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Assessment of Renal Hemodynamic Effects of Nesiritide in Patients With Heart Failure Using Intravascular Doppler and Quantitative Angiography

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OBJECTIVES We evaluated the magnitude and site of action of the nesiritide mediated renal vasodilatory effect in patients with heart failure (HF).

BACKGROUND Nesiritide, a recombinant human B-type natriuretic peptide is approved for the treatment of acute decompensated HF and has been shown to exert favorable hemodynamic, neurohormonal, and symptomatic effects. The renal effect of nesiritide in HF patients has not been well defined.

METHODS In 15 patients with acute decompensated HF, intravascular Doppler and quantitative angiography of the renal artery were used to assess the effect of nesiritide on renal artery diameter and velocity time integral as well as renal blood flow and vascular resistance. Nesiritide was administered intravenously at a standard dose of 2 μg/kg bolus followed by a continuous infusion at a rate of 0.01 μg/kg/min. Assessment of nesiritide effect was made at 15 min.

RESULTS Nesiritide infusion was associated with a significant central hemodynamic effect including a fall in mean pulmonary artery pressure (36 $\pm$ 12 mm Hg to 31 $\pm$ 13 mm Hg, $p < 0.001$), mean pulmonary capillary wedge pressure (21 $\pm$ 2 mm Hg to 15 $\pm$ 10 mm Hg, $p < 0.001$), and systemic vascular resistance (1,995 $\pm$ 532 dynes·s·cm^{-5} to 1,563 $\pm$ 504 dynes·s·cm^{-5}, $r < 0.001$), and an increase in cardiac output from 3.9 $\pm$ 1.2 l/min to 4.6 $\pm$ 1.6 l/min ($p = 0.001$). Nesiritide was also associated with a significant vasodilatory effect on the large conductance renal arteries resulting in an increase in renal artery diameter from 6.2 $\pm$ 0.7 mm to 6.7 $\pm$ 0.8 mm ($p < 0.001$). At the same time, there was a concomitant fall in mean renal artery pressure (99 $\pm$ 17 mm Hg to 89 $\pm$ 13 mm Hg, $p = 0.002$) and renal blood flow velocity time integral (27 $\pm$ 15 cm/beat to 23 $\pm$ 15 cm/beat, $p = 0.008$) and, therefore, no significant change in renal blood flow or renal vascular resistance.

CONCLUSIONS The nesiritide effect on the renal circulation in patients with HF is complex, with a marked vasodilatory action on the large, conductance renal arteries but a concomitant fall in velocity time integral and no effect on renal vascular resistance or renal blood flow. Lack of increase in renal blood flow may be due to a fall in renal blood pressure or an intrarenal vasoconstrictive effect. (J Am Coll Cardiol Img 2008;1:765–71) © 2008 by the American College of Cardiology Foundation

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Renal insufficiency is common in patients hospitalized for heart failure (HF) (1) and has a significant effect on the ability to correct volume overload with diuretics (2) and on short- and long-term outcome (3). Further worsening of renal function during the hospitalization results in prolongation of length of stay as well as increased morbidity and mortality (4). For these reasons, improvement of renal function or at least prevention of its deterioration is an important therapeutic goal in patients with acute decompensated heart failure (ADHF). Nesiritide, a recombinant human B-type natriuretic peptide (BNP), has been approved for the treatment of ADHF and has been shown to have favorable hemodynamic, neurohormonal and symptomatic effects in patients with ADHF (2,5). The effect of nesiritide on renal function, however, has not been fully understood, and available information is conflicting, with some studies demonstrating improvement (6) while others suggesting either no effect (7) or even deterioration (8). More mechanistic information is, therefore, needed in order to better understand the renal circulatory effects of nesiritide in patients with HF. The use of renal intravascular Doppler technique and quantitative angiography of the renal artery allows a direct measurement of changes in renal artery dimensions as well as in renal artery blood flow velocity (9) and provides an accurate assessment of the magnitude and location of the vasodilatory effect as well as changes in renal blood flow (RBF) (10,11). In this study we have used these techniques to assess the magnitude of the renal vasodilatory effect and the site of action of nesiritide in patients with HF.

