Complementary Roles of Color-Flow Duplex Imaging and Intravascular Ultrasound in the Diagnosis of Renal Artery Fibromuscular Dysplasia

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OBJECTIVES

The purpose of this study was to compare color-flow duplex imaging (CFDI), intravascular ultrasound (IVUS), and renal arteriography in diagnosing renal artery (RA) fibromuscular dysplasia (FMD) and correlating with the hemodynamic response to balloon angioplasty (BA) in patients with drug-resistant hypertension.

BACKGROUND

Renal arteriography is generally regarded as the gold standard for diagnosing RA FMD. The observation that CFDI and IVUS depicted endoluminal abnormalities suggestive of RA FMD in some patients with normal renal arteriograms prompted comparison of these modalities in a consecutive series of patients.

METHODS

Twenty hypertensive patients with CFDI suggestive of RA FMD (mid-to-distal flow derangement and velocity augmentation) underwent renal arteriography, IVUS, and BA, with both immediate and long-term blood pressure (BP) response assessment.

RESULTS

All patients were women, aged 31 to 86 years (mean 62 years). On IVUS, various endoluminal defects (eccentric ridges; fluttering membranes; spiraling folds) were depicted at locations predicted by CFDI and were uniformly identified at sites where arteriography depicted classic evidence of FMD (8 patients). However, similar defects were detected by IVUS when angiography was borderline (7 patients) or normal (5 patients). Balloon angioplasty eliminated (16 patients) or reduced (4 patients) the IVUS findings and lowered systolic BP in all (mean reduction 53 mm Hg, \( p < 0.0001 \)). This reduction was maintained during follow-up of 4 to 22 (mean 13) months (mean reduction 44 mm Hg, \( p < 0.0001 \)), independent of baseline angiographic appearance.

CONCLUSIONS

Both CFDI and IVUS depict the blood flow and endoluminal abnormalities of RA FMD. Balloon angioplasty eliminates or improves IVUS findings and produces substantial, sustained BP reduction, an effect that is independent of baseline arteriographic appearance, calling into question the legitimacy of arteriography as the diagnostic gold standard. (J Am Coll Cardiol 2003;41:1305–11) © 2003 by the American College of Cardiology Foundation

Renal artery (RA) stenosis is an important cause or component of hypertension and can be a major factor contributing to renal insufficiency and failure. A number of factors, including growing availability of therapeutic options, increasing awareness, and the evolution of reliable noninvasive diagnostic tools, have led to an increase in screening for this diagnosis. Included among these noninvasive tests is color-flow duplex imaging (CFDI), which can depict high flow velocities, kidney size, anomalous RA origin, the presence of accessory RAs, renal cysts and masses, and the incidental presence of an abdominal aortic aneurysm (1). In addition, CFDI can indicate whether RA obstruction is localized to the ostial/proximal arterial segment (typical of atherosclerosis) or in the middle or distal segments (the distribution more typical of other causes, most commonly fibromuscular dysplasia [FMD]). Several patients with severe, drug-resistant hypertension were found to have CFDI abnormalities that, by their mid-to-distal location, suggested renal artery FMD, but subsequent renal angiography demonstrated normal or nearly normal RAs, rather than the classic beaded appearance typical of this disorder (2,3). Intravascular ultrasound (IVUS) is a method for detecting endoluminal and arterial wall anatomy which can be underestimated or even completely inapparent on angiography. Therefore, in an attempt to explain the CFDI abnormalities in hypertensive patients whose renal arteriograms were not classically abnormal, a consecutive series of patients with CFDI evidence of RA flow derangements suggestive of RA FMD and who underwent subsequent renal arteriography were also studied with RA IVUS, and the impact of balloon

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angioplasty (BA) on IVUS findings and blood pressure (BP) was assessed.

