ABSTRACT

Renal failure is common in heart failure due to renovascular constriction and hypotension. We tested whether selective pharmacological renal artery vasodilation and active renal artery perfusion (ARP) could improve renal function without adverse effects on systemic blood pressure in a canine model of acute heart failure (AHF). AHF was induced by coronary microembolization in 16 adult mongrel dogs. In five dogs, selective intrarenal (IR) papaverine (1, 2, and 4 mg/min) was administered into the left renal artery. In six dogs, ARP was performed in the left renal artery to normalize mean renal arterial pressure followed by administration of IR papaverine (2 mg/min). In five dogs, ARP plus intravenous furosemide was tested. Urine output (UO) and cortical renal blood flow decreased during AHF and were restored by 2 mg/min IR papaverine (UO: baseline 4.2 ± 0.6, AHF 1.6 ± 1.3, IR papaverine 5.8 ± 1.1 ml/15 min; cortical blood flow: baseline 4.3 ± 0.2, AHF 2.4 ± 0.6, IR papaverine 4.2 ± 1.2 ml/min/g) with no significant change in aortic pressure. ARP also increased urine output and cortical renal blood flow (UO: baseline 5.0 ± 1.1, AHF 0.5 ± 0.4, ARP 3.8 ± 3.1 ml/15 min; cortical blood flow: baseline 4.0 ± 0.5, AHF 2.0 ± 0.8, ARP 3.52 ± 1.1 ml/min/g). A combination of these methods in AHF further increased urine output to twice the normal baseline (10.5 ± 7.5 ml/15 min). Addition of furosemide synergistically increased UO above that achieved with ARP alone (5.5 ± 2.6 versus 40.3 ± 24.7 ml/15 min, p = 0.03). In conclusion, ARP and selective renal vasodilation may effectively promote salt and water excretion in the setting of heart failure, particularly when systemic blood pressure is low.

Materials and Methods

All animals in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, 1996).

ABBREVIATIONS: AHF, acute heart failure; AoP, aortic pressure; ARP, active renal artery perfusion; Ccr, creatinine clearance; CO, cardiac output; IR, intrarenal; RAF, renal arterial flow; RAP, renal arterial pressure; UO, urine output; fr, French scale.
Surgical Procedures

Studies were performed in 16 adult mongrel dogs weighing 25 to 32 kg; additional dogs were used for preliminary studies as detailed in the text. The dogs were anesthetized (sodium pentobarbital, 30 mg/kg i.v.) and mechanically ventilated. In the supine position, the left femoral vein was cannulated for fluid infusion. Both femoral arteries were dissected for later cannulation. A micro-tipped manometer (Millar Instruments, Houston, TX) was inserted into the left ventricle through the right carotid artery to monitor left ventricular pressure. The left carotid artery was also cannulated with a micro-tipped manometer to measure aortic pressure (AoP). The right jugular vein was cannulated for central venous pressure measurement.

Through a midline laparotomy, both ureters were individually cannulated to quantify urine output and to obtain urine samples separately from each kidney. The abdominal wall was then tightly closed to prevent hypothermia and water loss.

Thereafter, the dog was repositioned in the right lateral position. The left subcostal space was entered to expose the left renal artery. A catheter (24-gauge Angiocath; BD Biosciences, Sandy, UT) was inserted into the left renal artery to measure renal arterial pressure (RAP) or to infuse pharmacologic vasodilators. An ultrasonic flow probe (Transonic Systems, Ithaca, NY) was placed around the left renal artery to monitor instantaneous changes in renal arterial flow.

The right renal artery was not instrumented so as not to interfere with the vessels and nerves of this kidney and to limit the surgical preparation to the minimum required. During these procedures, the extent of blunt dissection was minimized to prevent damage to the nerves and small vessels surrounding the kidney. The right kidney was left untouched to serve as control for the actively treated left kidney.

