DOI: 10.15825/1995-1191-2020-4-83-88

THE PROBLEM OF BIOCOMPATIBILITY AND THROMBOGENICITY IN MECHANICAL CIRCULATORY ASSIST DEVICES

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Patients suffering from end-stage congestive heart failure are in the severe category of cardiac patients. For many decades, there has been active development of circulatory assist devices. However, despite significant progress made in this area, the use of such devices is associated with several dangerous complications, one of which is thrombosis. The problem of creating biocompatible materials still remains unresolved. Analyzing the mechanism and risk of this complication allows to determine the ways of solving this problem.

Keywords: heart failure, heart transplantation, circulatory support, thrombosis, mechanical circulatory support devices.

Over 50 years have passed since the first heart transplant surgery was performed by Christian Barnard and his team at Groote Schuur Hospital [1].

Unfortunately, acute shortage of donor organs was and still remains the "Achilles' heel" of this treatment method. For instance, due to organ shortage, the number of heart transplants performed in the United Kingdom (UK) and in many Western countries has dropped sharply over the past decades. Moreover, the waiting list continues to increase [2]. In the UK, of the estimated 750,000 heart transplant candidates, only around 0.02% undergo transplantation. Consequent to this mismatch between supply and demand, almost 10% of patients on the heart transplant waiting list continue to die every year [3]. According to the Canadian Institute for Health Information, over the past 10 years, the annual mortality rate of patients awaiting heart transplantation was 16% [4]. In the United States of America, despite 35,000–64,000 patients requiring heart transplants, only 2,200–2300 operations are performed per year [5]. In the Russian Federation, data for 2018 shows that there were 823 patients on the waiting list, but only 282 heart transplants were performed during the year [6].

To solve this problem, many mechanical devices capable of effectively and safely providing circulatory support have been developed over the past few decades [7].

In the vast majority of cases, existing devices do not actually replace the heart, but function as a ventricular assist device (LVAD), providing the proper minute volume of blood circulation. Perhaps the main purpose of using LVAD today is to serve as a "bridge to transplantation". The use of circulatory support devices in patients with extremely poor prognosis of life expectancy can significantly improve the quality of life and increase survival to heart transplantation. According to the REMATCH randomized trial published in 2001, the annual survival rate of patients who received first-generation LVADs was 52% versus 25% in the medical drug therapy group. At 24 months, the trend continued, with 23% survival in the LVAD group and 8% in the medical therapy group. Currently, second- and third-generation LVADS provide similar 1-year survival (approximately 90%) compared to cardiac transplantation [8].

According to other studies, almost 70% of patients receiving LVAD support survive the waiting period for the donor organ, and in the case of implantation of the latest generations of devices, this figure reaches 79% [9, 10].

Since organ shortage was the main problem that prompted the development of circulatory assist devices, the predicted period of operation was rather short. However, subsequent development of technologies and production of biocompatible materials has significantly improved the safety of device models. Over time, there appeared a separate group of patients in whom regression of clinical signs of circulatory insufficiency and, as a consequence, absence of indications for heart transplantation, was observed against the background of previously implanted LVAD. This fact contributed to the consideration of mechanical circulatory support as a means of "destination therapy". In addition, the emergence of new LVAD models has achieved long-term circulatory support. This has led to restoration of full pumping function of the heart with the possibility of subsequent explantation of the device. According to some researchers, this "bridge to recovery" strategy has been successfully implemented in 5–10% of adult patients [11, 12].

The key problems preventing LVAD from becoming a complete alternative to heart transplant procedure are the development of biocompatible materials and a reliable pumping unit mechanism.

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The idea of prosthetics for the pumping function of the heart naturally guided engineers towards simulating pulsatile blood flow, synchronized with the heart's own rhythm. So, in 1975 the first generation of the HeartMate system (Thratec Corporation) was created.

In principle, this pump was an elastic chamber that changed its volume through a special installation using the force of an injected gas, liquid, or an electromechanical method. At the inlet and outlet of this chamber, valves were installed to ensure unidirectional blood flow. Like a living heart, during the filling phase, blood entered the elastic chamber of the pump, after which, during the ejection phase, it was released into the patient's arterial system. The first devices were rather bulky, required synchronization with the heart's own rhythm, and were difficult to operate. However, in spite of the fact that the pulsating nature of blood movement is physiological, in subsequent years in the clinical practice of using LVAD in adult patients, on-pulsating devices (more than 94%) became the most widespread devices [13].

Rotary blood pumps have several important advantages, one of them being that they do not require a large chamber volume to generate a working ejection comparable to the native heart ventricle. In subsequent pump generations, the flow was generated by rotating the impeller either as an axial (straight) or centrifugal (from the center to the tangential edge) flow. Rotary pumps consume significantly less energy, have fewer moving parts, and have no valves or cyclic drives. In second-generation designs, the main places of wear are bearings. For instance, it is known that the estimated service life of devices implemented by a rotor-supported bearing system is 1–2 years, at 9000–15000 rpm, and despite numerous attempts to adapt the operation of this part of the pump in specific blood conditions, most of the problems (thrombosis, breakage, exhaustion of the strength resource) have not been resolved [14].

