Anticoagulant Bridge Comparison in Mechanical Circulatory Support Patients

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Maintaining mechanical circulatory support (MCS) device patients in a specified therapeutic range for anticoagulation remains challenging. Subtherapeutic international normalized ratios (INRs) occur frequently while on warfarin therapy. An effective anticoagulant bridge strategy may improve the care of these patients. This retrospective review of MCS patients with subtherapeutic INRs compared an intravenous unfractionated heparin (UFH) strategy with a subcutaneous enoxaparin or fondaparinux strategy. Native thromboelastography (n-TEG) was used to evaluate anticoagulant effect with coagulation index (CI) as the primary outcome measure. Enoxaparin 0.5 mg/kg subcutaneously (SC) every 12 hours or fondaparinux 2.5–5 mg SC daily were compared with an initial UFH rate of 5 units/kg/hr and titrated to stated n-TEG goal range. The anticoagulant groups UFH, enoxaparin, and fondaparinux were found to be statistically similar with regard to frequency in n-TEG goal range, above range (hypercoagulability), or below range (hypocoagulability). Clinical outcomes were similar among groups with three gastrointestinal bleeds in UFH, one in enoxaparin, and one in fondaparinux groups. Device thrombosis occurred in one UFH patient, while UFH and fondaparinux groups had one ischemic cerebrovascular accident event each. These strategies provided comparable n-TEG results and clinical outcomes when compared with intravenous UFH. Low-dose enoxaparin or fondaparinux may provide an alternative anticoagulant bridging option in MCS patients presenting with subtherapeutic INR. *ASAIO Journal* 2019; 65:54–58.

Key Words: anticoagulation, mechanical circulatory support, bridge therapy, heart assist devices

Mechanical circulatory support (MCS) devices are gaining in popularity and have provided therapy for tens of thousands of end-stage heart failure patients worldwide. The standard anticoagulant remains warfarin for the majority of these patients. These patients have significant risks of both hemorrhagic and thromboembolic complications making this population among the most important to keep in a given therapeutic range. The prevalence of ischemic cerebrovascular accident (CVA) among left ventricular assist devices (LVADs) can range from 4 to 20%[1,2] and device thrombosis occurs in approximately 5–10% of MCS patients.[3,4] Meanwhile, gastrointestinal (GI) bleeding is quite common in LVAD because of a variety of factors and can be seen in up to 25% of this population.[5,6]

Maintaining the international normalized ratio (INR) in a set therapeutic range can theoretically minimize the above risks and yet remains challenging to do so. The recorded time in therapeutic range (TTR) for trials involving warfarin reinforces this therapeutic dilemma. The rates of TTR for major anticoagulant trials involving warfarin of 55–66%[7–9] reflect the widespread mediocrity in attaining anticoagulant goals. This provides ample opportunity for evaluation and possible advances in the methods of anticoagulant bridging in MCS patients who experience subtherapeutic INR. Until recently, the standard approach for bridging patients back to therapeutic INR has been inpatient intravenous unfractionated heparin (UFH). Drawbacks to this strategy include the following: delays to the start of therapy with admission to hospital and UFH set-up, variable times to reach a therapeutic-activated partial thromboplastin time (PTT) or anti-Xa range, unclear UFH goal ranges, costs of admission, and patient inconvenience. The availability of alternative agents that can be administered as an outpatient may provide some advantages. As well, the correct level of anticoagulation in MCS patients continues to evolve. We attempt to add to this knowledge base by reporting our experience with, and the testing of, the low molecular weight heparin—enoxaparin, or the synthetic pentasaccharide—fondaparinux. Potential advances in anticoagulant safety are possible since anecdotal reports of standard low molecular weight heparin dosing (1 mg/kg subcutaneously every 12 hours (q12hrs)) for bridge indication in MCS patients describe over-anticoagulation and hemorrhage.[10]

Herein we described an investigation of the anticoagulation response provided by low-dose enoxaparin or fondaparinux used to bridge MCS patients with subtherapeutic INR when compared with a traditional UFH bridge. The testing used in this report is through native thromboelastogram (n-TEG). Thromboelastogram has been reported to measure the anticoagulant effect for both enoxaparin and fondaparinux.[11–13] The analysis uses whole blood samples and attempts to report real-time hemostasis from patient samples that inherently contain multiple clotting factors, cytokines, and cellular contributors to a patient's propensity for thrombosis or bleeding. The use of TEG and similar point-of-care devices in cardiac surgery has shown benefit in reducing blood product use and interventions for postoperative bleeding complications.[14,15] The key elements of thromboelastography measure the R (initial reaction time), K (time to 20 mm amplitude), angle (the rate of speed between

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R and K), maximum amplitude (MA), and coagulation index (CI—the combined amalgamation of the aforementioned measures).

