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**Insights from Intravascular Pressure Measurement of Renal Artery Revascularization in Patients with Fibromuscular Dysplasia: the DYSART Study.**

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## ABSTRACT

**Introduction:** The indication of percutaneous renal transluminal angioplasty (PTRA) in fibromuscular dysplasia (FMD) is mainly based on renal artery stenosis (RAS) due to atherosclerosis criteria, which are not specific to FMD. Consequently, the selection of patients who could benefit from this treatment and its effectiveness remain uncertain. The aims of this study were to 1) report the effects of PTRA guided by transstenotic pressure measurements on hypertension 7 months after treatment, 2) assess the impact of pressure measurement to guide treatment efficacy in comparison to visual angiographic parameters, and 3) evaluate the reproducibility and accuracy of the stenosis measurement using a 4F catheter in comparison to a pressure guidewire.

**Methods:** This prospective multicentric study analyzed 24 patients with hypertension with RAS due to FMD that required PTRA. Clinical, duplex ultrasound (DUS) and angiographic indices were collected, and patients were followed up for 7 months ( $\pm 1$  month). Angiographic indices were measured twice both by a pressure guidewire and a 4F catheter. Assessment of procedural and clinical success of angioplasty was performed for all patients.

**Results:** Twenty-three patients (96%) had procedural success (considered as a post-PTRA translesional systolic gradient  $\leq 10$  mmHg or reduced by at least 80%) with a significant decrease in the systolic gradient after angioplasty (26.50 mmHg [16.75-38.75] vs. 0.00 [0.00-2.00],  $p < 0.01$ ). Three patients (12%) had complications, including two renal artery dissections and one partial renal infarction. Twenty-one patients (88%) were clinical responders to angioplasty at follow-up. Visual stenosis assessment showed a poor correlation with systolic gradient measurement before and after PTRA (R from -0.05 to 0.41,  $p = 0.06-0.82$ ). High correlations were found between pressure measurements made by a 4F catheter and guidewire (R from 0.64 to 0.89  $p \leq 0.003$ ).

**Conclusions:** In patients selected by clinical indicators and DUS, reaching a translesional systolic gradient  $\leq 10$ mmHg or reduced by at least 80% after angioplasty, promotes a high success rate for PTRA in hypertension due to FMD RAS.

**Clinical Relevance:** In the selected population, PTRA guided by transstenotic pressure showed a beneficial effect on hypertension management in 88% of patients with initial transstenotic gradient. Assessment of systolic gradient measurement is more reliable than visual stenosis assessment for guiding PTRA. Transstenotic pressure assessment using a 4F catheter is reproducible and highly correlated with assessments made through a pressure guidewire.

## **ABBREVIATIONS AND ACRONYMS**

DBP: diastolic blood pressure

DUS: duplex ultrasonography

FMD: fibromuscular dysplasia

MDCT: Multidetector CT-scan

Pa: aortic pressure

Pd: distal renal pressure

PTRA: percutaneous renal transluminal angioplasty

RAS: renal artery stenosis

SBP: systolic blood pressure

**KEYWORDS** : Renal Artery Obstruction; Hypertension, Renovascular; Fibromuscular  
Dysplasia.

## INTRODUCTION

Fibromuscular dysplasia (FMD) is a rare idiopathic systemic noninflammatory arterial disease that mainly affects renal and carotid arteries and causes stenosis, aneurysm, tortuosity or dissection. Symptomatic renal artery FMD is responsible for renovascular hypertension through stenosis, and its prevalence is approximately 4/1000, affecting mainly young women<sup>1</sup>.

Historically, FMD was distinguished on its histological appearance with the medial FMD being the most common (over 90% of all cases) compared to the intimal and adventitial types. Recent consensus moved from an histological to an angiographic classification, recognizing only focal and multifocal FMD, with medial FMD being the latter<sup>2</sup>.

To date, there is no consensus for defining renal artery stenosis (RAS) severity in FMD, and the diagnosis and treatment of RAS in FMD are based by default on what is known for atherosclerotic RAS<sup>2,3</sup>. The use of intravascular pressure measurements has been promoted for quantification of stenosis severity in atherosclerotic RAS because of low performance of angiographic assessment<sup>4</sup>. There is very sparse data on the subject for multifocal FMD, but the American Heart Association specifies that, due to an impossibility of visual angiographic assessment, the pressure gradient might be recorded<sup>2</sup>.

The transstenotic pressure measurement is considered as the reference for hemodynamic significant RAS, with a ratio of distal renal pressure (Pd) to aortic pressure (Pa)  $<0.90$  proposed as a threshold for defining a significant RAS, since it is associated with a release of renin<sup>5</sup>. The use of a 0.014" pressure guidewire is thought to provide more reliable assessment of stenosis significance<sup>6</sup>, but pressure guidewires require specific equipment for measurements, are expensive and not broadly available. Transstenotic pressure measurement could also be performed using a 4F catheter across the lesion<sup>7</sup>. However, a 4F catheter in a stenotic renal artery could result in an overestimation of the stenosis depending on its degree.

Despite sparse data specifically dedicated to FMD, percutaneous transluminal renal angioplasty (PTRA) effectively treats renal symptomatic FMD with a rate of hypertension cure of 36% and a 12% complication rate<sup>8</sup>. The hypothesis of the present paper is that in a selected FMD patient population based on Doppler ultrasonography (DUS) and clinical parameters, PTRA technical success guided by transstenotic pressure measurement should provide better results on arterial hypertension and subsequently be more precise in selecting whom to treat or not.

The objectives of the study were to 1) report the results of PTRA guided by transstenotic pressure measurements in hypertension in FMD patients, 2) assess the discrepancies between pressure measurement and visual angiographic parameters for the assessment of stenosis severity in FMD, and 3) evaluate the reproducibility and accuracy of the stenosis measurement using a 4F catheter in comparison to a pressure guidewire.



## **METHODS**

### **Patient population and study protocol**

This prospective multicenter study was approved by a national ethical committee. All patients were aware of the protocol, and gave informed consent (NCT02586870; 2015-A01244-45).

Patient recruitment was performed in four national reference centers for hypertension with expertise in FMD. All patients were recruited between November 2015 and August 2019.

