Role of cytokines in HF induced atrial arrhythmia

Yung-Kuo Lin, MD, PhD

Division of Cardiology, Department of Internal Medicine,
School of Medicine, College of Medicine
Outline

- NPs structure
- NP effects
- AF pathophysiology
- BNP levels and AF
- BNP modulates PV arrhythmogenesis
- Effects of NPs on electrical conduction
- Effects of ANP and mANP on atrial electrophysiology and arrhythmogenesis
- Effects of NPs on HF
- Conclusions
Natriuretic peptides

Clinical Science (2016) 130, 57–77
Structure of B-Type Natriuretic Peptide

Pro-BNP

N-terminal proBNP (1-76) BNP (77-108)
Structure and Known Functions of the Natriuretic Peptide Receptors (NPRs)

Source: Gardner, D. G. et al. Hypertension 2007;49:419-426
Illustration of the atrial fibrillation pathophysiology

- Altered hemodynamics
- Impaired cardiac function
- Vascular pathology
- Electrical remodeling
- Prothrombotic state
- Atrial dilatation
- Myocyte damage
- Atrial fibrosis

Genetics
NPs
Impaired cardiac function
NPs
NPs
Atrial fibrosis
Markers of inflammation
IL-6, CRP

Electrical remodeling
Prothrombotic state
Markers of coagulation
D-dimer

Prothrombotic state

AF

European Heart Journal (2013) 34, 1475–1480
BNP levels on AF

Community-based cohort studies – pooled CHARGE-US cohorts over 5 years of follow-up

- BNP, not CRP, substantially improved AF risk prediction beyond clinical factors in an independently replicated, heterogeneous population.
- BNP may serve as a benchmark to evaluate novel putative AF risk biomarkers.

- BNP levels correlate with AF burden in patients with lone AF and are strong predictors of recurrent arrhythmia after ablation.
- Elevated BNP levels may reflect increased cardiac chamber wall stress and/or intrinsic atrial disease, thus increasing the risk of arrhythmia recurrence.
**BNP EFFECTS**

- **Hemodynamic** (Balanced vasodilation)
  - Veins
  - Arteries
  - Coronary arteries

- **Neurohumoral**
  - Aldosterone
  - Endothelin
  - Norepinephrine

- **Renal**
  - Diuresis
  - Natriuresis

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BNP exert EP effects through NPR-A & NPR-B
Effects of BNP and CNP on SAN myocytes in the presence of the PDE 3 inhibitor - milrinone
**Background:** HF plays a critical role in the genesis of AF. A high BNP level occurs in patients with HF and in patients with AF. However, the role of BNP in the pathophysiology of AF is not clear. The purposes of this study were to evaluate the effects of BNP on pulmonary vein (PV) arrhythmogenesis.

**Methods and Results:** Whole-cell patch clamp and fluorescence were used to study the action potential, ionic currents, and calcium homeostasis in isolated single rabbit PV cardiomyocytes before and after a BNP infusion, with or without ODQ (10 μM), milrinone (50 μM), or ouabain (1 μM).
Effect of BNP on action potential morphology of PV cardiomyocytes
Effects of the BNP on the electrical activity of PV cardiomyocytes
Effects of BNP on the sodium current in PV cardiomyocytes

A

Baseline

BNP 100 nM

8 pA/pF

5 ms

(mV) -120 -80 -40 -20 0

lna (pA/pF)

P<0.005

B

(a) Baseline

After TTX 30 µM

Before TTX 30 µM

TTX-sensitive current

(b) BNP 100 nM

After TTX 30 µM

Before TTX 30 µM

TTX-sensitive current
Effects of BNP on Calcium Handling
Effects of ouabain, losartan, and BNP on PV cardiomyocytes
Effects of NPs on electrical conduction in the sinoatrial node (mice)

Effects of Wild-Type and Mutant Forms of ANP on Atrial Electrophysiology and Arrhythmogenesis

Hua R, et al. Circ Arrhythm Electrophysiol. 2015;8:1240-1254
Effects of Wild-Type and Mutant Forms of ANP on Atrial Electrophysiology and Arrhythmogenesis

L-type Ca2+ currents ($I_{Ca,L}$) Mouse RA

L-type Ca2+ currents ($I_{Ca,L}$) (NPR-C/−) mice.

