Effect of Renal Artery Stenting on Blood Pressure, Glomerular Filtration Rate and Left Ventricular Mass in Hypertensive Patients with Severe Atherosclerotic Renal Artery Stenosis

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Received 2016 October 23; Revised 2016 December 05; Accepted 2016 December 08.

Abstract

Background: Many small trials showed a significant improvement in blood pressure following renal artery stenting in patients with severe atherosclerotic renal artery stenosis, but data on renal function improvement is more conflicting. Recently, few trials have been conducted to evaluate the effect of this procedure on Left Ventricular Mass (LVM) and Left Ventricular Mass Index (LVMI).

Objectives: The aim of this study is to determine the effect of renal artery stenting on Blood Pressure, estimated Glomerular Filtration Rate (eGFR), Left Ventricular Mass (LVM), and Left Ventricular Mass Index (LVMI) in patients with severe atherosclerotic renal artery stenosis.

Methods: This is a prospective interventional study performed on forty patients with ischemic heart disease and medication resistant hypertension, who had severe (≥ 70%) atherosclerotic renal artery stenosis and underwent renal artery stenting. Blood pressure, LVM, LVMI and eGFR before renal artery stenting and after six months were assessed in these patients.

Results: There were significant reduction in systolic blood pressure (from 175.50 ± 17.28 mmHg to 137.30 ± 13.21 mmHg) (P < 0.001), and diastolic blood pressure (from 103.45 ± 8.91 mmHg to 84.30 ± 7.33 mmHg) (P < 0.001). Also, there were significant decrease in LVM (from 307.73 ± 108.13 g to 259.34 ± 92.17 g) (P = 0.004) and LVMI (from 174.70 ± 58.26 to 148.01 ± 49.77) (P = 0.004). LVM reduction was independent of SBP and DBP reduction (P = 0.376 and P = 0.196, respectively).

Conclusions: Renal artery stenting reduces Blood pressure and leads to regression of LVM independent of blood pressure reduction. Regardless of baseline eGFR, our study failed to find a significant increase in glomerular filtration rate.

Keywords: Atherosclerotic Renal Artery Stenosis, Renal Artery Stenting, Left Ventricular Mass (LVM), Left Ventricular Mass Index (LVMI), Estimated Glomerular Filtration Rate (eGFR)

1. Background

Atherosclerotic disease involves mainly the ostial-proximal stenosis of the main renal artery. Assessment of a general population by renal duplex ultrasound in individuals older than 65 years of age has revealed an approximately 7% prevalence of renal artery stenosis, which increases to 20% to 30% in high-risk populations (e.g., patients with known atherosclerotic vascular disease). Atherosclerotic renal artery stenosis is a progressive process usually with a loss of renal mass over time, despite management of hypertension.

Atherosclerotic renal artery stenosis is an important cause of hypertension, renal insufficiency, CAD, left ventricular hypertrophy, left ventricular failure and flash pulmonary edema.

Over the years, the impact of renal artery revascularization on blood pressure and renal function has been studied through numerous clinical trials. Some studies revealed no benefits of revascularization over medical treatment alone (1-3).

Many small trials showed a significant improvement in blood pressure following renal artery angioplasty, but data on renal function improvement is more conflicting (4-9).

Renovascular hypertension is an important cause of left ventricular hypertrophy and heart failure.

Left ventricular hypertrophy independently predicts morbidity and mortality, predisposing to heart failure, ventricular tachyarrhythmia, ischemic stroke, atrial fibrillation, and embolic stroke.

Recently, few trials have evaluated the effect of renal
artery stenting on left ventricular mass (LVM) and left ventricular mass index (LVMI) (10-13).

In the present study, while patients with ischemic heart disease and medication resistant hypertension underwent coronary artery angiography, renal artery angiography was also performed. In addition, in cases with severe renal artery stenosis, stents were placed at the site of renal artery stenosis.

2. Objectives

Objectives of the present study are to determine the impact of renal artery stenting on blood pressure, eGFR, LVM and LVMI in patients with severe atherosclerotic renal artery stenosis.