The inclusion criteria were (1) arterial hypertension (mean daytime systolic blood pressure, SBP  $\geq 135$  mmHg and/or diastolic blood pressure, DBP  $\geq 85$  mmHg as measured by a 24-hour ambulatory blood pressure measurement)<sup>9</sup> and (2) the presence of an RAS due to multifocal FMD of the main renal artery or accessory artery with a diameter  $\geq 5$  mm (defined using CT scan or DUS). Patients required renal angioplasty based on (i) recent onset of hypertension, (ii) resistant hypertension (hypertension treated with three antihypertensive drugs including one diuretic), (iii) poor compliance with medications or medication side effects, (iv) acute flash pulmonary edema, and (v) delayed onset of hypertension with a kidney size decrease or recent renal failure onset, especially after a renin-angiotensin system blocker.

The exclusion criteria were (i) patients with other causes of secondary hypertension (secreting tumor, adrenal gland hyperplasia, adrenal adenoma), (ii) patients with RAS from other causes, (iii) patients with focal FMD, (iv) patients with multifocal FMD of an accessory renal artery with a diameter  $< 5$  mm, (v) patients with involvement of a main renal artery collateral, (vi) patients with a stent in one renal artery, (vii) patients with renal artery dissection, (viii) patients with an aneurysm with a diameter more than twice the diameter of the concerned artery or aortic aneurysm  $> 45$  mm, (ix) patients with severe aortic atheroma, (x) patients in whom it was impossible to perform invasive pressure measurements, (xi) patients with a severe contrast media

allergy, (xii) patients with creatinine clearance MDRD  $< 40$  ml/min/1.73 m<sup>2</sup>, and (xiii) patients who were pregnant or breastfeeding.

### **Color duplex ultrasound**

DUS was performed in all patients prior to angiography using a commercial echography unit (Philips® Epic 5C X and IU22 MATRIX) with a 3.5 MHz transducer. All DUS was performed by the same experimental operator at each site. Images were acquired in the supine and lateral positions. Kidneys sizes were reported. The resistive index (RI) and systolic ascension time (SAT) were measured at the site of the RAS. After Doppler angle correction, peak systolic velocity (PSV), in the aorta and at the site of the stenosis, end-diastolic velocity (EDV) was measured to calculate the renal aortic ratio (RAR, ratio of PSV in aorta and PSV at the stenosis site) and the renal renal ratio (RRR, ratio of PSV at the proximal or mid segment of the renal artery and PSV at the distal segment of the renal artery). Assessment of velocity and all Doppler criteria were performed on the main artery and on the accessory renal artery with a diameter  $>5$  mm. Duplex studies were considered diagnostic if the entire renal artery was interrogated by velocity waveform analysis. All procedures were uploaded on a CD, allowing a centralized reading.

### **Multidetector CT-scan (MDCT)**

MDCT was performed prior to angiography using a commercial CT unit (Revolution EVO, GE Healthcare, Chicago, USA). CT angiography scans were performed after the administration of a bolus of 1 cc/kg of a nonionic contrast medium flushed with a bolus of 30 cc of a saline solution. The acquisition parameters were slice thickness=0.6 mm, pitch=1.3, reconstruction slice thickness=0.6 mm, peak voltage=120 kV, and automatic modulation of mAs. All MDCT interpretations were made by the same experimental radiologist at each site. Bilaterally, the

number of renal arteries, the diameter of the renal artery 10 mm after the ostium, which was considered the reference diameter of the renal artery, the maximal diameter of the renal artery, the stenosis percentage and involvement of collateral renal arteries by FMD were reported.

### **Renal angiography**

Renal angiography was performed by femoral access through a 6-F introducer sheath (Radiofocus® introducer II, Terumo, Tokyo, Japan). Quantitative renal angiography (QRA) was obtained by selective injection of 5-10 ml of contrast medium through a 6F-guiding catheter (RDC1, Cardinal Health, Dublin, Ireland). All procedures were performed by the same experimental operator at each site (A.J., M.S., F.T., H.R.). The number of renal arteries and involvement of the collateral artery were reported. No software was used for the percent diameter stenosis (DS) determination, which was visually graded by the operator in charge of the PTR, not blinded to his pressure measurements. All QRA acquisitions were uploaded on a CD for a centralized reading within one week after the exam to assess image quality.

### **Invasive renal pressure measurement**

Transstenotic pressure measurement was performed with a pressure guidewire, which was a 0.014" guidewire implemented with a pressure sensor (Verrata, Volcano, Rancho Cordova, CA, USA). Pa was measured through a guiding catheter, while Pd was assessed using the pressure guidewire advanced in a distal branch of the renal artery. Systolic, diastolic and mean pressures (Pa and Pd) were recorded. Systolic and mean gradients as well as Pd/Pa systolic and mean ratios were computed. All measurements were obtained under resting conditions (no pharmacologically induced hyperemia) twice and were obtained for the side requiring revascularization but also for the contralateral side. In addition, pressure measurements were realized using a 4F catheter (Cobra 2, Glidecath, Terumo Leuven, Belgium) positioned on the 0.014" pressure guidewire.

Pressure assessments were performed with the 0.014” pressure guidewire left in place to avoid recurrent catheterization of a diseased artery. 4F catheter measurements were performed twice to assess the reproducibility of the technique only on the side requiring angioplasty. PTRAs were performed with a monorail balloon (Ultra-soft SV, Boston Scientific, Natick, USA). The size of the balloon was selected based on the artery size on CT-scan. Procedural success was defined as a post angioplasty translesional systolic gradient  $P_d - P_a \leq 10 \text{ mmHg}^2$  or a reduction in systolic gradient by at least 80%. After the first angioplasty in case of procedural failure, a second PTRAs were performed with a balloon 0.5 mm larger than the first. In case of a second failure, the operator kept the right to decide to perform another angioplasty with a larger balloon or to stop the procedure. All per-procedure complications were reported.

