Correlation of Coagulation Pathway Parameters with BNP, Ejection Fraction and NYHA Class in Heart Failure

Nandini Nair1,3, Enrique Gongora2,4

1. Division of Cardiology, Scott and White Memorial Hospital, Temple, TX 76508.
2. Division of Cardiothoracic Surgery, Scott and White Memorial Hospital, Temple, TX 76508.
3. Division of Cardiology, Texas Tech Health Sciences Center, Lubbock, TX 79382.
4. Memorial Cardiac and Vascular Institute, Hollywood, FL 33021

Corresponding author:
Nandini Nair,
Division of Cardiology, Texas Tech Health Sciences Center, Lubbock, TX 79382.
Email: nandini.nair@gmail.com

Abstract

Background: The upregulation of inflammation and coagulation in addition to the sympathetic nervous system is known and reported in congestive heart failure. This study was undertaken to assess the correlations of the changes in coagulation parameters with functional class, ejection fraction and brain natriuretic peptide levels.

Methods: A small prospective study was conducted in dilated cardiomyopathy (DCM) patients. The protocol was approved by the Hospital IRB (Scott and White Memorial, Temple, TX 76508). Statistical analysis was conducted using the online Vassar stats system. Spearman’s rank order correlation was derived for all the correlations mentioned in this paper.

Results: PT, PTT, INR and d-dimer levels were significantly different in the two groups and correlated positively and significantly with BNP and New York Heart Association class. Statistically significant negative correlation was noted with ejection fraction. Fibrinogen levels did not correlate significantly with BNP, New York Heart Association class or ejection fraction.

Conclusions: Coagulation pathway parameters correlate significantly with BNP, functional class and ejection fraction in this study. The study is limited by its size and the fact that only dilated non-ischemic cardiomyopathy patients were included. Larger studies are required to further understand the complex interactions of biochemical pathways noted in heart failure.

Keywords: fibrinogen; d-dimer; PT; functional class

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Introduction

Up regulation of coagulation factors is a less understood phenomenon in congestive heart failure. Existing literature supports the fact that levels of von Willebrand factor, fibrinogen, ICAM, PECAM, P-selectin, d-dimer, fibrinogen, vascular cell adhesion molecules and platelet aggregation are significantly elevated in congestive heart failure [1-8]. The most frequently noted complication in congestive heart failure involves thromboembolism [9] which suggests pathological aberrations in the coagulation pathway as the disease progresses.

Hence this study was undertaken to assess the correlation between coagulation parameters and functional class as assessed by New York Heart Association classification. Correlation studies between coagulation and brain natriuretic peptide (BNP) were also done in these patients because BNP has been correlated well with NYHA functional class [10-12].

Methods

The study population consisted of 23 idiopathic dilated cardiomyopathy (DCM) patients and 9 control subjects. All DCM patients had normal angiographic studies. Plasma levels of BNP, PT, PTT, INR, fibrinogen, thrombin time, platelets and d-dimer were determined by clinical assays in the core laboratory of the hospital. Correlation analysis was performed between each of the above parameters and BNP, ejection fraction (EF) as well as functional status using New York Heart Association classification. The protocol was approved by Scott and White Hospital institutional board review. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee. None of the patients had a history of hypercoagulability or use of any anticoagulation therapy.
Statistical Methods

Spearman rank order correlations and t-test statistics were derived using the commercial VASSARStats.net online statistical analyses program [13]. Data was determined to be significant at p less than 0.05.

Results

Baseline characteristics of the study population are shown in Table I. The age of the control and DCM groups were not statistically significant. The DCM group had 84% males versus 56% in the control group. BNP in the control subjects was significantly lower than the DCM group as shown in Table I. LVDD and ejection fraction (EF) were also statistically different in the 2 groups as expected. Creatinine, thrombin time and platelets did not show any statistically significant difference between the 2 groups. The absolute values of creatinine were mildly abnormal in the DCM group. Thrombin time and platelets were within normal limits in the 2 groups.

