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Anti–Factor Xa and Activated Partial Thromboplastin Time Measurements for Heparin Monitoring in Mechanical Circulatory Support

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ABSTRACT

OBJECTIVES This study investigated the relationship between anti-factor Xa (anti-FXa) and activated partial thromboplastin time (aPTT) for monitoring intravenous unfractionated heparin (IV-UFH) in patients with continuous-flow left ventricular assist devices (CF-LVADs).

BACKGROUND CF-LVADs have become mainstream therapy for patients with advanced heart failure. Thromboembolic events, device thrombosis, and bleeding continue to be a challenge with this technology. Adequate anticoagulation is required to prevent these adverse events.

METHODS A prospective study of consecutive patients implanted with a CF-LVAD was conducted. Paired samples were considered concordant if aPTT values fell into expected ranges for subtherapeutic, therapeutic, and supratherapeutic anti-FXa levels. Heparin dosing was on the basis of anti-Xa levels.

RESULTS A total of 340 paired values from 38 patients were evaluated. Anti-FXa and aPTT were discordant in 253 samples (74.4%), with a high degree of variability in aPTT for any given anti-FXa level ($r^2 = 0.57$). Results were discordant in 104 samples (63.8%) from patients undergoing bridging therapy with warfarin and in 149 samples (84.2%) from patients with device obstruction and/or hemolysis ($p < 0.001$). The most common pattern of discordance was a supratherapeutic aPTT value despite a therapeutic anti-FXa level (49.1% for bridging vs. 75.8% for device obstruction and/or hemolysis; $p < 0.001$).

CONCLUSIONS Levels of aPTT were disproportionately prolonged relative to the corresponding anti-FXa levels in CF-LVAD patients, particularly those with device obstruction. Hemolysis and warfarin administration may falsely elevate aPTT, resulting in overestimation of heparin concentration and under-anticoagulation. Use of aPTT and anti-FXa to guide heparin therapy may lead to different estimates of heparin concentration in the same patient. (J Am Coll Cardiol HF 2015;3:314–22) © 2015 by the American College of Cardiology Foundation.

Thromboembolic events and gastrointestinal bleeding are serious complications in patients with continuous-flow left ventricular assist devices (CF-LVADs). Compared with initial experience, the rates of device thrombosis among patients who receive the HeartMate II LVAD (Thoratec Corporation, Pleasanton, California) have increased, with an associated higher mortality rate for medical management than for device exchange or urgent heart transplantation (1,2). Although specific causal factors have not been identified, patient characteristics, pump speed, pump design, or factors that reduce flow

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and heat dissipation from the bearings, coupled with inadequate anticoagulation, may be contributing factors (3).

Intravenous unfractionated heparin (IV-UFH) has been the mainstay for bridging therapy and for the treatment of suspected device obstruction and hemolysis in patients with CF-LVADs. In light of the risk of early device thrombosis, there is an urgent need to re-examine the way in which IV-UFH treatment is monitored (1,2). Measurement of activated partial thromboplastin time (aPTT) has been the criterion standard. However, because aPTT is susceptible to physiological and nonphysiological factors that do not reflect intrinsic heparin activity, patients may receive unintentionally high or low doses of heparin (4). In non-LVAD patients, anti-factor Xa (anti-FXa) has been suggested as an alternative measure because

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it may exhibit less variability and be less affected by other biological factors unrelated to UFH (5–8). Our institution transitioned to anti-FXa monitoring for all patients on IV-UFH in 2010. However, no comparison between aPTT and anti-FXa has been performed on patients receiving CF-LVADs. The aim of the present study was to prospectively evaluate the extent of agreement between these 2 methods by comparing simultaneous measurement of aPTT and anti-FXa levels in patients with CF-LVADs. Specifically, we hypothesized that a high level of discordance would be found between aPTT and anti-FXa.

METHODS

PATIENTS. Data were prospectively collected from consecutive patients with an implanted CF-LVAD who underwent therapy with IV-UFH between September 2012 and February 2014 at the University of Minnesota. Since 2010, our center has used anti-FXa monitoring to determine heparin dosing for all CF-LVAD patients. During the study period, both anti-FXa and aPTT concentrations were determined simultaneously in these patients to enable us to examine concordance; according to the standard care protocol for our center, only the anti-FXa values were used to guide clinical treatment. Our analyses included patients who were followed up for a minimum of 6 months. Patients were excluded from the analysis if they had advanced liver disease or an identified hypercoagulable state, were pregnant, were being treated with low-molecular-weight heparin, or were <21 years of age. The study was approved by the University of Minnesota institutional review board.