### **Clinical outcomes after angioplasty**

All patients were followed up for seven months ( $\pm$ one month) after angioplasty. Technical results and clinical outcomes of angioplasty were recorded in all patients. SBP, DBP, clearance creatinine (assessed by the MDRD equation), antihypertensive medication number, dose and type were recorded before and at follow-up. Patients were considered responders to angioplasty if at follow-up, mean day time DBP was  $<85 \text{ mmHg}$  and/or SBP was  $<135 \text{ mmHg}$  on 24-h measurement on the same or a reduced number of medications (or reduced number of defined daily doses)<sup>9</sup> or a DBP was reduced by at least 15 mmHg on the same or a reduced number of medications<sup>10</sup>. Patients were considered cured if DBP was  $<85 \text{ mmHg}$  and SBP was  $<135 \text{ mmHg}$  at the 24-h measurement without antihypertensive medication.

### **Statistical analysis**

Statistical analyses were performed with R software (Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 7.0 (GraphPad Software, Inc., San Diego, CA), and all testing was based on a 2-sided  $\alpha=0.05$  significance level. Quantitative variables are presented as

the mean  $\pm$  SD or median and interquartile range depending on the distribution normality, and qualitative variables as the number of patients and percentages. Continuous variables were analyzed by Student's t-test or the Mann-Whitney U test, and categorical variables were compared using the chi-square test or Fisher's exact test. To evaluate the impact of pressure guidewire measurements to guide treatment over visual stenosis assessment, correlation analysis was conducted between visual stenosis measurements and invasive pressure using either Pearson's r or Spearman's rho as appropriate. The intraobserver reliability for angiographic measurements was assessed using the intraclass correlation coefficient (ICC). The relationships between the measurements made through the pressure guidewire and 4F catheter were assessed using either Pearson's r or Spearman's rho, as appropriate for correlation testing, and Bland-Altman plots (plots of the differences between measurements against the mean).

## RESULTS

### Study population

A total of 31 patients were selected for the study. Five of them did not undergo angioplasty: one because of a withdrawal of consent before angiography, one secondary to material dysfunction, two because of bilateral stenosis and one because of renal artery aneurysm, resulting in the initial inclusion of 26 patients in the study. Two patients (8%) were lost to follow-up. Ultimately, a total of 24 patients were analyzed for outcomes (**Figure 1**). Characteristics of the studied population are presented in **Table I**. All of the patients analyzed underwent angioplasty (**Figure 2**). Among them, three patients (12%) had complications, including two renal artery dissections and one partial renal infarction.

### Angioplasty outcome

Procedural success was achieved in 23 patients (96%) with a median residual visual stenosis of 0.00% (0.00-40.00) and a median postprocedural transstenotic systolic gradient of 0.00 mmHg (0.00-2.00). Evolutions of angiographic indices before and after PTRAs are presented in **Table II**. All patients had a gradient decrease after PTRAs. The pre-PTRA systolic gradient was significantly higher (26.50 mmHg [16.75-38.75]) than the post-PTRA one (0.00 mmHg [0.00-2.00];  $p < 0.001$ ). The mean diameter of the treated renal artery measured on CT-scan was  $5.98 \pm 0.98$  mm. The mean diameter of the first balloon used was  $6.50 \pm 0.87$  mm. The systolic gradient measured after the first angioplasty was 5.00 (3.50-12.00) mmHg. Six patients (25%) underwent a second angioplasty based on the presence of a residual gradient measured with a pressure guidewire. The mean diameter of the second balloon was  $6.17 \pm 0.75$  cm. In one patient, the procedure was stopped by the operator despite the presence of a residual transstenotic gradient (17 mmHg) after 2 successive angioplasties using balloons with crescent diameters.

### **Clinical outcome: responders vs. nonresponders**

After angioplasty, 21 patients (88%) were responders to angioplasty, and 3 (12%) were nonresponders. The differences between responder and nonresponder characteristics are presented in **Table III**. Responders and nonresponders had a mean renal PSV of  $387.50 \pm 106.06$  cm/s vs.  $233.70 \pm 133.00$ , a mean IR of  $0.53 \pm 0.10$  vs.  $0.63 \pm 0.09$ , and a mean RAR of  $4.69 \pm 1.63$  vs.  $3.04 \pm 1.63$ , respectively. Among the 21 responders, 6 patients (29%) were cured of hypertension off antihypertensive medication, and the remaining (71%) had a decrease in BP measures with the same treatment or a decrease in the number and/or daily dose of antihypertensive medications. The three patients who experienced a complication during PTRAs were responders to PTRAs. The DUS criteria of the nonresponder patients are presented in **Supplemental Table I**. One of the nonresponders maintained an increased renal PSV (292 cm/s after PTRAs vs. 367 cm/s before PTRAs) and RAR (3.01 after PTRAs vs. 4.47 before PTRAs) and a decreased IR (0.55 after PTRAs vs. 0.53 before PTRAs) at follow-up, even though she had a procedural success with PTRAs.

### **Visual angiography assessment vs. pressure measurements**

Gradient measurements and angiographic visual assessment of the degree of the RAS did not show a significant correlation before and after PTRAs (R ranging from -0.05 to 0.41,  $p=0.06-0.82$ ) (**Figure 3**). Interestingly, the correlation between gradient measurements and visual stenosis assessment was worse for the post-PTRAs assessment, with no correlation between these two indices (R= -0.05 [-0.47;0.39],  $p=0.82$  between systolic gradient and visual stenosis assessment). These results showed that visual assessment is insufficient to assess the efficacy of PTRAs. Visual stenosis assessment showed a broad repartition of measurements both pre- and post-PTRAs (**Figure 4**).

#### **4F catheter vs. pressure guidewire in pressure measurements**

A high correlation was found between the gradient measured using a 4F catheter and the reference method using a pressure guidewire (**Figure 5**). As expected, the correlation of the pressure measurements between the pressure guidewire and the 4F catheter decreased when the severity of the stenosis increased due to the larger diameter of the 4F catheter compared to the guidewire (**Figure 6**). Of note, the 4F measurement overestimated the pressure guidewire measurement when the systolic gradient was higher than 20 mmHg. The highest concordance, with the lowest biases and narrowest limits of agreement, was found for the mean Pd/Pa ratio (bias -0.14, limits of agreement from -0.46 to 0.18). Bland-Altman plots for systolic gradient measurements showed a bias of 22.00 (limits of agreement from -23.241 to 67.41).

