Atherosclerotic Renovascular Disease

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1. Introduction

Atherosclerotic renovascular disease (ARVD), also known as atherosclerotic renal artery stenosis is increasingly recognized to be a cause of chronic renal failure. According to a recent administrative data regarding general population of the elderly greater than 65 years of age in the United States, the prevalence and incidence rates of ARVD were estimated 0.5% and 3.7 per each 1000 person-years respectively (Kalra et al., 2005). In addition, some epidemiological researches demonstrated that the prevalence among those with end-stage renal disease beginning renal replacement therapy was estimated from 5% to 22% (Rimmer & Gennari, 1993; Mailloux et al., 1994; Appel et al., 1995; van Ampting et al., 2003). Of note, ARVD is not only responsible to impaired kidney function but also reflects a status of patients at risk for systemic cardiovascular diseases (Kalra et al., 2005). It has been well known that a variety of risk factors for atherosclerosis share common pathway underlying atherosclerotic renal artery stenosis, coronary artery disease, and peripheral vascular disease. On the contrary, significant high-grade bilateral or isolated renal artery stenosis may cause renovascular hypertension estimating over 50% of ARVD populations by activation of renin-angiotensin-aldosterone system and lipoxygenase pathway that further deteriorate the kidney function (Romero 1997). A previous report uncovered that ARVD was estimated from 1% to 6% in patients with hypertension (Simon et al., 1972). In this regard, a vicious cycle will be established in the progression of renal arterial atherosclerosis, which is characterized by refractory hypertension, acute cardiac events (ie, heart failure, cardiogenic pulmonary edema or acute coronary syndrome), and hence leads to acute or chronic renal failure due to hypertensive or ischemic nephropathy (Buller et al., 2004). Therefore, an early alert of patients at risk for ARVD is critical in slowing down the rate of kidney function loss and providing treatment for underlying cardiovascular disease as well. In this chapter, we will fuel the readers with the classic knowledge in this field and propose the latest evidence-based medicine to manage patients with this disease.

2. The pathogenesis of atherosclerosis

Atherosclerosis is affected by the traditional risk factors including hypertension, smoking, hyperlipidemia, diabetes mellitus and family history of premature coronary artery disease systemically. Regionally, blood flow disturbances near arterial branches, bifurcations and curvatures result in complex spatiotemporal shear stresses that are associated with
atherosclerosis susceptibility (Davies, 2009). In these predisposed areas, hemodynamic shear stress, the frictional force acting on the endothelial cell surface is weaker than in protected regions. Studies have identified shear stress to be an important determinant of endothelial function and phenotype. High shear stress (>15 dyne/cm²) induces endothelial quiescence and an atheroprotective gene expression profile, while low shear stress (<4 dyne/cm²), which is prevalent at atherosclerosis-prone sites, stimulates an atherogenic phenotype (Malek et al, 1999). As we know, thrombosis formation in situ and distal embolic dislodge from great vessels, determined by the burden and the stability of atherosclerosis, are the two major mechanisms leading to target organ infarction. With recent substantial evidence, systemic inflammation caused by either external stimulus such as microbial infection or internal immunologic response may trigger acute vascular events via pathogenic athroma plaque rupture. Therefore, when and how to stabilize and regress the process of atherosclerosis becomes a critical step to prevent target organ damage.

