High N-Terminal Pro-B-Type Natriuretic Peptide Levels Are Associated with Reduced Heart Rate Variability in Acute Myocardial Infarction

Luc Lorgis1, Daniel Moreau2,3, Laurent Mock4, Bernadette Daumais1,2, Daniel Potard1,4, Claude Touzery1, Yves Cottin1,3, Marianne Zeller3*

1 Centre de Cardiologie, CHU Dijon, Dijon, France, 2 Service d’Exploration Fonctionnelle, CHU Dijon, Dijon, France, 3 Laboratoire de Physiopathologie et Pharmacologie Cardiométaboliques, INSERM UMR 866, UFR Médecine, Université de Bourgogne, Dijon, France, 4 Service de Cardiologie, Clinique de Fontaine les Dijon, Fontaine les Dijon, France

Abstract

Aim: We investigated the relationships between the autonomic nervous system, as assessed by heart rate variability (HRV) and levels of N-terminal Pro-B-type Natriuretic Peptide (Nt-proBNP) in patients with acute myocardial infarction (MI).

Methods and Results: The mean of standard deviation of RR intervals (SDNN), the percentage of RR intervals with >50 ms variation (pNN50), square root of mean squared differences of successive RR intervals (rMSSD), and frequency domain parameters (total power (TP), high frequency (HF), low frequency power ratio (LF/HF)) were assessed by 24 h Holter ECG monitoring. 1018 consecutive patients admitted <24 h for an acute MI were included. Plasma Nt-proBNP (Elecsys, Roche) was measured from blood samples taken on admission. The median (IQR) Nt-proBNP level was 681(159–2432) pmol/L. Patients with the highest quartile of Nt-proBNP were older, with higher rate of risk factors and lower ejection fraction. The highest Nt-proBNP quartile group had the lowest SDNN, LF/HF and total power but similar pNN50 and rMSSD levels. Nt-proBNP levels correlated negatively with SDNN (r = −0.19, p < 0.001), LF/HF (r = −0.37, p < 0.001), and LF (r = −0.29, p < 0.001) but not HF (r = −0.043, p = 0.172). Multiple regression analysis showed that plasma propeptide levels remained predictive of LF/HF (B(SE) = −0.065(0.015), p < 0.001), even after adjustment for confounders.

Conclusions: In conclusion, our population-based study highlights the importance of Nt-proBNP levels to predict decreased HRV after acute MI.

Introduction

After acute myocardial infarction (MI), B-type natriuretic peptide (BNP) and the N-Terminal fraction of its propeptide (Nt-proBNP) are major prognostic factors, independently of left ventricular ejection fraction (LVEF). [1,2] Modulation of Nt-proBNP is multifactorial, depending on left ventricular dysfunction, remodeling, on left intraventricular pressure, and residual myocardial ischemia. [3,4] Left ventricular remodeling is a complex process affected by many factors notably the autonomous nervous system (ANS) through sympathetic activation. [5]

ECG Holter analysis is a validated non-invasive approach to evaluate the level of sympathetic and vagal tone. Loss of ANS balance frequently associated with coronary artery disease, is characterized by a fall in vagal modulation and a rise in sympathetic modulation. Heart Rate Variability (HRV) reflects cardiovascular response to the ANS. After MI, reduced HRV is an independent predictive factor of mortality and sudden cardiac death. [6,7] Experimental studies in animals and humans strikingly showed that BNP infusion affects activity of the ANS through a decrease in sympathetic activity. [8,9]

However, the relationship between plasma levels of Nt-Pro-BNP and ANS evaluated by Holter ECG analysis has never been fully explored, in particular in acute MI.

In a large prospective study, we set out to analyze the relationship between ANS, evaluated by the high and low frequency spectral components of HRV and the level of Nt-ProBNP at the acute phase of MI.

