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PERSPECTIVE

Algorithm for the diagnosis and management of suspected pump thrombus

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Pump thrombosis is a dreaded complication of long-term implantable ventricular assist devices. No guidance exists regarding the diagnosis and management of this entity despite its significant morbidity. After considerable thought and deliberation, a group of leading investigators in the field of mechanical support propose an algorithm for the diagnosis and management of this vexing entity based on clinical symptoms and serologic and imaging studies.

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Continuous-flow pumps (CFPs) have emerged as the preferred mechanical circulatory support (MCS) modality for the long-term support of patients with advanced heart failure. Compared with previous pulsatile-flow technologies, the benefits of this mode of support include easier implantation, reduced infectious and bleeding complications, noiseless operation, and markedly improved reliability.[1] However, new challenges have arisen with the extended use of CFPs, including gastrointestinal bleeding, de novo aortic insufficiency, and pump thrombus. The latter is of particular interest because of the lack of guidance on the diagnosis and management of this entity as well as the high morbidity and mortality associated with its development.

Pump thrombosis denotes the development of clot within the flow path of any or all of the components that constitute the pump, including the titanium inflow cannula, the outflow graft, and the pump housing that contains the rotor. Thrombus can originate in the pump or travel from the left atrium or left ventricle (LV), or from right-sided cardiac chambers through a septal defect, and lodge in any or all of the pump components.

Pump-, patient- and management-related factors can contribute to the risk of pump thrombosis (Table 1). The former include atrial fibrillation, pre-existent LV thrombus not adequately removed at implant or de novo intracardiac thrombus, presence of mechanical valvular prostheses, sepsis, sub-therapeutic international normalized ratio (INR), inadequate anti-platelet therapy, and pro-coagulant states. Careful evaluation for the presence of these factors is mandatory because many can be potentially mitigated by interventions at the time of surgery, including ligation of the left atrial appendage in patients with atrial fibrillation, thorough removal of LV apical trabeculae and thrombus, and felt coverage of an aortic mechanical prosthesis if not exchanged for a biologic valve.

Pump factors that may predispose to pump thrombus include inflow cannula malposition, outflow graft kink or compression, and sustained low ventricular assist device (VAD) flows from such factors as low pump speeds or right-sided heart

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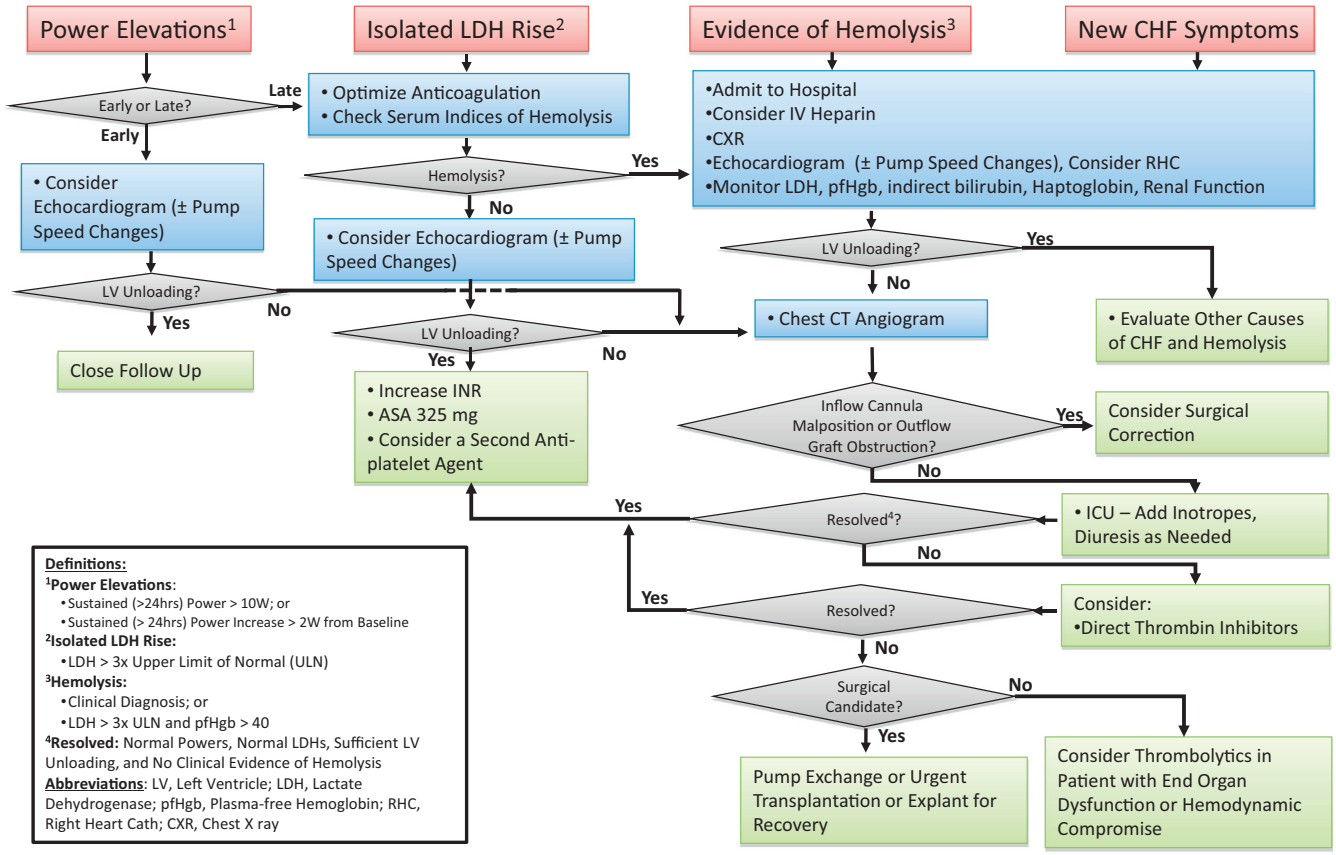

