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Argatroban in Short-Term Percutaneous Ventricular Assist Subsequent to Heparin-Induced Thrombocytopenia

David P. Webb, MS, CCP, LCP;*† Matthew T. Warhoover, MS, CCP, LCP;*†
Susan S. Eagle, MD;‡ James P. Greelish, MD;* David X. Zhao, MD;* John G. Byrne, MD*

**Vanderbilt Heart Institute, †Division of Perfusion Services, and ‡Department of Cardiothoracic Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee*

Abstract: Heparin-induced thrombocytopenia paradoxically is a transient pro-thrombotic disorder triggered by heparin exposure. If not treated appropriately, it can be life threatening because of its related thromboembolic complications. In particular, it presents a unique challenge in patients needing extracorporeal life support, because anticoagulation is essential for safe management. This case report describes the safe, efficacious use of Argatroban during short-term support of a patient with a percutaneously inserted left ventricular assist TandemHeart device.
Keywords: heparin-induced thrombocytopenia, Argatroban, TandemHeart, percutaneous ventricular assist device (pVAD).
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Heparin-induced thrombocytopenia (HIT) type II seems to be an ever increasing condition associated with the cardiac patient population. This is likely because of the frequency of which heparin is administered for the treatment of various medical conditions. The incidence of HIT type II is estimated to occur in ~1–4% of all cardiac surgical patients; however, the appearance of detectable antibodies is thought to be more frequent (1,2). HIT type II is characterized by thrombocytopenia resulting from an antibody-mediated platelet activation, which differentiates HIT type I (3–5). This immunological response is directly attributed to specific heparin-dependent IgG antibodies found in the plasma binding to heparin and platelet factor 4 (3–5). The result of this binding is platelet degranulation and endothelial interaction, which contributes to a variety of other clinical scenarios including deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, and limb artery occlusion (3–5). If not recognized and treated appropriately, HIT type II can be lethal.

Argatroban (GlaxoSmithKline, Research Triangle Park, NC) is thought to be a safe and efficacious therapeutic anticoagulant alternative for HIT type II patients with limited options. It is a small synthetic univalent direct thrombin inhibitor that binds reversibly to the active site of thrombin (6–9). In contrast to unfractionated heparin, Argatroban does not require a co-factor to elicit anticoagulation and currently has no reversal agent. After administration of Argatroban, both free and clot-bound inhibition of thrombin occurs (6–8). The elimination half-life is relatively short (39–51 minutes), although it may be increased with hepatic impairment because the liver is the primary site of metabolism (6,8,10). Unlike other direct thrombin inhibitors, Argatroban undergoes minimal renal clearance, making it ideal for patients with renal dysfunction (6–9). Although safe and effective dosing requirements have yet to be elucidated for the application of a short-term percutaneous ventricular assist device, it predictably increases the activated partial thromboplastin time (aPTT) and activated clotting time (ACT) in a dose and concentration-dependent fashion (6,8,11). Argatroban has been successfully used for anticoagulation during cardiopulmonary bypass, extracorporeal membrane oxygenation, and hemodialysis (12–14).

The TandemHeart ventricular assist device system (Cardiac Assist, Pittsburgh, PA.) is a continuous flow, afterload and preload dependent, centrifugal type extracorporeal pump (15–18). Unlike other ventricular assist devices, it can be inserted percutaneously by a cardiovascular surgeon in an operating room, a cardiologist in a cardiac catheterization laboratory, or either physician in a hybrid type cardiac surgical/catheterization suite. Typical left ventricular support uses a 21-F transseptal cannula inserted percutaneously through the right femoral vein and guided across the interatrial septum by transesophageal echo (TEE) to access the left atrium (Figure 1). The

Address correspondence to: David P. Webb, Chief/Program Director, Perfusion, Vanderbilt University Medical Center, 2971 TVC 1211 22nd Avenue SO, Nashville, TN 37232. E-mail: david.webb@vanderbilt.edu
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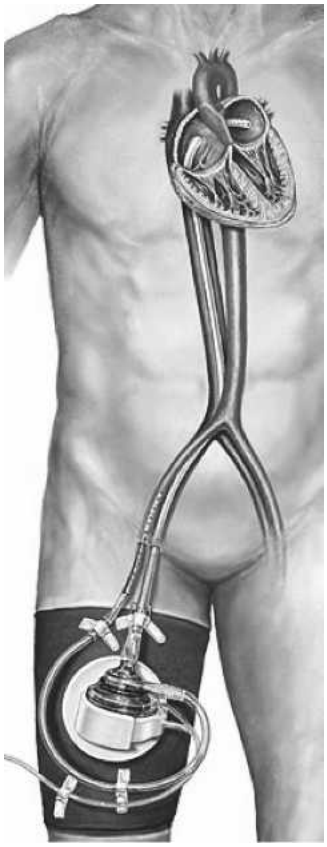

