (NPR-B) has been identified predominantly in nonmyocyte cells.16 Augmented expression of NPR-B occurs during development of cardiac hypertrophy after experimen-
pulmonary wedge pressure in previous work suggest that coronary sinus CNP and arterial CNP levels with pulmonary and peak troponin I concentration. The positive association of myocardial ischemic burden, as reflected by the Brandt score, with arterial CNP may, in contrast to CNP, arterial plasma NT-proCNP concentration in response to increasing myocardial wall tension. Because CNP potently suppresses both cardiac DNA and collagen synthesis in cardiac fibroblasts, these findings collectively suggest an important cardioprotective role for CNP in modulating cardiac fibrosis and extracellular matrix formation, in contrast to the natriuretic role for ANP and BNP.

Consistent with these findings, the current data demonstrate strong relationships between circulating CNP concentrations and measures of cardiac function, particularly pulmonary arterial pressure, LVEDP, and cardiac volume. Moreover, circulating CNP was independently related to myocardial ischemic burden, as reflected by the Brandt score and peak troponin I concentration. The positive association of coronary sinus CNP and arterial CNP levels with pulmonary artery pressure in the present study and of plasma CNP with pulmonary wedge pressure in previous work suggest that cardiac tissue CNP production occurs in response to elevated ventricular filling pressure and myocardial stretch. Given that CNP is secreted by cardiac fibroblasts, it is possible that cardiac CNP secretion directly reflects the burden of cardiac fibrosis in any given individual. In addition, cardiovascular disease may alter peptide catabolism via altered tissue blood flow in regions of peptide clearance and may accordingly influence CNP release and removal. Because echocardiography recordings were not simultaneous with plasma sampling, the relationship between CNP and cardiac volumes and LVEF might, in fact, be underestimated and possess stronger associations with cardiac function similar to those observed between CNP immunoreactivity and concurrently measured pulmonary artery pressure and LVEDP.

Gradients of CNP across the heart, reported here for the first time, did not correlate with any of the functional parameters measured in individual subjects; direct measurement of cardiac CNP secretion (coronary artery flow × cardiac arteriovenous peptide gradient) might further clarify whether cardiac CNP release is (or is not) related to differing cardiac filling pressures or the severity of myocardial ischemia. In contrast to CNP, arterial plasma NT-proCNP concentration did not correlate with measures of cardiac performance. The lower proportionate cardiac arteriovenous gradient, longer half-life in plasma, and multiple (net) tissue contributions compared with CNP presumably account for these differences.

Our observations show that significant net extraction of CNP occurs across renal, hepatic, and pulmonary tissue beds.

Table 3. Univariable and Multivariable Predictors of Arterial CNP Concentrations

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<td>Peak troponin I ≥0.03 μg/L</td>
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For multivariable, n=97 and adjusted $r^2=0.45$.

*Left ventricular end systolic volume and LVEDP were rotated through the model in place of LVEF and mean pulmonary artery pressure, respectively.

Figure 2. Scatter plots showing the relationship between mean pulmonary artery pressure and plasma arterial CNP (top) and NT-proCNP (bottom) immunoreactivity. The number of individuals, Pearson correlation ($r$), and $P$ values are shown for each analysis.
in humans, whereas the concentration of NT-proCNP is unaltered or increased in respective regional venous plasma. Small but highly significant positive NT-proCNP gradients were found across the liver and lower limb consistent with CNP synthesis across a broad range of tissues and compatible with generalized paracrine activity. In contrast, no site of net extraction of NT-proCNP was identified, compatible with generalized tissue release and intracirculatory degradation. Our findings fit with synthesis and release of both CNP forms by kidney, liver, and lung, but with more rapid degradation of CNP (eg, by tissue neprilysin or NPR clearance receptor). Because the arteriovenous gradient between artery and hepatic vein includes both hepatic and gut tissue, a net contribution of hepatic tissue to circulating CNP immunoreactivity masked by clearance in gut tissue is possible and might result in the net removal of CNP that we observed across this circulatory region. The opposing gradients for CNP (net clearance) and NT-proCNP (net release) across the hepatic circulation also suggest corelease of both CNP and NT-proCNP by hepatic tissue and clearance of CNP by the enteral circulation. Direct measurement of CNP in the portal vein would determine the relative contributions of gut and liver tissue to circulating C-type peptide immunoreactivity.

