Renal Artery Intervention by Nephrologists: A More Selective Approach

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Road Map

- Background
- Defining the Controversy
- The Nephrologists’ Perspective
- Future Directions
- Case discussion
Background

Table 2. Stages and Prevalence of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>90</td>
<td>5,900 3.3</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
<td>5,300 3.0</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
<td>7,800 4.3</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
<td>400 0.2</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure/ Dialysis</td>
<td>≤15 or dialysis</td>
<td>300 0.1</td>
</tr>
</tbody>
</table>


Percentages total >100% because NHANES III may not have included patients on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

For Stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >15 mg/g (women) on two measurements. Reproduced with permission.

ESRD Projected Prevalence
Background - Epidemiology

Up to 40% of selected hypertensive patients with end-stage renal disease (ESRD) have RAS.

Background – Clinical Presentation of RAS

- Hypertension
  - Abrupt onset of hypertension before the age of 50 years (suggestive of fibromuscular dysplasia)
  - Abrupt onset of hypertension at or after the age of 50 years (suggestive of atherosclerotic renal artery stenosis)
  - Accelerated or malignant hypertension
  - Refractory hypertension (not responsive to therapy with ≥3 drugs)

- Renal abnormalities
  - Unexplained azotemia (suggestive of atherosclerotic renal-artery stenosis)
  - Azotemia induced by treatment with an angiotensin-converting-enzyme inhibitor
  - Unilateral small kidney
  - Unexplained hypokalemia

- Other findings
  - Abdominal bruit, flank bruit, or both
  - Severe retinopathy
  - Carotid, coronary, or peripheral vascular disease
  - Unexplained congestive heart failure or acute pulmonary edema
Background – Pathophysiology of RAS

• Activation of the renin-angiotensin-aldosterone (RAA) system produces renal and systemic vasoconstriction, salt retention, and activation of the sympathetic nervous system.
• Other actions of angiotensin II (Ang II) promote pressor mechanisms, vascular remodeling, cardiac dysfunction, and tissue fibrosis.

Background – Progression of Disease
Background – Progression of Disease

• RAS > 50% ≠ Ischemic Nephropathy (no fibrosis resulting from hemodynamic changes)

• Ischemic Nephropathy ≠ RAS > 50% (small vessel disease)

The Controversy

• To intervene or not to intervene? – that is the question… And when?
The largest portion of this increase derives from procedures undertaken by cardiologists.*


<table>
<thead>
<tr>
<th>Physician Specialty</th>
<th>1996</th>
<th>1998</th>
<th>2000</th>
<th>% of Increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>2,380</td>
<td>5,069</td>
<td>9,220</td>
<td>387</td>
</tr>
<tr>
<td>Radiology</td>
<td>4,700</td>
<td>5,380</td>
<td>7,660</td>
<td>63</td>
</tr>
<tr>
<td>Surgery</td>
<td>300 (4)</td>
<td>490 (4)</td>
<td>760 (4)</td>
<td>153</td>
</tr>
<tr>
<td>Other</td>
<td>280 (4)</td>
<td>490 (4)</td>
<td>880 (5)</td>
<td>214</td>
</tr>
<tr>
<td>Total</td>
<td>7,660</td>
<td>11,400</td>
<td>18,520</td>
<td>142</td>
</tr>
</tbody>
</table>
The Controversy

• Recent guidelines from professional organizations lend support to the application of interventional vascular procedures into the renal arteries and inclusion of renal arteriography as part of coronary angiographic procedures.*


The Controversy

• CMS convened a meeting of its medical advisory group regarding treatment of RAS.

• The introductory statement read as follows: "In view of the uncertainty regarding optimal strategies for evaluation and management of atherosclerotic RAS, as well as the controversy about the risks and benefits of treatment, the CMS internally generated in February 2007 a national coverage analysis to examine the best treatment of RAS."
The Controversy

- CMS commissioned an analysis of published information regarding the benefits of revascularizing the kidney for atherosclerotic RAS by the Agency for Healthcare Research and Quality.

- The results of this analysis were published in December 2006: “The available information is insufficient to support benefits regarding mortality, progressive kidney disease, or cardiovascular events.

- “Thus, the published literature cannot support the observed, massive expansion of endovascular intervention.” *


The Controversy

- During the same time interval, at least four prospective, randomized trials for atherosclerotic RAS (ASTRAL, STAR, RAVE, CORAL) were started to examine the role of medical therapy alone as compared with medical therapy plus stent revascularization.

- In the United States, the National Heart, Lung, and Blood Institute of the National Institutes of Health is funding the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) trial. *

The Controversy

• This trial seeks to randomly assign 1080 patients to "optimal medical therapy" with or without renal artery stenting and evaluate clinical events including death, stroke, coronary artery disease events, congestive heart failure, kidney failure, and uncontrolled hypertension.

• A central premise of CORAL is that neurohormonal activation (mainly of the renin-angiotensin and sympathoadrenergic system) largely determines the morbidity from RAS.

