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Inflammatory Biomarkers are not Predictive of Intermediate-term Risk of Ventricular Tachyarrhythmias in Stable CHF Patients

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Summary

Background: Elevated levels of inflammatory biomarkers and brain natriuretic peptide (BNP) are associated with increased mortality in patients with heart failure (HF).

Hypothesis: The aim of the current study was to assess the correlation between circulating biomarkers and ventricular tachyarrhythmias among patients with HF.

Methods: Blood samples from 50 stable ambulatory HF patients with moderate to severe systolic left ventricular (LV) dysfunction and an implantable cardioverter defibrillator (ICD) were analyzed for interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hsCRP) and BNP. Thereafter, the patients were followed for a mean period of 152 ± 44 days, during which ventricular tachyarrhythmias were recorded by the ICDs.

Results: Follow-up data were obtained from 47 patients. Of them, 45 (96%) had ischemic cardiomyopathy, 38 (81%) had New York Heart Association class I–II, 43 (91%) were males, and the mean age was 68.6 ± 11.1 years. During follow-up, 5 patients (11%) had nonsustained ventricular tachycardia (NSVT), 6 patients (13%) had sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and 36 patients (76%) had no events. The circulating biomarkers' levels upon enrollment were not significantly different between patients who subsequently had NSVT or VT/VF and patients who were free of events.

Conclusions: No correlation was found between plasma levels of IL-6, TNF-α, hsCRP and BNP and ventricular arrhythmic events among stable HF patients during an intermediate term follow-up of 5.1 months. Further studies are still required to assess the association between these biomarkers and long-term risk of ventricular tachyarrhythmia.

Key words: heart failure, inflammatory biomarkers BNP, ventricular tachyarrhythmias

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Introduction

Accumulating evidence indicate that inflammatory cytokines play a role in the development of heart failure (HF) by adversely influencing heart contractility and inducing myocyte hypertrophy, apoptosis and fibrosis.[1–3] Inflammatory mediators are activated early in HF, with a progressive increment in serum in direct relation to worsening HF functional class.[3]

Circulating levels of inflammatory cytokines have been shown to predict adverse outcome in HF patients. Increased plasma concentrations of interleukin-6 (IL-6),[4–7] tumor necrosis alpha (TNF-α)[4,6,7] and C-reactive protein (CRP)[8–10] were all found to correlate with increased morbidity and mortality among patients with HF.

In addition to these biomarkers, brain natriuretic peptide (BNP), released by ventricular cardiomyocytes in response to myocardial tension and increased intravascular volume, was consistently shown to predict poor outcome [6,11] including sudden death [12,13] among HF patients.

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About one-half of deaths in HF patients are sudden, mostly due to VT degenerating to VF or immediate VF. Hence, a relationship between inflammatory markers or BNP and arrhythmic activity is suggested.

During the recent years, the implantable cardioverter defibrillator (ICD) has evolved as a promising therapy for life-threatening arrhythmias.[14–16] However, many patients who undergo ICD implantation would never be treated by their device. Therefore, there is a strong need to improve risk stratification of HF patients that would benefit the most from ICD implantation. An association between plasma biomarkers and ventricular tachyarrhythmias may be helpful in identification of patients at high risk to develop ventricular tachyarrhythmias, and assist in selection of HF patients for ICD implantation. Subsequently, the aim of the present study was to evaluate the correlation between plasma levels of IL-6, TNF-α, high-sensitivity CRP (hsCRP), and BNP and the risk to develop ventricular tachyarrhythmia among patients with HF.

Methods

Study Population

The study enrolled 50 consecutive stable ambulatory HF patients with moderate to severe systolic LV dysfunction and ICD that was implanted either for primary prevention (patients with severe LV dysfunction, nonsustained VT (NSVT) and inducible sustained VT (VT) or VF on electrophysiology study) or secondary prevention (patients with previous episodes of sustained VT or VF) of ventricular tachyarrhythmias.