Finally, the chest was entered through the left fifth intercostal space. The ascending aorta was dissected, and an ultrasonic flow probe (Transonic Systems) was placed to monitor instantaneous aortic blood flow and cardiac output. The pericardium was then opened and the heart exposed. The left atrial appendage and the thoracic descending aorta were each cannulated for colored microsphere injections and blood sampling, respectively, which were used to quantify regional blood flow within the two kidneys. The left anterior descending coronary artery was then dissected and cannulated in its proximal portion with a flexible silicon catheter (internal diameter, 1.0–1.3 mm; outer diameter, 1.8–2.3 mm); this cannula is used for injection of glass microspheres to induce AHF. The sternum was then reapproximated to prevent hypothermia and water loss.

In the dogs used to study ARP, the right femoral artery was cannulated with a 10-fr arterial cannula (Medtronic, Inc., Minneapolis, MN) to withdraw arterial blood following systemic heparinization (10,000 U i.v.). A 10-fr catheter with an ~1.0-ml balloon around the tip (Heartport, Redwood City, CA) and the femoral cannula were then connected to a centrifugal pump (BP-50, Medtronic, Inc.) that was primed with heparinized saline solution. Following induction of AHF, the catheter was inserted through the femoral artery to start ARP.

Protocol

Induction of Heart Failure. After making baseline recordings of hemodynamics (left ventricular, aortic, and central venous pressure), renal blood flow (both flow probe and microsphere assessments, as described below), and urine output and obtaining urine for later urinalysis, AHF was gradually induced by repeated injections of glass microspheres (~90-μm mean diameter, 25,000 microspheres/ml) every 5 min through the indwelling catheter in the left descending coronary artery (Knecht et al., 1997; Todaka et al., 1997). The number of such microsphere injections ranged between 5 and 11 with a median of 8. When cardiac output was decreased to half of the baseline value and this degree of cardiac output reduction was stable for 20 min, the second set of hemodynamic and urine assessments was performed (AHP study).

IR Papaverine. In five dogs, papaverine, a nonspecific smooth muscle relaxant and a known renal artery vasodilator, was administered selectively into the left renal artery through the indwelling catheter described above. Papaverine was continuously infused using an infusion pump (Harvard Apparatus Inc., Holliston, MA) starting at 1 mg/min. The infusion rate was increased to 2 and 4 mg/min. Hemodynamic measurements and urine output were monitored at each infusion rate; however, complete sets of measurements (including microsphere blood flow assessments and urine samples for analysis) were only performed during the 2 mg/min of papaverine infusion.

ARP. In six dogs, ARP was performed using a 10-fr catheter (with two lumens) inserted through the left femoral artery. After induction of AHP, the catheter was placed into the aorta, and perfusion was started through the larger catheter lumen at a rate of 100 ml/min to flush the system with heparinized blood. The catheter was then inserted into the left renal artery by manual guidance. The balloon at the tip of the catheter was inflated to occlude the proximal renal artery, and the perfusion rate was gradually increased until mean RAP reached its original baseline value. Renal arterial pressure was measured throughout the second lumen, which did not have flow. If this condition was stable, hemodynamic measurements were performed (ARP study).

ARP + IR Papaverine. Following the ARP study, continuous papaverine infusion into the perfusion cannula was started with an infusion rate of 2 mg/min. Since papaverine reduced RAP, the renal perfusion rate was adjusted so that RAP was maintained approximately at the original baseline value. The final set of hemodynamic and urine output measurements was performed under this condition.

ARP Plus Systemic Furosemide. Studies were performed in an additional five animals to test the additive effects of ARP and systematically administered furosemide. After the induction of acute heart failure as detailed above and the recording of baseline hemodynamics, furosemide (5 mg/kg i.v.) was administered, and repeat hemodynamics were obtained.

Data Analysis. Recorded signals included AoP, left ventricular pressure, central venous pressure, and cardiac output (CO) as detailed above. Renal arterial flow (RAF) and RAP were obtained only in the treated kidney. For the control untreated kidney and for both kidneys during IR papaverine infusion, AoP was regarded as equal to RAP. Regional blood flow was measured using colored microspheres (see below).