2.1 Systemic arterial atherosclerosis: the evidence from angiography and autopsy

Advanced atherosclerosis is highly prevalent among patients with ARVD characterized by coexistence with abdominal aortic aneurysm, severe coronary artery disease, ischemic stroke and peripheral vascular disease in post-mortem and angiographic studies (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>ANG (Patient: n)</th>
<th>Age (year)</th>
<th>CAD (%)</th>
<th>PAD (%)</th>
<th>ARVD (%)</th>
<th>Predictors</th>
</tr>
</thead>
</table>
| Crowley, 1998  | CAD: 14,152      | 61±12      | 63%     | NA      | 6.3% (bil: 1.3%) | Predictors for ARVD progression:  
  -Female gender, OR: 1.8  
  -PAD, OR: 1.8  
  -Hypertension, OR: 1.5  
  -Significant CAD, OR: 1.2 |
| Conlon, 2001   | CAD: 3,987       | 61±9       | 100%    | NA      | 9.1% (4.8%)* | -CAD: 2VD vs.1VD, OR: 1.9  
  -CAD: 3VD vs 1VD, OR: 2.5 |
| Liu, 2004      | CAD: 141         | 59±10      | 31%     | NA      | 18.4%    | -CAD vs. non-CAD, HR: 2.8 |
| Leandri, 2004  | CAD: 467         | 64±11      | 69%     | NA      | 9.0%     | -CAD: 2VD vs.1VD, OR: 2.8  
  -CAD: 3VD vs 1VD, OR: 3.0 |
| Buller, 2004   | ARVD: 837        | 67±10      | 68%     | -Carotid: 12%  
  -A.A.A or lower limb PAD: 12% | 14.4% (bil: 3.1%) | -Age per 10 year, OR:1.7  
  -Female gender. OR:1.9  
  -A.A.A or lower limb PAD, OR: 2.1  
  -Carotid, OR: 3.0 |
| Zhang, 2006    | CAD: 1,200       | 62±10      | 51%     | NA      | 9.7% (bil: 1.7%) | Age, hypertension, renal insufficiency, CAD |
| Ozkan, 2009    | PAD: 629         | 62±11      | 43%     | Aortoiliac, crural, femoropopliteal: 83% | 9.6%§ | Age, hypertension and aortoiliac stenosis |
Table 1. Associations between systemic atherosclerosis and ARVD: n: number; ANG: renal angiography; CAD: coronary artery stenosis >50%; ARVD: renal artery stenosis >50%; PAD: peripheral artery stenosis >50%; NA: not available; A.A.A: abdominal aortic aneurysm; carotid: carotid artery stenosis >50%; HR: hazard ratio; OR: odds ratio; VD: number of diseased coronary artery; § renal artery stenosis >60%; * renal artery stenosis >75%.

2.1.1 The nature course of ARVD

According to the shear stress rule, ostial and proximal lesions are mostly encountered and 20%-50% of cases are bilateral sites in ARVD (Safian & Textor, 2001). A significant progression of ARVD was observed in 11.1% of 14,152 subjects with high cardiovascular risks within a 2.6-year period in an angiographic study (Crowley et al, 1995) and in 35%-51% from 3 to 5 years in a dopplex ultrasonography study (Caps et al, 1998). From these reports, the predictors to disease progression include old age, female gender, hypertension, diabetes and the presence of significant coronary artery disease or peripheral vascular disease in which the odds ratios range from 1.2 to 2.1. On the other hand, patients with ARVD are associated with approximately 2-times risk of the occurrence of adverse coronary events and mortality as compared to those without ARVD in a long-term follow-up (Conlon et al, 2001; Edwards et al, 2005).

2.2 How to select patients at risk for prompt screening

As prescribed previously, patients at higher risk for atherosclerosis should receive an advanced step for screening the presence of ARVD (table 2).

Among these clinical features, the only statistically significant predictor to ARVD is the presence of abdominal bruit. The prevalence ranges from 6.5% to 31% in the healthy population (Watson & William, 1973), and 28% in hypertensive patients (Julius and Steward, 1967). However, in patients with angiographically proven ARVD, the prevalence increases up to 80% (Turnbull, 1995). Besides, the sensitivity of a systolic-diastolic abdominal bruit in the diagnosis of RAS has been reported from 39% to 63% and the specificity of 90% to 99% ((Turnbull, 1995). Thus, the presence of a systolic-diastolic bruit is highly suggestive of RAS and should be screened for, while the absence of a bruit does not exclude RAS (Rosener 2001).