Patients who have had an acute coronary syndrome or heart failure exacerbation during the month prior to enrollment and patients with an active inflammatory, infectious or malignant disease, were excluded from the study. The study protocol was approved by the institutional ethics review board at Rabin Medical Center and all patients signed an informed consent before recruitment. Demographic and clinical data were systematically collected including cardiovascular (CV) risk factors, past history of CV disease, LV function, New York heart association (NYHA) class, index event for ICD implantation, and chronic medical treatment. Cases ($n = 11$) were patients who developed VT, VF or NSVT during the study period.

Laboratory Analysis

Venous blood samples were drawn from the patients during routine follow-up visit in a single center outpatient ICD clinic between 8:00 and 12:00 AM, from January to August 2005. All biomarkers were analyzed in duplicate using standard commercial enzyme immunoassay kits: TNF-α and IL-6 (Quantikine HS, R&D, MN, USA), BNP (Phoenix pharmaceuticals, CA, USA). High-sensitivity C-reactive protein was determined by latex particle-enhanced immunoturbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany) with an automated analyzer Roche/Integra 800. All laboratory analyses were performed in a blinded fashion with respect to the identity of the patients.

Arrhythmia Analysis

All ventricular tachyarrhythmia events were analyzed using stored electrograms from the patient's ICDs during mean follow-up duration of 152 ± 44 days from enrollment.

The detection rate of NSVT, VT or VF for each patient was defined before enrollment to the study by the attending physician's decision at the time of ICD implantation or during the follow-up visits at the electrophysiology clinic.

VT was defined as consecutive ventricular premature beats (RR intervals of 400 to 300 ms) that persisted for more than 30 s and required termination with either antitachycardia pacing or defibrillation shock. NSVT was defined as 3 or more consecutive ventricular premature beats that did not persist for more than 30 s. VF was defined as ventricular tachyarrhythmia with RR interval of less than 320 to 285 ms requiring defibrillation shock for termination.

Statistical Analysis

Continuous variables were analyzed by one-way analysis of variance (ANOVA) comparing mean values of the three patients group. For categorical data, a Chi-square test was done. All p-values are two-sided and a level of 0.05 or less was considered as statistically significant. In cases where there are mutually exclusive outcomes (i.e. NYHA, LV dysfunction) a single p-value comparing differences between the three groups was done. Coefficient of variation was calculated in order to assess the variability of the biomarker concentrations in the patient population.

Results

Baseline Characteristics

The study enrolled 50 consecutive stable ambulatory HF patients with moderate to severe LV dysfunction and ICD. Three patients were lost to follow-up. None of the patients died during the study period, including those who were lost to follow-up. This was verified through the central Israeli internal ministry registry records. The mean follow-up duration of 47 patients was 152 ± 44 days. The mean age was 68.6 ± 11.1 years and 91% were males. The mean follow-up duration and baseline

TABLE 1 Baseline characteristics (n = 47)

	No events (n = 36)		NSVT (n = 5)		VT/VF (n = 6)		P
Age (yrs, mean ± S.D.)		69.2 ± 10.5		67.2 ± 5.4		73.3 ± 8.0	0.55
Follow-Up (days)		158 ± 44		134 ± 50		128 ± 29	0.19
	n	%	n	%	n	%	
Male gender	33	91.7	5	100	5	83.3	0.67
Index event							
VT	17	47.2	2	40	3	50	1.00
VF	9	25	0	0	1	16.7	0.67
Primary prevention	12	33.3	3	60	2	33.3	0.51
LV dysfunction							
Moderate	10	27.8	1	20	2	33.3	—
Severe	26	72.2	4	80	4	66.7	1.00
NYHA							
I	10	30.3	1	20	1	16.7	—
II	19	57.6	3	60	4	66.7	—
III	4	12.1	1	20	1	16.7	1.00
Ischemic CMP	35	97.2	5	100	5	83.3	—
Nonischemic CMP	1	2.8	0	0	1	16.7	0.42
Diabetes mellitus	3	8.3	2	40	2	33.3	0.054
Hypertension	15	41.7	1	20	2	33.3	0.77
Hyperlipidemia	22	61.0	1	20	4	66.7	0.23
Past CABG	14	38.9	4	80	3	50	0.21
Past CVA	5	13.9	0	0	1	16.7	1.00

Abbreviations: CABG = coronary artery bypass grafting, CMP = cardiomyopathy, CVA = cerebrovascular accident, LV = left ventricular, NSVT = nonsustained ventricular tachycardia, NYHA = New York heart association, VF = ventricular fibrillation, VT = ventricular tachycardia.