The doses evaluated for enoxaparin in this study are similar to those that have been used in MCS anticoagulant bridging elsewhere.[16] Fondaparinux used in MCS with heparin-induced thrombocytopenia has had documented success as well.[17,18] The reliable exposure and time to onset of anticoagulation provided by these agents provide a possible advantage for use in this setting. The ability to measure and compare the effects of these agents may provide greater confidence with their use.

Materials and Methods

This study was a retrospective chart review of MCS patients with subtherapeutic INRs implanted between November 1, 2013, and November 1, 2015. The project was approved through an Institutional Review Board within the Human Subjects Protection Program at the University of Arizona. Patients were included for review if sufficient data were available in the electronic health record and who required readmission for subtherapeutic INR at any time after discharge from initial MCS implant. A subtherapeutic value that required anticoagulant bridge therapy was defined as INR <1.8. Reasons for subtherapeutic bridge therapy were either unintentional or intentional INR reduction for invasive procedure. Native thromboelastogram data were compared among groups of patients who received either enoxaparin, fondaparinux, or a control group of intravenous UFH. The main outcome data point was the composite measure: CI (formula below), derived from n-TEG testing. The goal range is set at CI of either normal (0.0–1.87) or moderately hypocoagulable (−5.0 to 0.0). Patients who result in a hypercoagulable CI (>1.87) are thought to be at higher thromboembolic risk. Extended hypercoagulability was defined as CI >3.0, whereas extended hypocoagulability was defined as CI <−5.0, as these are approximately one standard deviation from the overall mean CI results. Dosing for enoxaparin bridge therapy was 0.5 mg/kg subcutaneously every 12 hours (dose adjusted to 0.5 mg/kg every 24 hours if creatinine clearance < 30 ml/min); no patient on hemodialysis was included. Patients were continued on parenteral anticoagulation until INR remained above lower limit of goal range for 24 hours. Goal INR was 2.0–3.0 for patients included in this analysis. If a patient was determined to have experienced heparin-induced thrombocytopenia, then fondaparinux was used for bridge therapy. Dosing for fondaparinux was initiated at 2.5 mg SC q24hrs and titrated, if necessary to 5 mg SC q24hrs based on n-TEG results. Thromboembolic and hemorrhagic outcomes were compared as number of ischemic CVAs, GI bleeding, or device thrombosis. These clinical outcomes were considered possibly related to a bridging strategy only if the event occurred within 3 months post bridge therapy. Gastrointestinal bleeding was defined as any bleed significant enough to require admission to hospital. Device thrombosis was recorded if patient required device exchange. Cerebrovascular accident was recorded as positive if evidence of new ischemic/infarction event on radiologic imaging.

Statistical analysis of demographic and clinical outcomes was performed using Kruskal–Wallis testing for continuous outcomes, whereas Fisher exact test measured categorical outcome values. For comparison of the CI probabilities between groups, a generalized linear mixed-effects model with random intercept to account for within subject correlation based on a multinominal distribution and cumulative logit link function. This model was chosen because multiple CI values were recorded for each patient.