Figure 1. Anatomical placement of a TandemHeart L-VAD.

transseptal cannula provides inflow of arterial blood to the pump. Blood is returned to the patient by a percutaneously inserted femoral arterial cannula.

The pump apparatus is dual chambered, with upper housing and lower housing assemblies (15,16). It weighs ~8 ounces and can deliver up to 5 L/min of blood flow at a maximum speed of 7500 rpm. An electromagnet driven motor propels blood in the upper chamber by a six-blade impeller that rotates on a lubricating fluid film (15,16). The lubricating fluid (normal saline) contains heparin or an alternative anticoagulant when needed and is continuously infused at a fixed rate of 10 mL/h into the lower inner housing chamber of the blood pump by a miniature positive displacement type infusion pump located on the console. This fluid boundary layer provides hydrodynamic bearing, local anticoagulation, and cooling of the blood. Because of the heat generated from the high rpms, the pump housing is also equipped with an integrated heat sink. The priming volume of the blood pump is negligible at ~10 mL.

CASE DESCRIPTION

A 35-year-old man with endstage idiopathic dilated cardiomyopathy presented to the emergency room with shortness of breath. A 12-lead EKG subsequently showed atrial fibrillation, which prompted a TEE. The TEE showed an ejection fraction (EF) of ~5–10%. The patient was admitted and worked up for orthotopic heart transplantation. Approximately 2 weeks into the admission, the patient was taken off Coumadin and placed on Lovenox (Sanofi-Aventis, Bridgewater, NJ) and heparin. Within 48 hours after initiating Lovenox and heparin, his platelet count fell ~50% (Figure 2). After a rapid decline in his platelet count, a diagnosis of HIT was considered, and the Lovenox and heparin were discontinued. The patient was subsequently placed on Argatroban after confirming a positive HIT antibody blood test (ELISA immunoassay). As his condition continued to decline and ~24

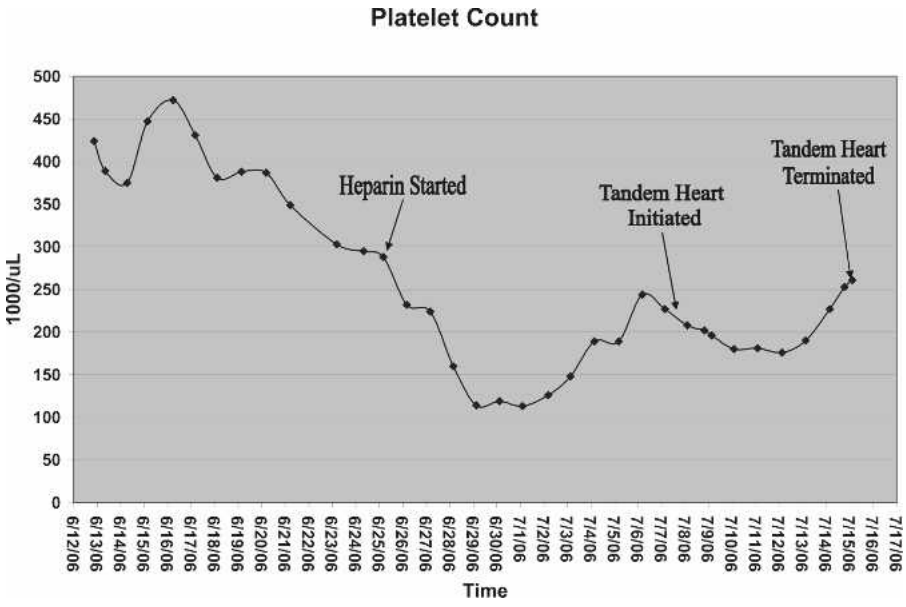

Figure 2. Platelet count relative to time course of events.

days into admission, a right heart catheterization and an additional TEE were performed, which showed pulmonary hypertension, moderate mitral valve regurgitation, and an EF of 5%. Because of signs of multiorgan system failure secondary to low cardiac output syndrome, the decision was made to insert a TandemHeart left ventricular assist device as a bridge to transplantation.

