Influence of Acute Renal Failure on Coronary Vasoregulation in Dogs

John G. Kingma, Jr., Chantal Vincent, Jacques R. Rouleau, and Iris Kingma

Coronary Physiology Research Group, Institut Universitaire de Cardiologie et Pneumologie, Department of Medicine, Laval University, Quebec City, Quebec, Canada

Impaired renal function is associated with an increased risk for cardiovascular events and death, but the pathophysiology is poorly defined. The hypothesis that coronary blood flow regulation and distribution of ventricular blood flow could be compromised during acute renal failure (ARF) was tested. In two separate groups (n = 14 each) of dogs with ARF, (1) coronary autoregulation (pressure-flow relations), vascular reserve (reactive hyperemia), and myocardial blood flow distribution (microparticles) and (2) coronary vessel responses to intracoronary infusion of select endothelium-dependent and -independent vasodilators were evaluated. In addition, coronary pressure-flow relations and vascular reserve after inhibition of nitric oxide and prostaglandin release were evaluated. Under resting conditions, myocardial oxygen consumption increased in dogs with ARF compared with no renal failure (NRF; 11.8 ± 9.2 versus 5.0 ± 1.5 ml O₂/min per 100 g; P = 0.01), and the autoregulatory break point of the coronary pressure-flow relation was shifted to higher diastolic coronary pressures (60 ± 17 versus 52 ± 8 mmHg in NRF; P = 0.003); the latter was shifted further rightward after inhibition of both nitric oxide and prostaglandin release. The endocardial/epicardial blood flow ratio was comparable for both groups, suggesting preserved ventricular distribution of blood flow. In dogs with ARF, coronary vascular conductance also was reduced (P = 0.001 versus NRF), but coronary zero-flow pressure was unchanged. Vessel reactivity to each endothelium-dependent/independent compound also was blunted significantly. In conclusion, under resting conditions, coronary vascular tone, reserve, and vessel reactivity are markedly diminished with ARF, suggesting impaired vascular function. Consequently, during ARF, small increases in myocardial oxygen demand would induce subendocardial ischemia as a result of a limited capacity to increase oxygen supply and thereby contribute to higher risk for adverse coronary events and mortality.

Mortality rates in acute renal failure (ARF) have remained unchanged in the past five decades (1). Several major clinical trials have documented that reduced renal function is associated with increased risk for cardiovascular events and death (2,3) in patients with acute or chronic renal disease (4). Renal disease also is an important risk factor for cardiovascular complications after myocardial infarction and cardiogenic shock (5). Renal failure modifies most factors that regulate cardiovascular function via direct hemodynamic effects, neurogenic reflexes, and circulating hormones (6). The loss of cardiovascular reserve as a result of renal disease may explain the high morbidity and mortality in patients with end-stage renal failure (4,7,8). Coronary autoregulation is an important homeostatic mechanism for maintenance of nutrient and oxygen delivery to the myocardium (9–11). Intrinsic autoregulatory mechanisms adjust tone within the microvasculature to maintain distribution of myocardial blood flow over a range of oxygen supply and demand requirements (9). Factors that are involved include intra- and extravascular compressive forces (12,13), left ventricular (LV) preload and afterload (14), LV volume, coronary collateral blood flow (15), neuronal status (16,17), arterial structure (18), and endothelial function (19); these factors can be modulated significantly under physiologic or pathologic conditions. Although it is established that underlying cardiac disease compromises kidney function in humans, it is not clear how impaired renal function affects coronary blood flow regulation, myocardial blood flow distribution, and cardiovascular reserve. We hypothesized that myocardial blood flow regulation could be compromised after onset of kidney dysfunction and thereby contribute to mortality in these patients. Studies were done using an in situ canine model of renal ischemia-reperfusion injury; total coronary blood flow (flow probe) and transmural (microparticles) myocardial blood flow regulation were evaluated. In addition, coronary vessel reactivity was assessed in response to intracoronary infusion of endothelium-dependent and -independent vasodilators before and after inhibition of nitric oxide (NO) and prostaglandin release.

