Treating the Pulmonary Circulation: Why, When and How

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Disclosure Information M Guazzi

Member of Advisory Board: Merck Sharpe, Pfizer

Speaker/Travel Fees: Bayer, Pfizer, Merck Sharpe
Do we have a current standard of care for Group 2 PH?

- Prevalence?
- Incidence?
- Therapy?

Guidelines for the Diagnosis and management of Heart Failure in Adults
Hunt SA et al 2009 – Circulation
Do we have a current standard of care for Group 2 PH?

- Prevalence?
- Incidence?
- Therapy?
Do we have a current standard of care for Group 2 PH?

9. Pulmonary hypertension due to left heart disease (group 2)

Most of the advances in the treatment of PH have been made in PAH. At the same time, virtually no progress has been made for the much more common forms of PH as encountered in patients with left heart diseases, lung diseases, or CTEPH. Despite the lack of data, drugs with proven efficacy in PAH are increasingly being...
“..It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.”

Mark Twain
Challenges in the Treatment of Group 2 PH

- When does PH become a target of treatment in cardiac patients?
- Which therapeutic opportunities and what perspectives?
When Treating PH and How are Pulmonary and Cardiac Objectives Interrelated?

- **Abnormal LV relaxation and stiffness**
  - **LVDP + Impaired volume regulation**
  - **LA and LV diastolic pressure**
  - **PCWP (Pulmonary congestion)**
  - **PA pressure**
  - **RV+RA pressure**
  - **RV failure**
  - **Systemic congestion (JVD, edema)**

- **Alveolar Edema**
- **Volume redistribution in pulm. vascular bed + Interstitial Edema**
- **Mitral Regurgitation**

- **Hydrostatic Pressure**
- **Alveolar-capillary membrane integrity**
- **Permeability**
- **Lynfatic drainage capacity**
**Clinical Case**

- Male, 38 years old
- First presentation at ER dept. for incoming dyspnea
- Severe hypertension (210/130 mmHg)
- $PO_2 = 92$ mmhg
- NTproBNP = 2390 pg/ml

\[
PASP = 54 \text{ mmHg} \quad \text{(RAP = 5 mmHg)}
\]

- $E/A = 5.0$
- $E/E' = 15.2$
Baseline

E/A = 5.0
E/E' = 15.2
PASP = 54 mmHg (RAP = 5 mmHg)

2-months post-therapy *
BP: 145/85 mmHg; NT-pro BNP: 870 pg/ml

E/A = 1.2
E/E' = 10.0
PASP = 51 mmHg (RAP = 5 mmHg)

*: Furosemide (50 mg), Ramipril (10 mg), Carvedilol (25 mg)
Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

A Community-Based Study

Carolyn S. P. Lam, MBBS,*† Véronique L. Roger, MD, MPH,* Richard J. Rodeheffer, MD,* Barry A. Borlaug, MD,* Felicity T. Enders, PhD,*† Margaret M. Redfield, MD*

Rochester, Minnesota; and Singapore, Singapore

PASP (Bernoulli eq.) and PCWP (11.96+0.596 x E/E1) estimated by Echo
A. PASSIVE Increase in Pulm. Pressure

- TPG < 12 mmHg; PCWP > 15 mmHg
- PAP
- RV
- LA

B. REACTIVE Pulm. Hypertension

- TPG ≥ 12 mmHg; PCWP > 15 mmHg
- PAP
- RV
- LA

C. OUT of PROPORTION Pulm. Hypertension

- TPG ≥ 12 mmHg; PCWP > 15 < 25 mmHg
- PAP
- RV
- LA
Pathobiology of Left-Sided PH at Different Stages

**REACTIVE Pulm. Hypertension**
- Enlarged and thickened pulmonary venules
- Arterial medial hypertrophy and intimal fibrosis
- Interstitial edema
- Lymphatic vessel dilatation
- No evidence of plexogenic vasculopathy except for few reported cases of severe mitral stenosis exposed to severe high PVRs.*

**OUT of PROPORTION Pulm. Hypertension**
- Initial or intermediate venular and arterial changes (?)

**PASSIVE Pulm. Hypertension**
- ??

Lung Capillary Remodeling and Endotelial Dysfunction in Diastolic HF and Left-Sided PH: Cellular Mechanisms

- Rat model of aortic banding for 9 weeks
- In vivo lung microcirculation studies

Kerem A et al Circ Res 2010;16:1103-1116
Endothelial Signaling Factors in PH

**Endothelium**

- **L-arginine**
  - e-NOS
  - **Nitric Oxide**
    - Receptor guanylyl cyclase
    - Soluble guanylyl cyclase
    - cGMP
    - cGMP-gated ion channels
    - PDE5
    - GMP

- **Pre-proendothelin**
  - Proendothelin
  - **Endothelin-1**
    - ETα
    - ETβ
    - Hypertrophy
    - Vasoconstriction
    - Protein kinase G
    - cGMP binding proteins

- **Arachidonic acid**
  - Prostacyclin synthesis
  - Prostacyclin

- **Natriuretic Peptides**
  - GTP
  - ATP

**Smooth muscle**

- cAMP
  - PDE3
  - AMP
  - Adenilate cyclase
  - ATP
Challenges in the Treatment of Group 2 PH

> When does PH become a target of treatment in cardiac patients?

