The long-term outcomes of percutaneous therapy for renal artery fibromuscular dysplasia

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Background: **Percutaneous intervention for symptomatic renal artery fibromuscular dysplasia (FMD) has replaced surgical therapy as first-line treatment. This study evaluates the factors that impact long-term anatomic and functional outcomes of endovascular therapy for symptomatic renal artery FMD.**

Methods: **Records of patients who underwent renal artery angioplasty for FMD between January 1990 and December 2007 were retrospectively analyzed. Indication for intervention was poorly controlled hypertension (diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg, or both, taking >2 antihypertensive medications). Twenty-nine women (average age, 45 years [range, 18-80]; 86% with a history of hypertension <8 years) underwent 38 attempted interventions. Sixty-six percent of contralateral kidneys were normal (31% had a ≤60% stenosis), 13% had >60% stenosis, and the remainder were nonfunctioning or absent. Creatinine was >1.5 mg/dL in 4%, 24% had hyperlipidemia, 17% had metabolic syndrome, and 4% were considered diabetic.**

Outcomes: **All interventions were successfully performed. Stent placement was required in 13% for technical failure and flow-limiting dissection. Seventy-three percent of these lesions were in the proximal renal artery, with the remainder in the middle renal artery. Technical success (<30% residual stenosis) was achieved in all vessels. There were no periprocedural or 90-day deaths. The procedurally related complication rate was 8%. Median follow-up was 2 years. All patients were alive at follow-up. Primary and assisted primary patency rates were 66% and 87% at 5 years. Restenosis was considered a 50% reduction in luminal area on angiography during follow-up. The restenosis rate was 28% at 5 years (10 vessels underwent repeat percutaneous intervention). Immediate clinical benefit was seen in hypertension in 72% (improved or cured ≤3 months) and was maintained in 73% at 5 years by life-table analysis. Proportional hazard analysis showed the predictors of long-term clinical benefit were duration of hypertension <8 years, creatinine <1.5 mg/dL, ipsilateral kidney size >9 cm, functional status of the contralateral kidney, a fasting blood glucose <110 mg/dL, triglycerides <150 mg/dL, and high-density lipoprotein >50 mg/dL. Neither age <50 years nor statin administration appeared significant.**

Conclusions: **Percutaneous endovascular intervention for clinically symptomatic FMD in the renal arteries is technically successful, safe, and durable. Most patients have immediate clinical benefit, with continued long-term results out to 5 years. It appears that the presence of existing renal pathology and markers of prediabetic state are associated with recurrence of hypertensive symptoms. (J Vasc Surg 2008;48:865-71.)**

Fibromuscular dysplasia (FMD) can result in significant hypertension in women aged between 15 and 50 years old but only accounts for <10% of cases of renovascular hypertension.[1] First described in 1938,[2] FMD frequently involves the distal main renal artery and its branches.[1] Medial fibroplasia represents the most common dysplastic lesion. Medial hyperplasia may be indistinguishable angiographically from intimal fibroplasia. Intimal fibroplasia occurs in <10% of patients with arterial fibrodysplasia. Adventitial (periarterial) hyperplasia is the rarest type of fibrodysplastic lesion.

Although FMD has been shown to affect multiple arterial beds, the frequency of involvement in renal arteries is 60% to 70%, with bilateral disease occurring in 35% of patients. The natural history of renal FMD is progression in up to 37% of patients,[3] but this progression only rarely results in occlusion of the renal artery.[4] Patients with FMD do demonstrate a significant decrease in mean cortical thickness and reduced renal length compared with similar patients with essential hypertension. As many as 63% of patients with FMD experience a loss of renal mass, but the incidence of renal failure remains remarkably low.[3,5] Renal artery atherosclerosis, in contrast, is a significant cause of progressive renal dysfunction leading to ischemic nephropathy and loss of functioning renal mass.[6]

