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*EP & Arrythmia*

# Changes of Atrial Natriuretic Peptides after Defibrillation Threshold Testing Predicted Future Ventricular Arrhythmia Event

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***Background:*** We investigated the change of natriuretic peptides during defibrillation threshold (DFT) testing and its relationship with future ventricular arrhythmia (VA) events in patients implanted with an implantable cardioverter defibrillator (ICD).

***Methods:*** Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP) were measured in 21 patients (mean age 61 ± 13 years; 67% male) undergoing ICD implantation. Blood samples of the patients were drawn at pre-implantation, 30 minutes, 60 minutes, and 24 hours after DFT testing. The patients were followed and divided into two groups according to the occurrence of VA in 18 months. The biomarker levels and their changes were compared in patients with and without further VA.

***Results:*** The pre-implantation ANP levels were higher at pre-implantation and increased significantly at 30 minutes after DFT testing (Δ30minANP) among patients with VA events. The BNP and CNP levels did not change significantly after DFT testing in both groups. The area under curve was 0.82 for the change in Δ30minANP determining further ventricular events. The optimal Δ30minANP cutoff value was 0.51 pg/ml, with sensitivity of 0.83 and specificity of 0.68. Multivariable analysis confirmed that patients with Δ30minANP more than 0.51 pg/ml have a higher risk of further ventricular events (hazard ratio 39.8, 95% confidence interval: 2.87-553.01, p = 0.006). The pre-implantation ANP level could not predict future VA events (hazard ratio 1.06, 95% CI: 1.00-1.14, p = 0.06).

***Conclusions:*** The increase of ANP concentration after DFT testing predicted future VA events after ICD implantation while the BNP and CNP levels did not predict future VA events.

**Key Words:** Atrial natriuretic peptides • Brain natriuretic peptides • Defibrillation threshold testing • Implanted implantable cardioverter defibrillator • Ventricular arrhythmia

## INTRODUCTION

Defibrillation threshold (DFT) testing has been used to confirm effective device function during implantable cardioverter defibrillator (ICD) implantation. Myocardial injuries related to DFT testing, for example, elevation of cardiac enzymes and serum brain natriuretic peptide (BNP) levels have been reported.[1] Natriuretic peptides are markers of atrial and ventricular hemodynamic stress. Several studies indicated that both atrial natriuretic peptide (ANP) and BNP levels decreased after sinus rhythm was restored by cardioversion in patients

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with atrial fibrillation.[2-5] The c-type natriuretic peptide (CNP), secreted by the endothelium and myocardium, is structurally related to atrial and brain natriuretic peptides,[6] and its levels increase in patients with chronic heart failure related to clinical severity.[7] The changes of these natriuretic peptides after DFT testing were not completely investigated and the correlations of these changes with clinical outcomes were not well-studied. Since ICD was given to patients for terminating serious ventricular arrhythmias (VA), the occurrence of VA can be considered as one of the major outcomes. We hypothesized that the change of natriuretic peptides in response to DFT testing predicted future VA events after ICD implantation. The current investigation aimed to study the changes in natriuretic peptides levels after DFT testing and its correlation with VA events after implantation.

## METHODS

Twenty-three consecutive patients undergoing elective ICD implantation were enrolled in this study. The indications for ICD implantation were secondary preventions for VA caused by arrhythmogenic right ventricular dysplasia, long QT syndrome, ischemic heart disease, dilated cardiomyopathy and idiopathic ventricular fibrillation with aborted sudden cardiac death. Patients with clinical evidence of acute myocardial infarction within 40 days, and end-stage renal disease requiring hemodialysis were excluded. The ICD implantations were performed by experienced electrophysiologists according to the standard protocol. In brief, all patients underwent the surgical procedures after local anesthesia and conscious sedation. The ICD pockets were created subcutaneously in the left subclavian area. Operators were tasked to obtain a minimum R wave of 5.0 mV and a high-voltage impedance within the reference range. After the ICD implantation, DFT testing was performed with a shock ranging from 10 joules (J) to 15J after the ventricular tachyarrhythmia was induced by T wave shock. If ventricular tachyarrhythmia was terminated by the first shock, we repeated testing with decreased shock energy by 5J. If ventricular tachyarrhythmia was not terminated by the first shock, a rescue endocardial shock of 25-41 J or an external shock was delivered immediately. Repeated testing was performed with an increased shock energy by 5J. For example, if sinus rhythm was restored with the shock energy of 15J, repeated testing with 10J was performed. If sinus rhythm was not restored with the shock energy of 15J, a rescue endocardial shock of 25J was delivered. If sinus rhythm was restored with the shock energy of 25J, repeated testing with 20J would be performed. The DFT was defined as the lowest shock energy required to achieve at least 2 successful terminations of induced ventricular tachycarrhythmia from 3 attempts.