In the third-generation devices, mechanical wear has been reduced by magnetic suspension of the rotor. This innovative design has greatly improved overall reliability and durability. Lower total weights and volumes of implantable devices make the third-generation systems applicable to patients with a small body surface area (small women and children). Without valves, a pump bag compression and bearing source, the third-generation rotary pumps are much quieter than their predecessors.

While rotary pumps are free of some of the disadvantages of pulsatile LVADs, they come with a number of unique biocompatibility issues. The high rotor speeds (~5000–10000 rpm), required to generate a flow rate of ~5 liters per minute, expose the blood cells to high peak shear stresses. And although these stresses are of a very short duration, they can lead to hemolysis and platelet activation. That is why, from this point of view, centrifugal disc-type pumps, allowing to develop the design capacity at minimum (less than 3000 rpm) rotor revolutions, minimizing the risk of blood hemolysis, are better [15, 16].

Besides hemolysis, one of the main problems limiting the long-term use of any LVAD model is thromboembolic complications. The difficulty in analyzing thromboembolic complications is due to differences in the understanding of assessment criteria. Thromboembolic complications range from focal tissue necrosis, detected only on histological studies, to persistent neurologic symptoms (stroke). Data published in 2009 by INTERMACS described 199 neurological, 14 arterial, and 33 venous thrombotic complications in 483 LVAD patients over a two-year period. In this report, central nervous system events were the leading cause of death (11%), which further emphasizes the difficulty of addressing the biocompatibility problem and its present urgency [17].

One of the ways to combat major complications was to reduce the area of the inner surface of the pump in order to reduce the blood-contacting surface area. Thus, the surface area of the latest generations of pumps was significantly reduced (for HeartMate I, the blood-contacting surface area varied from 400 to 500 cm^2). However, despite this, the problem of thromboembolism still remains unsolved. Another way of tackling this problem was to accelerate endothelialization of the inner surface of the pump, for example, despite the large blood-contacting surface area, a textured surface was successfully used in the HeartMate XVE model. The blood- and tissue-contacting surfaces of titanium cannulas were covered with sintered titanium microspheres 50–75 μm in diameter (Fig.), and 25 mm xenopericardial valves (Medtronic) were installed at the pump inlet and outlet. The diameter of the fibrils of the fully textured polyurethane surface of a flexible diaphragm was approximately 18 μm.

Despite the fact that the idea of using a textured surface seemed risky at first, this concept turned out to be an original solution to the biocompatibility problem. The clots of heterogeneous composition, rapidly forming and tightly fixed on the inner surface, containing platelets, monocytes, macrophages, lymphocytes and multipotent circulating cells created optimal conditions for early (about 7 days) formation of pseudo-intima, significantly reducing the risk of thromboembolism [18].

In this case, formation of the neointima, apparently, occurred due to the natural drift of pluripotent cells by the blood stream. At the same time, it was shown that the forming neointima does not exceed 150 μm in thickness within a year after implantation [19].

The resulting pseudointima does not have antithrombotic properties. However, Spanier et al. suggested that such a surface could work by creating a stable prothrombotic and potentially pro-inflammatory environment that induces continued coagulation through the tissue factor pathway. An enhanced fibrinolytic response by the body, which has been described many times in literature, serves as a natural autoanticoagulation to prevent the develop-