Materials and Methods
Male mongrel dogs that weighed 20 to 25 kg were used in this study; animals were acclimatized for 7 d before the day of first surgical...
Renal Ischemia-Reperfusion Injury Preparation

Dogs were premedicated with acepromazine maleate (Atravec, 0.5 mg/kg, intramuscularly); cefazolin sodium (Kefzol, 22 mg/kg, intravenously) and butorphanol (0.2 mg/kg, intramuscularly) were given 30 min before surgery and every 2 h during the surgical intervention for antibiotic prophylaxis and analgesia, respectively. Anesthesia was induced with sodium pentobarbital (Somnotol, 30 mg/kg, intravenously); maintenance doses were administered as needed. Dogs were intubated and mechanically ventilated (Harvard Apparatus, Boston, MA). ARF was produced using a modified Goldblatt model. Briefly, through a lower abdominal section, the spleen was removed (20); the kidneys were exposed and dissected free of perirenal tissue. All branches of the right renal artery were stripped and ligated; small branches of the left renal artery were similarly stripped and ligated and an inflatable vascular occluder (4 to 5 mm; In Vivo Metrics, Healdsburg, CA) was positioned on the main artery. The silastic tubing was tunnelled subcutaneously into a pouch in the dorsal interscapular region, and the abdominal wound was closed in layers. Buprenorphine (0.2 mg/kg, intramuscularly) was given to relieve postoperative pain. After 24 h of recovery, the vascular occluder on the left renal artery was inflated (glycerine was used to ensure complete occlusion) for 45 min; glycerine subsequently was removed from the tubing to allow reperfusion of ischemic tissues. Butorphanol (0.1 mg/kg, intramuscularly) was administered to all dogs to relieve potential discomfort during these manipulations. Dogs with no renal failure (NRF; controls) underwent the same surgical procedure described above, but the left renal artery was not occluded.

Extent of renal failure was confirmed by increases in plasma urea nitrogen (mmol/L) and creatinine (µmol/L) in venous blood samples that were drawn daily (a.m.). Blood was collected in precooled vials with sodium pentobarbital (Somnotol, 30 mg/kg, intravenous); acepromazine maleate (Atravec, 0.5 mg/kg intramuscularly); cefazolin sodium (Kefzol, 22 mg/kg, intravenously); and 800 µmol/L, dogs ($\geq$ 8 d of postrenal artery occlusion) were sedated with acepromazine maleate (Atravec, 0.5 mg/kg intramuscularly) and butorphanol (0.1 mg/kg intramuscularly). Dogs were anesthetized using sodium pentobarbital (30 mg/kg intravenously), intubated, and mechanically ventilated; atelectasis was prevented by maintaining an end-expiratory pressure of 5 to 7 cmH2O. Arterial blood pH, PaO2, and PCO2 were monitored regularly and kept within normal physiologic limits. Body temperature was kept at 38 ± 1°C by a water-jacketed Micro-Temp heating blanket (Zimmer, Dover, OH) and was monitored with probes placed in the abdomen and trachea. A left thoracotomy was performed in the fifth intercostal space. Heparin-filled catheters were inserted into the internal thoracic artery (for reference arterial blood withdrawal), the left atrium (for injection of microspheres), the coronary sinus (for venous blood withdrawal), and both femoral arteries and veins. A 5F micropumped pressure transducer (Millar MPC500) was placed in the LV cavity through the apex to measure LV pressure and its first derivative; a 7F Pigtail catheter was placed in the aortic root via the left femoral artery to measure aortic pressure. A segment of the left main coronary artery was dissected free proximal to the first major marginal branch and a Doppler probe (Transonic Systems Inc., New York, NY) was positioned to measure changes in coronary blood flow. A snare (for reactive hyperemia) was placed distal to the probe along with a micrometric screw occluder (for construction of coronary pressure flow relations [PFR]). Piezoelectric crystals (5 MHz; Triton Technologies, San Diego, CA) were positioned in the posterior ventricular wall to assess myocardial wall thickening as described previously (21). Two catheters were inserted into the coronary artery distal to the screw occluder to allow infusion of drugs and measurement of coronary perfusion pressure (22). Heparin sodium (200 U/kg intravenously) was administered every 2 h during the experimental protocol. The chest cavity was covered with plastic film to prevent undue cooling.

