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Assessment of Coagulation and Hemostasis Biomarkers in a Subset of Patients With Chronic Cardiovascular Disease

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Abstract

Measurement of a single marker of coagulation may not provide a complete picture of hemostasis activation and fibrinolysis in patients with chronic cardiovascular diseases. We assessed retrospective orders of a panel which included prothrombin fragment 1.2 (PF1.2), thrombin: antithrombin complexes, fibrin monomers, and D-dimers in patients with heart assist devices, cardiomyopathies, atrial fibrillation and intracardiac thrombosis (based on ordering ICD-10 codes). During 1 year there were 117 panels from 81 patients. Fifty-six (69%) patients had heart assist devices, cardiomyopathy was present in 17 patients (21%) and 29 patients (36%) had more than 1 condition. PF1.2 was most frequently elevated in patients with cardiomyopathy (61.1%) compared to those with cardiac assist devices (15.7%; $P = 0.0002$). D-dimer elevation was more frequent in patients with cardiac assist devices (98.8%) compared to those patients with cardiomyopathy (83.3%; $P = 0.014$). Patients with cardiomyopathy show increases of PF1.2 suggesting thrombin generation. In contrast, elevations of D-dimers without increase in other coagulation markers in patients with cardiac assist devices likely reflect the presence of the intravascular device and not necessarily evidence of hemostatic activation.

Keywords

heart disease, coagulation, prothrombin factor 1.2, D-dimer, fibrin monomers

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Introduction

The National Patient Safety Goals from the Joint Commission encourage American hospital administrations to conduct internal reviews of anticoagulation safety practices.[1] A variety of tests can be used to monitor the coagulation system. Most hospital laboratories offer measurement of D-dimer as a marker of recent or ongoing fibrinolysis and clinicians may use the results to assess risk of thrombosis.[2] Importantly, D-dimer values above the reference range can be seen in a variety of situations not necessarily related to activation of the coagulation system, including advanced age[3,4] and in the presence of intravenous catheters.[5] This stresses the importance of the test's negative predictive value, as D-dimer results within the reference range allow clinicians to rule-out certain conditions such as disseminated intravascular coagulation (DIC), pulmonary embolism, or deep vein thrombosis. Fibrin monomers are another analyte frequently offered by clinical laboratories. Increased levels of fibrin monomers indicate active cleavage of fibrinogen to fibrin and reflect concentration of thrombin activity.[6] Levels of fibrin-monomers may predict left atrial appendage thrombosis in elderly patients with acute ischemic stroke.[7] Concentrations of fibrin monomers vary in some hypercoagulable states (e.g., pregnancy, hormone replacement, chemotherapeutic agents, anti-angiogenesis medications) but are reliably increased in patients with DIC and malignancies.[8,9] Some use fibrin monomers to monitor anticoagulant treatment.[10,11]

Activation of the coagulation system upstream of fibrin monomer generation can be assessed by measuring prothrombin fragment 1.2 (PF1.2) and thrombin-antithrombin complexes (TATs). PF1.2 assesses ongoing activation and

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Table 1. ICD 10 Used With Descriptors.

ICD-10 code	Descriptor
Z95.811	Presence of heart assist device
I42.9	Cardiomyopathy, unspecified, including primary and secondary causes and can be accompanied by heart failure or tachycardia
I51.3 or I23.6	Intracardiac thrombosis, not elsewhere specified (independent of location)-OR- Thrombosis of atrium, auricular appendage, mural and ventricle or following complications of an acute myocardial infarction
I48	Persistent atrial fibrillation or flutter, independent of chronicity (persistent), paroxysmal, atypical or other

Abbreviation: ICD, International Classification of Disease.