To evaluate renal responses to each treatment, measurement of urine output (UO) over 15-min periods and urinalysis, including urine creatinine and sodium, were performed. Arterial blood samples were also obtained for serum creatinine and sodium at the same time point as urine sampling. UO was measured two to three times and averaged. Creatinine clearance (Ccr) was calculated according to the standard equation Ccr (ml/min) = urine creatinine (mg/dl)/serum creatinine (mg/dl) × urine output (ml/min). Excretion of sodium was calculated as the following: sodium excretion (μmol/min) = urine output (ml/min) × urine sodium (μmol/ml).

Microsphere Analysis. To assess the regional blood flow in the kidneys, 1.5 or 2.0 ml of colored microsphere solution (15-μm diameter, 3 × 10^6 microspheres/ml in a saline suspension with 0.01% Tween 80 and thimerosal, Dye-Trak; Triton Technology, Inc., San Diego, CA) was injected into the left atrium. Blood samples were obtained during microsphere injections at a constant rate of withdrawal (7 ml/min) from the indwelling catheter in the descending aorta.

At the end of the experiment, both kidneys were excised, and six tissue samples from the cortex and three samples from the medulla in each kidney were obtained. These samples were digested, and the microspheres were retrieved by filtration of the digestate. The dye on the microspheres was then itself digested into solution using dimethylformamide, and the photometric absorption of the resulting sample was measured by a diode array spectrophotometer (model 8452A; Hewlett Packard, Palo Alto, CA). The composite spectrum
was resolved at the peak frequencies into the contributions from the individual colored microspheres using a matrix inversion technique (Kowalik et al., 1991). The number of microspheres in each sample was calculated according to the optical density at the wavelength corresponding to each dye color using standardization curves generated from known quantities of microspheres from the same batch of spheres. Regional renal blood flow (milliliters per minute per gram) was calculated using the following equation:

$$\text{RBF} = \frac{F_{\text{ref}}}{M_{\text{sample}}} \times \frac{\text{OD}_{\text{sample}}}{\text{OD}_{\text{ref}}}$$

where $F_{\text{ref}}$ represents the rate at which arterial blood is withdrawn from the femoral artery (i.e., from the reference sample, which was always 7 ml/min); $\text{OD}_{\text{ref}}$ represents the optical density of the dye solution obtained from this reference sample; $M_{\text{sample}}$ represents the mass of the respective kidney sample; and $\text{OD}_{\text{sample}}$ represents the optical density at the corresponding wavelength of the dye solution obtained from the kidney sample.

**Statistical Analysis**

All data are presented as means and standard deviations. Statistical comparisons were performed with analysis of variance using Bonferroni-Dunn correction to account for multiple comparisons.

**Results**

**IR Papaverine.** The changes in AoP (equivalent to RAP in both kidneys), CO, left RAF, and UO during the initial induction of heart failure and then during IR papaverine infusion are shown in Fig. 1. As intended, CO was decreased to 50% of the baseline value by repeated coronary embolizations (Fig. 1A). AoP also decreased significantly after induction of AHF (Fig. 1B). RBF measured in the left renal artery, which was naturally perfused from the aorta in this protocol, was also decreased (Fig. 1C) as renal artery resistance increased from $0.40 \pm 0.10$ to $0.55 \pm 0.19$ mm Hg · min/ml ($p = 0.05$, paired $t$ test). However, since renal blood flow is autoregulated down to a blood pressure of 60 to 70 mm Hg (Kastner et al., 1984; Woods et al., 1987; Persson et al., 1990; Young et al., 1990), it decreased proportionately and slightly less than did total CO.