Coronary PFR and Distribution of Myocardial Blood Flow

Under resting conditions ($n = 14$ dogs), a reactive hyperemic response to 20 s of total occlusion of the left circumflex artery was recorded to assess coronary vascular reserve; circumflex artery diastolic pressure was recorded at both zero flow and peak flow. After return to baseline, coronary PFR were constructed by incremental (5- to 10-mmHg increments) lowering of arterial pressure; the autoregulatory break point (LPL) for each curve was determined as described previously (23). Coronary pressures were not allowed to fall below the LPL to avoid potential preconditioning effects. Distribution of myocardial blood flow was determined using radiolabeled microspheres (15 µm; NEN, Boston, MA) at baseline (i.e., intact coronary tone) and at the LPL as described in earlier experiments from our laboratory (16). Immediately after each microsphere injection, arterial and coronary sinus blood samples were drawn simultaneously to evaluate blood gases, pH, hematocrit, percentage of oxygen saturation, and oxygen content. The same experimental protocol was repeated in each dog during treatment with N$^\text{-}$nitro-L-arginine methyl ester (L-NAME) (50 µg/kg per min, intracoronary [IC] at a rate of 1 ml/min for 12-min with an infusion pump) and L-NAME (as above) + indomethacin (INDO) (5 mg/kg intravenous bolus) to evaluate potential contribution of NO and prostanoids on blood flow regulation in these dogs as described previously (24,25).

In Vivo Coronary Dose-Response Experiments

Peak reactive hyperemic responses to a 20-s coronary occlusion were recorded to assess coronary vascular reserve ($n = 14$ dogs), as described above. For assessment of the effects of ARF on endothelium-dependent and -independent vasoactivity acetylcholine chloride (0.1 to 10 µg/min IC; Sigma, St. Louis, MO), bradykinin acetate (0.03 to 1.0 µg/min IC; Sigma), adenosine (1.0 to 100.0 µg/min IC; Sigma), and l-arginine (0.0 to 30.0 mg/min IC) (Sigma) dissolved in normal saline (solutions prepared fresh daily) were infused into the circumflex coronary artery with a precision pump injector (1 ml/min; Harvard Apparatus, Holliston, MA) for 2 min (24); data were recorded when coronary blood flow was stable. Normal saline was infused at the same rate to determine the effects of vehicle on coronary blood flow. The response to a single dose
of nitroglycerin (100 µg/min IC; SABEX, Boucherville, QC, Canada) also was evaluated. The same experimental protocol was repeated in each dog during combined treatment with L-NAME (50 µg/kg per min, IC at a rate of 1 ml/min for 12 min with an infusion pump) and INDO (5 mg/kg intravenous bolus); however, only a single dose of each agonist was injected: Adenosine (30 µg/min IC), acetylcholine (5 µg/min IC), and bradykinin (0.33 µg/min IC). The sequence of drug administration was randomly selected with the exception that nitroglycerin was always administered at the end of each study because of long-lasting effects. At least 5 min was allowed between injections for return to steady-state hemodynamic values.

Postmortem Preparation
At the end of each experiment, the left main circumflex artery was ligated and Monastral blue dye was injected into the circumflex artery to delineate its vascular bed. Under deep anesthesia, cardiac arrest was induced by intra-atrial injection of saturated potassium chloride. For assessment of regional blood flow distribution (see Coronary PFR and Distribution of Myocardial Blood Flow section), the heart was excised, fixed in 10% buffered formaldehyde (pH 7.4), and subsequently processed as described previously (21). The left kidney also was removed and fixed in formalin; tissue samples were obtained from the cortex. Radioactivity in reference arterial blood and cardiac and renal tissue samples was measured in a multichannel NaI(TI) γ-well counter (Auto-Gamma 5003 Cobra II; Packard Instruments, Meriden, CT) with standard window settings. All samples were counted for 2 min, and nuclide activity was corrected for background and decay. Overlap corrections were made using the inversion matrix technique; the matrix was derived from radioisotope standards made from small aliquots of the microsphere stock and assayed simultaneously with the blood and tissue samples. Blood flow (ml/min per 100 g) was calculated using PCGERDA computer software (version 1.02; Packard Instruments).

Statistical Analyses
Hemodynamic, coronary blood flow, and myocardial contractile function data were obtained directly from strip chart recordings. Overall comparisons of blood flow data under control (no treatment), L-NAME, or L-NAME+INDO conditions were made using ANOVA for repeated measures. The Student-Newman-Keuls multiple range test, with α ≤ 0.05, was performed on all main-effect means to identify significant differences between interventions. A similar approach was used to assess differences between vascular responses to adenosine, acetylcholine, bradykinin, and l-arginine. End-diastolic wall thickness (EDT; onset of positive dP/dt) and end-systolic wall thickness (EST; approximately 20 ms before peak negative dP/dt) also were evaluated (26); because contractile function varies with the respiratory cycle, all measurements were determined at end expiration. Percentage of systolic myocardial wall thickening (SWT) was calculated using the equation SWT (%) = EST – EDT/EDT × 100. Values from five consecutive, artifact-free beats were averaged and normalized to preocclusion values.

