Renal artery stenosis – is routine intervention indicated?

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University of Florida College of Medicine, and
NF/SGVHS
20-50 rule of medicine

- Over a continual cycle of 20 years, 50% of what we think we know is found to be wrong...

- Less “cynical” version,
  - If, and only if,
  - Our minds are open to new ideas
  - Are we going to be able to provide better care in the future than we do now.
Three phases of a medical intervention

- Can we do it?
- Does it work?
- Is it better than other therapies?
General agreement exists that ...

- Renal artery stenosis alters renal function
  - Increased renin release, leading to hypertension
General agreement exists that...

- Renal artery stenosis alters renal function
  - Increased renin release, leading to hypertension
  - Decreased renal perfusion, leading to ischemic nephropathy
General agreement exists that:

- PTRA ± stenting and surgery have high rates of anatomic success
- These interventions improve BP control and GFR in a subset of people
Question for today is not “is RAS bad,” but “when and how to intervene?”

- For hypertension, which controls BP better?
  - “Routine intervention”
    - PTRA stent in all
  - “Salvage Intervention”
    - Medical therapy, possibly followed by intervention if BP remains poorly controlled
Question for today is not “is RAS bad,” but “when to intervene?”

- RAS is associated with high mortality and morbidity
  - Does intervention alter mortality or morbidity?
- What about “drive-by angiograms?”
  - What is the natural history of “incidentally identified” renal artery stenosis
Easy decisions

- Fibromuscular dysplasia
- Young adult with severe hypertension
# Demographics in FMD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% present, or Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>100%</td>
</tr>
<tr>
<td>CKD (creatinine &gt; 1.3 mg/dl)</td>
<td>19%</td>
</tr>
<tr>
<td>Female:Male</td>
<td>81% : 19%</td>
</tr>
<tr>
<td>Age</td>
<td>45 (19-70)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4%</td>
</tr>
<tr>
<td>Smoker</td>
<td>29%</td>
</tr>
</tbody>
</table>

Pathogenesis of FMD remains unknown

- Cigarette smoking and a history of hypertension are associated with an increased risk of this condition.
- No association with previous oral contraceptive use or endogenous sex hormones abnormalities.
- More common among:
  - First-degree relatives of patients with fibromuscular dysplasia of the renal arteries
  - Persons with the angiotensin-converting–enzyme allele ACE-I.

BP response is excellent

BP response is excellent and typically long-lasting

Recurrence may be higher than expected

Results very good, but not 100%

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of Patients</th>
<th>Technical Success Rate</th>
<th>Effect on Blood Pressure</th>
<th>Months of Follow up</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sos et al (^5)</td>
<td>1983</td>
<td>11</td>
<td>97 %</td>
<td>59 % 14 %</td>
<td>16 (4-40)</td>
<td>6 %</td>
</tr>
<tr>
<td>Baert et al (^7)</td>
<td>1990</td>
<td>22</td>
<td>81 %</td>
<td>58 % 21 %</td>
<td>26 (6-72)</td>
<td>NR</td>
</tr>
<tr>
<td>Tegtmeyer et al (^59)</td>
<td>1991</td>
<td>66</td>
<td>100 %</td>
<td>39 % 39 %</td>
<td>39 (1-121)</td>
<td>13 %</td>
</tr>
<tr>
<td>Bonell et al (^60)</td>
<td>1995</td>
<td>105</td>
<td>89 %</td>
<td>22 % 63 %</td>
<td>43 (0-168)</td>
<td>11 % major</td>
</tr>
<tr>
<td>Jensen et al (^61)</td>
<td>1995</td>
<td>10</td>
<td>97 %</td>
<td>39 % 47 %</td>
<td>12 (NR)</td>
<td>1 % major</td>
</tr>
<tr>
<td>Davidson et al (^62)</td>
<td>1996</td>
<td>21</td>
<td>100 %</td>
<td>52 % 22 %</td>
<td>NR</td>
<td>13 %</td>
</tr>
<tr>
<td>Klow et al (^63)</td>
<td>1998</td>
<td>49</td>
<td>92 %</td>
<td>26 % 44 %</td>
<td>9 (1-96)</td>
<td>0 %</td>
</tr>
<tr>
<td>Berrer et al (^64)</td>
<td>2002</td>
<td>27</td>
<td>100 %</td>
<td>74 % 26 %</td>
<td>10 (NR)</td>
<td>7 %</td>
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<td>Surow et al (^65)</td>
<td>2003</td>
<td>14</td>
<td>95 %</td>
<td>79 % 21 %</td>
<td>NR</td>
<td>28 %</td>
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<td>de Frass nette et al (^66)</td>
<td>2003</td>
<td>70</td>
<td>94 %</td>
<td>14 % 74 %</td>
<td>39 (1-204)</td>
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NR denotes not reported.
The percentage shown is the total for cured and improved.