L-type Ca2+ currents ($I_{Ca,L}$) human right atrial myocytes

Hua R, et al. Circ Arrhythm Electrophysiol. 2015;8:1240-1254
Effects of Wild-Type and Mutant Forms of ANP on Atrial Electrophysiology and Arrhythmogenesis

Hua R, et al. Circ Arrhythm Electrophysiol. 2015;8:1240-1254
Carperitide and Atrial Fibrillation After Coronary Bypass Grafting

The Nihon University Working Group Study of Low-Dose HANP Infusion Therapy During Cardiac Surgery Trial for Postoperative Atrial Fibrillation

Akira Sezai, MD, PhD; Mitsuru Iida, MD, PhD; Isamu Yoshitake, MD, PhD; Shinji Waku, MD, PhD; Shunji Osaka, MD, PhD; Haruka Kimura, MD, PhD; Hiroko Yaoita, MD; Hiroaki Hata, MD, PhD; Motomi Shiono, MD, PhD; Toshiko Nakai, MD, PhD; Tadateru Takayama, MD, PhD; Satoshi Kunimoto, MD, PhD; Yuji Kasamaki, MD, PhD; Atsushi Hirayama, MD, PhD

*Circ Arrhythm Electrophysiol. 2015;8:546-553*
INTRAVENOUS NESIRITIDE, A NATRIURETIC PEPTIDE, IN THE TREATMENT OF DECOMPENSATED CONGESTIVE HEART FAILURE

WILSON S. COLucci, M.D., URI ELKAYAM, M.D., DARLENE P. HORTON, M.D., WILLIAM T. ABRAHAM, M.D., ROBERT C. BOURGE, M.D., ALLEN D. JOHNSON, M.D., LYNNE E. WAGONER, M.D., MICHAEL M. GIVERTZ, M.D., CHANG-SENG LIANG, M.D., PH.D., MATTHEW NEIBAUR, M.D., W. HERBERT HAUGHT, M.D., AND THIERRY H. LEJEUMENT, M.D., FOR THE NESIRITIDE STUDY GROUP*

TABLE 2. CHANGES IN BASE-LINE HEMODYNAMIC VALUES AT SIX HOURS IN THE EFFICACY TRIAL.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PLACEBO (N=42)</th>
<th>NESIRITIDE</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.015 µg/kg/min (N=43)</td>
<td>0.030 µg/kg/min (N=42)</td>
</tr>
<tr>
<td>Pulmonary-capillary wedge pressure (mm Hg)</td>
<td>+2.0±7.2</td>
<td>-6.0±7.2‡</td>
<td>-9.6±6.2‡</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>+0.4±4.6</td>
<td>-2.6±4.4‡</td>
<td>-5.1±4.7‡</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn·sec·cm⁻⁵)</td>
<td>+161±481</td>
<td>-247±492‡</td>
<td>-347±499‡</td>
</tr>
<tr>
<td>Cardiac index (liters/min/m²)</td>
<td>-0.1±0.47</td>
<td>+0.2±0.49§</td>
<td>+0.4±0.69‡</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>+0.3±11</td>
<td>-4.4±10.2</td>
<td>-9.3±12.6‡</td>
</tr>
<tr>
<td>Systolic pulmonary-artery pressure (mm Hg)</td>
<td>+1.7±8.2</td>
<td>-9.4±10.3‡</td>
<td>-12.9±12.5‡</td>
</tr>
<tr>
<td>Mean pulmonary-artery pressure (mm Hg)</td>
<td>+2.0±5.9</td>
<td>-7.0±6.9‡</td>
<td>-7.7±7.6‡</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn·sec·cm⁻⁵)</td>
<td>+26±197</td>
<td>-62±100</td>
<td>-2±142</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>+1.4±7.5</td>
<td>-1.6±7.1</td>
<td>+0.0±8.8</td>
</tr>
</tbody>
</table>
Conclusions

- BNP – a marker of HF as well as AF.
- BNP regulates PV electrophysiological characteristics and impairs sodium and calcium homeostasis.
- Activation of cyclic GMP, inhibiting PDE3 and Na\(^+\)/K\(^+\) - ATPase might participate in BNP modulation of PV electrophysiology in the pathophysiology of HF-related atrial arrhythmogenesis.
- NPs regulate electrical conduction and atrial electrophysiology and arrhythmogenesis.
- mANP causes AF and wild-type ANP is antiarrhythmic.
- In together with ARB, NP might improve HF without increase of AF.
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Taipei, Taiwan

17-20 October 2018

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