All statistical procedures were performed using the SAS statistical software package (SAS Inc., Cary, NC) (27). P < 0.05 was used to indicate a significant difference in mean values.

Results
Thirty-four dogs were entered into these studies; six dogs (one NRF and five ARF) died during the 8-d postsurgical period and were excluded from the study. Twenty-eight dogs were used in the data analysis. Body weights were not significantly different between NRF and ARF dogs. Coronary PFR and distribution of myocardial blood flow were evaluated in 14 dogs; in an additional 14 dogs, endothelial function was assessed directly by intracoronary injection of endothelium-dependent and -independent vasodilators.

Biochemical Variables and Blood Gases
Plasma levels of plasma urea nitrogen, creatinine, and renin activity were markedly augmented in all ARF dogs; plasma potassium and calcium levels were not changed, as shown in Table 1. Blood gas values for arterial and coronary sinus blood are summarized in Table 2. Partial pressure of oxygen in coronary sinus blood was lower (P = 0.005) in dogs with ARF compared with controls; arterial and coronary sinus carbon dioxide levels were similar. Arterial blood pH was more alkaline in dogs with ARF (P = 0.008 versus NRF), but oxygen saturation and hematocrit were not different.

Cardiac Hemodynamics and Wall Thickening
Heart rate, LV pressure (systolic/diastolic), and SWT in the posterior ventricular wall are summarized in Table 3. Development of ARF was associated with a significant increase in systolic LV pressure (125 ± 25 versus 104 ± 9 mmHg in NRF); mean heart rate was similar between the two experimental groups. Heart rate–arterial BP index (15.8 ± 4.6 versus 12.7 ± 2.3 bpm × mmHg per 10⁻⁵; P = 0.032) and myocardial oxygen consumption (11.8 ± 9.2 versus 5.0 ± 1.5 ml O₂/min per 100 g; P = 0.001) were significantly elevated in ARF dogs. Treatment with L-NAME and L-NAME+INDO resulted in a further increase of myocardial oxygen consumption in NRF dogs, but this effect was not observed in animals with ARF. SWT did not change for either experimental group under control conditions but was markedly reduced in both groups after treatment with L-NAME and L-NAME+INDO.

Coronary Pressure-Flow Relations, Reactive Hyperemia, and Distribution of Blood Flow
Figure 1 summarizes the effects of ARF on coronary pressure-flow relations during autoregulation. Baseline coronary

Table 1. Physical and biochemical data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NRF (n = 14)</th>
<th>ARF (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg) at day 1</td>
<td>25 ± 2</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>Body weight (kg) at day 8</td>
<td>26 ± 2</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>82.6 ± 12.8</td>
<td>849.3 ± 229.8b</td>
</tr>
<tr>
<td>Plasma urea nitrogen (mmol/L)</td>
<td>4.2 ± 1.0</td>
<td>53.0 ± 15.5b</td>
</tr>
<tr>
<td>Renin activity (ng/ml per h)</td>
<td>2.24 ± 1.36</td>
<td>10.8 ± 7.5b</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.4 ± 0.3</td>
<td>4.54 ± 0.72</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.39 ± 0.08</td>
<td>2.53 ± 0.26</td>
</tr>
</tbody>
</table>

aAll values are mean ± 1 SD. ARF, acute renal failure; NRF, no renal failure.

bP < 0.05 versus NRF.
Table 2. Summary of hematocrit, blood gas, oxygen saturation and pH data

