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Relationship of extent and nature of dysfunctional myocardium to brain natriuretic peptide in patients with ischemic left ventricular dysfunction*

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Abstract

We studied the relationship between brain natriuretic peptide (BNP) levels and viable myocardium and ischemic myocardium, regional scar and regional contractile function. Fifty-nine patients underwent dobutamine echocardiography and magnetic resonance imaging and resting BNP levels were determined. By magnetic resonance imaging, total extent of dysfunctional myocardium correlated strongest with BNP ($r = 0.60$, $p < 0.0001$). The extent of scar, viability and ischemia also correlated. At dobutamine echocardiography, a composite of dysfunctional and ischemic myocardium was the strongest correlate of BNP ($r = 0.48$, $p < 0.0001$), with less strong correlations by global parameters. The extent of dysfunctional myocardium, rather than its nature determines BNP levels.

Abbreviations: BNP – brain natriuretic peptide; DbE – dobutamine echocardiography; MRI – magnetic resonance imaging; CrCl – creatinine clearance; WS-MRI – LV systolic global wall stress; EDV – end diastolic volume; ESV – end systolic volume

Introduction

Brain natriuretic peptide (BNP) is known to correlate with left ventricular systolic function (ejection fraction, LV volumes, cardiac index, LV global wall stress), myocardial mass, pulmonary artery wedge and mean pulmonary artery pressure [1–6]. However, little is known about the role of chronic ischemia or chronic reduction in coronary flow reserve in the release of BNP and the subsequent BNP levels, or indeed the relationship between BNP and the myocardial characteristics of scar, viability and ischemia. Thus, we sought to study the relationship between BNP levels on the one hand and regional contractile function, scar, and viable and ischemic myocardium on the other.

Methods

Fifty-nine patients (age 34–77) with previous infarction and varying amounts of ischemic LV dysfunction (ejection fraction 48 ± 15%) were studied a median of 107 days after myocardial infarction. We performed dobutamine echocardiography (DbE) and magnetic resonance imaging

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(MRI) to measure contractile function, volumes and late contrast enhancement [7], and measured resting BNP levels (Biosite, San Diego, CA) [8]. Patients with coronary revascularization, valvular disease of more than moderate severity or any contraindication to DbE or MRI were excluded. Serum creatinine was 90 ± 30 micromol/l and creatinine clearance (CrCl) was 66 ± 24 ml/min [9, 10]. No patient had a clinical event between the time of the index infarction and subsequent investigations.

Resting MRI was obtained to assess contractile function, volumes and late contrast enhancement. LV systolic global wall stress (WS-MRI) was calculated from the following formula: WS-MRI = $0.133 \times \text{SBP} \times [1 + (3 \times (\text{LVESV index}/\text{LV mass index})]$ [11]. To analyze contrast enhancement on MRI a modification of standard American Society of Echocardiography segmentation [12] was used: the LV was divided into 128 subsegments after dividing 32 segments into 4 layers, from epicardium to endocardium, reflecting the transmural extent of scar (Figure 1). Contrast enhancement identified regions of old myocardial infarction that have been organized into scar. Viable myocardium was defined as the presence of regional dysfunction with absence of hyperenhancement. Myocardium that had reduced resting contractile function (hypokinesis, akinesis or dyskinesis) was defined as dysfunctional myocardium. Note dysfunctional myocardium was therefore composed of both scar and viable myocardium. Myocardium that had normal contractile function and was non-enhancing was classified as normal.

DbE images were interpreted by the consensus of two observers using the standard American Society of Echocardiography 16 segment model [12]. Segments with resting contractile dysfunction were defined as dysfunctional myocardium. Segments were considered viable if they were dysfunctional at rest and augmented function at low dose (5 – 10 mcg/kg/min). Segments were defined as scar if they were dysfunctional at rest and failed to augment at low dose. Segments were defined as ischemic if function deteriorated at any dose, however, for the purposes of our analysis, segments with resting dysfunction were not counted as ischemic.