The correlation coefficients between the first and second measurements of the systolic gradient were 0.95 (0.88-0.98),  $p < 0.01$  with the guidewire and 0.96 (0.88-0.99),  $p < 0.01$  with the 4F catheter. Likewise, the correlation was 0.97 (0.93-0.99),  $p < 0.01$  and 0.95 (0.86-0.98),  $p < 0.01$  for the systolic ratio with the guidewire and the 4F catheter respectively.



## DISCUSSION

The main findings of this study are that 1) in a selected population with initial transstenotic gradient, angioplasty guided by transstenotic pressure showed a beneficial effect on hypertension management in 88% of patients; 2) the normal transstenotic ratio ( $>0.90$ ) and gradients were restored after angioplasty in patients who presented a clinical response to angioplasty; 3) systolic gradient measurement is more reliable than visual stenosis assessment in guiding angioplasty; and 4) transstenotic pressure assessment using a 4F catheter is reproducible and highly correlated with those made through a special pressure guidewire.

Multifocal fibromuscular dysplasia is the second leading cause of renovascular hypertension after atherosclerosis. The etiology of fibromuscular dysplasia is still a matter of debate: hormonal factors have been suggested<sup>11</sup> as well as autosomal dominant inheritance and a contribution of smoking<sup>12</sup>. Most guidelines on the detection and management of renal artery stenosis are based on atherosclerotic patients due to its frequency (80-90% of renal artery stenosis)<sup>13</sup>, although the pathophysiology is different. Fibromuscular dysplasia is a noninflammatory vascular disease with ischemia of the vasa vasorum<sup>14</sup>. Histologically, it is characterized by the alteration of a thinned medial wall layer and thickened fibromuscular collagenic ridges leading to the so-called “string of beads” appearance (80-90%)<sup>12,13</sup>.

Angiography is still the gold-standard for identifying fibromuscular dysplasia renal artery stenosis<sup>8,15</sup>. In contrast to atherosclerotic renal stenosis, where the usefulness of invasive treatment is restricted to highly selected patients, there is no consensus about those in fibromuscular dysplasia<sup>12</sup>. Invasive treatment by angioplasty<sup>16</sup> in fibromuscular dysplasia should be proposed for uncontrolled hypertension with medication or renal impact, such as impaired renal function or ischemic nephropathy<sup>8,15</sup>. In the present study, only three patients (12%) did not present clinical success of angioplasty, which suggests that our selection criteria are relevant for

hypertension management in fibromuscular dysplasia patients. Interestingly, all of them were male, which might be a point to investigate in a larger study since the low number of nonresponders in our population did not allow us to formally conclude in a sex effect in clinical response. Two of the three nonresponders to angioplasty had doppler criteria suggesting less severe renal artery stenosis than the responders. The third nonresponder patient maintained doppler criteria suggestive of significant stenosis at follow-up, which may imply a place for duplex ultrasonography in fibromuscular dysplasia patient selection for renal angioplasty.

In addition to clinical success, we also looked for procedural success. Due to a lack of consensus on the definition of renal angioplasty success in fibromuscular dysplasia patients<sup>8</sup>, we considered procedural success a postinterventional translesional systolic gradient  $\leq 10$  mmHg or a reduction in systolic gradient by at least 80%. A systolic gradient  $< 10$  mmHg is considered normal<sup>2</sup>, and we voluntarily based our criteria on a more stringent threshold for our patients compared to the previously reported translesional systolic pressure gradient of 20 mmHg<sup>10</sup>. We also considered a reduction of 80% as a reduction deemed to be sufficient. Based on our definition of success, we thus found 23 (96%) patients with successful angioplasty. Moreover, we did not use the previously reported residual stenosis  $< 30\%$  criterion<sup>10,17,18</sup> as a criterion for procedural success since it was initially developed in patients with atherosclerotic stenosis and visual assessment in fibromuscular dysplasia patients remains challenging. We therefore investigated the correlation between visual assessment of stenosis and invasive measurements of translesional gradients.

These two methods did not show good correlation, and the correlation coefficients were lower post-angioplasty. Moreover, especially post-angioplasty, the results for visual stenosis assessment were too scattered, compared to those for systolic gradient measurements, to be able to know if the stenosis was treated. These findings thus suggest that visual stenosis assessment is not reliable to attest the efficacy of renal angioplasty and that measurements of gradients are necessary to

guide the procedure in fibromuscular dysplasia. All our angiographic indices were evaluated with a pressure guidewire and a 4F catheter, and one of our aims was to investigate the correlation between these two. Significantly high correlations were found for all angiographic indices tested by the guidewire and the 4F catheter. Moreover, similar to the pressure guidewire for low-degree stenosis, our results suggest that the 4F catheter was prone to overestimate the severity of significant stenosis. This was expected since a 4F catheter placed distally to the lesion may partially obstruct the flow because of its diameter and therefore overestimate the transstenotic pressure gradient<sup>4</sup>. Additionally, reported measurements using a 4F catheter suggest that overestimation is larger in gradients higher than 20 mmHg. On the other hand, 4F catheter seems reliable to detect transstenotic systolic gradient around 10 mmHg, which was one of our criterion for procedural success. These preliminary results suggest that renal angioplasty in fibromuscular dysplasia could be successfully guided by pressure measurement using a 4F catheter, thus reducing the procedure cost but have to be confirmed with larger studies. The intraobserver correlation coefficients also suggest reliable repeated measurements, both with the pressure guidewire and the 4F catheter, when made by the same medical operator.

The present study has several limitations, such as the limited number of patients. Fibromuscular dysplasia is not a common disease, and recruitment of such patients is difficult. In our population, we had a low number of nonresponders, which did not allow us to statistically compare them to the responders; however, we suggest that duplex ultrasonography criteria might have an important role in patient selection for renal angioplasty.

## CONCLUSIONS

In renal artery stenosis due to multifocal fibromuscular dysplasia, reaching a residual systolic transstenotic gradient  $\leq 10$  mmHg or reduced by at least 80% promotes up to 80% success in hypertension management. Gradient assessment, which is better than visual stenosis assessment, can be confidently performed with a 4F catheter instead of a 0.014" pressure guidewire.