> Which therapeutic opportunities and what perspectives?
Which Pharmacological Therapy for Left-Sided PH?

1. Prostanoids

2. Endothelin receptor antagonists

3. Modulators of NO pathway (Inhaled NO..)

4. Modulators of cGMP pathway:
   - Phosphodiesterase 5 inhibitors
   - Activators and stimulators of soluble GC
Prostanoids in Heart Failure (1)

- Improved hemodynamics during short term administration of PGI2 \(^1\), PGE \(^2,3,4\), iloprost \(^2\)

- Epoprostenol improves exe. capacity in moderate to severe HF (VO\(_2\)) \(^5\)

Flolan International Randomised Survival Trial (FIRST) \(^6\)

N= 471 pts - EF < 25% - NYHA III/IV - iv epoprostenol (mean dose 4 ng/kg/min) vs conventional therapy. Primary end-point: SURVIVAL
Ppa 36 mmHg- PCWP 16 (c) vs 26 (t) mmHg.

Hemodinamic improvement (PCWP, CI) \(^1,2\)

*Early termination*—trend towards higher mortality in the treated group

# Endothelin Receptor Antagonists in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of pts/ NYHA class/ EF</th>
<th>Study duration</th>
<th>Primary END-POINT</th>
<th>Pulm. hemo. end-point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACH-1 (Bosentan)</td>
<td>370 / III-IV / &lt; 35%</td>
<td>26 weeks (174 pts)</td>
<td>Clin. status @ 26 w</td>
<td>No</td>
<td>Early term. (safety, abn LFT)</td>
</tr>
<tr>
<td>ENABLE 1-2 (Bosentan)</td>
<td>1613 / III-IV / &lt; 35%</td>
<td>18 weeks on average (312 pts)</td>
<td>All cause Mort./HF hosp</td>
<td>No</td>
<td>Fluid ret. ↑ hosp.</td>
</tr>
<tr>
<td>HEAT (Darusentan)</td>
<td>157 / III / &lt; 35%</td>
<td>3 weeks</td>
<td>Syst. and Pulm. Hemo</td>
<td>No</td>
<td>PCWP↓, PVR↓, CI ↑, ↑ doses trend to ↑ mortality</td>
</tr>
<tr>
<td>EARTH (Darusentan)</td>
<td>642 / II-IV / &lt; 35%</td>
<td>24 weeks</td>
<td>Change in LVESV @ 24 w + functional status</td>
<td>No</td>
<td>No benefits, trend to ↑ mortality</td>
</tr>
</tbody>
</table>
Inhaled NO in Heart Failure

- Studies performed primarily in post-LVAD and post-HTX pts \(^1,2,3\)
- In stable HF, reported improvement in exercise \(\text{VO}_2\) \(^4\)

Short half life – continuous administration needed - PH rebounds with brief interruptions \(^5\)

Cases of acute pulmonary edema in pts with poorly compliant LV \(^6,7\)

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First demonstration that selective PDE5 inhibition is an effective approach to modulate NO signaling

PDE5 inhibition by Sildenafil is now approved for the cure of idiopathic pulmonary hypertension

Group 2 PH next step ?!
# PDE5 Expression in Different Vascular Beds

## Table 1. Functions of PDEs and Cardiovascular Effects of Specific Inhibitors

<table>
<thead>
<tr>
<th>Family</th>
<th>Enzyme Main Functions</th>
<th>Selective Inhibition</th>
<th>Vessel Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contractility</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>PDE1</td>
<td>Regulates smooth muscle contraction, sperm function, immune cell activation, neuronal signaling</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PDE2</td>
<td>Regulates aldosterone secretion, long-term memory, endothelium barrier function under inflammation</td>
<td>↑</td>
<td>...</td>
</tr>
<tr>
<td>PDE3</td>
<td>Regulates platelet aggregation, cardiac and vascular smooth muscle contractility, renin release, oocyte maturation; mediates insulin signaling (antilipotic effects)</td>
<td>↑ ↑ ↑ ↓ │ ↓ ↓ ↓ ↓ ↓</td>
<td></td>
</tr>
<tr>
<td>PDE4</td>
<td>Has a role in brain function, vascular smooth muscle proliferation, fertility, vasodilation, cardiac</td>
<td>↑</td>
<td>...</td>
</tr>
<tr>
<td>PDE5</td>
<td>Is a well-established regulator of vascular smooth muscle contraction especially in lung and corpus cavemosum; is involved in the control of platelet aggregation; may regulate cGMP signaling in the brain</td>
<td>↑</td>
<td>↓ ↓ ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>PDE6</td>
<td>Is involved in the transduction of signal of the eye photoresponse and in melatonin release regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE7</td>
<td>Has a role in T-cells and other inflammatory cells activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE8</td>
<td>May be involved in T-cell activation and sperm function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE9</td>
<td>Has been postulated to regulate the NO-cGMP signaling in brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE10</td>
<td>Is considered a regulator of cGMP in the central nervous system and may be involved in the learning and memory processes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE11</td>
<td>May play a role in sperm development and function</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|        |                                                                                                                 | Corpus Cavemosum |
|        |                                                                                                                 | ...             |