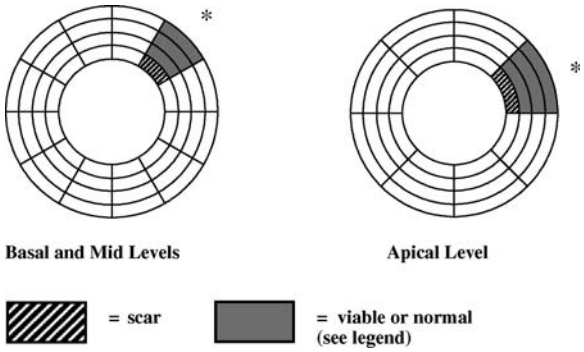

Figure 1. Schematic diagram illustrating regional analysis by MRI. The diagram on the left represents short axis left ventricular slices at the basal and mid levels. The diagram on the right represents the slices at the apical level. The basal and mid slices have been divided into 12 segments. This is a simple modification of the standard American Society of Echocardiography segmentation [12], the first modification being that the number of segments has been doubled by dividing all the standard segments in half making 32 segments. The concentric circles (see diagram) then divide each of these 32 segments into 4 layers giving a total of 128 subsegments. Using delayed contrast enhancement scar was identified. The amount of scar was quantified by counting the number of subsegments that contained scar. In the segments marked with asterisks, the hashed shaded area represents scar of one subsegment in each of the segments. If the segment had resting contractile dysfunction then the gray shaded subsegments were defined as viable myocardium. If the segment had normal resting contractile function then the gray shaded subsegments were defined as normal myocardium.

Results

Of the 59 patients with LV dysfunction after infarction, 52% had undergone thrombolysis and none had undergone primary angioplasty. The infarct size was significant, evidenced by an average creatine kinase level of > 2000 IU/L. The selected patients were significantly limited by LV dysfunction (LVEF by MRI: 48 ± 15%), the majority being in functional class II for dyspnea (47%), with a mean exercise capacity of 5 METS. The BNP levels ranged from 2.1 to > 1300 pg/ml with a mean of 209 ± 279 pg/ml. Serum creatinine ranged from 50 to 220 micromol/l with a mean of 90 ± 30 micromol/l and CrCl (corrected for lean body weight) ranged from 24 to 145 ml/min with a mean of 66 ± 24 ml/min.

Details of the MRI findings (32 segment model) and echocardiographic findings are summarized in Tables 1 and 2 respectively. Thinning (assessed by MRI and defined as thickness < 6 mm) was present in only 8% of segments showing resting dysfunction 58 segments out of 1888 by MRI (equivalent to 29 out of 944 segments by echocardiography).

The correlations of log BNP with imaging parameters are summarized in Figure 2. The extent of both scar and viable myocardium by MRI correlated moderately well with log BNP, although the strongest correlate of BNP was the total extent of dysfunctional myocardium ($r = 0.60$, $p < 0.0001$). Other left ventricular parameters (mass, EDV, ESV, EF and systolic wall stress) were less strongly associated with Log BNP (Table 1). Additionally, there was no meaningful correlation of BNP or log BNP with a range of clinical factors except age with log BNP ($r = 0.37$, $p = 0.004$) and CrCl ($r = -0.45$, $p < 0.0001$), age and CrCl being covariates ($r = -0.612$, $p < 0.001$). Of the clinical parameters and MRI parameters, the best independent predictors of BNP were the extent of dysfunctional myocardium by MRI together with CrCl ($r = 0.68$, $p < 0.001$). The extent of dysfunctional myocardium ($\beta = 0.53$) had a stronger association than CrCl ($\beta = -0.30$).

Table 1. Means and ranges of MRI parameters and correlations with log BNP. subsegts – subsegments; LVESV – left ventricular end systolic volume; LVEDV – left ventricular end diastolic volume; LVEF – left ventricular ejection fraction; WS-MRI – left ventricular systolic global wall stress; CrCl – creatinine clearance (corrected for lean body weight).