AoP did not change significantly during selective left renal artery papaverine infusion with either 1 or 2 mg/min papaverine infusions, although at 4 mg/min there was an approximately 10% decrease in AoP compared with the preceding AHF state (AHF 78 ± 15 versus 61 ± 18 mm Hg during 4 mg/min papaverine, $p = 0.082$). RAF tended to improve during IR papaverine infusion (AHF, 148 ± 47 versus 208 ± 37 ml/min during 2 mg/min papaverine, $p = 0.034$). However, with 4 mg/min IR papaverine, RAF did not increase and even decreased due to a slightly lower aortic perfusion pressure. UO was significantly improved with 2 mg/min IR papaverine compared with UO measured during the AHF state (Fig. 1D).

![Fig. 1. A, cardiac output. B, systemic aortic pressure (equivalent to renal arterial pressure). C, renal arterial flow in the left renal artery. D, urine output (control kidney, black bars; treated kidney, white bars). Papa 1, 2, and 4, intrarenal papaverine at infusion rates of 1, 2, and 4 mg/min, respectively. Data are from five dogs. † $p < 0.05$ versus baseline in the same kidney; # $p < 0.05$ versus AHF.](image-url)
However, with 4 mg/min papaverine, UO did not increase as significantly as did RBF.

Since papaverine infused at 2 mg/min provided the best RAF and UO, measurements of cortical and medullary blood flow (by colored microspheres), Ccr, and sodium excretion were performed with this dose. Both cortical (Fig. 2A) and medullary flows (Fig. 2B) were significantly improved by IR papaverine in the treated kidney compared with those during AHF. Interestingly, regional renal blood flow also tended to improve in the control kidney, although these results did not reach statistical significance. Also, Ccr improved in both kidneys, although significantly more so in the treated kidney in which Ccr returned to the baseline normal value (Fig. 2C). However, sodium excretion was not improved by IR papaverine (Fig. 2D).

**ARP with and without IR Papaverine.** Figure 3 shows changes in AoP (which equals changes in RAP in the control kidney), RAP and RAF in the treated kidney, CO, UO, regional blood flow, Ccr, and sodium excretion during ARP with and without IR papaverine. The changes in systemic hemodynamics, RAP, RAF, and UO after induction of AHF were similar to those in the first groups of animals (Fig. 1).

As intended, RAP was restored to its normal value by ARP (Fig. 3B). Furthermore, ARP did not cause a decrease in AoP, and there was no change in total CO. Importantly, UO was also restored to its baseline value (Fig. 3C), even though RAF measured by flow probe in the treated kidney was only mildly improved (Fig. 3D). However, cortical blood flow measured by the colored microsphere technique was restored by ARP (Fig. 3E), whereas medullary flow (Fig. 3F) remained depressed. Finally, creatinine clearance increased to above baseline, whereas sodium excretion was improved only slightly (Fig. 3, G and H, respectively).

With addition of 2 mg/min IR papaverine to ARP, UO was further increased compared with that during ARP alone, reaching roughly twice the baseline value. Sodium excretion was also increased with only mild changes in cortical and medullary flows as well as creatinine clearance.

**Synergism with Systemic Diuretics.** Five additional experiments were performed to test the combined effect of ARP and diuretics. In this protocol, ARP was performed as described above followed by systemic administration of furosemide (5 mg/kg i.v.). Urine output, which was decreased during acute heart failure and restored by ARP, was further enhanced by systemic administration of furosemide. Urine output, which was decreased during acute heart failure and restored by ARP, was further enhanced by systemic administration of furosemide (ARP, 5.5 \pm 2.6 versus ARP + furo-

