Blood Compatibility of Metals and Alloys Used in Medical Devices

W. VAN OEVEREN, P. SCHOEN, C. A. MAIJERS
University of Groningen, Department of Biomedical Engineering and HaemoProbe BV, Groningen, The Netherlands

Summary

A literature survey was performed to evaluate the current knowledge of the blood compatibility of metals or alloys used for devices that come in contact with the blood. Results of straightforward blood compatibility studies such as those proposed by the International Standardization Organization have not often been published. Also, comparisons between various metals and/or other materials have not been systemically performed, although more is known about the blood compatibility of different polymers. After sifting data from various in vitro studies, animal experiments and clinical reports, it is concluded that most metals seem to be less blood compatible than artificial polymers. On the other hand, ceramics consisting of oxidized metals and carbon alloys appear to be as compatible as or even better than polymers.

Key words

Metals, blood compatibility, implantable devices

Introduction

aortic wall had extensive reactions to silver and copper [7]. However, another study revealed the limitations of gold by showing greater platelet adhesion and diffusion, as well as greater platelet microvesicle generation on gold as compared to titanium [8]. Moreover, on gold the expression of CD11b by polymorphonuclear neutrophils increased continuously, indicating an inflammatory reaction [9]. In contrast to gold, CD11b expression on graphite was only transient. Taken together, these results indicate that gold cannot be considered the most favorable metal to be used as a naked surface, since induction of an inflammatory reaction impairs healing and endothelial growth at the site of implantation.

Silver

The poor biocompatibility of silver has been demonstrated by the recent failure of silver-coated heart valve textile to become incorporated by tissue ingrowth. The antimicrobial properties of silver legitimated its use on heart valve textile [10], although the cytotoxic effects of silver were known [11]. Blood compatibility data for silver is limited to surface microscopy of large bore catheters for extracorporeal detoxification [12]. Importantly, silver may become chemically modified after implantation to result in the formation of highly thrombogenic silver nitrate. Notably, the latter product has been used as the activator in model studies to investigate antithrombotic compounds [13]. Because of its cytotoxicity and possible thrombogenicity, silver is not a metal that should be used in direct contact with blood.

Stainless steel

Stainless steel (316L) is the most commonly used metal for endovascular devices. Its mechanical properties significantly contribute to its applicability, but the blood compatibility results also appear better than that of some other metals. For instance, stainless steel stents are more blood compatible than tantalum stents [14]. However, stainless steel can also be further optimized, since several studies showed that polymer coating of stainless steel stents reduced deposition of platelets and thrombus mass by more than 60 % [15,16]. The reported reduction by stainless steel of the partial thromboplastin time by 50 % or more, indicating activation of the clotting system, would be considered unacceptable in view of the requirements for newly developed biomaterials.

Tantalum

After stainless steel, tantalum was introduced as the metal for the construction of stents. Due to tantalum's high radiopacity, implantation of tantalum stents is greatly facilitated. Initial studies showed similar blood compatibility for tantalum and stainless steel [17], although later studies indicated that stainless steel possesses superior blood compatibility [14]. Clinical studies indicated that a high incidence of thrombotic complications could occur after tantalum stent implantation if anticoagulation and anti-platelet therapy was insufficient [18]. Also, post-stent antithrombotic therapy was required, including both anticoagulants and platelet inhibitors or ticlopidine plus aspirin [19]. Polymer-coating of tantalum stents with polyurethane or parylene reduced the deposition of platelets by 5 to 50 % relative to platelet deposition on uncoated stents [20].

Titanium

In the human body, titanium exists only for a short period of time in its unmodified form, and relevant blood compatibility data are therefore obtained with titanium nitride or titanium oxide.

Titanium oxide appears to reduce fibrinogen deposition due to its semi-conductive nature. This effect is explained by the similar electronic structures of fibrinogen and titanium [21]. In a comparative study with low-temperature isotropic pyrolytic carbon (LTI carbon), not only reduced deposition of fibrin, but also a 50 % reduction in microscopically counted platelets was observed for titanium oxide [21]. Transvenous inferior-vena-cava filters made of stainless steel, titanium or titanium-nickel all showed approximately 25 % early thrombosis in clinical use, measured via ultrasound scanning [22]. This incidence of early thrombosis was unexpectedly high, and difficult to reduce with the current devices, since antithrombotic medication is often contra-indicated in patients requiring a vena cava filter.