Easy decisions about RAS

- Fibromuscular dysplasia
  - Young adults with severe hypertension
- ARF with ACE-I or ARB use
  - Exclude intravascular volume depletion
Hard decisions

- Atherosclerotic renal artery stenosis

- Why
  - Different cases being identified
  - Natural history has changed due to changes in medical therapy
    - Lipid-lowering medications
    - Better anti-hypertensive medications
    - Improved recognition of cigarette hazards
Mechanism of hypertension differs in acute and chronic RVH

How much renal artery stenosis do you need to alter renin release?

How much renal artery stenosis do you need to alter renin release?

Changes in blood pressure attributed to revascularization

- SBP: Change in BP (mmHg) = -21
- DBP: Change in BP (mmHg) = -6
Renal artery stenosis interventions in Medicare beneficiaries

Number of procedures

- Angioplasty/stent
- Surgery

Modified from Murphy, Am. J. Roent. 2004
Medicare (CMS review) 2007
Changes in blood pressure attributed to revascularization

Observational Series n=1058
Prospective Series n=210

SBP
-21

DBP
-6
-3
Randomized, controlled trials of PTRA for renal artery stenosis

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SNRASCG Protocol

- A total of 135 eligible patients were identified, of whom 55 (44%) were randomized.
- Eligible patients had sustained hypertension, with a minimum diastolic BP of 95 mm Hg on at least two anti-hypertensive drugs.
- Renal artery stenosis was defined by renal angiography as at least 50% stenosis in the affected vessel.
- All patients were observed during an initial 4-week run-in period on a fixed drug regimen and subsequent changes measured from this 4-week baseline.

SNRASC CG Results – unilateral RAS

Does stenting alter event-free survival?

After adjusting for age, smoking, previous Cardiovascular disease and heart failure.

EMMA criteria

- Men and women younger than 75 years,
- DBP readings >95 mm Hg on at least three occasions and/or receiving antihypertensive treatment,
- Creatinine clearance >50 mL/min.
- Anatomic inclusion criteria, from the qualifying angiogram immediately before randomization.
  1. Atherosclerotic nature of the RAS,
  2. RAS of either ≥ 75% without thrombosis or of ≥60% with a positive lateralization test (lateralized intravenous pyelography, renal scintigraphy, or renal vein renin determination
  3. Not been previously dilated; and
  4. A functional kidney on the opposite side exhibiting a normal main artery or an arterial diameter reduction <50%.
EMMA Study

EMMA Study

Oscillometric device

24-hour ambulatory BP

Sphygmomanometer

angioplasty better  medication better

angioplasty better  medication better

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DRASTIC Study

- PTRA SBP
- PTRA DBP
- Medical SBP
- Medical DBP

Baseline: 179, 104, 103
3 months: 169, 99, 101
12 months: 160, 93, 96

DRASTIC Study – decreased number of medications with PTRA

Baseline | 3 months | 12 months
---|---|---
Medical | 2.0 | 2.5 | 2.4
PTRA | 2.0 | 1.9 | 1.9

