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Orignal Article

Thrombus on the inflow cannula of the HeartWare HVAD: an update☆

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ABSTRACT

Background: The HeartWare HVAD (Medtronic, Minneapolis, MN) is a continuous-flow left ventricular assist device (LVAD) approved by the FDA in 2012 as a bridge to transplant in patients with end-stage left ventricular heart failure. The current inflow cannula has a smooth outer surface near the inflow edge and a sintered collar of titanium microspheres near the pump. A previous case series of HVAD patients bridged to transplant revealed thrombus on the outer surface of the inflow cannula in 8 of 8 patients, predominantly at the smooth-sintered interface, that was associated with a clinical stroke rate of 12.5%.
Design: Cases of HVAD devices removed at the time of heart transplant were identified in the surgical pathology database. The gross and microscopic findings were reviewed along with clinical data.
Results: A total of 22 patients with 24 HVAD implants diagnosed with dilated cardiomyopathy (13 patients), ischemic heart disease (4 patients), lymphocytic myocarditis (2 patients), hypertrophic cardiomyopathy (2 patients), and congenital valvular disease (1 patient) were included. Two patients received two HVADs to provide biventricular support. All patients received post-implantation anti-coagulation with an INR goal of 2 to 3. Gross pathologic examination revealed thrombi on the outer aspect of the HVAD inflow cannula in 23 of 24 devices (96%). The inflow cannula of the one device that did not develop thrombus was positioned such that the smooth-sintered interface was buried in the ventricular myocardium and not in contact with blood in the ventricular chamber. Complications during the period of device support included 9 thromboembolic events (41%) including 6 ischemic strokes (27%), 2 intracoronary thromboembolic events and 1 splenic infarct. Patients suffered strokes 4 to 174 days (mean 82) after HVAD placement and had thrombus on the inflow cannula ranging in size from 0.1–2.5 cm (axial), 0.4–4.5 cm (circumferential) and 0.1–0.5 cm (thickness). Histologic evaluation revealed bland, partially organized thrombi without evidence of infection. Other complications included driveline infections (9%), non-driveline related bacteremia (9%) and hemorrhage (5%).
Conclusions: We report here an extension of our original study to a total of 22 patients with 24 HVAD implants who were all successfully bridged to transplant. We validate the very high prevalence of thrombus around the HVAD inflow cannula, associated with a clinical thromboembolic event in over a third of the patients, the majority of which were strokes. The nidus for thrombus formation appears to be the smooth-sintered interface of the HVAD inflow cannula.

1. Introduction

The use of mechanical circulatory support devices to successfully bridge heart failure patients to transplant has exponentially risen during the last decade, while heart transplant cases have remained for the most part constant at about 2500 per year in the United States [1]. Recent data demonstrate lower complication rates and improved outcomes over this time, especially with newer continuous flow left ventricular assist devices (LVADs) as compared to the first generation pulsatile devices [2]. In 2012, the U.S. Food and Drug Administration approved the HeartWare Ventricular Assist Device (HVAD, Medtronic, Inc., Minneapolis, MN) for patients with refractory left ventricular failure patients awaiting heart transplant. To date, over 10,000 HVADs have been implanted worldwide.

The HVAD was the first implantable centrifugal flow device in the US, with important design differences from commercially available axial flow devices [3]. The pump is smaller and resides directly on the epicardial surface of the left ventricle, with the inflow cannula residing