2.2.1 Differential diagnosis

Some clinical situations have to been addressed in the differential diagnosis of ARVD (table 3).
**Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical findings</strong></td>
<td>- Abdominal or flank bruit</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td></td>
</tr>
</tbody>
</table>
*International Diabetes Federation:*  
- Central obesity is defined as waist circumference with ethnicity specific values or if BMI is >30 kg/m², central obesity can be assumed and waist circumference does not need to be measured.  
- And any two of the following:  
  - Triglycerides: > 150 mg/dl, or specific treatment for this lipid abnormality.  
  - HDL cholesterol: < 40 mg/dl in males, < 50 mg/dl in females, or specific treatment for this lipid abnormality  
  - BP: systolic BP > 130 mmHg or diastolic BP > 85 mmHg, or treatment of previously diagnosed hypertension.  
  - FPG > 100 mg/dl, or previously diagnosed type 2 diabetes. If FPG > 100 mg/dl, OGTT glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome |
| **Hypertension**    |  
- Refractory hypertension (BP > 160/95 mm Hg while receiving three or more antihypertensive agents) or associated acute pulmonary edema  
- Accelerated hypertension (increase in BP > 15% in 6 months)  
- Severe hypertension (DBP > 115 mm Hg or Grade III or IV retinopathy)  
- Recent-onset (within the last 2 years) hypertension  
- Onset of hypertension after age 60 |
| **Renal insufficiency** |  
- Elevated serum blood urea nitrogen > 20 mg/dl or creatinine > 1.4 mg/dl  
- Cockcroft-Gault CrCl < 50 ml/min without clear etiology  
- Acute renal failure attributable to ACEI or ARB therapy |
| **Atherosclerosis**  |  
- Abdominal aortic atherosclerosis or lower extremity artery stenosis  
- Peripheral artery disease or carotid artery stenosis / ischemic stroke  
- Coronary artery disease > 2 vessel disease |

Table 2. Patients at risk for further ARVD screening. BP: blood pressure; DBP: diastolic BP; FPG: Fasting plasma glucose; OGTT: oral glucose tolerance test; CrCl: creatinine clearance; ACEI: ACE inhibitors; ARB: angiotensin II receptor blockers.

<table>
<thead>
<tr>
<th>Clinical situations</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal bruit</td>
<td>Splenic arteriovenous fistula, hepatic cirrhosis, hepatoma, abdominal aortic aneurysm and coarctation, celiac artery compression syndrome, intestinal ischemia, and pancreatic carcinoma</td>
</tr>
</tbody>
</table>
| Progressive renal insufficiency or renovascular hypertension | - Benign hypertensive nephrosclerosis  
- Atheroembolic renal disease |
| Renal artery stenosis                          | - Renal artery dissection  
- Fibromuscular dysplasia |

Table 3. Differential diagnosis of ARVD.
Most of these clinical situations could be differentiated correctly by the image study such as computed tomography and renal angiography. They are not necessary mutually exclusive and may be coexisted. For instance, benign hypertensive nephrosclerosis, a renal parenchymal disease can be present together with ARVD. Atheroembolic renal disease is associated with aortic manipulation or occurs spontaneously. The clinical features include abrupt decline of renal functions and evidence of atrial fibrillation with extrarenal embolism (Hazanov, 2004). Fibromuscular dysplasia (FMD) characterized by fibrous thickening in arterial wall usually involves 60%-75% of renal and 25%-30% of carotid artery stenosis (Luscher et al, 1981; Gray et al 1996) and is responsible for 25% cases of renovascular hypertension (Pickering, 1989). In angiographic findings, FMD demonstrates classic images of “string-of-beads” appearance, aneurism, and focal or tubular stenosis. In contrast to ARVD, FMD occurs predominantly in young women of childbearing age and involves the middle and distal portion of main renal artery (Das et al, 2007).

