Renal Circulatory Effects of Adenosine in Patients With Chronic Heart Failure

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Objectives. We sought to study the renal circulatory effects of adenosine in patients with chronic congestive heart failure (CHF).

Background. Renal blood flow (RBF) is often reduced in patients with chronic CHF and may lead to decreased renal function. The cause of reduced RBF is multifactorial and involves systemic as well as local vasoregulatory mechanisms. Stimulation of renal adenosine A1 receptors in animal models has resulted in a significant vasoconstriction of afferent and efferent glomerular arterioles and deterioration of renal function. Although adenosine serum levels have been shown to be elevated in patients with CHF, their effect on the renal circulation in this patient population has not been studied.

Methods. Nine patients with CHF from left ventricular systolic dysfunction were studied. The effects of adenosine at a dose of 10−5 mol/liter infused directly into the main renal artery on heart rate, renal artery blood pressure, renal artery cross-sectional area (measured by intravascular ultrasound), renal Doppler blood flow velocity (measured by a Doppler flow wire in the renal artery), RBF and renal vascular resistance (RVR) were evaluated.

Results. Infusion of adenosine resulted in no significant effect on heart rate or renal artery blood pressure but caused a substantial increase in RVR (11,204 ± 1,469 to 31,494 ± 3,911 dynes·cm−2, p = 0.0005), which led to a marked fall in RBF in every patient (mean values 376 ± 36 to 146 ± 22 ml/m2, p = 0.0002). These changes in RVR and RBF were associated with no significant change in renal artery cross-sectional area (0.389 ± 0.040 to 0.375 ± 0.033 cm2, p = 0.3).

Conclusions. Stimulation of renal adenosine receptors in patients with CHF results in marked renal vasoconstriction that leads to an important reduction in RBF. Lack of change in renal artery cross-sectional area suggests that adenosine affects intrarenal resistance blood vessels rather than large conductance vessels. These results may indicate a rationale for investigation of renal adenosine receptor blockade for enhancement of RBF and improvement of renal function in patients with chronic CHF.

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JACC Vol. 32, No. 1
July 1998:211–5

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Reduction of renal blood flow (RBF) is common in patients with congestive heart failure (CHF) and is the principal determinant of impaired glomerular filtration rate in these patients (1,2). Although a fall in RBF accompanies a decline in cardiac output in these patients, intrarenal hemodynamic variables are also mediated by local vasoregulatory mechanisms (2,3). An understanding of such mechanisms is a prerequisite for any attempt to develop therapeutic strategies for enhancement of RBF and improvement of renal function in patients with CHF.

Adenosine is an ubiquitous nucleoside that is present in normal kidneys (4,5). The physiologic effects of endogenous adenosine are mediated by activation of two major subtypes of membrane-bound receptors, allowing an important regulation of renal hemodynamic variables and function (4–8). Although exposure to adenosine leads to a marked vasodilatory effect in most vascular beds, the vasoregulatory effect of the drug in the kidney is more complex and heterogenous (8). Adenosine administration in various animal models resulted in different effects (9–11). The drug decreased RBF in salt-depleted rats (9) but increased RBF in sodium-loaded rats. Similarly, studies in humans demonstrated inconsistent results (12–14). Although adenosine was reported to dilate the renal vasculature in healthy subjects (14) and in patients with hypertension (13), it decreased renal flow in patients undergoing general anesthesia (12). However, no information is available regarding the effect of adenosine on the renal circulation in patients with CHF. An understanding of the effects of adenosine may be important for future development for therapeutic interventions for enhancement of renal function in such patients. The present study was therefore designed to evaluate the effect of exogenous adenosine on renal hemodynamic variables in patients with chronic symptomatic CHF.

Methods

Patients. Nine patients with a history of CHF from left ventricular (LV) systolic dysfunction who underwent diagnostic cardiac catheterization were included in the study. All...
patients were of male gender, and their age ranged from 30 to 64 (mean 46 ± 5 SEM). The etiology of CHF was coronary artery disease in four patients and unknown in five. LV systolic dysfunction was diagnosed by either contrast or radionuclide ventriculography, and mean LV ejection fraction was 26 ± 4%.

The group mean hemodynamic values as measured during cardiac catheterization were heart rate 88 ± 7 beats/min, mean arterial blood pressure 92 ± 3 mm Hg, mean right atrial pressure 9 ± 2 mm Hg, mean pulmonary artery pressure 30 ± 4 mm Hg, mean pulmonary artery wedge pressure 19 ± 3 mm Hg, cardiac index 3.3 ± 0.4 liters/min per m², systemic vascular resistance 1,480 ± 355 dynes•cm⁻² and pulmonary vascular resistance 192 ± 68 dynes•cm⁻².