Patients were stratified for analysis on the basis of whether treatment with IV-UFH was initiated because of subtherapeutic international normalized ratio (INR) values (bridging cohort) or because of suspected device thrombosis and/or hemolysis (device obstruction/hemolysis cohort). Patients at our center did not receive bridging therapy with heparin immediately after device implantation (9); warfarin therapy was routinely started ~48 h postoperatively. Simultaneous samples for aPTT measurement were drawn when anti-FXa was in the desired therapeutic range, with a minimum of 3 consecutive simultaneous measurements. Heparin dosing was on the basis of anti-FXa levels according to an institutional protocol for dose adjustment; however, clinical teams could further refine dose adjustments on the basis of desired anti-FXa level. To confirm accuracy, the protocol allowed for repeat testing when results were outside laboratory-established therapeutic ranges and with subsequent heparin dose changes.

LABORATORY ASSAYS. Hemostasis tests were conducted on blood collected in 3.2% sodium citrate on a STA-R Evolution analyzer (Diagnostica Stago, Parsippany, New Jersey) with reagents from Diagnostica Stago. Determination of INR was performed with rabbit brain thromboplastin (STA-Neoplastine CI Plus), and measurements of aPTT were performed with cephalin plus silica (STA-PTT Automate). Lactate dehydrogenase (LDH) levels were determined with VITROS Chemistry Products LDH slides on a VITROS 5600 Integrated Chemistry System (Ortho Clinical Diagnostics, Raritan, New Jersey). The normal LDH range in our laboratory is 325 to 750 U/l.

Heparin was measured with a chromogenic anti-FXa activity assay. Before January 2013, heparin concentrations were determined with STA-Rotachrom calibrated with STA-Hepanorm H and STA-Calibrated HBPM/LMWH. In January 2013, the method was changed to STA-Liquid Anti-FXa calibrated with STA-Multi Hep Calibrators.

The laboratory therapeutic range for aPTT was established in 2005 by using blood samples from 59 random patients who received IV-UFH heparin, excluding samples with anti-FXa <0.1 U/ml or >1.0 U/ml, INR >1.3, or aPTT <36 s or >150 s. The aPTT heparin therapeutic range was established on the basis of correlation studies between aPTT and anti-FXa (10–12). The anti-FXa therapeutic ranges used by our institution corresponded to 0.15 to 0.35 U/ml for low intensity and 0.3 to 0.7 U/ml for high intensity (12–14); this was our comparison group. The aPTT heparin therapeutic range was subsequently verified at annual lot changes

ABBREVIATIONS AND ACRONYMS

anti-FXa = anti-factor Xa

aPTT = activated partial thromboplastin time

CF-LVAD = continuous-flow left ventricular assist device

INR = international normalized ratio

IV-UFH = intravenous unfractionated heparin

LDH = lactate dehydrogenase

by correlation between old and new lots. No shift in the range was observed over the time period of the study.

DOSING PROTOCOLS. Heparin dosing protocols were developed on the basis of previously established recommendations for clinical practice (12,15). The bridging cohort had a target anti-FXa level between 0.15 U/ml and 0.35 U/ml (low intensity), and the device obstruction/hemolysis cohort had an anti-FXa target between 0.3 and 0.7 U/ml (high intensity). Because of the overlap in therapeutic ranges, 0.3 U/ml was considered the separation point in our concordance analyses, although all pairs of results were analyzed on a continuum.

Our dosing protocol called for the initial heparin dose to be determined on the basis of the anti-FXa level 6 h after infusion start, with repeat testing 6 h after dose change and subsequent measurements once daily. Heparin therapy was discontinued if there was evidence of bleeding or, in the case of transitioning to warfarin, when therapeutic warfarin levels were reached (determined by measuring INR). For supratherapeutic anti-FXa levels >0.7 U/ml, the protocol specified holding infusion for 60 min, then a dose reduction by 300 U/h; for levels >1.31 U/ml, infusion was held for 60 min, then a dose reduction by 350 U/h. Subtherapeutic levels were rechecked after 6 h. For levels <0.1 U/ml, the protocol stipulated a bolus of 50 U/kg and a dose increase by 300 U/h; for levels 0.1 to 0.14 U/ml, the protocol called for a bolus of 30 U/kg and an increase by 150 U/h. All samples were drawn per institutional protocol, with aPTT checked when anti-FXa was in the therapeutic range or with a change in heparin dosing.

