Intravenous nicorandil improves symptoms and left ventricular diastolic function immediately in patients with acute heart failure: a randomized, controlled trial


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Disclosure Information: No conflict of interest
Background (1)

- Acute heart failure syndrome (AHFS) management and outcome have not changed over the past decade.

- Recent guidelines for the treatment of AHFS have recommended pharmacotherapy with vasodilators as preferable to inotropic agents in patients without excessively low blood pressure.

- Acute therapy with vasodilators can improve both hemodynamics and symptoms, but those effects have not been enough to improve clinical outcome.

- The safety and efficacy of combined therapy of vasodilators in AHFS has not been well studied.
Nicorandil is a vasodilator that has nitrate-like properties and activates ATP-sensitive potassium channels and results in balanced venous and arterial vasodilation.


**Nitrate-like action**
- Reduce preload by dilating vein

**K<sub>ATP</sub> channel opener**
- Reduce afterload by dilating arteries

**Background (2)**

- **Nitroglycerin**
  - CH<sub>2</sub>—ONO<sub>2</sub>
  - CH—ONO<sub>2</sub>
  - CH<sub>2</sub>—ONO<sub>2</sub>
Intravenous administration of nicorandil by bolus injection followed by continuous infusion improves PCWP and CI in AHFS patients immediately and continuously as a potent vasodilator with combined preload and afterload reduction.

(Kato K et al. Jpn Pharmacol Ther 2008;36:S25-S34)
(Tanaka K et al. J Cardiol 2010;56:291-299)

Intravenous administration of nicorandil resulted in significantly less development of hemodynamic tolerance over a 24-hour period than nitroglycerin.

(Larsen AI et al. Am Heart J 1997;134:435-441)
A bolus intravenous administration of nicorandil improves immediately PCWP and CI in patients with AHFS

Kato K et al. *Jpn Pharmacol Ther* 2008;36:S25-S34

PCWP

- Intravenous administration of nicorandil (0.2mg/kg) over 5min
- PCWP reduced by 30%

Cardiac Index

- CI increased by 15%

*: p<0.05, **: p<0.01 (vs Baseline), Mean±S.E.
This prospective, randomized study was conducted to evaluate the acute efficacy and safety of combined therapy of vasodilators (low-dose carperitide and nicorandil) in patients with AHFS.
Study Design

Subjects:
Hospitalized 118 patients with AHFS in our institution

Design:
Prospective, randomized, controlled trial

Groups:
Control group: Standard therapy
NCR group: Nicorandil + Standard therapy

Nicorandil; 0.2mg/kg bolus, followed by continuous infusion of 0.2mg/kg/hr for 24 hours
Standard therapy: All patients received intravenous administration of carperitide (hANP) which was administered with an initial dose of 0.0125μg/kg/min.
Inclusion and Exclusion Criteria

**Inclusion criteria:**
- Dyspnea at rest or with minimal activity
- Over 20 years of age

**Major exclusion criteria:**
- Hypotension at baseline (SBP < 90mmHg)
- Significant lung disease that could interfere with interpretation of dyspnea
- Acute coronary syndrome
- Severe renal and/or hepatic dysfunction
Study protocol

Admission/Baseline

Enrolment/Randomization/Initial treatment (\(O_2\), diuretics, NTG)

Before

Control group (n=59)
(low dose carperitide)

NCR group (n=59)
(Nicorandil in addition to low dose carperitide)

24h

<1hr from admission

24hrs RX

Safety:

- Systolic blood pressure

Efficacy:

- Symptoms and clinical signs
- Echocardiographic findings
## Baseline Characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=59)</th>
<th>NCR group (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>74.7±11.1</td>
<td>75.7±12.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Male gender</td>
<td>34 (57.6)</td>
<td>28 (47.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1±5.4</td>
<td>23.1±4.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure readmission</td>
<td>24 (40.7)</td>
<td>17 (28.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (71.2)</td>
<td>45 (76.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 (27.1)</td>
<td>15 (25.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (39.0)</td>
<td>24 (40.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (15.3)</td>
<td>13 (22.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>20 (33.9)</td>
<td>18 (30.5)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Values are numbers (%) or mean±SD.
<table>
<thead>
<tr>
<th></th>
<th>Control group (n=59)</th>
<th>NCR group (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical findings and symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP on admission (mmHg)</td>
<td>148.1±29.3</td>
<td>154.1±30.3</td>
<td>0.27</td>
</tr>
<tr>
<td>DBP on admission (mmHg)</td>
<td>85.4±18.6</td>
<td>88.1±21.6</td>
<td>0.47</td>
</tr>
<tr>
<td>HR on admission (bpm)</td>
<td>96.3±22.3</td>
<td>101.1±21.6</td>
<td>0.24</td>
</tr>
<tr>
<td>NYHA class (I/II/III/IV)</td>
<td>0/1/10/47</td>
<td>1/4/9/46</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>21 (36.2)</td>
<td>25 (43.9)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>824 (400-1575)</td>
<td>744 (493-1360)</td>
<td>0.98</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5±1.0</td>
<td>1.4±0.8</td>
<td>0.57</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>11.3±2.3</td>
<td>11.2±2.5</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Values are numbers (%), mean±SD. and median (IQR)
## Baseline Characteristics (3)