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure
BNP = B-type natriuretic peptide
HF = heart failure
MRBP = mean renal arterial blood pressure
RAD = renal artery diameter
RAP = right atrial pressure
RBF = renal blood flow
RVR = renal vascular resistance
VTI = velocity time integral

METHODS

Patient selection. The study included 15 patients admitted to the Los Angeles County/University of Southern California Medical Center for ADHF. All patients were clinically stable at the time of the study and underwent diagnostic cardiac catheterization for clinical indications after initial treatment.

All patients had left ventricular systolic dysfunction, documented either by radionuclide ventriculography or by echocardiography. Patients with a systolic blood pressure less than 95 mm Hg or those who required treatment with other intravenous vasoactive medications were excluded. In addition, because of the risk of contrast nephropathy, patients with serum creatinine ≥133 μmol/l (1.5 mg/dl) were also excluded.

Study protocol. All patients signed a written consent approved by the institutional research committee. For safety reasons, oral intake including medications was not allowed the morning of the test. A balloon-tipped, triple lumen pulmonary artery (Swan-Ganz) catheter was placed into the pulmonary artery and a 6-F guiding catheter was placed in the proximal portion of the renal artery. After full heparinization, a 0.014-inch Doppler-tipped Flowire (Volcano Therapeutics, Rancho Cordova, California) was introduced into the guiding catheter and the tip positioned in the main renal artery or one of its major branches. Catheter position in the artery was confirmed with a small amount (1 to 3 ml) of contrast. Position of the flow wire was manipulated to achieve the highest possible flow velocity, and the wire was then locked to prevent any change in its position. Renal artery pressures were measured directly with the aid of the guiding catheter, fluid-filled pressure tubing, and standard transducers. RBF was measured by quantitative renal angiography and intravascular Doppler flow measurement. The spectral Doppler flow velocity (velocity time integral [VTI]) was continuously recorded on a high-quality, super VHS videotape for subsequent analysis, and average peak flow velocity was measured based on 15 to 20 beats to correct for changes related to respiration (Fig. 1). Renal artery lumen diameter (RAD) was measured blindly by quantitative angiography (QCA Heartlab, Westerly, Rhode Island) approximately 5 mm distal to the tip of the Flowire (Volcano Therapeutics) (Fig. 2).

After the placement of both catheters, baseline hemodynamic measurements, which included heart rate, renal arterial blood pressure, right atrial pressure (RAP), pulmonary arterial and pulmonary capillary wedge pressures, were performed along with thermodilution cardiac output. Cardiac index, systemic and pulmonary vascular resistances, as well as mean renal arterial blood pressure (MRBP) were calculated by standard formulas. In addition, renal artery Doppler blood flow velocity was recorded, and renal artery angiogram using 2 to 3 ml of contrast was performed. Renal artery blood flow was calculated using the following formula: RBF (ml/min) = heart rate (beats/min) × VTI × (π × (RAD^2/4), and renal artery vascular resistance (RVR) was calculated as: 80 × (MRBP − RAP)/RBF. Nesiritide (Scios Inc., Fremont, California) at a standard dose of 2-μg/kg intravenous bolus was