2.3 The screening and diagnostic modality

With the progression of the technology, a variety of modalities emerge for screening and diagnosis of ARVD (table 4). In addition to renogram and nuclear scintigraphic captopril renogram, dopplex ultrasonography has been used successfully to detect the presence of renal artery stenosis due to the non-invasive and contrast-free characteristics. However, it is usually limited by a wide operator-dependent variation, obesity of patient and time consuming. Magnetic resonance (MR) angiography increases the comparability between examinations (Fig. 1A). Both of the sensitivity and specificity are estimated within 90-95%. Till now, multi-detector computed tomography (MDCT) angiography (Fig. 1B) almost replaces the role of catheter angiography as the first diagnostic tool for ARVD because of its high utility and detection rate in evaluation of other abdominal problems.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Sensitivity/specificity</th>
<th>PPV/NPV</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renogram</td>
<td>75% /75%</td>
<td>50-75% /60%</td>
<td>Almost for screening only</td>
</tr>
<tr>
<td>Captopril renogram</td>
<td>83-90% / 80-93%</td>
<td>70-92% /60-100%</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Dopplex ultrasonography</td>
<td>75-90% /62-90%</td>
<td>60% /95%</td>
<td>Wide operator-dependent variation, time consuming</td>
</tr>
<tr>
<td>MR angiography</td>
<td>88-95% / 90-95%</td>
<td>60-75% /90-98%</td>
<td>Gadolinium-induced renopathy</td>
</tr>
<tr>
<td>MDCT angiography</td>
<td>94-100% / 93-100%</td>
<td>71-100% /95-100%</td>
<td>Contrast-induced renopathy</td>
</tr>
<tr>
<td>Catheter angiography</td>
<td>100%</td>
<td>100%</td>
<td>Contrast-induced renopathy, bleeding, arterial dissection, distal embolism</td>
</tr>
</tbody>
</table>

Table 4. Diagnostic modalities for ARVD. PPV: positive predictive value; NPV: negative PV.

2.4 Therapeutic indications

As we know, ARVD is highly associated with systemic atherosclerosis and occurs after the occurrence of coronary artery disease and peripheral artery disease. Accordingly, an early medical intervention and risk factors reductions to prevent the development of ARVD in the
presence of systemic atherosclerosis and many risk factors is important. On the other hand, a critically unilateral or bilateral stenosis of renal artery disease may need further mechanical manipulations such as renal angioplasty, stenting and bypass surgery. We will describe the two parts of therapy in detail in the following paragraphs.

2.4.1 Medical treatment

Life style modification and a control of established risk factors is the golden rule for most atherosclerotic vascular disease including diabetes, obesity, hypertension, low density lipoprotein cholesterol (LDL-C), inflammation and smoking. However, no reports prove the effect of medical control to reduce the occurrence of ARVD or prevent disease progression. It is reasonable that medical treatment should be started in middle-aged persons at risk to prevent ARVD. The choice of pharmacological agents and the goal aimed to achieve with or without vascular events will be listed in table 5.

Among the antihypertensive agents, ACE inhibitors or angiotensin II receptor blockers (ARBs) are observed with the most effectiveness in control of the blood pressure for patients with ARVD (Dworkin & Jamerson, 2007). Surgical intervention should be considered if refractory hypertension persists. However, adequate control of blood pressure by chronic administration of antihypertensive drugs can not be guaranteed the prevention of stenotic lesions progression and post-stenotic renal atrophy.

2.4.2 Interventional treatment

Renal artery revascularization for bilateral or unilateral disease in a single viable kidney is indicated in the following situations (Greco & Breyer, 1997; Textor, 2004).

1. Severe or refractory hypertension
2. Recurrent episodes of acute pulmonary edema
3. Unexplained progressive renal insufficiency
4. Progressive renal function impairment with optimal blood pressure control.

Beyond these criteria mentioned above, the procedure of revascularization should be performed after weighing the benefits against the hazards. Therefore revascularization
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<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Medications</th>
<th>(non) CVD / Goal</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Insulin, secretagogues, sensitizers, α-glucosidase inhibitors, peptide analogs</td>
<td>Non-CVD/ HbA1c&lt; 6.5 % CVD/ LDL-C &lt; 7.0 %</td>
<td>Adverse cardiovascular effects and metabolic abnormalities of anti-diabetic agents</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ACEI/ ARB, BB, CB, diuretics</td>
<td>Non-CVD/ BP&lt; 120/85 mg/L CVD/ BP&lt; 140/90mg/dl</td>
<td>-A J-curve relationship between hypertension and cardiovascular mortality -ACEI/ARB should be used carefully in bilateral ARVD</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Statin, fibrates, resins, niacin, ezetimibe,</td>
<td>Non-CVD/ LDL-C&lt; 100 mg/L CVD/ LDL-C &lt; 70mg/dl</td>
<td>Multi-drug interaction and dose effect related rhabdomyolysis</td>
</tr>
<tr>
<td>Inflammation</td>
<td>-Antiplatelet agents -Statin -Investagated drugs</td>
<td>Non-CVD/ hs-CRP&lt; 2mg/L CVD/ not established</td>
<td>According to the JUPITER trial only (Ridker et al, 2008)</td>
</tr>
</tbody>
</table>