### Lab data acquisition and analysis

Four blood samples, 2 ml for each, were collected from each patient for measurement of ANP, BNP, and CNP. These samples were collected at pre-implantation, 30 minutes, 60 minutes, and 24 hours after DFT testing. Details of the quantification of plasma natriuretic peptides in this laboratory have been previously described.[8,9] In brief, blood samples were collected into chilled test tubes containing ethylene diamine tetraacetic acid (EDTA) and aprotinin (0.6 TIU per ml blood; Phoenix Pharmaceuticals, Mountain View, CA, USA). Samples were immediately centrifuged and plasma stored at -80 °C until later measured. The plasma levels of naturiuretic peptides were determined by the technician, who was unaware of the patients' clinical data using radioimmunoassay method with commercially available kits (Phoenix Pharmaceuticals, USA), conducted according to the manufacturer's manual. The intra-assay co-efficient of variation was 7.5% for ANP, 6.5% for BNP, and 6.9% for CNP. The lower limit of detection was 1 pg/ml.

The changes of natriuretic peptides after DFT testing were calculated by the natriuretic peptides levels collected at a certain time point minus those collected at pre-implantation. For example, the change in ANP at 30 minutes (Δ30minANP) was calculated as the ANP level at 30 minutes after DFT testing minus the level at pre-implantation. The change in ANP at 60 minutes (Δ60minANP) was calculated as the level at 60 minutes after DFT testing minus the level at pre-implantation. The change in ANP at 24 hours (Δ24hrANP) was calculated as the level at 24 hours after DFT testing minus the level at pre-implantation. The changes of BNP or CNP levels were calculated in the same fashion.

### Follow up

The first patient visit occurred 7 days after implantation to ascertain the ICD wound condition. Then, the patients were followed up at 4 weeks after ICD implantation and then every 3 months for more than 18 months at the cardiovascular clinic with ICD interrogation. The interrogation reports were incorporated with the medical charts. If there were VA events with high ventricular rate of more than 180 beats per minute and more than 8 consecutive beats observed by the device, the patient was assigned to the group with VA events. If concurrent atrial high rates of more than 180 beats per minute were noted during the VA events, the intracardiac electrograms were printed and reviewed by one electrophysiologist to determine whether the VA events were actual VA, or high ventricular rate driven by supraventricular tachycardia. The exact date of the first VA event was recorded. If there were no VA events observed by the device, the patient was assigned to the group without VA. The change of natriuretic peptide levels in patients with VA events were compared with those in patients without the events. Informed consent for the study and ICD implantation were obtained from all patients before enrollment. The study protocol was approved by the Institutional Review Board of this hospital (MMH-I-S-231).

### Statistical analysis

The data are presented as the mean value and standard deviation for normally distributed continuous variables and proportions for categorical variables. The differences between continuous values were assessed using paired 2-tailed t test for continuous variables. The chi-square test was used for the comparison of categorical variables. To compare biomarker measurements between groups, the Mann-Whitney Test was used. To compare the change of biomarker measurements between time points within a group, the Wilcoxon signed-rank test was used. Cox proportional hazards regression analysis was used to evaluate the association of variables with VA events. The variables regarded as significant predictors ($p < 0.05$) for future VA with univariate analysis and the variables previously reported to be associated with VA occurrence were subjected to the Cox proportional hazards regression analysis. The receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of the increment in ANP at 30 minutes for detection of VA events. VA events event-free curves were drawn using the Kaplan-Meier method and were compared using the log-rank test; additionally, all of the tests were two-sided. A p-value of 0.05 or less was considered an indication of statistical significance.