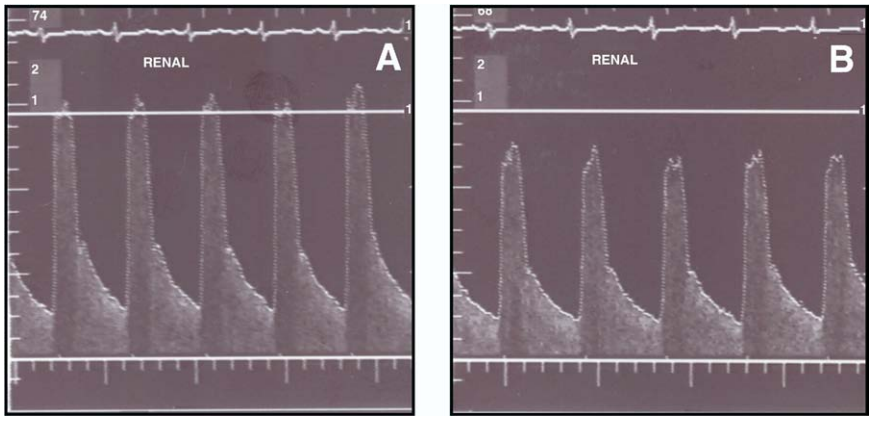

Figure 1. Example of Renal Artery Blood Flow Velocity Measured by Intravascular Doppler Technique

Renal blood flow velocity as measured with a Doppler Flowire (Volcano Therapeutics) at baseline **(A)** and during nesiritide infusion **(B)**.

then administered via a peripheral intravenous line followed by a continuous infusion at a rate of 0.01 μg/kg/min. All of the measurements and calculations mentioned in the preceding text were repeated in every patient at 15 min of nesiritide infusion. Assessment of nesiritide effect was done at 15 min in order to avoid an excessive prolongation of the patient procedures. The rest of the diagnostic tests including left heart catheterization and angiography were performed after the completion of the study protocol.

Data analysis. Because of the relatively small number of cases and lack of normality of distributions, the nonparametric Wilcoxon signed rank test was performed to compare measured and calculated parameters between the baseline and at 15 min of nesiritide infusion in all 15 patients. All group values were presented as mean ± SD. A probability value of <0.05 was considered as statistically significant.

RESULTS

General information. Of the 15 patients who were enrolled into the study, there were 4 female subjects and 11 male subjects. Mean age was 53 ± 16 years, ranging from 24 to 78 years. The etiology of HF was coronary artery disease in 6 patients and nonischemic cardiomyopathy in the others. None of the patients were found to have angiographic evidence

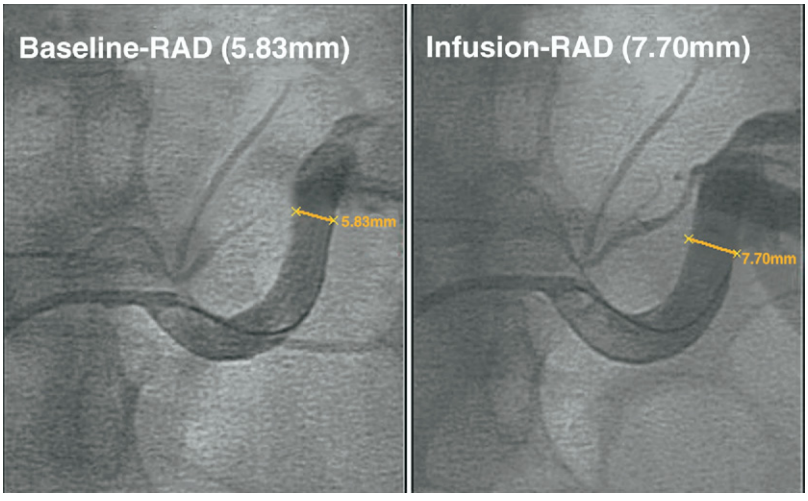

Figure 2. Example of a Quantitative Angiography of the Renal Artery

Renal artery diameter (RAD) as obtained by quantitative angiography at baseline and during nesiritide infusion.

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Table 1. Measurements of Systemic and Renal Hemodynamic Parameters at Baseline and 15 min After Intravenous Infusion of Nesiritide in 16 Patients With HF