The DCM subjects were maintained on optimum medical therapy. No statin use was noted in the subjects. The lipid profile did not show any significant differences.

In this pilot study parameters that were significantly different between the two study groups showed a statistically significant correlation with BNP levels. PT, PTT, INR and d-dimer levels were significantly different in the two groups and correlated positively and significantly with BNP as shown in Table II. PT PTT INR and d-dimer not only correlated positively with BNP but also correlated positively with New York Heart Association classification of functionality (Table III) and reached statistical significance in our analyses. Correlation with ejection fraction was negative as expected. PT, PTT, INR, and d-dimer achieved statistically significant correlation with ejection fraction as shown in Table IV. Interestingly fibrinogen levels did not correlate significantly with BNP, New York Heart Association class or ejection fraction in the study. There were no statistical differences in AST (p=0.2) or alkaline phosphatase (p=0.18) and borderline significant difference in total bilirubin (p=0.04) between the control and DCM groups.

C-reactive peptide (CRP) was significantly elevated (p=0.01) in the DCM group (22+/-15mg/L) as compared to control group subjects (3.3+/-2.2mg/L). The lipid profile in the two groups were not significantly different in the control versus DCM groups with respect to total cholesterol (163+/-27 vs 157+/-24, p=0.13) and triglycerides (87+/-30 versus 108+/-19 ,p=0.2). The HDL was significantly higher in the control group versus the DCM subjects (53+/-10 versus 37+/-4 p=0.007). No subjects were on statins at the time of the study.

Discussion

Congestive heart failure has been recognized as a complex syndrome in which the coagulation and inflammatory pathways are up regulated and functionally abnormal. This has been found in animal and human systems [14-16]. However it remains a less understood phenomenon especially with relevance to coagulation. In our analysis, we noted a significant correlation with BNP levels and NYHA functional class between the parameters we assessed. A significant negative correlation with ejection fraction was also noted.

It has been postulated using animal models such as the murine system that increase in the anticoagulation parameters is a protective mechanism in heart failure in the setting of hypercoagulable and pro inflammatory states [17]. The other explanation for increased anticoagulation is the dysfunction of the right ventricle and passive congestion of the liver that follows. However in our study, liver functions as suggested by total bilirubin, AST and ALT did not show any statistical differences between the two groups. The lipid profile was not different except for higher HDL levels in the control subjects.

Role of oxidative stress, inflammation and blood viscosity changes in diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) seems intriguing and appears to point to a common tenet with heart failure with reduced ejection fraction (HFrEF). It has been noted in many studies that there exists a great similarity between the 2 types of heart failure with respect to morbidity and mortality. Additionally, evidence maybe slowly building up to prove the similarity between HFrEF and HFpEF.

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<th>Table I. Baseline characteristics of study population</th>
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<td>Age (years)</td>
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<td>Gender</td>
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<td>Creatinine (mg/dl)</td>
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*p<0.05 was considered significant

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<th>Table II. Correlation of Coagulation Parameters with BNP</th>
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<td>Coagulation Parameter</td>
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*p<0.05 was considered significant
It therefore seems logical to apply similar treatment strategies for both types of heart failure [20,21]. Increased oxidative stress and inflammation go hand in hand with worsening diastolic dysfunction [22]. Further studies would therefore be needed in heart failure with preserved ejection fraction to delineate the roles of oxidative stress and coagulation parameters in diastolic dysfunction leading to florid heart failure. It is very likely that the same effects would be seen in the HFrEF patients.

Limitations of this study include the small sample size which included only non-ischemic dilated cardiomyopathy patients. The correlations of coagulation pathway parameters with NYHA class is interesting and opens a new area of investigation if these molecules can be used as a biomarker panel along with BNP to guide therapy. Larger studies appear to be needed in this area to better understand the pathophysiological ramifications of these observations which will help in development of better therapeutic targets.

Declarations of Interest
The authors Drs. Nandini Nair and Enrique Gongora have no conflicts of interest to disclose.

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