[Editorial]

Graphene coating onto mechanical heart valve prosthesis and resistance to flow dynamics

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Cardiovascular diseases account for three of the four leading causes of death in the world. One of the most common forms is heart valve disease, affecting about 3-6% of the population over 65 years [1]. The state of the art treatment is heart valve replacement either with mechanical or biological prostheses[2]. Heart valve prostheses are currently among the most widely used cardiovascular devices (projected number of valve replacements: 850 000 per year by 2050) in Western countries[3]. However, the ideal valve substitute does not exist and each of the currently available prosthetic valves has inherent limitations[4]. Mechanical prostheses provide an extremely long-term durability but, at the same time, bear a high risk of thrombosis, which makes permanent anticoagulation therapy necessary leading to possible haemorrhagic complications. The alternative biological prostheses are made of porcine or bovine pericardium, providing good biocompatibility without a need for anticoagulation but they are prone to degeneration and, therefore, require more revision operations. Factors used to determine which valve is most suited for a patient include the patient's age, contraindication to anticoagulation, comorbidities, need of associated procedures, availability of a given replacement, patient agreement, and surgeon expertise[5,6]. With changing demographics and lifestyle choices, the demand for a more durable and biocompatible prosthesis is on the rise. The research in the field of valvular heart disease substitute is thus booming.

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Mechanical valves are the preferred valves for individuals under the age of 65 due to their high durability and longevity. There have been many different developments for mechanical heart valves since their inception in the 1950s. According to recent reports, bileaflet mechanical valves are the most widely implanted valves, accounting for 85% of the mechanical valves implanted. The low profile of the bileaflet mechanical valves allows them to be implanted into smaller hearts without obstruction of other structures such as the mitral valve or coronaries[2]. Bileaflet valves have good haemodynamics with a low transvalvular pressure gradient and minimal regurgitation, and they are durable, showing a low rate of mechanical failure. All mechanical valves have three components: (1) the cloth-covered sewing ring, generally made of pyrolytic carbon; (2) the occluder, made of various metallic alloys, usually incorporating titanium and covered up by pyrolytic carbon; (3) the retaining mechanism, which keeps the occluder in place. The exposure of any of these artificial surfaces (sutures, sewing ring, occluder, and valve housing) to the circulating blood can promote thrombus formation[7].

Efforts to reduce the thrombogenicity of artificial valves and its anticoagulant-related risks have prompted new prosthetic valve design and surface/compound modification but still, these improvements are not satisfactory and valve thrombosis remains a major problem in implanted patients. As an example, the ATS Open Pivot valve (Minneapolis, MN, USA), introduced in 2000, has featured a change in the pivot design with no longer recesses or cavities in the pivot area where potential thrombus can form[8]. The On-X valve, marketed by the Medical Carbon Research Institute (Austin, TX, USA), a more recent mechanical valve introduced in the US and intended to function with less anticoagulation, also brings some innovative design features (a length-to-diameter ratio close to that of native heart valves, a smoothed pivot recess that allows the leaflets to open at an angle of 90° relative to the valve housing and a two-point landing mechanism during valve closure) to reduce thrombogenicity. The use of the On-X valve in aortic position has recently provided some promising and encouraging data[9].

The main disadvantage of the previous metals or metal alloys used in prosthetic valves was that they could corrode due to chemical reactions with the body enzymes and acids, which might trigger toxic, inflammatory, or allergic responses in patients[10]. Besides, the corrosion process could also degrade the structural integrity of the metallic devices, resulting in premature failure. Therefore, how to protect metals from alteration in a biological environment was one of the critical issues to be addressed for the sustainable biomedical application of metals. Metal alloys consisting of stainless steel or titanium have often been used to give mechanical strength and for their corrosion resistance properties. However, these materials have a very limited biocompatibility as they create highly thrombogenic surfaces. The introduction of pyrolytic carbon from the General Atomic Company as a suitable valve material has been likely the most important breakthrough in the engineering process of mechanical valves for either surface coating (by depositing gaseous hydrocarbons—usually methane—onto a heated graphite substrate at temperatures of between 1800 and 2300°C) or entire leaflets and housings of the valves (made from 100% pyrolytic carbon using fluidized bed processes)[11]. Due to its strength, excellent resistance to wear and reduced thrombogenicity, pyrolytic carbon has become the main component of commercial mechanical cardiac valves for more than three decades.