Based on our findings, transstenotic measurements during angioplasty should be as systematic as patient selection on doppler ultrasonography to reach good clinical results.

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Figure 1

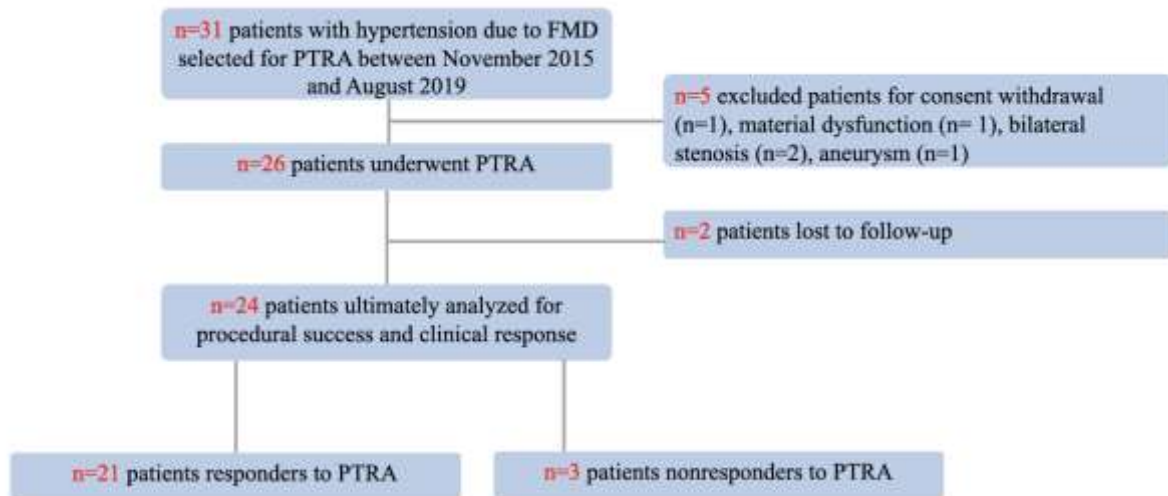