Variable	Mean ± SD		p Value
	Baseline	Infusion	
HR (beats/min)	79 ± 16	81 ± 16	0.444
SRBP (mm Hg)	135 ± 28	123 ± 22	0.003
DRBP (mm Hg)	79 ± 12	71 ± 10	<0.001
MRBP (mm Hg)	99 ± 17	89 ± 13	0.002
RAP (mm Hg)	9 ± 6	7 ± 5	0.061
SPA (mm Hg)	55 ± 19	49 ± 22	0.001
DPA (mm Hg)	26 ± 8	22 ± 9	<0.001
MPA (mm Hg)	36 ± 12	31 ± 13	<0.001
PCWP (mm Hg)	21 ± 8	15 ± 10	<0.001
CO (l/min)	3.9 ± 1.2	4.6 ± 1.6	0.001
CI (l/min/m^2)	2.2 ± 0.5	2.5 ± 0.6	<0.001
SVR (dynes·s·cm^{-5})	1,995 ± 532	1,563 ± 504	<0.001
PVR (dynes·s·cm^{-5})	315 ± 157	305 ± 157	0.632
VTI (cm/beat)	27 ± 15	23 ± 15	0.008
RAD (mm)	6.2 ± 0.7	6.7 ± 0.8	<0.001
RVR (dynes·s·cm^{-5})	14,568 ± 7,334	13,609 ± 6,654	0.45
RBF (ml/min)	623 ± 326	647 ± 412	0.15

CI = cardiac index; CO = cardiac output; DPA = diastolic pulmonary artery (pressure); DRBP = diastolic renal blood pressure; HF = heart failure; HR = heart rate; MPA = mean pulmonary artery (pressure); MRBP = mean renal blood pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAD = renal artery diameter; RAP = right atrial pressure; RBF = renal artery blood flow; RVR = renal vascular resistance; SPA = systolic pulmonary artery (pressure); SRBP = systolic renal blood pressure; SVR = systemic vascular resistance; VTI = velocity-time integral.

of renal artery atherosclerotic disease. Left ventricular ejection fraction ranged from 10% to 38% (mean: 25 ± 9%). Mean serum creatinine was 97 ± 18 μmol/l (1.1 ± 0.2 mg/dl) and MRBP was 99 ± 17 mm Hg.

All patients were on oral furosemide and angiotensin-converting enzyme inhibitors, 12 patients were also on digoxin (75%), 10 patients on beta-blockers (69%), 8 on aspirin (56%), 2 on spironolactone (12%), and 1 patient on nitrates (6%).

Baseline versus 15-min infusion. Results of the analyses between baseline and 15 min of nesiritide infusion are shown in Table 1. There were significant reductions in renal arterial blood pressures and pulmonary arterial pressure as well as in pulmonary capillary wedge pressure and a borderline significant reduction in RAP (p = 0.06). In addition, calculated value of systemic vascular resistance was also decreased, while cardiac output and cardiac index were significantly increased. There was no significant change in heart rate and pulmonary vascular resistance. Nesiritide infusion also resulted in a significant increase in RAD, but at the same time, a fall in VTI (Fig. 3). These renal circulatory effects were not associated with a significant change in either RBF (Fig. 4) or RVR.

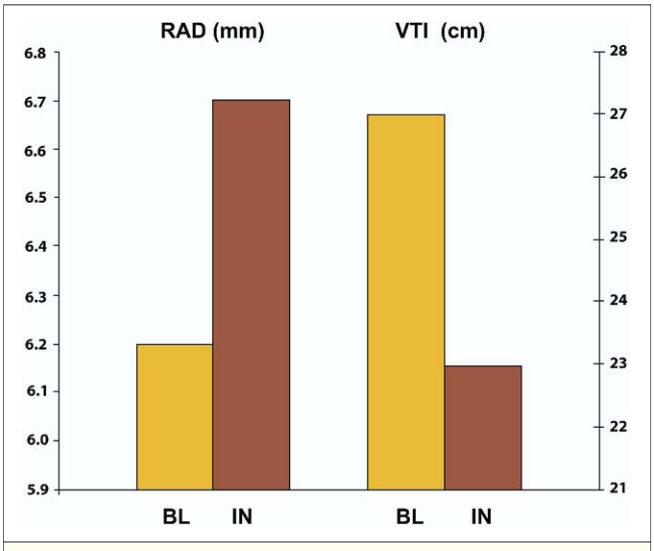

Figure 3. Mean Values of RAD and VTI

Mean group values of renal artery diameter (RAD) and velocity time integral (VTI) at baseline (BL) and at 15 min of nesiritide infusion (IN) at a dose of 0.01 μg/kg/min after intravenous bolus administration of 2 μg/kg. Continuous infusion of nesiritide was associated with a progressive significant dilation of the RAD (6.2 ± 0.7 mm to 6.7 ± 0.8 mm, p < 0.001), but at the same time a significant fall in VTI (27 ± 6 cm to 23 ± 15 cm, p < 0.001).