Thromboelastography was performed on a model 5000 whole blood hemostasis analyzer (Haemoscope Corporation, Niles, IL). It is performed without the use of kaolin activator at our institution. Thus, it is referred to as "native" TEG. Samples are collected in buffered sodium citrated 3.2% vials. This study reports n-TEG results in terms of millimeter. Normal values are as follows: 1) R, 16–32 mm measured in distance at a rate of 2 mm/min to onset of coagulation; 2) K, 4–9 mm measured in distance at a rate of 2 mm/min to a standard clot strength of 20 mm; 3) MA, 51–66 mm maximum clot strength (millimeter amplitude); 4) angle (ANG), 40–64 degrees mm proportional to the rate of clot growth; and 5) CI, normal values are between 0.00 and 1.87 (formula: $CI = -0.2454R + 0.0184K + 0.1655MA - 0.0241\alpha - 5.0220$).[19]

Results

A total of 46 courses of anticoagulant bridging occurred in 29 MCS patients with subtherapeutic INR. Patient groups were similar with regard to age, weight, gender, renal function, and concomitant antiplatelet therapy. The more recent patients, treated with enoxaparin or fondaparinux, were compared with historical control patients treated with UFH. There were nine HeartMate II LVAD, 19 HeartWare LVAD, and one total artificial heart patient. The average age was 59.4 years in 16 male and six female patients. The average initial subtherapeutic INR was 1.62 (**Table 1**). Patients who were treated with fondaparinux had positive heparin/platelet-factor 4 antibody optical densities by enzyme-linked immunosorbent assay (ELISA) (>0.4 optical density), all other study group patients received enoxaparin. The average duration of enoxaparin courses was 2.9 ± 2.1 days, and 3.7 ± 2.3 days for fondaparinux. Duration of UFH therapy in the control group was a mean of 5.7 ± 4.8 days (**Table 1**).

There were no statistically significant differences in the proportion of patients who fell within, or out of, stated CI goal ranges by n-TEG. Mechanical circulatory support patients on intravenous UFH recorded a goal range CI 61.4% of the time when compared with 61.3% for enoxaparin and 60.0% for fondaparinux (**Table 2**). This equivalency existed despite more frequent titrations of dose for heparin when compared with enoxaparin or fondaparinux groups. No statistically significant difference existed among UFH, enoxaparin, or fondaparinux groups in the amount of extended hypercoagulability or hypocoagulability that occurred. Extended hypercoagulability occurred in 3.9% of UFH patients when compared with 3.7% for enoxaparin and 6.8% for fondaparinux patients. Extended hypocoagulability was measured 22.0%, 22.7%, and 13.4% of the time for UFH, enoxaparin, and fondaparinux groups, respectively. The mean activated PTT among UFH bridged patients was 52.8 seconds (approximately 1.5 times institutional upper limit of normal range), while enoxaparin-treated patients had a mean peak anti-Xa value of 0.35 IU/ml. Coagulation indices were plotted against day of therapy in **Figure 1**. This showed differences between a more consistent goal range for UFH over time compared with a trend toward hypocoagulability for enoxaparin and fondaparinux over time (UFH *versus* enoxaparin) $p < 0.05$ and (UFH *versus* fondaparinux) $p < 0.001$.

Table 1. Summary of Patient Characteristics by Treatment Group

	Heparin	Enoxaparin	Fondaparinux	*p**
No. of patients	15	11	3	
Age (years)	52	64.7	63.4	0.36
Weight (kg)†	84.5	84.3	89.3	0.75
Female	4 (26.7%)	2 (27.3%)	0	1.00
CrCl (ml/min)	66 ± 18	78 ± 29	58 ± 6	0.07‡
Aspirin	14 (93.3%)	9 (90.0%)	2 (66.7%)	0.33
Dipyridamole	5 (33%)	4 (36%)	1 (33%)	0.99
Initial INR	1.52	1.61	1.63	0.50
Bridge courses	24	16	6	
Duration (days)	5.7 ± 4.8	2.9 ± 2.1	3.7 ± 2.3	0.07
Mean PTT (seconds)	42.4 ± 8.3†	—	—	—
Anti-Xa (IU/ml)	—	0.35 ± 0.27†	—	—

Average dosing = unfractionated heparin: 6.2 units/kg/hr ± 2.6 (mean) IV, enoxaparin: 0.5 mg/kg every 24 hours subcutaneous, fondaparinux: 2.5 mg every 24 hours subcutaneous (16 doses), 5 mg q24hrs (four doses).

*Derived from Kruskal–Wallis test for continuous outcomes and Fisher exact test for categorical outcomes.

†Mean ± SD.

‡Median ± interquartile range.