TABLE 1 Demographic and Clinical Characteristics of Patients With CF-LVADs (N = 38)

Age (yrs)	57 ± 16
Male	30 (78.9)
White	4 (10.5)
Body mass index (kg/m^2)	30.8 ± 7.7
Coronary artery disease	18 (47.4)
Hypertension	26 (68.4)
Diabetes mellitus	17 (44.7)
Chronic obstructive pulmonary disease	9 (23.7)
Stroke	8 (21.1)
Atrial fibrillation	15 (39.5)
Creatinine	1.45 ± 0.84
Lactate dehydrogenase at admission	985 (540–4,736)
Plasma hemoglobin at admission	15 (15–347)
Low INR at admission (on the basis of target level)	25 (65.8)
INR value at admission	1.96 (1.10–5.98)
ASA dose before admission	81 (0–325)

Values are mean ± SD, n (%), or median (range).
ASA = acetylsalicylic acid; CF-LVAD = continuous-flow left ventricular assist devices; INR = international normalized ratio.

EVALUATION OF CONCORDANCE. The primary endpoint was the extent of concordance/discordance between aPTT and anti-FXa in patients with CF-LVADs requiring IV-UFH. Blood samples for aPTT and anti-FXa were drawn simultaneously during the hospital stay; any samples not drawn simultaneously were excluded from the analysis. Pairs were considered concordant if aPTT values fell into the following expected ranges: for anti-FXa <0.15 U/ml, the corresponding aPTT range should be <45 s; for anti-FXa 0.15 to 0.29 U/ml, aPTT should be 45 to 60 s; for anti-FXa 0.3 to 0.7 U/ml, aPTT should be 61 to 100 s; and for anti-FXa >0.7 U/ml, aPTT should be >100 s. The number and percent of concordant and discordant pairs were determined. To examine the effects of conditions that may influence aPTT, we compared concordant and discordant pairs in samples from patients with INR <1.5 versus those with INR ≥1.5, as well as in samples from patients with LDH levels <2.5 versus ≥2.5 times the upper limit of normal (750 U/l). Concentrations of various coagulation factors in patients with discordant values were also measured.

CLINICAL OUTCOMES. Major bleeding and thromboembolic events within 30 days after starting IV-UFH therapy were assessed. Major bleeding was defined as fatal bleeding, a drop in hemoglobin of >2 g/dl, transfusion of >2 red blood cell units, or symptomatic bleeding in a critical organ. Rates of device exchange, urgent heart transplantation, and death before September 2014 were reported.

STATISTICAL ANALYSIS. Analyses were conducted by using Stata version 13 (Stata Corp., College Station, Texas). Descriptive statistics were used, and comparisons of concordance were performed by using chi-square tests or the Fisher exact test where appropriate. Assessment of continuous laboratory values was conducted by using the Wilcoxon rank sum test. Linear regression analysis was used to evaluate the relationship between aPTT and anti-FXa. To mitigate the effect of outliers, values were averaged from patients with >4 consecutive simultaneous specimens using a single value for each individual. The coefficient of determination (r^2) was calculated to estimate the proportion of the variation in aPTT that could be accounted for by using anti-FXa.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. A total of 340 samples from 38 patients with CF-LVADs were analyzed for concordance of anti-FXa and aPTT values. The patients' demographic and clinical characteristics are shown in Table 1.

OVERALL CONCORDANCE IN CF-LVAD PATIENTS. Mean aPTT was 127 ± 68.7 s (median 109 s; range 34 to 240 s), and mean anti-FXa was 0.34 ± 0.20 U/ml (median 0.3 U/ml; range 0.1 to 0.8 U/ml). The mean heparin dose was 1,495.5 ± 415 U/h.

Overall, aPTT and anti-FXa were concordant in 87 samples (25.6%) and discordant in 253 samples (74.4%), with the most common pattern being a supratherapeutic aPTT (>100 s) despite a therapeutic anti-FXa value (Table 2). Of 185 samples with an aPTT >100 s, 125 (67.6%) had a corresponding anti-FXa value within the therapeutic range.

Linear regression analysis of the relationship between anti-FXa and aPTT using all samples resulted in an r^2 of 0.57 (Figure 1). Of the 38 patients, 32 had >4 consecutive simultaneous specimens. Using the mean value of each patient's specimens to produce a single value per patient, the r^2 was 0.61.

