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Color Doppler sonography in the study of chronic ischemic nephropathy

M. Meola [a,*], I. Petrucci [b]

[a] S. Anna School of Advanced Studies, Nephrology and Dialysis Unit, Department of Internal Medicine, University of Pisa, Italy
[b] Nephrology and Dialysis Unit, Department of Internal Medicine, University of Pisa, Italy

KEYWORDS
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Abstract In western countries, the risk of cardiovascular disease has increased considerably in recent decades. This trend has been paralleled by an increase in cases of atherosclerotic renal disease, which is related to the improved prognosis of cardiovascular diseases, aging, and the increasing mean age of the general population. It is reasonable to expect that in the near future, there will be a sharp increase in the number of elderly patients with atherosclerotic vascular disease in chronic dialysis programs. The result will be a dramatic rise in the social and economic costs of dialysis that could constitute a true clinical emergency. In this epidemiologic scenario, one of the most important targets of 21st century nephrology will be the early diagnosis of chronic ischemic nephropathy and the development of new and more effective strategies for its treatment.

Color Doppler (CD) ultrasonography has displayed high sensitivity, specificity, and positive and negative predictive values in the diagnosis of this disease in selected population, making it an ideal tool for use in screening programs. Eligibility for screening should be based on clinical criteria. For the most part, it will be aimed at adults (especially those who are elderly) with atherosclerotic vascular disease involving multiple districts and chronic kidney disease (CKD), stage 2—3, in the absence of a documented history of renal disease. In these patients, hypertension may be a secondary manifestation or a symptom of the ischemic nephropathy itself. The objectives of sonographic screening should be (1) to identify subjects in the population at risk who are affected by stenosis of the main renal artery (RAS); (2) to identify and characterize patients without RAS who have chronic ischemic nephropathy caused by nephroangiosclerosis and/or atheroembolic disease. The former group will require second-level diagnostic studies or angioplasty with stenting; the latter can be managed conservatively. The most important CD parameters in the workup of suspected RAS are those that are direct signs, i.e., increases in peak systolic velocity (PSV) and diastolic velocity (DV), spectral broadening, and an altered renal:aortic ratio (RAR). Their assessment requires full-length sampling of the renal artery and is associated with greater practical/technical difficulties. Measurement in triplicate of the PSV in the ostial, medial, and hilar segments of both arteries and bilateral measurement of parenchymal resistance indices are usually sufficient to detect the presence

* Corresponding author. Nephrology and Dialysis Unit, Department of Internal Medicine, University of Pisa, via Roma, 67, 56100 Pisa, Italy.
E-mail address: mmeola@int.med.unipi.it (M. Meola).

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of stenosis and refer the patient for second-level studies. Important parameters for estimating the severity of a stenosis include the renal:aortic ratio (>3.5), disappearance of the early systolic peak in segmental vessels, lateralization of the resistance index ($\Delta RI > 0.05$), and the evaluation of the acceleration index (AI) and acceleration time (AT). Second-level imaging studies (CT angiography, MR angiography) are still indispensable for precise definition of the location and extension of the stenosis and the therapeutic approach during digital subtraction angiography (DSA). In the absence of direct or indirect signs of RAS, increases in the intraparenchymal resistance indices ($RI > 0.75—0.80$; $PI > 1.50$) associated with systemic atherosclerotic disease are indicative of microcirculatory damage related to nephroangiosclerosis or atheroembolic disease.

Sommario Nei Paesi occidentali il rischio di malattie cardiovascolari è notevolmente aumentato negli ultimi decenni. Di pari passo, il miglioramento prognostico delle malattie cardiovascolari, l'invecchiamento e l'aumento della vita media della popolazione generale stanno rivelando un crescente numero di casi di malattia renale cronica d'origine vascolare. È del tutto plausibile pensare che nei prossimi anni il numero di pazienti anziani con malattia vascolare aterosclerotica, che sarà inserito nei programmi di dialisi cronica, aumenterà rapidamente. Questo farà lievitare in modo drammatico i costi sociali ed economici della dialisi configurando una vera emergenza clinica. In questo scenario epidemiologico, la diagnosi precoce della malattia ischemica cronica del rene e la definizione di nuove strategie terapeutiche rappresenterà uno dei *target* più importanti della nefrologia di questo secolo.

Il color-Doppler (CD) per le sue caratteristiche di sensibilità, specificità, per il valore predittivo positivo e negativo può essere considerato il test di screening della malattia ischemica cronica del rene. Lo screening ecografico deve avere un duplice obiettivo: (1) individuare nella popolazione a rischio i casi di stenosi dell'arteria principale da indirizzare alle indagini di secondo livello e all'angioplastica con stenting; (2) individuare e alle caratterizzare, da assenza di stenosi dell'arteria principale, i casi di malattia ischemica cronica da nefroangiosclerosi e/o ateroembolia da avviare alla terapia conservativa. Lo screening deve essere guidato dalla preselezione clinica e deve essere preferibilmente rivolto a soggetti adulti e anziani con vasculopatia aterosclerotica polidistrettuale e insufficienza renale cronica di media gravità in assenza di storia clinica di nefropatia. In questi pazienti l'ipertensione può essere sia una manifestazione secondaria sia un sintomo associato alla malattia ischemica cronica del rene.

I segni diretti, in altre parole l'aumento della velocità di picco sistolico (VPS) e della velocità telediastolica (VD), la dispersione spettrale e un indice reno-aortico alterato sono i parametri più indicativi per la diagnosi di stenosi. La determinazione di questi parametri impone il campionamento dell'arteria renale in tutto il suo tragitto ed espone alle maggiori difficoltà pratiche. Un triplice campionamento delle VPS nel tratto ostiale, mediale e ilare in entrambe le arterie e una valutazione bilaterale degli indici di resistenza parenchimale sono sufficienti per escludere o confermare una stenosi e avviare il paziente all'indagine di secondo livello. Alla presenza di stenosi un rapporto reno-aortico >3,5, la scomparsa del picco sistolico precoce nei vasi segmentari, la lateralizzazione degli indici di resistenza ($\Delta RI > 0{,}05$) e la determinazione degli indici d'accelerazione (AT e AI) possono migliorare il giudizio diagnostico sulla severità della stenosi. Il ricorso a tecniche morfologiche di secondo livello come l'angio-TC o l'angio-RM è in ogni caso indispensabile per definire esattamente la sede, l'estensione della stenosi e la strategia terapeutica durante l'angiografia.

In assenza di segni diretti o indiretti di stenosi dell'arteria principale, l'incremento degli indici di resistenza intraparenchimali ($IR > 0{,}75—0{,}80$; $IP > 1{,}50$) associato a malattia aterosclerotica sistemica indica che il danno morfologico interessa prevalentemente il microcircolo ed è espressione di nefroangiosclerosi o ateroembolia.

Introduction

Color Doppler ultrasonography (CDUS) is widely used to screen for chronic ischemic nephropathy (CIN) (also known as chronic renovascular disease), which can be caused by renal artery stenosis (RAS) or by atherosclerotic involvement/atheroembolism of the microarterioles supplying the renal parenchyma [1,2]. In subjects at risk for CIN, the objectives of the CDUS examination include (1) the assessment of renal morphology; (2) detection of the presence of stenosis involving one or both of the main renal arteries; (3) identification of

cases requiring angioplasty as opposed to conservative medical treatment; (4) evaluation of atherosclerotic damage in other arteries (aorta, epiaortic arteries, arteries of the lower extremities); and (5) characterization of the chronic ischemic damage caused by nephroangiosclerosis and/or atheroembolism [3,4]. In short, the examination should document or exclude the presence of RAS and determine whether the ischemic nephropathy is due to atherosclerotic involvement of the microcirculation in the absence of RAS. The so-called ''vascular patients'' most commonly referred to nephrology, internal medicine, or general medicine outpatient clinics are elderly who have survived various types of cardiovascular events and present diffuse, polymorphic atherosclerotic disease with or without history of CKD stage 2—3. In these subjects, hypertension may be caused by or simply associated with CIN [1,2].

Definitions

There is no real consensus regarding the meaning of the terms *chronic ischemic nephropathy* or *chronic renovascular disease* [5,6]. In the literature, many authors use these terms to refer exclusively to the progressive ischemic damage inflicted on the kidney by atherosclerotic forms of renal artery stenosis (RAS) [2]. It is important to recall that, although the vast majority of RASs (90%) are indeed caused by atherosclerosis, 10% of all cases are the result of dysplasia. Regardless of its etiology, RAS can be the cause of *secondary hypertension*, which can be corrected by renal angioplasty with *stenting* [1,2].

Atherosclerotic involvement of the main renal artery is most commonly found in the ostial and paraostial segments. It develops within an atherosclerotic milieu, and it may be associated with various degrees of nephroangiosclerosis and/or cholesterol atheroembolic disease, which are capable of causing considerable ischemic damage even in the absence of RAS. Therefore, the terms *chronic ischemic nephropathy* and *chronic renovascular disease* should include not only those forms of the disease caused by stenotic involvement of the main renal artery but also the chronic parenchymal ischemia resulting from injury to the microcirculation (nephroangiosclerosis, atheroembolism), with or without RAS [1,2].

Epidemiology

In Western countries, recent decades have witnessed increases in the average life expectancy, improvements in the prognosis of cardiovascular disease, and general population aging that have contributed to the growing prevalence of chronic kidney disease (CKD) caused by ischemic processes. In coming years, an increasing number of elderly subjects with cardiovascular disease will enter long-term renal dialysis programs, provoking a clinical emergency that can be expected to increase the socioeconomic costs of dialysis. Epidemiologic studies show that requests for hemodialysis for adult/elderly patients are motivated primarily by the presence of ''vascular disease,'' diabetic nephropathy, or CKD of unknown cause (Fig. 1). The latter includes various types of parenchymal, glomerular, or tubulo-interstitial damage, but in adults and elderly individuals it is often aggravated by atherosclerosis, diabetes, and/or hypertension.

The prevalence in the general population of RAS as a cause of renovascular hypertension is only 2—4% [1,2], but figures as high as 30—40% are observed in selected subgroups, e.g., patients with systemic atherosclerosis involving one or more districts (ischemic heart disease, chronic peripheral vascular disease of the lower extremities, carotid artery stenosis or occlusion, atherosclerotic or dissecting aneurysms of the aorta, accelerated hypertension with CKD, Takayasu's arteritis) [1,2,7—9]. In older patients, smokers, and subjects with elevated serum cholesterol levels, the number of vessels affected by peripheral arteriopathy is closely correlated with the prevalence of RAS, which is very common in patients with involvement of more than five arterial districts [7]. As noted above, atherosclerosis is responsible for around 90% of all cases of RAS although the most common cause of RAS in young women is fibromuscular dysplasia.

In the Italian Dialysis and Renal Transplant Registry, vascular diseases currently represent the main cause of CKD and new requests for long-term dialysis in patients over 60; their prevalence ranges from 25% to 30% (Fig. 1). Based on epidemiologic data, unilateral or bilateral RAS alone accounts for only a portion of the cases of vascular disease reported among CKD patients. In a 1996 review of 7200 cases of CKD in North America, only 1.24% were caused by RAS. Fourteen percent of the subjects of Caucasian origin in this study population had CKD caused by hypertensive nephroangiosclerosis [10]. Based on their study of a smaller series, Appel et al. paint a very different picture in which the prevalence of RAS among dialysis patients over 50 years of age is 22% [11]. The longitudinal Cardiovascular Health Study was designed to assess RAS — including risk factors, associated morbidity and cardiovascular mortality — in the general population over 65 years of age. The prevalence of RAS in these subjects was 6.8% (6.0% for unilateral cases, 0.8% for bilateral stenosis; 5.5% among women versus 9.1% in men) [12].

