Functional Assessment of the Circulation of the Single Kidney
Lilach O. Lerman, Martin Rodriguez-Porcel

Abstract—Functional alterations in the renal circulation that can contribute to abnormal renal perfusion have been demonstrated in various models of renal injury. To detect impairments in renal vascular function, renal flow reserve can be determined by repeated measurements of renal blood flow (RBF) during pharmacological challenge with short-acting vasodilators that should increase RBF in kidneys that are not severely damaged structurally. Among the invasive techniques for such measurements, the most readily available is probably the intravascular Doppler, which can be employed during renal angiography for rapid evaluation of changes in RBF during intrarenal injections of vasoactive substances. High-resolution tomographic imaging techniques, like electron-beam x-ray computed tomography, further offer the potential for noninvasive measurements of renal parenchymal perfusion and function, in association with either intrarenal or systemic injections of vasoactive substances. Acetylcholine is a potent short-acting renal vasodilator that can be useful to assess the response of the renal microcirculation, define renal flow reserve, and examine the endothelium-dependent responses of RBF. Such assessments of the function of the renal circulation can assist in evaluation of patients with systemic or renal disease for early detection and monitoring of renovascular injury. (Hypertension. 2001;38[part 2]:625-629.)

Key Words: renal circulation • renal blood flow • computed tomography • acetylcholine

Under normal conditions, basal renal vascular tone is well regulated by many vasoactive systems that keep renal blood flow (RBF) in equilibrium, including the endothelium-derived relaxing factor NO, prostaglandins, and the renin-angiotensin system. Therefore, at an early stage of renal disease, RBF may be normal, and impaired renal vascular tone may become evident only as an attenuated response during stimulus with vasoactive substances or physiological challenges. The mechanisms of the attenuated response have been postulated to include decreased release of vasodilators (eg, NO, prostaglandins) and co-existing vasoconstrictors (eg, thromboxane, angiotensin II), which may be released or rendered unopposed during challenge. The altered functional response may precede structural renal damage and can serve as a marker for abnormal handling of daily challenges by the kidney. Such impairment has been demonstrated in various models of renal injury, like hypertension, hypercholesterolemia, renal artery stenosis, ischemia and reperfusion, acute renal failure, diabetes mellitus, and aging. Hence, utilization of vasodilators to examine renal flow reserve (RFR) can serve to disclose subtle functional vascular alterations and may allow early detection and monitoring of renovascular injury. For example, residual responsiveness of the intrarenal circulation to challenge may also reflect renal viability and may conceivably predict success of subsequent therapy (eg, revascularization).

Evaluation of the reactivity of the single-kidney circulation entails rapid and successive measurements of single-kidney RBF, as well as availability of rapid-onset and short-acting renal vasodilators that could evoke a sufficient increase in RBF and/or distinguish normal from diseased kidneys. In the coronary or peripheral circulation, such assessment is often performed by measurement of vascular diameter, blood flow, or blood velocity under resting conditions and subsequently during pharmacological challenge with endothelium-dependent (eg, acetylcholine or bradykinin) or -independent (eg, nitroglycerin) vasodilators. Flow measurements in the forearm circulation are usually performed by strain-gauge plethysmography or intravascular Doppler, and in the coronary circulation, by the latter, both in conjunction with intra-arterial drug infusion. Although a similar approach could be useful to assess the renal circulation in patients with renal injury, it has been less commonly applied in the kidney. In this review we summarize techniques that have been previously used or are potentially useful to quantify RBF, that pharmacologically challenge the renal circulation, and that in combination measure single-kidney RFR in humans.

Measurements of Single-Kidney RBF
Diverse techniques have also been used for measurement of RBF, but some were either incapable of single-kidney measurements without ureteral catheterization (eg, p-aminohippuric...
showed an exaggerated renal vasodilator response3 to this calcium channel blocker, and their first-degree relatives significant reduction in renal vasomotion in response to a observed that patients with essential hypertension showed a increased basal renal vascular resistance (RVR) or mild disease but observed a potentiated response in patients with increased basal renal vascular resistance (RVR) or mild essential hypertension and no structural damage. They later observed that patients with essential hypertension showed a significant reduction in renal vasomotion in response to a calcium channel blocker, and their first-degree relatives showed an exaggerated renal vasodilator response6 to this drug, which was attributed to abnormal flux of calcium into renal arterioles.6 More recently, intrarenal infusion of adenosine in essential hypertension or renal artery stenosis was shown to induce a dose-dependent vasodilatation, which was more prolonged in patients with renal artery stenosis, suggesting a potentiated mechanism for adenosine-induced vasodilatation.7

However, this methodology is invasive because it involves injection of the 133Xe directly into the renal artery and external counting with a scintillation probe.8,9 In addition, its washout curves cannot be reliably used for compartmental flow measurements.

