Heart Failure with Preserved Ejection Fraction: New Insight into Mechanisms and Potential Therapy

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21st Annual Heart Failure 2017 – an Update on Therapy

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Disclosure

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Amgen, Merck, MyoKardia, Axon, AstraZeneca, Actelion

Off-Label/Investigational Uses
None
Outline

• Review key mechanisms that cause the clinical syndrome of HFpEF
• Review new therapies being evaluated to treat HFpEF
Therapies that work in HFrEF have failed in HFpEF

Borlaug & Redfield Circulation 2011
The Key Pathophysiologic Target in HFpEF

The graph illustrates the changes in PCWP (mmHg) over time for both HFpEF and Control groups. The data points are marked with error bars, and the graph shows a significant increase in PCWP for the HFpEF group compared to the Control group at various time points (Baseline, Leg Raise, 20W, Peak, 1 min Recovery). The statistical significance is denoted by * and p<0.0001.
But it’s not just filling pressures…

- Cardiac output (L/min)
- Stroke volume (ml)
- Heart Rate (bpm)

Graphs showing significant differences between control and HFpEF groups. P < 0.001 for each comparison.

Borlaug Eur Heart J 2016
What causes these hemodynamic limitations?
NO-cGMP-PKG: Central to HFpEF

Comorbidities
- Metabolic syndrome
  - Obesity
  - Type 2 DM
  - Hypertension
- Renal insufficiency

Systemic inflammation
- CRP
- IL1RL1
- GDF15

Multiorgan involvement
- PH
- \(\Delta(A-VO_2)_{EX}\)
- Na\(^+\) retention

Endothelium-cardiomyocyte signaling
- ONOC
- ROS
- NO
- VCAM
- E-selectin
- Leukocytes
- TGF-\(\beta\)
- Fibroblasts
- Myofibroblasts
- Collagen
- Cardiomyocytes

CONCLUSIONS

Patients with heart failure and a preserved ejection fraction who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than did patients who received placebo. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT02053493.)
Inorganic Nitrite: An Alternative NO source
Hypothesis: $\text{NO}_2^-$ would improve exercise hemodynamics in HFpEF

- Base Hemos
- Exercise Hemos 20W x 5 min
- Re-base Hemos
- Base $\text{NO}_2^-$
- Exercise 20W x 5 min, $\text{NO}_2^-$
- Base placebo
- Exercise 20W x 5 min, placebo

Randomized: IV $\text{NO}_2^-$ or NS

Borlaug, Koepp et al. J Am Coll Cardiol 2015
**Acute benefits from IV NO\textsubscript{2} in human HFpEF**

**Rest**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nitrite</th>
</tr>
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<tbody>
<tr>
<td>ΔPCWP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.0001</td>
<td>p=0.007</td>
</tr>
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</table>

**Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nitrite</th>
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<tbody>
<tr>
<td>ΔPCWP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.0002</td>
<td>p=0.0005</td>
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**ΔCO (L/min)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nitrite</th>
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<td>p-value</td>
<td>p=0.007</td>
<td></td>
</tr>
</tbody>
</table>

Borlaug et al. *J Am Coll Cardiol* 2015
Similar Benefits with Beetroot (NO$_3^-$) and with Inhaled NO$_2$
Next Steps:

INDIE-HF
INABLE-HFpEF
Other pathways to enhance cGMP-PKG

Solomon *Lancet* 2012
PH & RVD in HFpEF are viable targets

Lam, Redfield JACC 2009

Melenovsky, Borlaug Eur Heart J 2014
Abnl RV-PA coupling even in early stages

- ΔPVR (WU) - HFpEF vs Control: ΔPVR (WU) decreases significantly in HFpEF compared to Control, with p = 0.006.

- ΔPAC (ml/mmHg) - HFpEF vs Control: ΔPAC decreases significantly in HFpEF compared to Control, with p = 0.006.

- mPAP (mmHg) vs Cardiac Output (l/min) - HFpEF vs Control: mPAP increases significantly with decreased Cardiac Output in HFpEF compared to Control, with p < 0.0001.

- ΔRV S' (cm/s) - HFpEF vs Control: ΔRV S' decreases significantly in HFpEF compared to Control, with p < 0.05.

Borlaug et al. *Eur Heart J* 2016
Much to gain from PA vasodilation in HFrEF

**Acute Response to β-agonist**

- **∆PA mean (mmHg)**
  - Controls: 0 mmHg
  - HFrEF: 2 mmHg
  - p < 0.0001

- **∆PVR (WU)**
  - Controls: -1.5 WU
  - HFrEF: -1.0 WU
  - p = 0.002

- **∆PAC (ml/mmHg)**
  - Controls: 0.5 ml/mmHg
  - HFrEF: 1.0 ml/mmHg
  - p = 0.008

- **RV s’ (cm/s)**
  - Baseline: 5 cm/s
  - 5 ug: 10 cm/s
  - 10 ug: 15 cm/s
  - p = 0.6

Andersen Circ Heart Fail 2015
PAP reduces HF hospitalizations in HFpEF

NNT = 2
over 18 months
Next Steps:

BEAT-HFpEF (albuterol)
SERENADE (macitentan)
Why should patients with HFrEF get all the devices?
Chronotropic Incompetence is common in HFpEF
Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure

