Renal Interventions: Indications and Outcomes

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Clinical scenarios

Which patient would likely benefit from renal artery revascularization?

- **Patient A** – 60 y/o male with 20 year hx of htn; on 2 drug therapy for 10 years. Cr 1.0. 70% right RAS
- **Patient B** – 55 y/o female w/ 10 year hx of htn. On 2 drug therapy. Recently increased to 3 drugs. Cr 1.6 (Cr. 1.2 in year prior) 70% RAS.
- **Patient C** – 65 y/o diabetic male with 2 drug hypertension. CRI for 15 years. Current Cr. 1.8. 80% RAS.
Objectives:

- Background
- Pathophysiology
- History and Physical Findings
- Evaluation
- Indications for Intervention
- Outcomes
Renovascular disease
  - Vasculitis
  - Fibromuscular dysplasia
  - Atherosclerosis
Atherosclerotic RAS (ARAS)
- Most common cause of RAS in the adult
- Estimated to effect ~1 million in US
- Prevalence thought to be 7–25%, increasing with each decade of life
- Prevalence likely to increase with increased life expectancy
  - Hypertensive pts (DBP > 100 mmHg) upwards of 50–60%
- Evidence that ARAS
  - Sequela of generalized atherosclerosis
  - Marker of future atherosclerotic events

Background cont.

- ARAS
  - More common in patients with DM, HTN, hypercholesterolemia, and smokers
  - Associated with PVD and CAD (85% have some extra-renal disease)
  - Bilateral in 1/3
  - Progressive
Natural History of ARAS
- Progressive disease in 30–70% over 10 years
  - ~10% with interval renal artery occlusion
- Renal Loss
  - Progressive renal atrophy in 14–49%
  - > 26% loss over 14.4mo in pts with >60% RAS
- Ischemic Nephropathy
  - Reported in 14–43% azotemic pts >45y/o
  - Pts starting RRT, cause in up to 25%
  - Dialysis dependent ischemic nephropathy
    - High mortality (30%/year, median survival 27months)
Progression of Disease

76 y/o male with NIDDM, PVD, and HTN

Baseline

Three years later
Main clinical syndromes of ARAS
- Renovascular hypertension
- Ischemic nephropathy
- Cardiac disturbance syndromes (flash pulmonary edema, refractory CHF, unstable angina)
Pathophysiology

- ARAS
  - Renal Hypoperfusion ➔ progressive tissue loss ➔ ischemic nephrophathy
  - Activation of RAAS ➔
    - Incr. Renin ➔ AT1 ➔ AT2 ➔ systemic hypertension, LVH, diastolic dysfunction
    - Aldosterone ➔ fluid retention ➔ flash pulmonary edema, CHF
Pathophysiology cont.

- Simplistic view
- Much more complex
  - Not all lesions symptomatic
    - 49–77% prevalence of ARAS at autopsy
    - Only ~5% hypertension secondary to renovascular dz
  - Not all lesions progress
    - 60–70% lesions do not progress
    - Concurrent small vessel disease can make hemodynamically significant lesions physiologically unimportant
History and Physical Findings

History:

- Age >50
- HTN: short duration (<1 year), sudden worsening, difficult to control (>3drugs)
- Hx of athero in other distributions
- Azotemia of short duration or sudden rise in creatinine following initiation of ACE-I
- Flash pulmonary edema/recurrent CHF despite normal EF
- Unstable angina
- Abdominal or flank bruit
H&P cont.

- Laboratory
  - Hyperkalemia (r/o aldosteronoma)
  - Hyperlipidemia
  - Proteinuria usually absent (may be present sec. to hyperperfusion of contralateral kidney)
Evaluation

- Non-Invasive studies:
  - Duplex US
  - CTA
  - MRA
  - Renal Scintigraphy
  - DSA
Indications for Treatment

- Renovascular hypertension
  - Onset of hypertension >60 y/o
  - Refractory hypertension (>3 drug)
  - Accelerated hypertension
  - Malignant hypertension
  - Renal salvage (solitary kidney, bilateral disease)
  - Recurrent pulmonary edema
Indications for Treatment

- Ischemic Nephropathy
  - Unexplained decrease in renal function
  - Decreasing renal mass
  - Decrease renal fxn or ARF after starting antihypertensive medication (ACE inhib)
  - Bilateral disease
  - Sudden onset of renal insufficiency
Case 1

71 y.o FEMALE → DIALYSIS X 1 MOS; RT = 6cm; LT = 9.8cm

BOTH RAs → OCCLUDED

OFF DIALYSIS @ 3 WKS

RENAral ARTERy STENTING
Case 2

- 66 y/o woman with HX of renal insufficiency (baseline Cr 1.9 mg/dl) and HTN that was medically controlled
- Presents with CHF (mild LV dysfunction on echo, MI ruled out)
- Noted to have Cr 3.2mg/dl
- **What would you do next?**
Duplex ultrasound