<table>
<thead>
<tr>
<th></th>
<th>Hct</th>
<th>PO2a</th>
<th>SatO2a</th>
<th>PO2cs</th>
<th>pHa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRF</td>
<td>ARF</td>
<td>NRF</td>
<td>ARF</td>
<td>NRF</td>
</tr>
<tr>
<td>Baseline</td>
<td>39 ± 1</td>
<td>37 ± 10</td>
<td>94 ± 24</td>
<td>96 ± 22</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>LPL</td>
<td>40 ± 2</td>
<td>37 ± 11</td>
<td>102 ± 25</td>
<td>90 ± 18</td>
<td>92 ± 15</td>
</tr>
<tr>
<td>LPL-LN</td>
<td>37 ± 2</td>
<td>38 ± 11</td>
<td>113 ± 20</td>
<td>102 ± 3</td>
<td>98 ± 1</td>
</tr>
<tr>
<td>LPL-INDO</td>
<td>38 ± 2</td>
<td>37 ± 11</td>
<td>117 ± 26</td>
<td>131 ± 26</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>P (groups)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.005</td>
<td>0.008</td>
</tr>
<tr>
<td>P (interventions)</td>
<td>NS</td>
<td>0.005</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P (interaction)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*All values are mean ± 1 SD. Hct, hematocrit (vol %); PO2a, PO2cs, partial pressure of O2 (mmHg) in arterial and coronary sinus blood; SatO2a, oxygen saturation of arterial blood (%); pHa, acidity/alkalinity of arterial blood. LPL, autoregulatory break point; LN, N^\text{"n}-nitro-L-arginine methyl ester; INDO, indomethacin; LPL-LN, LPL during treatment with L-NAME; LPL-INDO, LPL during treatment with LN + INDO. P value using ANOVA with df of 7,42.

Table 3. Summary of myocardial oxygen demand parameters and oxygen consumption

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LVPsys</th>
<th>LVPdias</th>
<th>RPI</th>
<th>SWT</th>
<th>MVO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRF</td>
<td>ARF</td>
<td>NRF</td>
<td>ARF</td>
<td>NRF</td>
<td>ARF</td>
</tr>
<tr>
<td>Baseline</td>
<td>122 ± 12</td>
<td>125 ± 21</td>
<td>104 ± 9</td>
<td>125 ± 25</td>
<td>4 ± 4</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>LPL</td>
<td>118 ± 9</td>
<td>131 ± 20</td>
<td>104 ± 8</td>
<td>124 ± 23</td>
<td>3 ± 2</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>LPL-LN</td>
<td>96 ± 19</td>
<td>121 ± 34</td>
<td>143 ± 17</td>
<td>132 ± 20</td>
<td>7 ± 3</td>
<td>4 ± 3</td>
</tr>
<tr>
<td>LPL-INDO</td>
<td>94 ± 18</td>
<td>102 ± 39</td>
<td>146 ± 17</td>
<td>145 ± 36</td>
<td>8 ± 3</td>
<td>4 ± 4</td>
</tr>
<tr>
<td>P (groups)</td>
<td>0.072</td>
<td>NS</td>
<td>0.075</td>
<td>0.032</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>P (interventions)</td>
<td>0.021</td>
<td>0.001</td>
<td>0.076</td>
<td>NS</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>P (interaction)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*All values are mean ± 1 SD. HR, heart rate (beats/min); LVPsys/dias, left ventricular pressure during systole/diastole (mmHg); RPI, heart rate arterial pressure index (beats/min × mmHg/1000); SWT, systolic wall thickening (%); MVO2, myocardial oxygen consumption (mL O2/min per 100 g). P value using ANOVA with df of 7,42.

blood flow (cf. Table 4) was higher in ARF dogs (57 ± 20 versus 38 ± 12 ml/min; P = 0.006 versus NRF); diastolic circumflex artery pressure was 93 ± 8 and 111 ± 25 mmHg (P = 0.003), respectively, in NRF and ARF dogs. There was little change in coronary blood flow as perfusion pressure was incrementally reduced over the autoregulatory plateau (this shows intact autoregulation). The autoregulatory break point (LPL) was higher in ARF dogs (60 ± 17 versus 52 ± 8 mmHg; P = 0.003 versus NRF dogs); inhibition of NO and prostaglandin release produced a further rightward shift of the LPL in ARF dogs. During reactive hyperemia, blood flow increased from 38 ± 12 to 209 ± 18 ml/min in NRF and from 57 ± 20 to 178 ± 20 ml/min in ARF dogs; flow repayment duration was significantly longer in ARF dogs (156 ± 49 versus 126 ± 32 s in NRF; P = 0.001). Reduced peak blood flow levels in ARF dogs occurred even though diastolic coronary perfusion pressures were much higher in these animals (reduced vascular conductance). The endocardial/epicardial blood flow ratio (determined from microsphere blood flow data) was not different between the two experimental groups over the autoregulatory range; this suggests that distribution of blood flow across the LV wall was preserved. Diastolic coronary artery pressures at zero flow were similar for both experimental groups at baseline (11 ± 4 mmHg in NRF versus 12 ± 4 mmHg in ARF dogs); these values increased significantly in both groups during treatment with L-NAME and L-NAME+INDO (cf. Table 5). Vascular conductance (i.e., slope of the flow-pressure relation) also was significantly lower in ARF dogs; further reductions in vascular conductance were observed for this group during treatment with L-NAME and L-NAME+INDO.