Methods

Patients

The participants were recruited from the RICO (observatoire des Infarctus de Côte-d’Or) database, a French regional survey for acute MI. [10] Briefly, RICO survey collects data from all the consecutive patients hospitalized <24 h for acute MI in all public centres or privately funded hospitals of one eastern region. The
present study included all the consecutive patients admitted between 1st July 2001 and 31st March 2008 who underwent a 24-hour Holter ECG recording during the hospitalization. Patients with a pacemaker (n = 8), atrial fibrillation (n = 83) or heart rate dysfunction (n = 6) were excluded. The present study complied with the Declaration of Helsinki and was approved by the ethics committee of University Hospital of Dijon. Each patient gave written consent before participation.

Data collection
Cardiovascular risk factors, hemodynamic parameters, i.e. heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, Killip class, history of MI and acute treatments were prospectively collected. LVEF was determined by echocardiography using the Simpson method at 3–6 days.

Biological data
Nt-proBNP levels were measured from blood samples taken at admission, kept at room temperature for 30 min then centrifuged at 2500 rpm at 4°C for 10 min. The median time from symptom onset to blood sampling was 180 (85–466) min. Plasma level of Nt-proBNP was determined by chemoluminescence (Elecsys 2010, Roche). Inter and intra-assay coefficient of variation were both <3%. The lowest detection limit of the assay was at 0.6 pmol/L. The limit for the detection of cross-reactivity with the other natriuretic peptides (ANP, BNP and CNP) was less than 0.01%. Peak Creatine Kinase (CK) was determined by blood sampling at 8-hour intervals during the first 48 h (Dimension analyzer, Roche). Creatinine clearance was calculated from plasma creatinine levels assessed from blood sample taken on admission. [11]

Holter ECG data
24-hour (Holter) ECG was performed at 5±2 days. Long ECG tracing were recorded and analysed by two experienced observers using a Synelfast digital recorder Holter (Elam medical and Spieder Viers, le Plessis Robinson, France), with seven surface electrodes signals (acquisition sampling rate : 1000 Hz). After classifying the QRS morphology, the RR intervals (longest and shortest) were confirmed manually until no QRS sequences were incorrectly labeled. Only sequences with normal QRS characteristics were analyzed for HRV study.

Analysis of the temporal domain analyzed the indexes 1) rMSSD: root mean square successive difference between each value and the preceding value. 2) pNN50: % of successive intervals in which the difference exceeds 50 ms. 3) SDNN: standard

Table 1. Characteristics of the study population according to Nt-proBNP quartiles.

|               | Q1    | Q2    | Q3    | Q4    | P   |
|---------------|-------|-------|-------|-------|-----|
| Median Nt-proBNP (25th–75th), pg/ml | 70 (39–107) | 356 (238–479) | 1238 (945–1640) | 5605 (3451–11284) | p <0.001 |
| N = 254 | N = 255 | N = 255 | N = 254 |
| Age (years) | 55 (47–64) | 64 (52.5–73) | 65 (54–75) | 76 (65.25–81) | <0.001 |
| Sex female   | 37 (15%) | 53 (21%) | 77 (30%) | 120 (47%) | <0.001 |
| Hypertension | 78 (31%) | 129 (51%) | 132 (52%) | 161 (63%) | <0.001 |
| Diabetes     | 44 (17%) | 41 (16%) | 56 (22%) | 75 (30%) | 0.001 |
| Body mass index (kg/m²) | 26 (24–29) | 26 (24–29) | 26 (24–29) | 25 (22–28) | 0.001 |
| Dyslipidemia | 106 (42%) | 117 (47%) | 127 (50%) | 101 (40%) | 0.103 |
| History of myocardial infarction | 13 (5%) | 27 (11%) | 26 (10%) | 33 (13%) | 0.023 |
| Current smoker | 121 (48%) | 94 (37%) | 83 (34%) | 54 (21%) | <0.001 |