**Study protocol.** All patients signed a consent form approved by the research committee of the Los Angeles County/University of Southern California Medical Center. After completion of diagnostic cardiac catheterization, an 8F angioplasty multipurpose or Judkins right coronary artery guiding catheter was placed in the proximal portion of the renal artery, and the catheter position confirmed with a small amount of angiographic contrast medium (Hexibrix, Mallinckrodt Medical). A Doppler guide wire (0.018-in. [0.045 cm]) (Flow-wire, Cardiometrics) was then introduced into the guiding catheter through a valved sidearm connector and its tip positioned in the main renal artery. A 3.5F intravascular ultrasound catheter (Mansfield, Boston Scientific) was then placed in a similar fashion and was positioned next to the Doppler wire. Images were obtained with a commercially available intracoronary ultrasound imaging system (Sono Intravascular, Hewlett-Packard) at 30 frames/s and recorded on 0.5-in. high quality super VHS videotape for subsequent off-line analysis. Renal artery lumen planimetry was later performed from the taped images, and cross-sectional area was determined with specially designed software. The spectral Doppler renal blood flow velocities were recorded, and the velocity–time integral was measured as the area under the outermost portion of the spectral velocity envelope. To correct for changes related to respiration and cardiac cycle, 15 to 30 beats were used for measurements of both renal artery cross-sectional area and Doppler velocity–time integral, and average values are reported.

Renal blood flow (in ml/min) was calculated as the product of the renal artery cross-sectional area and the velocity–time integral using the following formula: Flow = Heart rate per minute × Velocity–time integral × Cross-sectional area. Renal vascular resistance (RVR) was calculated as follows: 80 × (Mean renal artery blood pressure/RBF).

Renal artery pressures were measured directly with the aid of the arterial catheter, fluid-filled pressure tubing and standard transducers. Infusion of adenosine was performed through the arterial catheter directly into the renal artery. Adenosine (Fujisawa) was mixed in 5% dextrose in water to achieve a blood concentration of 10⁻⁵ mol/liter, assuming an average RBF of 600 ml/min in patients with CHF (15). Baseline measurements were performed after 3 min of renal intraarterial infusion of 5% dextrose in water and included the measurements of renal artery blood pressures, heart rate, intravascular ultrasound and Doppler flow velocity. After baseline hemodynamic measurements, infusion of adenosine into the renal artery was started, and measurements were repeated at 2 to 3 min.

**Data analysis.** A paired Student t test was used to determine the effect of exogenous adenosine on heart rate, renal artery blood pressures, renal artery cross-sectional area, Doppler velocity–time integral and calculated RBF and RVR. Results are expressed as mean value ± SE; p ≤ 0.05 was considered statistically significant.

**Results**

Administration of adenosine into the renal artery was not associated with any significant changes in both heart rate (86 ± 7 to 85 ± 8 beats/min, p = NS) and renal artery blood pressure (92 ± 4 to 91 ± 4 mm Hg, p = NS) (Fig. 1). The Doppler-measured velocity–time integral (Fig. 2 and 3) was reduced by 59 ± 5% from 25 ± 5 to 10 ± 2 m (p = 0.001). Calculated RBF

**Figure 1.** Effect of intrarenal artery administration of adenosine on mean group values of heart rate and mean renal artery pressure. BL = baseline.
was markedly reduced in all patients (Fig. 4). The group mean value for RBF was reduced 61 ± 4% from 376 ± 36 to 146 ± 22 ml/m² (p = 0.0002). RVR (Fig. 5) calculated from renal artery pressure and RBF demonstrated a 171 ± 113% increase from 11,204 ± 1,469 to 31,494 ± 3,911 dynes·cm² (p = 0.0005). In contrast to these findings, no change was seen in renal artery cross-sectional area (Fig. 6) on intravascular ultrasound (0.389 ± 0.040 vs. 0.375 ± 0.033, p = 0.3).

### Discussion

Adenosine is an ubiquitous nucleoside that is present in the kidneys (5). Adenosine receptors have been identified in glomeruli, cortical collecting tubule cells and the renal papilla and seem to play a regulatory role both in normal renal physiology as well as in abnormal conditions (4–7,16–21). Although adenosine is a potent vasodilator in most vascular beds, its renal circulatory actions are complex. The net circulatory effects depend on the balance between the vasoconstrictive effect of adenosine A₁ receptors and the vasodilatory effect mediated by adenosine A₂ receptors (8). In addition, salt balance and renin activity have been shown to play a role (9). RBF is often reduced in patients with CHF and may lead to impairment of renal function (1,2). Although the effect of adenosine on renal circulation has been studied in various animal models and in humans, no information is available regarding the renal circulatory effects of this substance in patients with CHF. Our study, which is to our knowledge the first attempt to evaluate the effect of exogenous adenosine on the renal circulation in patients with CHF, demonstrates a marked vasoconstrictive effect of adenosine on the renal circulation, resulting in a substantial increase in RVR and a concomitant fall in RBF in all patients.

Although the present study does not provide mechanistic insight into the renal vascular and hemodynamic effects of adenosine in patients with CHF, previous studies (18–20) demonstrating the ability to block responses to exogenous adenosine in vitro indicate that the vasoconstrictive effect is receptor mediated. Furthermore, animal studies (8,19,21) using specific adenosine receptor antagonists have confirmed that the vasoconstrictor effect of adenosine is due to the exclusive presence of receptors of the A₁ subtype in the kidney. Activation of these receptors has been reported (18,22) to lead to an inhibition of adenyl cyclase activity and to decreased intracellular cyclic adenosine monophosphate (AMP) levels. At the same time, the observation that adenosine results in some tissues in stimulation and in others in inhibition of cyclic AMP production led to the conclusion that these responses were mediated by different receptor types. Numerous studies have confirmed the presence of vasodilating adenosine A₂ receptor subtype both in preglomerular and postglomerular...
The stimulation of A2 receptors has been shown (18) to lead to vasodilation secondary to an increase in intracellular cyclic AMP levels.