Table 5. Modifiable risk factors for ARVD. CVD: cardiovascular disease including myocardial infarction and ischemic stroke; ACEI: ACE inhibitors; ARB: angiotensin II receptor blockers; BP: blood pressure; BB: beta-blocker; CB: calcium receptor blocker; JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; CRP: C-reactive protein.

should be aimed for patients with a reversible status of chronic renal insufficiency and resistant hypertension instead of reduing their mortality. A review literature has demonstrated that half of patients with ARVD have no change in renal function, while one fourth improve and one fifth deteriorate their renal function after renal stenting (Fig.1A & B) (Leertouwer et al, 2000).

Fig. 2. An atherosclerotic ostial lesion at right renal artery. Panel A: catheter renal angiography (An arrowhead indicates a lesion from ostial to proximal right renal artery; Panel B: post-percutaneous transluminal angioplasty with stenting (An arrowhead indicates stenting site of right renal artery).
Accordingly, only 20-25% of patients may be eligible for elective renal revascularization. There have some image, histology and clinical evidence to select patients with ARVD having benefits to undergo renal artery revascularization which is described as follow (Novick et al, 1987; Muray et al, 2002).

1. Visualization of the collecting system either on an intravenous pyelogram or during the pyelogram phase after renal arteriography
2. Kidney length ≥9 cm.
3. The presence of intact glomeruli on frozen section biopsy at the time of surgery.

There are three methods for renal artery revascularization (table 6).

<table>
<thead>
<tr>
<th>Revascularization</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA without stenting (Connolly et al, 1994)</td>
<td>Non-ostial lesions</td>
<td>-65-70% success rate for lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-35-50% improvement of renal functions</td>
</tr>
<tr>
<td>PTA with stenting (ASTRAL investigators, 2009; Stone et al, 2011; White, 2010; Davies et al, 2009)</td>
<td>Ostial and non-ostial lesions</td>
<td>-Significantly lower restenosis rate than PTA alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-98.8% success rate for lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-10.6-19% TVR rate within 5-10 years period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Inconclusive results of the improvement of renal functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Complication rate: 9% in 24 hours; 20% in 1 month; mortality rate &lt;1%</td>
</tr>
<tr>
<td></td>
<td>-Early primary branching of the main renal artery</td>
<td>-55-65% improvement of lesions of renal functions</td>
</tr>
<tr>
<td></td>
<td>-Aortic reconstruction near the renal arteries</td>
<td>-In-hospital mortality rate: 3-10%</td>
</tr>
</tbody>
</table>

Table 6. Comparison of three types of revascularization intervention. PTA: percutaneous transluminal angioplasty; TVR: target vessel revascularization; ASTRAL: Angioplasty and Stenting for Renal Artery Lesions; ACC/AHA: American College of Cardiology Foundation/American Heart Association.

3. Conclusion

ARVD reflecting a status of systemic atherosclerosis is associated with chronic renal disease. Life style modification and risk factors reduction are important for the primary prevention of ongoing renal dysfunction and secondary prevention of subsequent cardiovascular events. Some clinical features of patients at risk for ARVD should be highlighted and both medical treatment and mechanical procedures should be taken as early as possible if uncontrolled hypertension leading to end-organ damage or progressive renal insufficiency develops.
4. Acknowledgement

We thank Dr. Yu-Guang Chen, Tri-Service General Hospital for his kindly providing the image of MDCT angiography.

5. References


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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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