The main impetus for the treatment of FMD is control of hypertension and its attendant complications. The treatment for most patients can be primarily managed medically. Revascularization is reserved for those patients who have recent onset of hypertension (<1 year), with the primary goal to cure the hypertension, those in whom blood pressure control has proved difficult, those intolerant of antihypertensive therapy, those who are not compliant with their antihypertensive medication, and those who have demonstrated a loss of renal volume leading to a diagnosis of ischemic nephropathy.[7]

The primary mode of intervention is by balloon angioplasty, with surgery reserved for recalcitrant lesions. Few

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reports, however, address the factors that affect the long-term durability or clinical effectiveness of percutaneous transluminal renal angioplasty (PTRA) for renal artery FMD. The purpose of this study is to evaluate the factors that influence the long-term anatomic and functional outcomes of endovascular therapy for symptomatic renal artery FMD.

METHODS

Study design. We performed a retrospective analysis of records from patients who underwent PTRA for all causes between January 1990 and December 2007, and those with FMD of the main renal artery were identified. Patients with aneurysmal disease and branch vessel disease were excluded. Indication for intervention was poorly controlled hypertension, defined as diastolic blood pressure (DBP) >90 mm Hg or systolic blood pressure (SBP) >140 mmHg, or both, taking >2 antihypertensive medications. For each patient, demographics, existing comorbid conditions, and risk factors for atherosclerosis were identified. Freedom from recurrent hypertension and factors influencing clinical benefit were measured.

Treatment algorithm. Patients with hypertension underwent a diagnostic study to identify the presence of renal artery stenosis. Procedures were performed within a service line, and interventionalists were drawn from vascular surgery, interventional cardiology, and interventional radiology. This diagnostic study consisted of standard angiography, magnetic resonance angiography (MRA), renal isotope scan, or duplex ultrasound (DUS) imaging. The DUS criteria to identify renal artery stenosis has been previously described.[8-10] Angiography was performed in the presence of clinical criteria as defined by Rundback et al[11] and a ≥60% stenosis on DUS or MRA or a positive renal scan.

The angiographic analysis was generally performed through a femoral or transaxillary approach. The lesions were crossed with a soft, atraumatic guidewire through an SOS Omni or Simmons catheter (Angiodynamics, Queensbury, NY). Balloon angioplasty was performed under systemic heparinization (40 to 60 U/kg intravenously), with the use of a 0.035-inch guidewire and 4- to 7-mm balloons. A balloon size 10% larger than the renal artery diameter was typically selected. Guiding catheters were used when extra support was deemed necessary. Primary stenting was not used in this series. Stenting was only used for technical failure and flow-limiting dissection.

Interventions were performed in patients with renal artery stenosis ≥50% by angiography, regardless of comorbidities. The treatment of patients not categorized into the clinical criteria referenced was managed medically. Nonfunctioning kidneys were not treated. In the presence of bilateral disease, the clinical criteria for treatment of both kidneys were the same as those for solitary renal artery stenosis. Bilateral >50% disease was treated at the same setting.

Patients were followed up at 6-month intervals after the procedure. Blood pressure, serum creatinine level, and number of antihypertensive medications were identified during these intervals. To assess postprocedural patency, each patient had at least one DUS study ≤1 month, a second at 6 months, and a DUS evaluation every 6 months thereafter. If the DUS showed ≥60% stenosis and the patient had recurrent symptoms of poorly controlled hypertension (DBP >90 mm Hg or SBP >140 mm Hg, or an increase in antihypertensive medications >2), angiography was performed and restenosis was treated if it was ≥50%. Median follow-up was 2 years (mean, 3.3; range 0.7-14.4 years) with a median of 4 DUS scans (range, 2-98 scans).