BRIDGING VERSUS SUSPECTED DEVICE OBSTRUCTION/HEMOLYSIS. The bridging cohort consisted of 24 patients with CF-LVADs who were treated with IV-UFH because of a subtherapeutic INR with no evidence of device obstruction. The median time from implantation to data collection in the bridging group was 293 days (range 17 to 1,381 days); mean aPTT was 93.6 ± 48.1 s (median 82.5 s; range 34 to 240 s); and mean anti-FXa was 0.26 ± 0.17 U/ml (median 0.22 U/ml; range 0.10 to 0.78 U/ml). The device obstruction/hemolysis cohort consisted of 14 patients. The median time from implantation to data collection was 113 days (range 27 to 1,627 days); mean aPTT was 167 ± 68.4 s (median 174 s; range 36 to 240 s); and mean anti-FXa was 0.44 ± 0.19 U/ml (median 0.46 U/ml; range 0.1 to 0.86 U/ml). The mean baseline LDH concentration measured 1 month after device implantation was significantly higher in the device obstruction/hemolysis cohort (mean 839 U/l; range 691 to 945 U/l) than in the bridging cohort (mean 699 U/l; range 588 to 967 U/l; $p < 0.001$).

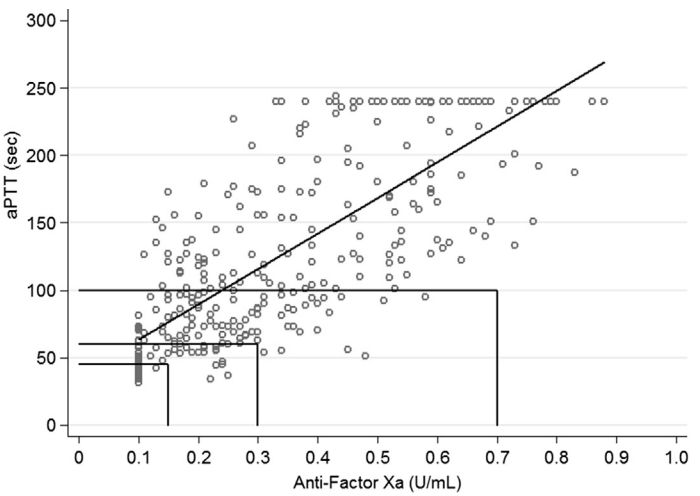
Of the 163 samples from the 24 patients in the bridging cohort, anti-FXa and aPTT were concordant in 59 (36.2%) and discordant in 104 (63.8%) (Table 3). Discordant aPTT values were supratherapeutic compared with therapeutic anti-FXa values in 28 samples (49.1%). Linear regression analysis revealed an r^2 of 0.48. In contrast, of 177 samples from patients with suspected device obstruction and/or hemolysis (Table 4), anti-FXa and aPTT were concordant in 28 (15.8%) and discordant in 149 (84.2%). Discordant aPTT values were supratherapeutic compared with therapeutic anti-FXa values in 97 samples (75.8%). In the linear regression analysis, r^2 was 0.49. In the device obstruction/hemolysis group, there was a clustering of aPTT values >240 s, despite a therapeutic anti-FXa. The level of discordance was significantly higher in the device obstruction/hemolysis group versus the bridging cohort ($p < 0.001$).

TABLE 2 All CF-LVAD Patients (340 Samples From 38 Patients) According to aPPT Level

	Anti-Factor Xa, U/ml	Concordant, n (%)	Discordant, n (%)
<45 s	<0.15	22 (88.0)	0
	0.15–0.29	0	3 (12.0)
	0.3–0.7	0	0
	>0.7	0	0
45–60 s	<0.15	0	24 (46.2)
	0.15–0.29	23 (44.2)	0
	0.3–0.7	0	5 (9.6)
	>0.7	0	0
61–100 s	<0.15	0	10 (12.8)
	0.15–0.29	0	43 (55.1)
	0.3–0.7	25 (32.1)	0
	>0.7	0	0
>100s	<0.15	0	5 (2.7)
	0.15–0.29	0	38 (20.5)
	0.3–0.7	0	125 (67.6)
	>0.7	17 (9.2)	0
Total	–	87 (25.6)	253 (74.4)

Number and percent of concordant and discordant activated partial thromboplastin time (aPTT) values are shown for each anti-factor Xa level.
Other abbreviations as in Tables 1 and 2.

FIGURE 1 Anti-FXa and aPTT Pairs in 38 Patients With CF-LVADs Treated With UFH



$r^2 = 0.57$. anti-FXa = anti-factor Xa; aPTT = activated partial thromboplastin time; CF-LVAD = continuous-flow left ventricular assist device; IV-UFH = intravenous unfractionated heparin.