INR, international normalized ratio; PTT, partial thromboplastin time; q12hrs, every 12 hours; q24hrs, every 24 hours; SC, subcutaneous; SD, standard deviation.

The most prevalent clinical outcome was GI bleeding. This occurred in three (20%) of UFH patients, as compared to one (9%) with enoxaparin and one (33%) with fondaparinux (**Table 3**). One patient in the fondaparinux experienced both an ischemic CVA and a GI bleed. There was one patient in the UFH group who experienced an ischemic CVA. Each patient who experienced a CVA recovered without residual neurologic deficits. One patient in the UFH group suffered a device thrombosis that required surgical exchange.

Discussion

The anticoagulation goals for MCS patients continue to be investigated. If an artificial surface on a dynamic pump can create a thrombogenic environment in the blood, then returning the patients' hemostatic balance back to a "normal" level with anticoagulation would be the ideal amount of pharmacotherapy necessary. Thus, based on this measure of whole blood coagulability (n-TEG), we can tailor the amount of anticoagulation to achieve "normocoagulability." This testing modality has directed us toward generally more conservative doses of anticoagulation in MCS patients both postoperatively and in bridging scenarios. In more than 2 decades of experience monitoring MCS anticoagulation, n-TEG values in the normal to moderately hypocoagulable range have been employed. This consistently employed method of analysis has allowed for a familiarity that has allowed for ease of historical comparisons that provide continuing quality improvement and analyses.[20] The added expense to perform this test will not be required in every instance of subtherapeutic INR. Our findings have provided some confidence for dosing these alternative subcutaneous agents in the outpatient setting.

The results presented here show equivalence by n-TEG, in the amount of anticoagulation provided by traditional intravenous (IV) UFH use as compared with a low-dose enoxaparin or fondaparinux strategy. These doses of enoxaparin/fondaparinux show a measured effect on n-TEG samples. Keeping the peak values in the normocoagulable to moderately hypocoagulable ranges has allowed for evidence of acceptability in this cohort of patients. A greater sample size would be required to display differentiation in clinical outcomes. Advantages of the subcutaneous administration of enoxaparin or fondaparinux lie in the potential for faster time to treatment when compared with admission to hospital and initiation of intravenous (IV) UFH treatment. It is particularly convenient if the patient has readily available subcutaneous drug at home or a nearby dispensary. The potential benefits derived from avoiding hospital admission include decreased nosocomial risks as well as less direct or indirect costs to patient, family, and institution. However, one must be cognizant of the trustworthiness in the patient's adherence to medical advice as an outpatient, to avoid the deleterious outcomes

Table 2. Comparison of CI Categories From Native Thromboelastogram (Observed % Frequencies by Probability Model)

CI	Heparin	Enoxaparin	Fondaparinux
Extended hypocoagulability (CI ≤ –5.0)	28 (22.0%)	9 (22.7%)	2 (13.4%)
Goal range (–5.0 < CI ≤ 1.87)	66 (61.4%)	22 (61.3%)	11 (60.0%)
Hypercoagulability (1.87 < CI ≤ 3.0)	15 (12.7%)	4 (12.3%)	5 (19.7%)
Extended hypercoagulability (CI > 3.0)	6 (3.9%)	2 (3.7%)	0 (6.8%)
p	Ref	0.93	0.34

Goal range = normocoagulability CI (0–1.87) or moderate hypocoagulability (–5.0 to 0.0). Heparin group = 24 courses of bridging, enoxaparin group = 16 courses of bridging, and fondaparinux group = six courses of bridging. *P* values calculated with heparin group as a reference. Proportion of CI values within each category by drug treatment group compared by generalized linear mixed-effect model with random intercept to account for within-subject correlation based on a multinominal distribution and a cumulative logit function.

CI, coagulation index.