Although both arterial plasma CNP and NT-proCNP immunoreactivity were inversely related to eGFR, the latter proved to be an independent predictor of arterial NT-proCNP concentration and not CNP. This difference may relate to differing effects of renal transit on the 2 peptides. CNP is particularly vulnerable to enzymatic degradation by neprilysin that is abundant in renal tissue, especially in brush-border vesicles of proximal tubular cells. Tubular reuptake and subsequent degradation after glomerular filtration may account for both the “loss” of immunoreactivity across the kidney and the low CNP immunoreactivity measurable in human urine.

Plasma NT-proCNP exhibits no net change across the kidney or lungs in contrast to positive gradients at every other site. Notably, these 2 locations are sites of net CNP clearance. The fall in CNP and lack of positive gradient in NT-proCNP suggest that both tissues may be relatively inert with respect to endothelial release of C-type peptides into plasma. Alternatively, both may be sites in which the concurrent but differing mechanisms of CNP versus NT-proCNP clearance are more active than elsewhere. In contrast, the transhepatic gradients of the 2 peptides are frankly opposite with net release of NT-proCNP but clearance of CNP. Presumably, the enterohepatic vasculature releases both peptides concurrently, but in the case of CNP, local clearance by neprilysin and/or other mechanisms exceeds arterial delivery and local release with a consequent net fall between the artery and hepatic vein. The coreleased NT-proCNP is not subject to the same degree of local clearance with a consequent net increase in plasma levels during enterohepatic transit. Focused studies of specific tissue handling of CNP forms and their relation to contrived changes in regional blood flow and GFR are needed to clarify these observations.

Although the arteriovenous gradients of CNP and NT-proCNP are small, measured in picomolar terms, the data consistently indicate net clearance or production of C-type peptides across multiple circulatory regions, generally with very small P values. Importantly, small changes in circulating levels of vasoactive peptides can exert extremely powerful trophic and hemodynamic effects, as has been documented previously for other vasoactive peptides (eg, angiotensin II). Although the present data cannot evaluate the biological importance of the peptide arteriovenous gradients observed at the tissue level, small arteriovenous gradients may represent organ spillover and reflect major interorgan differences in tissue peptide levels and important paracrine/autocrine activity.

Limitations
The small but significant increase in arterial CNP and NT-proCNP immunoreactivity during the 20-minute sampling period in the current study was similar to increases in CNP and NT-proCNP over time in a similar experimental protocol. Increasing natriuretic peptide immunoreactivity over time may relate to the duration of supine posture causing increased peptide release because of redistribution of circulating volume to the thorax and subtle increments in intracardiac volumes and wall tension. Measurements of regional blood flow would be required to calculate absolute values of peptide secretion and clearance but were not practical in the current study.

Perspectives
This study clarifies the release and clearance sites of 2 circulating products (CNP and NT-proCNP) of the propeptide proCNP in humans. Findings of net release of both CNP and NT-proCNP imply important contributions from the heart and head/neck tissues to circulating concentrations. Arterial plasma CNP immunoreactivity, by positively reflecting left ventricular filling pressures and ischemic burden, opens the way to further in vivo studies of the possible cardioprotective paracrine role of CNP in the heart. Net release of NT-proCNP, most obvious from the heart and head/neck, occurs from multiple sites, whereas significant CNP extraction is found across renal, hepatic, and pulmonary tissue. Taken together, these data suggest net cosecretion of CNP and NT-proCNP into the human circulation with differing clearance mechanisms. The absence of site-specific arteriovenous falls in NT-proCNP suggests predominantly intracirculatory degradation.

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Disclosures
None.

References


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