Intravascular Doppler
This invasive technique provides percutaneous single-kidney measurements of blood velocity using an intrarenal Doppler wire, and synchronous documentation of renal arterial diameter enables calculation of RBF.10 This provides accurate velocity measurements of in small straight tubes <4.76 mm in diameter.11 However, in larger or more tortuous tubes and for flow rates >200 mL/min (which are common in the renal artery), it may underestimate blood flow, probably because of suboptimal positioning and wire instability or because of deformed flow profiles.11 Flow in collateral and accessory renal arteries may also be missed by Doppler measurements obtained within the main renal artery.

Despite its potential limitations, this technique is useful for rapid and sequential quantification of RBF. Important studies using the intravascular Doppler technique in humans have shown that intrarenal acetylcholine resulted in a significant vasodilatory effect on both conductance and resistance renal blood vessels and led to a marked reduction in RVR and enhancement of RBF.12 Nitroglycerin, an exogenous NO donor, caused a small and selective vasodilatory effect on renal conductance vessels and failed to decrease RVR and thus to increase RBF.12 In patients with chronic congestive heart failure, intrarenal adenosine induced marked reduction in RBF, mainly via a vasoconstrictor effect on intrarenal resistance vessels.10 Similarly, in patients with cardiovascular risk factors, adenosine decreased—whereas acetylcholine, papaverine, and nitroglycerin increased—Doppler-derived RBF, with acetylcholine showing the greatest efficacy for renal vasodilatation.13 In hypertensive patients, isosorbide dinitrate increased RBF velocity and disclosed heterogeneous responses between the 2 kidneys,14 and the renal microcirculation response to papaverine showed variability among patients.15 Studies in pigs have shown that intrarenal isosorbide dinitrate and papaverine significantly increase RBF, but the response was greater with papaverine, probably because papaverine dilates small resistance vessels whereas isosorbide dinitrate dilates conductance vessels. Both drugs induced a significant decrease in mean arterial pressure (MAP).16 These studies also reinforced the observation that RFR is less marked than the coronary circulation.16 While coronary flow reserve (hyperemic-to-basal blood flow ratio) is up to 4 or 5, RFR of >2.5 is difficult to achieve, possibly because of the lower basal RVR compared with the coronary vascular resistance.

Although intrarenal injections of vasodilators have been very useful to examine renovascular reactivity, this invasive approach is no longer mandated. Development of fast, high-resolution imaging techniques now allows repetitive measurements of RBF17 and detection of small changes induced by intravenously injected vasoactive agents. Furthermore, these methods hold a potential to measure concomitant renal function and regional perfusion, and thereby assess the coupling of renal hemodynamics and function.

Computed Tomography Techniques
Tomographic imaging techniques using intravenously injected indicators may potentially have useful clinical applications, because their cross-sectional capability allows assessment of the circulation of the single kidneys noninvasively, bilaterally, and simultaneously. High spatial resolution coupled with dynamic imaging of indicators (inodinated or radioactive) allows evaluation of regional renal function and/or RBF,18 and measurements of parenchymal flow circumvent the potentially confounding presence of collateral and accessory renal arteries. Techniques applied to the kidneys include positron emission tomography (PET),19 magnetic resonance imaging (MRI),20 and x-ray computed tomography.17,21,22

Positron Emission Tomography
PET involves exposure to radioactivity, its tracers are difficult to produce, and its relatively low spatial resolution limits measurements of medullary perfusion. However, it is one of the few techniques capable of quantification of RBF and cortical blood flow in vivo.23 Using this technique, Middlekauff et al have shown that cortical RBF decreases and RVR increases in response to static handgrip exercise and that exogenous adenosine produces reflex renal vasoconstriction,29,24 which were exaggerated in heart failure.25 Juillard et al26 have also shown
that PET provided reliable measurement of RBF in pigs using 15O-labeled water, a short-life tracer that allows repeated measurements. These investigators further demonstrated that during infusion of dopamine and angiotensin II, PET could detect the increase or decrease in RBF, respectively, suggesting that this method could be used to assess the reactivity of the renal circulation.

