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,1 including the endothelium-derived relaxing factor NO, prostaglandins, and the renin-angiotensin system.2 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 alterations3 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,4 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...
calcium channel blocker, and their first-degree relatives
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
a blunted increase in RBF in response to graded doses of
vasodilators.6 More recently, intrarenal infusion of aden-
osine 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 diam-
eter enables calculation of RBF.10 This provides accurate
time velocity measurements of small straight tubes <4.76 mm
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 vasodilation.13 In hypertensive patients, isosorbide
dinitrate increased RBF velocity and disclosed heterogeneous
responses between the 2 kidneys,14 and the renal microcircu-
lation response to papaverine showed variability among
patients.15 Studies in pigs have shown that intrarenal isosor-
bide dinitrate and papaverine significantly increase RBF, but
the response was greater with papaverine, probably because
papaverine dilates small resistance vessels whereas isosor-
bide 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 mea-
surements of RBF17,19 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 in-
jected indicators may potentially have useful clinical appli-
cations, because their cross-sectional capability allows as-
sessment of the circulation of the single kidneys
noninvasively, bilaterally, and simultaneously. High spatial
resolution coupled with dynamic imaging of indicators (io-
dinated 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 measure-
ments 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 adeno-
sine 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 mea-
surements. 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 dy-
namic 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 den-
sity 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 exten-
sively used to study renal perfusion and function by 
intravenous injection of nonionic contrast. The high spatial 
and temporal resolution of EBCT enables accurate, reproduc-
ible, and noninvasive quantification of single-kidney volume 
and cortical, medullary, and papillary perfusion in hu-
mans and 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 re-
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\(^{37,40}\) (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\(_2\)- and A\(_3\)-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.\(^{44}\) In normal subjects, intrarenal adenosine reduced RBF,\(^{45}\) and in chronic congestive heart failure, increased RVR and decreased RBF.\(^{10}\) However, in both essential and renovascular hypertensive patients, intrarenal adenosine induced a dose-dependent increase in RBF.\(^{7}\) 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,\(^{15}\) nitroglycerin,\(^{13}\) isosorbide dinitrate,\(^{14}\) or sodium nitroprusside\(^{46}\) 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,\(^{3,5,6,12,13,17–49}\) the prototypical endothelium-dependent vasodilator of the microcirculation, appears to be associated with greater RFR attended by a smaller and more transient decrease in MAP.

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, whereas the dose of sodium nitroprusside required to increase RBF was accompanied by a small but sustained decrease in MAP.\(^{37,40}\) Intrarenal 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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**References**


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