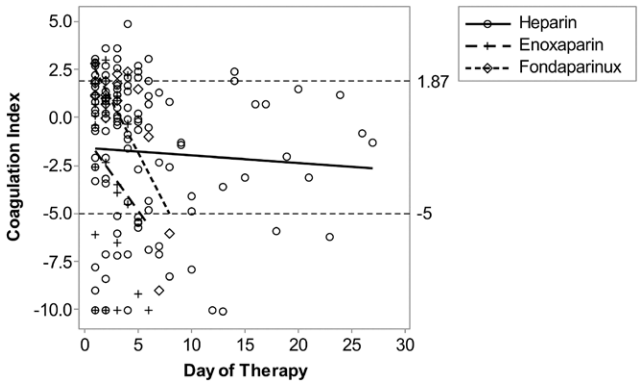

Figure 1. Coagulation index *versus* day of anticoagulation bridge therapy. Goal range (coagulation index: –5.0 to 1.87). Both enoxaparin and fondaparinux extrapolate to extended hypocoagulability (<–5.0) as days of therapy progress, whereas heparin remains within stated goal range (likely due to more frequent dose titrations and shorter half-life). A linear mixed-effects model with day of therapy and drug type show (UFH *versus* enoxaparin) $p < 0.05$ and (UFH *versus* fondaparinux) $p < 0.001$. Analysis of correlated data points, R^2 (= 0.05). UFH, unfractionated heparin.

from lack of prompt and adequate anticoagulation. Another potential drawback to an anticoagulant given on periodic intervals as opposed to a continuously infused UFH might be the pharmacokinetic characteristics. The peak *versus* trough effect of the scheduled drugs will create differences in anticoagulant activity throughout the day. Data presented here in the interval-dosed group generally reflect "peak" CI values. In contrast, five CI values were 12 hours or greater from drug administration, and all of these were in hypercoagulable or normocoagulable CI range. Whether this translates into a clinically significant effect remains uncertain. Also, a noticeable accumulation of anticoagulant effect is a possibility with these medications that rely heavily upon renal elimination. Particularly, fondaparinux carries the characteristic of a longer half-life that can be susceptible to drug build-up with repeated dosing. This was observed in a patient treated with 8 days of fondaparinux. **Figure 1** indicates the trend toward accumulation of enoxaparin and fondaparinux as the days of therapy progress. From a potency standpoint, the initial fondaparinux dose of 2.5 mg never produced an extended hypocoagulable response on the first day of testing. Goal range CI was generally attained only after repeated doses of 2.5 mg or an increase to 5 mg amounts. In comparison, enoxaparin doses of 0.5 mg/kg subcutaneously twice per day provided adequate initial dosing to maintain patients within the CI goal range relatively soon after initiation. All data in **Figure 1** represent CI's early in the dosing interval (<12 hours from time of administration). It remains to be seen whether peak values correlate with clinical effect or does a more thorough measure of drug exposure better reflect efficacy (*i.e.*, area under the curve).

Table 3. Summary of Clinical Outcomes by Anticoagulant Bridge Group

	Heparin	Enoxaparin	Fondaparinux	*p*
Ischemic CVA	1 (6.7%)*	0	1 (33%)*	0.31
GI bleeding	3 (20%)†	1(9%)*	1 (33%)*	0.30
Device thrombosis	1 (6.67%)*	0	0	1.00

Events occurring within 3 months of anticoagulant bridge therapy for subtherapeutic INR among 15 patients in the heparin group, 11 patients in the enoxaparin group, and three patients in the fondaparinux group.

*HeartWare LVAD.

†Two HeartMate II and one HeartWare LVADs.

CVA, cerebrovascular accident; GI, gastrointestinal; INR, international normalized ratio; LVAD, left ventricular assist device.

Thromboelastogram results in terms of CI were the primary measure of hemostasis in these patients. Generally, the subjects who achieved the stated CI goal range generated anti-Xa levels in the enoxaparin group to a mean value of 0.35 ± 0.27 IU/ml. This was similar to anti-Xa peak goal ranges (0.2–0.4 IU/ml) used elsewhere for the anticoagulation of MCS patients during the immediate postoperative period.[21]

The limitations from this report are the small sample size, retrospective protocol, and the historical bias comparing traditional bridge therapy *versus* more recent practice. We must also consider that the results provided by thromboelastogram do not exclusively reflect amount of anticoagulation used, rather it represents a combination of physiologic hemostatic forces in the setting of anticoagulation. If the patient is prone to hypocoagulability, there may be little anticoagulation needed to maintain a patient within n-TEG goal ranges. Thus, patient physiology can confound these results and predispose the practitioner to be slightly more or less aggressive with anticoagulation. The reader should also be aware that standard goal ranges for the "native" thromboelastogram (n-TEG) used in this report are different from other standard (kaolin)-activated thromboelastogram values.