Definitions. The definitions used in the study are as follows:

- Coronary artery disease was defined as a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations.
- Cerebrovascular disease included a history of stroke, transient ischemic attack, or carotid artery revascularization.
- Hypercholesterolemia was defined as a fasting cholesterol level >200 mg/dL.
- Diabetes was defined as a fasting plasma glucose level >110 mg/dL or an HbA_{1c} >7%. Patients with diabetes were characterized as having insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus.
- Hypertension was defined as a SBP >140 mm Hg or DBP >90 mm Hg on three occasions during a 6-month period.
- Metabolic syndrome was defined as previously described,[12] consisting of insulin resistance or impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity, with the exception of abdominal circumference, which was not routinely recorded. We substituted a body mass index score ≥30.0 kg/m^2 as a positive score instead of an abdominal circumference >102 cm for men or >88 cm for women.
- An elevated serum creatinine level was defined as ≥1.5 mg/dL on two consecutive values during a 3-month period.
- Chronic renal insufficiency was defined as a persistent serum creatinine level >1.5 mg/dL for >6 months.
- Estimated glomerular filtration rate (eGFR) was defined as $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if African American). The baseline serum creatinine was the value recorded closest to the procedure.

Patients were considered to have a "nonfunctioning kidney" if any two of the following local criteria used at our institution during the study period were met: (1) a DUS scan identified a pole-to-pole length of <9 cm, with no renal flow in the main renal artery and parenchymal peak systolic velocity <10 cm/s, (2) surgically or congenitally absent kidney, or (3) no visible nephrogram on contrast arteriogram. The renal resistive index was defined from DUS imaging as (1 − [end diastolic velocity/peak systolic velocity]) × 100.

An endoluminal procedural success was a residual stenosis of <30%. Failures were residual stenosis ≥30%, by angiographic measurement, including lesions unable to be dilated or crossed, and occlusion ≤30 days. Restenosis was considered a 60% reduction in luminal area as determined by DUS imaging or a 50% reduction in luminal area as determined by angiography, or both, during follow-up. A death ≤30 days of the procedure was considered procedurally related.

Response in the hypertensive patient was defined as follows: "Cured" patients became normotensive after intervention (DBP <90 mm Hg and SBP <140 mm Hg) without medications. "Improved" patients became normotensive after intervention (DBP <90 mm Hg or SBP <140 mm Hg, or both) on the same (or reduced) number of medications, or had a DBP 15 mm Hg below baseline with the same or reduced number of medications. "No effect" patients had no change or did not meet these criteria for cure or improvement of presenting hypertension after intervention and were considered a treatment failure. For the purposes of this report, responders were patients in whom an improved or cured hypertension was demonstrated ≤3 months of intervention, and nonresponders were patients in whom no effect on their hypertension was demonstrated. Recurrence of hypertension was defined as a recurrence of DBP >90 mm Hg or SBP >140 mm Hg, or a >20% increase of postprocedural baseline DBP that was not treatable by repeat angioplasty.[11]

Statistical analysis. We performed our analysis on an intention-to-treat basis. Measured values are reported as percentages or means ± 1 standard deviation. Survival, cumulative patency, and clinical benefit rates are calculated using life-table analysis and reported using the Society for Vascular Surgery criteria. Standard errors are reported in life-table analyses. The log-rank test was used to determine differences between life tables. The Cox proportional hazards model was used for the time-dependent outcomes of death, patency, and long-term freedom from recurrent hypertension. The proportional hazards assumption was checked and confirmed for the significant covariates using log (-log [survival]) curves. Logistic regression models were used for outcomes measured shortly after the procedure, including complications and short-term clinical benefits. The dependence of each covariate on the outcome was first checked separately using the χ^2 test. Covariates with the significance level of $P \leq .10$ were included in the multivariate stepwise analysis.

RESULTS

Patient population. The study comprised 29 women who were a mean age of 45 years (range 18-80 years), with 69% were aged <50 years. A total of 38 interventions were attempted (9 were for bilateral lesions). A history of hypertension <8 years was present in 86%, 24% had hyperlipidemia, 17% had metabolic syndrome, 4% were considered diabetic, and 4% had a serum creatinine level >1.5 mg/dL (Table I). Sixty-six percent of contralateral kidneys were normal (31% had a ≤60% stenosis), 13% had >60% stenosis, and the remainder were nonfunctioning or absent (Table II).