Clinical data
Heart rate | 73 (64–85) | 72 (62–82) | 80 (69–90) | 84 (72–100) | <0.001 |
| SBP (mmHg) | 140 (124–158) | 139 (120–157) | 145 (129–162) | 133 (119.5–157) | 0.026 |
| DBP (mmHg) | 83 (72–95) | 80 (70–90) | 80 (70–97) | 80 (69–90) | 0.01 |
| Anterior wall infarction | 80 (31%) | 75 (29%) | 83 (33%) | 125 (49%) | 0.001 |
| LVEF (%) | 60 (52–66) | 59 (50–63) | 55 (46–64) | 46 (35–55) | <0.001 |
| ST-elevation MI | 156 (61%) | 140 (55%) | 159 (62%) | 167 (66%) | 0.085 |
| Heart failure (Killip class >1) | 31 (12%) | 30 (12%) | 53 (21%) | 127 (50%) | <0.001 |

Acute treatments
β-blockers | 212 (83%) | 212 (83%) | 204 (80%) | 172 (68%) | 0.001 |
| Amiodarone | 10 (4%) | 10 (4%) | 17 (7%) | 27 (11%) | 0.005 |

Biological data
Peak CK (UI/L) | 863 (241–2607) | 808 (221–2158) | 729 (278–2548) | 517 (215–1448) | 0.005 |
| Creatinine clearance, mL/min | 92 (75–114) | 82 (63.2–105) | 79.3 (57–105) | 52 (35–71) | <0.001 |

Data are presented as N(%) or median (25th–75th). P values correspond to one-way ANOVA.
LVEF: Left Ventricular Ejection Fraction.
CK: Creatine Kinase.
Nt-proBNP: N-terminal pro B type Natriuretic Peptide.
MI: Myocardial Infarction.
doi:10.1371/journal.pone.0044677.t001

Data collection
Cardiovascular risk factors, hemodynamic parameters, i.e. heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, Killip class, history of MI and acute treatments were prospectively collected. LVEF was determined by echocardiography using the Simpson method at 3±1 days.

Biological data
Nt-proBNP levels were measured from blood samples taken at admission, kept at room temperature for 30 min then centrifuged at 2500 rpm at 4°C for 10 min. The median time from symptom onset to blood sampling was 180 (85–466) min. Plasma level of Nt-proBNP was determined by chemoluminescence (Elecsys 2010, Roche). Inter and intra-assay coefficient of variation were both <3%. The lowest detection limit of the assay was at 0.6 pmol/L. The limit for the detection of cross-reactivity with the other natriuretic peptides (ANP, BNP and CNP) was less than 0.01%. Peak Creatine Kinase (CK) was determined by blood sampling at 8-hour intervals during the first 48 h (Dimension analyzer, Roche). Creatinine clearance was calculated from plasma creatinine levels assessed from blood sample taken on admission. [11]
deviation of all of the RR intervals between two normal QRS complexes.

Spectral analysis used the Fast Fourier Transform to convert the different successive RR intervals in the frequency domain. Low frequencies (LF, between 0.04 and 0.15 Hz) are affected by both vagal and sympathetic activity, whereas high frequencies (HF, between 0.15 and 0.4 Hz) are affected by vagal tone. The LF/HF ratio is therefore considered an indicator of sympathovagal balance; Oscillations in very low frequencies VLF (range 0.00 to 0.04 Hz) reflect peripheral vaso-motor regulation. Total power (TP), combining the sum of all of the frequencies, is a global measure ANS activity.

**Statistical analysis**

Data are expressed as medians (1st–3rd quartile) or percentages (n (%)). Categorical variables were compared using the Chi-2 test and continuous variables using ANOVA. A correlation analysis was carried out using a Spearman or Pearson test. We used backward multivariate linear regression analysis to predict LF/HF. Variables associated with the LF/HF ratio in univariate analysis were included as covariables in the model (inclusion at 1%, and an exclusion at 5%). For not normal distribution, variables were log-transformed. The best linear adjustment was selected for inclusion in the model. Analyses were performed using SPSS 12.0 (SPSS Inc, Illinois, USA).