3. Methods

A total of 65 patients with severe ischemic heart disease who were resistant to medical therapy and had coronary angiography indications were surveyed in Ghaem hospital between 2010 and 2014. Also, these patients had severe arterial hypertension that didn't have a good response to medication treatment. According to this situation, simultaneous with coronary angiography, renal artery angiography was performed in these patients.

Of these 65 patients, 40 cases [12 males (30%), and 28 females (70%)] had severe renal artery stenosis. Drug resistant hypertension is defined as blood pressure > 140/95 mmHg despite optimal medical treatment with at least three different types of antihypertensive drugs (one of them was a diuretic) with maximum effective dose except in the presence of a contraindication for a duration of at least three months. Atherosclerotic disease involves mainly the ostio-proximal stenosis of the main renal artery. In the presence of severe (≥70%) proximal renal artery stenosis (atherosclerotic), stents were placed at the sites of stenosis.

Patients were excluded from this study if they had the following criteria:
- eGFR < 15 mL/min
- Non-atherosclerotic stenosis, (non ostial and proximal stenosis of renal artery)
- Other arterial lesions in the abdominal aorta that need surgery
  - Coagulopathies
  - Presence of any contraindication for usage of aspirin, thienopyridin or heparin
  - Severe and refractory heart failure
  - Presence of implantable cardioverter defibrillator (ICD) or pacemaker
- Any arrhythmia interfering with left ventricular echocardiographic parameters evaluation
- History of myocardial infarction
- Hypertrophic or restrictive cardiomyopathy
- History of renal transplantation, hemodialysis, peritoneal dialysis,

Blood pressure measurement was according to American Heart Association's (AHA) guidelines and was recorded before the intervention and 1 day, 1 week, 1, 3 and 6 months after the intervention. Blood pressure improvement was defined as reduction in systolic blood pressure (SBP) values of > 10 mmHg and diastolic (DBP) of > 5 mmHg. If changes in BP values were considered insignificant (changes in SBP and DBP values within the ranges of 10 and 5 mmHg respectively), a reduction in the number or doses of antihypertensive drugs is considered as blood pressure improvement. Blood pressure deterioration was defined as an increase in SBP and DBP values or an increase in the number or doses of antihypertensive drugs.

The sample size of our study was calculated as 40 cases according to the study of Dervisoglu et al. (6). After dividing the patients into two groups based on their baseline GFR (group 1: 15 < eGFR < 60 mL/min & group 2: eGFR ≥ 60 mL/min), changes in renal function in each group was studied.

Based on the study of Rzeznik et al. (11), a decrease of ≥15 gr in LVM was defined as significant regression.

eGFR was calculated using Modification of Diet in Renal Disease (MDRD) (14) formula as the following:

eGFR (mL/min) = 175 × (Scr) - 1.154 × (Age) - 0.203 × (0.742 if female) × (1.212 if African American)

To measure M-mode echocardiographic parameters, the patients were examined in left lateral decubitus position with Vivid 3 GL.Echocardiography System (USA, 2004), prob: 2.5 - 3.5 MHz through parasternal long axis according to the American Society of Echocardiography’s guidelines.

LVM was calculated using formula of Penn (15) as the following:

LV mass (Penn) = 1.04 ([LVIDd + PWTd + IVSTd]3 - [LVIDd]3) - 13.6 g

(LVIDd: left ventricular internal dimension during diastole, IVSTd: interventricular septal thickness during diastole, PWTd: posterior wall thickness during diastole)

In order to calculate LVMI, the following formulas were used:

\[ LVMI = \frac{LV M}{BSA} \]  

(1)

Mosteller formula (16):

\[ Body \ Surface \ Area \ (BSA) = \left( \frac{Height \ (cm) \times Weight \ (kg)}{3600} \right)^{1/2} \]  

(2)
3.1. Angioplastic Procedure

In most cases, angioplasty and stent placement was performed by femoral approach (brachial approach was used for one patient due to anatomical variation). Success rate was 100% (residual Stenosis < 30%). No major complications including abdominal aorta or renal artery dissection, acute renal artery obstruction, and so on were occurred. The diameter of renal artery stents was all based on size of vessels on angiography. These stents had diameter between 4.5 to 6 mm and length of 12 to 18 mm.