[a] Two patients had both VT and VF as an index event.

characteristics were not different between patients who subsequently developed significant ventricular arrhythmic event and those who did not (Table 1).

Medical Treatment

Most patients received beta-blockers (74%), statins (85%), diuretics (70%) and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (87%). Fifty-five percent of the patients received antiarrhythmic therapy. The medical therapy did not differ between patients who had had a ventricular arrhythmic event and those who were free of any ventricular arrhythmic events (Table 2).

Arrhythmic Events

During the follow-up period, 36 patients (76%) did not have any ventricular tachyarrhythmia, 3 patients had sustained VT (6.5%), 3 patients had VF (6.5%), and 5 patients had NSVT (11%). Of these, 1 patient had intractable VT that was resistant to a variety of antiarrhythmic medications, and necessitated VT ablation and 1 patient had recurrent episodes of VF that required prolonged hospitalization with intravenous antiarrhythmic therapy and recurrent direct current shocks.

The indication for ICD implantation in all 3 patients who subsequently had VT was sustained VT, in 3 patients who had VF was VF (1 patient) and primary prevention (2 patients), in 5 patients who had NSVT was sustained VT (2 patients) and primary prevention (3 patients) (Table 1).

Biomarkers Levels

Plasma biomarkers concentrations in patients with and without arrhythmic event are summarized in Table 3. The baseline plasma levels of IL-6, TNF-α, CRP or BNP were not different between patients who subsequently developed sustained VT/VF, NSVT, and patients who did not have any ventricular arrhythmic event during mean follow up period of 152 days.

The power of the one-way ANOVA results to detect a significant difference in biomarker levels between patients without events, patients with NSVT and patients with VT/VF for hsCRP, BNP, IL-6 and TNF-α was 96, 91, 66.4 and 62.4% respectively.

The interindividual variability of the biomarker concentrations assessed by coefficient of variation was relatively wide for TNF-α (131.74%) and CRP (113.23%), but less broad for BNP (55.3%) and IL-6 (87.1%).

TABLE 2 Baseline medical treatment (n = 47)

	No events (36)		NSVT (5)		VT/VF (n = 6)		P
	n	%	n	%	n	%	
β-blockers	26	72.2	5	100	4	66.7	0.52
Ca channel blockers	5	13.9	1	20	0	0	0.60
Digoxin	6	16.6	1	20	1	16.7	1.00
Statins	30	83.3	4	80	6	100	0.63
ACE inhibitors	22[a]	61.1	3	60	4	66.7	1.00
ARBs	10	27.8	2	40	2	33.3	0.86
Loop diuretics	15[b]	41.7	3	60	3	50	0.78
Spironolactone	12	33.3	3	60	3	50	0.44
Disothiazide	4	11.1	1	20	1	16.7	0.43
Antiarrhythmic therapy							
Amiodarone	18	50	3	60	3	50	1.00
Sotalol	1	2.8	0	0	1	16.7	0.42

Abbreviations: ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, NSVT = nonsustained ventricular tachycardia, VF = ventricular fibrillation, VT = ventricular tachycardia.
[a] Two patients received combined treatment with ACE inhibitor and ARB.
[b] Eleven patients received concomitant treatment with spironolactone and loop diuretics and 1 patient received combined treatment of spironolactone and disothiazide.

TABLE 3 Plasma biomarkers levels (n = 47)

	No events (36)	NSVT (5)	VT/VF (n = 6)	P
IL-6 (pg/mL)	2.40 ± 1.77	1.90 ± 0.45	3.71 ± 4.59	0.40
TNF-α (pg/mL)	3.88 ± 5.58	8.45 ± 7.52	3.04 ± 2.55	0.27
hsCRP (mg/L)	0.41 ± 0.48	0.47 ± 0.60	0.44 ± 0.42	0.96
BNP (ng/mL)	3.66 ± 1.78	3.27 ± 0.89	3.90 ± 3.90	0.90

Abbreviations: BNP = brain natriuretic peptide, hsCRP = high sensitivity C reactive protein, IL-6 = Interleukin 6, NSVT = non-sustained ventricular tachycardia, TNF-α = tumor necrosis factor-α, VF = ventricular fibrillation, VT = ventricular tachycardia.