METHODS

From January 1998 to April 2000, twenty patients being screened for RA stenosis because of uncontrolled, drug-resistant, or new-onset hypertension were found by noninvasive ultrasound evaluation (CFDI) of their RAs to have abnormalities suggesting FMD. These abnormalities included high flow velocity, high flow velocity ratio relative to adjacent aortic flow velocity, and abnormal, nonlaminar flow patterns (such as aliasing and spiraling flow) localized to the middle and/or distal segments of the affected RA. All CFDI was performed in an ICALV (Intersocietal Commission for Accreditation of Vascular Laboratories)-certified laboratory by certified vascular sonographers using a curvilinear C5–2 MHz imaging probe as part of the HDI 5000 (Advanced Technology Laboratories, Bothell, Washington) cardiovascular ultrasound machine. Patients were imaged in the supine position with an average study time of about 40 min. Whereas, in the past, bowel gas or obesity would occasionally interfere with such an examination, newer imaging apparatus and the ability to image from multiple sonographic windows have nearly eliminated this obstacle to obtaining diagnostic studies. No patients undergoing RA ultrasound evaluation during the time course of patient acquisition in this series failed to have fully diagnostic studies, either because of bowel gas or body habitus. Routine evaluation included the following: 1) long and transverse views of the aorta with recording of peak mid-systolic blood flow velocity, and 2) two-dimensional views with color-flow and spectral Doppler interrogation of the origin, proximal, middle, and distal segments of the RA. Peak systolic velocities ≥200 cm/s and RA:aorta systolic flow velocity ratio ≥2.0 were the flow velocity criteria utilized to indicate hemodynamically significant FMD. In our laboratory, diastolic blood flow velocities have not been found to be helpful in evaluating these patients and were not utilized in this analysis. In general, however, greater weight was given to the qualitative appearance of blood flow derangement than to these numerical criteria.

Subsequently, these patients underwent selective renal arteriography with 6F internal mammary artery diagnostic catheters via a transfemoral approach. Contrast medium (Omnipaque) was injected selectively into each RA at the rate of 4 ml/s for 10 cc volume. Each RA was imaged in the standard anterior–posterior projection as well as the 10° to 20° right anterior oblique projection for the right RA and 10° to 20° left anterior oblique projection for the left RA, respectively, to minimize overlap of branches and to view the ostium clearly, without overlap of the adjacent aorta. In some patients, cranial and caudal angulations were also used when required to fully assess the arteriographic anatomy. Images were obtained with an Integris X-ray system (Phillips, Eindhoven, Holland) on 35-mm film at 15 frames/s and also stored in a digital archive. The arteriograms were reviewed by three cardiologists and assigned to one of three descriptive categories.

The first category (abnormal) was defined by the presence of classic arteriographic findings of FMD, namely a beaded appearance produced by multiple, eccentric, cleft-like stenoses appearing beyond the most proximal segment of the RA. The second category (normal) comprised those arteriograms with no evidence of FMD or other stenosis or luminal irregularity. The third category (borderline) was intermediate between these two and consisted of those angiograms that did not show the classic findings of FMD but were not entirely normal, such as mild luminal narrowing or mild scalloping of the lumen edge. Differences among interpreters (which were infrequent) were resolved by consensus. A specific evaluation of intraobserver variability was not undertaken. Inasmuch as all patients were included in this analysis on the basis of abnormal CFDI, none of the three angiographic interpreters were blinded to the general nature of the noninvasive test results, but the specific findings were not available at the time of arteriographic characterization.

All patients in this series underwent IVUS examination to assess for the presence of endoluminal abnormalities. All imaging was performed by the interventional cardiologist at the time of arteriography and angioplasty using a 3.2F 20–MHz Sonicath IVUS imaging catheter (Boston Scientific/Medi-Tech, Natick, Massachusetts). The IVUS findings were correlated with angiography and CFDI results. All patients then underwent balloon angioplasty at sites indicated by these imaging methods. In all cases, noncompliant balloon catheters (UltraThin Diamond, Boston Scientific/Medi-Tech) were used, the diameter chosen to exceed the normal reference segment by 0.5 to 1 mm. These balloon catheters were introduced into the artery through an 8F guiding catheter (Medtronic PK1 Renal Guide Catheter), and correct positioning of the balloon catheter was assessed by injection of contrast from the guide catheter. Following balloon dilation, IVUS and angiography were repeated to evaluate the impact of the angioplasty procedure on the ultrasound and arteriographic findings. Blood pressure was monitored over the next 12 to 24 h, and antihypertensive agents were revised, when appropriate, based on BP response before discharge from the hospital. Both BP and antihypertensive therapy were monitored over a follow-up interval ranging up to 22 months.
long-term group and individual BP responses were assessed using the Student t test and chi-square methods.