- U/S demonstrates no hydronephrosis
- Kidneys measure 9.5 cm bilaterally
- Question of bilateral renal artery occlusion
- Angiogram? Contrast?
Bilateral RA occlusion
Distal left RA reconstituted

How would you treat this?
Left occlusion traversed and stented
No further intervention at that time
CHF resolved
Plavix for 30 days and aspirin for life
Cr improved to 2.2 mg/dl at 4 weeks
Further management...
Returned for Intervention on Right Side

Successfully crossed and stented the right RA occlusion
8 Week F/U

- Baseline Cr. 3.2, CR 2.2 after left PTRA, and then 1.2mg/dl after bilateral renal PTRA
- No further episodes of CHF
Treatment options

- Numerous studies
- Conflicting data
- Lack of good randomized controlled trials

- Medical therapy
- Surgical revascularization
- Percutaneous revascularization
  - Balloon angioplasty
  - Stent placement
Comparative trials:

- Surgical revascularization and stenting are better than PTA alone at restoring RA patency.
- Neither demonstrate better clinical outcomes.

- Renal artery stenting has better primary success as well as long term patency than PTA alone.
  - Primary success (<50% residual stenosis)
    - 88% for stent placement
    - 57% for PTA
  - 6 month patency
    - 86% for stent
    - 52% for PTA

PTA/Stenting effects on Hypertension

- Benefit in 49–70%
- 10–20% cured (off all meds @ 1 year)

Benefit for Renal Insufficiency

- Renal function improves in 26% (25/96)
- Renal function stable in 36.5% (35/96)
- Renal function worsens in 37.5% (36/96)
Clinical trials

1998–2000

- 3 separate RCT’s
  - 1998– Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) n=25
    - Conclusion: No significant differences for hypertension
  - 1998– Essai Multicentrique Medicaments vs Angioplastie (EMMA) trial, n=23
    - Conclusion: No differences for hypertension but more adverse events with angioplasty
    - 27% crossover from medical therapy to PTA
  - 2000– Dutch Renal Artery Stenosis Intervention Cooperative Study Group (DRASTIC) n=56
    - Conclusion: No significant difference in BP c/w BMT.
    - 44% crossover (medical Rx to PTA)
2003– Nordmann AJ et al.

- Meta–Analysis of RCT’s
- Used the data from SNRASCG, EMMA, DRASTIC
- N= 210 patients

Findings:
- Significant decrease in BP after PTA (SBP ~7mmHg)
- Higher patency rate (52% vs 19% after 12 months)
- Use fewer antihypertensive medications
- Appeared to have fewer major cardiovascular and renovascular complication (OR 0.27)
- NO significant effect on renal function
2003 – Ramos et al.

- Prospective, non-randomized trial
- N = 105
- mean f/u 371 days
- Affects of renal function on outcome after PTAS
- Stenosis > 70% with pressure gradient > 30mmHg

Findings:
- Overall, significant reductions in SBP and DBP; modest improvement in GFR
- Subgroup analysis:
  - Lower GFR ➔ Stat. signif improvement in GFR, NS BP reduction
  - Higher GFR ➔ sig reduction of BP, NS change in GFR
1999– Angioplasty and Stenting for Renal Artery Lesions (ASTRAL trial)
Largest multicenter, randomized, unblinded clinical trial
57 hospitals (53 UK, 3 Aus, 1 NZ)
N=806 randomized to revascularization + medical Rx or medical Rx alone.
Median f/u 34 months
ASTRAL trial

Selection criteria
- Screen for Si/Sx of ARAS
- Imaged (CT/MR) U/S, labs

Eligibility:
- Substantial ARAS (>50%) in at least one renal artery
- If pt’s doctor “was uncertain that the patient would definitely benefit from revascularization.”
Outcome measures:

- Primary:
  - Renal function

- Secondary:
  - BP
  - **Time to 1st renal event** (new onset acute kidney injury, dialysis, tx, nephrectomy, death from renal failure)
  - **Time to 1st CV event** (MI, CVA, death from CV causes, angina, CHF, fluid overload, CABG, other peripheral a. procedure)
  - Overall mortality
Supplementary Appendix Figure 1: CONSORT Diagram for ASTRAL – Patient Recruitment and Follow-up

Randomized (N=806)

403 Revascularization
- 335 (83%) attempted revascularization
  - 317 (95%) revascularizations successfully completed
  - 18 (5%) failed revascularization procedures
    - failure to cross stenosis (n=13)
    - lesion undilatable (n=5)
- 68 (17%) not revascularized
  - minimal stenosis* (n=33)
  - lesion occluded since randomization (n=4)
  - patient not suitable for revascularization (n=6)
  - patient refused/withdrew consent (n=12)
    - other (n=8)
    - unknown (n=5)

403 Medical Therapy
- 379 (94%) remain on best medical management
- 24 (6%) have crossed-over and undergone revascularization

9 were lost to follow up
11 were withdrawn
103 deaths

11 were lost to follow up
7 were withdrawn
106 deaths
Findings:

- **Renal Function**
  - Slope of the reciprocal of Cr (rate of functional decline) favored revascularization (p=0.06)
  - Mean serum Cr 0.02mg/dl lower for revascularization group (ns p=0.64)

- **Blood Pressure**
  - Overall, SBP decreased in both groups (.27mmHg/yr) with no significant difference b/n groups
  - However, # of antihypertensive medications was significantly lower in revascularization group (p=0.03)
Findings cont.