TABLE 3 CF-LVAD Patients Receiving Heparin for Bridging (163 Samples From 24 Patients) According to aPPT Level

	Anti-Factor Xa, U/ml	Concordant, n (%)	Discordant, n (%)
<45 s	<0.15	19 (90.5)	0
	0.15–0.29	0	2 (9.5)
	0.3–0.7	0	0
	>0.7	0	0
45–60 s	<0.15	0	14 (40.0)
	0.15–0.29	19 (54.3)	0
	0.3–0.7	0	2 (5.7)
	>0.7	0	0
61–100 s	<0.15	0	7 (14.0)
	0.15–0.29	0	27 (54.0)
	0.3–0.7	16 (32.0)	0
	>0.7	0	0
>100 s	<0.15	0	5 (8.8)
	0.15–0.29	0	19 (33.3)
	0.3–0.7	0	28 (49.1)
	>0.7	5 (8.8)	0
Total	–	59 (36.2)	104 (63.8)

Number and percent of concordant and discordant aPTT values are shown for each anti-factor Xa level.

Abbreviations as in Tables 1 and 2.

COMPARISON GROUP. In 59 patients without an LVAD who were selected at random, the mean anti-FXa level was 0.36 ± 0.16 U/ml (range 0.12 to 0.79 U/ml), and the mean aPTT was 66.7 ± 20.5 s (range 41.7 to 135.2 s). Anti-FXa and aPTT values were concordant in 39 samples (67.2%) (Table 5), and r^2 was 0.66. The level of discordance was significantly higher in patients with CF-LVADs versus the comparison group ($p < 0.001$).

FACTORS INFLUENCING aPTT. Of the 340 paired aPTT and anti-FXa values from 38 patients, 313 (92%) had an INR from the same day. The proportion of samples with an INR ≥1.5 was significantly higher among discordant sample pairs than among concordant sample pairs ($p < 0.001$) (Figure 2). There was no significant difference in LDH between low versus high INR as measured at admission (968 U/l [range 646 to 2,529 U/l] vs. 1,034 U/l [range 727 to 2,032 U/l]; $p = 0.78$).

The proportion of samples with LDH concentrations ≥2.5 times the upper limit of normal (750 U/L) was significantly higher among discordant sample pairs than among concordant sample pairs ($p < 0.001$) (Figure 3). Fourteen patients had an aPTT ≥200 s determined at >2 consecutive measurements. These patients were most likely to have markedly elevated LDH levels; their mean LDH concentration was 2,041 U/l (range 1,000 to 3,678 U/l), which was significantly higher than the mean of 801 U/L (range 629 to 1,060 U/l) in patients with aPTT <200 s ($p = 0.008$).

To evaluate the biochemical basis for discordance, coagulation factors II, V, VII, VIII, IX, X, XI, and XII

TABLE 4 CF-LVAD Patients With Suspected Device Thrombosis and/or Hemolysis (177 Samples From 14 Patients) According to aPPT Level

	Anti-Factor Xa, U/ml	Concordant, n (%)	Discordant, n (%)
<45 s	<0.15	3 (75.0)	0
	0.15–0.29	0	1 (25.0)
	0.3–0.7	0	0
	>0.7	0	0
45–60 s	<0.15	0	10 (58.8)
	0.15–0.29	4 (23.5)	0
	0.3–0.7	0	3 (17.7)
	>0.7	0	0
61–100 s	<0.15	0	3 (10.7)
	0.15–0.29	0	16 (57.1)
	0.3–0.7	9 (32.1)	0
	>0.7	0	0
>100 s	<0.15	0	0
	0.15–0.29	0	19 (14.8)
	0.3–0.7	0	97 (75.8)
	>0.7	12 (9.4)	0
Total	–	28 (15.8)	149 (84.2)

Number and percent of concordant and discordant aPTT values are shown for each anti-factor Xa level.

Abbreviations as in Tables 1 and 2.

TABLE 5 Comparison Group Treated With Unfractionated Heparin (59 Samples From 59 Patients) According to aPPT Level

	Anti-Factor Xa, U/ml	Concordant, n (%)	Discordant, n (%)
<45 s	<0.15	1 (33.3)	0
	0.15–0.29	0	2 (66.7)
	0.3–0.7	0	0
	>0.7	0	0
45–60 s	<0.15	0	1 (4.0)
	0.15–0.29	14 (56.0)	0
	0.3–0.7	0	10 (40.0)
	>0.7	0	0
61–100 s	<0.15	0	0
	0.15–0.29	0	4 (14.8)
	0.3–0.7	22 (81.5)	0
	>0.7	0	1 (3.7)
>100 s	<0.15	0	0
	0.15–0.29	0	0
	0.3–0.7	0	2 (50.0)
	>0.7	2 (50.0)	0
Total	–	39 (67.2)	20 (33.9)

Number and percent of concordant and discordant aPTT values are shown for each anti-factor Xa level.