Does intervention improve quality of life? Results from DRASTIC study

- MOS Short-form general health survey, validated Dutch form
- EuroQol instrument, validated Dutch version
- Physical symptoms questionnaire for hypertension and anti-hypertensive treatment, validated Dutch form
- Measurements at time of randomization, 3 months and 12 months

Quality of life results – changes from baseline at 3 months

Quality of life results – changes from baseline at 12 months

P Krijnen, et al. J Hum Hypertension
19:467-470, 2005
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Angioplasty and Stenting for Renal Artery Lesions
Study design

- Recruitment from 2000 – 2007
- 806 patients
- 56 centers
Entry criteria

- At least one ARVD lesion suitable for balloon angioplasty and/or stent.
  - Confirmed by intra-arterial angiography, magnetic resonance angiography or computerized tomography.
- No previous revascularization procedure for ARVD.
- The medical team responsible for the patient’s care is substantially uncertain about whether early revascularization is clinically indicated.
  - In particular, it should be unlikely that revascularization will become definitely indicated within the next 6 months.
Study size

- 80% power to detect 20% in rate of renal function loss
- Originally powered to enroll 1000 patients over 5 years
- Less crossover, mortality and loss to follow-up than predicted
- Size reduced to 750 patients
Study design

- Diagnosis of ARVD (unilateral or bilateral)
  - Revascularization not contraindicated

- Uncertain whether to revascularize
  - INFORMED CONSENT & RANDOMIZATION

- Revascularization with angioplasty and/or stent insertion (and medical treatment)

- No Revascularization
  - Medical treatment only

- Follow-up at 1-3 months, 6-8 months, 1 year, then annually.
  - Renal function, Blood Pressure, Renal and vascular events, Mortality

*Journal of Human Hypertension* (2007) 21, 511–515
## Baseline characteristics

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<th>Characteristic</th>
<th>Mean</th>
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<tr>
<td>Age</td>
<td>71</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>2.03 mg/dl</td>
</tr>
<tr>
<td>eGFR</td>
<td>40 ml/min/1.73m²</td>
</tr>
<tr>
<td>BP at randomization</td>
<td>150/76</td>
</tr>
<tr>
<td>% stenosis</td>
<td>76%</td>
</tr>
<tr>
<td>Male : Female (%)</td>
<td>63% : 37%</td>
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<tr>
<td>Follow-up</td>
<td>2.3 yrs</td>
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Primary outcomes at 1 yr

Change in serum creatinine

Improvement in BP

Improvement in SBP and DBP
Secondary outcomes

Number of events, n

Renal Events
- Medical: 47
- Stenting: 46

CV Events
- Medical: 107
- Stenting: 95

Mortality
- Medical: 81
- Stenting: 79
Pre-specified subgroup analyses for renal function preservation

- Baseline creatinine
  - < 150 µmol/L
  - 150-250 µmol/L
  - > 250 µmol/L

- eGFR
  - < 30
  - 30-45
  - > 45

- % RAS,
  - < 70%
  - 71-89%
  - > 90%

- Length of affected kidney

- Renal function worsening
  - Creatinine ↑ 20% or > 100 µmol/L in previous yr
Pre-specified subgroup analyses for renal function preservation

- Bilateral RAS or RAS >70% in solitary kidney (130 at 1 yr)
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<tr>
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<td>806 studied</td>
<td>2.3 years</td>
<td></td>
<td>Negative</td>
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Summary

- At present, no evidence that PTRA ± stent, as a general rule, improves:
  - BP control,
  - Quality of life,
  - Renal function, or
  - Mortality

- Use PTRA ± stenting for:
  - FMD
  - Recurrent flash pulmonary edema
  - ARF with ACE-I and/or ARB not due to volume depletion
  - Very resistant hypertension of recent origin (?)