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**Fig. 2.** A, cortical blood flow (control kidney, black circles; treated kidney, white circles). B, medullary blood flow (control kidney, black circles; treated kidney, white circles). C, creatinine clearance (control kidney, black bars; treated kidney, white bars). D, sodium excretion (control kidney, black bars; treated kidney, white bars). *p < 0.05 versus control kidney; †p < 0.05 versus baseline in the same kidney; #p < 0.05 versus AHF.
semide 40.3 \pm 24.7 \text{ ml/15 min}, p = 0.03; p value decreased to 0.0001 after logarithmic transformation of the data to equate the variances about the mean values). In contrast, only a mild increase in urine output was observed in the control kidney (ARP 1.5 \pm 1.1 versus 6.4 \pm 9.1 \text{ ml/15 min}, p = \text{N.S.}). These data only reflect acute effects of diuretic administration, and it is generally the case that only long-term effects of diuretics should be considered (to account for possible rebound effects), and it has not been determined whether these effects are sustained. Nevertheless, it should be noted that these effects were dramatic in the perfused kidney compared with the control kidney.

**Discussion**

Both selective intrarenal papaverine administration and ARP can increase cortical renal blood flow and restore natriuresis, diuresis, and creatinine clearance in a canine model of acute heart failure. Intrarenal papaverine also increased urine output in the untreated kidney, but the effect, which
could be due to a systemic effect of papaverine, was less than 50% of that seen in the treated kidney. Combining selective vasodilator therapy and active renal artery perfusion further increased urine output to twice the baseline normal values while maintaining systemic arterial pressure.

Renal failure (oliguria or anuria and azotemia despite maximal medical therapy) due to decreased aortic pressure and increased renovascular resistance occurs commonly without intrinsic renal disease in the setting of acute heart failure. Renal failure leads to sodium and water retention, edema in the lungs, and abdominal viscera, factors that interfere with normal organ function and contribute importantly to the clinical deterioration in acute heart failure. When renal failure occurs in the setting of acute heart failure, more aggressive therapies such as ultrafiltration and hemodialysis are sometimes used. Pharmacologic therapies used to increase blood pressure (such as norepinephrine or pressor doses of dopamine) cause further renovascular constriction; thus, despite increasing blood pressure, these agents may cause further deterioration of renal function (see Guidelines for the Evaluation and Management of Heart Failure, 1995; Pool, 1998). Thus, approaches that can improve renal function in the setting of acute heart failure could have a significant impact on patient outcome.

**Intrarenal Papaverine.** Prior studies have investigated the utility of selective intrarenal administration of vasodilators. Bugge et al. (1991) reported that IR papaverine (4 mg/min) infused into denervated canine kidneys increased RBF by 50% and increased sodium excretion 6-fold at a normal renal arterial pressure (~120 mm Hg). However, they reported that IR papaverine could not improve RAF at low RAPs (~40–60 mm Hg) although sodium excretion could be maintained at the normal level (Bugge et al., 1991). Similarly, Baer et al. (1970) also described that IR papaverine (6 mg/min) increased RAF by 50% and increased sodium excretion 3-fold at the control pressure (~100 mm Hg), whereas RAF was only mildly increased at an RAP of ~50 mm Hg with significant improvement of sodium excretion (Baer et al., 1970). In the current study, although using the lower dose of 2 mg/min for IR papaverine infusion compared with other reports (Baer et al., 1970; Bugge et al., 1991), we observed favorable effects in the intact preparation on RBF (in both cortex and medulla), creatinine clearance, and urine output with minimal changes in systemic arterial pressure.

However, compared with the reports described above, sodium excretion was not fully restored by IR papaverine even with the relatively higher mean renal perfusion pressures (~70 mm Hg). One possible explanation is the lower papaverine dose used in the present study. However, a more important factor might be the difference in experimental models. In the prior reports, renal artery perfusion pressure was decreased using a renal artery occluder in normal dogs. In contrast, we used an acute heart failure model that likely stimulates baroreflexes leading to neurohormonal activity and causing more sodium reabsorption. Although papaverine is considered to exert its effects by maintaining sodium chloride reabsorption in the macula densa even under low renal perfusion pressures (Bugge et al., 1991), it was not the dominant factor in the present study.