**Magnetic Resonance Imaging**

MRI has been used to measure flow through both the main renal artery and the renal parenchyma. Recording dynamic changes in signal intensity or disappearance rate after administration of gadopentetate dimeglumine has also been used to assess renal function, although nonlinearity of the paramagnetic contrast material concentration with tissue density limits quantitative measurements. MRI measurements have been obtained under various clinical conditions, but few of them examined RFR. MRI successfully demonstrated that dipyridamole decreased medullary more than cortical perfusion, and aminophylline attenuated a decrease in cortical flow following extracorporeal shockwave lithotripsy.

**Electron-Beam Computed Tomography**

Electron-beam computed tomography (EBCT) has been extensively used to study renal perfusion and function by intravenous injection of nonionic contrast. The high spatial and temporal resolution of EBCT enables accurate, reproducible, and noninvasive quantification of single-kidney volume and cortical, medullary, and papillary perfusion in humans and in animal models. Furthermore, single-kidney tubular dynamics and glomerular filtration rate can be synchronously obtained to allow comprehensive evaluation of the kidney. The main limitations of this technique are related to exposure to radiation and x-ray contrast agents.

Measurements of RBF in normal animals during infusion of vasoactive substances showed a prompt increase in response to intrarenal bradykinin and secretin and to systemic furosemide, acetylcholine, and sodium nitroprusside. The response to both latter drugs was attenuated in pigs with
hypercholesterolemia and hypertension\textsuperscript{37,40} (Figure), suggesting that early renal injury also impairs endothelium-independent vasodilation or that subtle impairments are detectable using smaller doses or systemic administration of the drugs.

Choice of Vasoactive Substance

Compared with other vascular beds, the renal vasculature shows unique responses to vasoactive substances. For example, adenosine is a potent and short-acting vasodilator of coronary microvessels and is commonly used to define coronary flow reserve. In the kidney, on the other hand, the \( A_1 \)- and \( A_2 \)-adenosine receptors tend to have opposite effects on afferent arteriolar resistance and renin secretion, and exogenous adenosine can dose dependently either constrict or dilate the normal renal vasculature.\textsuperscript{44} In normal subjects, intrarenal adenosine reduced RBF,\textsuperscript{45} and in chronic congestive heart failure, increased RVR and decreased RBF.\textsuperscript{10} However, in both essential and renovascular hypertensive patients, intrarenal adenosine induced a dose-dependent increase in RBF.\textsuperscript{7} Hence, exogenous adenosine has differential renovascular effects and, unlike in the coronary vessels, does not constitute a reliable vasodilatory challenge.

In contrast, various endothelium-dependent and -independent (NO donors and smooth muscle relaxants) induce a substantial increase in RBF. Endothelium-independent vasodilators like papaverine,\textsuperscript{15} nitroglycerin,\textsuperscript{13} isosorbide dinitrate,\textsuperscript{14} or sodium nitroprusside\textsuperscript{46} induce an effective increase in RBF, but even intrarenal injections are often limited by profound systemic effects that restrict interpretation of RBF or achieving maximal RFR. Among these, papaverine dilates the renal microcirculation and is more likely to achieve a substantial decrease in RVR and RFR than conduit vessel dilators. However, acetylcholine,\textsuperscript{3,5,6,12,13,47–49} the prototypical endothelium-dependent vasodilator of the microcirculation, appears to be associated with greater RFR and is often limited by profound systemic effects that restrict interpretation of RBF or achieving maximal RFR. Among these, papaverine dilates the renal microcirculation and is more likely to achieve a substantial decrease in RVR and RFR than conduit vessel dilators. However, acetylcholine,\textsuperscript{3,5,6,12,13,47–49}

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Indeed, using EBCT, we have observed that systemic administration of acetylcholine effectively increased RBF (Figure, part a) accompanied by only a transient decrease in MAP.\textsuperscript{16} Intravenous bolus injections of acetylcholine also dose dependently increased RBF (measured using intravascular Doppler) more effectively than papaverine, in association with smaller decrements in MAP (Figure, part b), suggesting that acetylcholine may be a suitable challenge for RFR.

In summary, assessment of renal circulatory function can assist in evaluation of patients with systemic or renal disease. Tomographic imaging techniques, like EBCT, offer the advantage of noninvasive measurements of renal regional perfusion and function. Determination of RFR can be achieved by repeated measurements of RBF during pharmacological challenge with short-acting vasoactive substances like acetylcholine, which can also be used to assess endothelium-dependent RBF and has few systemic hemodynamic effects.
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Hypertension. 2001;38:625-629
doi: 10.1161/hy09t1.095205
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/3/625

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