## RESULTS

### Patient characteristics

Twenty-three consecutive patients who underwent elective ICD implantation were enrolled into this study. The indications for ICD implantation were as follows: arrhythmogenic right ventricular dysplasia in 1 patient; long QT syndrome in 1 patient; idiopathic ventricular tachyarrhythmia with aborted sudden cardiac death in 3 patients; ischemic heart disease-related ventricular tachycardia in 8 patients and dilated cardiomyopathy with VA in 10 patients. Two patients with end-stage renal disease were excluded. Table 1 shows the baseline characteristics of the patients. Among 21 patients, VA was induced successfully in all patients and a total of 71 electrical shocks (mean: $3.55 \pm 0.81$ per patient) were delivered for DFT testing. The mean DFT was $14.42 \pm 3.78$J and mean duration of induced VA was $29.9 \pm 5.84$ seconds. There were no differences in the number of shocks, mean DFT and duration of induced VA between the groups (Table 1). No patients required external defibrillation to abolish the induced VA and to restore normal sinus rhythm. There were no procedural complications, and all patients were discharged with cardiovascular clinic follow-up.

### Follow up

The patients were followed for 18 months ($536 \pm 55$ days). One patient passed away due to decompensated heart failure after a follow-up period of 294 days. There were 9 patients who had VA events observed by the ICD in 18 months.

### Changes of natriuretic peptides

The mean ANP level at pre-implantation was significantly higher in the group with future VA events ($26.28 \pm 28.85$ vs. $10.23 \pm 7.66$, $p = 0.02$). The mean ANP levels

**Table 1.** Baseline characteristics of the patients with and without future VA

| | Patients with future VA events (n = 9) | Patients without future VA events (n = 12) | p value |
|---|---|---|---|
| Age (years) | 62.3 ± 11.6 | 60.5 ± 15.1 | 0.77 |
| Male gender (%) | 6 (66.7%) | 8 (66.7%) | 1.00 |
| LVEF (%) | 44.1 ± 14.7 | 44.4 ± 10.4 | 0.55 |
| HTN (%) | 3 (33.3%) | 4 (33.3%) | 1.00 |
| Kidney disease (%) | 3 (33.3%) | 2 (16.7%) | 0.38 |
| Diabetes (%) | 2 (22.2%) | 4 (33.3%) | 0.58 |
| Smoking (%) | 3 (33.3%) | 2 (16.7%) | 0.38 |
| ACEI (%) | 4 (44.4%) | 2 (16.7%) | 0.16 |
| ARB (%) | 3 (33.3%) | 4 (33.3%) | 1.00 |
| Beta blocker (%) | 3 (33.3%) | 5 (41.7%) | 0.70 |
| Amiodarone (%) | 4 (44.4%) | 5 (41.7%) | 0.90 |
| Underlying heart diseases | | | 0.72 |
| DCM | 5 (55.5%) | 5 (41.7%) | |
| IHD | 3 (33.3%) | 4 (33.3%) | |
| ARVD | 0 (0%) | 1 (8.3%) | |
| Long QT syndrome | 0 (0%) | 1 (8.3%) | |
| Idiopathic VT | 1 (11.1%) | 1 (8.3%) | |
| Number of shocks | 3.6 ± 1.1 | 3.5 ± 0.5 | 0.65 |
| DFT (joules) | 14.8 ± 4.8 | 14.2 ± 3.0 | 0.72 |
| Duration of induced VA (seconds) | 29.4 ± 7.0 | 30.3 ± 5.1 | 0.76 |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARVD, arrhythmogenic right ventricular dysplasia; DCM, dilated cardiomyopathy; DFT, defibrillation threshold; HTN, hypertension; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; VA, ventricular arrhythmia; VT, ventricular tachyarrhythmia.

at 30 minutes, at 60 minutes, and at 24 hours after DFT testing were not significantly different between the groups. The Δ30minANP was significantly higher in the group with VA events than that in the group without VA events (3.01 ± 4.18 pg/ml vs. -0.76 ± 1.70 pg/ml, p = 0.03). The Δ60minANP was also higher with borderline significance (10.40 ± 12.89 vs. 0.45 ± 4.59, p = 0.05). Those ANP increments were not observed in the group without VA events. The changes in ANP level at 24 hours were not significantly different between the groups (Table 2).