RESULTS

Data were reviewed on 20 consecutive patients being evaluated for drug-resistant or new-onset hypertension and having abnormal CFDI RA blood flow suggestive of FMD. All were women. Ages ranged from 31 to 86 years (mean 62 years). In the outpatient evaluation of these patients prior to angioplasty, systolic BP ranged from 138 to 240 mm Hg (mean 178 mm Hg). In all patients, the directly measured BP recorded at the time of the invasive procedure equaled or exceeded these outpatient BP recordings. Baseline creatinine level was normal (≤1.5 mg/dl) in all patients.

Before angioplasty, all patients were being treated with at least two (mean 2.6) antihypertensive medications (alpha-blockers, beta-blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, diuretics, and nitrates) (Table 1).

Patients were selected for invasive evaluation and treatment on the basis of abnormal CFDI suggestive of FMD. The flow abnormalities were localized to the middle segment of the artery in 14 patients and in the middle and distal segment of the artery in 6. Abnormalities were unilateral in 8 patients and bilateral in 12, consisting of normal, nonlaminar flow patterns including aliasing and spiraling flow as depicted by the color-flow pattern. These color-flow abnormalities were supplemented by spectral Doppler flow-velocity derangements indicative of RA obstruction, including augmentation of flow velocity at the site of disturbed flow on CFDI (1.8 to 7.3 m/s) and high flow velocity ratio relative to flow velocity in the adjacent aorta (> 3.5 in 10 RAs, between 2.5 and 3.5 in 14 RAs).

Renal arteriography was classic for FMD in only 8 patients. Among the remaining 12 patients, 7 had borderline angiographic abnormalities, and 5 had normal arteriograms. In all patients, IVUS demonstrated endoluminal abnormalities, including discrete, fixed, eccentric ridges; fluttering membranes; and/or spiraling longitudinal folds. These abnormalities were localized to those segments that were abnormal on CFDI, but they were uniformly absent in the proximal RA segments where CFDI indicated normal flow abnormalities were localized to the middle segment of the artery in 14 patients and in the middle and distal segment of the artery in 6. Abnormalities were unilateral in 8 patients and bilateral in 12, consisting of normal, nonlaminar flow patterns including aliasing and spiraling flow as depicted by the color-flow pattern. These color-flow abnormalities were supplemented by spectral Doppler flow-velocity derangements indicative of RA obstruction, including augmentation of flow velocity at the site of disturbed flow on CFDI (1.8 to 7.3 m/s) and high flow velocity ratio relative to flow velocity in the adjacent aorta (> 3.5 in 10 RAs, between 2.5 and 3.5 in 14 RAs).

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flow patterns. In all patients whose angiograms demonstrated the classic appearance of FMD, IVUS revealed these surface abnormalities, and CFDI demonstrated deranged blood flow patterns at the sites depicted angiographically (Fig. 1). However, in all patients with borderline or normal angiograms, IVUS identified qualitatively similar, and essentially indistinguishable, defects at sites predicted by CFDI (Figs. 2 and 3, respectively). In some patients whose contralateral RAs were normal or borderline and whose CFDI was normal, IVUS was performed and was uniformly normal (Fig. 4A). A typical IVUS image demonstrating discrete, fixed, eccentric ridges in a patient with FMD is shown in Figure 4B.