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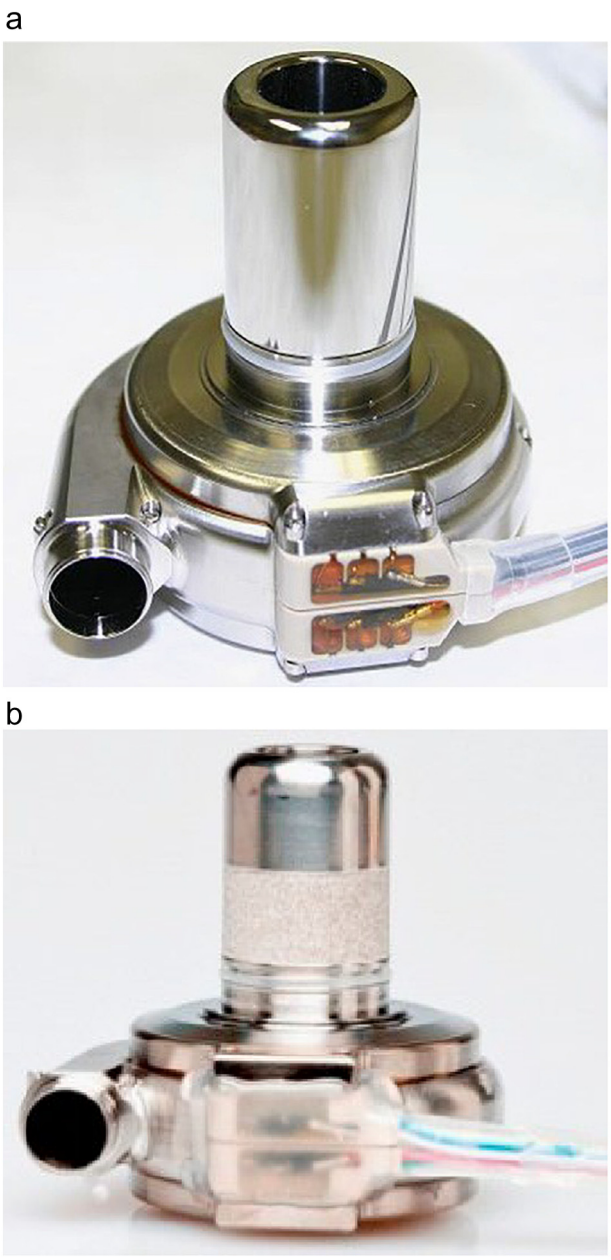

Fig. 1. A, The original HVAD inflow cannula was covered by a smooth, polished titanium surface. B, The modified HVAD inflow cannula has a collar of sintered titanium microspheres covering the half of the cannula nearest the pump with the remainder of the cannula the original smooth surface. *Images from Najjar* et al., *J Heart Lung Transplant 2014.*

within the left ventricular cavity; the driveline is also thinner. The rotor design produces continuous, centrifugal flow with a magnetically levitated impeller rather than the axial flow system of the Thoratec HeartMate II, for example, which requires inflow and outflow bearings to support and align the impeller. The smaller pump size and driveline, intrathoracic positioning and flow characteristics of the HVAD were thought to be advantageous in reducing common device complications such as infection, thrombosis and bleeding. The HVAD ADVANCE trial demonstrated non-inferiority (91% patient survival at 6 months) to other commercially available devices in a bridge to transplant setting [4–6]. In addition, a recent study of 1051 HVAD patients (mean support time 314 days) who were successfully bridged to transplant showed no post-transplant survival differences compared to patients bridged with the HeartMate II [7].

The original HVAD inflow cannula had a smooth, polished titanium outer surface, which raised concerns about the increased risk of cerebrovascular accidents secondary to device-related thromboemboli [8]. Examination of the polished smooth surface showed failure of endothelialization and tissue ingrowth, resulting in largely unorganized thrombus on the inflow cannula. In rare cases, thrombus growth and accumulation led to complete obstruction of the inflow cannula, requiring device exchange. Preliminary clinical trials data reported an ischemic stroke rate, presumably from device-related thromboemboli, in 8% of patients. Therefore in 2011, a change in the HVAD design was implemented in an attempt to promote non-thrombotic passivating tissue overgrowth on the outer surface of HVAD inflow cannula; the smooth, polished titanium surface was replaced with one incorporating a collar of sintered titanium microspheres (9, Fig. 1).