The average BNP and CNP levels at pre-implantation, 30 minutes, 60 minutes, and 24 hours after DFT testing were not significantly different between the groups. There was a trend towards higher increment of BNP at 60 min (Δ60minBNP) in the group with VA events; however, statistical significance was not reached (9.34 ± 17.36 vs. -2.28 ± 8.91, p = 0.06). Other increment or decrement of BNP and CNP levels were not significantly different between the groups (Table 2).

### Increment in ANP level after DFT testing determining future VA events

To obtain the cut-offs for changes of natriuretic peptide, receiver operating characteristic (ROC) curve analysis was used to create dichotomous variables for values of changes of natriuretic peptide (Figure 1). The area under curve was 0.82 and the optimal Δ30minANP cut-off value was 0.51 pg/ml, with sensitivity and specificity of 0.83 and 0.68, respectively.

### Criteria for predicting future VA events

We performed multivariate analysis to evaluate the risk factors for VA events after ICD implantation. Proportional hazard regression analysis was done for common risk factors including age, gender, left ventricular systolic function, the usage of angioangiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker or amiodarone, and Δ30minANP (Table 3, Model 1). The results showed that patients with Δ30minANP by more than 0.51 pg/ml have a higher risk of further VA events (hazard ratio 39.8, 95% CI: 2.87-553.01, p = 0.006). The ANP level at pre-implantation could not predict the future VA events (hazard ratio 1.06, 95% CI: 1.00-1.14, p = 0.06) (Table 3, Model 2). We divided the participants into two groups according to the Δ30minANP (≥ 0.51 vs. < 0.51 pg/ml) and performed Kaplan-Meier analysis. The cumulative event-free sur-

**Table 2.** Mean levels and the changes of natriuretic peptides after DFT testing

| | Patients with future VA events (n = 9) | Patients without future VA events (n = 12) | p value |
|---|---|---|---|
| Pre-implantation ANP (pg/ml) | 26.28 ± 28.85 | 10.23 ± 7.66 | 0.02 |
| Δ30minANP (pg/ml) | 3.01 ± 4.18 | -0.76 ± 1.70 | 0.03 |
| Δ60minANP (pg/ml) | 10.40 ± 12.89 | 0.45 ± 4.59 | 0.05 |
| Δ24hrANP (pg/ml) | 5.37 ± 14.88 | 0.46 ± 3.74 | 0.36 |
| Pre-implantation BNP (pg/ml) | 66.71 ± 52.78 | 38.08 ± 45.53 | 0.37 |
| Δ30minBNP (pg/ml) | 4.46 ± 11.03 | -2.08 ± 10.60 | 0.19 |
| Δ60minBNP (pg/ml) | 9.34 ± 17.36 | -2.28 ± 8.91 | 0.06 |
| Δ24hrBNP (pg/ml) | -9.68 ± 18.17 | -11.64 ± 38.58 | 0.89 |
| Pre-implantation CNP (pg/ml) | 7.09 ± 4.54 | 5.51 ± 3.21 | 0.15 |
| Δ30minCNP (pg/ml) | -0.29 ± 1.37 | -0.02 ± 0.81 | 0.88 |
| Δ60minCNP(pg/ml) | -0.55 ± 1.42 | -0.08 ± 0.99 | 0.38 |
| Δ24hrCNP (pg/ml) | -0.34 ± 2.69 | -0.09 ± 1.18 | 0.77 |

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; DFT, defibrillation threshold; VA, ventricular arrhythmia.

Δ30minANP, ANP level at 30 min after DFT testing – ANP level at pre-implantation; Δ60minANP, ANP level at 60 min after DFT testing – ANP level at pre-implantation; Δ24hrANP, ANP level at 24 hours after DFT testing – ANP level at pre-implantation; Δ30minBNP, BNP levelat 30 min after DFT testing – BNP level at pre-implantation; Δ60minBNP, BNP level at 60 min after DFT testing – BNP level at pre-implantation; Δ24hrBNP, BNP level at 24 hours after DFT testing – BNP level at pre-implantation; Δ30minCNP, CNP level at 30 min after DFT testing – CNP level at pre-implantation; Δ60minCNP, CNP level at 60 min after DFT testing – CNP level at pre-implantation; Δ24hrCNP, CNP level at 24 hours after DFT testing – CNP level at pre-implantation.