**Results**

The baseline characteristics classified according to Nt-proBNP quartiles are presented in table 1. Among the 1018 participants, the median Nt-proBNP level was at 682 (159–2432) pg/ml. Patients with the highest Nt-proBNP quartile were almost 20 y older and with a higher rate of CV risk factors, except for smoking, and history than patients from the lowest quartiles. Patients from the highest quartile were also characterized by increased heart rate, lower SBP levels on admission and higher rate of anterior infarction. With increasing levels of Nt-proBNP, LVEF gradually decreased, while patients with HF increased. Beta-blockers were less given in patients with the highest levels of the propeptide, while amiodarone was more used. Infarct size, as assessed by biological markers (i.e. CK), was lower in the highest quartiles of propeptide.

HRV parameters (i.e. SDNN, LF/HF, LF, VLF and total power) gradually decreased with increasing Nt-proBNP (Q4 to Q1) (table 2). However, pNN50, rMSSD and HF values were similar whatever the propeptide quartiles (table 2). Median values for LF, HF and LF/HF according to the Nt-proBNP quartiles are presented in figure 1. Variations in the LF/HF ratio are mainly due to variations in LF, since high frequencies do not vary significantly (p = 0.172).

In correlation analysis, the level of Nt-proBNP was associated with SDNN (r = 0.19, p<0.001), LF/HF ratio (r = −0.37, p<0.001), and LF (r = −0.29, p<0.001) but not HF (r = −0.04, p = 0.172) (figure 2).

Multiple linear regression analysis showed that plasma levels of NT proBNP were independently associated with LF/HF, even after adjustment for confounding factors (table 3).

**Discussion**

This large prospective study in patients after MI is the first to report that high levels of Nt-proBNP at admission is strongly predictive of deterioration in HRV, as evidenced by a marked decrease in the LF/HF ratio.

**Figure 1.** Heart rate variability parameters in spectral analysis according to of Nt-proBNP quartiles: Low Frequency (LF), High Frequency (HF) and Low frequency/High Frequency (LF/HF) ratio. P values correspond to one-way ANOVA.

doi:10.1371/journal.pone.0044677.g001
Heart rate variability determinants

HRV temporal and spectral analysis is a strong and independent prognosis marker after acute MI. [6,7]. Although HRV early decreases after MI, HRV parameters are stable from the second to fifth day after MI. [12] In addition, HRV is a useful tool for risk stratification for both short and long term prognosis. [13] In our study, older age and women were associated with decreased LF/HF ratio, consistent with findings showing that vagal modulation diminishes with increasing age. Moreover, men have a greater HRV than women, although this difference disappears after age 50. [14]

In patients under cardiac rehabilitation program, LF/HF ratio was improved by roughly 50% in patients taking betablockers corresponding to a more favorable sympathovagal balance. [15] Propranolol treatment for 1 month induced a greater increase in

| Table 2. Distribution of heart rate variability indexes according to Nt ProBNP quartiles. |
|------------------|------------------|------------------|------------------|------------------|
|                  | Q1 (N = 254)     | Q2 (N = 255)     | Q3 (N = 255)     | Q4 (N = 254)     |
| PNN50 (ms)       | 3.71 (0.96–10.63)| 4.00 (1.01–10.76)| 2.99 (0.67–9.44) | 2.66 (0.88–9.76) |
| rMSSD (ms)       | 25.8 (18.0–36.7)| 27.7 (18.9–38.5)| 25.0 (17.7–36.3) | 28.1 (18.6–41.4) |
| SDNN (ms)        | 89.7 (70.6–114.9)| 86.0 (66.0–113.9)| 80.2 (59.7–100.3)| 73.5 (55.1–94.9) |
| TP (ms²)         | 2326 (1286.50–3830.75)| 1851 (1057–3480)| 1722 (733–3152.5) | 1226 (569.5–2373.0)|<0.001 |
| LF/HF            | 3.85 (2.52–5.70)| 3.33 (1.82–4.76)| 2.62 (1.41–4.5) | 1.67 (0.95–3.01) |
| LF (ms²)         | 412 (212–848)| 330 (152–739) | 267 (102–608.5) | 170.5 (71.25–439.5) |
| HF (ms²)         | 105 (51–226)| 98 (46–226) | 94 (36–228) | 89 (44.25–235) |
| VLF (ms²)        | 988 (488–1714)| 787 (411–1333) | 557 (290–1128) | 440 (170–840) |