PDE indicates phosphodiesterase.
DOC? CAN YOU WRITE ME A PRESCRIPTION FOR SOME OF THAT VIAGRA?

SAY NO!
PDE5-Inhibition: Hemodynamic Effects


Acute Effects of Sildenafil on Exercise PVR
Chronic Sildenafil Effects on Exercise Pulmonary Hemodynamic in Systolic HF

Subset of HF pts randomized to 12 weeks sildenafil (50 mg/3 times day)

Lewis et al. Circ Heart Fail 2011 in press
PDE-5 Inhibition: Intrapulmonary Selective Vasodilatation

Sildenafil
PDE-5 Inhibition: Comparison of Acute Effects with Other Pulmonary Vasodilators

Sildenafil Efficacy and Safety in Advanced HF with LVAD

138 HF pts with severe left-sided PH (PVR > 3 Woods) evaluated for HTX

LVAD

- 58 no changes in PVR
- 26 (Sildenafil 50 mg/3 times a day)
- ↓ PVR (from 5.87 to 2.97 Wood Unit; P<0.0001)
- ↓ Mean PAP (from 36.5 to 24.3 mmHg; P<0.0001)

80 significant ↓ PVR

32 (Placebo)

Tedford RJ et al Circ Heart Fail 2008;1:213-219
## Reversal of Left-Sided PH with LVAD

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>TIME, days</th>
<th>Post LVAD Changes in mean PAP, mmHg</th>
<th>Post LVAD Changes in PVR, WU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallagher et al 1991</td>
<td>16</td>
<td>61</td>
<td>/</td>
<td>-2.3</td>
</tr>
<tr>
<td>Smedira et al 1996</td>
<td>63</td>
<td>/</td>
<td>-11</td>
<td>-1.3</td>
</tr>
<tr>
<td>Nguyen et al. 2001</td>
<td>3</td>
<td>/</td>
<td>-30</td>
<td>-2.7</td>
</tr>
<tr>
<td>Martin et al 2004</td>
<td>6</td>
<td>/</td>
<td>-43</td>
<td>-2.7</td>
</tr>
<tr>
<td>Salzberg et al 2005</td>
<td>6</td>
<td>/</td>
<td>-18</td>
<td>-2.9</td>
</tr>
<tr>
<td>Zimpfer et al. 2007</td>
<td>35</td>
<td>42</td>
<td>/</td>
<td>-3.1</td>
</tr>
<tr>
<td>Etz et al. 2007</td>
<td>10</td>
<td>182</td>
<td>-18</td>
<td>-2.6</td>
</tr>
<tr>
<td>Liden et al 2009</td>
<td>11</td>
<td>239</td>
<td>/</td>
<td>-2.3</td>
</tr>
<tr>
<td>Mikus et al 2011</td>
<td>150</td>
<td>180</td>
<td>-16</td>
<td>-1.96</td>
</tr>
</tbody>
</table>

-26 mmHg  
-2.4 WU
Transpulmonary cGMP Release in HF Patients with High PVR: Acute Effects of Sildenafil (40 mg)

Melenowsky V et al. JACC 2009;54:595-600
• Rat model of aortic banding for 9 weeks
• In vivo lung microcirculation studies

**Capillary remodeling**  |  **Capillary/Arterioles Wall Thick.**  |  **Capillary NO release to ACh**
---|---|---

[Sham image]

<table>
<thead>
<tr>
<th>Size Range</th>
<th>Mean Wall Thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ø &lt;150 µm</td>
<td><img src="chart.png" alt="" /></td>
</tr>
<tr>
<td>Ø 150-250 µm</td>
<td><img src="chart.png" alt="" /></td>
</tr>
<tr>
<td>Ø 250-1000 µm</td>
<td><img src="chart.png" alt="" /></td>
</tr>
</tbody>
</table>

**Sham**

**CHF**

**CHF + Sildenafil**
RV Shape

Sham

CHF

CHF + sild

RV Systolic Function

Pulm. Acceleration Time (ms)