Table I. Patients characteristics, indications, and comorbidities by response to treatment

Characteristics	*Response*	*No Response*	P
Patients, No.	21	8	. . .
Kidneys treated, No.	27	11	. . .
Bilateral disease, No.	6	3	. . .
Age			
Mean average ± SD, years	47 ± 16	43 ± 22	.02
<50 years, %	71	63	.09
Hypertension duration <8 years, %	86	63	<.05
Blood pressure, mean ± SD mm Hg			
Systolic	169 ± 20	180 ± 36	.2
Diastolic	92 ± 13	91 ± 14	.3
Antihypertensive drugs, mean ± SD	2 ± 1	3 ± 1	.5
Comorbidities, %			
Smoking history	19	13	.09
Diabetes mellitus	5	0	<.05
Hyperlipidemia	19	38	<.05
Metabolic syndrome	14	25	<.05
Cerebrovascular	10	13	.2
Creatinine >1.5 mg/dL	5	13	<.05
Hormone replacement therapy	10	8	.12
Metabolic syndrome variables, %			
Hypertension	100	100	
Body mass index >27 kg/m^2	28	13	<.05
Fasting blood glucose ≥110 mg/dL	19	25	<.05
HDL ≤50 mg/dL	13	35	<.05
Triglycerides ≤150 mg/dL	19	25	<.05

HDL, High-density lipoprotein; *SD,* standard deviation.

Immediate outcomes (<3 months). Of the 38 planned interventions, technical success, as defined by <30% residual stenosis on angiographic imaging, was achieved in all vessels; however, placement of a stent occurred in 13% because of technical failure and flow-limiting dissection. The proximal renal artery was the location for 73% of these lesions, with the remainder in the middle renal artery. No branch vessels of the main renal artery were treated. There were no periprocedural 30-day or 90-day deaths.

The procedure-related complication rate was 8%; all were minor and included one patient each with groin hematoma, groin pseudoaneurysm, and arteriovenous fistula. Hypertension was "improved" or "cured" ≤3 months of intervention in 72% of the patients (Table III). Significant differences were seen in the population of responders vs nonresponders in duration of hypertension (<8 years), presence of hyperlipidemia, worsening stage of chronic kidney disease, smaller ipsilateral kidney, contralateral renal artery stenosis (>50%), and bilateral higher resistive indices within the kidney (Tables I and II). These factors all correlated with response. When we specifically looked at metabolic syndrome as a discrete variable, it was not signif-

Table II. Kidney disease, functional parameters, and ipsilateral and contralateral variables according to response to treatment

Variable	*Response*	*No response*	P
Kidney stage, %			
1 (eGFR ≥90[a])	29	38	.1
2 (eGFR 60-89[a])	52	25	<.05
3 (eGFR 30-59[a])	19	25	<.05
4 (eGFR 15-29[a])	0	13	<.05
5 (eGFR <15[a] or dialysis)	0	0	
Functional parameters			
Creatinine, mean ± SD mg/dL	0.9 ± 0.01	1.3 ± 0.1	<.05
eGFR, mean ± SD[a]	78.0 ± 1.1	74.6 ± 4.3	
eGFR <30[a], %	0	13	<.05
eGFR 30-60[a], %	24	12	<.05
eGFR >60[a], %	76	75	.2
Ipsilateral kidney variables			
Kidney size, mean ± SD cm	10.4 ± 0.04	9.7 ± 0.05	<.05
Resistive index, mean ± SD	0.65 ± 0.004	0.70 ± 0.01	<.05
Contralateral kidney anatomy, %			
Normal	71	50	<.05
Stenosis (>60%)	19	50	<.05
Nonfunctioning	10	0	<.05
Contralateral kidney variables			
Kidney size, mean ± SD cm	9.6 ± 0.02	9.6 ± 0.1	.3
Resistive index, mean ± SD	0.66 ± 0.005	0.68 ± 0.01	<.05

eGFR, Estimated glomerular filtration rate; *SD*, standard deviation.
[a]The eGFR is calculated as mL/min/1.73 m^2.