At papaverine infusion rates of 4 mg/min, mean RAP decreased further to ~60 mm Hg and RAF decreased. Therefore, even with selective IR infusion, an infusion rate at which systemic effects are observed is ultimately reached, and the resulting hypotension limits improvements in renal function and would likely have deleterious effects on other organs as well.

**Active Renal Perfusion.** ARP was considered as a means of restoring normal RAF and RAP to the hypoperfused kidney in the setting of acute heart failure. Indeed, ARP restored urine output, sodium excretion, and cortical blood flow. However, we did not observe full normalization of creatinine clearance or medullary flow, perhaps because of a coexistence of renovascular constriction induced by the heart failure state.

Nevertheless, the effect of ARP seemed to be mediated by restoration of renal perfusion pressure rather than improved renal blood flow. Since the medullary blood flow is not auto-regulated as efficiently as cortical blood flow, when medullary blood flow is increased following elevation of renal perfusion pressure, hydrostatic pressure within the vasa recta capillaries and renal interstitium is elevated. This pressure elevation inhibits reabsorption of fluid and sodium from the proximal tubule and/or from the thin descending limb (Firth et al., 1990). Therefore, maintenance of renal perfusion pressure seems to be important for obtaining natriuresis, and this was only achieved in the present studies with ARP.

**ARP Plus IR Papaverine.** As described above, the decrease in RAP limited the effectiveness of papaverine to enhance natriuresis. On the other hand, increased renal vascular resistance limited, to a certain degree, the effectiveness of ARP to restore all aspects of renal function. Since selective renal vascular vasodilation and active perfusion are potentially complementary strategies, we tested the effect of combining these methods. ARP plus IR papaverine significantly increased sodium excretion and urine output to as much as twice their respective normal baseline values. Nevertheless, this strategy still showed incomplete improvement in medullary renal blood flow. Therefore, it is possible that the mechanisms of enhanced natriuresis might be a combination of the pressure natriuresis and pharmacologic inhibition of sodium reabsorption and might be only partly due to vasodilation.

Based upon these results, we propose that selective drug infusion and/or active perfusion could provide a new therapeutic approach to treating renal dysfunction in the setting of acute heart failure. IR papaverine infusions could be carried out using specially designed catheters via a percutaneous approach. Relatively low rates of selective papaverine infusions were effective in improving renal function without inducing systemic hypotension. However, if insufficient effects are observed, ARP (with continued drug infusion), which is a more aggressive therapy requiring active pumping and pressure monitoring, could be an alternative approach.

**Limitations.** In the present studies, only one kidney was treated with either selective IR drug infusion or ARP to provide an appropriate control to assess the effects of therapy. In the clinical setting, however, it would be desirable to treat both kidneys to achieve maximal clinical effects. Also, the present study only examined acute effects, whereas therapeutically, it would be desirable to devise a means of providing such therapies over longer time periods for patients with chronic heart failure. The results obtained in the present study may not apply in the setting of chronic heart failure against the backdrop of standard chronic heart failure.
therapies. The results of the present study could also be influenced by the fact that they were obtained in the setting of significant surgical preparation and with various organs exposed; these conditions could cause a loss of effective circulating blood volume due to bleeding and serous leakage. For example, there were some differences in baseline sodium excretion between the first and second set of experiments (compare Figs. 2D and 3H). This could reflect some differences in experimental preparation that were not controlled for. Such factors would not be encountered in the clinical setting and could influence results.

**Conclusion.** In conclusion, renal blood flow and urine output could be restored by IR papaverine with mild improvement of sodium excretion. On the other hand, active renal perfusion improved natriuresis in spite of limited recovery of renal blood flow. Combining these methods helped to overcome individual limitations and further improved natriuresis. Most importantly, these benefits were achieved without deleterious effects on systemic arterial pressure. Since renal dysfunction remains a common consequence of acute heart failure responsible for significant morbidity and mortality, therapies to specifically and more aggressively treat renal dysfunction in heart failure, particularly in already hypotensive patients, could represent an important new approach to this condition.

**References**


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