These epidemiological data demonstrate, first of all, that the clinical definition of chronic ischemic nephropathy is still ambiguous, and second, that RAS is the cause of only a small percentage of the cases requiring dialysis. In fact, in most cases, the vascular disease is the result of various forms of systemic atherosclerotic disease characterized by extensive involvement of the microcirculation rather than the main renal artery. These cases are under-represented in the literature published over the past 15 years, which is instead full of articles on RAS — its diagnosis, treatment (including revascularization techniques), and clinical follow-up. Few reports specify that chronic renal hypoperfusion can also occur *in the absence of stenosis*, as the result of atherosclerotic remodelling of the arterial microcirculation. In these cases, chronic, progressive ischemic damage is caused by increased vascular resistance in parenchymal vessels. The latter is caused by various overlapping factors (vessel remodelling, repeated episodes of cholesterol atheroembolism, and reduction of the cross-sectional area of the microcirculation) whose combined effects increase parenchymal vascular impedance and prevent normal perfusion.

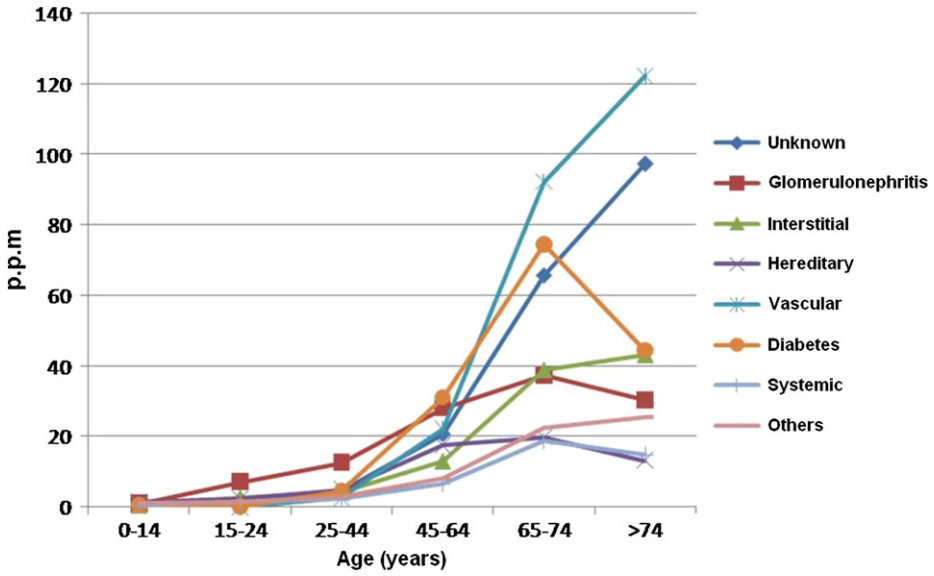

Fig. 1 Italian Registry of Renal Transplants — 2006: age-related distribution of primary renal diseases requiring the initiation of dialysis. Abscissa: patient age in years; ordinate: number of patients entering dialysis in Italy during 2006 per 1,000,000 inhabitants (ppm).

Hemodynamic changes in main renal artery stenosis

Morphologic criteria of critical stenosis

Before we consider the hemodynamic consequences of arterial stenosis, we must define the morphological and functional characteristics of the condition referred to as *critical arterial stenosis*. Experimental data show that the stenosis of an artery is the result of a pathologic process involving the vessel wall, which becomes hemodynamically significant when the cross-sectional area of the vessel is reduced by more than 75—85% [13]. On digital subtraction angiography (DSA) (which has all the limitations of a two-dimensional imaging method, i.e., difficulties in defining vessel margins and in measuring the reference diameter), stenosis is considered critical when it narrows the vessel lumen by more than 50%. The significance of an angiographically detected area of stenosis varies with its length and irregularity, as well as with the characteristics of the distal vascular bed and the presence or absence of efficient collateral circulation [7]. CDUS is less effective than arteriography for the geometric assessment of stenosis. The renal arteries are generally examined with convex 2.5—3.5-MHz transducers, and the spatial resolution that can be achieved with these probes is far inferior to that offered by the high-resolution (7.5—14 MHz) transducers used to examine superficial vessels [14]. CDUS documents the presence of RAS indirectly by revealing its hemodynamic effects, that is, changes in blood-flow velocity that occur at the level of the narrowed segment. This explains the enormous difficulties that arise when one attempts to compare angiographic data with hemodynamic findings obtained with CDUS.

Hemodynamic criteria of stenosis

From the hemodynamic point of view, a gradual reduction of the perfusion pressure by as much as 40% usually has no real effect on the glomerular filtration rate (GFR) or on renal blood flow (RBF) thanks to the autoregulatory mechanisms that control the intrarenal circulation. In contrast, a sudden drop in the perfusion pressure of more than 40% is followed by an abrupt decrease in the GFR. In general, the autoregulatory mechanisms become ineffective when perfusion pressure drops by more than 40% and systolic pressure falls below 70—80 mmHg [8]. Experimental arterial stenosis of >75% reduces perfusion pressure by approximately 40% [8,9]. Under these conditions, ischemia activates the renin—angiotensin—aldosterone system and provokes secondary hypertension, which is initially renin-dependent. It later becomes volume-dependent following the onset of secondary increases in aldosterone levels. It is important to recall that hypersecretion of renin stimulates the secretion of aldosterone by the adrenal cortex, and this leads to sodium and water retention that increases blood volume. Therefore, stenosis of the renal artery is considered hemodynamically significant when it produces a drop in perfusion pressure that is capable of activating the renin—angiotensin—aldosterone system [8,9,14,15].

Geometric features of renal arteries favouring ostial stenosis

The renal arteries originate from the aorta at the level of the second lumbar vertebra, approximately 1.5—2.0 cm from the origin of the superior mesenteric artery. The right renal artery arises from the anterolateral aspect of the aorta, curves forward and runs toward the renal hilum, passing behind the inferior vena cava. The left renal artery arises from the posterolateral aspect of the aorta and runs obliquely, alongside the homolateral renal vein, toward the left lumbar fossa. In the axial plane, the angles of bifurcation between the aorta and the renal arteries normally range from −26° to 70° (mean 24° ± 15°) on the right and from −75° to 38° (mean 5° ± 16°) on the left [16]. In the sagittal and coronal planes, the mean angles of bifurcation

are $-65^\circ \pm 39^\circ$ (range, from 30° to -120°) and $-76^\circ \pm 36^\circ$ (range, from 20° to -120°), respectively, on the right; corresponding figures for the left renal artery are $18^\circ \pm 23^\circ$ (range from -20° to 70°) and $173^\circ \pm 28^\circ$ (range, from 100° to 220°) [17].

The geometry of the origins of the renal arteries from the aorta has never been faithfully reproduced in flow-simulation studies or experimental hydraulic models. Although the angles of origin of these arteries are not precisely 90°, the experimental flow model that provides the most faithful reproduction of the hemodynamic conditions in this area is the right-angle junction (T-junction) [18,19]. In experimental studies conducted with a 3-mm-diameter glass T-junction model, the paths of the tracer (i.e., 50-μm polystyrene spheres in aqueous glycerol) demonstrate the appearance of separation flows at the inner wall of the daughter tube and on the opposite wall of the main tube, just downstream from the branch. The stationary motions and spiral-shaped vortices in both the main and collateral vessels lower the mean levels of wall shear stress [18,19]. This is per se sufficient to justify the development of atheromatous plaques in the ostial and paraostial regions of the vessel (Fig. 2). However, the process can be accelerated by various factors, including the presence of systemic atherosclerosis, diabetes, advanced age, and possibly also by individual variations in the angle of bifurcation between the two vessels.

Direct hemodynamic effects of RAS

The direct hemodynamic effects of RAS vary with the magnitude and geometric characteristics of the obstruction. The changes in blood flow have been characterized in experimental models and computer-simulation studies (Fig. 3) [20,21]. According to the principle of continuity of Leonard, the flow velocity of a fluid increases proportionally to decreases in the caliber of the channel it flows through. The increase of velocity that occurs in the narrowed segment (critical stenosis) is known also as *Venturi effect*. Therefore, blood flow in the two segments of the artery is represented by the equation $Q = V_0A_0 = V_sA_s$, where Q stands for the flow upstream from the stenosis, and the mean spatial velocities in the prestenotic and stenotic segments are represented by V_0 and V_s, respectively, and the cross-sectional areas of these two segments are A_0 and A_s. Consequently, the ratio between the mean spatial velocities in the stenotic segment and those of the prestenotic segment equals the reciprocal of the ratio between the cross-sectional areas of the two segments (i.e., $V_s/V_0 = A_0/A_s$).

- These *variations in flow velocity* are the basis of Doppler detection of stenosis. The flow diagram shown in Fig. 3 highlights a second consideration: if a sudden increase in the flow rate is needed to get the blood through the stenotic segment of the artery, the stream lines must of necessity converge in the prestenotic segment. This convergence causes flow disturbances and broadening of the flow velocity of the red cells; more importantly, it modifies the Doppler angle, and this can result in underestimations of the magnitude of changes in flow velocity and of the severity of the stenosis [14,21]. Downstream from the stenosis, the behavior of the stream lines is reversed: here the blood is forced to flow from a narrowed segment of the vessel into a larger-caliber segment. This situation results in the appearance of stationary movements and reverse flow next to the vessel wall. In accordance with the

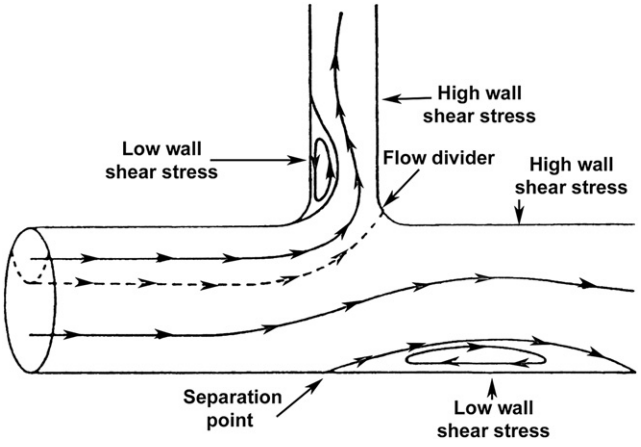

Fig. 2 Variations in flow at a 90° T-junction. The stream lines shown in the diagram were videorecorded in an experimental model in glass filled with a aqueous glycerol solution containing polystyrene microspheres (50 μm in diameter). The dotted lines show separation flows at the point where the collateral vessel arises from the main vessel. The flow divider generates stationary recirculation flow on the side opposite to the branching vessel and on the side opposite to the main branch. In the diagram, the points along the vessel wall where shear stress is increased or decreased are shown. (Adapted with permission from Karino T, Motomiya M, Goldsmith HL. J Biomech 1990;23:537.).