DISCUSSION

Quantitative angiography and intravascular Doppler techniques have been extensively used for evaluation of coronary anatomy (12) and for the assessment of coronary blood flow reserve (13). These techniques have also been validated and used for the measurements of changes in RAD and RBF (9–11,14–16). Our group has used these methods to gain further insight into the renal circulatory effect of various therapeutic interventions in patients with HF (10,17,18). The use of these techniques in the present study has indicated that compared with its systemic effect the renal circulatory action of nesiritide is more complex. A bolus administration followed by continuous infusion of the standard recommended dose of the drug was associated with a progressive dilation of the large conductance renal arteries, but at the same time a fall in VTI and, therefore, no significant change in RBF and only a small and statistically insignificant fall in RVR. The findings of this unique response to nesiritide are similar to the previously described effect of natriuretic peptides in animal experimentations and in healthy humans. Burnett et al. (19) and Maack et al. (20) examined the effect of synthetic atrial natriuretic peptide on the renal circulation in anesthetized dogs and reported a

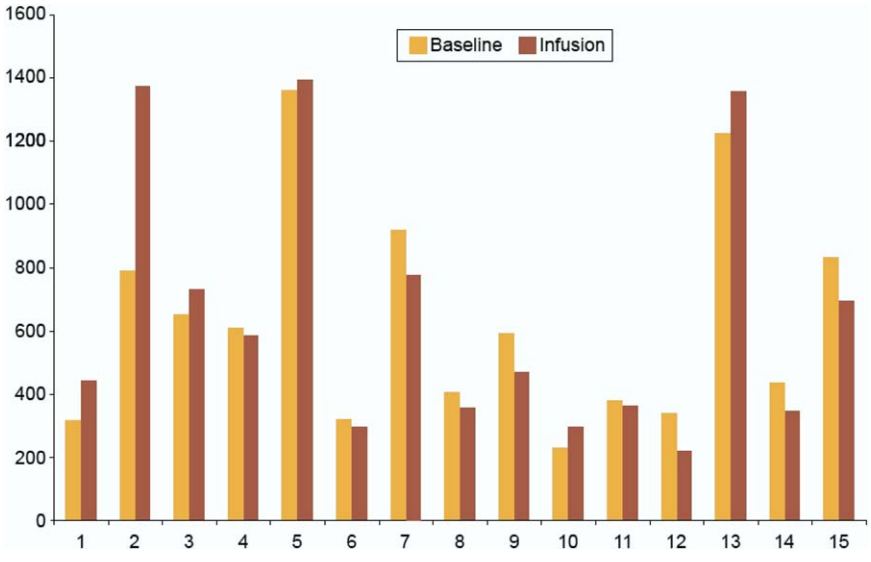

Figure 4. Effect of Nesiritide on RBF

Individual values of renal blood flow (RBF) in ml/min at baseline **(orange)** and at 15 min of nesiritide infusion **(brown)** in the 15 patients studied. Mean values were 631 ± 336 ml/min at baseline and 647 ± 412 ml/min during the infusion ($p = 0.15$).

transient increase in RBF, which was followed by a decline to or below baseline values with a continuous infusion. A number of studies in normal volunteers has shown an increase in glomerular filtration rate in response to BNP administration; the effect on RBF, however, was variable (21–24).