After BA, the defects identified by IVUS were completely eliminated in 16 patients and qualitatively improved in 4 (reduced number, length, and/or extension into the lumen). Although not all patients were subjected to CFDI after angioplasty, Figure 5 is an example of CFDI and flow velocities before and after treatment. Overnight, during the 12- to 24-h period after angioplasty, systolic BPs fell into the range of 90 to 180 mm Hg (mean 125 ± 22 mm Hg). The mean individual decrease in systolic pressure was 53 mm Hg (p < 0.0001), with all patients having had a drop of at least 30 mm Hg. After balloon angioplasty, the mean number of antihypertensive medications was reduced to 1.8.

DISCUSSION

About RA FMD. Renal artery stenosis is the most common cause of secondary hypertension and may be present in up to 10% of patients presenting with hypertension (4). By far, the most commonly reported etiology of RA stenosis is atherosclerosis, accounting for greater than 90% of diagnoses in most series. Atherosclerosis most commonly narrows the RA at the ostium and/or within its proximal segment. In contrast, FMD, representing the second most common cause of RA stenosis, is detected at an earlier age, affects women up to eight times more commonly than men, and generally spares the proximal RA, typically being localized in the middle and distal segments and occasionally extending into primary branches (5). Most often, it occurs in the absence of clinically apparent atherosclerosis, although these two lesions can coexist in the same RA. Renal artery FMD can also be accompanied by FMD in other medium-to-large arteries, most notably the internal carotid artery.

Harrison and McCormack (5) originally defined the classification system for FMD according to the layer of the arterial wall involved (intimal, medial, subadventitial fibroplasias, and fibromuscular hyperplasia). They noted that most adults present with medial dysplasia, and it is the dissection of this layer that leads to the complication and development of narrowing in the arterial lumen, thus predisposing to flow abnormalities. Histologically, medial fibroplasia appears as areas of thinned media and thickened fibromuscular ridges of collagen deposition without a lipid

Figure 2. (A) Right renal artery angiogram with subtle irregularities at the edges of the arterial lumen, producing a slightly scalloped appearance. (B) Transverse view at the level of the origin of the right renal artery showing laminar flow in the proximal segment (red), becoming turbulent in the middle segment, beginning with the first curve on the angiogram. (C) Intravascular ultrasound in the middle segment of the right renal artery, demonstrating a membrane (arrow). Ao = aorta.

Figure 3. (A) Normal left renal arteriogram. (B) Transverse view at the level of the left renal artery with normal flow proximally (blue) and a narrowing and turbulent flow (spiraling mosaic pattern) in the mid-portion. (C) Intravascular ultrasound demonstrating a membrane in the artery (arrow). Ao = aorta.
or inflammatory component. The internal elastic lamina is nonexistent. Angiographically, the “string of beads” appearance is seen (6). This classic appearance of FMD is the most common form, representing 85% of all recognized cases (7). These lesions are generally located in the distal two-thirds of the main RA and sometimes extend into the branches. The etiology of FMD is unknown (8,9).

**Diagnosis of RA stenosis.** Many screening tests are available for detecting RA stenosis, including measurement of plasma renin activity (10), captopril-stimulated plasma renin activity (11), nuclear renography (12), intravenous pyelography (13), magnetic resonance angiography (14), digital subtraction angiography (15), spiral computed tomographic (CT) imaging (16), and renal arteriography with renal vein renin sampling (13). The reported sensitivities and specificities range from 75% to 95%. In general, however, these detection methods have been evaluated in...
patients with atherosclerotic RA stenosis; they have not been validated as screening tools for RA FMD. The "gold standard" for the diagnosis of RA fibromuscular dysplasia is the classically abnormal renal arteriogram or a pathologic specimen (2).

Noninvasive imaging modalities available to identify FMD include duplex ultrasonography, contrast-enhanced magnetic resonance angiography (MRA), and spiral CT angiography. Leung et al. (14) evaluated 60 patients using duplex ultrasonography, contrast-enhanced MRA, and conventional angiography for diagnosing renovascular disease (including atherosclerosis and FMD). They reported 85% to 95% sensitivity and specificity in diagnosing RA stenosis with duplex ultrasonography and contrast-enhanced MRA versus angiography ("gold standard"). They noted that MRA was similar to conventional angiography in providing only an outline of the arterial lumen, which might not adequately depict FMD. They postulated that future improvements in MRA and cross-sectional reconstruction might be more helpful. Leung and colleagues also noted that duplex ultrasonography was able to provide arterial flow and hemodynamic information, which is not available with MRA.