The patient's clinical laboratory values and physical attributes the afternoon of the TandemHeart insertion were as follows: Hgb, 10.7 g/dL; HCT, 36.0%; BUN, 21 mg/dL; Creat, 1.2 mg/dL; Plt, 227 thou/μL; aPTT, 65.1 seconds; prothrombin time (PT), 30.4 seconds; international normalized ratio (INR), 2.9; glucose, 137 mg/dL; Na^+, 137 mEq/L; K^+, 3.8 mEq/L; Cl^-, 96 mEq/L; height, 180 cm; weight, 104.9 kg; BSA, 2.29 m^2.

CASE MANAGEMENT

Before the patient's arrival, the hybrid surgical/catheterization suite was purged of all heparin and/or heparin impregnated lines. During the routine "Time Out," discussion revolved around the patient's HIT status and the plan to use Argatroban. The TandemHeart circuit was set up and prepared according to the manufacturer's recommendations with the exception of heparin. In place of 90,000 USP heparin, 7000 μg of Argatroban was used in a 1-L normal saline bag to provide local anticoagulation for the lubricating film of the blood pump apparatus.

On arrival, the patient was prepared and draped in a routine sterile fashion. After percutaneous puncture of the right femoral vein, a standard Brockenbrough catheter was used to gain access into the left atrium through the fossa ovalis. The position of the Brockenbrough catheter within the left atrium was confirmed by manual dye injection. The Brockenbrough catheter was exchanged for a stiff guide wire for introduction of a two-stage dilator followed by insertion of the 21-F transseptal inflow cannula. Preceding cannulation, the patient was administered a 3500-μg bolus dose of Argatroban to achieve an ACT of ~400 seconds (Figure 3). The ACT was elevated per manufacturer's recommendations for cannula insertion. TEE was used to confirm placement of the 21-F transseptal cannula before suturing to the skin. Positioning of the 21-F transseptal cannula is critical because deoxygenated blood will be circulated if allowed to migrate back into the right atrium.

A 17-F Biomedicus arterial perfusion cannula (Medtronic, Minneapolis, MN) was percutaneously inserted in the left femoral artery and advanced into the lower abdominal aorta. After carefully de-airing, both cannulae were attached to the pump using standard techniques. Once the entire circuit was completely free of air, the arterial clamp was removed, and the pump was initiated at 3000 rpm and gradually increased to ~5000 rpm. A pump speed of 5000 rpm was enough to provide ~4.0 L/min of flow and to maintain slight ejection of the left ventricle. Some left ventricular ejection is advisable to help avoid hemostasis and thrombus formation.

After insertion of the TandemHeart, the patient was transferred to the Cardiovascular Intensive Care Unit (CVICU). While in the CVICU, the Argatroban infusion rate was titrated to maintain an aPTT at or near 2.5 times normal per the manufacturer's recommendations (Figure 4). At this level of anticoagulation, the patient developed no systemic thromboembolization or bleeding complications. The patient was maintained on the TandemHeart