Data are presented as median (25th–75th). P values correspond to one-way ANOVA.

Figure 2. Correlation analysis between Nt-proBNP circulating levels and heart rate variability parameters on 24 h holter ECG; A: SDNN: Standard Deviation of the NN interval (SDNN); B: Low frequency (LF); C: High frequency (HF =; D: Low frequency/high frequency (LF/HF) ratio. P values correspond to one-way ANOVA. LF and HF are log-transformed values.

doi:10.1371/journal.pone.0044677.g002
HF than with placebo. [16] In addition, LF/HF ratio increased in the placebo group but decreased in the betablocker group, suggesting sympathetic inhibition. An increase in LF/HF ratio in patients under metoprolol or atenolol 3 weeks after an acute MI has also been reported. [17] In our study, most (i.e. 80%) patients were on beta-blocking therapy, resulting in a more favorable LF/HF ratio. To the best of our knowledge, no studies have clearly demonstrated the beneficial effect of beta-blockers on HRV at such early stage after the acute phase of MI.

Sympathetic activity by spectral analysis

High frequency index (i.e. HF) reflects parasympathetic modulation, and considered as mainly influenced by respiration. LF power is probably driven by both the sympathetic and parasympathetic nervous system. Moreover, LF power is also considered as an index of sympathetic modulation of the heart rate. Although LF/HF ratio is recognized as an index of vagosympathetic balance, caution must be taken on the interpretation of this ratio. [18] because reduced LF and the LF/HF ratio may rather correspond to a decreased response of the sinus node to ANS modulations and baroreflex dysfunction, rather than an increase in sympathetic activity. In humans, LF power may also primarily reflects baroreflex modulation rather than sympathetic tone. [19] In our study, LF/HF ratio alteration across the quartiles was mostly driven by a decrease in LF, with similar HF levels. Hence, the decreased predominance of LF suggests a gradual decrease in sympathetic tone with increasing NT-proBNP levels.

Nt-proBNP and ANS

BNP have a wide spectrum of favorable effects including diuretic, natriuretic, and hypotensive properties, and inhibition of the Renin-Angiotensin-Aldosterone System and of endothelin secretion. Thus, infusion of BNP has been proposed as a novel therapy for heart failure. Natriuretic peptides are known to induce natriuresis and diuresis, and inhibit activity of the Renin-Angiotensin-Aldosterone System and of endothelin secretion. Hence, in patients with heart failure, LF/HF is reduced, indicating an impairment of autonomic reactivity and the attenuation of responses correlated strongly with impairment of left ventricular function. [20] Hence, in patients with impaired left ventricular function, the pathophysiologic mechanisms of LF/HF ratio and of reduced LF oscillations are complex. [21] Further studies are needed to specifically address the relationship between the propeptide, sympathetic nerve activity and LF oscillations in such patients.