In another study by Beregi et al. (16), the role of helical CT angiography was used to evaluate RA FMD. They evaluated 20 patients with conventional and helical CT angiography. Helical CT angiography using transverse sections and maximum-intensity projection reconstructions identified RA FMD but was limited by the difficulty in visualizing distal lesions. They concluded that conventional angiography with pressure measurements should be the gold standard to depict physiologically significant FMD.

**Study implications.** Our observations suggest that RA FMD may be more common than traditional diagnostic methodologies would suggest. The CFDI can indicate the functional significance of an RA stenosis by measuring blood flow velocity augmentation across the lesion (17). Although customary measures of severity, such as percent diameter stenosis, can, at least with atherosclerotic obstruction, be obtained more clearly with arteriography, it has been shown that hydraulic assessment is a better predictor of response to revascularization (16). Our findings further show that CFDI can suggest that FMD is the cause of renovascular hypertension by virtue of localizing flow disturbance beyond the proximal RA segment and depicting unusual flow patterns, most often spiraling, not usually seen in atherosclerotic obstruction, although such patterns can occur (in the proximal segment) with atherosclerosis in complex lesions such as tandem stenoses or serpigenous lumens. Finally, our observations call into question the traditional regard for renal arteriography as the gold standard for diagnosing RA FMD. Whereas in patients with classically abnormal arteriograms, CFDI and IVUS demonstrate confirmatory findings, qualitatively similar ultrasound observations can be made when angiography is borderline or even normal. Moreover, the effects of BA on BP and on IVUS abnormalities were, in this series of patients, independent of the appearance of the baseline arteriogram.

The seeming failure of conventional angiography to detect lumen surface abnormalities capable of detection with IVUS and whose flow-disturbing effects can be demonstrated with CFDI is not surprising. Though a space-occupying atherosclerotic obstruction is generally well demonstrated angiographically, very short, planar, cleft-like lesions can escape angiographic detection in all but one optimal view in which the cleft is parallel to the X-ray beam (15). It perhaps should not be surprising that the occasionally delicate, diaphanous, and membranous intimal folds so clearly seen on IVUS can escape angiographic detection when surrounded on both surfaces by contrast medium.

There are several limitations in these observations. The number of patients is small and represents a single-center experience. The series is defined by patients with CFDI suggesting nonproximal RA obstruction with certain patterns of flow derangement. The prevalence of similar IVUS findings in normal patients (normal BP, no CFDI evidence of RA stenosis of any type) or in patients with atherosclerotic RA stenosis is unknown, although there were no such findings in segments that appeared normal by CFDI and angiography in this series. However, the consistent finding of IVUS-depicted lumen surface abnormalities in locations of substantial flow derangement demonstrated by CFDI, coupled with their disappearance or reduction after BA, which produced a uniform BP improvement, independent of the renal arteriographic pattern, suggests that further exploration in larger numbers of patients is warranted.

**Conclusions.** The diagnosis of RA FMD has traditionally been made on the basis of a classic appearance on arteriography. The findings of this study indicate that FMD can be present when angiography is borderline or even normal. The use of CFDI can demonstrate RA flow patterns suggestive of FMD, and IVUS can depict the various luminal surface abnormalities representative of this disorder. These ultrasound imaging modalities correlate very closely with the BP response to angioplasty. The findings call into question the traditional regard for renal arteriography as the gold standard for diagnosing RA FMD, and they suggest that CFDI and IVUS should be studied further in larger numbers of patients and in multiple centers to define their role in the diagnosis of this disorder.

**IN MEMORIAM**

Dr. Manohar Gowda died in September 2002.

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