In the left kidney, cortical blood flow was reduced in ARF dogs (2.7 ± 1.8 versus 8.4 ± 0.9 ml/min per g in NRF; P = 0.001). Treatment with L-NAME decreased cortical blood flow values (1.7 ± 0.6 in ARF versus 4.4 ± 0.6 ml/min per g in NRF; P = 0.001) in both experimental groups; this effect was exacerbated further with L-NAME+INDO (1.5 ± 0.8 versus 3.4 ± 0.9 ml/min per g; P = 0.02).

Dose-Response Relations to Endothelium-Dependent and -Independent Vasoactive Drugs

Adenosine, acetylcholine, and bradykinin produced dose-dependent increases in coronary blood flow in all dogs without significantly affecting heart rate or mean arterial pressure; however, vasodilatory responses to each of these compounds was markedly reduced in ARF dogs (P < 0.05 versus NRF; Figure 2). Intracoronary infusion of l-arginine increased coronary blood flow in NRF dogs but had no effect in ARF dogs even at the
coronary autoregulation is preserved but the lower autoregulatory break point shifts to a higher coronary perfusion pressure; (2) coronary vascular reserve and coronary vascular conductance are markedly diminished; and (3) coronary vessel reactivity to either endothelium-dependent or -independent vasodilators is substantially reduced, suggesting loss of vascular function in ARF dogs. All of these effects are exacerbated during combined blockade of NO and prostaglandin release.

Vascular endothelium plays a crucial role in regulation of vascular tone, inflammation, and thrombosis; endothelial dysfunction contributes to pathophysiology of atherosclerosis (28) and acute cardiovascular syndromes (29). Coronary reserve is markedly reduced in patients with congestive heart failure, diabetes, and nephropathy (30). These changes are attributed mostly to increases in LV mass, circulating neurohumoral factors, and anemia. In our study, peak reactive hyperemic responses were similar for both study groups, but coronary vascular reserve was blunted in ARF dogs. Under resting conditions, coronary autoregulation and myocardial blood flow distribution were maintained in both ARF and NRF dogs; however, the autoregulatory break point in ARF dogs was shifted to a higher diastolic coronary pressure as a result of the reduction of coronary vascular conductance because coronary pressure at zero flow was similar in these experimental groups both at baseline and during combined treatment with L-NAME+INDO. Increases in myocardial oxygen demand combined with a higher LPL markedly diminish the ability to maintain uniform distribution of blood flow across the LV wall (13,31). With ARF, higher levels of myocardial oxygen demand would trigger maldistribution of ventricular blood flow and result in subendocardial ischemia.

The endothelium produces many compounds that modulate coronary vascular tone in relation to myocardial oxygen demand. The balance between oxygen supply and demand in the heart is postulated to be controlled by the coronary venous oxygen tension (32); a relation has been shown between coronary venous oxygen levels and mediators of vascular dilation in normal dogs. During exercise, blockade of adenosine (including KATP channels) and NO synthesis produces a parallel downward shift of the coronary venous Po2 versus myocardial oxygen consumption relationship. Inhibition of prostaglandins alone did not affect this relationship; however, this does not exclude a potential effect of prostaglandins during disease (32). With ARF, the observed reduction in coronary venous Po2 may reflect diminished efficacy of local coronary metabolic mediators: (1) Reduced bioavailability of NO to vascular smooth muscle cells as a result of structural alterations in the vessel or microvessel wall, (2) increased destruction of NO as a result of overproduction of reactive oxygen intermediates in the vessel wall (33), and (3) impaired dilation to NO donors (e.g., nitroglycerin) as a result of defective vascular smooth muscle cell function at the level of the soluble guanylate cyclase/cyclic guanosine monophosphate signaling pathway. During ARF, we documented that combined blockade of NO synthase and cyclooxygenase further reduced vessel reactivity and coronary vascular conductance, indicating a role for prostaglandins. The overall impact of these factors is a mismatch between myocardial oxygen supply and demand that could explain the in-