Study limitations

The delay between the propeptide and HRV measure HRV may influence the findings since HRV parameters are not all stable during the first two weeks after AMI. However, as shown by Carpeggiani et al., [28], the significance between admission and discharge (13±7 d) was obtained on a large paired analysis, and a large delay between the 2 HRV measures and therefore this significant increase may not apply to our study population. Moreover, LF/HF was stable during the study duration since neither LF/HF ratio nor the normalized powers did change during hospitalization (Discharge: 3±3 vs admission: 3±6). Therefore, Nt-proBNP measured at admission could predict long-term deterioration of spectral HRV balance. The main strength of this study is the use of a large regional population-based registry, reflecting the daily clinical practice in the setting of acute MI, with prospectively collected data including comprehensive analysis of all the parameters that could potentially influence HRV. This registry, however, suffers from the usual limitations of observational, non randomized studies, and therefore determines correlations, rather than causal relationships. The observation of a decreased HRV in patients with high NT-proBNP levels must therefore be interpreted with a fair amount of caution. However, the adjustment for a wide range of possible confounding factors limits the risk of bias in our conclusions. Hence, although we cannot exclude the impact of other unmeasured confounding factors, we may think that the observed effects on HRV are robust and reliable.

Conclusion

Our study showed for the first time a strong association between high levels of NT-proBNP and diminished HRV after an acute MI, even after adjustment for confounding factors. In addition, our results provide further insights on the pathophysiological effects of the propeptide, and its interplay with the sympathetic nervous system. Further experimental studies are needed to fully explore the physiological pathways involved in such effects and to determine their prognosis and therapeutic impact.

| Table 3. Multivariate analysis of factors associated with Log LF/HF. |
|----------------|----------------|----------------|----------------|
| Variable       | Beta           | Standard Error | p              |
| Log NT-proBNP  | 0.055          | 0.015          | <0.001         |
| Beta-blocker   | 0.062          | 0.026          | 0.020          |
| Female         | 0.127          | 0.025          | <0.001         |
| Age            | 0.009          | 0.001          | <0.001         |

doi:10.1371/journal.pone.0044677.t003

Nt-ProBNP and Heart Rate Variability in AMI

High frequency index (i.e. HF) reflects parasympathetic modulation, and considered as mainly influenced by respiration.
Acknowledgments

We wish to thank Anne Cécile Lagrost, Florence Bichat, Aline Chaqnon and Juliane Berchoud for research assistance and Philip Bastable for English assistance.