thrombin formation, while TATs are produced as a result of binding of thrombin to antithrombin. Ota et al explored the use of PF1.2 and TAT in conjunction with D-dimer and soluble fibrin and have found that PF1.2 was elevated in more than 50% of patients with thrombosis.[12] These parameters have been applied to define risk of thrombosis and determine the need for anticoagulation in patients with atrial fibrillation.[10] In our seven-hospital system, providers may order D-dimer and fibrin monomers as single tests or as a panel, called the markers of coagulation and hemostasis activation (MOCHA), which include PF1.2, TAT, fibrin monomers and D-dimer. The MOCHA panel is ordered primarily by the following inpatient and outpatient services: hematologists seeing patients with hypercoagulable diseases (accounting for over 50% of orders), providers in the stroke clinic (over 30%), the cardiology service (approximately 6%), and other services (10%) including general medicine, rheumatology, and hepatology. We have used the panel to study patients with stroke[13] and during the SARS-CoV2 pandemic.[14]

The great majority of the MOCHA panel results from patients from the cardiology service are abnormal and the 4 conditions for which they are ordered include presence of heart assist devices, cardiomyopathies, atrial fibrillation, and intracardiac thrombosis. The objective of this study was to identify the variations present in MOCHA panel parameters for the above 4 conditions and perform a correlation with anticoagulation treatment.

Methods

Using the data warehouse, we selected all MOCHA panels that occurred over a 1-year period and were associated with ICD-10 (International Classification of Disease) codes corresponding to cardiac assist devices, cardiomyopathy, atrial fibrillation, or intracardiac thrombosis (Table 1 presents the specific codes and their descriptor). The ICD-10 is the 10th revision of the classification of diseases managed by the World Health Organization. Collection of data from the clinical chart included demographic information and anticoagulation treatment. Results were segregated into their diagnostic ICD-10 groups; however, some patients had more than 1 code associated with their panel result. When this occurred, we only counted the patient once in the category of cardiac assist devices as all these patients had the ICD-10 code for the device plus another code (cardiomyopathy or thrombosis).

Plasma samples for testing MOCHA parameters were obtained in coagulation tubes containing 3.2% sodium citrate. D-dimer levels were measured using high sensitivity latex dimer assay (Instrumentation Laboratories, Bedford, MA). PF1.2 and TATs were measured using Enzygnost ELISA kit (Siemens Healthcare, Tarrytown, New York, NY). Soluble fibrin monomer assays were performed using latex immunoassay (Stago, Parsippany, NJ).

We calculated the following for each parameter: the mean, median, range, and number of results that were above the reference range. A 2 tailed Fisher exact test using the online GraphPad calculator (https://www.graphpad.com/quickcalcs/contingency1.cfm) was used to calculate P values when comparing number of abnormal results for each of the parameters. Based on the evaluation of the MOCHA markers taken together, the sample results were segregated into 3 groups and correlated with the anticoagulation received at the time the MOCHA panel was performed. These groups included:

A. Patients with increased PF1.2 independent of elevation of the other parameters were considered to have prothrombin conversion to thrombin.
B. Patients with increased D-dimer together with elevated TATs and/or fibrin monomer suggested clot formation and fibrinolysis.
C. Patients with only D-dimer, or TAT, or fibrin monomer elevation were considered to have a non-specific panel.

The study was performed in accordance with Emory's institutional review board (IRB). The IRB defined that a consent form was not necessary as physicians ordered the tests as part of the patient's treatment and independent of this retrospective study. In addition, the study was deemed an expedited IRB review as results present patient data in aggregate.

Results

A total of 117 MOCHA panels from 81 patients were reviewed. This included 47 males and 34 women with an average age of 51 years (range 19-85). The most frequent ICD-10 code was for cardiac assist device (56 patients) followed by cardiomyopathy (17 patients). Upon chart review, diagnoses of the patients with the ICD-10 related to cardiomyopathy included coronary artery disease (7 patients), ischemic heart disease (3), cardiogenic shock (2), valvular insufficiency (1), sickle cell vaso-occlusive disease (1), sinus tachycardia (1), hypertrophic cardiomyopathy (1), and viral myocarditis (1). There were 29 patients with more than 1 ICD-10 code assigned; 24 had an ICD-10 code for cardiac assist device and cardiomyopathy while 5 had cardiac assist device and intracardiac thrombosis. Table

Table 2. Demographics for Each ICD-10 (International Classification of Disease) Category With the Number of Patients Tested.