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=59)</th>
<th>NCR group (n=59)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral medication on admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I/ ARBs</td>
<td>32 (54.2)</td>
<td>32 (54.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>20 (33.9)</td>
<td>19 (32.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Statins</td>
<td>16 (27.1)</td>
<td>13 (22.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>27 (45.8)</td>
<td>29 (49.2)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>IV medication during the first 24 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carperitide</td>
<td>59 (100.0)</td>
<td>59 (100.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dose (μg/kg/min)</td>
<td>0.021 (0.015-0.030)</td>
<td>0.024 (0.017-0.030)</td>
<td>0.13</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>44 (74.6)</td>
<td>47 (79.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2 (3.4)</td>
<td>3 (5.1)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are numbers (%).
Changes in blood pressure over time

*All patients (n=118)*

![Graph showing changes in blood pressure over time for systolic and diastolic blood pressure (SBP and DBP) for control and NCR groups.](image-url)

- **Blood pressure (mmHg)**
  - Systolic BP
  - Diastolic BP

- **Time points:** Before, 1h, 2h, 6h, 24h

- **Groups:** Control (SBP), NCR (SBP), Control (DBP), NCR (DBP)
Changes in dyspnea by 5-point Likert

* : p<0.01, ** : p<0.001 (vs. Control group), mean ±SD

1= not short of breath, 2= mildly short of breath, 3= moderately short of breath,
4= severely short of breath, 5= very severely short of breath
# Echocardiographic parameters at baseline and 1h after treatment

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>NCR group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1h</td>
<td>p value</td>
<td>Baseline</td>
<td>1h</td>
<td>p value</td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>104.0 ± 33.0</td>
<td>94.8 ± 30.6</td>
<td>0.003</td>
<td>109.0 ± 38.2</td>
<td>88.1 ± 35.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ea (cm/s)</td>
<td>5.1 ± 2.5</td>
<td>4.7 ± 2.1</td>
<td>0.031</td>
<td>4.5 ± 2.7</td>
<td>4.9 ± 2.7</td>
<td>0.031</td>
</tr>
<tr>
<td>E/Ea ratio</td>
<td>25.5 ± 17.5</td>
<td>24.3 ± 15.3</td>
<td>0.473</td>
<td>30.3 ± 17.1</td>
<td>20.7 ± 10.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DcT (cm)</td>
<td>150.3 ± 46.4</td>
<td>166.3 ± 57.3</td>
<td>0.017</td>
<td>144.9 ± 65.7</td>
<td>184.4 ± 66.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

E, early transmitral diastolic velocity; Ea, early diastolic mitral annular tissue Doppler; DcT, deceleration time of E velocity; IVC, maximum inferior vena cava diameter.
Changes in echocardiographic parameters at 1h after treatment

**Control group**

**NCR group**

- **E (cm/s)**
  - Control: -20.9
  - NCR: -9.3
  - *p*=0.027

- **Ea (cm/s)**
  - Control: -20.9
  - NCR: 0.4
  - *p*=0.002

- **E/Ea ratio**
  - Control: -9.6
  - NCR: -1.3
  - *p*=0.003

- **DcT (cm)**
  - Control: 15.9
  - NCR: 42.0
  - *p*=0.026
Summary

Safety:
- This combined therapy of vasodilators (low-dose carperitide and nicorandil) could be safely administered to patients with AHFS in the urgent phase without excessively low BP, even in patients with lower baseline BP.

Efficacy:
- Administration of nicorandil to standard therapy improved echocardiographic findings (E↓, E/Ea↓, DcT↑) rapidly, resulted in relief dyspnea in patients with AHFS.
Clinical perspective

It was suggested that Nicorandil could become a second-line vasodilator agent in patients with AHFS who do not respond rapidly to a first-line vasodilator.