- Renal Events
  - 73 events in 57 pts in revascularization group
  - 80 events in 58 pts in BMT group

- Cardiovascular events
  - 238 events in 141 pts in revascularization group
  - 244 events in 145 pts in BMT group

- Overall Survival
  - 103 deaths in revascularization group
  - 106 deaths in BMT group
Results:

- **Revascularization:**
  - 95% success
  - 95% pts received stent
  - 38 (9%) periprocedural complications (<24hr) – 19 serious
    - 1 pulmonary edema
    - 1 AMI
    - 5 renal embolization
    - 4 renal artery occlusions
    - 4 renal artery perforations
    - 1 femoral artery aneurysm
    - 3 cholesterol emboli ➔ periph gangrene/amputations
Results cont.

- Revascularization
  - 55 (20) adverse event (24hr–30days) 12 serious
    - 2 deaths (cardiac causes)
    - 4 groin hematoma/hemorrhage req. hospitalization
    - 5 Acute kidney injury
    - 1 renal artery occlusion
Conclusions:

- No evidence of a worthwhile clinical benefit in the initial years following revascularization in patients with ARAS.
- The upper confidence limits for a benefit from revascularization with respect to renal function were below levels that would be considered clinically relevant.
- No significant improvements in blood pressure or reductions in renal or cardiovascular events or mortality were seen.
- Revascularization was associated with substantial risks
Methodological Problems

- Unusual enrollment criteria of having an “uncertain indication” for renal revascularization
- Selection bias that favored enrollment of mild to moderate RAS (41% had < 70% stenosis)
  - No pressure gradient measurements
- Primary endpoint of progressive loss of renal function
  - 25% patients had normal renal function; 15% with only mildly impaired function
- Intention-to-treat analysis
  - 17% of revascularization group never received a stent
  - 6% of BMT group crossed over to stent
  - Further weakening any benefit from the revasc group
Methodological Problems cont.

- No Core laboratories
- Major procedural complication rate (9%) was 3–4 fold higher than that previously reported in other trials.

Table 1. Technical Success Rate and Complications of PRI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Procedure Success (%)</th>
<th>Death (%)</th>
<th>Dialysis (%)</th>
<th>Major Comp (%)</th>
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<tbody>
<tr>
<td>Tuttle et al⁵</td>
<td>148</td>
<td>98</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Rocha-Singh et al⁶</td>
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<td>97.3</td>
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<td>Blum et al⁵</td>
<td>68</td>
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<tr>
<td>White et al⁶</td>
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<td>99</td>
<td>0</td>
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<tr>
<td>Dorros et al⁶</td>
<td>163</td>
<td>99</td>
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<td>Ivanovic¹⁰</td>
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<tr>
<td>Zeller¹¹</td>
<td>215</td>
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<td>0</td>
<td>0</td>
<td>2.80</td>
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<tr>
<td>Total/average</td>
<td>1 023</td>
<td>98.8±1</td>
<td>0.24±0.2</td>
<td>0.09±0.2</td>
<td>2.34±1.5</td>
</tr>
</tbody>
</table>

Major Comp indicates major complication (death, myocardial infarction, emergency surgery, need for dialysis, or blood transfusion).
Future Developments

- CORAL Trial
  - Multicenter RCT started in 2006
  - Optimum medical therapy vs. stenting with optimum medical therapy
  - Primary entry criteria:
    - ARAS of >60% with pressure gradient of >20mmHg
    - ARAS of >80% regardless of gradient
    - Systolic hypertension >155mmHg on >2meds
  - Randomization of 1080 patients
  - With and without use of embolic protection device
The role of percutaneous renal intervention in the setting of ARAS is uncertain.

There are certainly groups of patients who benefit from renal intervention. Patient selection is key.

More insight into the pathophysiology of RAS with regards to outcome measurements is needed.

Data from the CORAL study will likely determine the fate of renal artery interventions.
Best outcomes for renal artery PTA/Stenting:
- Appropriate history (refractory to 3 drug HTN or rising creatinine w/o explanation)
- Lateralized on NM or U/S (with low RI)
- <65 y/o
- Male, Non-smoker, Non-DM
- Tight stenosis
- Vessel size greater than or equal to 6 mm best
- Stented if ostial lesion
- Kidney size >7–9 cm
Renal–angiotensin system is more than just simple plumbing

Component of renin related to innervation
- May guide/alter future therapy
- Sympathetic ablation
References