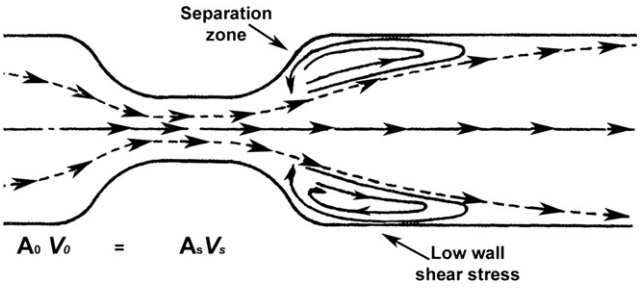

Fig. 3 Direct hemodynamic effects of stenosis. The hemodynamic effects of stenosis vary depending on the severity and geometric characteristics of the obstruction. The diagram shows the variations that occur in continuous laminar flow (Poiseuille-type) at the level of a simple arterial stenosis, symmetrical with regular margins. According to the principle of continuity, blood flow in the prestenotic and stenotic segments of the artery is represented by the equation $Q = V_0A_0 = V_sA_s$, where Q stands for the flow upstream from the stenosis; the mean spatial velocities in the two segments are represented by V_0 and V_s, respectively; and the cross-sectional areas of these two segments are A_0 and A_s. Consequently, $V_s/V_0 = A_0/A_s$. Flow velocity in the stenotic segment must necessarily increase (Venturi effect).

Law of Laplace, the increase in vessel-wall tension promotes progressive weakening of the vessel that results in post-stenotic dilatation. On the other hand, the marked reduction in parietal shear stress related to stationary flow facilitates the development of thrombosis and progression of the stenosis toward complete occlusion. Two to three centimeters downstream from the stenosis, the parabolic profile of the stream lines is restored. All of the hemodynamic changes described above are clearly represented in the Doppler spectrum, where a dramatic increase in systo-diastolic velocity in the stenotic segment is associated with broadening of Doppler spectrum due to turbulence and stationary flows within the stenotic segment and downstream from it (Fig. 4).

- The effects of the stenosis on blood flow depend not only on the degree of obstruction but also on the characteristics of the vascular beds proximal and distal to the area of stenosis. In any case, the mean arterial flow at rest is jeopardized only when the caliber of the arterial lumen is reduced by more than 75—80%. This observation has prompted a number of attempts to use Doppler sonography to characterize changes in flow velocity at the point of stenosis and to estimate the degree of stenosis based on the morphology of the spectral waveform. Unfortunately, all attempts to stage stenoses based on the morphology of the spectral curve have failed, and these approaches have been abandoned in favor of simpler, less precise criteria that can be repeatedly evaluated with ease and are associated with lower margins of error.

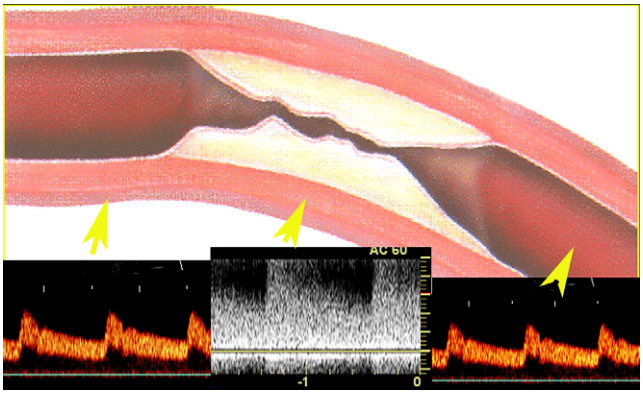

Fig. 4 Direct hemodynamic effects of stenosis. The stenosis causes marked, violent acceleration of the flow. The Reynolds numbers in the stenotic segment are very high, and the laminar flow thus becomes turbulent, vorticose. The phenomena, which are well known in hydrodynamics, are reflected in the results of the Doppler spectral analysis. The spectral curve at the level of the stenosis displays violent systo-diastolic acceleration associated with marked spectral broadening. Upstream, the tracing is normal although the amplitude is reduced in cases of closed stenosis. Immediately downstream, the acceleration tends to diminish. In the separation zone, the stationary recirculation flow facilitates the development of thrombosis and the formation of post-stenotic dilatation (increased transmural pressure). Laminar flow is restored 1—2 cm downstream from the stenosis.

The *changes in pressure* that occur within the stenotic segment are highly complex and are beyond the scope of the present review. In general, the drop in pressure that occurs at the level of the stenosis depends on three distinct factors. It can be calculated as follows: $\Delta P = \Delta P_s + \Delta P_c + \Delta P_e$, where ΔP_s is the loss of pressure caused by the stenosis, which functions like series resistance in an electrical circuit. It is calculated in accordance with Poiseuille's law. ΔP_c represents the loss of kinetic energy related to compression of the flow, and ΔP_e is the drop in pressure caused by post-stenotic dilatation of the vessel [22]. The relative magnitudes of these three variables depend on the geometry of the stenosis. In cases of stenosis involving a cardiac valve, the only relevant variable in the equation is ΔP_e. In the study of RAS, the decrease in pressure across the stenotic segment has no practical implications because Doppler measurements of trans-stenotic changes in flow velocity are not possible in the renal arteries, which are located far from the body surface. In contrast, in the assessment of a stenotic heart valve, Doppler velocitometric data are very useful for estimating the transvalvular loss of pressure. Trans-stenotic changes in the systolic pressure of the main renal artery observed on angiography have been used to validate the direct and indirect flow velocitometric parameters commonly used in the diagnosis of RAS [23]. A peak systolic velocity (PSV) exceeding 200 cm/s and a renal:aortic ratio greater than 2.5 are significantly correlated with trans-stenotic systolic pressure gradients of 24 mmHg.

Hemodynamic effects of increases in peripheral resistance

The spectral curve recorded in a normal renal artery is a low-resistance curve characterized by rapid initial systolic acceleration followed by gradual, progressive deceleration with rapid modulations. The normal PSV in this artery is 100 ± 20 cm/s; the DV is 30—40 cm/s [3,4,7]. Diastolic flow is continuous, and the spectrum never reaches the zero line (abscissa). The lowermost portion of the area under the curve, i.e., that lying between the zero-flow line and the line that connects the bases of the systolic wave, represents continuous systo-diastolic flow, i.e., the blood flow that is indispensable for the maintenance of organ function (Fig. 5).

The Doppler spectral waveform registers variations in the flow velocity of the blood column caused by the discontinuous action of the heart. Therefore, the morphology of the curve is closely related to cardiac movements, but it also varies as a function of total circulatory impedance. It is important to note that when the forces that oppose flow are not constant, when they adapt to an intermittent, dynamic action, the term *impedance* — as applied to electrical circuits — is conceptually more appropriate than *resistance*. If the heart rate and systolic force of the left ventricle are stable, the total circulatory impedance (like the resistance of a complex electrical circuit) represents the sum of the resistance forces, i.e., *hydraulic resistance*, *wall compliance* (electrical capacitance), and the *inertia and viscosity of the blood* (electrical inductance) (Fig. 6). In a given individual, the inertia and

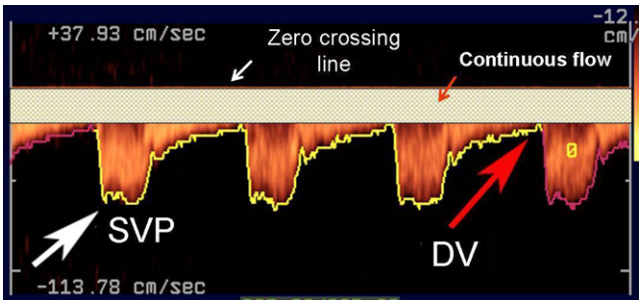

Fig. 5 Doppler spectral curve. Monophasic spectral curve. The terminal circulation of the kidney is characterized by low resistance with a sharp systolic acceleration followed by gradual diastolic deceleration with multiple modulations. The acceleration of the wave that follows does not begin at the zero line (abscissa): it is superimposed on a substantial amount of continuous diastolic flow. The line joining the two bases of a given complex is referred to as the theoretical zero-flow line. The lowermost portion of the area under the curve, i.e., that lying between the abscissa and this theoretical zero-flow line represents continuous systo-diastolic flow that is indispensable for the maintenance of organ function.

viscosity of the blood are constants. Consequently, total impedance represents the sum of hydraulic resistance and arterial compliance.

Hydraulic resistance is derived from Poiseuille's law (which corresponds to Ohm's law in the field of electrical conductance). It is defined by the following relation: $R = 8L\eta/\pi r^4$, where R is the resistance that opposes flow, L is the length of the conduit, η the viscosity of the blood, and r the radius of the conduit [24]. If the inertia of the blood mass and the length of the system are constants, the magnitude of the hydraulic resistance is largely related to arteriolar vasomotility and to the state of the arteriolar walls. In fact, Poiseuille's law states that, if the pressure gradient remains constant and the radius of the conduit is reduced by half, blood flow, which is inversely proportional to the fourth power of the radius, will decrease by a factor of 16 [24]. In other words, blood flow and the pressure gradient required to maintain a given blood flow are strongly influenced by even minimal changes in the diameter of the vessel. In the presence of a mean arterial pressure of 100 mmHg, the total vascular resistance in the normal kidney is 100 mmHg/600 ml/min, or 0.17 peripheral resistance unit — a value that is 8.5 times higher than that of the entire systemic circulation [25]. It should come as no surprise that a single kidney (which accounts for only 1% of total body weight) is characterized by total peripheral resistance so much higher than that of the entire systemic circulation since the kidney is supplied by a terminal circuit whereas the systemic circulation includes a myriad of alternative and collateral pathways. Under normal conditions, the level of resistance provided by the intrarenal microcirculation allows extremely high blood-flow rates (approximately 600 ml/min per kidney), and the Doppler spectral curve includes an elevated component representing continuous flow. In young, healthy subjects, tracings of the segmental, interlobar, and arcuate arteries are rounded with a protracted, blunt-tipped systolic peak and a very low-resistance index (RI $<$ 0.60) [26]. Aging, hypertension, diabetes, and above all atherosclerotic disease cause progressive hardening of the tunica media [10—12,26]. In animals' models and in humans with stabilized hypertension, changes in the arterial microcirculation (arteries with ∅ ranging from 100 μm to 400 μm, arterioles with a ∅ $<$100 μm) consist in increases in the thickness of the vessel wall and narrowing of the lumen [27]. Numerous experimental studies have demonstrated that the structural changes involving small arteries are the result of a dual process that includes remodelling followed by cell growth. Both processes increase the thickness of the tunica media and the tunica media:lumen ratio. An increase in this ratio is not necessarily synonymous with an increase in wall thickness, but it may result from rearrangement of the musculo-elastic layer around a shrinking lumen. This

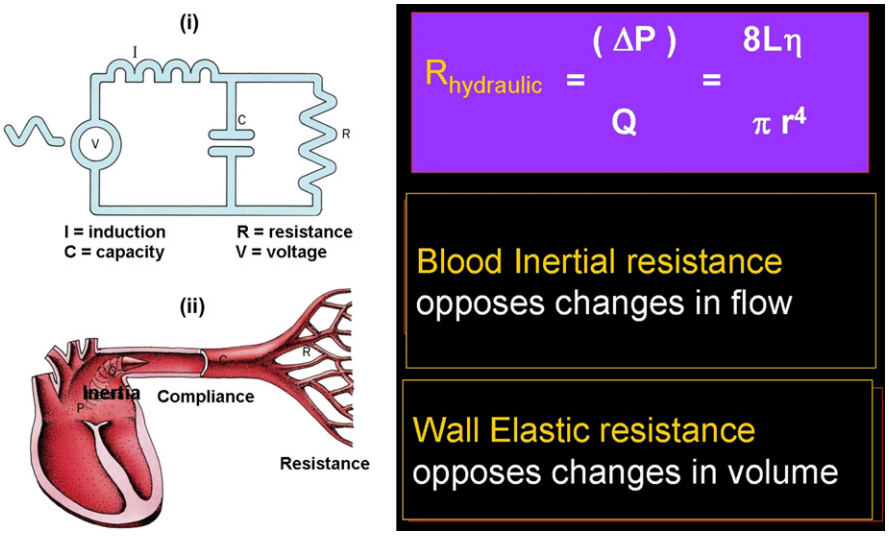

Fig. 6 Circulatory impedance. The total circulatory impedance is the sum of the forces of resistance, that is *hydraulic resistance*, *wall compliance* (electrical capacitance), and the *inertia and viscosity of the blood* (inductance).

process is known as eutrophic inward remodelling, and it leads ultimately to marked increases in wall stiffness and decreases in the cross-sectional area of the arterioles, which result in decreased flow [27,28].