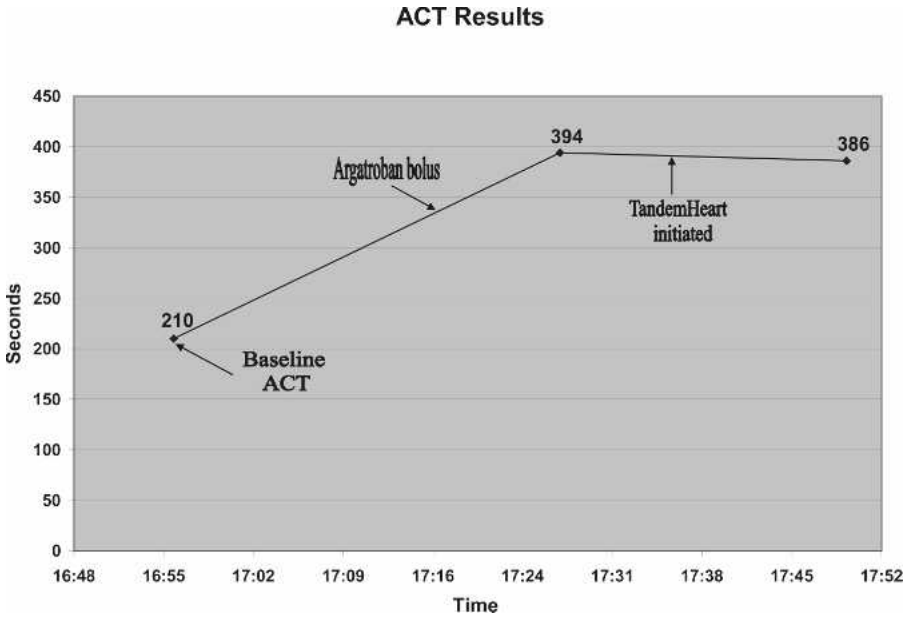

Figure 3. Argatroban ACT results over time during TandemHeart insertion.

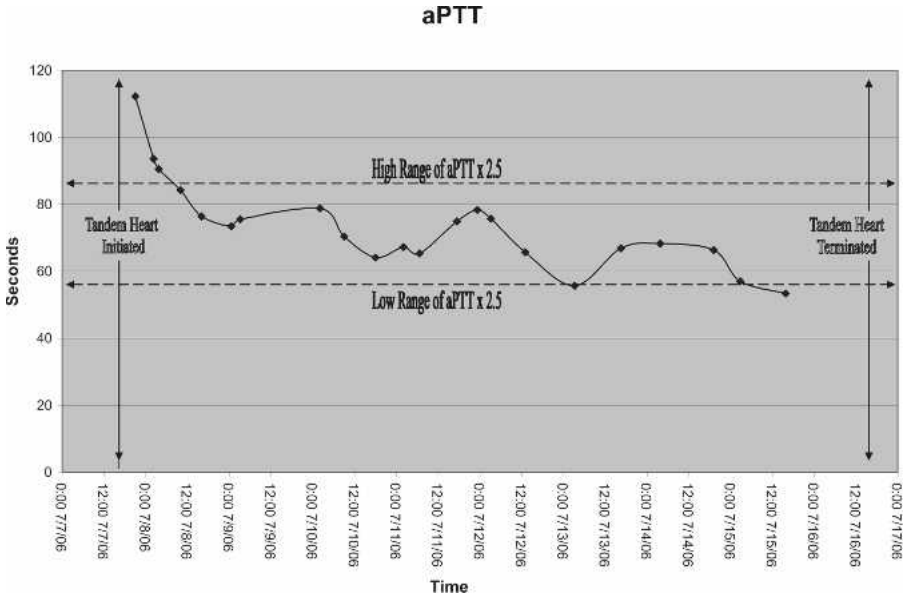

Figure 4. Argatroban aPTT results over time showing optimal therapeutic range from 55 to 85 seconds.

for 9 days while a suitable donor heart was aggressively pursued. Because multiple positive HIT assays were confirmed throughout the course of VAD support, Argatroban was used for anticoagulation during conventional bypass and orthotopic heart transplantation.

DISCUSSION

The TandemHeart is a simplistic centrifugal pump system with extensive back-up and fault management features for safe and user-friendly operation. It is designed to decrease ventricular wall tension, myocardial oxygen consumption, and atrial filling pressure while increasing cardiac output. It has been used to treat acute cardiogenic shock caused by myocardial infarction, post-cardiotomy support, high-risk catheter-based interventions, and as a bridge to definitive therapy (15–17). The most unique aspect of the TandemHeart is that it can be inserted percutaneously by either a cardiovascular surgeon or cardiologist. Although there are many ventricular assist devices available today, the TandemHeart is an excellent option from a cost, safety, and ease-of-use perspective. In addition, it has proved suitable for short-term left ventricular support provided there is reasonable right ventricular function. This made the TandemHeart seem to be the most suitable device given the circumstances.

With the frequency of which heparin is used for medical therapies and/or procedures, it is likely that cardiac teams will encounter more HIT type II patients. HIT type II is a condition that can create serious complexities for patients needing extracorporeal life support, because of anticoagulation requirements. Argatraban, a viable alternative to heparin, has been shown to be safe and efficacious. It was not only beneficial in speeding platelet recovery and count, but also showed excellent anticoagulation properties in preventing systemic thromboembolization. Both aPTT and ACT tests were useful for managing and monitoring appropriate therapeutic levels. Furthermore, it may be most useful in patient with kidney dysfunction because it undergoes minimal renal clearance unlike other direct thrombin inhibitors.

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