TAPSE (mm)

sham

CHF

CHF+sil
Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction: a Target of Phosphodiesterase-5 Inhibition in a 1-year Duration Study

Study Hypothesis

Pre-capillary pulmonary hypertension and RV function may benefit from chronic PDE5-inhibition

- Randomized, Double-blind, placebo-controlled trial
- **Primary Outcome**: Changes in pulmonary hemodynamics (PVR, mean PAP, mean PCWP, arterial elastance) and RV function (Frank Starling, MSEJR, TAPSE) @ 6 and 12 months
- **Secondary Outcome**: Changes in lung volumes and alveolar gas diffusion (DM). Changes in LV systolic and diastolic function. Q. of Life

44 pts with hypertensive heart disease and signs and symptoms of HF (average LVEF 60±4 %)

*Circulation* 2011 in press
### Effects of PDE5 Inhibition on Pulmonary Hemodynamics and RV Function in HFpEF

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RAP (mmHg)</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>Mean PWP (mmHg)</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Pulm. Art. Elastance (mmHg/ml)</td>
<td>0.69</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>RV function/dimensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV maximal short axis</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>RV MSEJR (mL/sec)</td>
<td>242</td>
<td>231</td>
</tr>
</tbody>
</table>

* * §

*Circulation* 2011 in press
Effects of PDE5 Inhibition on RV Contractility in HFrEF

Baseline

6 months

Stroke Volume (mL·beat⁻¹)

RV End-Diastolic Pressure (mmHg)

Placebo
Sildenafil

Placebo
Sildenafil

Circulation 2011 in press
Effects of PDE5 Inhibition on Quality of Life in HFpEF

BREATHLESSNESS

FATIGUE

EMOTIONAL FUNCTION

* $ P<0.01 \text{ vs Baseline}

$ P<0.01 \text{ vs Placebo}

Placebo  Sildenafil

Circulation 2011 in press
PDE-5 Inhibition: Side Effects and Safety Profile in HF

Chronic studies (sildenafil from 25 to 50 mg/three times day):
- Guazzi M et al JACC 2007
- Lewis S et al Circulation 2007
- Behind et al J Card Fail 2008
- Tedford RJ et al Circ Heart Failure 2008
- Lewis S et al Circ Heart Failure 2011
- Guazzi M et al Circulation 2011

Acute studies (sildenafil 50 mg):
- Katz SD et al JACC 2000 (48)
- Piccirillo G et al. Am Heart J 2002 (20)
- Bocchi EA et al. Circulation 2002 (23)
- Alaeddini J et al Am J Cardiol 2004 (14)
- Guazzi M et al JACC 2004 (16)
- Lepore JJ Chest 2005 (11)
- Hirata K et al. Am J Cardiol 2005 (20)
- Katz SD et al. Am J Cardiol 2005 (63)
- Hryniwicz K et al Clin Sci 2005 (16)
- El-Hesayen A et al. Eur J Heart Fail 2006 (10)
- Lewis S et al Circulation 2007 (13)
- Melenowsky et al JACC 2009 (46)

N=316 pts

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>N, cases</th>
<th>Chronic (sildenafil from 25 to 50 mg/three times day)</th>
<th>Acute (sildenafil 50 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3 %</td>
<td>No patients discontinued</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>4 %</td>
<td>No patients discontinued</td>
<td></td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>0.3%</td>
<td>No patients discontinued</td>
<td></td>
</tr>
<tr>
<td>Myalgia (Back pain)</td>
<td>0.3%</td>
<td>No patients discontinued</td>
<td></td>
</tr>
</tbody>
</table>

N=132 pts

No patients discontinued
What Kind of HF Patients Have Been Investigated in PDE5 Inhibitors Clinical Trials?

- Stable systolic and diastolic HF (Male-NYHA II-III)
- Primarily mild to moderate left-sided PH
- Initial experience on advanced HF
- Patients optimally treated with antifailure therapies
- **No experience in acute HF**
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials
Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (Relax Trial)

- Study Design: Randomized, placebo-controlled, double blind
- Study population: 190 pts with HF-EF > 50%
- Primary Outcome: Exercise capacity (VO₂)
- Secondary Outcome: LV mass, symptoms

190 pts

- Placebo
- Sildenafil (20 mg x 3)
- Sildenafil (60 mg x 3)

12 weeks 24 weeks

September 2008

Clinical Trials.gov Identifier: NCT00763867
Summary and Outlook

- There are not specific Guidelines at this time for the treatment of Group 2 PH.

- Advances in molecular pharmacology in the field of cGMP signaling are intriguing and growing evidence suggests that PDE5 inhibition may have promise.

- There remains a truly unmet need for novel, safe and effective therapies for Group 2 PH.