An artery's ability to adapt to the volume of blood it contains depends on the visco-elastic properties of the vessel wall. The term *compliance* refers to the variation in volume related to the variations in arterial pressure, as specified in the following equation: $C = \Delta V/\Delta P$, where C stands for compliance, ΔV represents change in the volume of the vessel, and ΔP, variations in pressure. In contrast, *distensibility* is defined as the change in volume (ΔV) related to changes in pressure (ΔP) based on the initial volume of the vessel, as shown in this formula: $D = \Delta V/\Delta PV$, where D is distensibility, ΔV stands for the change in vessel volume, and ΔPV, for the variation in pressure as a function of the initial volume. *Stiffness* is the reciprocal value of distensibility, i.e., $S = 1/D$. All of these parameters are dependent on the value of the arterial pressure.

The increased stiffness of the arterial wall and the reduced cross-sectional area of the microcirculation are the fundamental causes of the chronic ischemic damage produced by nephroangiosclerosis and atheroembolism in the absence of RAS. It is important to recall that district blood flow (Q) is defined by the relation $Q = A \times V_m$, where A is the cross-sectional area of the vessel and V_m, the mean flow velocity of the blood. Blood flow is thus directly proportional to the cross-sectional area of the vessel: if the latter area decreases, there will be a proportional decrease in flow. If on the other hand flow remains constant, based on the equation shown above, variations in A and V_m will be inversely proportional to one another [24]. In other words, hardening of the arterioles reduces the *compliance* of the system whereas remodelling of the microarterioles increases its *total hydraulic resistance* [29], and both factors increase total impedance. In the kidney, these morphological changes lead to reduced perfusion in certain districts, like that associated with benign and malignant nephroangiosclerosis, and a marked increase in the difference between systolic and diastolic flow velocities. The difference between systolic and diastolic blood-flow velocities is simply the expression of the increased *pulse pressure* and *pulse wave velocity*, i.e., the velocity at which the wave is propagated along the vessel wall. Variations in velocity are detected on color Doppler as a marked increase in the resistivity indices as a result of the decrease in diastolic flow.

Technique for examining the renal vessels

Patient preparation

Ideally, the patient should be examined after an 8-h fast preceded by several days on a low-fiber diet. If prolonged fasting is contraindicated by the presence of insulin-dependent diabetes, liquid feedings should be administered with the insulin injections. The administration of anti-gas drugs in a patient with fecal stasis in the colon is of little use. Color Doppler sonography of the renal arteries requires an examination strategy that will reduce the risk of technical failures, but sometimes, despite all efforts, complete sampling is not possible, e.g., in patients who are obese, non-cooperative, or suffering from chronic heart failure (NYHA 2-4) or chronic respiratory disease. The difficulties that arise are related in part to the depth and courses of the renal arteries, in part to the frequency of supernumerary vessels (20—25%), and in part to the fact that the entire course of each artery has to be explored under conditions of complete apnea. Atherosclerotic stenoses commonly affect the ostial and paraostial segments of the main branch, but fibrodysplastic changes (intimal, mediointimal, adventitial) usually involve the middle, distal, and perihilar segments of the artery. In addition, the hemodynamic variations caused by stenosis tend to disappear 1—2 cm downstream from the restriction. Consequently, sampling errors can result in the underestimation or non-recognition of a critical stenosis.

In daily practice, the duration of a color Doppler examination of the renal arteries varies with the training and experience of the operator, the number of examinations he/she does each day, and the type of equipment used. In general, a good operator can complete the study of the arteries and intraparenchymal resistivity indices within 15 min (range 5—20 min). If the examination requires more than 20 min, it should be repeated after more complete preparation and cleansing of the intestine. In fact, the operator's level of concentration and patience tend to decrease rapidly when faced with a difficult case, particularly when the patient has also been incorrectly prepared for the examination or subjected to an excessively short period of fasting.

Scanning planes and technique for examination of the native kidney

The renal artery can be examined in various scanning planes: (1) transverse or axial scans carried out at the epi-mesogastric level; (2) subcostal scans performed with the patient in the right or left lateral decubitus position; (3) coronal scans along the aorta done with the patient in the left lateral decubitus position; and (4) coronal scans of the kidney and hilum with the patient in the lateral decubitus position. An approach that is useful in one case may be nonproductive in another: through daily experience, the operator acquires the ability to ''find'' the right solution for sampling each artery. In clinical practice, ''the end justifies the means.'' The goal in this case is the uniform insonation of the vessel at an appropriate Doppler angle, and operators should use whatever scanning planes allow them to record the Doppler signal under the given set of circumstances (including the conditions of the patient). Challenges of this type are a test of the sonographer's skill, experience, and ''creativity,'' and they account in large part for the operator-dependency of the results obtained with this imaging modality.

Axial scans allow the operator to identify the renal ostium, the artery's anatomic relation to the homolateral renal vein, and the presence of any accessory arteries (although this is not always easy). In this plane, the insonation angle for scanning the ostial segment of the right renal artery is far from optimal (50—60°), but that of the left artery is ideal (<30—45°) (Fig. 7). In subcostal scans, which are carried out in the right and left semilateral decubitus positions, the right and left renal arteries extend

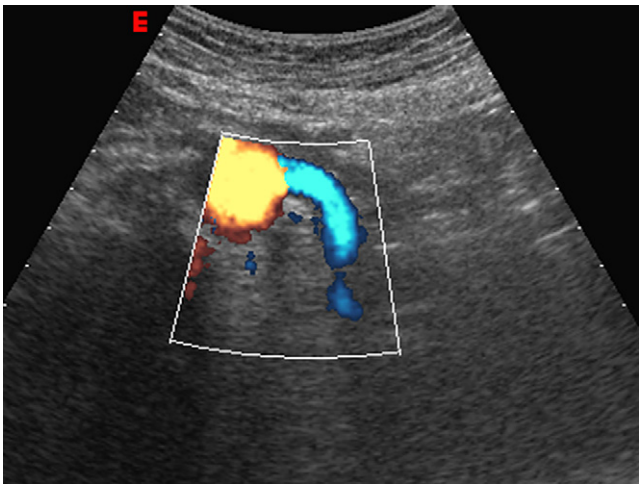

Fig. 7 Axial scan of the left renal artery. Axial scans allow the examiner to identify the pedicle from which the artery originates, the artery's anatomic relation to the homolateral renal vein, and the presence of any accessory arteries (although this is not always easy). In this plane, the insonation angle of the ostial segment of the right renal artery is unfavorable (50—60°), but that of the left renal artery is ideal (<30—45°).

full length and can be sampled at appropriate angles (<20—30° on the right, >40° on the left) (Fig. 8). A coronal scan along the aorta with the patient in the left lateral decubitus is undoubtedly one of the most spectacular scans: it depicts the ostia of both arteries, any supernumerary branches that may be present (Fig. 9), and the aorta and renal vessels' relations to the medial diaphragmatic column. The advantage of this scan is that it allows sampling of the ostia of the arteries with very low angles of insonation (<20—25°), although in brachytypes and patients who are obese, the low frequencies used (2.5 MHz) do not always produce high-quality images. Coronal scans of the right and left kidney along the mid-posterior axillary line with the patient in the right/left lateral decubitus position provides a panoramic view of the segmental vessels (Fig. 10a, b)

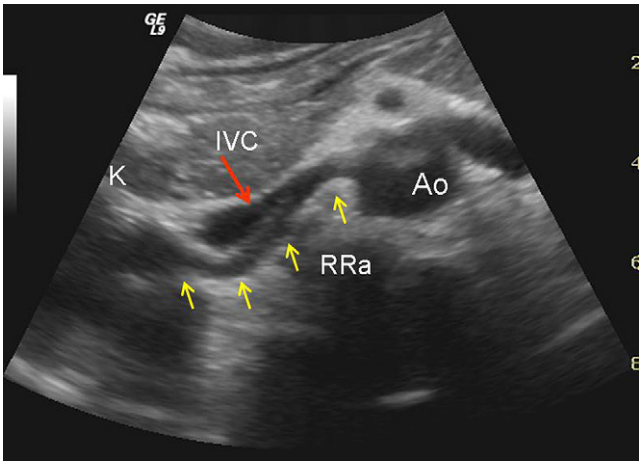

Fig. 8 Axial scan of the right renal artery. K = renal hilum; Ao = aorta; IVC = inferior vena cava; RRa = right renal artery.

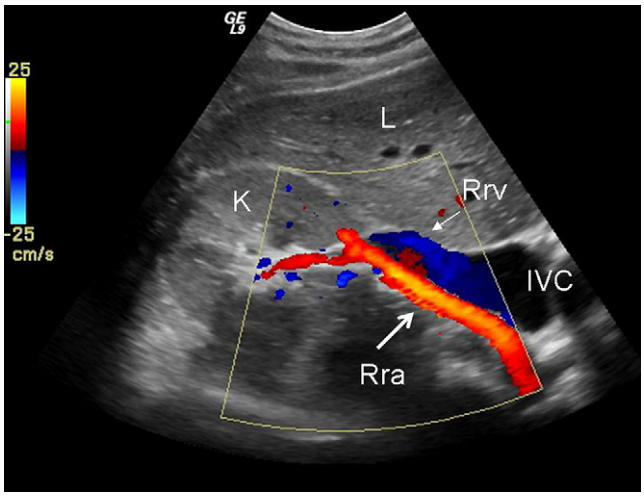

Fig. 9 Right subcostal scan with the patient in the left semilateral decubitus. Right renal artery and vein.

and of the artery and vein at the hilum. In this scan, arterial blood flows centrifugally and venous blood flows centripetally with respect to the transducer so the arteries and veins are depicted in red and blue, respectively. Coronal scans can often capture spectacular images of the renal artery in its full length, including its origin from the aorta. Although the kidney acts as an acoustic window, the vascular pedicle and the initial segment of the artery are not always optimally defined. The depth of field in this scan requires the use of low frequencies, and this decreases the quality of the images obtained. Its main advantage is that allows rapid sampling of the interlobar arteries next to the mesorenal column and calculation of the intraparenchymal resistivity indices. All scans described above require alternating or combined use of B-mode, color/power Doppler, and Doppler spectral analysis. In general, examination of the ostial and paraostial segments of the artery will reveal a large part of the atherosclerotic stenosis; the middle and distal segments must be examined to exclude the presence of fibrodysplastic or distal atherosclerotic forms.