In the first formal pathologic evaluation of HVADs following implementation of the inflow cannula design change, our group reported the presence of thrombus in the outer aspect of the HVAD inflow cannula in 100% of the explanted devices from 8 patients who were

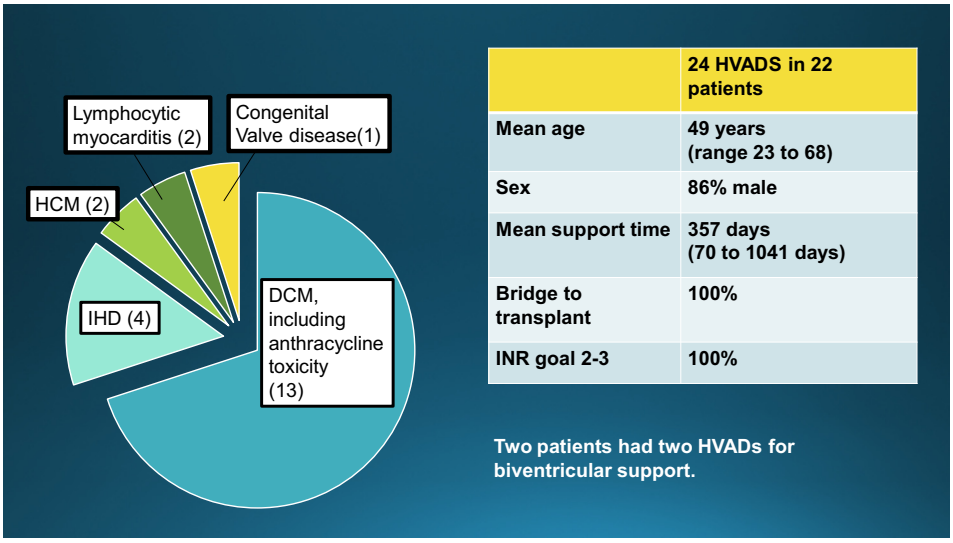

Fig. 2. Demographics and clinical parameters for HVAD patients.

successfully bridged to transplant [10]. These thrombi were associated with embolic events in 3 patients (38%), including a stroke in 1 patient (12.5%). In the present study, we report an extension of this original study to a total of 22 patients with 24 HVAD implants over a three-year period; the study confirms the very high prevalence of cannula-associated thrombus in the explanted devices.

2. Methods

This study was approved by the institutional review board of the Brigham and Women's Hospital (BWH). Using the surgical pathology database, all cases of HVADs removed at the time of heart transplant at BWH from December 2013 to May 2017 were identified. A retrospective review of the gross and microscopic findings of explanted HVADs, along with clinical data and adverse events was undertaken. The clinical data collected included patient demographics, indication for HVAD, device support time, and major complications.

3. Results

A total of 22 patients (19 men and 3 women, mean age 49, range 23 to 68 years) with 24 HVAD implants (mean support time 357 days, range 71 to 1041 days) were evaluated; the details of the first 8 of these have been previously reported [9]. The most frequent indication for HVAD implantation was dilated cardiomyopathy, which included chemotherapy-induced cardiotoxicity patients (Fig. 2). Two patients had two concurrent HVADs implanted for biventricular support. All 22 patients were successfully bridged to transplant.

Most of the HVADs used as LVADs had the inflow cannula placed in the left ventricular apex (19/22) with the remainder (3/22) placed in an inferior/posterior (diaphragmatic) position (Fig. 3a-b). The HVADs used as RVADs were placed in the right atrium (1/2) or right ventricle (1/2). Gross pathologic examination revealed unorganized thrombus on the outer aspect of the HVAD inflow cannula (thrombus size 0.1–2.5 cm (axial), 0.4–4.5 cm (circumferential) and 0.1–0.5 cm (thickness)) in 23 of 24 devices (96%). The thrombi were centered on the junction between the polished and sintered interface of the inflow cannula (Fig. 3c-d) and generally extended above and/or below the interface (Fig. 3e-f). The inflow cannula of the one device that did not develop thrombus was positioned such that the polished-sintered interface was buried in the ventricular myocardium and not in contact with blood in the ventricular chamber (Fig. 4). The gross examinations of the other portions of the HVADs were unremarkable, without evidence of thrombus within the outflow graft or pump, or mechanical component damage. No additional thrombi were seen elsewhere in the explanted hearts.