MRI parameters	Mean ± SD	Range	*r*	*p*
Dysfunctional myocardium (subsegts)	60 ± 36	0–128	0.601	< 0.0001
Scar (subsegts)	22 ± 14	0–66	0.476	< 0.0001
Viable myocardium (subsegts)	38 ± 30	0–124	0.500	< 0.0001
Normal myocardium (subsegts)	68 ± 36	0–128	−0.601	< 0.0001
LVESV (ml/m^2)	48 ± 29	12–164	0.438	0.001
LVEDV (ml/m^2)	87 ± 29	34–187	0.308	0.018
LVEF (%)	48 ± 15	12–76	−0.451	< 0.0001
LV mass (g)	162 ± 49	71–356	0.08	0.55
LV mass (g/m^2)	82 ± 22	48–176	0.233	0.076
WS-MRI (dynes/mm^2)	346 ± 103	158–576	0.350	0.007
CrCl (ml/min)	66 ± 24	24–145	−0.449	< 0.0001

Table 2. Means and ranges of DbE parameters and their correlation with log BNP.

Dobutamine echo parameters	Mean ± SD	Range	*r*	*p*
Dysfunctional myocardium (segments)	5 ± 3	1–13	0.456	< 0.0001
Scar (segments)	3 ± 3	0–12	0.376	0.003
Viable myocardium (segments)	2 ± 2	0–10	0.143	0.276
Ischemic myocardium (segments)	3 ± 3	0–13	0.232	0.075
Viable + ischemic myocardium (segments)	4 ± 3	0–15	0.166	0.206
Dysfunctional + ischemic myocardium (segments)	7 ± 3	2–16	0.484	< 0.0001
Normal myocardium (segments)	9 ± 3	0–14	–0.484	< 0.0001
CrCl (ml/min)	66 ± 24	24–145	–0.449	< 0.0001

At DbE, the extent of dysfunctional myocardium, and the extent of scar and viability and ischemia were all correlates of log BNP (Table 2). The strongest correlation was with a composite of dysfunctional and ischemic myocardium, the composite being defined as the number of segments in a given left ventricle that were dysfunctional plus the number of segments in the same left ventricle that were ischemic ($r = 0.48$, $p < 0.0001$). In a multivariate model of DbE variables, the composite of dysfunctional myocardium and ischemia was the only variable that was independently associated with log BNP ($r = 0.49$, $p < 0.0001$). In a multivariate model of the clinical and echo parameters, the best independent predictors of BNP were the extent of dysfunctional myocardium by echo, the extent of ischemic myocardium together with CrCl (predicted log BNP, $r = 0.61$, $p < 0.001$). The combination of extent of dysfunctional myocardium ($\beta = 0.33$) and extent of ischemic myocardium ($\beta = 0.27$) had a stronger association than CrCl ($\beta = -0.33$) (Table 3).