	Number of patients with only 1 ICD code	Age average (range)	Females	Number of panels ordered	Number (percent) of panels repeated per patient	Number of repeats within 4 weeks
Heart assist device	56[a]	51 (19-74)	22	89	22 with 2; 5 with 3 to 5 (48%)	17
Cardiomyopathy	17	53 (31-85)	7	18	1 (6%)	0
Intracardiac thrombosis	4	39 (22-55)	2	5	1 (25%)	1
Atrial fibrillation	4	61 (44-77)	3	5	1 (25%)	1

[a]29 patients had more than one ICD-10 code assigned, 24 of them had a second code of cardiomyopathy, and 5 had a second code of thrombosis.

Table 3. Results of Markers of Coagulation and Hemostasis Panel for Each of the ICD-10 Code.

		Heart assist device	Cardiomyopathy	Intracardiac thrombosis	Atrial fibrillation	*P* value[a]
Normal ranges in parenthesis	Total number of measurements	89	18	5	5	
Prothrombin fragment 1.2 (1.2 65-288 pmol/L)	Mean	187	460	310	240	
	Median	144	324	312	272	
	Range	66 to >1200	71 to >1200	203 to 423	85 to 348	
	Number abnormal (%)	14 (15.7)	11 (61.1)	3 (20)	2 (40)	$P \leq .001$
Thrombin anti-thrombin (1-5.5 mcg/L)	Mean	7.4	45	18.9	8.9	
	Median	6.6	7.9	10	6.3	
	Range	2.5 to >60	5 to >60	5.2 to >60	5.1 to 15	
	Number abnormal (%)	63 (70.7)	15 (83.3)	4 (80)	3 (60)	$P = .38$
Fibrin monomers (<6mcg/ml)	Mean	21.4	49	12.2	64	
	Median	7	7	7	7	
	Range	<7 to >150	<7 to >150	<7 to 29	<7 to >150	
	Number abnormal (%)	48 (55.3)	9 (50)	3 (60)	2 (40)	$P = 1.00$
D-dimer (<574 μg/mL FEU)	Mean	3548	8445	3184	2114	
	Median	1994	1262	875	930	
	Range	552 to 22453	<220 to >60,000	258 to 7331	353 to 7170	
	Number abnormal (%)	88 (98.8)	15 (83.3)	3 (60)	4 (80)	$P = .014$

Abbreviation: ICD, International Classification of Disease; FEU, fibrin equivalent unit.
[a]*P* value comparing number of abnormal results for heart assist devices to each of the other diagnostic codes.

2 presents demographic data, total number of patients, and number of measurements for each ICD-10 code. The table also shows the number of repeat MOCHA panels that these patients had, including repeats occurring within a 4-week period. Patients with cardiac assist devices had repeat testing more frequently compared to the other groups.

Table 3 shows the results for the different parameters for the MOCHA panels for each ICD-10 code. Of note, PF1.2 was most frequently elevated in patients with cardiomyopathy compared to the other ICD-10 codes. This difference was statistically significant compared to the patients with cardiac assist devices ($P \leq .001$). Also of note, was the high frequency of D-dimer elevation in patients with cardiac assist devices ($P = .014$, compared with cardiomyopathy patients). Analysis of the 24 patients with both cardiomyopathy and cardiac assist device ICD-10 codes showed similar biomarker behavior to that observed in patients with only cardiac assist device for the majority the parameters. Specifically, all showed elevated D-dimer and only 4 showed an increase in PF1.2.

Table 4 presents the correlation of the 3 MOCHA interpretation groups with the anticoagulation treatment, changes that occurred in those patients after repeat testing, and location (inpatient versus outpatients). Most of the patients with cardiomyopathy were considered to have prothrombin conversion, while those patients with cardiac assist devices were considered to have clot formation with fibrinolysis ($P \leq .001$). Twenty-four patients with cardiac assist devices had repeat testing. In these 24 patients, their panels changed from either prothrombin conversion or clot formation with fibrinolysis to either a non-specific panel or clot formation with fibrinolysis. Review of anticoagulation treatment showed that all patients with cardiac assist devices (56) were anticoagulated. Fifty (89%) patients were on warfarin while the remaining 6 (11%) patients were on heparin due to recent device implantation. Of the 50 patients on warfarin, 12 (24%) were considered to have prothrombin conversion while 22 (39%) had a non-specific panel. Of the 17 patients with cardiomyopathy, 9 (53%) were receiving anticoagulation primarily with heparin, low