Discussion

Although increased plasma levels of IL-6,[4–7] TNF-α,[7,17] CRP[8–10] and BNP[12,13] are all correlated with increased mortality in patients with chronic HF, the current study revealed that plasma levels of IL-6, TNF-α, CRP or BNP were not predictive of ventricular tachyarrhythmias in patients with moderate to severe systolic LV dysfunction.

IL-6

IL-6 was found to predict long-term mortality[4,5,7] and long-term cardiac death[6] in chronic HF whereas, in the present study, IL-6 was not found to predict intermediate-term risk of ventricular arrhythmias among HF patients. Yet, none of the previous studies showed a correlation between IL-6 and sudden death, and the majority of the patients in the previous studies had NYHA class III–IV, whereas 81% of the patients in our study had NYHA class I–II.

In agreement with our findings, IL-6 was not found to predict 6-months' cardiovascular death among HF patients[18] and it was not a significant predictor of mortality when added to the known prognostic factors including the traditional cardiovascular risk factors, NYHA and LV function.[19]

TNF-α

So far, TNF-α was shown to predict cardiac mortality in patients with NYHA class III–IV,[6] and 1.1–2.7 years all cause mortality in stable HF patients and patients with NYHA III–IV.[7,20] These data together with the negative results of our study suggest that TNF-α may be related to nonarrhythmic death or may still be associated with arrhythmic death among unstable HF patients with NYHA III–IV. Further studies are still required to test this hypothesis.

C-reactive Protein

Elevated CRP was correlated with increased long-term all-cause mortality in patients with ischemic and nonischemic HF[9,21] and CV mortality in patients with

ischemic HF.[22] On the contrary, CRP was not found to predict mortality among outpatient population of HF patients during follow-up of 24 months.[23] In accordance with the latter study, in the present study hsCRP was not predictive of ventricular tachyarrhythmias among patients with stable HF during intermediate-term follow up. Yet, the correlation between CRP and long-term risk of ventricular tachyarrhythmias should be further evaluated.

Brain Natriuretic Peptide

Mechanical stretch of the myocardium triggers the release of BNP and also contributes to arrhythmogenesis and sudden cardiac death (mechano-electric feedback) in patients with LV dysfunction and elevated filling pressure.[24]

In earlier studies, BNP was found as an independent predictor of sudden death in patients with severe LV dysfunction and as an independent predictor of future appropriate ICD therapies in HF patients[12,25], whereas in the current study BNP was not associated with ventricular tachyarrhythmias during mean follow-up of 5.1 months. In the light of the previous studies, and the mechano-electric feedback, we attribute our negative results to the stable clinical condition of our patient cohort and to the intermediate-term follow-up duration of the study.

Limitations

The main limitation of the current study is the relatively low rate of malignant ventricular arrhythmic events of 13%, which is attributed to the stable clinical condition of the study population and the relatively short follow-up duration. However, our aim was to assess the value of circulating biomarkers among ambulatory, stable HF patients and not among patients with severe HF, who are more prone to arrhythmic events. Another limitation is the relatively modest power of the study for IL-6 and TNF-α (66.4 and 62.4%, respectively). Therefore, further larger and longer-term studies are needed to establish the precise role of these two biomarkers in risk assessment of HF patients. Yet, the power to detect a significant difference in hsCRP or BNP concentration was very high and exceeded 90%.

Conclusions

Identifying HF patients at increased risk for sudden death is an important issue in the era of ICD therapy, and additional tools for patient risk stratification are still required. According to the present study IL-6, TNF-α, hsCRP and BNP did not predict intermediate-term risk of ventricular tachyarrhythmias in stable HF patients; however, further prospective studies are needed in order to establish the role of these biomarkers as predictors of long-term risk of ventricular arrhythmias among HF patients.

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