Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients

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SHIFT Trial 2010: Selective heart rate reduction by ivabradine improved outcome in patients with systolic heart failure (EF≤35%).

Aim of this study was to investigate whether selective heart rate reduction with ivabradine reduces afterload in patients with systolic heart failure thereby possibly contributing to the beneficial outcome of the SHIFT trial.
Methods

• 275 patients with systolic heart failure (EF ≤35%) treated either with placebo (n=132) or ivabradine (7.5mg bid; n=143) were included and retrospectively analyzed.

• Effective arterial elastance (Ea), vascular compliance (VC) and end-systolic elastance (Ees) are important parameters of ventricular-arterial interaction. These parameters were calculated non-invasively at baseline and after 8 months of treatment using Echo data and blood pressure measurements of the SHIFT echocardiographic substudy.
Definition of the pressure-volume parameters

Effective arterial elastance (Ea) = \( \frac{P_{es}}{SV} \approx TPR \times HR \)

End-systolic elastance (Ees) non-invasive single beat analysis according to Sunagawa et al., Ann Bio Eng 1984 and Chen et al., JACC 2001

Vascular compliance (VC) = \( \frac{SV}{PP} \)

Coupling ratio = \( \frac{Ea}{Ees} \)
The effective arterial elastance (Ea) represents resistive and pulsatile load of the heart.

Theoretically, heart rate can modulate Ea i.e. afterload burden.

End-systolic elastance (Ees) represents cardiac contractility.

Aims of the study →

1.) Does selective heart rate reduction with ivabradine reduce afterload (Ea↓) in patients with systolic heart failure?

2.) Does selective heart rate reduction influence vascular-ventricular interaction?
## Baseline demographics of the studied patients

<table>
<thead>
<tr>
<th>Demographics a. clinical data</th>
<th>All (n=275)</th>
<th>Ivabradine (n=143)</th>
<th>Placebo (n=132)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7 (11.1)</td>
<td>60 (10.8)</td>
<td>59.4 (11.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Male</td>
<td>224 (81.5%)</td>
<td>119 (83.2%)</td>
<td>105 (79.5%)</td>
<td>0.43</td>
</tr>
<tr>
<td>NYHA II</td>
<td>153 (55.6%)</td>
<td>82 (57.3%)</td>
<td>71 (53.8%)</td>
<td>0.55</td>
</tr>
<tr>
<td>NYHA III+IV</td>
<td>122 (44.4%)</td>
<td>61 (42.7%)</td>
<td>61 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>28.6 (5.3)</td>
<td>28.5 (5.2)</td>
<td>28.7 (5.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Heart rate</td>
<td>71 (11.4)</td>
<td>71 (11.8)</td>
<td>71 (11.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP, mmHg)</td>
<td>122 (15)</td>
<td>123 (15.7)</td>
<td>121 (14.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP, mmHg)</td>
<td>76 (8.6)</td>
<td>76 (9.2)</td>
<td>76 (8.0)</td>
<td>0.81</td>
</tr>
</tbody>
</table>
Effects of heart rate on compliance and Ea by tertiles at baseline (n=275)

Vascular compliance (VC)

Effective arterial elastance (Ea)

Vascular compliance (VC)

Effective arterial elastance (Ea)

p<0.001 for trend

p<0.001 for trend
Effect of ivabradine on HR and stroke volume after 8 mths. of treatment

Heart rate (bpm)

- Baseline
- After 8 months

Stroke volume (ml)

- Baseline
- After 8 months

# p<0.05 Iva baseline vs. 8 mths. of treatment; * p<0.05 placebo vs. Iva 8 mths.
Effect of ivabradine on vascular compliance and Ea after 8 mths. of treatment

Vascular compliance (VC) (ml/mmHg)  Effective arterial elastance (Ea) (mmHg/ml)

baseline  after 8 months  baseline  after 8 months

# p<0.05 lva baseline vs. 8 mths. of treatment; * p<0.05 placebo vs. lva 8 mths.
Effect of ivabradine on Ees and coupling ratio Ea/Ees after 8 mths. of treatment

End-systolic elastance (Ees) (mmHg/ml)

Coupling ratio (Ea/Ees)

# p<0.05 Iva baseline vs. 8 mths. of treatment; * p<0.05 placebo vs. Iva 8 mths.
Effect of ivabradine on end-diastolic volume (EDV) after 8 mths. of treatment

# p<0.05 Iva baseline vs. 8 mths. of treatment
Summary

The studied patients at baseline demonstrated:

- A rightward shift in the PV diagram with increased EDV of about 170 ml (normal < 155 ml*)
- A marked increase in Ea of 2.0 mmHg/ml (normal 1.2-1.3#)
- A decreased Ees of 1.0 mmHg/ml (normal 1.7#)
- An abnormal high coupling ratio (Ea/Ees) of 2.4 (normal 0.7#)

After 8 months ivabradine reduced Ea, increased VC with improvement of the coupling ratio (Ea/Ees) and stroke volume while Ees remained unchanged and EDV was reduced.

* Oh JK, The Echo Manual 3rd Ed. 2006; # Redfield MM et al., Circulation 2005
Conclusion

• Heart rate modulates cardiac afterload indicated by the alterations of effective arterial elastance (Ea).
• Selective heart rate reduction with ivabradine reduced effective arterial elastance mainly by improving vascular compliance (VC).
• Ivabradine did not alter Ees, a load-independent marker of left ventricular contractility.
• Higher stroke volumes of the patients of the ivabradine group may therefore depend on improved ventricular-arterial coupling.
275 patients
EF < 35%

132 patients treated with Ivaa
143 patients treated with placebo

Treatment scheme

Baseline

Placebo or ivabradine treatment

8 month visit

EA/ VC were calculated according to heart rate tertiles