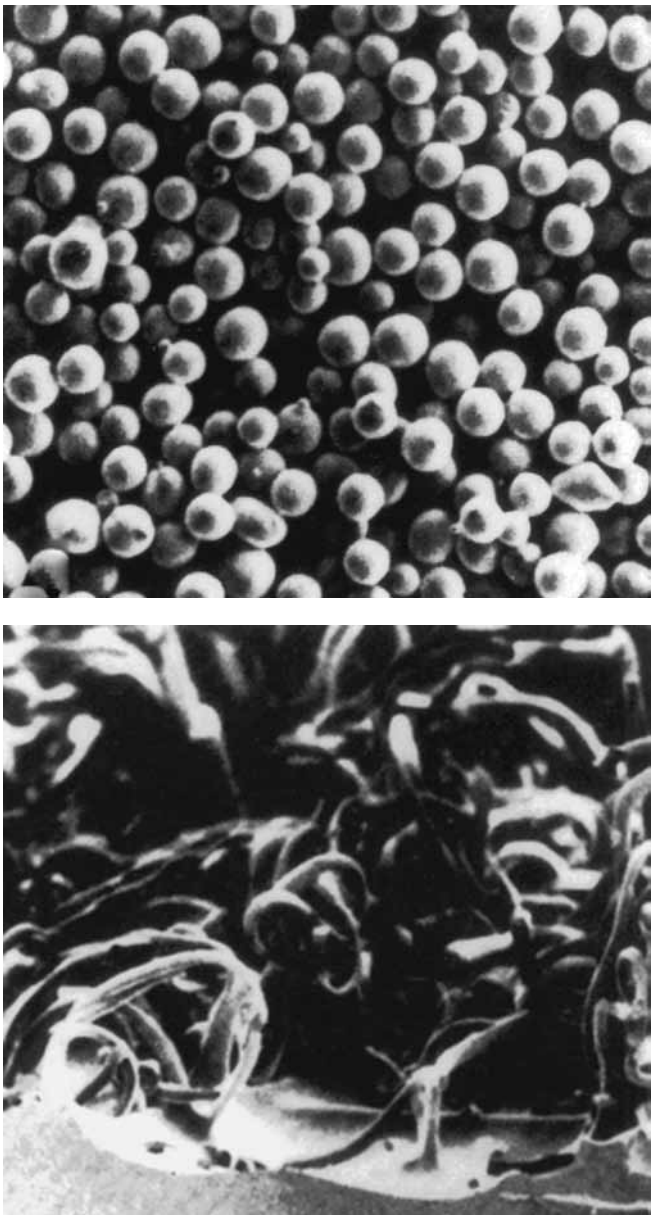

Fig. Textured surface of the HeartMate XVE

ment of thromboembolic syndrome. In addition, impressive clinical results recorded by the first generation of the pump is due to the fact that the formed thrombi are much less likely to migrate due to the stronger adhesion to the extracellular matrix present on the surface.

Unfortunately, this concept of natural surface modification cannot be implemented in smaller continuous flow pumps, and it is likely that the smaller blood-contacting surfaces of these pumps could offset any potential increased risk.

The HeartMate II has the highest efficacy and safety record of any LVAD implanted. It has been implanted in over 10,000 patients in about 300 different clinics around the world. In patients under 70 years of age without cardiogenic shock, diabetes, and renal failure, the HeartMate II circulatory support showed a 1-year and 2-year survival of 80% and 70%, respectively, which is comparable to heart transplantation outcomes. Moreover, the PREVENT study showed a 4.8% risk of thrombosis for this device in the first 6 months after implantation. According to Kreuziger et al., HeartMate II thrombosis occurs in 10% of patients after implantation [20–22].

The main cause of thrombosis in these cases is the heat generated in the inflow part of the bearing unit. This is where thrombotic masses were found most often; apparently, this was associated with the heat released during rotor rotation, protein denaturation and fibrin deposition. Histological analysis of the thrombi found around the inlet bearing in HeartMate II showed high levels of fibrin, which supports the coagulation theory of thrombosis. Administration of warfarin therapy by reducing the concentration of clotting factors II, VII, IX and X helped to reduce the likelihood of thrombosis [23, 24].

However, artificial surfaces can directly activate proteins of the internal pathway – factors XI and XII, on which warfarin has no effect, whereas the activity of the internal pathway was significantly affected by the nature of the flow generated by LVAD. An absolute 40–50% decrease in clotting factors XI and XII after pulsatile LVAD implantation has been proven [25].

The latest-generation HeartMate III (Abbott, Chicago, IL) with a fully magnetic rotor suspension has software that allows for generation of a pulsatile flow. The first large study conducted in 10 centers (Europe, Kazakhstan, Canada, Australia) showed excellent outcomes: no hemolysis, no thrombosis or failure within 12 months, not a single case of stroke was recorded [26, 27]. According to Krabatsch et al., there was a 92% 6-month survival and an 81% 12-month survival [28].

However, according to a study published in 2018 by Konstantin et al., comparing three different LVADs – HeartMate II, HeartMate III, and HeartWare, the overall 30-day survival rate was 70.4%, annual survival 51.9% and 5-year survival 38% with no significant difference in complication rates between these three LVAD models. Despite the significant advantages of latter pump generations, the probability of death from pump thrombosis and subsequent embolic stroke was 24% within 3 months after implantation [29, 30].

Since the risk of thrombus formation mainly determines the hemodynamic flow profile in pump cavities, the available theoretical evidence and previously performed experimental studies create obvious prerequisites for considering Tesla-turbine disc pumps (viscous friction pumps) as circulatory assist devices [31].

In such devices, centrifugal force creates a uniform hydraulic velocity profile and ensures pumping of a liquid medium without pulsations and vibrations with formation of a boundary layer. The boundary layer not only transfers kinetic energy to the fluid between the discs, but also acts as a molecular buffer between the disc surface and blood. An element-free blood plasma layer is formed

around the surfaces of the rotating discs, minimizing the contact of blood cells with the disc surface [32, 33].

Despite encouraging results of the first trials of the new disc pump model showing minimal blood cell injury, largely due to modification of the a-C:H:SiO_x film surface, an understating of the risk of thrombus formation and the incidence of other complications remain unclear [34, 35].

CONCLUSION

At present, none of the existing LVAD models can ensure complete absence of thromboembolic complications and hemolysis. Analysis of literature data and recent experiments on adaptation of implantable materials show that the problem is still a highly urgent one.

The authors declare no conflict of interest.

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The article was submitted to the journal on 2.06.2020