• This trial has had difficulty meeting enrollment goals.

Why Are Nephrologists Averse to RAS Intervention?

• Nephrologists have moved toward a more conservative clinical stance in recent years, perhaps as a pragmatic counterweight to enthusiastic interventional specialties.*

Why Are Nephrologists Averse to RAS Intervention?

Table 1: Summary of Reviewed Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Intervention</th>
<th>Studies, n</th>
<th>Quality, n</th>
<th>Applicability, n</th>
<th>Participants, n</th>
<th>Year of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>Angioplasty with stent placement versus medical therapy</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized trials</td>
<td>Angioplasty without stent placement or combination of angioplasty with and without stent placement versus medical therapy</td>
<td>2*</td>
<td>2</td>
<td>1</td>
<td>103</td>
<td>1992-1995</td>
</tr>
<tr>
<td>Comparison studies</td>
<td>Renal denervation versus medical therapy</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>1996-2003</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Medical treatment</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Natural history</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>724</td>
<td>1990-1999</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Angioplasty with stent placement</td>
<td>21</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>1996-2002</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Angioplasty without stent placement</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>473</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Surgical revascularization</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>931</td>
<td>1996-2002</td>
</tr>
</tbody>
</table>

Table 2: Effects of Renal Artery Revascularization versus Medical Treatment Alone on Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Strength of Evidence</th>
<th>Studies (Participants), n</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Weak</td>
<td>1 (95)</td>
<td>No large difference in mortality up to 5 years between revascularization and medical treatment</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Moderate</td>
<td>1 (870)</td>
<td>1 (69)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Acceptable</td>
<td>2 (102)</td>
<td>0 (87)</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>Weak</td>
<td>1 (65)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Weak</td>
<td>1 (65)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>
Why Are Nephrologists Averse to RAS Intervention?

Retrospective outcomes data to define RF

Current Limitations of Our Knowledge

- It is not clear why some patients deteriorate after renal revascularization.
- The selection of patients for revascularization is controversial because of uncertainty regarding the likely outcomes.
- There is no good test to predict whose GFR will decline and whose will improve.
- Misconceptions about the natural course of CKD progression.
Future Directions

• It is almost certain that many, if not most, patients now being subjected to endovascular stenting of the renal arteries have only limited benefit, regarding either BP response or improvement in kidney function. *


Future Directions

• The subset of patients with "critical" renal artery stenosis stand to have major clinical benefit from restoring kidney perfusion and major adverse outcomes if not detected and treated. *

• The definition of "critical " has historically been radiographic or hemodynamic.

Future Directions

<table>
<thead>
<tr>
<th>Questions</th>
<th>Tools for Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of vascular occlusion?</td>
<td>Quantitative angiography, translesional gradients, intravascular ultrasound</td>
</tr>
<tr>
<td>Treatable?</td>
<td>Vessel location, associated disease, accessory vessels, aneurysm, occlusion</td>
</tr>
<tr>
<td>Responsible for disease?</td>
<td>Evident activation of pressor systems (e.g., renin) Duration of change (e.g., BP) renal function; other measures of tissue ischemia (e.g., BOLD MR, PET energy consumption); activation of fibrogenic, inflammatory, or oxidative pathways</td>
</tr>
<tr>
<td>Benefit from revascularization?</td>
<td>Rapidity of evolution, preexisting injury (e.g., hypertension, diabetes, other kidney disease), comorbid disease risk, associated procedural risk to kidney (e.g., atheroembolic potential), response to other medical therapy Risk for disease progression, salvageability of kidney function (resistive index, BOLD MR)</td>
</tr>
</tbody>
</table>

Future Directions

• Most imaging procedures focus on the first two items—the anatomic severity and approachability of renal vascular lesions.

• It is likely that the third and fourth items—diagnostic measures to evaluate the role of vascular occlusive lesions in generating disease and the likelihood of clinical benefit after restoration of vessel patency—are more important.
Future Directions

• A recognized drawback of clinical treatment trials is the intermixture of high-risk and low-risk patients into the "average" of the entire cohort.*

• A definition of the RF associated with good and bad outcomes is necessary.


Risk Factors for Outcomes

• Pre-intervention GFR
• Initial size of the treated kidney
• Vascular resistive index
• Patient age
• Lateralization to the affected kidney
### Inclusion/Exclusion Criteria

#### Inclusion Criteria
1. Documented history of systolic hypertension, $\geq 155$ mmHg on two or more antihypertensive medications
2. One or more RAS
   a. $\geq 60\%$ and $< 80\%$ by angiography with a $\geq 20$ mmHg systolic pressure gradient utilizing a $\leq 4-F$ diameter device, or
   b. $\geq 80\%$ and $< 100\%$ by angiography
New Algorithm

Case Presentation: RAS

- 62 yo female with DM, RCC s/p right nephrectomy, CKD, CAD, now requiring CABG. Sent for evaluation of RAS found on MRA. Cr = 2.2.
Exchange Method

Bare-wire Method
Renal artery intervention → CABG

Creatinine

Thank you