Patients were admitted at least 1 day before the procedure. The contrast agent used for all patients was Iodixanol (Visipaque). Special precautions were taken toward those more susceptible to contrast agent nephropathy. Patients were hydrated with normal saline 50 - 100 cc/hr according to their medical condition. 5 - 10000 unit intravenous bolus of heparin was given immediately before the procedure. The patients who had been taken aspirin and clopidogrel daily, continued the same doses, others were given 300 mg chewable aspirin and 600 mg clopidogrel a day before the intervention. Aspirin 80 mg/d indefinitely and clopidogrel 75 mg per day were continued for at least 2 months after the intervention. Atorvastatin (40 - 80 mg) was also added to the drug regimen.

3.2. Statistical Analysis

IBM SPSS Statistics software (version 20) was used for statistical analysis. Continuous variables were expressed as mean ± SD and discrete variables as numbers and percentages. Depending on the results of Kolmogorov-Smirnov (KS) test, evaluation of normality of data distribution was performed before and six months after the intervention. Significance of changes was examined by paired sample t-test or Wilcoxon test. If the changes were proved to be statistically significant, linear regression model was used for evaluating the impact of suspected continuous variables.

4. Results

No major complications such as dissection in abdominal aorta or renal arteries, acute embolic event, acute cardiovascular event or deaths were reported during 6-month follow-up. Due to gradual increase in blood pressure (after the primary reduction) in 2 (5%) patients, duplex ultrasound and renal artery Doppler were performed and restenosis of renal arteries was revealed in these two cases. Restenosis was confirmed by renal artery angiography in these patients and balloon angioplasty without stent deployment was performed. Demographic data of the studied patients were recorded in Table 1.

Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics of Patients</th>
<th>Age, years ± SD</th>
<th>Male, N (%)</th>
<th>SBP, mmHg ± SD</th>
<th>DBP, mmHg ± SD</th>
<th>eGFR, ml/min ± SD</th>
<th>LVM, g ± SD</th>
<th>LVMI ± SD</th>
<th>Hypertension, N (%)</th>
<th>Diabetes Mellitus, N (%)</th>
<th>Hyperlipidemia, N (%)</th>
<th>Smoking, N (%)</th>
<th>BMI &gt; 25 kg/m², N (%)</th>
<th>eGFR ≥ 60 ml/min, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64.11 ± 6.59</td>
<td>12 (30)</td>
<td>175.50 ± 17.28</td>
<td>103.45 ± 8.19</td>
<td>68.53 ± 26.70</td>
<td>307.73 ± 108.13</td>
<td>174.70 ± 58.26</td>
<td>40 (100)</td>
<td>24 (60)</td>
<td>26 (65)</td>
<td>4 (10)</td>
<td>27 (67.5)</td>
<td>22 (55)</td>
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4.1. Blood Pressure

Blood pressure reduction was significant in all follow-up intervals. After six months, the mean SBP decreased from 175.50 ± 17.28 mmHg to 137.30 ± 13.21 mmHg (P < 0.001), and DBP from 103.45 ± 8.19 mmHg to 84.30 ± 7.33 mmHg (P < 0.001) (Table 2).

According to the definition of BP improvement in our study, as previously discussed in methods for both systolic and diastolic BP, BP improved in 87.5% of patients, and no significant changes or increase in BP were occurred in the remaining of 12.5%. The mean number of antihypertensive drugs decreased from 3.72 ± 0.46 to 2.74 ± 1.12 (P < 0.001) (Table 3). LVM reduction was independent of SBP and DBP reduction (P = 0.376, P = 0.196, respectively).

In 21 (52.5%) patients, there was a reduction in the number of drugs (antihypertensive medication was stopped in 2 cases) and in 14 (35%) patients, we used the same number of drugs, but the doses were decreased.