All patients received post-implantation anti-coagulation with an INR goal of 2 to 3, and were monitored by a dedicated anticoagulation service. Complications during the period of device support included 9 thromboembolic events (41%) including 6 strokes (27%). Patients suffered strokes 4 to 174 days (mean 82) after HVAD implantation. The distribution of strokes was variable in the brain, and none of these patients had a previous history of stroke or transient ischemic attack prior to HVAD implantation. The other three embolic complications included two intracoronary thromboemboli and a splenic thromboembolic infarct. Additional complications included driveline infections (9%), non-driveline related bacteremia (9%) and hemorrhage (5%).

Histological evaluation of the HVAD inflow cannula thrombi revealed bland, laminated, largely unorganized thrombus (Fig. 5), and no evidence of infection was identified grossly or microscopically. Histological evaluation of the two [2] cases of clinical intracoronary thromboemboli demonstrated multifocal healing infarcts with associated organizing intravascular thromboemboli dating to the time after HVAD implantation. The indication for HVAD implantation was dilated cardiomyopathy in these patients, and there was no evidence of coronary artery disease upon pathologic examination of the heart. Two [2] additional cases histologically demonstrated patchy subacute myocardial infarctions that would date to after the time of HVAD implantation in patients with ischemic heart disease; while these were suggestive of intracoronary thromboemboli, they were not felt to be definitive enough to adjudicate to the pump and were not considered as thromboembolic events in our study.

Clinical imaging after HVAD implantation (chest x-rays, computed tomography scans, and echocardiography studies) and post-explant pathologic evaluation were reviewed to assess the position of the cannula relative to the cardiac chambers and to assess for other intracardiac thrombi. With the exception of one inflow cannula that showed sub-optimal positioning with a horizontal lie directed towards the posterior wall, the remaining patients demonstrated good positioning. Of note, three cases were specifically positioned with the pump residing on the posterior/diaphragmatic aspect of the left ventricle, with the inflow cannula directed more anteriorly. Although thrombus was present on the inflow cannula of all three of these cases, these patients did not suffer stroke or any other embolic complication. No additional intracardiac thrombi were present on clinical imaging studies. Carotid ultrasonography was not performed on any of the patients.