Graphene differs from other carbon materials by the presence of unique physical, chemical, biological, electronic and quantum mechanical properties[12]. Graphene is a chemically inert and impermeable flat atomic monolayer composed of sp^2-bonded carbon atoms, which is able to confer an effective oxidation resistance to the underlying metallic material[13]. In view of its properties, graphene can be considered as an excellent protective coating candidate for metals allowing their electrochemical passivation. This monolayer of graphene has remarkable structural integrity, impeding even helium gas at high pressure to penetrate through the monolayer in air, and precluding the contact of surrounding fluid, i.e. blood, with the device substrate[14]. The biocompatibility of graphene-made protection films has already been demonstrated both in vitro and in vivo, and, therefore, graphene coating can adequately be adapted to implanted metal materials such as mechanical valves[15]. Graphene also has interesting anti-bacterial properties[16]. Large-scale synthesis of high quality and uniform graphene films can be achieved through chemical vapour deposition. By using a sacrificial polymer (i.e., poly(methylmethacrylate), such a graphene monolayer can be transferred from the chemical vapour deposition support (usually Cu foil) onto the medical device (figure 1). After transfer, van der Waals interactions between the graphene sheet and the substrate mediate coating adhesion[17].

An additional chemical challenge for the development of cardiac valve coating is to obtain a coating that resists the flow dynamics and stress inherent to the cardiac pump function. Today some advanced strategies consider using additional organic derivatives, such as thiol derivatives self-assembled on metal surface, to effectively enhance the hydrodynamic resistance of graphene protection[18]. In the paper of Arokiaraj et al., a graphene monolayer prepared by chemical vapour deposition was directly transferred onto four metallic cardiac valves (Medtronic ATS bi-leaflet valves) by using poly(methylmethacrylate) as sacrificial layer[19]. After

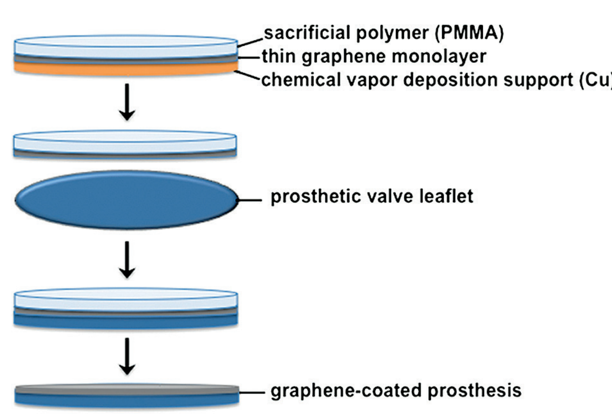

Fig. 1 Example of graphene monolayer transfer onto valve prosthesis.

Graphene deposited by chemical vapour deposition (CVD) on a copper (Cu) foil is spin coated by poly(methylmethacrylate) (PMMA) before removing the Cu by chemical etching.
The resulting PMMA/graphene membrane can then be applied to the valve substrate before removal of the PMMA sacrificial layer.

thermal treatment of the device graphene sheet, three of the four coated valves were submitted to stringent fatigue tests, i.e. accelerated wear test over 40 million cycles. Remarkably, even after such stringent treatment, the study demonstrated that the graphene coating remains attached to two out of the three coated valves, but its presence could not be demonstrated in the third valve. The authors mentioned the importance of the thermal treatment, improving the adhesion of the graphene layer when high temperatures are reached. As the valve leaflet substrates are composed of pyrolytic carbon, they can withstand high temperatures. However, this heating step might appear as a limitation since parts of the valvular peripheral ring were damaged when the temperature exceeded 100°C. In the present study, no anchoring additive was used to improve coating adhesion, which was only achieved by thermal treatment. Therefore, the use of adapted additional anchoring material could be envisioned to reach efficient anchorage at low temperature. Although only very few numbers of samples were used, this study represents the very first demonstration of the resistance to drastic flow of a graphene monolayer coating applied to prosthetic cardiac valves. It should be noted that the haemocompatibility and thrombogenicity properties of the graphene-coated valves remain to be tested. Nevertheless, due to the unique properties of graphene in terms of biocompatibility and of possible conjugation with bioactive molecules with local action or progressive controlled drug release, i.e. anticoagulation agents, the coating strategy described here offers quite interesting promises for the future evolution of prosthetic cardiac valves and other medical implants.

CONFLICT OF INTEREST: none.

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