4.2. Estimated Glomerular Filtration Rate

The reduction in the mean eGFR from 68.53 ± 26.70 ml/min to 66.70 ± 19.63 ml/min that was observed 6 months after stenting was not statistically significant (P = 0.533). After dividing the patients into two groups based on their baseline eGFR (group 1: 15 < eGFR < 60 ml/min...
Table 2. Comparison of Systolic and Diastolic Blood Pressure Values Before (at Baseline) and 7 Days, 1, 3 and 6 Months After Renal Artery Stenting

<table>
<thead>
<tr>
<th>Time</th>
<th>SBP, mmHg ± SD</th>
<th>P value</th>
<th>DBP, mmHg ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (before stenting)</td>
<td>175.50 ± 17.28</td>
<td></td>
<td>103.45 ± 8.91</td>
<td></td>
</tr>
<tr>
<td>at 7 Days</td>
<td>149.75 ± 15.16</td>
<td>&lt; 0.001</td>
<td>91.22 ± 7.76</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>at 1 Month</td>
<td>147.26 ± 12.02</td>
<td>&lt; 0.001</td>
<td>90.64 ± 6.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>at 3 Months</td>
<td>139.57 ± 11.20</td>
<td>&lt; 0.001</td>
<td>85.00 ± 5.56</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 6 Months</td>
<td>137.30 ± 13.21</td>
<td>&lt; 0.001</td>
<td>84.30 ± 7.33</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 3. Comparison of Number and Percentage of Type of Anti-hypertensive Medications Users Before and 6 Months After Stent Insertion in Renal Arteries

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Before RAS, No. (%)</th>
<th>6 Months After RAS, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>αB</td>
<td>1 (2.50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ACEI</td>
<td>24 (60.0)</td>
<td>18 (45.0)</td>
</tr>
<tr>
<td>ARB</td>
<td>13 (32.5)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>BB</td>
<td>38 (95.0)</td>
<td>34 (85.0)</td>
</tr>
<tr>
<td>CCB</td>
<td>32 (80.0)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>36 (90.0)</td>
<td>25 (62.0)</td>
</tr>
</tbody>
</table>

Abbreviations: αB, Alpha adrenergic blocker; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BB, Beta adrenergic blocker; CCB, Calcium channel blocker.

including 14 patients (35%) & group 2: eGFR ≥ 60 mL/min with 26 patients (65%), no patients in these groups showed significant improvement (P = 0.296 and P = 0.332, respectively).

4.3. Left Ventricular Mass (LVM) and Left Ventricular Mass Index (LVMI)

Reduction in mean LVM (from 307.73 ± 108.13 g to 259.34 ± 92.17 g, P = 0.004), and mean LVMI (from 174.70 ± 50.26 to 148.01 ± 49.77, P = 0.004) were significant over the 6 months. Also, mean PWTd (from 1.22 ± 0.34 cm to 1.12 ± 0.23 cm, P = 0.027) and mean IVSTD (from 1.28 ± 0.21 cm to 1.17 ± 0.23 cm, P = 0.007) were significantly reduced over the 6 months. The decrease in LVIDd was not significant (from 5.02 ± 0.66 cm to 4.86 ± 0.64 cm, P = 0.063) (Table 4).

Left ventricular hypertrophy regressed in 25 (62.5%) cases, it did not change significantly in 5 (12.5%) while it progressed in 10 (25%) patients (significant change in LVM was defined as a decrease or increase of ≥ 15 gram in it).

5. Discussion

The present study along with many other recent trials (4-8) have shown that once percutaneous renal artery revascularization (PTRA) is done in an experienced center, although still an invasive procedure, it can be accompanied by high success rate and few complications.

In our study, both SBP and DBP were reduced significantly, and although great sampled clinical trials like DRASTIC, STAR and ASTERAl (1-3) revealed no benefits of revascularization over medical treatment alone, many other small trials showed a significant improvement in blood pressure following renal artery stenting.

