B-type Natriuretic Peptide in VHD: a Non-imaging Helper for the Cardiologist

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Sart Tilman Liège, BELGIUM
Conflict of Interest Disclosure

None
BNP Molecular Forms and Processing


BNP and its inactive amino terminal portion are neurohormones released by the ventricles in response to increased LV wall stress
Volume overload
Pressure overload
Wall stretch

Cardiac Myocyte

Furin
NT-BNP<sub>1-76</sub>
BNP<sub>77-108</sub>
proBNP<sub>1-108</sub>
Pre-proBNP
BNP mRNA

Elimination:
- Enzymatic: neutral endopeptidase
- Receptor mediated: CNP-receptors

T<sub>1/2</sub>=22min

Secretion

BNP<sub>77-108</sub>

N-terminal proBNP<sub>1-76</sub>
## Characteristics of an ‘ideal’ biomarker

<table>
<thead>
<tr>
<th>Specific</th>
<th>Predictive</th>
<th>Robust</th>
</tr>
</thead>
<tbody>
<tr>
<td>High myocardium/serum ratio</td>
<td>Long half-life in blood</td>
<td>Rapid, simple, and accurate</td>
</tr>
<tr>
<td>Not present in non-cardiac tissue, even pathologically</td>
<td>Release proportionate to extent of injury</td>
<td>Non-invasive / accessible / unexpensive</td>
</tr>
<tr>
<td>Sensitive</td>
<td></td>
<td></td>
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<tr>
<td>Zero baseline</td>
<td></td>
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<tr>
<td>Marker of ‘early,’ reversible cardiotoxicity</td>
<td></td>
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<tr>
<td>Immediate release with injury</td>
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</table>
The Place of BNP in current VHD Guidelines

ESC Guidelines

In Aortic stenosis:

“Natriuretic peptides have been shown in preliminary studies to predict symptom-free survival in AS.”

In Mitral regurgitation:

“Preliminary series have also suggested the value of elevated BNP levels as predictors of long-term outcome but this also remains to be validated”
**BNP level in AS**

BNP level is correlated with AS severity:
- ++ with AVA
- +- with pressure gradient

BNP is correlated with the consequences of AS on LV

Qi et al. AHC 2001
Lim et al. Eur Heart J, 2004
BNP level is well associated with the symptomatic status.

Bergler-Klein et al. Circulation 2004
Gerber et al. Circulation 2003
BNP level and Symptoms in AS

- BNP is more powerful than AS severity parameters to identify symptoms
- BNP level may predict the occurrence of symptoms:

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Developing Symptoms (n=14)</td>
<td>Patients Remaining Asymptomatic (n=29)</td>
<td>Patients Developing Symptoms (n=14)</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>188 (56–420)</td>
<td>64 (27–161)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTbNP, pmol/L</td>
<td>131 (50–202)</td>
<td>31 (19–56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NTbNP, pmol/L</td>
<td>131 (20–505)</td>
<td>31 (14–28)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bergler-Klein et al. Circulation 2004
**BNP for Risk Stratification in asymptomatic AS**

Risk Score for Predicting Outcome in Patients With Asymptomatic Aortic Stenosis

Jean-Luc Monin, MD, PhD; Patrizio Lancellotti, MD, PhD; Mehran Monchi, MD; Pascal Lim, MD; Emmanuel Weiss, MD; Luc Piérard, MD, PhD; Pascal Guéret, MD

- 107 pts followed in Créteil
- Risk score according to independent variables
- Validation in Liège (107 pts)

Score = (Peak velocity x 2) + (nat log BNP x 1.5) + 1.5 (if female)

Monin et al. Circulation, 2009
BNP level in LF/LG AS

BNP is significantly elevated in LF AS, even in paradoxical LF/LG AS. BNP level >550pg/mL strong predictor of outcome in LF/LG AS.

Lancellotti, Magne et al. JACC, 2012

Derivation (n=160) and validation (n=134) cohorts of asymptomatic severe AR and no LV dilatation/dysfunction

Combined end-point defined as LV dysfunction, symptoms or death

Baseline BNP < 130 pg/mL

Baseline BNP ≥ 130 pg/mL

HR = 6.7 (2.3-16.6)

p < 0.0001

Follow-up, years

BNP level in Aortic Regurgitation

Pizarro et al. JACC, 2011
**BNP level in Aortic Regurgitation**

**Follow-up, years**

- ERO<50mm² + BNP<130pg/mL
- ERO≥50mm² + BNP<130pg/mL
- ERO<50mm² + BNP ≥ 130pg/mL
- ERO≥50mm² + BNP ≥ 130pg/mL

**P Value**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP ≥130 pg/ml</td>
<td>6.9 (2.52-17.57)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESD/BSA ≥24 mm/m²</td>
<td>3.4 (1.88-11.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>EROA ≥50 mm²</td>
<td>4.3 (2.4-12.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>EDD ≥35 mm/m²</td>
<td>2.1 (0.88-13.7)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Multivariate predictors of Cardiac events
BNP level in Mitral Regurgitation

BNP level is not related to MR itself but to the atrial and ventricular consequences of MR

124 patients with primary MR; BNP vs. MR severity (ERO): r=0.17, p=0.06

Detaint et al. Circulation, 2005
**BNP level in Mitral Regurgitation**

**Determinants of BNP level**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BNP, Multivariate Analysis (P)</th>
</tr>
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<tbody>
<tr>
<td>LA volume</td>
<td>0.0001</td>
</tr>
<tr>
<td>AF</td>
<td>0.006</td>
</tr>
<tr>
<td>ESVI</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Impact of BNP level on survival**