Although the administration of exogenous adenosine in the present study resulted in a substantial reduction of RBF in all patients, it was not associated with any significant change in the size of the large renal artery as determined by intravascular ultrasound. These findings suggest that the vasoconstrictive action of adenosine in the kidney is due to its effect on small resistance vessels rather than on large conductance vessels. This conclusion is supported by animal experiments (18,21) demonstrating adenosine-mediated vasoconstriction of afferent and efferent glomerular arterioles reflecting the presence of adenosine A1 receptors on these intrarenal blood vessels.

The present study was designed to evaluate the direct effect of adenosine on the renal circulation. The drug was infused into the renal artery to avoid renal changes mediated by potential systemic effects (14,23,24). Lack of any systemic effect was evidenced by the stability of heart rate and systemic blood pressure demonstrated during adenosine infusion. Edlund et al. (14) reported a small increase in heart rate observed during adenosine infusion into the renal artery in normal subjects. These investigators postulated an activation of afferent nerves to the central nervous system induced by adenosine receptors in the kidney. However, this suggestion is not supported by our results demonstrating a lack of a significant change in heart rate during intrarenal adenosine infusion.

Study limitations. The present study was designed to evaluate the renal circulatory effect of exogenous adenosine at a dose comparable to that used to achieve an effect in other vascular beds (25) and at a previously evaluated concentration in the kidney tissue (26). A dose-related effect of adenosine has been demonstrated by Inscho et al. (27) who reported vasoconstriction of afferent arteriolar vessels with a lower concentration and vasodilation at a higher concentration from stimulation of the lower affinity adenosine A2 receptors. It is therefore unclear whether the results of our study can be applicable to the effect of endogenous adenosine. However, it has been suggested (6,28) that under physiologic conditions, the extracellular free adenosine concentration is low and is predominantly mediated by A1 receptor activity. This suggestion is further supported by a reported reduction in the glomerular filtration rate caused by A1 receptor-mediated afferent arteriolar vasoconstriction found when endogenous adenosine production is stimulated by pharmacologic maneuvers (21,22,29). Although the luminal presentation of exogenous adenosine to the renal vascular cells should be similar to that of circulating endogenous adenosine, the adventitial presentation of intrarenally produced adenosine may result in a different action. However, the use of topicaly applied adenosine, which approaches the vasculature through the interstitial compartment and is probably more indicative of the effect of endogenous adenosine, has also been reported (30) to produce a renal vasoconstrictive effect similar to that seen in our study.

An additional limitation of the study could be related to the use of angiotensin-converting enzyme (ACE) inhibitors as part of CHF therapy. Numerous reports (17,31) have indicated that angiotensin II may be an important modulator of adenosine-induced renal hemodynamic effect. Although ACE inhibitors were discontinued at least 14 h before the initiation of our study, a residual effect of these drugs could have attenuated the vasoconstrictive action of adenosine.

Clinical implications. Reduction of RBF is common in patients with chronic CHF and is an important cause of acute and chronic renal dysfunction. The results of the present study demonstrate a significant renal vasoconstrictive effect mediated by stimulation of adenosine receptors. These findings may indicate a possible role for inhibition of adenosine receptors as a therapeutic target aiming to increase RBF in patients with chronic CHF. Such a possibility seems to be supported by numerous studies (6,32,33) in animals and humans demonstrating a significant increase in RBF and improvement of the glomerular filtration rate with the use of adenosine A1 receptor antagonists. An additional benefit of renal adenosine receptor blockade shown in various animal models and in normal human subjects has been a significant diuretic and natriuretic effect (6,28,33–35). Yamagata et al. (34) have also demonstrated in anesthetized dogs that the diuretic and natriuretic effect of adenosine, which was mediated mainly by inhibition of reabsorption of water and sodium at tubular sites, was associated with only a minimal kaliuretic effect.

Conclusions. The results of the present study demonstrate a potent vasoconstrictive effect of adenosine on the renal circulation in patients with CHF, leading to a marked increase in RVR and a reduction in RBF. Lack of effect on the luminal cross sectional area of the large conductance renal arteries indicates that adenosine exerts its vasoconstrictive effect on the intrarenal resistance blood vessels. This effect is likely to be due to stimulation of adenosine A1 subtype receptors in the kidney. The findings of this study and previous reports on enhancement of RBF, glomerular filtration rate, urine production and sodium excretion with adenosine A1 receptor antagonists may suggest a rationale for the investigation of adenosine A1 receptor blockade for enhancement of RBF and improvement of renal function in patients with chronic CHF.
We thank the cardiac catheterization laboratory staff at the Los Angeles County/University of Southern California Medical Center for their commitment to the performance of this study.

References