Stenosis of the renal artery in a transplanted organ

Stenosis of the renal artery in a patient who has undergone kidney transplant is a relatively frequent finding (1—23% depending on the series), and it generally involves the anastomotic segment of the artery. It can develop from 3 months to 2 years after transplantation as the result of iatrogenic scarring provoked during explantation, vessel clamping, or creation of an end-to-side anastomosis with the common iliac artery. Less commonly, multiple segments (or even the full length) of the artery are affected by the stenosis. In these cases, RAS is usually the result of traumatic damage to the intima produced by catheterization of the artery during the cold ischemia stage, but it can also be caused by torsion or kinking of the vessel following graft implantation [30]. Clinically speaking, RAS produces secondary hypertension that can be corrected with PTRA in 1—5% of all patients with severe hypertension, but it can also lead to transplant dysfunction or loss. These

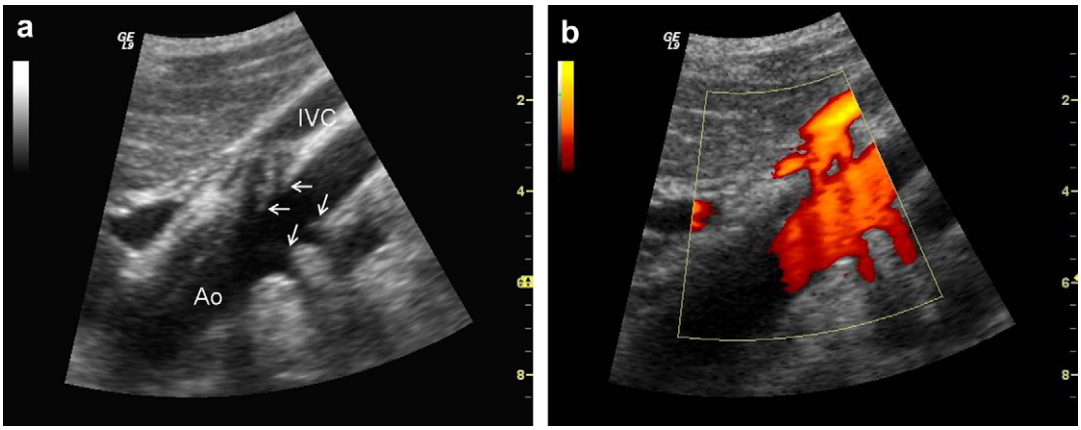

Fig. 10 (a, b). Coronal scan along the aorta with the patient in the left lateral decubitus. Ao = aorta; IVC = inferior vena cava; white arrows = ostia of the renal arteries (double bilateral district).

clinical findings stress the importance of full-length examinations of the renal arteries. The sensitivity of color Doppler in these cases can be markedly reduced if the vessel is stretched or kinked as a result of surgery. In both cases, the examination reveals accelerations that are not always indicative of critical stenosis. Above all, it is important to recall that kidney transplant ischemia may be the result of stenosis of the common iliac artery caused by clamp-related trauma to the intima.

Color Doppler technique

To minimize the risk of technical failures, the operator should develop a systematic examination approach. The first step is to identify in B-mode the *anatomic window*, collateral branches of the aorta, and the veins of the supramesocolic region. The origin of the superior mesenteric artery from the aorta is an important landmark for two reasons: first, a very acute angle at this junction can cause compression or entrapment of the left renal vein (nutcracker syndrome); second, it is located 1.0—1.5 cm from the renal ostia.

Next the Doppler color box is opened. Its dimensions should be limited to facilitate the Doppler analysis and improve the sensitivity and frame rate. At this point the operator should carefully adjust the color Doppler functions: the pulse repetition frequency (PRF) should be set at 1.5—3.0 KHz; transmission frequency at 2.3—2.8 MHz; and the wall filter at 100 Hz. The color gain and depth of field should be adjusted according to the patient's body type [3,4]. If the CD settings are correct, image will be ''clean,'' with uniformly red or blue tones and no aliasing or color-bleeding (leakage of color into the perivascular tissues) [14]. Movement of the transducer, the patient's breathing, and movement of the intestinal loops can all cause flash artifacts [14].

The next step involves activation of the spectral analysis mode. The sample volume can then be placed within the lumen of the renal artery and the velocity/time (V/t) spectral waveform recorded. The size of the sample volume should be adjusted to allow uniform insonation of the vessel (2—4 mm) without provoking oversampling and undersampling artifacts. In this case as well, care should be taken in adjusting the Doppler spectral settings: PRF (3—6 KHz), Doppler frequency (4—8 KHz), gain, depth of field, wall filter. If the colorimetric map is normal and the velocitometric waveform shows a VPS < 100 cm/s, the intraparenchymal RI can be calculated and compared to exclude the possibility of lateralization of the vascular resistance, and the examination is over. If aliasing or a perivascular color bruit is noted in the ostial, middle or hilar segments of the artery [3,4], spectral analysis must be focused on them. Multiple V/t waveforms should be recorded at optimal Doppler angles ($<60^{\circ}$) because the diagnosis of stenosis is based exclusively on the absolute flow velocities observed. Premature bifurcation or kinking can cause false accelerations that are a source of error. The appearance of *aliasing on spectral analysis*, that is the inversion of the apical portion of the V/t curve on the side opposite to the *zero-flow line*, may be the result of an incorrect PRF setting, but it can also reflect an increase in the velocity of blood flow [14]. If the PRF setting is right, *aliasing* is a useful artifact that indicates increased flow velocity and the presence of stenosis. Spectral ambiguity can be eliminated by adjusting the PRF, by moving the zero line of the V/t curve, or by reducing the depth of field [14].

When the color box is opened over the renal parenchyma, a rich radial or fan-shaped network of blood vessels appears. Segmental arteries and veins radiate from the hilum toward the parenchyma, giving rise to the arcuate vessels and the interlobar arteries. Cortical *blushing*, which is especially evident on power Doppler or *dynamic-flow* studies, consists of the appearance of network of thin vessels that pulsate rhythmically with the systolic/diastolic expansions of the parenchymal vessels (Fig. 11). Parenchymal blushing is a reflection of the systo-diastolic vasomotility of the intrarenal vessels; therefore it tends to diminish with age or in the presence of pathological remodelling of the microcirculation and marked increases in vessel stiffness. The intraparenchymal RI and PI should ideally be measured in an interlobar vessel, adjacent to the renal column (Fig. 12). In young subjects, the RI is usually less than 0.60 and the PI < 1.20. Both indices tend to increase in the presence of stabilized arterial hypertension, advanced age, diabetes, or interstitial nephropathies. In chronic interstitial nephropathy, the RI and PI generally exceed 0.70 and 1.20—1.50, respectively; values near or above

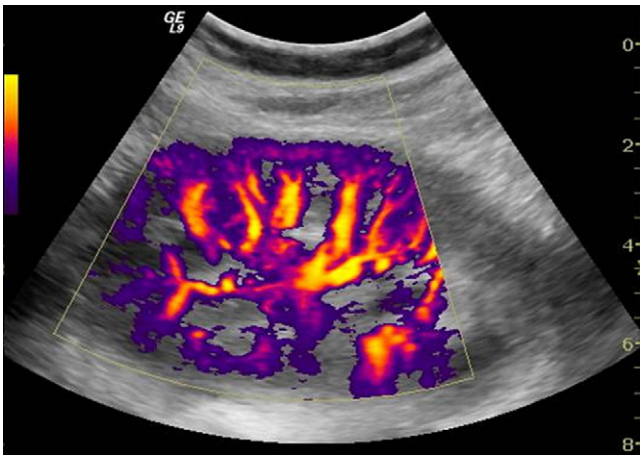

Fig. 11 Coronal scan of the left kidney. Interlobar and interlobular segmental vessels. Perfusional cortical *blushing*, which is especially evident on power Doppler or *dynamic-flow* studies, consists of the appearance of a network of thin vessels that pulsate rhythmically with the systolic/diastolic expansions of the parenchymal vessels.

0.80 and 1.50 are indicative of primary vascular nephropathy, nephroangiosclerosis, and atheroembolism [31]. Intraparenchymal resistance is more commonly expressed with the RI than with the PI. In fact, the former index is considered a more precise indicator of circulatory resistance downstream to the point of measurement whereas the latter is more indicative of variations in the wall pulse in the various arterial districts and therefore, vascular stiffness.

In short, CDUS simplifies the study of the renal vessels by reducing the time needed to record the spectral waveforms

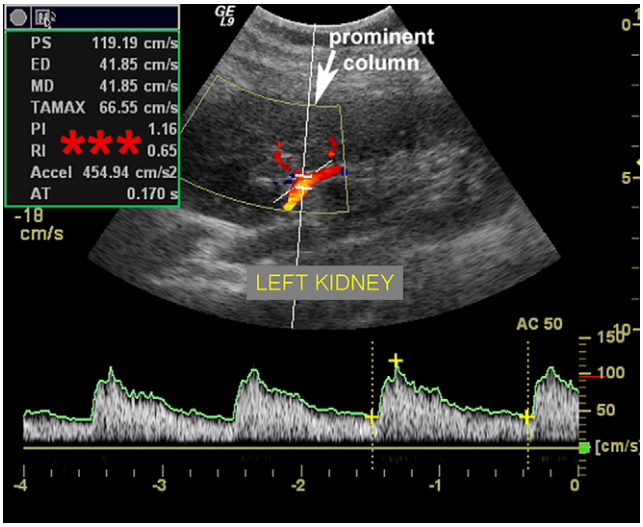

Fig. 12 Measurement of the resistance index and the pulsatility index. The spectral curve was recorded in an interlobar vessel next to the renal column. The resistivity indices (the values are indicated with asterisks) were calculated with the formula $IR = (S - D)/S$; $IP = (S - D)/V_{mean}$.

in the various segments of the main artery. On digital scanners, CD and spectral analysis settings (PRF, frequency, gain) can be regulated separately, and this feature has improved Doppler sensitivity. The dynamic color-coded map provides only semiquantitative information on blood flow, but it depicts the course of the vessels and provides immediate information on their patency and the direction of their flow. The appearance of *aliasing* with oversaturation and anomalous, non-progressive color changes (e.g., red tending toward yellow or blue or light blue) indicates the presence of abnormal accelerations with vortices. Although these signs are typical of critical stenosis, they are nonspecific in that they provide only semiquantitative information (changes in mean flow velocity). By recording the spectral curve at the critical points identified during the CD examination, one obtains quantitative measurements of systolic and diastolic flow velocities that are indispensable for diagnosis and can be easily repeated. The examination of the renal arterial circuit ends with full-length exploration of the interlobar arteries and calculation of the resistivity indices [14].

Color Doppler findings in chronic renal disease caused by stenosis of the main renal artery

An ideal screening test should be noninvasive, repeatable, low cost and have a high negative predictive value [32]. CD has many of these characteristics. In the first place, it is a low cost examination without risk to the patient, well tolerated and capable of furnishing information that reduces and rationalizes recourse to second-level diagnostic studies. Second, it is highly sensitive and specific. In recently published series, it displayed sensitivity and specificity of 90—95% and a negative predictive value of >95% when used in a population in which the prevalence of disease was >20% [33]. Consequently, the use of screening CDUS in the diagnosis of CIN is gaining increasing support. In the series published in the 1990s, sensitivity and specificity values reported for Doppler were highly discordant. This favored persistence of the view that CD is characterized by low reliability and strong operator dependence. It is possible, however, that the wide variability that characterized findings published during that period was a reflection of the lack of consensus on Doppler parameters, the lack of intra- and interobserver validation, the level of technology of the equipment used, differences in the prevalence of RAS in the populations examined and finally the location and severity of the stenoses [34].