Table 4. Correlation of Results for Each ICD-10 Code and Anticoagulation Being Received.[a]

	Anticoagulation	Prothrombin conversion (A)	%	Formed clot with fibrinolysis (B)	%	Non-specific changes (C)	%	Repeated panel that changed
Device (56 patients)	Warfarin (mostly outpatients)	12	21	17	30	22	39	5 went from A to B; 18 went from B to C
	Heparin (mostly inpatients)	2	4	1	2	2	2	1 went from B to C
Cardio-myopathy (17 patients)	Warfarin (outpatients)	0	0	0	0	2	12	1 repeated with no change
	Heparin (mostly inpatients)	6	35	0	0	1	6	0
	Platelet inhibitors (outpatients)	3	18	0	0	1	6	0
	No anticoagulation (outpatients)	2	12	0	0	2	12	0
Intra-cardiac thrombosis (4 patients)	Warfarin (outpatient)	1	25	0	0	0	0	1 repeated went from A to C
	Heparin (mostly inpatients)	2	50	1	25	0	0	0
Atrial fibrillation (4 patients)	Heparin (inpatients)	0	0	1	25	1	25	0
	Tranexemic acid (inpatient)	1	25	0	0	0	0	0
	Apixaban (outpatient)	1	25	0	0	0	0	1 repeat went from A to C

Abbreviation: ICD, International Classification of Disease.

[a](A) Increase in PF1.2 independent of elevation of the other parameters. (B) Increased D-dimer together with increased TAT and/or fibrin monomers. (C) Only D-dimer, TAT, or fibrin monomers elevated were considered as non-specific.

molecular heparin, or warfarin; 4 (23%) were receiving platelet inhibitors (aspirin or P2Y12 inhibitors); and the remaining 4 were not receiving anticoagulation or antiplatelet therapy. Of the 9 patients receiving anticoagulants, 6 (54%) were considered to have prothrombin conversion, which was the same as 3 of the 4 patients receiving platelet inhibitors and 2 of the 4 patients not receiving platelet inhibitors or anticoagulation treatment. Lastly, all of the 8 patients with thrombosis or atrial fibrillation were receiving anticoagulant treatment and 4 (50%) were considered to have prothrombin conversion.

Discussion

Our results demonstrate that patients with cardiac assist devices commonly have D-dimer elevations, while increases in other MOCHA parameters are infrequent. Over 50% of MOCHA panels were interpreted as non-specific in this group, as there was only elevation of D-dimer. Increases of D-dimer are expected in this group of patients as even the insertion of an antecubital line can result in elevations of this marker.[5] Also notable was the fact that patients with dual ICD-10 codes behaved mostly as patients with cardiac assist devices which may be due to the fact that they were adequately anticoagulated. In a previous analysis of cardiac assist devices in our institution, D-dimers were elevated when measured at baseline, during routine visits after the device had been in place, and when patients had a thrombotic event.[15] Of relevance, others have found that patients with recent myocardial infarcts that had reduction of D-dimer, either by pharmacological means or spontaneously, had a decreased risk of new ischemic events.[16] This literature suggests that normalization or decrease of D-dimer may have significant value in patients with cardiac assist devices. Although not all patients with cardiac assist devices had repeat tests in our study, these were the patients with more frequent repeat testing suggesting that clinicians monitor patients using this biomarker panel.

In our series the frequency of elevation of fibrin monomer was similar for each ICD-10 code. Elevated values occurred in approximately half of our cases independent of the ICD-10 code. Some researchers have found that fibrin monomer had higher sensitivity than the other MOCHA parameters to predict deep venous thrombosis after surgery, others have found a strong association with ischemic heart disease, while others have found increased levels of fibrin monomer in patients with thrombi in the left atrial appendage.[7,17,18] Our study could not corroborate results from the previous studies including heart thrombosis as we did not have enough patients with isolated intracardiac thrombi. In our study the percent of cases with increased levels of TATs was higher compared to fibrin monomer, but the frequency of increase (around 70%) was similar in all the ICD-10 codes. Many laboratories do not offer measurement of TATs.