![Graph showing survival rates with BNP levels](image)

*Detaint et al. Circ, 2005*
### BNP level in Asymptomatic MR

<table>
<thead>
<tr>
<th></th>
<th>Derivation Set</th>
<th>Validation Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BNP &lt;105 pg/ml</td>
<td>BNP ≥105 pg/ml</td>
</tr>
<tr>
<td>(n = 130)</td>
<td>(n = 37)</td>
<td>p Value</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61 ± 6</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Male</td>
<td>77 (59)</td>
<td>24 (64)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (9)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (15)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>139 ± 22 (93-170)</td>
<td>135 ± 18 (90-155)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 10 (62-98)</td>
<td>69 ± 11 (55-89)</td>
</tr>
<tr>
<td>NFL, n (%)</td>
<td>2 (1.5)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Exercise capacity (METs)</td>
<td>9.5 (8.5-11)</td>
<td>9.0 (8.0-12)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>68 (65-72)</td>
<td>65 (63-68)</td>
</tr>
<tr>
<td>End-diastolic diameter/BSA (mm/m²)</td>
<td>33 (25-38)</td>
<td>40 (29-46)</td>
</tr>
<tr>
<td>End-systolic diameter/BSA (mm/m²)</td>
<td>18 (14-23)</td>
<td>24 (19-29)</td>
</tr>
<tr>
<td>Regurgitant volume (ml/beat)</td>
<td>65 (63-70)</td>
<td>76 (66-84)</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>49 (46-55)</td>
<td>58 (49-64)</td>
</tr>
<tr>
<td>EROA (mm²)</td>
<td>53 (46-61)</td>
<td>65 (47-74)</td>
</tr>
<tr>
<td>AV/BSA (cm²/m²)</td>
<td>65 (42-73)</td>
<td>76 (49-84)</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>24 (18-30)</td>
<td>32 (24-38)</td>
</tr>
</tbody>
</table>

**BNP is a good marker of advanced stage of the disease**

*Pizarro et al. JACC, 2009*
**BNP level in Asymptomatic MR**

Multivariate predictor of combined end-point

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>BNP ≥105 pg/ml</td>
<td>4.6 (2.7–11.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>End-systolic diameter/BSA &gt; 22 mm/m²</td>
<td>3.4 (1.6–10.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>EROA &gt; 55 mm²</td>
<td>4.2 (2.1–11.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Follow-up, years

Combined end-point,%

Baseline BNP < 105 pg/mL vs. ≥ 105 pg/mL

Validation cohort

Pizarro et al. JACC, 2009
LV Longitudinal Function and BNP Level

Bi-centric study, n=135 asymptomatic MR (moderate & severe) with no LV dysfunction/dilatation

Prognostic importance of brain natriuretic peptide and left ventricular longitudinal function in asymptomatic degenerative mitral regurgitation

Julien Magne,1 Haifa Mahjoub,2 Luc A Pierard,1 Kim O’Connor,1,2 Charles Pirlet,1 Philippe Pibarot,2 Patrizio Lancellotti1

LV GLS, %

Whole cohort (n=135) BNP Quartiles

Q1 Q2 Q3 Q4

-20±4% -23.3±3 -21.2±3* -19.6±3 † ‡ † ‡

-16.5±4 † ‡ §

p<0.0001

Log BNP vs. LV GLS, %

r=0.64 p<0.0001

Magne et al. Heart 2012
BNP and Impact on Outcome

KM curves: median of BNP

- BNP <41pg/ml
  - 75±6%
- BNP >41pg/ml
  - 21±8%

Follow-up, months

Cardiac Event-free Survival, %

p<0.0001

HR=3.5, 95%CI: 1.7-7.2, p=0.001

Multivariable Analysis

- Q4
  - HR=8.8, 95%CI: 2.1-36.7, p=0.002
- Q3
  - HR=8.5, 95%CI: 2.2-32.5, p=0.002
- Q2
  - HR=3.5, 95%CI: 0.9-14.1; p=0.075
- Q1
  - HR=1, 95%CI: 1-1
Exercise BNP and Impact on Outcome

BNP level significantly increase during exercise

Exercise BNP is determined by ex. LV longitudinal function

Magne et al. Submitted 2012
**Exercise BNP and Impact on Outcome**

**Exercise BNP level and outcome**

- Tertile 1 (Ex. BNP: 5-29 pg/mL)
- Tertile 2 (Ex. BNP: 30-62 pg/mL)
- Tertile 3 (Ex. BNP: 63-412 pg/mL)

**Prediction of cardiac events, $\chi^2$**

**Incremental prognostic value of exercise BNP**

- Demographic and echo. data: 24.3
- Resting BNP: 35.8
- Exercise BNP: 45.6

$p=0.02$

Magne et al. Submitted 2012
### BNP in VHD: Take Home Messages

- **In severe AS**, BNP is a powerful predictor of the occurrence of symptoms and of poor outcome in asymptomatic pts (when combined with AS severity and gender).

- **In LF/LG AS**, BNP $>550$ pg/mL is associated with significant reduced survival.

- **In severe AR**, BNP $>130$ pg/mL multiplies by 7 the risk of cardiac events.

- **In severe primary MR**, BNP $>105$ pg/mL multiplies by 4.5 the risk of cardiac events.

- **In asymptomatic primary MR**, exercise BNP level may have important incremental prognostic value.
DON’T MISS

5-8 December 2012
MAICC – Athens, Greece

Abstract submission deadline
31 May

Early bird registration
30 September
Thank you for your attention.

“In these matters the only certainty is that nothing is certain.”

Pliny The Elder, 23 AD-79 AD