Table III. Outcomes according to response to treatment

Outcome	*Response*	*No response*	P
Immediate clinical benefit, %			
Deterioration	0	0	
No Change	0	100	<.05
Improved	81	0	<.05
Cured	19	0	<.05
Long-term outcomes, %			
Vessel occlusion	0	38	<.05
Vessel restenosis	14	13	.2
Absolute recurrence	14	25	<.05
Ipsilateral reintervention	14	13	.2

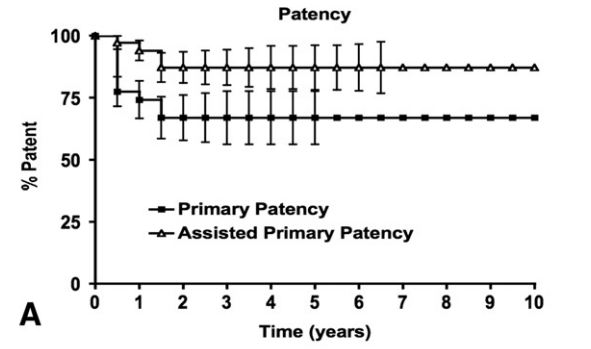
icantly associated with poor outcomes when all-comers were identified; however, when the group was stratified, more patients in the nonresponder group were diagnosed as having metabolic syndrome, and the predominant features were abnormal fasting blood glucose, low high-density lipoprotein (HDL), and elevated triglycerides (Table I).

Outcomes (>3 months). All patients were alive at follow-up. No chronic renal impairment developed during follow-up. Primary and assisted primary patency rates determined by serial DUS imaging were 66% and 87% at 5 years (Fig, *A*). Assisted primary and secondary patency rates were equal (Fig, *A*). The restenosis rate was 28% at 5 years (Fig, *B*). Stent placement did not influence patency, restenosis, or symptom recurrence. Ten vessels underwent repeat percutaneous intervention for recurrent symptoms. Reintervention by balloon angioplasty for restenosis in those patients with recurrent symptoms, defined as poorly controlled hypertension (DBP >90 mm Hg or SBP >140 mm Hg or an increase in antihypertensive medications of >2), was successful in all cases.

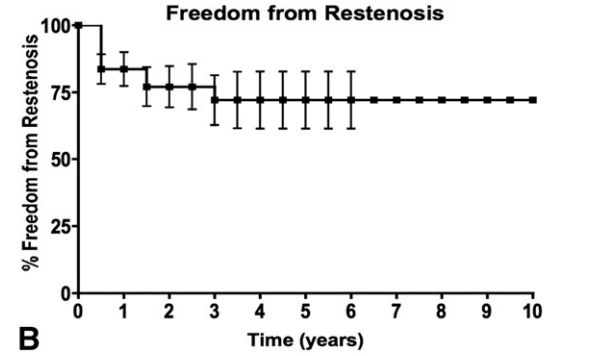
Development of restenosis was associated with low HDL levels (≤50 mg/dL, female; relative risk [RR], 2.35; 95% confidence interval [CI], 1.32-4.52; $P = .004$); elevated triglycerides levels (≥150 mg\dL; RR, 2.2; 95% CI, 1.84-2.86; $P = .004$); eGFR <30 mL/min/1.73 m^2 (RR, 1.74; 95% CI, 1.09-3.24; $P = .004$); and age >55 years (RR, 2.78 (95% CI, 1.51-131.50; $P < .003$).