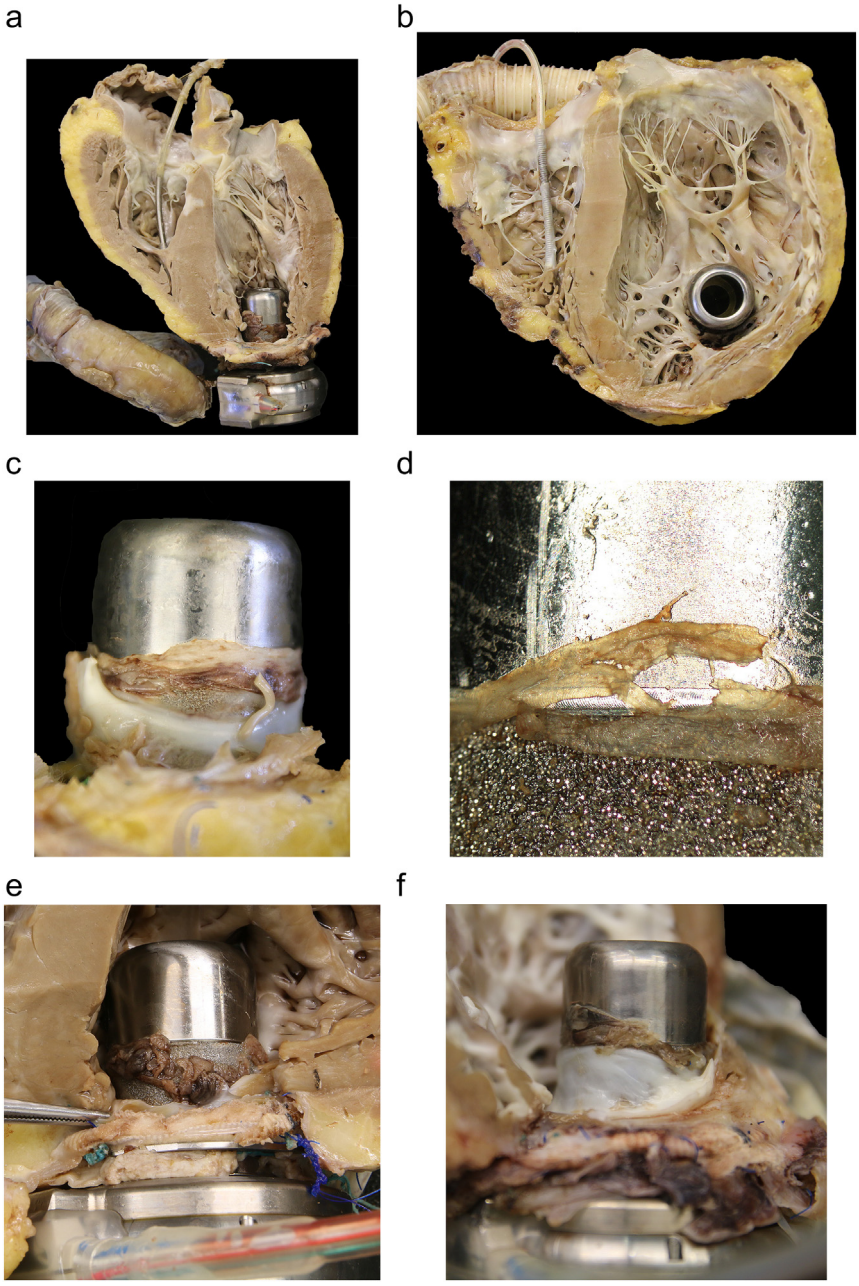

Fig. 3. Gross evaluation of HVAD devices. A, HVAD placed in the left ventricular apical position. Thrombus can be seen on the cannula. B, HVAD placed in the diaphragmatic position. Thrombus can be seen on the aspect of the cannula nearest the apex. C. Thrombus present at the junction of the smooth and sintered portions of the cannula with pannus on the sintered portion. D. Close-up view of smooth-sintered interface with loosely adherent thrombus. E. Thrombus at the smooth-sintered interface extending onto the sintered portion of the cannula. F. Thrombus at the smooth-sintered interface extending onto the smooth portion of the cannula.

4. Discussion

We report here an extension of our initial pathologic case series to include a total of 24 HVADs explanted at time of heart transplant. Our results validate the very high prevalence of thrombus around the HVAD inflow cannula. The nidus for thrombus formation appears to be the smooth-sintered interface of the HVAD inflow cannula, regardless of positioning axis. This gross finding was associated with a clinical thromboembolic event in almost half the patients, the majority of which were ischemic strokes (6 of 9, 27%). The stroke rate was not significantly different between men and women, and none of our patients suffered complications of a hemorrhagic stroke.

A recent study (ENDURANCE) comparing the HVAD to the Thoratec HeartMate II showed non-inferiority for the HeartWare HVAD overall for destination therapy, but reported a significantly increased stroke rate of 30% in the HVAD cohort [11]. Although the stroke rate was comparable to our study, half of the strokes were reported as hemorrhagic. It is not entirely clear from imaging studies whether the reported hemorrhagic strokes evolved from an ischemic/thromboembolic etiology in these patients who were chronically anticoagulated. Notably, the patients in our study were relatively healthier because they received devices intended as bridge to transplant, and did not have a previous neurological history, compared to the ENDURANCE destination therapy patients, 19% of whom in the HVAD arm had already suffered a stroke or transient ischemic attack. Other studies of patients who have received HVADs report ischemic stroke rates ranging from 7% to 29% (Table 1). The current work, combined with our previous study [10] are the only studies to provide confirmation of device-related thrombus through gross evaluation of HVAD explants. We suspect that, given the low incidence of reported HVAD in-pump thrombosis, the etiology of the