References

1. de Lemos JA, Morrow DA, Bentley JH, Ormland T, Sabatine MS, et al (2001) The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 345: 1014–1021.
2. Omland T, Persson A, Ny L, O'Brien R, Karlsson T, et al (2002) N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 106: 2913–2918.
3. Levin ER, Gardner DG, Samson WK (1998) Natriuretic peptides. N Engl J Med 339: 321–328.
4. Martinez-Ramayor A, Richards AM, Burnett JC, Januzzi JL (2008) Biology of the natriuretic peptides. Am J Cardiol 101: 3–8.
5. Neumayr RH, Hauptman PJ (2009) beta-Adrenergic receptor blockers and heart failure risk after myocardial infarction: a critical review. Curr Heart Fail Re 6: 220–229.
6. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59: 256–262.
7. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE (1992) Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 85: 164–171.
8. Toader E, McAllen RM, Cividjian A, Woods RL, Quintin L (2007) Effects of systemic B-type natriuretic peptide on cardiac vagal motoneuron activity. J Physiol Heart Circ Physiol 293: H3465–H3470.
9. Brunner-La Rocca HP, Kaye DM, Woods RL, Hastings J, Eder MD (2001) Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol 37: 1221–1227.
10. Zdiller M, Steg PG, Ravin J, Laurent Y, Janin-Manificat L, et al (2008) Relation between body mass index, waist circumference, and death after acute myocardial infarction. Circulation 118: 482–490.
11. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Natl Clin Pract Nephrol 16: 31–41.
12. Doululas AD, Flather MD, Pipilis A, Campbell S, Stuart F (2001) Evolutionary pattern and prognostic importance of heart rate variability during the early phase of acute myocardial infarction. Int J Cardiol 77: 169–179.
13. Bigger JT Jr, Fleis JL, Rolnitzky LM, Steinman RC (1993) Frequency domain measures of heart period variability to assess risk late after myocardial infarction. J Am Coll Cardiol 21: 729–736.
14. Bonnemerie H, Wiegand UKH, Brandes A, Kluge N, Katus HA (2003) Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. J Cardiovasc Electrophysiol 14: 791–799.
15. Malaffato G, Facchini M, Sala L, Branzi G, Bragato R, et al (1998) Effects of cardiac rehabilitation and beta-blocker therapy on heart rate variability after first acute myocardial infarction. J Am Coll Cardiol 81: 834–840.
16. Lamport R, Ickovics JR, Viscodi CJ, Horovitz RJ, Lee FA (2003) Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. Am J Cardiol 91: 137–142.
17. Large J, Wemmerblom B, Tygesen H, Karlsson T, Hjalmarson A (1997) Heart rate variability after acute myocardial infarction in patients treated with atenolol and metoprolol. Int J Cardiol 60: 157–164.
18. Eckberg DL (1997) Sympathovagal balance: a critical appraisal. Circulation 96: 3234–3239.
19. Rahman F, Prechlik S, Gross D, Sewell L, Goldstein DS (2011) Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Clin Auton Res 21: 133–141.
20. Chan NY, Seyed N, Takano K, Levi R (2012) An unsuspected property of natriuretic peptides: promotion of calcium-dependent catecholamine release via protein kinase g-mediated phosphodiesterase type 3 inhibition. Circulation125: 290–297.
21. Kasama S, Toyama T, Hatori T, Sumino H, Kumaoka H, et al (2007) Effects of intravenous atrial natriuretic peptide on cardiac sympathetic nerve activity and left ventricular remodeling in patients with first anterior acute myocardial infarction. J Am Coll Cardiol 49: 667–674.
22. Alyan O, Kacmaiz F, Ozdemir O, Maden O, Topaloglu S, et al (2008) Effects of cigarette smoking on heart rate variability and plasma N-terminal pro-B-type natriuretic peptide in healthy subjects: is there the relationship between both markers? Ann Noninvasive Electrocardiol 13: 137–1344.
23. Perkonska J, Hannekoski S, Junttila MJ, Jokinen V, Tapalainen J, et al (2010) Predictors of long-term risk for heart failure hospitalization after acute myocardial infarction. Ann Noninvasive Electrocardiol 15: 250–258.
24. Makikiillo TH, Haikuri HV, Hintze U, Videbaek J, Mitrami RD, et al (2001) DIAMOND Study Group (Danish Investigations of Arrhythmia and Mortality ON Dofetilide). Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. Am J Cardiol 87: 178–182.
25. Tapalainen JM, Lindgren KS, Makikiillo TH, Vuolteenaho O, Leppaluoja J, et al (2004) Natriuretic peptides as predictors of non-sudden and sudden cardiac death after acute myocardial infarction in the beta-blocking era. J Am Coll Cardiol 43: 757–763.
26. Patel H, Ozdemir RA, Patel M, Xiao HB, Poole-Wilson PA, et al (2011) Impairment of autonomic reactivity is a feature of heart failure whether or not the left ventricular ejection fraction is normal. Int J Cardiol 151:34–39.
27. Scalvini S, Voherrani M, Zannelli E, Pagan M, Mazuero G, et al (1998) Is heart rate variability a reliable method to assess autonomic modulation in left ventricular dysfunction and heart failure? Assessment of autonomic modulation with heart rate variability. Int J Cardiol 67:9–17.
28. Carpeggiani C, L’Abbate A, Landi P, Michelassi C, Raciti M, et al (2004) Early assessment of heart rate variability is predictive of in-hospital death and major complications after acute myocardial infarction. Int J Cardiol 96:361–366.

Author Contributions

Conceived and designed the experiments: DM LL LM YC. Performed the experiments: BD YC. Analyzed the data: DP DM. Contributed reagents/materials/analysis tools: CT. Wrote the paper: MZ.