In response to therapy, 72% of patients demonstrated immediate clinical benefit, with improved or cured hypertension ≤3 months of procedure. This clinical benefit was maintained in 71% ± 9% of patients at 5 years by life-table analysis (Fig, *C*). When only those patients who demonstrated immediate clinical benefit were analyzed, clinical benefit was maintained in 73% ± 9% at 5 years by life-table analysis. A significant relationship was found between the presence of restenosis and loss of clinical benefit (odds ratio, 0.008; 95% CI 0.0004-0.167; $P < .0001$). Angiographically significant restenosis was found in only 64% of patients with recurrent symptoms (odds ratio, 0.0084; 95% CI, 0.0004-0.1658). We did not encounter any patients with asymptomatic restenosis during follow-up.

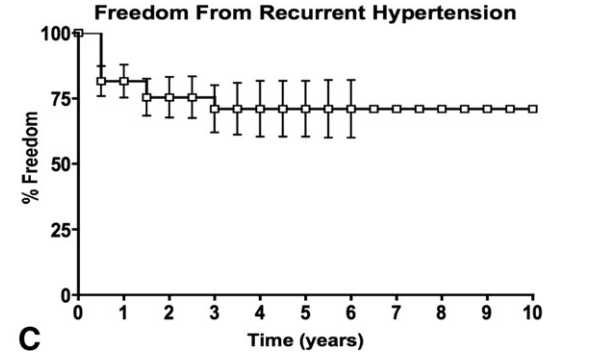
Proportional hazard analysis showed the predictors of long-term clinical benefit were duration of hypertension <8 years (RR, 1.23; 95% CI, 1.01-2.98, $P = .02$), eGFR >60 mL/min/1.73 m^2 (RR, 26.5; 95% CI, 18.1-34.5, $P = .01$), ipsilateral kidney size >9 cm (RR, 1.41; 95% CI, 1.1-3.3; $P = 0.03$), status of the contralateral kidney (RR, 1.53; 95% CI, 1.1-1.96, $P = .04$), a fasting blood glucose <110 mg/dL (RR 1.53, 95% CI 1.17-2.34, $P = .04$),



Years	0	1	2	3	4	5	6	7	8	9	10
Primary	38	25	18	13	10	10	9	7	2	2	2
Assisted	38	32	25	19	13	12	11	7	2	2	2



Years	0	1	2	3	4	5	6	7	8	9	10
Restenosis	38	29	23	17	12	12	11	9	3	3	3



Years	0	1	2	3	4	5	6	7	8	9	10
Symptoms	38	31	23	18	12	12	12	9	7	3	3

Fig. A, Life-table analysis of primary and assisted primary patency of the renal vessels intervened on for symptomatic fibromuscular dysplasia. **B,** Life-table analysis of freedom from restenosis. **C,** Life-table analysis of freedom from recurrent hypertension. Recurrence was defined as a recurrence of diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg or a >20% increase of postprocedural baseline diastolic blood pressure that was not treatable by repeat angioplasty. Values are mean ± standard error of the mean. The number at risk at each time interval is shown below each figure.

triglycerides <150 mg/dL (RR 6.67, 95% CI 1.86-10.03, $P = .004$), and HDL >50 mg/dL (RR 3.89, 95% CI 2.12-6.39, $P = .024$); the latter three are markers of the prediabetic state and associated with metabolic syndrome. Neither age <50 years nor administration of statins appeared to be significant. Categorization of the status of the contralateral kidney by occlusion of the renal artery vs surgically absent kidney did not influence freedom from recurrent symptoms.

DISCUSSION

PTRA has become the treatment of choice for patients with renal artery FMD limited to the main renal artery.[3] Most these patients have medial fibroplasia. In the current cohort of patients with FMD and hypertension, PTRA was technically successful and was associated with no major complications and a low morbidity rate. There was a 100% technical success rate, whereas published reports indicate technical success rates for PTRA in these circumstances of 83% to 100%.[13-19] Success rates with open revascularization are 89% to 97%. No anatomic injuries or acute functional injuries occurred. In contrast with the FMD population, acute functional injury, defined as a persistent increase in the serum creatinine level of ≥0.5 mg/dL at 1 month after the procedure, associated with atheroembolism during renal intervention for atherosclerotic disease, is now recognized as an important clinical problem.[20-22] Patient survival in this cohort was 100% during follow-up, no new patients developed chronic renal impairment, and those with a pre-existing serum creatinine level >1.5 mg/dL did not demonstrate worsening of renal function.