The severity of renal artery stenosis (≥ 70% in our study and many others compared with ≥ 50% in DRASTIC, STAR and ASTERAl) may play an important role in causing different results.

The impact of renal artery stenting on renal function is still a matter of debate. Despite dividing the patients into two groups based on their baseline eGFR, our study failed to show any significant improvement in renal function. In two different studies by Dervisoglu et al. (6) and Ramos et al., (9) lower baseline eGFR was associated with better outcome in renal function after successful renal artery stenting. Also, the last guidelines on peripheral vascular disease published by European Society of Cardiology (ESC) in 2011, eGFR < 30 mL/min or the rise in creatinin > 0.5 mg/dL were as a point to consider interventional procedures.

Proteinuria more than 1 g/d, renal atrophy, severe parenchymal kidney disease and severe disseminated intrarenal arteriolar disease were associated with poor outcome following percutaneous transluminal renal artery angioplasty (PTRA) (17).

In our study, decrease in LVM reduction was independent of SBP and DBP reduction.

Left ventricular hypertrophy regressed in 25 (62.5%), it did not change significantly in 5 (12.5%) while it progressed in 10 (25%) patients.

Symonides et al. (1999), Zeller et al. (2007), Corriere et al. (2009) and Rezeznic et al. (2011) also found that PTRA had improved left ventricular hypertrophy (10, 11, 13, 18), while no significant reduction in LVM occurred in 84 patients participating in the study of Marcantoni et al. in 2012 (12). The reduction in systolic blood pressure was reported as an important associated factor in LVM improve-
ment in the clinical trial by Symonides et al. (13). But like the present study, Zeller et al. and Rzeznik et al. (10, 11) also failed to find any correlation between BP reduction and LVM (or LVMI) improvement. In one study in which LVM regression was associated with blood pressure reduction, the degree of decrease in hypertension was much greater (13). In the clinical trial by Symonides et al. (13), SBP and DBP were decreased by 20 mmHg and 12 mmHg.

The function of aldosterone in causing left ventricular hypertrophy, independent of high blood pressure can be helpful in interpreting these findings (10). This hypothesis is strengthened by the finding of Duprez et al. (19) that they determined the effect of aldosterone on left ventricular hypertrophy, independent of arterial hypertension impact on it.

Zeller et al. (10) and Rzeznik et al. (11) demonstrated that reduction in IVSTD and PWTD also play an important role in LVM improvement, a finding that was similar to the results of our study.

5.1. Limitations of the Study

1. Due to small number of patients in this study, future studies with larger samples along with multicenter research trials are recommended.
2. Lack of a control group with primary hypertension, and that changes in left ventricular hypertrophy in them are compared with the patients in our study.
3. Measurement of aldosterone, plasma renin, and urinary catecholamine was not carried out to confirm theory of the effect of endocrine changes in regression of left ventricular hypertrophy.

5.2. Conclusion

The present study suggests that renal artery revascularization in patients with renovascular hypertension and ischemic heart disease reduces left ventricular mass and left ventricular mass index, independent of the improvement in blood pressure, but our study failed to show any improvement in renal function.

Acknowledgments

The authors would like to appreciate the deputy research of Mashhad University of Medical Sciences which supported this paper financially.

References


Table 4. LVDD, IVSTD, PWTD, LVM and LVMI at Baseline and 6 Months After Renal Artery Stenting

<table>
<thead>
<tr>
<th></th>
<th>LVDD (cm)</th>
<th>IVSTD (cm)</th>
<th>PWTD (cm)</th>
<th>LVM (gr)</th>
<th>LVMI (gr/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>5.02</td>
<td>1.28</td>
<td>1.22</td>
<td>307.73</td>
<td>174.70</td>
</tr>
<tr>
<td><strong>At 6 Months</strong></td>
<td>4.86</td>
<td>1.17</td>
<td>1.12</td>
<td>108.13</td>
<td>148.01</td>
</tr>
<tr>
<td><strong>P-Value</strong></td>
<td>0.063</td>
<td>0.007</td>
<td>0.027</td>
<td>0.004</td>
<td>0.004</td>
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