Concerning thromboembolism associated with left ventricular assist devices

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1. Introduction

Cardiac surgeons are obligated to find solutions for patients with end-stage cardiac failure. Cardiac transplantation has provided the most successful option thus far but demand far exceeds the supply of donor hearts and demand is projected to increase while supply will level off, or perhaps decline [1]. Because of this shortfall in donor hearts there has been continued effort and emphasis on development of alternatives to cardiac transplantation [2]. Recently it was estimated that by the year 2010 between 35,000 and 70,000 patients in the USA alone would be candidates for permanent cardiac replacement or support [3].

2. Early experience

Early versions of blood pumping devices, most containing silicone rubber blood sacs, experienced major problems with thrombosis. [4] Dacron-flocked surfaces were promulgated as a solution, the theory being that the formation of a ‘pseudo-intimal’ lining on these devices would be non-thrombogenic [5]. Early efforts with textured surfaces resulted in impaired diaphragm flexibility, hemolysis, and embolization [6], but these problems seem to have been resolved in the more modern devices. A major breakthrough in materials was made with the introduction of segmental polyurethanes in 1967. That led to adoption of this ‘smooth’ material for almost all devices [7]. Problems related to blood sac calcification, soft tissue pannus at the atrial cuff, and major thrombosis problems were gradually resolved with the introduction of low profile valves, and a host of iterative improvements in geometry, design, control systems, power sources, and driving systems. We are now to the point where calves implanted with these devices, the most common animal model used, can routinely survive for up to a year without demonstrable adverse effect [8].

A 1992 report on the clinical use of total artificial hearts from 1969 to 1991 listed 11 different models and a total of 230 devices implanted in 226 patients at 39 different centers [9]. The devices were used from <24 h to 603 days, mean 26 days. Thirty day survival in these patients was 58%. Infection occurred in 36% of the patients. Clinically diagnosable thromboembolic events occurred in 9%. Death most often resulted from sepsis (33%), multigang failure (cause not reported) (32%), pulmonary failure (12%), and neurological events (9%) [9]. It is not clear from this report, if the 9% thromboembolic and 9% neurological events are the same events.

3. Thromboembolism

Thromboembolism and infection are the most frequently cited major complication associated with these blood pumping devices [10–20]. The Thermo Cardio Systems Heart Mate 1000 IP left ventricular assist device (LVAD) (a textured-surface device) was used in 57 patients in 11 different clinical centers and resulted in thromboembolic cerebrovascular complications in only two patients [21]. Another series using this same device reported results on 223 patients with only six suffering thromboembolic events [22]. A different group of investigators, using this same device, found minimal thromboembolic complications despite the absence of anticoagulation. However they found evidence of significant thrombin generation and fibrinolysis. They concluded their patients demonstrated activation of the coagulation cascade [23]. Transcranial Doppler monitoring was used in 14 patients who received the Heart Mate 1000 LVAD. Thirty-five studies were...
obtained, from fourteen patients, from the left middle cerebral artery, for a duration of 30 min per study. One patient who suffered a fatal stroke averaged 0.03/min high intensity transient signals (HITS). The 13 asymptomatic patients registered an average of 0.016 HITS/min [11]. That would translate to about 0.8 HITS per day, on average. Another study using this technique but using different blood pumping devices recorded ten ischemic cerebrovascular events and two peripheral thromboembolic events during multiple observation periods in six patients. HITS were found in 143 of 170 (84.1%) monitoring periods ranging from 30 min to 3 h [10].

Molecular biology techniques were used to study the pseudo-intima formed on 11 textured surface devices following explantation. No clinical thromboembolic events had been reported from these patients. The pseudo-intima was composed of patches of cellular tissue intermingled with areas of compact fibrinous material and islands of collagenous tissue containing fibroblast-like cells. Many of the latter cells contained microfilaments with dense bodies suggestive of myofibroblasts [18]. From what we know about initiation of the thrombosis cascade this is not a description of a non-thrombotic surface [24]. RNA hybridization analysis of this surface demonstrated that the colonizing cells actively expressed genes encoding fibronectin, actin, and types I and III collagen, all known activators of thrombosis [18].

The critical issue seems to be the definition of thromboembolism. In most patient studies the end-point seems to be clinical neurological, renal or hepatic signs of thromboembolic disease. Reports of definitive studies with significant numbers relating to platelet turn-over times, or related problems seems to be increasing. The mechanistic details of how these protein biofilms enhance or limit long term function of these devices needs careful and systematic study.

Animal studies show evidence of enhanced activation of the fibrinolytic system which could help explain the lack of clinical significance, i.e. shed microemboli are ‘neutralized’ by body defense mechanisms before causing permanent injury [17]. Platelet survival was measured with 111In-labeled autologous platelets in nine calves with TAHs and five with LVADs. Platelet survival was found to be significantly shortened compared to control animals [26]. Fibrinogen survival was measured with 131I-labeled homologous fibrinogen in six calves with TAHs and three with LVADs and was found to be normal when compared to controls [26]. Radioisotope labeled autologous platelets have been used to quantify platelet sequestration and organ microembolism in prosthetic valve implantation studies, but this technology has apparently not been used to evaluate these problems in blood pumping devices to date [27].

Recent advances in our understanding of host/materials interactions should lead to easier and more useful methods of evaluating blood pumping devices for potential problems. The antigen CD62, also called GMP-140 or PAD-GEM, is a glycoprotein exposed on the external surface of platelets after platelet activation. Using flow cytometry and immunohistochemical techniques CD62 has been used to quantify numbers of activated platelets in ventricular assist device patients [28]. Flow cytometry has also been used to demonstrate that macrophages are activated by exposure to foreign surfaces [29].

The role the white blood cell population plays in adverse responses to cardiovascular devices remains to be completely elucidated. We do know that both cellular and molecular responses are initiated when these devices are implanted. As a result of these responses protein biofilms are deposited on the foreign material surfaces. These protein biofilms include an increasingly long list of adhesion molecule proteins that have been shown to interact with white blood cells, particularly polymorphonuclear cells, but also with lymphocytes and platelets [30]. Protein biofilms may also provide hospitable sites for infectious agents to attach and grow as well as being sequestered from antimicrobial therapy. As the successful use of these devices increases the incidence of infection related problems seems to be increasing. The mechanistic details of how these protein biofilms enhance or limit long term function of these devices needs careful and systematic study.

References