Figure 2

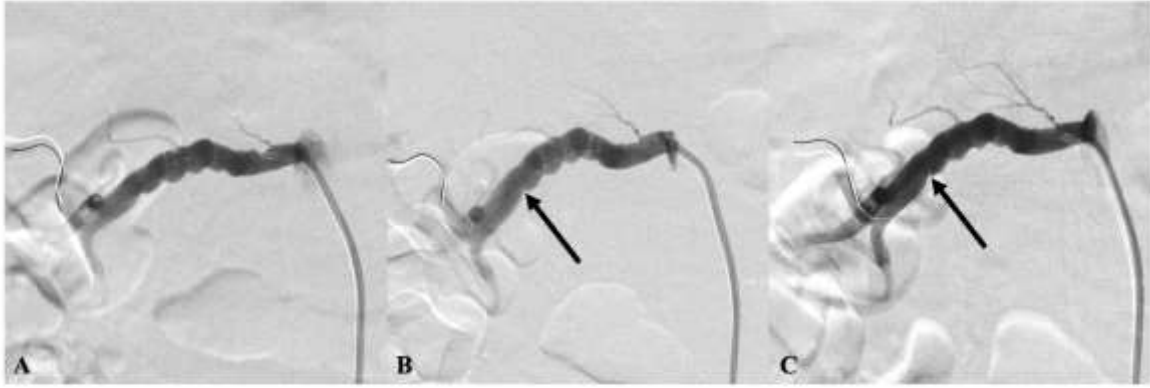


Figure 3

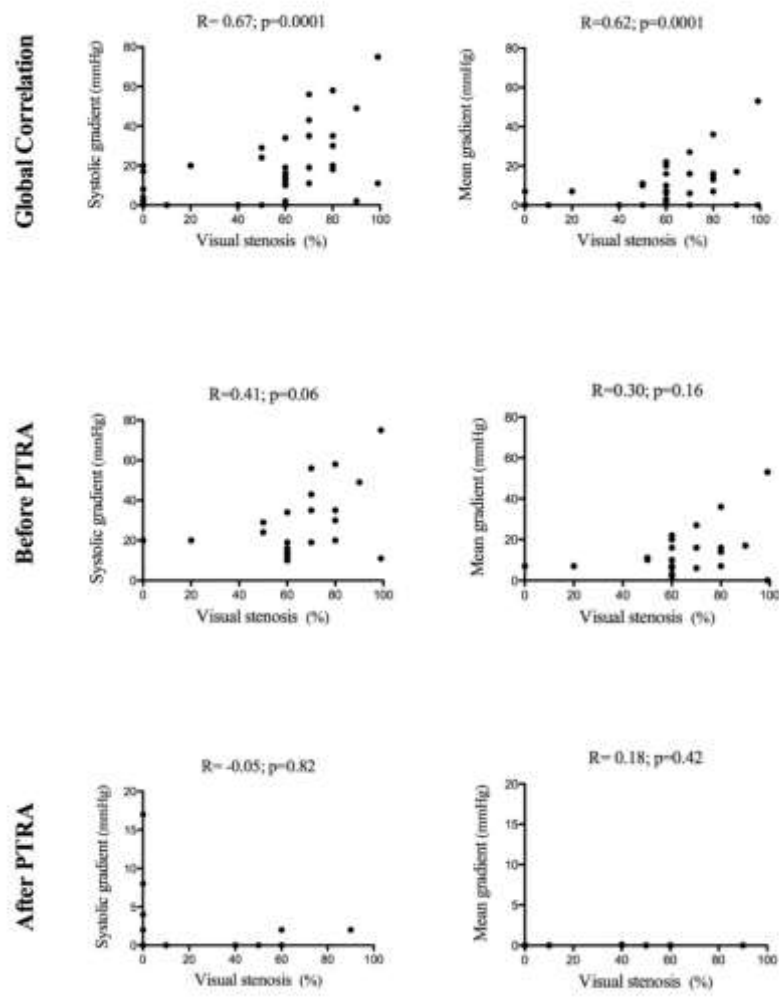


Figure 4

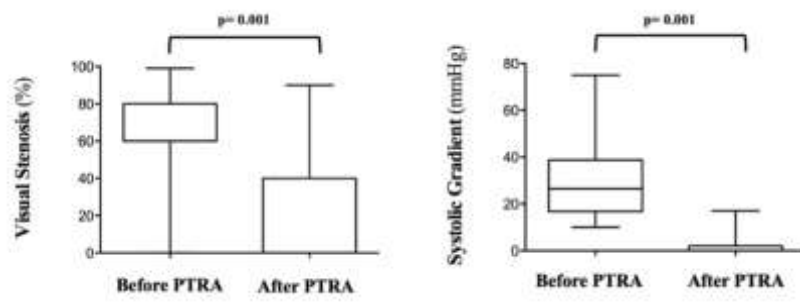


Figure 5

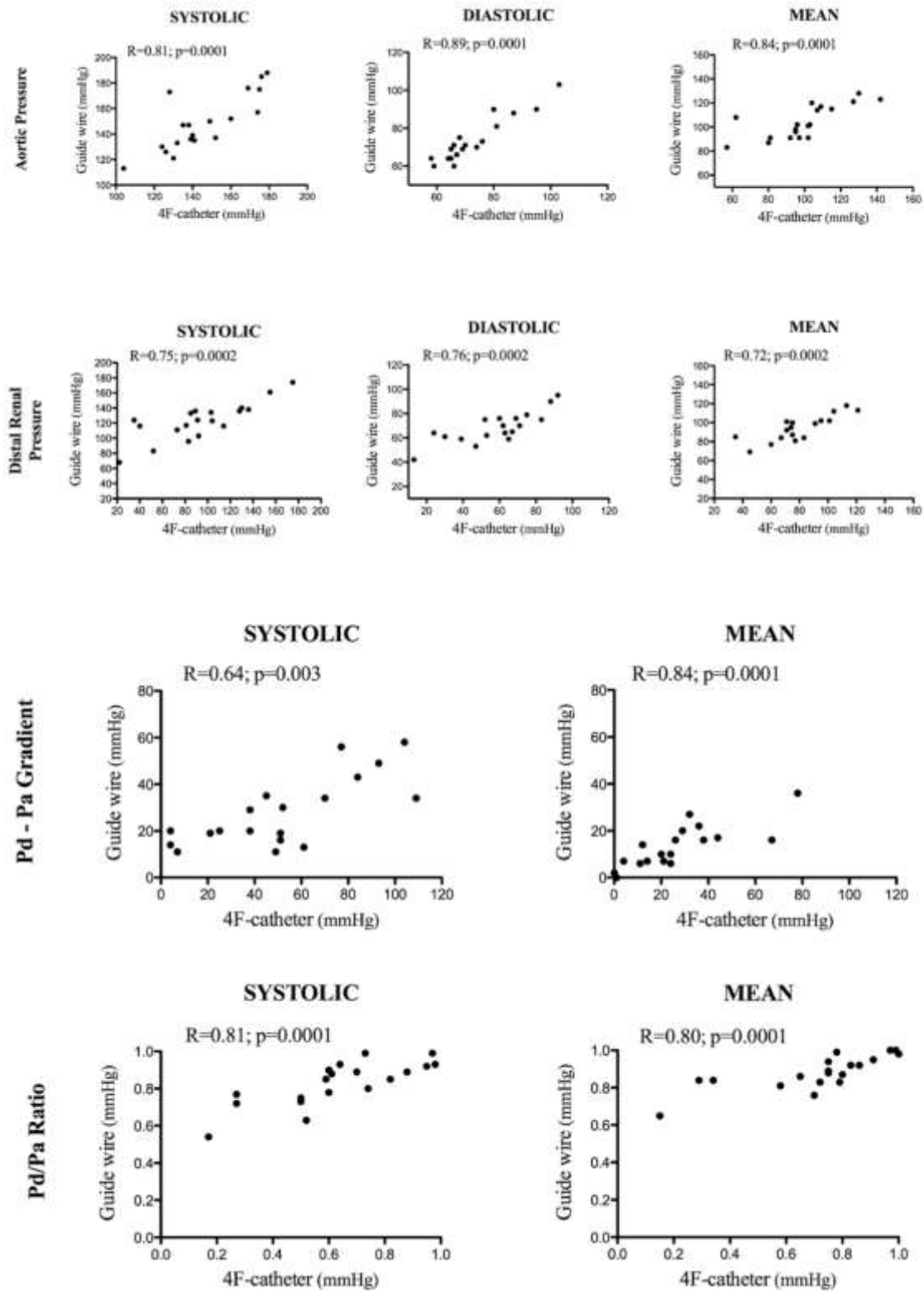
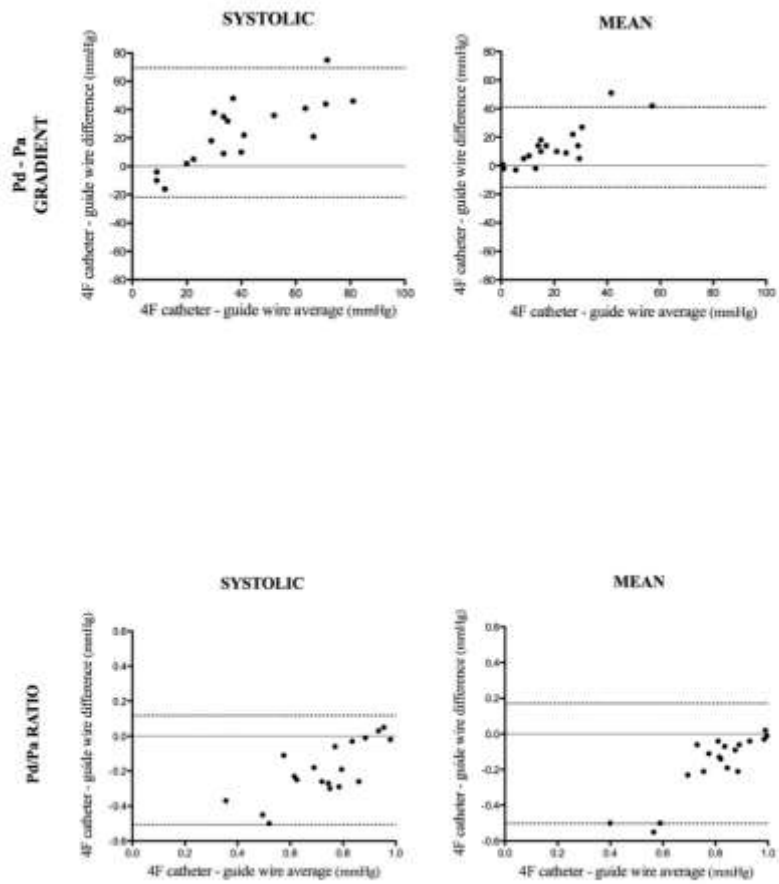