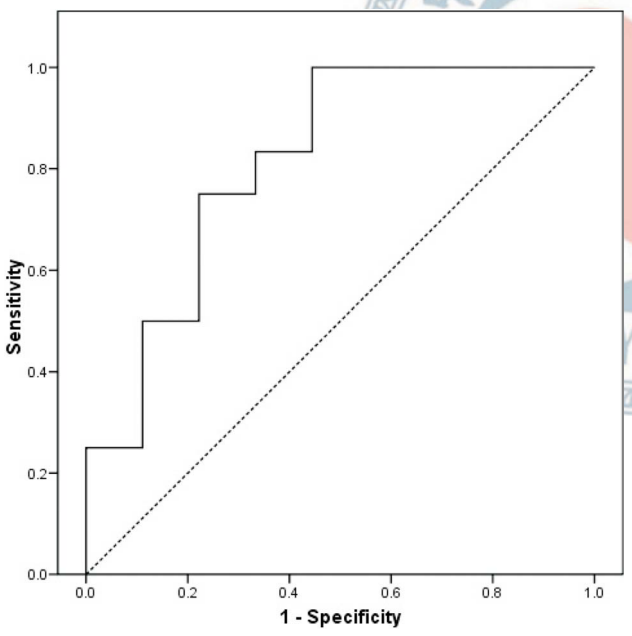


***Figure 1.*** *Receiver operating characteristic curve analysis of Δ30minANP levels determining future VA event occurred during follow-up. Area under the curve was 0.82 and the Δ30minANP cut point was 0.51 pg/ml with sensitivity of 0.83 and specificity of 0.68.*

vival probabilities in the group with Δ30minANP ≥ 0.51 pg/ml (n = 9) and in the group with Δ30minANP < 0.51 pg/ml (n = 12) were 22.2% and 76.9%, respectively (log-rank test, p = 0.009) (Figure 2).

## DISCUSSION

The main findings of the current study are as follow: 1) The mean ANP level at pre-implantation and the increment in ANP levels at 30 minutes after DFT testing were associated with VA events in the 18 months following ICD implantation; and 2) the BNP and CNP levels did not change significantly after DFT testing.

### Atrial natriuretic peptides and ventricular arrhythmia

In the normal human heart, ANP is mainly synthesized in and secreted from the cardiac atrium response to atrial distension, and serves to maintain sodium homeostasis and inhibit activation of the renin-angiotensin-aldosterone system.[10] The plasma level of ANP is increased due to either atrial or ventricular pressure overload with positive correlation to pulmonary capillary wedge pressure,[11] and it surges faster than BNP and CNP.[12] It has also been observed that the increase in ANP level during VA was associated with increased right atrial pressure.[13] Invasive recordings of the pulmonary capillary wedge pressure, right atrial pressure and/or

**Table 3.** Proportional hazard regression analysis of variables associated with future VA event occurred among ICD implanted patients*

| Model 1 | Hazard ratio (95% CI) | p value |
|---|---|---|
| Age (≥ 60 vs. < 60 years) | 0.95 (0.28-1.04) | 0.25 |
| Gender (men vs. women) | 0.35 (0.02-5.85) | 0.46 |
| LVEF (< 40 vs. ≥ 40%) | 1.18 (0.17-8.22) | 0.87 |
| ACEI (yes vs. no) | 2.52 (0.26-24.17) | 0.42 |
| ARB (yes vs. no) | 0.23 (0.02-2.94) | 0.26 |
| Beta-blocker (yes vs. no) | 1.24 (0.19-8.21) | 0.82 |
| Amiodarone (yes vs. no) | 5.60 (0.56-55.67) | 0.14 |
| Δ30minANP (≥ 0.51 vs. < 0.51 pg/ml) | 39.8 (2.87-553.01) | 0.006 |
| **Model 2** | **Hazard ratio (95% CI)** | **p value** |
| Age (≥ 60 vs. < 60 years) | 4.86 (0.39-60.72) | 0.22 |
| Gender (men vs. women) | 0.21 (0.01-3.09) | 0.25 |
| LVEF (< 40 vs. ≥ 40%) | 0.81 (0.13-5.21) | 0.83 |
| ACEI (yes vs. no) | 3.95 (0.45-34.7) | 0.22 |
| ARB (yes vs. no) | 2.07 (0.24-17.7) | 0.51 |
| Beta-blocker (yes vs. no) | 0.33 (0.04-2.48) | 0.28 |
| Amiodarone (yes vs. no) | 1.30 (0.14-12.35) | 0.82 |
| ANP at pre-implantation (pg/ml) | 1.06 (1.00-1.14) | 0.06 |