Abbreviations as in Tables 1 and 2.

were measured simultaneously with anti-FXa and aPTT in 10 consecutive patients with discordant levels (Table 6). All patients had a supratherapeutic aPTT compared with anti-FXa. Factor VIII was elevated in 9 of 10 patients. One had a low factor V value (58%), whereas 2 patients had low factor XII values. Low levels of factors II, VII, IX, and X were observed in patients receiving warfarin who had an elevated INR.

CLINICAL OUTCOMES. There were no significant differences between the bridging and suspected obstruction/hemolysis cohorts in major bleeding, thromboembolic events, or mortality at 30 days after IV-UFH administration (Table 7).

Of the 14 patients in the suspected obstruction/hemolysis cohort group, 11 had confirmed device thrombosis at the time of device exchange, urgent transplantation, or death, including 1 patient who received thrombolytic agents for device obstruction and died of an intracranial hemorrhage, 1 who died at device exchange after an embolic cerebrovascular accident, and 1 who died of a preservation injury resulting in cardiogenic shock at the time of transplant. The remaining 3 patients had hemolysis and were discharged; of these, 2 had no recurrent hemolysis (1 patient at 9 months and the other at the 11-month follow-up). The third patient was readmitted for hemolysis 5 months after IV-UFH treatment.

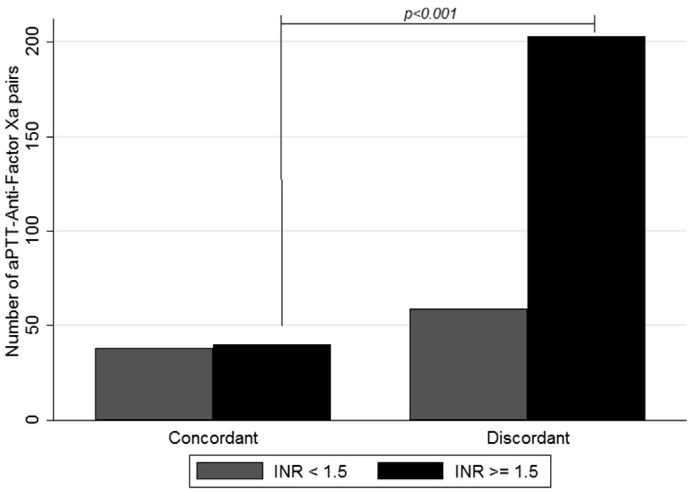
DISCUSSION

This observational study examined the extent of concordance between aPTT and anti-FXa in a prospective cohort of 38 consecutive CF-LVAD patients treated with IV-UFH. Anti-FXa and aPTT levels were discordant in 74.4%, most commonly with supratherapeutic aPTT despite therapeutic anti-FXa levels, especially in the device obstruction/hemolysis group. For any given anti-FXa value, a wide range of aPTT values was measured, and only about one-half of the variation in aPTT could be accounted for by anti-FXa.

Evidence supporting monitoring methods for UFH in CF-LVADs is scarce. Although aPTT is considered the standard criterion, its validity as a measure for therapeutic UFH levels in CF-LVADs should be questioned. Our data are consistent with previously published reports of variation in aPTT when monitoring UFH in patients without ventricular assist devices, with the predominant pattern of discordance being a high aPTT relative to a therapeutic anti-FXa level (5,6,8,16,17). Although heparin therapy is effective in venous thrombosis (18), in patients with CF-LVAD and device thrombosis (in whom medical management carries a 50% mortality [2]), the paucity of data on heparin management and the possibility of under-anticoagulation on the basis of aPTT monitoring can have serious implications.

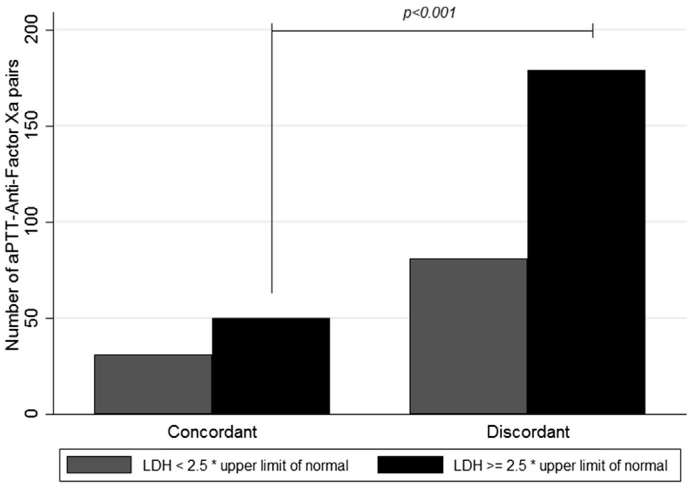
The balance of hemostasis in patients with CF-LVADs is complicated, with multiple variables influencing aPTT and anti-FXa levels. The presence of