Figure 1 Algorithm for the diagnosis and management of pump thrombus.

dysfunction. Moreover, rotary pumps can generate local areas of heat at the inflow and outflow bearings that, without adequate cooling from surrounding blood flow, can make them pro-thrombotic. Constant washing of the pump by blood at adequate flow rates dissipates the generated heat and reduces areas of stagnation and hence is a critical factor in maintaining adequate hemocompatibility.

The incidence of pump thrombus reported in the initial and extended clinical trials of the 2 available continuous-flow technologies ranges from 0.014 to 0.03 events per patient-year.[1–5] More recently however, published and anecdotal reports,[6–13] as well as discussion within the MCS community, all suggest that pump thrombus may be a growing and vexing problem. Because of the small number of patients reported and the heterogeneity of devices and treatment modalities used to diagnose and treat pump thrombus, firm recommendations on the diagnosis and management cannot be formalized. Furthermore, whether the problem of pump thrombus is actually increasing or simply related to a rapidly growing number of patients being currently supported by CFPs remains unknown.

Key to the diagnosis of pump thrombus is the use of routine laboratory (to diagnose hemolysis) and imaging modalities. Lactate dehydrogenase (LDH) levels greater than 3 times the upper limit of normal and/or plasma free hemoglobin (pfHb) greater than 40 mg/dL should raise concern for possible thrombus. Plain chest X-ray imaging may reveal malposition of the inflow cannula, a malaligned outflow graft protector, or pulmonary vascular congestion suggestive of heart failure. An echocardiogram can document signs of sub-optimal LV unloading, including a dilated ventricle, severe mitral regurgitation, and frequent aortic valve opening and/or elevated right ventricular systolic pressure. Serial recording of LV end-diastolic diameter with increasing VAD speeds (so-called ramp study) may diagnose pump thrombus or other obstructions to blood flow within the rotary pump and cannula system.[14] Finally, chest computed tomography angiography can suggest a possible mechanical etiology for a suspected pump thrombus, including malpositioned inflow or kinked outflow graft, or can definitively diagnose pump thrombus by lack of contrast in outflow graft.

Right-heart catheterization can confirm elevated right-sided pressures, whereas left-sided heart catheterization with a pigtail catheter in the LV can be used to observe the presence or absence of contrast flow across the pump and into outflow graft. In the absence of inflow cannula or outflow graft abnormalities, failure to unload the LV with increased pump speeds is highly suggestive of pump thrombus within the rotating mechanism, particularly in the presence of elevated indices of hemolysis.

Management algorithm

Eager to address pump thrombus, a multidisciplinary group of physicians have met regularly to devise an algorithm for the diagnosis and management of pump thrombus. The proposed algorithm, shown in Figure 1, suggests a stepwise approach to guide diagnosis and treatment according to clinical presentation.

Table 1 Factors That May Increase Propensity to Pump Thrombus Formation in Continuous-Flow Pumps

Pump-related
1. Intrinsic heat generated by rotational movement of pump
2. Blood-contacting surface interactions
3. Shear stress-induced platelet activation
4. Regions of flow field stasis
5. Thrombus formation at cannulation site
6. Outflow graft impingement by outflow protector (now corrected)
7. Inflow cannula migration and malposition

Patient-related
1. Atrial fibrillation
2. Pre-existent atrial or ventricular thrombus
3. Presence of left sided mechanical prosthesis
4. Infection or sepsis
5. Non-compliance
6. Low flow due to:
   a. Cannula positional change over time (weight gain or loss, bending torso)
   b. Right-sided heart failure
   c. Hypovolemia
   d. Hypertension
7. Hypercoagulable state:
   a. Protein C deficiency
   b. Protein S deficiency
   c. Anti-thrombin deficiency
   d. Plasminogen deficiency
   e. Lupus anti-coagulant
   f. Heparin-induced thrombocytopenia
   g. Activated protein C deficiency
   h. Factor V Leiden
   i. Prothrombin G20210A mutation
   j. Malignancy