In our series, the PF1.2 marker showed significant differences between heart assist devices and cardiomyopathy. This analyte was elevated in less than 15% of patients with cardiac assist devices while it was elevated in over 60% of patients with

cardiomyopathy. The lower frequency of PF1.2 elevation in our patients with heart assist devices likely indicates that these patients were adequately anticoagulated. Patients with cardiomyopathy had very frequent elevation of PF1.2 suggesting prothrombin conversion and thrombin generation. This marker is not routinely offered by laboratories. Increased amounts of PF1.2 have been found to predict occurrence of deep venous thrombosis in patients with cancer.[9] Ota et al found it to be elevated in patients with thrombosis, up to 3 days postoperative, and in patients with liver transplants.[12] The use of this marker was explored in patients with atrial fibrillation and mitral stenosis showing that lower levels can be expected when the patients were receiving anticoagulation treatment.[19] Lower levels of PF1.2 were observed in patients being on hemodialysis that were anticoagulated with warfarin.[20] Furthermore, patients with recent myocardial infarcts and elevated PF1.2 benefited when anticoagulation was given compared to those with recent myocardial infarcts and normal PF1.2.[16]

Laposata et al surveyed physicians regarding the need and usefulness of interpretation of complex coagulation panels, finding that interpretations have "... saved them time and improved the diagnostic process ... helped prevent a misdiagnosis or ... impact the differential diagnosis."[21] At our institution we provide an interpretation of the MOCHA panel results within the clinical context. When laboratory testing indicates prothrombin conversion into thrombin, we interpret this as an activation of the coagulation cascade. Elevations of only D-dimer are considered non-specific. Others, using this MOCHA panel, have shown elevations of all parameters in uncomplicated pregnancies, while in patients with cancer increases in MOCHA parameters have been strongly associated with active disease and poor survival.[8,22] In our institution, the MOCHA panel in patients with COVID-19 showed that elevation in PF1.2 and TAT was associated with admission to the ICU, while D-dimer and fibrin monomers were increased in patients with poor outcomes.[14] Clinicians find value in the panel and its interpretation, as evidenced by the continued ordering of the panel for patients with cardiac conditions, including use of repeated measures. Though, it was not clear from our review of charts what triggers physicians to repeat testing in some patients but not others.

Results of the MOCHA panel could be used to guide anticoagulation treatment. The INR (International normalized ratio) has been used to adjust warfarin treatment and an early study showed correlation of INR and PF1.2, although results change with age.[23] Our patients with cardiac devices were all anticoagulated; nevertheless, up to one third showed prothrombin conversion independent of the use of warfarin or heparin. Of note, patients in the group with cardiac assist devices that had repeat MOCHA testing showed changes to what appeared to be lesser activation of the coagulation cascade. Similarly, our cases with ICD-10 codes of thrombosis and atrial fibrillation were all anticoagulated but still 1 half showed prothrombin conversion. The only ICD-10 group with patients without anticoagulant or antiplatelet treatment was the cardiomyopathy group.

There are several limitations to this study, including being retrospective as upon review of charts it was difficult to define how clinicians responded to results from the MOCHA profile. This was mainly because it was not stated in the clinicians' notes that a change in anticoagulation was made based on the MOCHA results although changes appeared temporally related. Another limitation is having a small number of patients particularly for the ICD-10 codes of thrombosis and atrial fibrillation and flutter. Lastly, other heart devices such as pacemakers, artificial valves, and left arterial closure devices were not included in the ICD-10 codes studied.

In conclusion, patients with cardiomyopathy tend to have increased levels of PF1.2 indicating prothrombin conversion. In comparison, patients with cardiac assist devices had increased D-dimer while their PF1.2 was mostly within reference range, suggesting adequate anticoagulation in this group of patients. A prospective, real-time study of a cohort of patients with cardiac conditions would likely be useful to further identify how clinicians respond to MOCHA parameter results.

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