Figure 6



**Table I. Clinical baseline characteristics.**

|  | <b>Baseline</b>  |
|--|------------------|
| Patients (n)                           | 24               |
| Age (years)                            | 48.54 ± 13.11    |
| Sex (M/F)                              | 3 (12%)/21 (88%) |
| Number of cardiovascular risk factors* |                  |
| 0                                      | 7 (29%)          |
| 1                                      | 7 (29%)          |
| 2                                      | 7 (29%)          |
| 3                                      | 2 (8%)           |
| 4                                      | 1 (4%)           |
| Systolic blood pressure (mmHg)**       | 152.80 ± 18.35   |
| Diastolic blood pressure (mmHg)**      | 91.13 ± 13.07    |
| Number of antihypertensive drugs       |                  |
| 0                                      | 0 (0%)           |
| 1                                      | 5 (21%)          |
| 2                                      | 9 (38%)          |
| 3                                      | 4 (17%)          |
| 4                                      | 5 (21%)          |
| 5                                      | 1 (4%)           |
| Antihypertensive drugs type            |                  |
| Renin-angiotensin system blocker       | 17 (71%)         |
| Calcium inhibitor                      | 16 (67%)         |

|  |                       |
|--|-----------------------|
| Thiazide diuretic                        | 11 (46%)              |
| Beta blockers                            | 9 (38%)               |
| Others                                   | 5 (21%)               |
| Total treatment dose (mg/day)            | 170.00 (55.00-240.00) |
| eGFR (MDRD, ml/min/1.73 m <sup>2</sup> ) | 79.12 ± 12.44         |

*Values are the mean ± SD or median (interquartile range) or n (%)*

*M: male, F: female; eGFR : estimated glomerular filtration rate*

*\*Including age >50/>60 years old for male/female; smoking; dyslipidemia; diabetes mellitus; familial history.*

*\*\*Mean daytime blood pressure measured by a 24-hour ambulatory blood pressure measurement*



**Table II. Evolution of invasive pressure measurement before and after PTRA.**

| n=24                           | Before PTRA         | After PTRA        | P-value         |
|--------------------------------|---------------------|-------------------|-----------------|
| <b>Pa (mmHg)</b>               |                     |                   |                 |
| Systolic                       | 154.00 ± 29.45      | 162.40 ± 30.42    | <b>0.02</b>     |
| Diastolic                      | 76.88 ± 13.37       | 77.41 ± 13.10     | 0.70            |
| Mean                           | 108.40 ± 19.76      | 111.60 ± 21.14    | <b>0.13</b>     |
| <b>Pd (mmHg)</b>               |                     |                   |                 |
| Systolic                       | 126.00 ± 33.44      | 155.20 ± 29.26    | <b>&lt;0.01</b> |
| Diastolic                      | 70.25 ± 14.50       | 75.95 ± 15.55     | <b>0.05</b>     |
| Mean                           | 94.29 ± 22.08       | 109.00 ± 21.90    | <b>&lt;0.01</b> |
| <b>Pd - Pa gradient (mmHg)</b> |                     |                   |                 |
| Systolic                       | 26.50 (16.75-38.75) | 0.00 (0.00-2.00)  | <b>&lt;0.01</b> |
| Mean                           | 12.50 (7.00-19.25)  | 0.00 (0.00-0.00)  | <b>&lt;0.01</b> |
| <b>Pd/Pa ratio</b>             |                     |                   |                 |
| Systolic                       | 0.82 ± 0.14         | 0.96 ± 0.03       | <b>&lt;0.01</b> |
| Mean                           | 0.87 ± 0.12         | 0.97 ± 0.03       | <b>&lt;0.01</b> |
| <b>Visual stenosis (%)</b>     | 60.00 (60.00-80.00) | 0.00 (0.00-40.00) | <b>&lt;0.01</b> |

*Values are the mean ± SD or median (interquartile range)*

*Pa: aortic pressure; Pd: distal renal pressure; PTRA: percutaneous renal transluminal angioplasty*

**Table III. Comparison between responders and nonresponders to angioplasty.**

|  | <b>Responders</b><br>n=21 | <b>Nonresponders</b><br>n=3 |
|--|---------------------------|-----------------------------|
| <b>Clinical baseline characteristics</b>   |                           |                             |
| Age (years)                                | 48.71 ± 13.85             | 47.33 ± 7.51                |
| Sex (M/F)                                  | 0 (0%)/21 (100%)          | 3 (100%)/0 (0%)             |
| Number of cardiovascular risk factors      | 1.29 ± 1.11               | 1.33 ± 1.16                 |
| Systolic blood pressure (mmHg)*            | 152.70 ± 18.60            | 153.00 ± 20.30              |
| Diastolic blood pressure (mmHg)*           | 92.19 ± 12.77             | 83.67 ± 15.50               |
| Number of antihypertensive drugs           | 2.52 ± 1.25               | 2.33 ± 0.58                 |
| Total treatment dose (mg/day)              | 170.00 (72.50-241.00)     | 92.50 (7.50-177.50)         |
| eGFR (MDRD, ml/min/1.73 m <sup>2</sup> )   | 78.99 ± 13.02             | 80.45 ± 3.46                |
| <b>DUS baseline indices (treated side)</b> |                           |                             |
| Kidney size (cm)                           | 104.90 ± 9.51             | 99.33 ± 8.14                |
| IR   | 0.53 ± 0.10               | 0.63 ± 0.09                 |
| SAT (ms)                                   | 126.60 ± 46.84            | 168.00 ± 19.97              |
| Aortic PSV (cm/s)                          | 85.00 ± 17.75             | 76.67 ± 6.81                |
| Renal PSV (cm/s)                           | 387.50 ± 106.06           | 233.70 ± 133.00             |
| EDV (cm/s)                                 | 137.70 ± 67.85            | 67.33 ± 38.00               |
| RAR  | 4.69 ± 1.63               | 3.04 ± 1.63                 |
| RRR  | 3.40 ± 1.41               | 1.95 ± 0.64                 |
| <b>Angiographic indices (treated side)</b> |                           |                             |