FIGURE 2 aPTT-anti-Xa Pairs Stratified by INR



Proportion of concordant and discordant sample pairs with an international normalized ratio (INR) <1.5 or ≥1.5 in 313 sample pairs. Abbreviation as in Figure 1.

FIGURE 3 aPTT-anti Xa Pairs Stratified by LDH



Proportion of concordant and discordant sample pairs with a lactate dehydrogenase (LDH) concentration <2.5 or ≥2.5 times the upper limit of normal (750 U/l). Abbreviation as in Figure 1.

TABLE 6 Coagulation Factor Levels in 10 Patients With Discordant aPTT and Anti-Factor Xa Levels

	Coagulation Factor Levels, %											
Patient #	II	V	VII	VIII	IX	X	XI	XII	aPTT, s	Anti-Factor Xa, U/ml	INR	LDH, U/l
1	84	98	94	118	25	10	67	86	240	0.52	3.00	1,840
2	44	58	104	219	49	24	89	99	157	0.6	1.79	2,088
3	68	123	101	307	103	43	81	63	163	0.54	1.37	1,963
4	30	116	77	365	64	16	143	88	138	0.51	2.14	4,960
5	82	83	134	253	113	82	78	43	180	0.71	1.17	2,383
6	60	88	121	216	79	55	65	34	136	0.34	1.09	3,622
7	70	98	55	800	138	100	97	84	71	0.10	1.31	8,818
8	29	105	16	339	40	13	102	109	46	0.10	3.40	1,224
9	32	148	23	332	33	20	95	106	54	0.10	2.34	523
10	42	76	31	236	43	15	65	105	137	0.33	2.48	1,659

Normal assay ranges for factors II, V, VII, VIII, IX, X, and XI, 60% to 140%; factor XII, 50% to 186%; international normalized ratio (INR), 0.86 to 1.14; and lactate dehydrogenase (LDH), 325 to 750 U/l. Patient 9 was in the bridging cohort, and the remaining 9 patients were in the device obstruction/hemolysis cohort.

Other abbreviation as in Table 1.

specific conditions may determine which assay provides the best insight into the degree of anticoagulation. Poor correlation between anti-FXa and aPTT could result from administration of other coagulants, liver disease, vitamin K deficiency, acute phase response with elevated factor VIII concentrations, factor deficiencies, lupus anticoagulant agent, or elevated platelet factor 4 (16). Our study highlights 3 such conditions: hemolysis (as illustrated by elevated LDH levels), concurrent warfarin therapy, and coagulation factor deficiency.

Chromogenic assays such as the anti-FXa assay are influenced by conditions that color the plasma, such as hemolysis, hyperbilirubinemia, and hyperlipidemia (19). In our patients, discordance between aPTT and anti-FXa was associated with LDH values ≥2.5 times the upper limit of normal. High levels of hemolysis, icterus, or lipemia may cause false lowering of the anti-FXa in some chromogenic assays; these conditions were not present in our cohort, and plasma-free hemoglobin levels were usually well below the limit of interference per manufacturer's instructions. The same condition may even affect tests in opposite directions. For example, liver disease can lead to multiple factor deficiencies, including antithrombin deficiency, which may increase aPTT but decrease anti-FXa levels.

The concomitant use of warfarin with UFH can lengthen aPTT. Although discordance rates were higher for our patients with INR values ≥1.5, 20% of samples from patients with an INR <1.5 were also discordant. A prospective study by Kearon et al. (7) found that for every increase of 1.0 in the INR, the aPTT increased by 16 s. Price et al. (6) found that 42% of data pairs from 539 patients had a high aPTT value relative to anti-FXa, and data pairs with a high aPTT were most likely associated with an INR ≥1.5. Because aPTT reflects the effects of both UFH and warfarin, reducing the heparin dose in response to a high aPTT may result in clinically relevant subtherapeutic heparin levels (7). In patients with bridging protocols on the basis of aPTT monitoring, the highest incidence of device thrombosis occurs in the first 3 months, possibly because therapeutic heparin concentrations may not be achieved with concomitant warfarin administration (1). In patients with hemolysis and/or suspected device obstruction, aPTT-based monitoring may overestimate heparin concentrations, resulting in heparin underdosing and failure to respond to IV-UFH therapy. The high failure rates reported with medical therapy may be a reflection of these circumstances. Furthermore, the magnitude of the aPTT discordance observed in our CF-LVAD patients with INR >1.5 was out of proportion to what has been reported in the non-CF-LVAD literature (6,7).