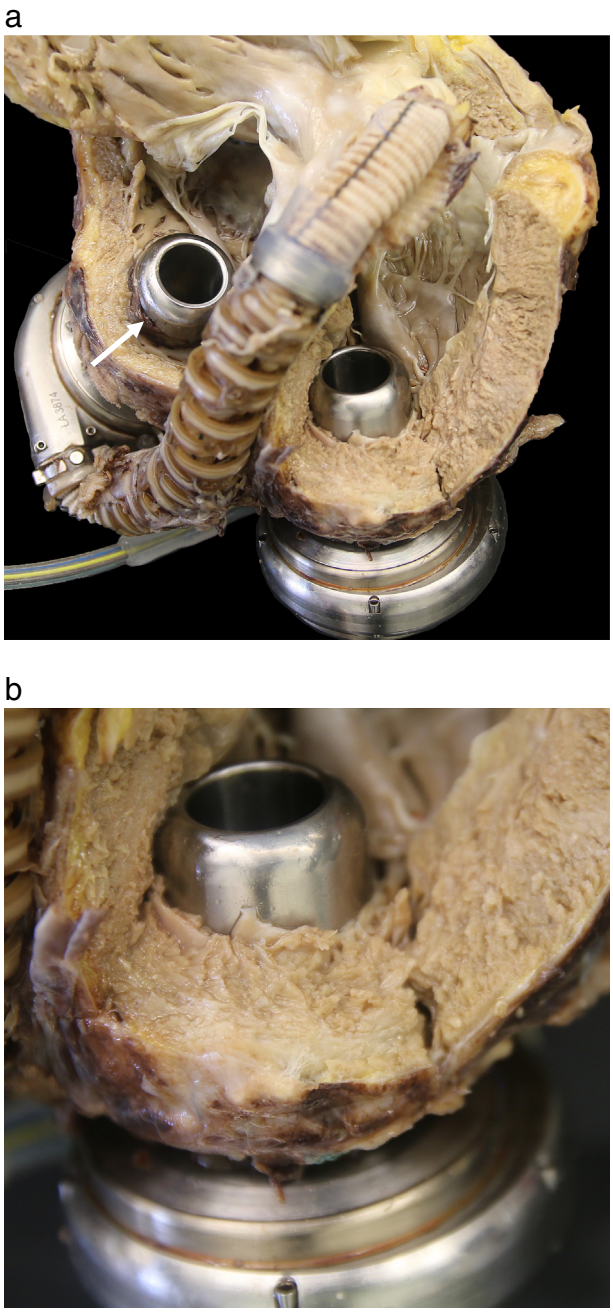

Fig. 4. A, The inflow cannula of the one device that did not develop thrombus was in the left ventricle of a patient with biventricular support. There is thrombus on the surface of the right ventricular inflow cannula (arrow). B, The left ventricular cannula was positioned such that the smooth-sintered interface was buried in the left ventricular myocardium and did not contain thrombus.

strokes in our series is embolization of the thrombus on the outer aspect of the inflow cannula, as there was no pathologic evidence (on explant) or clinical/imaging evidence to suggest another source.

With the goal of reducing thrombosis, the principle design change in the HVAD inflow cannula design replaced the smooth titanium surface with a segment of sintered titanium microspheres to promote tissue ingrowth. However, introduction of this feature produced a discontinuity at the smooth-sintered interface that would be in contact with the blood in the ventricular chamber. Jamiolkoswki et al. [12] specifically studied the effect of geometric irregularities in titanium alloys, as might be seen at the smooth-sintered interface, by flowing reconstituted fresh human blood over defined crevices (approximately 50 to150 μm in width). The greatest levels of platelet deposition occurred in the distal corners of small crevices (between 50 and 90 μm), with computational simulations demonstrating that areas of stagnation and circulation increased as the ratio of the width to depth of the crevices decreased. Our finding that thrombus involves, and in some cases is confined to, the junction between the polished and sintered interface of the inflow cannula suggests that changes in biomaterial properties, particularly the step from the sintered to non-sintered areas and potentially the porosity of the roughened surface, in the setting of altered flow characteristics at the ventricular apex, significantly contribute to thrombus formation.