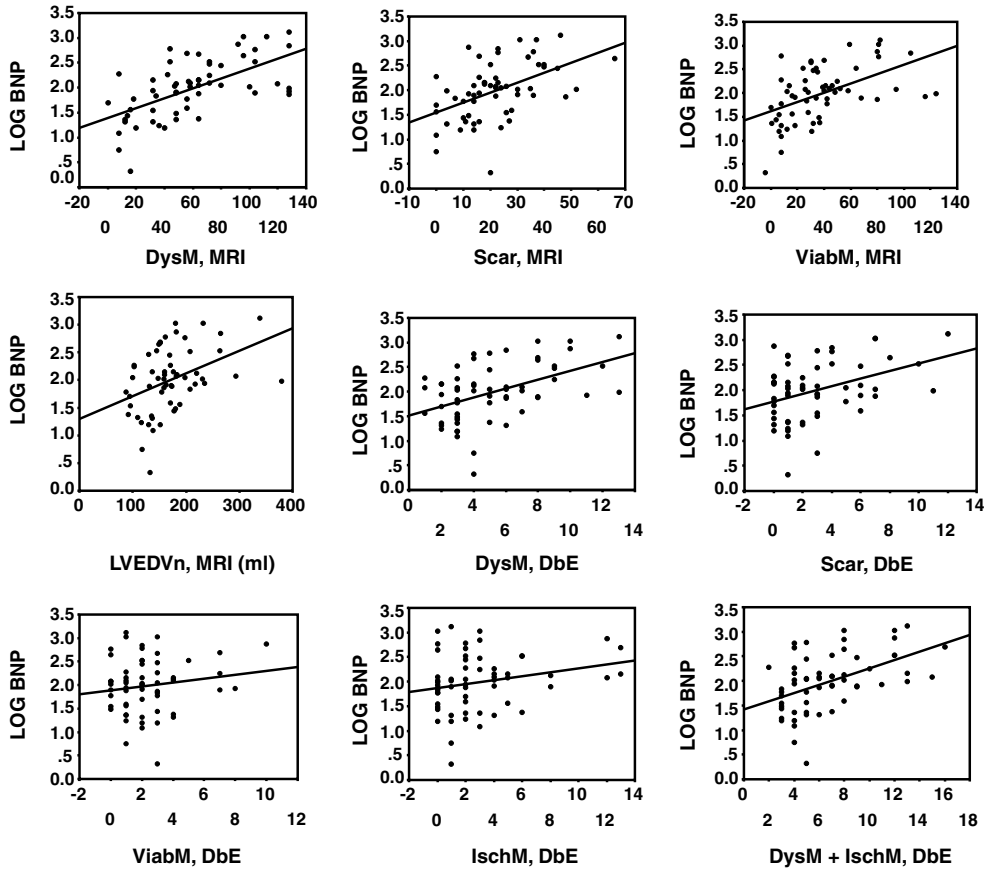

Figure 2. Scatter plots of MRI parameters and DbE parameters versus log BNP. *Abbreviations:* DysM – dysfunctional myocardium; ViabM – viable myocardium; LVEDVn – left ventricular end diastolic volume normalized; IschM – ischemic myocardium.

Discussion

The results of this study indicate that the extent of dysfunctional myocardium correlates moderately with BNP levels (log BNP) and this correlation exceeds that of BNP with characteristics of the ventricle as a whole (e.g. volumes, ejection fraction, mass and calculated systolic wall stress). These findings are consistent with the additive prognostic significance of regional indices to that of global left ventricular ejection fraction [13, 14]. The results also suggest that the extent of dysfunctional myocardium rather than its nature determines BNP levels, although there is also an association with the extent of inducible ischemia.

Table 3. Multivariate models for prediction of log BNP.

	B	β	p	r
Dysfunctional myocardium, MRI	0.00857	0.572	0.001	0.675
Creatinine clearance	−0.00704	−0.295	0.006	
Dysfunctional myocardium, DbE	0.633	0.332	0.007	0.607
Ischemic myocardium, DbE	0.0473	0.269	0.015	
Creatinine clearance	−0.0079	−0.332	0.008	

BNP is thought to be produced mainly locally in the left ventricle in direct response to increased wall tension [15, 16]. Normal ranges for BNP are complex and evolving and are probably still imperfectly defined [3, 17–21], although, 40 out of 59 (68%) of the BNP levels were above one of the recently published 'normal ranges' (5th -95th percentiles in pg/ml; women 8–155, men 4–86) [18].

However, the augmented expression of natriuretic peptides in patients with dilated cardiomyopathy is not due solely to global ventricular wall stress but is also influenced by regional conditions and is associated with structural changes in the myocytes [22]. Moreover, BNP-expressing myocytes are located in the subendocardium, with a gradient of BNP immunostaining from endocardium to epicardium [22, 23].

The mechanism of the association of BNP levels with regional dysfunction is unclear. Acute ischemia has certainly been shown to be associated with raised BNP levels [24–26], and the extent of stress induced ischemia has been demonstrated to be proportional to the BNP level during exercise [24]. The association of regional function with resting levels that we have shown may attest to the contribution of recurrent episodes of transient stunning. Supporting this, Morita et al. has demonstrated raised BNP levels in levels in patients with acute myocardial infarction, the height of the BNP level reflecting the degree of LV dysfunction [27].

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