Does intensive medical treatment improve outcomes in aortic dissection?

Frank A Loderer professor of medicine©, Janet T Powell professor of vascular biology and medicine©, Christoph A Mitterer professor of internal medicine/cardiology©

**Medical rx of acute aortic dissection (Hiratzka, Circulation 2010)**

“Aggressive” lowering of:
- SBP to < 100 or 120 mm Hg
- HR to < 60 bpm

1st line: IV β-blockers
Essentially unchanged over past 50 yrs

**Rx of HTN emergencies has changed: JNC 6 & 7**

- ↓ BP ≤ 25% initially
- to 160/100 mm Hg within next 2–6 hrs
- “avoiding excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia”.

**First-line β-blockers**

- Meta-analyses: worse outcomes in other settings
  - HTN rx (Wiysonge, JAMA 2013 & latter 2014):
    - no longer 1st line in NICE, ESH/ESC, JNC8
  - Peri-op β-blockers: 27%↑ in 30d mort (Bouri, Heart’14)
  - 2014 Cochrane review on β-blockers for chronic Type B dissection
    - no RCTs on medical therapy for dissection
    - “There is no strong source of evidence that one type of medication is superior to another”
How we got here: Wheat & Palmer, 1965

**TABLE I**—CLINICAL COURSE OF 20 PATIENTS WHO DEVELOPED SYMPTOMS WITHIN 24 HOURS OF BEGINNING NEW ANTITENSURF DICHRONIC MEDICATIONS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Antihypertensives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.L.</td>
<td>40</td>
<td>M</td>
<td>Headache</td>
<td>Hydralazine</td>
<td>SD</td>
</tr>
<tr>
<td>L.M.</td>
<td>50</td>
<td>F</td>
<td>Hypertension</td>
<td>Hydralazine</td>
<td>SD</td>
</tr>
<tr>
<td>S.W.</td>
<td>60</td>
<td>M</td>
<td>Headache</td>
<td>Hydralazine</td>
<td>SD</td>
</tr>
<tr>
<td>P.R.</td>
<td>70</td>
<td>M</td>
<td>Hypertension</td>
<td>Hydralazine</td>
<td>SD</td>
</tr>
</tbody>
</table>

The focus on inotropic effect (dP/dt)

- Beaven/Murphy BMJ 1956: AD occurred in 9 of 44 pts with severe HTN treated with hexamethonium (BP drug with positive inotropic effect)
- CF Simpson: Negative inotropes (reserpine & later propranolol) prevented aortic dissection in turkey model (chronic doses that did not affect BP or HR).

(Implied?) Withholding surgery might be more palatable if we substitute “intensive” medicine.

The only direct comparison? Mills 1979, Am J Surg

**TABLE II**—Survival of Patients

<table>
<thead>
<tr>
<th>Survival Type</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgically Treated (n = 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial 29</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>At 2 hr</td>
<td>14 (47%)</td>
<td>5 (100%)</td>
<td>10 (33%)</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>At 1 wk</td>
<td>3 (50%)</td>
<td>11 (85%)</td>
<td>2 (50%)</td>
<td>26 (65%)</td>
</tr>
<tr>
<td>At 1 mo</td>
<td>4 (50%)</td>
<td>8 (67%)</td>
<td>9 (50%)</td>
<td>21 (52%)</td>
</tr>
<tr>
<td>At 1 yr</td>
<td>4 (50%)</td>
<td>4 (50%)</td>
<td>4 (25%)</td>
<td>12 (30%)</td>
</tr>
</tbody>
</table>

Medically Treated (n = 17) Initial |        |         |          |       |
| Initial 8 | 0 | 2 | 6 | 16 |
| At 2 hr | 3 (100%) | 3 (100%) | 2 (67%) | 8 (89%) |
| At 1 wk | 1 (33%) | 7 (78%) | 8 (50%) | 16 (88%) |
| At 1 mo | 0 | 1 (33%) | 3 (33%) | 4 (25%) |
| At 1 yr | 0 | 3 (100%) | 3 (100%) | 6 (67%) |

Non-surgically (excluding Wheat) Treated (n = 22) Initial |        |         |          |       |
| Initial | 0 | 2 | 8 | 10 |
| At 2 hr | 8 (89%) | 3 (60%) | 8 (100%) | 19 (86%) |
| At 1 wk | 5 (56%) | 0 | 6 (75%) | 11 (50%) |
| At 1 mo | 4 (44%) | 0 | 4 (50%) | 8 (36%) |
| At 1 yr | 1 (11%) | 0 | 3 (38%) | 4 (18%) |

More early research

- Other small case series followed with ‘OK’ outcomes
  - Type A & B not distinguished before 1970, so hard to compare surgical and medical treatment
  - ‘Intimal tears’ in synthetic ‘aortas’ extended with ↑ intensity of pulsatile (but not laminar) flow
  - Extension of intimal tear made in dogs ↓ by drugs that ↓ both BP & inotropic force

Aorta vs patient

- These studies suggested beneficial effect on the aorta but did not address overall effect on the patient
- Austen 1967: “the complications due to hypotensive therapy were significant”
- Were more lives saved by preventing extension than were lost to hypotension?

BP reduction is often clearly needed, but what about more moderate regimens?
Since then: only a few case series

- Genoni, Eur J Cardiothorac Surg 2001
- von Kodolitsch, Circulation 2003 (IMH)
- Kodama, Circulation 2008
- IRAD, Am J Cardiol 2012
- Melby, J Clin Hypertens 2013

Pts who met some specified goal of intensive therapy during or after hospitalization had fewer adverse events over next few years

- e.g. IRAD: Rx at hospital discharge assoc with longer survival: β-blockers after Type A, CCBs after Type B

Concerns:

- Small numbers of outcomes (20-54) per study
- Possible post-hoc selection of predictors and/or outcome measures
- Missing data (esp. IRAD)
- Likelihood that worse outcomes were caused by the reasons pts were not on the drug or at goal
  - Intensive therapy appears to have been the intention for all patients

Conclusions

- Intensive therapy used for AD for 50 years
- No reliable evidence regarding whether it is helpful or harmful
- An RCT is clearly needed
  - Compare to rx rec for HTN emergencies
  - Factorial w EVR?
    [vs. med for Type B, open for Type A]