* The Δ30minANP and the ANP at pre-implantation were analyzed separately because of significant overlap of these 2 items.
Abbreviation as Table 1 and Table 2.

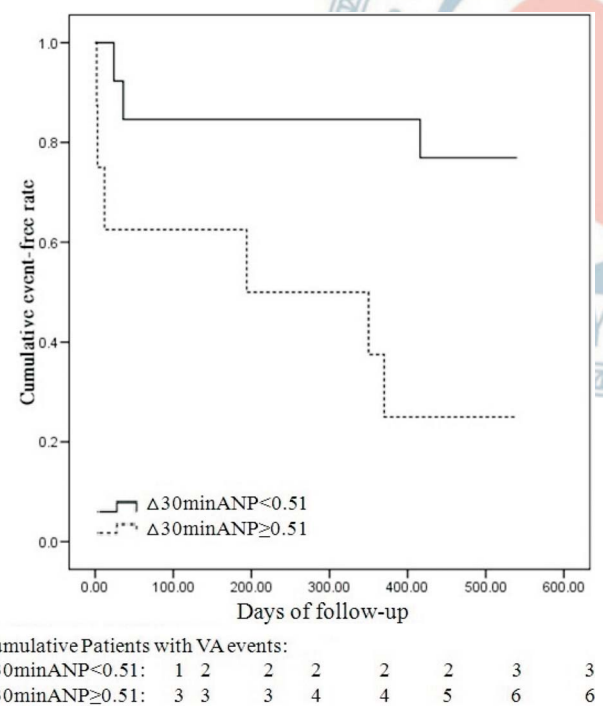


***Figure 2.*** *Kaplan-Meier plots for VA event-free curves grouped by Δ30minANP. All participants were divided into two groups according to the Δ30minANP (≥ 0.51 vs. < 0.51 pg/ml). Cumulative VT event-free rates in the Δ30minANP ≥ 0.51 pg/ml (n = 9) and Δ30minANP < 0.51 pg/ml (n = 13) were 22.2% and 76.9%, respectively (log-rank test, p = 0.009).*

left ventricular end-diastolic pressure would help to clarify this observed variability. The study performed by Crozier et al. showed that stable ventricular tachyarrhythmia-induced increases in ANP to peak levels at 20 minutes or later and reversion to sinus rhythm resulted in the decrease in ANP levels with an apparent half-life of 7 minutes.[14] In the study undertaken by Twidale et al. in 15 patients with spontaneous ventricular tachyarrhythmia and histories of myocardial infarction, plasma concentrations of ANP fell slowly and yet were still significantly raised 24 hours after reversion to sinus rhythm.[15] These studies suggested that ventricular tachyarrhythmia is related to increased ANP level. It has been demonstrated that the administration of ANP could suppress cesium-induced ventricular tachyarrhythmia in rabbits.[16] The protective effect of the exogenous ANP against cesium-induced ventricular tachycardia may be explained by not only a reduction in pressure overload but also the diverse action of ANP on the cardiovascular system. It suggests that the endogenous ANP might serve as a marker for VA burden. To our knowledge, there were no prior studies investigating the change of ANP after DFT testing. In this study, we found that the most significant increment of ANP level was ob-

served at 30 minutes after DFT testing in patients with future VA events and no significant differences were noted at 24 hours, although ventricular tachycarrhythmia was induced with a short duration. In studies performed in patients with induced sustained VA, the increase in ANP levels were observed when the tachycardia cycle length was around 320~335 ms and the duration greater than 30 seconds.[13,17] In the setting of DFT testing, the duration of ventricular tachyarrhythmia depends on the ICD charging times, which were usually less than 10 seconds every time.[18] Even if the first and second shock failed to restore sinus rhythm; the patients were successfully cardioverted at the third shock with total ventricular tachyarrhythmia duration less than 30 seconds in our study.