Rationale and Design of the Randomized Trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I)

Ted Feldman, MD; Jan Komtebedde, DVM; Daniel Burkhoff, MD, PhD; Joseph Massaro, PhD; Mathew S. Maurer, MD; Martin B. Leon, MD; David Kaye, MD; Frank E. Silvestry, MD; John G.F. Cleland, MD; Dalane Kitzman, MD; Spencer H. Kubo, MD; Dirk J. Van Veldhuisen, MD; Franz Kleber, MD; Jean-Noël Trochu, MD, PhD; Angelo Auricchio, MD, PhD; Finn Gustafsson, MD, PhD; Gerd Hasenfuß, MD; Piotr Ponikowski, MD; Gerasimos Filippatos, MD; Laura Mauri, MD, MSc; Sanjiv J. Shah, MD

Borlaug *Circ Heart Fail* 2010

Hasenfuß, Kaye *Lancet* 2016
One more kooky idea…
Could we target the pericardium?

Exercise

\[ P = 0.0003 \]

\[ P = ae^{bv} \]

<table>
<thead>
<tr>
<th>Pericardium</th>
<th>( a ), mmHg</th>
<th>( b ), mmHg/ml</th>
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<tbody>
<tr>
<td>Present</td>
<td>(-1.0 \pm 1.6)</td>
<td>(0.085 \pm 0.040)</td>
</tr>
<tr>
<td>Absent</td>
<td>(0.3 \pm 1.0^*)</td>
<td>(0.055 \pm 0.022^*)</td>
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Percutaneous Pericardial Resection
A Novel Potential Treatment for Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD; Rickey E. Carter, PhD; Vojtech Melenovsky, MD, PhD; Christopher V. De Simone, MD, PhD; Prakriti Gaba, BS; Ammar Killu, MBBS; Niyada Naksuk, MD; Lilach Lerman, MD, PhD; Samuel J. Asirvatham, MD

Background—People with heart failure and preserved ejection fraction develop increases in left ventricular (LV) end-diastolic pressures during exercise that contribute to dyspnea. In normal open-chest animal preparations, the pericardium restrains LV filling when central blood volume increases. We hypothesized that resection of the pericardium using a minimally invasive epicardial approach would mitigate the increase in LV end-diastolic pressure that develops during volume loading in normal and diseased hearts with the chest intact.

Methods and Results—Invasive hemodynamic assessment was performed at baseline and after saline load before and after pericardial resection in normal canines with open (n=3) and closed chest (n=5) and in a pig model with features of human heart failure and preserved ejection fraction with sternum intact (n=4). In closed-chest animals, pericardiotomy was performed using a novel subxiphoid procedure. In both experimental preparations of normal dogs, pericardiotomy blunted the increase in LV end-diastolic pressure with saline infusion, while enhancing the saline-mediated increase in LV end-diastolic volume. With chest intact in the pig model, percutaneous pericardial resection again blunted the increase in LV end-diastolic pressure secondary to volume expansion (+4±3 versus +13±5 mmHg; P=0.014), while enhancing the saline-mediated increase in LV end-diastolic volume (+17±1 versus +10±2 mL; P=0.016).

Conclusions—This proof of concept study demonstrates that pericardial resection through a minimally invasive percutaneous approach mitigates the elevation in LV filling pressures with volume loading in both normal animals and a pig model with diastolic dysfunction. Further study is warranted to determine whether this method is safe and produces similar acute and chronic hemodynamic benefits in people with heart failure and preserved ejection fraction. (Circ Heart Fail. 2017;10:e003612. DOI: 10.1161/CIRCHEARTFAILURE.116.003612.)

Key Words: blood volume ■ heart failure ■ hemodynamics ■ humans ■ pericardium
Pericardial Resection Abrogates the increase in LVEDP with saline loading

**Normal Dogs**

\[ \text{ΔLVEDP (mmHg)} \]

Before

\[ 0 \]

5

10

15

20

25

After

\[ p=0.003 \]

\[ 0 \]

5

10

15

20

25

\[ \text{ΔLVEDV (mmHg)} \]

Before

\[ 0 \]

20

40

60

After

\[ p=0.09 \]

\[ 0 \]

20

40

60

**HFpEF Pigs**

\[ \text{ΔLVEDP (mmHg)} \]

Before

\[ 0 \]

5

10

15

20

25

After

\[ p=0.019 \]

\[ 0 \]

5

10

15

20

25

\[ \text{ΔLVEDV (mmHg)} \]

Before

\[ 0 \]

20

40

60

After

\[ p=0.055 \]

\[ 0 \]

20

40

60

Borlaug et al. *Circ Heart Fail* 2017
Summary: Lots of Hope for HFpEF

- Therapies aimed at pathophysiology
  - $\uparrow$LVFP, $\downarrow$CO reserve, RV-PA uncoupling
- Novel Therapies Targeting cGMP-PKG
  - Inorganic Nitrite, LCZ696
- Targeting PH & RVD
  - ET antagonists, $\beta$-adrenergic agonists
- New Device approaches under investigation
  - Pacing, IASD, pericardiectomy
Thanks for your attention