Although the mechanism of lack of increase in RBF despite a significant augmentation in cardiac output and a clearly documented nesiritide-mediated vasodilation of the conductance renal arteries is not entirely clear, there are a number of possible explanations. Since renal blood pressure showed a significant decline during continuous nesiritide infusion, the decrease in VTI and lack of improvement in RBF may be related to this finding. This possibility is supported by a study by La Villa et al. (23) who reported a significant increase in RBF during infusion of BNP in healthy volunteers at a dose that did not affect the systemic blood pressure. The relation between RBF and renal perfusion pressure may also be supported by recent studies by Riter et al. (25), who demonstrated a favorable effect on both urine output and renal function of a small (one-half of the standard dose), nonhypotensive dose of nesiritide in patients with decompensated HF. Low-dose nesiritide was also reported to have a favorable effect on renal function in 2 recent studies evaluating the effect of the drug in patients undergoing cardiopulmonary bypass surgery. Chen et al. (26) demonstrated prevention of activation of aldosterone as well as worsening of renal function observed in patients receiving placebo with an infusion of a low-dose nesiritide in a group of patients undergoing cardiopulmonary bypass surgery. Similarly, Mentzer et al. (6) demonstrated a nesiritide-mediated renal protective effect with prevention of worsening renal function and augmentation of urine output in patients with HF undergoing cardiac surgery. The patients in the later study received continuous infusion of nesiritide at the standard dose but without the initial bolus, which was associated with no significant reduction in systemic blood pressure compared with that in placebo. The results of these studies suggest the need for further investigation of the potential benefits of a smaller, nonhypotensive dose of nesiritide.

An additional potential explanation for the lack of significant changes in both RBF and RVR seen in our study may also be an alteration of intrarenal vasoregulation. Natriuretic peptide-mediated constriction of the efferent arterioles concomitant to dilation of the afferent renal arterioles have been well documented in animal experimentations (27–30). A slower time course of atrial natriuretic peptide-induced vasoconstriction of efferent arterioles, compared with a prompt vasodilatory response of the afferent arterioles in pre-constricted preparations, has been reported by Camargo et al. (30) in isolated, perfused rat kidneys and has been suggested to be the result of a secondary release of endothelin (31,32).

The circulatory effect of nesiritide as demonstrated in the present study may not be unique to the renal circulation. Michaels et al. (33) who examined the effect of intravenous nesiritide administration on human coronary arteries also showed a differential vasodilatory effect on the conductance and resistance arteries. While the epicardial conductance coronary arteries showed a gradual dilation that maximized at 15 min of infusion, the average peak blood flow velocity, which is affected mostly by dilation of the resistance vessels, demonstrated a significant decrease with continued infusion.

Study limitations. It should be noticed that the method used in this study for the evaluation of renal artery blood flow is likely to represent an underestimation of total RBF and is, therefore, not suitable for accurate measurement of this parameter or RVR but rather for assessment of their relative changes. Reasons for underestimation include the need to position the Doppler wire in a secondary renal artery is some patients due to the presence of a short renal artery with early bifurcation or double main renal arteries. Additionally, the underestimation may result from an inability to divert the wire to the central portion of the flow in order to record the maximum flow velocity especially in a large vessel such as the renal artery (Fig. 2) (34). In spite of these limitations, this method has been shown to accurately assess changes in flow, which are likely to be proportional to changes in total RBF (10,11, 14,17,18). An additional limitation is related to the fact that the study was performed in clinically stable patients as part of diagnostic cardiac catheterization and that the effect of contrast used for renal artery angiography on the vascular effect of nesiritide is not known; for these reasons the results of this study may not be completely applicable to symptomatic patients with ADHF who are treated with nesiritide early after admission.

CONCLUSIONS

The results of our study suggest a complex effect of intravenous nesiritide on the renal circulation in patients with HF. The drug had a substantial vasodilatory effect on the large, conductance renal arteries but not on the small resistant vessels. As a result of these effects, continuous nesiritide infusion was not associated with a significant impact on either RVR or RBF. Lack of increase in RBF in spite of a significant increase in cardiac output and RAD may be related to a fall in renal blood pressure due to the systemic effect of the drug and to a delayed vasoconstrictive response of the intrarenal efferent renal arterioles.

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Key Words: heart failure ■ nesiritide ■ intravascular Doppler ■ kidney.