Surface modification of a titanium alloy for reduced thrombogenicity in cardiovascular devices

Sang Ho Ye, Joshua R. Woolley, Carl A. Johnson Jr, Trevor A. Snyder and William R. Wagner.
McGowan Inst. for Regenerative Medicine, Depts. of Bioengineering & Surgery, Univ. of Pittsburgh, Pittsburgh, PA 15219.

Introduction: Although titanium alloys (e.g. Ti4Al6V) have exhibited good biocompatibility in a variety of settings, including cardiovascular devices, thrombosis and thromboembolism remain problematic for ventricular assist devices (VADs) that utilize this (and other) blood contacting surfaces. We are currently developing a rotary VAD for use in infants [1]. This pump will have very small blood path dimensions, a high surface area to volume ratio, and be fabricated from Ti4Al6V for the main pump housing and rotor. Our objective was to develop a surface modification strategy that could reduce platelet deposition onto this surface. The approach focused on attaching phosphorylcholine (PC) groups, which others have shown to exhibit excellent biocompatibility and anti-thrombogenicity when applied as surface modifying agents [2].

Methods: TiAl6V4 coupons were cleaned ultrasonically with water and acetone. The surfaces were then modified using one of two techniques. In the first method surfaces were passivated with nitric acid, silanated with 3-aminopropyltriethoxysilane (APTES), and then modified by immersing for 24h at 60˚C in a solution of a copolymer comprised of 70mol% methacryloyloxyethyl-phosphorylcholine (MPC) and 30mol% methacrylic acid (MA). This copolymer, referred to as PMA70 had a Mw=5.5x10^5. The surface modified with this technique was referred to as Ti-PMA70-1. In the second method surfaces were treated with H_2O-vapor plasma by radio frequency glow discharge (50W, 5min) and then silanated with APTES. Samples were then immersed in PMA70 solution at 60˚C for 24h after adding a condensation reagent ((1-ethyl 3-(3-dimethylaminopropyl) carbodiimide) hydrochloride (EDC) to facilitate immobilization of the PMA70 via a condensation reaction between surface amines and PMA70 carboxyl groups. Samples treated in this manner were referred to as Ti-PMA70-2.

The modified TiAl6V4 coupons (Ti-PMA70-1 and Ti-PMA70-2) were rinsed with ethanol and water 3 times, and then further rinsed by stirring in deionized water for 24h. The surface composition of the coupons was analyzed by an X-ray photoelectron spectroscopy (XPS). The acute in vitro blood biocompatibility of the modified surfaces was evaluated by continuous rocking for 50min at 37˚C in fresh, minimally anticoagulated (1.5 u/mL heparin) ovine blood. The ovine blood was treated with mepacrine at 10um final concentration to fluorescently label the platelets prior to contacting the test surfaces. Mural thrombotic deposition was assessed macroscopically and with epi-fluorescence microscopy.

Results: The surface atomic composition of the modified TiAl6V4 samples is shown in **Table 1**. The data support the successful modification of the Ti4Al6V surfaces with PMA70 given the presence of Si and P, which are attributed to APTES and PMA70 respectively. The Ti-PMA70-2 had slightly higher percentages of Si and P than Ti-PMA70-1 ($p<0.05$). The H_2O-vapor plasma treatment may have more effectively created hydroxyl groups on the surface [3], or the use of EDC may have better coupled PMA70 to the surface to explain this observation. In **Fig. 1A** representative images of modified and control surfaces after ovine blood contact demonstrate the marked difference between Ti-PMA70-1 and Ti-PMA70-2, which had relatively low thrombotic deposition, and the heavy or moderate deposition seen on unmodified Ti4Al6V or polystyrene respectively. Ti-PMA70-2 appeared to have slightly less deposition than Ti-PMA70-1. These results were supported by the images in **Fig. 1B** where control surfaces had heavy and nearly complete surface coverage with fluorescent platelets, while the modified surfaces had only sparse and small thrombi.

Table 1. Atomic percentage (composition) as determined by XPS

	C	O	Ti	Si	P
Ti-PMA70-1	30.7 (±2.3)	47.5 (±0.8)	9.6 (±0.9)	2.1 (±0.5)	0.8 (±0.2)
Ti-PMA70-2	38.2 (±3.4)	43.2 (±2.4)	5.9 (±0.8)	5.0 (±0.6)	1.1 (±0.2)

Mean value ± S.D. (n=3)

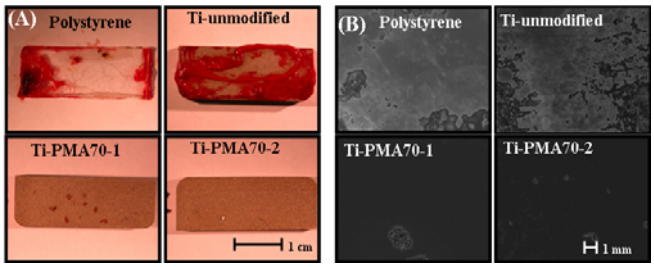

Fig. 1. (A) Macroscopic and (B) microscopic images of modified and unmodified TiAl6V4 coupon samples after blood contact for 50 min. Scale bars = 1cm for (A) and 1mm for (B).

Conclusion: TiAl6V4 surfaces were modified with a phospholipid polymer (PMA70) that was associated with decreased acute thrombotic deposition in vitro. This technique is amenable to the modification of surfaces in a pediatric VAD and may enable the necessarily aggressive design of these devices in terms of their relatively small blood flow paths and the need for cautious anticoagulation in this patient population.

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References:

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