**Natriuretic peptides and DFT testing**

We observed that the increase of ANP after DFT testing was found in patients with future VA events. It has been reported that induced ventricular fibrillation and shock delivery would cause an increase in BNP level in patients with systolic heart failure [mean left ventricular ejection fraction (LVEF) = 26.1%] who received ICD implantation for primary prevention.[19] Additional shocks after DFT testing would cause significant increases in BNP levels from pre-implantation to 8-12 hours in patients with impaired LV contractility (mean LVEF = 28%). However, conflicting results existed. The study performed by Toh et al. showed that for patients with either preserved (mean LVEF = 61%) or impaired LVEF (mean LVEF = 27%) undergoing ICD implantation, DFT testing transiently impaired cardiac function and hemodynamics, but there were no significant changes in cardiac biomarkers including BNP.[20] While age itself is a risk factor for increased BNP level, it is noted that the populations in the former two studies were relatively older (mean age of 68.2~71.4 years) than the population in the latter (mean age of 55~57 years). The patients in our study were also relatively young, with a mean age of 60~62 years and the indications for ICD were all secondary prevention. These different factors of the study populations may cause different results regarding the BNP levels after DFT testing.

CNP is mainly expressed in the central nervous system, bone and vasculature.[21] There have been no prior studies that investigated the change in CNP level in patients with ventricular tachyarrhythmia undergoing ICD implantation. Our study showed that the CNP levels did not change significantly after DFT testing and were unrelated to the future VA events.

**ANP, BNP and future VA events**

Previous studies did not include the outcomes of the patients with elevated ANP after DFT testing. We observed that the patients with increased ANP at pre-implantation and after induced ventricular tachyarrhythmia and DFT testing were prone to have VA events during follow-up. This finding may be explained in that the patients with increased ANP had worse ventricular compliance than those without increased ANP. While ANP is increased due to either atrial or ventricular pressure overload, either ventricular systolic or diastolic dysfunction may cause changes in ANP levels.[22,23] Elevation of ANP has also been observed in patients with acute or chronic heart failure,[11] and heart failure itself is a prognostic factor for VA.[24]

Several studies indicated that LV systolic function and baseline BNP levels could predict outcomes including malignant arrhythmia and sudden cardiac death[25-29] as well as future appropriate therapies[30] after ICD implantation. Christ et al. showed that natriuretic peptides carried more prognostic value than the LVEF.[28] However, Klein et al. analyzed the results from the Prospective Analysis of Risk Factor for Appropriate ICD Therapy (PROFIT)-Study, and demonstrated that LVEF less than 40%, QRS-duration more than 150 ms and atrial fibrillation were independent predictors for VA occurrence, whereas there was no relationship between N-terminal pro-brain natriuretic peptide and VA occurrence in secondary prophylactic ICD patients.[31] In our study, neither the LVEF nor the BNP could predict the future VA events, although there was a trend toward higher increment of BNP at 60 min (Δ60minBNP) in the group with VA events. In fact, this might be explained by the difference in the characteristics of the study populations with wide variation in the baseline BNP levels.

**Clinical implication**

Measurement of ANP level at pre-implantation and 30 minutes after DFT testing could identify those patients with higher risk for future VA events. More aggressive antiarrhythmia drugs and monitoring for those

patients at risk could be necessary, especially in the first 18 months after ICD implantation. Furthermore, ANP is more sensitive than BNP, and CNP as a risk surrogate in such patient population.

### Study limitations

There were several limitations in this study. First, the patient population was small, with different stages of myocardial diseases. Further study with a large population and homogeneous disease entity is necessary. Secondly, concurrent hemodynamic monitoring, including pulmonary capillary wedge pressure and right atrial pressure, which represented the patient's myocardial preload status, was not done in this study.

## CONCLUSIONS

In patients undergoing ICD implantation for secondary prevention, the mean ANP levels at pre-implantation and the increment in ANP levels at 30 minutes after DFT testing were associated with future VA events in the following 18 months.

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