Renal scintigraphy with captopril is widely considered a screening test for RAS although it is more time-consuming and expensive and poorly tolerated by the patient. Scintigraphy requires adequate preparation with drug washout, the choice of the radionuclide (Tc-MAG_3, Tc-DTPA or I^{131}-OIH), standardization of the dose and route of administration of the ACE-inhibitor [35]. Therefore, although some authors maintain that this method can be used to screen selected populations [35,36], its actual role is quite limited due to the complexity of the testing protocol and the absence of standardized diagnostic criteria. Even today it certainly plays a fundamental role in the functional diagnosis of renovascular hypertension.

From a practical point of view, CD studies of the renal arteries should not be performed indiscriminately on all hypertensive patients: it should be reserved for those cases in which there is a strong clinical suspicion of RAS [37]. Cases requiring screening should be selected in accordance with the clinical criteria established in the literature (Table 1) [37].

B-mode ultrasonography does not play a primary role in the study of RAS [38], but it can reveal significant renal asymmetry (differences in the coronal diameters of the kidneys of >1.5 cm), loss of renal mass (parenchymal thinning), flattening of the mesorenal column, which are in any case nonspecific signs of chronic ischemia [38]. The echogenicity of the ischemic kidney varies from diffuse, uniform hypoechogenicity to fine, diffuse hyperechogenicity. In those forms of ischemic nephropathy in which involvement of the microcirculation is predominant, the coronal diameter is close to normal (10.0–10.5 cm) and the thickness of the parenchyma only moderately reduced; the cortex and medulla exhibit diffuse, inhomogeneous hyperechogenicity that is often associated with sclerolipomatosis of the sinus and simple cysts. In other cases, the morphology of the kidney is almost normal, and involvement of the microcirculation is manifested only by marked increases in the intraparenchymal resistance indices. Occasionally, the morphologic assessment reveals hyperechoic/mixed plaques in the ostial and paraostial segments, anomalies like kinking or premature bifurcation, and in rare cases, aneurysms or irregularities involving the walls of the middle segment that are caused by fibrodysplasia. A pedicle with a diameter <4 mm is often associated with a double arterial district. The morphological study of the aorta can reveal atheromatous disease ranging from mild to severe, which causes irregular wall margins, aneurysms (saccular, fusiform) of various sizes. Morphological assessment of the adrenal glands is difficult, but a skilled operator can reveal adrenal masses (pheochromocytomas, adenomas).

From a hemodynamic point of view, variations occurring within and immediately downstream from the stenotic segment can alter the morphology of the V/t curve. Within the stenotic segment, there is a significant increase in the peak systolic and diastolic velocities; the flow pattern changes from laminar to vorticose with dispersion of the red-cell velocity in the Doppler spectrum (broadening of the spectrum and disappearance of the systolic/diastolic window) (Fig. 13) [34]. Downstream from the stenosis, vortices and spectral broadening prevail. At a short distance from the stenosis, normal hemodynamics are restored. Progression of the stenosis is accompanied by accentuation of the phenomena described above and additional increases in PSV (systolic jet). All of this occurs within an empirical limit defined by Reynolds' law: once this limit is reached, the pressure-related energy upstream to the stenosis is no longer sufficient to overcome the resistance of the stenosis, and it is dispersed as thermal energy in the casual, erratic movement of the blood (vortices and eddies). Under these conditions, terminal, post-stenotic waveforms are recorded in and downstream to the stenotic segment, and the systo-diastolic range is markedly reduced [14]. When the lumen is

Table 1 Clinical criteria for selection of patients to be screened for chronic ischemic nephropathy (modified from Ref. [37])

1. Hypertensive patients

- Women <50 years of age with no family history of hypertension
- Young patient with recent-onset hypertension that responds poorly to multidrug therapy
- Men >50 years of age with severe, recent-onset hypertension and signs/history of atherosclerotic disease in one or more vascular districts
  - Ischemic heart disease
  - Chronic peripheral arteriopathy
  - Steno-obstruction of epiaortic vessels
  - Dissecting aortic aneurysm
  - Recognized cardiovascular risk factors (e.g., diabetes, smoking, dyslipidemia)
- Patients with malignant or accelerated hypertension

2. Patients with urinary anomalies

- Increase in serum creatinine that cannot be attributed to medical nephropathy in a patient aged >50 years with a history of atherosclerotic disease involving one or more districts
- Rapid, significant increase in serum creatinine or acute renal failure after use of ACE-inhibitors, with or without loop diuretics, for recent-onset hypertension
- Asymmetrical kidney or monolateral terminal kidney
- Decreased serum potassium associated with hypertension

3. Suspicious clinical signs

- Abdominal murmur near the umbilicus
- Severe retinopathy
- Ischemic cardiopathy, peripheral or epiaortic arteriopathy
- Acute or unexplained congestive heart failure or
- Repeated episodes of rapid-onset pulmonary edema (*flash pulmonary edema*)
- Occasional discovery of an abdominal aortic aneurysm

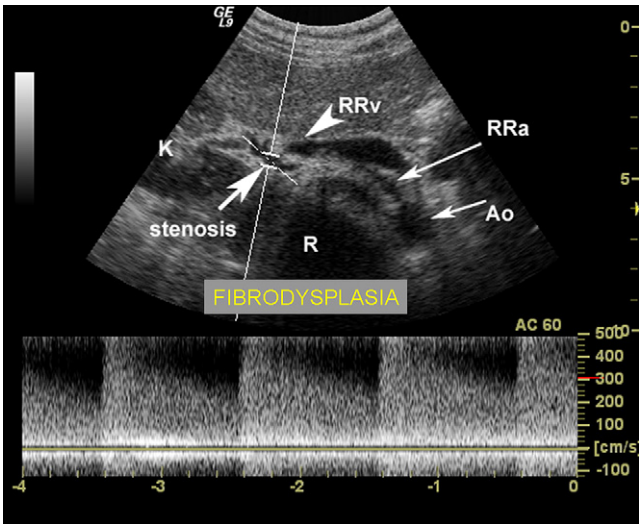

Fig. 13 *V/t* curve in hemodynamically significant stenosis. From a hemodynamic point of view, variations occurring within and immediately downstream from a stenotic segment can alter the morphology of the *V/t* curve. Within the stenotic segment, there is a significant increase in the peak systolic and diastolic velocities; the flow pattern changes from laminar to vorticose with dispersion of the red-cell velocity in the Doppler spectrum (spectral dispersion and disappearance of the systolic window). The case reported refers to a fibrodysplastic stenosis of the distal segment of the right renal artery.

completely occluded, orthodromic flow disappears, and stump-flow may be observed.

On all scanners, the Doppler signal is represented by means of spectral analysis of velocity or color-code flow mapping. The Doppler-shift (δF), i.e., the variation in soundwave frequency that occurs when ultrasounds encounter a blood column in motion, varies as a function of velocity and direction of blood flow and falls within the KHz range, i.e., within the range of audible frequencies. Therefore, it can be amplified and reproduced as a characteristic sound (bruit), which becomes louder and increasingly harsh as the degree of stenosis increases. This sign is generally considered to be of enormous importance, a red flag that immediately attracts the attention of the examiner. The Doppler parameters used to define critical stenosis are now fully standardized in the international literature although they still need to be subjected to intra and inter-observer validation in each diagnostic Doppler laboratory. These criteria can be divided into major (or direct) criteria and minor (indirect) criteria; there are also intra- and extrarenal parameters [33]. The major (or direct) criteria are based on the demonstration of variations in flow velocity caused by the stenosis in the ostial/paraostial or middle-hilar segment of the main vessel. Because absolute PSV and DV values vary with the Doppler angle, quantitative analysis of the *V/t* curve cannot furnish a precise definition of the severity or degree of the stenosis, but it can distinguish hemodynamically critical forms (i.e., those that cause ischemia and trigger the renin–angiotensin cascade) from those that are non-significant. The cut-off recommended in the literature corresponds to a stenosis of more than 60%, and it was calculated by comparing velocitometric parameters with angiographic stenoses >50%. PSV values >180 cm/s and DVs > 90 cm/s with a Doppler angle between 20° and 60° are generally regarded as indicative of significant stenosis [39]. The rate of false positives drops dramatically when these values are recorded with insonation angles <30°. Table 2 shows the criteria for diagnosis of stenosis recommended by Zierler and Strandness in their 1996 paper in the *American Journal of Hypertension* [40]. If the PSV is >180 cm/s and the RAR < 3.5, the degree of stenosis is probably <60%; vice versa, when the PSV is >180 cm/s and the RAR > 3.5, the stenosis is considered to be >60% [40]. The results of this study are fully consistent with our own experience. Based on validation against MR angiography, the direct criteria used in our CD lab to identify stenosis are a PSV > 180–200 cm/s and a DV > 90 cm/s; the indirect criteria are spectral broadening of the *V/t* curve and an RAR > 3.5. The use of contrast medium and analysis of time/intensity curves are of little value in the diagnosis of RAS. Although there are no data available on the use of parametric sonographic perfusion imaging to measure renal tissue perfusion, this approach might lead to new prospects in the clinical assessment of RAS, indications for revascularization, and post-treatment follow-up [41,42].

The diagnosis of total occlusion is sometimes quite difficult; it is based on the complete absence of Doppler signals and, rarely, on the appearance of stump-flow signal. The presence of a thin ejection jet with a demodulated, terminal *V/t* curve (characterized by a reduced-amplitude systolic signal and the absence of a diastolic signal) is indicative of preocclusive stenosis. If these findings are associated with loss of the renal mass (reduced corticomedullary thickness, longitudinal renal diameter <9 cm), the chances of saving the kidney with revascularization are limited. In cases of progressive stenosis, the longitudinal diameter of the kidney has been estimated to decrease by 1 cm/year. Acute obstruction caused by primary or secondary thrombosis of the main renal artery determines irreversible renal injury within 3–4 weeks [40].

The search for direct signs of stenosis requires full-length sampling of the main artery. In the predigital era, when scanners were not particularly sensitive, it was often impossible to sample the entire length of the artery; in those days, the examinations were often lengthy and complicated. In an attempt to simplify the diagnosis of RAS, many authors have attempted to identify semiquantitative, easy-to-calculate parameters that are not dependent on the Doppler angle.

Table 2 Criteria for the diagnosis of renal artery stenosis

Stenosis[a] (%)	PSV (cm/s)	RAR
Normal[b]	<180	<3.5
<60	>180	<3.5
>60	>180	>3.5
Occlusion	No signal	–

Elaborated by Zierler and Strandness (see Ref. [40]).
PSV – peak systolic velocity; RAR – renal:aortic ratio.
[a] Percentage reduction of the free diameter of the renal artery.
[b] PSV: 100 ± 20 cm/s and RAR: 1–1.5.