|                                |                     |                     |
|--------------------------------|---------------------|---------------------|
| Systolic Pa (mmHg)             | 149.40 ± 24.25      | 186.30 ± 48.01      |
| Diastolic Pa (mmHg)            | 75.86 ± 13.04       | 84.00 ± 16.37       |
| Mean Pa (mmHg)                 | 105.30 ± 16.13      | 130.30 ± 32.62      |
| Systolic Pd (mmHg)             | 119.80 ± 28.56      | 170.00 ± 37.32      |
| Diastolic Pd (mmHg)            | 68.19 ± 13.24       | 84.67 ± 17.62       |
| Mean Pd (mmHg)                 | 89.90 ± 18.03       | 125.00 ± 27.18      |
| Systolic Pd-Pa gradient (mmHg) | 30.00 (16.00-40.00) | 20.00 (19.50-22.00) |
| Mean Pd-Pa gradient (mmHg)     | 16.00 (7.00-20.00)  | 7.00 (6.50-9.00)    |
| Systolic Pd/Pa ratio           | 0.80 ± 0.14         | 0.92 ± 0.06         |
| Mean Pd/Pa ratio               | 0.86 ± 0.12         | 0.96 ± 0.04         |

*Values are the mean ± SD or median (interquartile range) or n (%)*

*DUS: duplex ultrasonography; EDV: end-diastolic velocity; eGFR : estimated glomerular filtration rate; F: female; IR: resistive index; M: male; Pa: aortic pressure; Pd: distal renal pressure; PSV: peak systolic velocity; RAR: renal aortic ratio; RRR: renal renal ratio; SAT: systolic ascension time*

*\*Mean daytime blood pressure measured by a 24-hour ambulatory blood pressure measurement*

**Supplemental Table I. DUS criteria of nonresponder patients to angioplasty.**

| <b>Patient</b> | <b>IR</b> | <b>SAT<br/>(ms)</b> | <b>Aortic<br/>PSV<br/>(cm/s)</b> | <b>Renal<br/>PSV<br/>(cm/s)</b> | <b>EDV<br/>(cm/s)</b> | <b>RAR</b> | <b>RRR</b> |
|----------------|-----------|---------------------|----------------------------------|---------------------------------|-----------------------|------------|------------|
| 1              | 0.53      | 155                 | 82                               | 367                             | 95                    | 4.47       | 2.4        |
| 2              | 0.71      | 191                 | 69                               | 233                             | 83                    | 3.38       | 1.2        |
| 3              | 0.66      | 158                 | 79                               | 101                             | 24                    | 1.27       | 1.5        |

*DUS: duplex ultrasonography; EDV: end-diastolic velocity; IR: resistive index; PSV: peak systolic velocity; RAR: renal aortic ratio; RRR: renal renal ratio; SAT: systolic ascension time.*

## FIGURE LEGENDS

**Figure 1.** Flowchart.

**Figure 2.** Angiography before and after successful angioplasty.

Digital subtraction angiography (DSA) of the right renal artery in a 63-year-old female with fibromuscular dysplasia with resistant hypertension and good clinical results after angioplasty.

A. Preangioplasty DSA showing the typical “string of beads” appearance of pathologic renal artery with maximal stenosis visually estimated at 80% and with a systolic translesional gradient measurement of 16 mmHg by a pressure guide wire.

B. Postfirst angioplasty (6 mm balloon) angiography showing no significant decrease in visual stenosis at the site of angioplasty (arrow), with a systolic gradient of 12 mmHg.

C. Postsecond angioplasty (7 mm balloon) angiography showing no modification of the visual stenosis compared to the second angioplasty (arrow) but with a restoration of a normal systolic gradient, measured after angioplasty at 9 mmHg.

**Figure 3.** Correlation between visual stenosis and invasive pressure gradient assessment.

Correlation plots between visual stenosis assessment and invasive Pd-Pa gradient measurements by pressure guide are depicted.

*Pa*: aortic pressure; *Pd*: distal renal pressure; *PTRA*: percutaneous renal transluminal angioplasty.

**Figure 4.** Evolution of visual stenosis and invasive systolic gradient measurement before and after PTRA.

Comparison of visual stenosis and invasive systolic gradient measurement both before and after PTRA. Box plot shows median and interquartile range. Upper and lower whiskers are maximum and minimum values, respectively. Round symbols show the 5th/95th percentile values.

*PTRA*: percutaneous renal transluminal angioplasty

**Figure 5.** Correlation between 4F catheter and pressure guide wire indices.

Correlation plots between invasive angiographic measures by 4F catheter and pressure guide wire. Scatter plots of measurements by the 2 methods are depicted.

*Pa*: aortic pressure; *Pd*: distal renal pressure

**Figure 6.** Bland-Altman plots for comparison between the 4F catheter and pressure-guide wire for mean Pd/Pa ratio measurements.

Bland – Altman plots for invasive angiographic measures by 4F catheter and pressure guide wire. Averages  $\pm 1,96$  SD are indicated by the continuous and dashed lines, respectively.

*Pa*: aortic pressure; *Pd*: distal renal pressure

**Table I.** Clinical baseline characteristics.

**Table II.** Evolution of invasive pressure measurement before and after PTRA.

**Table III.** Baseline characteristics of responders and nonresponders to angioplasty.

**Supplemental Table I.** DUS criteria of nonresponder patients to angioplasty.