Virchow's triad — blood contacting surface, blood flow characteristics, and intrinsic coagulability — are frequently used as a framework for understanding thrombus formation in medical devices. The HVAD inflow cannula acts as a thrombogenic surface by virtue of not being lined by healthy endothelial cells, and because the protrusion of the inflow cavity into the ventricular cavity alters the pattern of normal blood

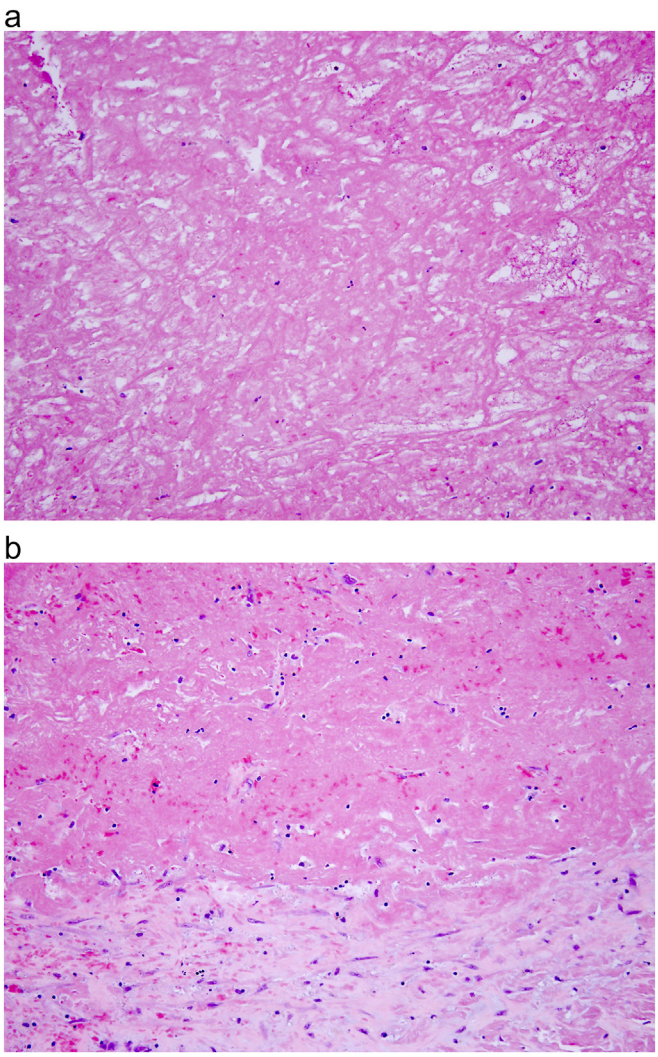

Fig. 5. A, Histologic image of bland, laminated unorganized thrombus from the outer aspect of the HVAD inflow cannula (H&E stain, 200× magnification). B, Histologic image of thrombus with area of organization at bottom of image (H&E stain, 200× magnification).

flow. We previously proposed [10] that a combination of factors likely contributes to thrombus formation including stasis between the inflow cannula tip and myocardium, changes in mechanical compliance in the ventricular wall due to the rigid epicardial pump, changes in flow characteristics along the cannula surface due to the discontinuity gap between the sintered and non-sintered material surfaces, heat dissipation from the pump through the cannula, and vibratory mechanical forces transferred to the cannula from the pump; many of these have been investigated independently for several types of inflow cannulas [13–15]. Patient-specific factors can lead to hypercoagulability by modifying the coagulation cascade and/or platelet function, including genetic factors (e.g., Factor V Leiden mutation, prothrombin G20210A mutation) and acquired conditions (e.g., antiphospholipid antibody syndrome, malignancy). However, our data seem to indicate that the only predisposing factor to HVAD cannula thrombosis is having a device with an exposed smooth-sintered interface.

Table 1
Previous studies comparing stroke rates in the Heartware HVAD device

Study	N	Ischemic/thromboembolic stroke	Hemorrhagic stroke
Strueber et al., 2011	50	0	6%
Ozbaran et al., 2012	10	0	10%
Lalonde et al., 2013	13	15%	23%
Nishi et al., 2014	10	0	10%
Peng et al., 2014	7	29%	14%
Teuteberg et al., 2014	382	7%	8%
Rogers et al., 2017	296	15%	15%
Glass et al., this study	22	27%	0

In summary, we report here an extension of the original study to a total of 22 patients with 24 HVAD implants who were all successfully bridged to transplant. We validate the very high prevalence of thrombus around the HeartWare HVAD inflow cannula associated with a clinical thromboembolic event of 41%, the majority of which were strokes. The nidus for thrombus formation appears to be the smooth-sintered interface, and the findings should be informative for future design modification.

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