One of the more important indirect, extrarenal signs, which is now widely used, consists in what is improperly referred to as the renal:aortic ratio (RAR) [34]. It is more precisely the ratio of PSV in the main renal artery to the PSV recorded in the aorta right below the emergence of the superior mesenteric artery. At this level, owing to the presence of lumbar lordosis, the aorta follows an oblique, posteroanterior course, and the *V/t* curve recorded here is of the resistive type with a small reverse wave. Sampling of the aorta must be carried out with an insonation angle of 45—55° and a volume sample that is large enough to represent moderate dispersion of velocity. PSV in the aorta is clearly lower than that recorded in the renal arteries due to the difference in caliber. In a normal subject the RAR ranges from 1.0 to 1.5. It tends to increase with age and with increasing vessel *stiffness*. If the PSV in the renal artery does not exceed 180 cm/s and the RAR is $\leq$3, diagnosis of RAS becomes difficult and the degree of stenosis needs to be evaluated with MR angiography or CT angiography or with follow-up CD. In patients with stenosis caused by fibrodysplasia, which is characterized by greater elasticity and compliance, the RAR criteria established in atherosclerotic RAS are not always applicable.

In cases of severe narrowing (>75—80%), sampling of the hilar vessels reveals typical flattening of the early systolic peak and lengthening of the systolic plateau, which characterize the parvus-tardus sign [43]. The *parvus-tardus* sign is not constant; it is the expression of the complex interaction that occurs between compliance and the forces of vascular resistance downstream from the stenosis. When it is present and associated with marked lateralization of the resistance forces, it not only represents a highly sensitive marker of stenosis but it also indicates that the ischemic kidney is protected by substantial vasodilatation that is modulated by the autoregulatory mechanisms [44]. In these cases, the probability of successful revascularization is quite high even though the stenosis is preocclusive.

Using translumbar scans, Handa et al. analyzed systolic acceleration times (AT), systolic acceleration indices (AIs), and acceleration:time ratios (ATR) in *V/t* curves recorded in the main renal artery [45]. This technique was associated with a very high rate of success: 98% in cases of RAS, with 100% sensitivity and 93% specificity. The high sensitivity and specificity figures reported by Handa et al. have been confirmed in part in more recent clinical and experimental studies [46]. Nonetheless, calculation of the AT and AI is not widely used probably because use of the translumbar approach with the patient prone makes it quite difficult to examine the renal arteries in brachytypes and obese subjects, and the angle of incidence being used can never be identified with any precision.

RAS represents an accessory series resistance in the terminal renal circuit. Theoretically, downstream from a preocclusive stenosis, there should be a reduction in the best known semiquantitative Doppler parameters, the resistance indices of Planiol and Pourcelot and Gosling's pulsatility index (IP), but in spite of the decrease in perfusion pressure in this area, there is not always a clear decrease in resistivity. In fact, the forces of resistance in the parenchymal microcirculation are influenced by multiple factors such as age, use of antihypertensive drugs, preexistent parenchymal damage, remodelling of the microcirculation (atherosclerotic disease, hypertension, and diabetes), heart rate, and cardiac output. For this reason, vasomotility does not always coincide with the theoretical behavior based on the principles of hemodynamics. The resistance indices should be calculated as the mean of three measurements made at the level of the interlobar arteries at three different points in the parenchyma. *Lateralization of the RI > 0.12 is* considered to be a reflection of unilateral stenosis [39,47].

In any case, the resistance indices are currently the only Doppler parameters that can provide information on the vasomotility and total vascular impedance of the parenchymal circulation. If the microcirculation is not markedly compromised, resistance in the kidney is quite low (RI < 0.60) during the initial phases of ischemia. The ischemic kidney is incorrectly said to be ''protected'' by the hemodynamic adaptation of the intrarenal circulation (Fig. 14a—c). These conditions are ideal for revascularization. If the hypoperfusion stabilizes and becomes chronic, the renal mass decreases progressively as a result of parenchymal, interstitial, and vascular damage, and progressive increases in resistance are inevitable. Therefore, an elevated RI (>0.75—0.80) should be considered an almost absolute contraindication to revascularization, especially when the coronal diameter of the kidney is <9 cm. The concomitant presence of RAS and atherosclerotic damage to the microcirculation, which is reflected by a significant increase in the RI (>0.80), also represents a less than ideal setting for performing revascularization [39,48].

Based on a critical analysis of the current literature, the long-term results of revascularization in terms of renal function (RF) and arterial pressure are by no means certain. For this reason, the experts maintain that, in determining whether or not stenosis is critical, it is important to consider other factors such as the response to multidrug treatment of hypertension, the evolution of the RF, and quality of life. Therefore, in addition to the usual morphological and hemodynamic criteria, these clinical factors should also be used to decide whether or not to revascularize a hemodynamically significant stenosis. The advantage of treating preocclusive stenosis is even less clear; this practice is as controversial as revascularization for RAS patients with stable blood pressure and normal renal function [49]. Most cases of RAS associated with hypertension and CKD can be managed with conservative medical treatment without increasing the risk of mortality or aggravating the kidney disease. In these cases, RF and renal mass (diameter) should be closely monitored, particularly when the stenosis is bilateral or when the patient has only one kidney. In other words, the benefits of revascularization in cases of severe stenosis have not been clearly demonstrated, so the decision to treat preocclusive stenosis should be based exclusively on clinical criteria [49].

The role of second-level studies in the diagnosis of RAS

Spiral CT angiography furnishes high-quality vascular images with 2- and 3-dimensional reconstructions that are similar to those offered by DSA. The use of standardized protocols for studying the renal arteries is associated with

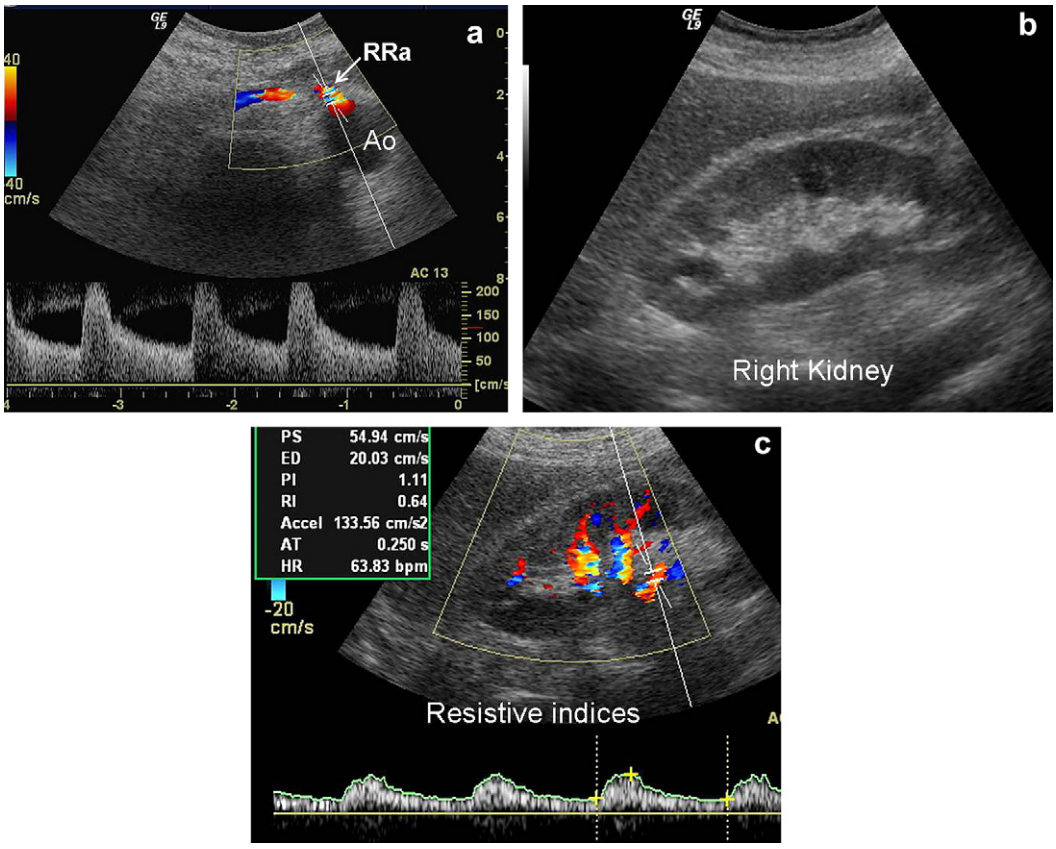

Fig. 14 Atherosclerotic RAS and intraparenchymal resistivity indices. The resistivity indices are the only Doppler parameters that provide information on the vasomotility and the total vascular impedance of the parenchymal vessels. A kidney without marked microcirculatory changes, in the precocious phases of the ischemia, shows very low-resistance indices (RI < 0.60). In the case reported (78-year-old woman with wrinkled right kidney and a creatinine clearance of 53 ml/min), (a) the right renal artery shows stabilized, non-progressive stenosis that is close to being critical. In the B-Mode image (b) the kidney has a normal aspect. The intraparenchymal RIs are low (0.64) because of reactive vasodilatation, which protects the kidney from ischemia (c).

a significant increase in sensitivity and specificity (90—98%) [50], and accuracy is comparable to that of DSA [49,51]. The advantages of Angio-CT over Angio-MRI include better visualization of wall calcifications, which can be distinguished from noncalcified plaques (useful information when angioplasty is being planned), direct visualization of metal stents (position, patency, intimal hyperplasia), and a lower cost. Nonetheless, Angio-CT is not suited for use as a screening method because it is in any case expensive and time-consuming (particularly the postprocessing image reconstruction) and exposes the patient to ionizing radiation and potentially nephrotoxic iodated contrast media.

Vascular studies based on MRI have changed dramatically over the last few years as a result of technical and methodological advances and the introduction of ultrafast sequences, phase-array coils, and paramagnetic contrast media. The sequences traditionally used in the study of vascular structures, time-of-flight (TOF) and phase-contrast (PC), rely on saturation or cancellation of the signal in stationary tissues to produce selective images of blood vessels, but they also have several drawbacks, including long acquisition times, saturation of flow, a high rate of motion artifacts, limited view fields, and they cannot be used to evaluate the renal parenchyma. The recently introduced technique of contrast-enhanced 3-dimensional Angio-MRI has eliminated many of these problems. It involves T1 shortening by means of high-velocity intravenous administration of paramagnetic contrast medium. The image is acquired when the concentration of contrast medium in the vessel is at its highest, which renders the technique flow-independent. Broad fields of view in the coronal plane can also be used to visualize the entire vascular tree. With high magnetic field MR scanners equipped with high-performance gradients, the examination can be carried out during a single breath-hold, which eliminates the problem of breathing artifacts and allows selective visualization of the arteries or veins. The images can also be re-elaborated in any anatomic plane by means of dedicated software.

In the diagnosis of RAS, contrast-enhanced Angio-MRI has exhibited high rates of sensitivity and specificity (100% and 89% according to Snidow, 100% and 97% according to DeCobelli, 100% and 96% in the study of Schonberg). Like digital angiography (which is still regarded as the gold standard for detection of RAS), contrast-enhanced MR angiography furnishes information that is exclusively morphologic; the addition of sequences that can provide functional and hemodynamic data are thus a useful complement. For this reason, despite its limitations, phase-contrast Angio-MRI is still included in protocols for the study of the renal arteries. It

can provide functional information related above all to the quantification of flow, which is a useful supplement to contrast-enhanced MR angiographic findings. With this sequence, only the blood flow itself is visualized; the vessels appear as structures characterized by high signal intensity. In the presence of stenosis, flow turbulence causes a drop in signal intensity known as the flow void, which causes rapid spin dephasing. This allows the examiner to determine whether or not the RAS is hemodynamically significant. The major limitation of the phase-contrast technique is a relatively high rate of false positive results related to the presence of physiologic turbulence (due to vessel kinking or abrupt changes in the orientation of the vessel). It has also been shown to overestimate the degree of stenosis in some cases. Both of these problems can be overcome by combining phase-contrast sequences with those of contrast-enhanced MR angiography.