The methodology used here provides some evidence for an alternative anticoagulant bridge strategy when compared with intravenous UFH. The equivalence shown in enoxaparin and fondaparinux groups based on n-TEG results implies a similar conservative level of anticoagulation when compared with our traditional UFH protocol. A patient's inherent thromboembolic or bleeding risk should be considered when choosing an anticoagulant strategy. Further study should be undertaken to continue to improve the anticoagulation management of MCS patients.

References

1. Morgan JA, Brewer RJ, Nemeh HW, et al: Stroke while on long-term left ventricular assist device support: Incidence, outcome, and predictors. *ASAIO J* 60: 284–289, 2014.
2. Backes D, van den Bergh WM, van Duijn AL, Lahpor JR, van Dijk D, Slooter AJ: Cerebrovascular complications of left ventricular assist devices. *Eur J Cardiothorac Surg* 42: 612–620, 2012.
3. Starling RC, Moazami N, Silvestry SC, et al: Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med* 370: 33–40, 2014.
4. Slaughter MS, Rogers JG, Milano CA, et al; HeartMate II Investigators: Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 361: 2241–2251, 2009.
5. Draper KV, Huang RJ, Gerson LB: GI bleeding in patients with continuous-flow left ventricular assist devices: A systematic review and meta-analysis. *Gastrointest Endosc* 80: 435–446. e1, 2014.
6. Harvey L, Holley CT, John R: Gastrointestinal bleed after left ventricular assist device implantation: Incidence, management, and prevention. *Ann Cardiothorac Surg* 3: 475–479, 2014.
7. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365: 883–891, 2011.

8. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361: 1139–1151, 2009.
9. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 365: 981–992, 2011.
10. Connors JM: Anticoagulation management of left ventricular assist devices. *Am J Hematol* 90: 175–178, 2015.
11. White H, Sosnowski K, Bird R, Jones M, Solano C: The utility of thromboelastography in monitoring low molecular weight heparin therapy in the coronary care unit. *Blood Coagul Fibrinolysis* 23: 304–310, 2012.
12. Zmuda K, Neofotistos D, Ts'ao CH: Effects of unfractionated heparin, low-molecular-weight heparin, and heparinoid on thromboelastographic assay of blood coagulation. *Am J Clin Pathol* 113: 725–731, 2000.
13. Martinez B, Giacomello R, Paniccia R: Thromboelastographic monitoring of fondaparinux in surgical patients. *Crit Care* 17 (suppl 2): 356, 2013.
14. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 88: 312–319, 1999.
15. Royston D, von Kier S: Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during cardiopulmonary bypass. *Br J Anaesth* 86: 575–578, 2001.
16. Borden M, Kiernan MS, Pham DT, DeNofrio D, Sylvia L: Bridging with half-therapeutic dose enoxaparin in outpatients with left ventricular assist devices and sub-therapeutic international normalized ratios. *J Heart Lung Transplant* 34: 860–862, 2015.
17. Velagic V, Samardzic J, Baricevic Z, et al: Management of heparin-induced thrombocytopenia with fondaparinux in a patient with left ventricular assist device. *Int J Organ Transplant Med* 5: 83–86, 2014.
18. Gellatly RM, Leet A, Brown KE: Fondaparinux: An effective bridging strategy in heparin-induced thrombocytopenia and mechanical circulatory support. *J Heart Lung Transplant* 33: 118, 2014.
19. TEG® 5000 Thromboelastograph Hemostasis System. Operator's Manual. Copyright © 1999–2007 by Haemoscope Corporation Niles, IL.
20. Copeland JG, Arabia FA, Tsau PH, et al: Total artificial hearts: Bridge to transplantation. *Cardiol Clin* 21: 101–113, 2003.
21. Sandner SE, Riebandt J, Haberl T, et al: Low-molecular-weight heparin for anti-coagulation after left ventricular assist device implantation. *J Heart Lung Transplant* 33: 88–93, 2014.