We had a 100% technical success rate after intervention according to angiographic criteria. One caveat on this result should be mentioned. Currently, many authors now recommend that because the degree of stenosis associated with FMD cannot always be estimated by angiographic appearance alone, translesional pressure measurements or immediate postprocedural duplex sonography, or both, should be performed to better describe technical success.

The current study showed a cumulative patency rate 87% at 5 years. Restenosis developed in 14% of the vessels, with an actuarial restenosis rate of 28% at 5 years. Reintervention by balloon angioplasty for restenosis was successful in all cases. Reported restenosis rates after PTRA for FMD are 7% to 27%.[13-19] Clinical factors associated with restenosis after initial PTRA, include increased body mass index and duration and degree of hypertension.[23] We did not identify either factor as a significant variable in the development of restenosis.

Oertle et al[24] have shown that about one-third of patients treated by PTRA for FMD who subsequently return during follow-up with deterioration of or recurrent arterial hypertension have no angiographic demonstrable restenosis, whereas 15% of patients without deterioration of or recurrent arterial hypertension have angiographic demonstrable restenosis. Our data confirmed that approximately one-third of patients with recurrent symptoms do not demonstrate restenosis and that the presence of restenosis in asymptomatic patients is very low. However, the

relatively high rate of occlusion in the nonresponders should prompt early reimaging of the renal vessel and should prompt more frequent duplex imaging.

Diabetes and insulin resistance have been shown to be independent predictors of early restenosis after coronary stenting.[25-28] In the current study, dyslipidemia (low HDL and high triglyceride levels), low eGFR (<30 mL/min/1.73 m^2), and patients aged >55 years were factors associated with the development of restenosis.

The clinical success, defined as cured or improved hypertension after PTRA, was 72%. Hypertension cure rates of 14% to 59% and hypertension improvement rates of 21% to 63% have been reported.[13-19] The incidence of "no effect" with endoluminal intervention ranges from 7% to 30%.[3] With open surgery, cure of hypertension can be obtained in 33% to 63% of patients, with improvements in hypertension noted in 24% to 57%. The incidence of failure (ie, "no effect" on hypertension) is 3% to 33%. Successful outcome appears to be associated with an age <50 years, the absence of associated coronary and carotid stenosis, and duration of hypertension of <8 years. In the current study, we identified the duration of hypertension as a significant factor related to successful outcome. However, we also identified an association with decreased long-term clinical benefit and a cluster of variables associated with prediabetic state, including fasting blood glucose >110 mg/dL, triglycerides >150 mg/dL, and HDL ≤50 mg/dL. This is a novel finding. An important finding in this cohort was that statin therapy did not influence outcomes.

These data would suggest that surveillance for and aggressive correction of both the prediabetic state and dyslipidemic should be considered in patients presenting with symptomatic FMD. There are limitations to the current study. The patient number is relatively small but does represent one of the largest series in the literature. We only treated main renal artery disease and did not include patients with branch vessel disease.

CONCLUSION

Percutaneous endovascular intervention for clinically symptomatic FMD in the main renal artery is technically successful and safe. There are excellent cumulative patency and low restenosis rates. Most patients experience an immediate clinical benefit, with continued long-term results in >70%. It appears that the presence of existing renal pathology and markers of prediabetic state are associated with restenosis and with recurrence of hypertensive symptoms.

AUTHOR CONTRIBUTIONS

Conception and design: MD
Analysis and interpretation: WS, MD
Data collection: EP, IM, JN, WS, AL, MD
Writing the article: WS, AL, MD
Critical revision of the article: EP, IM, JN, WS, AL, MD
Final approval of the article: EP, IM, JN, WS, AL, MD
Statistical analysis: WS, MD
Obtained funding: MD
Overall responsibility: MD

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