Management-related
1. Sub-therapeutic international normalized ratio
2. Absence of anti-platelet therapy
3. Inflow cannula malposition at implant
4. Infection management
5. Low flow due to:
   a. Low speed setting to manage gastrointestinal bleeding and/or aortic insufficiency
   b. Sub-optimal hypertension management

Patients may present with (1) asymptomatic sustained power elevations; (2) isolated elevation of LDH or pfHb; (3) clinical signs of hemolysis (hemoglobinuria with tea-colored urine); and/or (4) symptoms of heart failure (with or without hemodynamic abnormalities including shock). Asymptomatic sustained power elevations (defined as power $\geq$10 watts, or power $>$2 watts above baseline for $>$24 hours) can occur frequently in the early post-operative period and are of uncertain significance. A bedside echocardiogram with a ramp study to confirm LV unloading with increased speed can be considered. Serum LDH should be obtained but may be elevated due to concomitant blood transfusions in the peri-operative setting. Early postoperative institution of aspirin and warfarin therapy, with heparin bridging to an INR of 2.0 $\pm$ 0.5, is recommended.

Patients presenting with isolated LDH elevations or de novo power elevations that appear *late* in the clinical course should be promptly evaluated for frank hemolysis. Presence of the latter mandates hospital admission and further diagnostic testing as well as consideration of institution of intravenous heparin. If an echocardiogram and ramp study suggest appropriate LV unloading, other causes for heart failure symptoms and/or hemolysis must be sought. However, if adequate LV unloading is not documented, a chest computed tomography angiogram to evaluate the position of the inflow cannula and outflow graft and document unimpeded flow of contrast from the LV cavity through the outflow and into the ascending aorta should be obtained. If inflow cannula malposition or outflow graft kink are diagnosed, surgical correction should ensue.

In the absence of pump inflow or outflow abnormalities, the inability to unload the LV on a ramp study must be attributed to pump thrombus, and the patient should be transferred to an intensive care unit for close monitoring and initiation of intravenous heparin and inotropic/diuretic therapy as needed depending on heart failure symptoms. Resolution of findings (power spikes, hemolysis, and/or heart failure) can be followed by up-titration of anti-thrombotic therapy with acetylsalicylic acid (325 mg) and Coumadin to an INR target of 2.5 $\pm$ 0.5. Consideration can be given to the addition of a second anti-platelet agent (clopidogrel, dipyridamole). Up-titration of antithrombotic therapy must be guided by the patient's coexistent comorbidities and potential risks of bleeding diathesis.

Persistent hemolysis, power spikes, and/or heart failure symptoms may be addressed with more aggressive anti-thrombotic therapy with direct thrombin inhibitors, although the only evidence of the effectiveness of these interventions at this time is anecdotal. If hemolysis persists despite aggressive anti-thrombotic therapy, consideration should be given to pump exchange if the patient is deemed a surgical candidate. Excellent results have been attained by a limited upper abdominal approach with peripheral cardiopulmonary bypass for isolated pump exchange.[15]

Urgent listing for transplantation can be pursued if the estimated waiting time is no more than a few days and heart failure symptoms can be managed readily. In the presence of low output state and progressive heart failure, urgent device exchange is mandatory, although a high morbidity and significant 30-day mortality can be expected. If the patient is not deemed to be a surgical candidate, systemic thrombolytic therapy may be attempted in the presence of end-organ dysfunction or hemodynamic compromise. Prognosis under these circumstances is poor.

Finally, patients presenting with obvious pump thrombosis with red alarms, pump stoppage, and in shock unresponsive to battery and controller exchanges require emergent pump exchange without further diagnostic studies.

Recent anecdotal institutional data (Frank Pagani, MD, Ulrich Jorde, MD, and Scott Silvestry, MD, personal communication, January 2013) suggest that serial sampling of LDH and pfHb levels may allow early recognition of potential pump thrombus.[16] These observations need to be validated in multicenter studies to determine if early diagnosis

could lead to interventions that could alter the natural history of early pump thrombus formation. Prospective evaluation for potential risk factors for the development of hemolysis and pump thrombus with particular attention of power spikes and patient- and pump-related factors is warranted.

Limitations

At the time of this writing, 2 continuous-flow LVADs have been approved in the United States. Most of the experience with this algorithm is based on the Heart Mate II (Thoratec, Pleasanton, CA) LVAD. Nevertheless, principles and lessons drawn from this may be applied to other rotary pumps in clinical use. Furthermore, there is a lack of objective data, such as from randomized clinical studies, to know if the therapeutic algorithm being proposed is effective. It is important to remember that this algorithm is based on the opinions and collective experience of experts in the field. As mentioned earlier, the adverse implications of thrombus are critical, such that we feel compelled to publish these recommendations as a starting platform to address this vexing problem.

Disclosure statement

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