MR angiography uses a relatively low-osmolarity contrast medium that is less nephrotoxic and less allergenic than those used in conventional angiography. It is also less expensive than DSA and does not use ionizing radiations, and these features make it more suitable for post-angioplasty follow-ups. Its advantages over CT angiography include large volume acquisition with a single breath-hold and the generation of functional and hemodynamic data. It can also use simpler, more rapid image-reconstruction algorithms because unlike CT, MR images do not include bone and other calcified structures with signal intensities similar to that of blood vessel. However, MR angiography cannot be used on patients who have vascular stents, and the equipment needed to perform it is not widely available in Italy, particularly the more sophisticated MR scanners.

Color Doppler findings in chronic renal disease caused by nephroangiosclerosis and/or atheroembolic disease

The term *nephroangiosclerosis* is used to refer to the ischemic tubulo-interstitial damage caused by progressive loss of the interstitial and glomerular microarterioles. The pathogenesis of this disease is multifactorial [52], and it shows a predilection for the black race. A dominant role is undoubtedly played by arterial hypertension, including stabilized forms (benign nephrosclerosis) and those termed malignant or accelerated (malignant nephrosclerosis). Age, male sex, smoking, genetic background, metabolic disturbances (dyslipidemia, hyperuricemia, hyperhomocysteinemia), eating habits (high-salt diet), cocaine abuse, exposure to lead and cadmium, insulin-resistance, and hantavirus infections have all been implicated in the development of nephroangiosclerosis. The benign form mainly affects the tunica media, causing dystrophic remodelling of the vessel wall and narrowing of the lumen. The predominant lesion in malignant nephroangiosclerosis — as in other forms of vasculitis — is fibrinoid necrosis. Numerous observational studies have revealed vascular lesions like those of nephroangiosclerosis in the kidneys of patients who are completely normotensive. This observation has led some to hypothesize that nephroangiosclerosis is a primary renal disease and a cause rather than an effect of hypertension [52].

On B-mode ultrasonography, the nephroangiosclerotic kidney has an almost normal coronal diameter (approximately 9.5—10 cm), but the corticomedullary design is disrupted and the echogenicity is diffusely increased. Acquired cysts of various size and sclerolipomatosis of the renal sinus are frequent. On color Doppler, the PSV and DV of the paraostial and initial segments of the main renal arteries are not indicative of stenosis. The waveform complexes are characterized by a marked difference between the PSV and DV, which reproduces changes in the pulse pressure and reflects the marked, diffuse increases in vascular impedance (Fig. 15a—d). From the hemodynamic point of view, it is important to recall that accentuation of the pulsatile component of the spectral curve suggests reduction of the continuous flow as well as loss of *compliance* and reduction of the cross-sectional area of the vessels of the microcirculation. The latter alteration markedly increases vascular impedance and decreases overall renal blood flow [48]. Nephroangiosclerosis develops within an atherosclerotic *milieu, and it* is frequently associated with atherosclerotic involvement of the lumbar aorta. For this reason, it may well be associated with atheroembolic episodes favored by invasive procedures or use of anticoagulants.

Renal atheroembolic disease involves occlusion of small arteries by the release of cholesterol emboli resulting from the fragmentation of atheromatous plaques involving the walls of the aorta or one of its major branches. Detachment and fragmentation of these plaques can occur spontaneously or as a result of invasive diagnostic/therapeutic procedures and the use of anticoagulants. The kidney is the main target of these emboli owing to its anatomical proximity to the aorta and its rich blood supply. Atheroembolic kidney disease often remains unrecognized because it mainly strikes elderly subjects who are frequently poor candidates for a renal biopsy. It is reasonable to expect an increase in the frequency of this disease in coming years because invasive vascular procedures (endoprostheses, stenting) and thrombolytic therapy (e.g., for myocardial infarction) are being used in an increasing number of elderly patients with severe atheromatous disease of the aorta [53,54]. The acute injury produced by atheroembolism consists in localized ischemia resulting from the occlusion of small vessels (arcuate and interlobular arteries, microarterioles measuring 150—200 μm in diameter) associated with inflammation of the vessel wall. In experimental models, the initial inflammatory reaction (which develops within the first 24 h) characterized by polymorphonuclear cell infiltrates and eosinophilia is followed (48 h) by the arrival in the obstructed lumen of macrophages and multinucleated giant cells. Over time, the vessel wall undergoes endothelial proliferation and concentric fibrous thickening of the media and intimal layers. The ischemic damage is sustained by remodelling of the vessel wall and the persistent presence of cholesterol crystals within the lumen. Sclerohyalinosis of the glomeruli, tubular atrophy, and multiple areas of infarction cause various forms of CKD that are more or less progressive depending on the severity and frequency of atheroembolism and the amount of parenchyma affected.

From a morphological point of view there are no specific signs of this disease on B-Mode sonography, especially when

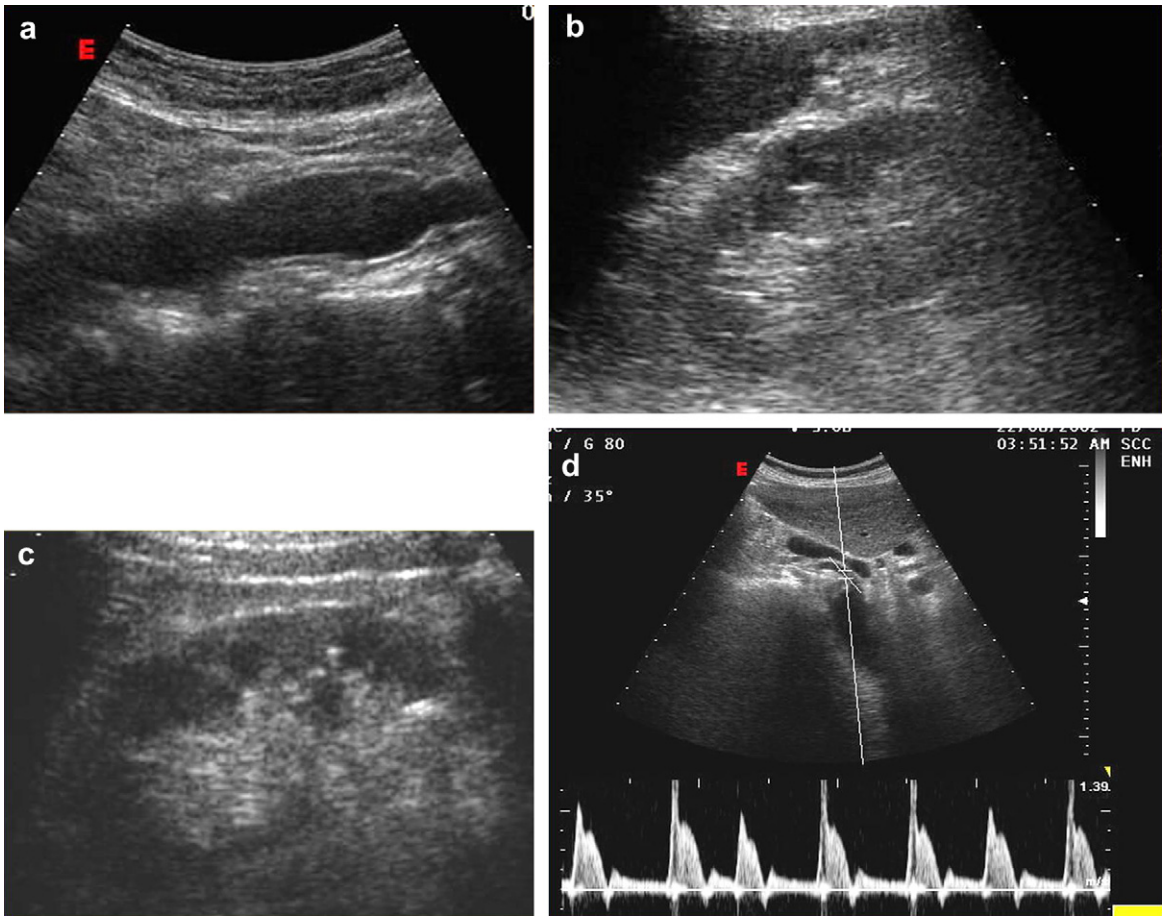

Fig. 15 Nephroangiosclerosis. *V*/*t* curve in the main renal artery. Seventy-four-year-old male with moderate hypertension and serum creatinine 2.3 mg/dL. The morphologic examination revealed sclerotic dilatation of the lumbar aorta (a), kidneys with diameters in the lower normal range (b, c), and mild sclerolipomatosis of the renal sinus. In the paraostial and initial segments of the main renal artery, the VPS and VD are not indicative of stenosis (60—70 cm/s). The velocitometric complexes show a marked systo-diastolic differential, which reflects marked diffuse increases in the parenchymal vascular impedance (d). RI in the interlobar arteries varied from 0.78 to 0.80.

the features of atheroembolism overlap with nephroangiosclerosis, age-related parenchymal damage, and senile diabetes. In general, morphologic examination of the aorta and large vessels in these cases reveals severe mixed atheromatosis characterized by flat or vegetating plaques with hyperechoic or mixed structures. The most common forms of atheroembolism are those occurring in patients with normal renal function subjected to invasive procedures or anticoagulant therapy. The structural aspects of the kidneys may be almost normal; the parenchyma hypoechoic or finely hyperechoic. The diagnosis is generally suggested by the patient history and confirmed by CD-PD studies, which in the acute phase reveal a diffusely hypoperfused kidney with pulsating cortical blushing caused by the markedly increased resistance. In these cases (as in those involving nephroangiosclerosis) the *V*/*t* curves for the main renal artery and the periphery are characterized by a dramatic drop in amplitude and a marked difference between systolic and diastolic flow velocities. The presence of an intraparenchymal RI $>$ 0.75—0.80 and eosinophilia in an elderly patient with atherosclerosis and rapidly deteriorating renal function who has recently undergone invasive vascular procedures or heparin treatment is highly suggestive of atheroembolism [55].

Conclusions

Color Doppler ultrasonography is a noninvasive imaging technique that is well tolerated and can be repeated as needed. It depicts the course of vessels and simplifies recording of the spectral curve, which is indispensable for quantitative analysis of a Doppler signal. In recent years, digital technology has been exploited to improve the sensitivity and accuracy of the Doppler examination, reducing its duration and the percentage of studies that are unsuccessful.

Color Doppler plays a primary role in the diagnosis and follow-up of the majority of renovascular diseases. It is used as a screening test for chronic ischemic disease caused by RAS or by atherosclerotic remodelling of the renal microcirculation. The most diagnostically relevant parameters are peak systolic and diastolic velocities, spectral dispersion, and the RAR. Comparative assessment of the

resistance indices (RI and PI) and the parvus-tardus sign is useful for determining whether a case should be managed conservatively or with stenting. Second-level studies are indispensable for treatment planning and morphological diagnoses. In the absence of RAS, an RI of >0.80 and a PI of >1.50 are indicative of nephroangiosclerosis and/or atheroembolism, i.e., they reflect increases in total impedance caused by remodelling of the microcirculation and reduction of the total cross-sectional area of the vessels with an increase in total peripheral resistance.

Conflict of interest statement

The authors have no conflict of interest.

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