Our data provide some initial insight regarding the biochemical basis for discordance on the basis of coagulation factors. Of 10 consecutive patients with discordance who had factors analyzed, 1 patient had

TABLE 7 Outcomes in Patients With Heparin for Bridging Therapy Versus for Suspected Device Obstruction/Hemolysis

	Bridging Cohort (n = 24)	Device Obstruction/ Hemolysis Cohort (n = 14)	p Value
Gastrointestinal tract bleeding, within 30 days	4 (16.7)	0	0.28
Intracranial hemorrhage, within 30 days	0	1 (7.1)	0.13
Thrombotic event, within 30 days	0	2 (14.3)	0.13
Device exchange	0	9 (64.3)	<0.001
Transplant	2 (8.3)	3 (21.4)	0.34
Death	3 (6.3)	3 (21)	0.70

low factor V value (58%), and 2 patients had low factor XII values. Although low factor XII is not accompanied by abnormal bleeding, it may be associated with marked prolongation of aPTT, making this test unreliable for monitoring heparin levels (20). There is a complex interaction between factor XII levels and thrombosis, with no clear relationship; however, data from a large registry revealed a U-shaped association of factor XII plasma levels with mortality from cardiovascular disease (20,21). Furthermore, 9 of 10 patients tested had elevated levels of factor VIII, which is an independent marker of increased thrombotic risk and has been shown to be elevated in non-CF-LVAD patients with heparin resistance, lowering the aPTT and possibly leading to over-anticoagulation (17). However, in our cohort, elevated factor VIII was not associated with heparin resistance; on the contrary, most patients had supratherapeutic aPTT levels despite a therapeutic anti-FXa.

Anti-FXa has disadvantages for monitoring heparin therapy because it does not reflect the complete anticoagulant properties of heparin. For example, effects of prothrombin and other coagulation factors are not assessed. Low endogenous antithrombin levels could lead to underestimation of UFH concentrations and therefore over-anticoagulation in some assays (22). Hence, aPTT may be a better marker of the global level of anticoagulation in situations of low antithrombin levels (5).

Given our small sample size, the study design, and small number of bleeding events, we were unable to draw firm conclusions regarding the safety of our anti-FXa–monitoring protocol relative to an aPTT-monitoring protocol. However, despite consistent supratherapeutic aPTT levels in the device obstruction/hemolysis cohort, in the absence of thrombolytic agents, no major bleeding episodes occurred. Both of our thrombotic events occurred in the setting of low-intensity heparin infusion. All 4 episodes of major gastrointestinal bleeding in the bridging cohort occurred with re-challenge of IV-UFH during an admission for gastrointestinal bleeding. One of the benefits of measuring heparin by using the anti-FXa method instead of aPTT is the low specificity of a prolonged aPTT to predict bleeding (23,24). Thus, in our experience, an anti-FXa–based monitoring protocol has been used to stabilize patients with acute device thrombosis and bridge patients to device exchange or urgent transplantation without excessive bleeding complications or thromboembolic events.

STUDY LIMITATIONS. This trial was a single-center, nonrandomized study in a small cohort of patients. It was designed to test for discordance between anti-FXa and aPTT, and not for superiority of 1 monitoring-based regimen over the other. Furthermore, no post-hoc correction was used for multiple testing. Despite these limitations, the results provide critical information regarding monitoring IV-UFH and offer insight into the potential biochemical basis for discordance between anti-FXa and aPTT.

CONCLUSIONS

Concordance between aPTT and anti-FXa in patients with CF-LVADs was low, typically with a supratherapeutic aPTT relative to anti-FXa. Despite this finding, bleeding and thromboembolic events in our cohort were low. Our findings indicate that, particularly during hemolysis and warfarin administration, aPTT may overestimate heparin concentration, because aPTT is influenced by other factors involved in hemostasis. Thus, anti-FXa may provide a more accurate estimate of heparin concentration. Further investigation is required before recommendations can be made about optimal testing protocols in bridge patients versus those with device thrombosis, given the mitigating factor (hemolysis) that differentiates the 2 conditions. These data suggest a great opportunity remains to better understand the most efficacious and safe way to monitor heparin therapy in patients with CF-LVADs.

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