**Discussion**

This study presents several new findings regarding the effects of ARF on blood flow regulation in the heart. Results show that (1) higher dosages (P < 0.05 versus NRF). Percentage change in circumflex artery blood flow in response to a single dose of adenosine, acetylcholine, and bradykinin was substantially reduced in both experimental groups after combined treatment with L-NAME+INDO (Table 6). Vascular responses to intracoronary nitroglycerin (endothelium independent) also were substantially reduced in ARF dogs (177 ± 14% versus 260 ± 25 in NRF; P = 0.01) before and after combined treatment with L-NAME+INDO.
creased cardiovascular risk observed with renal failure. In an earlier study, Ruschitzka et al. (34) reported significant endothelial dysfunction in renal arteries of rats 24 h after acute renal ischemia-reperfusion injury. Our results, although consistent with these findings, support the view that vascular smooth muscle cell dysfunction can contribute to overall vascular dysfunction (35).

Renal ischemia is associated with significant increases of vasoactive compounds in plasma (e.g., angiotensin II, bradykinin) (36); treatment with angiotensin-converting enzyme inhibitors facilitates release of NO and prostanoids in these patients (19,37). Plasma and tissue levels of endothelin also are augmented in ARF (34,38) as a result, in part, of limited clearance by the lungs and kidneys; although endothelin may be partly responsible for the reduced vessel function, other, unknown uremic toxins also may play a role. In our study, renal blood flow was significantly reduced in ARF dogs; combined treatment with L-NAME+INDO further reduced renal perfusion that could trigger a greater release of vasoactive compounds that may have contributed to the lower coronary conductance. Increased production of reactive oxygen intermediates after renal ischemia-reperfusion injury may promote endothelial dysfunction as elevated levels of reactive oxygen species quench synthesis of NO and limit bioavailability. Exogenous antioxidants have been shown to augment bioavailability of NO in animal models of ARF (39). In our study, vascular responses to agonists that stimulate both NO-dependent and independent mechanisms were markedly diminished in ARF dogs; reduced bioavailability of NO may be responsible, but plasma NO levels were not measured directly. That intracoronary infusion of L-arginine was unable to elicit a blood flow response suggests that other pathways that are involved in production of NO could be suppressed in ARF dogs.

Like most studies, this one has limitations. First, experiments were carried out in an experimental model of renal failure; plasma creatinine levels increased >10-fold in most animals and is indicative of severe renal impairment. In humans, when plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure. With plasma creatinine levels double, clearance is reduced to 50%; a 10-fold increase in plasma creatinine levels likely would reduce clearance levels to approximately 10% of normal values. ESRD is considered when GFR is 15 ml/min or less (normal of 120) in humans. As such, dogs that were used in our study were considered to be in moderate to severe renal failure.
conventional techniques, including the Modification of Diet in Renal Disease (40) and the Cockcroft and Gault equations (41), have not been validated in canines.

Acquired coagulopathy in patients with renal disease can result in thrombosis, bleeding, or a combination of both (42). Coagulation parameters could have influenced blood rheology or vessel reactivity in these studies; however, the similarity of hematocrit levels between the two experimental groups reduced the possibility that a change in blood viscosity was responsible for coronary blood flow alterations in ARF dogs.

Conclusion

Our data demonstrate that under resting conditions, coronary vasodilatory reserve is reduced (diminished coronary vascular conductance), vascular reactivity to endothelium-dependent or -independent compounds is compromised, and the autoregulatory break point is increased after acute renal ischemia-reperfusion injury. These factors would contribute to the higher risk for adverse coronary events in patients with renal failure if increases in myocardial oxygen demand cannot be met because of limited coronary vascular reserve.

Acknowledgments

These studies were supported by an operating grant from the Kidney Foundation of Canada (J.G.K. and J.R.) and the Heart and Stroke Foundation of Quebec (J.G.K.).

We appreciate the expert surgical (André Blouin), technical (Lynn Atton), and animal care (Guy Noel and Justin Robillard) assistance of the staff at the Laval Hospital Research Center.

References


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/