Titanium nitride has been tested for its blood compatibility with regard to leukocyte adhesion, and appeared to retain no leukocytes [23]. Additionally, platelet retention was as low as with silicone elastomer, but comparisons to more blood compatible materials have

not been made [24]. In vivo experiments with titanium nitride heart-valves in sheep showed some depositions of fibrin and platelets [25].

Nickel-titanium alloy (nitinol) has attracted special attention due to its memory functions. It must be noted that nitinol has an outer surface of titanium (oxide), whereas nickel is not exposed to blood. Therefore, the blood compatibility characteristics are expected to be rather similar to those of titanium oxide. Based on the hypothesis that a semi-conductor prohibits fibrin and platelet deposition, nitinol is expected to be thromboresistant, unless its semi-conductive nature is lost in the alloy. In a clinical study with nitinol intravascular clot filters, the effects on the clotting system and on platelet adhesion were shown to be similar to those induced by stainless steel [26]. An experimental study with stented rabbits showed significantly more thrombus formation on stainless steel than on nitinol [27]. However, grafting of polyethylene oxide (PEO) on nitinol reduced the fibrinogen adsorption by as much as 99 %, and significantly reduced platelet adhesion, which once more shows the superior thromboresistent effects of polymers as compared to those of metals like nitinol [28].

Further evidence that nitinol, too, can only safely be implanted during antithrombotic treatment was provided in experiments that included the use of platelet inhibitors aspirin and clopidogrel in a porcine stent model: combined treatment with these inhibitors reduced stent thrombosis 95 - 98 % [29]. An effective coating such as PEO could thus limit the use of systemic treatment by medication.

Zirconium

Zirconium applied in an alloy with titanium or niobium retained less fibrinogen than stainless steel, but the activation of prekallikrein, indicating contact activation, was significantly higher on zirconium alloys than on stainless steel and pyrolytic carbon [30].

Aluminum

Aluminum alloys or oxide have been tested in an application for implantable blood pumps. The aluminum alloys react with platelets similarly to or better than titanium. The adhesion of platelets to titanium-aluminum alloy as determined by the binding of GpIIIa antibody was less than to polyethylene [31]. This is one of the few examples were a metal shows similar or better blood compatibility than a polymer. In this study silicon carbide was similar to titanium aluminum alloy with respect to a reduced platelet binding.

Carbon

Pyrolytic (LTI) carbon has been used as surface coating for artificial heart valves for more than 20 years. However, platelet spreading on these surfaces has been shown and the activation of the clotting system is considerable, resulting in fibrin formation on the surface [32]. This appeared to be mainly due to the electrical interactions of the interface and the clotting proteins. Carbon has more recently been applied in an alloy with silicon by means of plasma enhanced chemical vapor deposition (PECVD) process [33]. Similar to the findings considering the semiconductor effects of titanium oxide [21] the blood compatibility was improved considerably after coating with silicon carbide, shown by reduced fibrin formation and platelet deposition [34]. Tantalum stents coated with silicon carbide have been applied successfully in patients, even without antiplatelet medication during the implantation procedure [35], while these silicon carbide coated tantalum stents demonstrated significantly less platelet adhesion than stainless steel stents [14].

Conclusion

No thorough comparisons between metals can be made, since the reported studies have evaluated the blood compatibility of different materials and no consistent reference materials were included. Furthermore, most studies report only limited blood compatibility tests. Apparently, the possible induction of an inflammatory reaction initiated by complement activation or granulocyte activation is not frequently tested, although it is an important contributor to intimal hyperplasia [36]. Still, in general, it could be stated that the more noble metals appear to be less blood compatible than ceramics and silicon carbide products. Most naked metals had a poor blood compatibility in direct comparison to polymers, which was most often tested after polymer coating of the metals, indicating that the mechanical properties of metals are still considered essential for stent or valve construction. A thorough evaluation of blood compatibility of metals is warranted to quantify their thrombotic and inflammatory properties.

References

[1] Lavelle SM, Iomhair MM. Antithrombotic effect in vivo of thrombotic substances adsorbed on a platinum surface. Technol Health Care. 1996; 4: 389-91.

[2] Kim TS, Park JH, Lee Y, et al. An experimental study on thrombogenicity of various metallic microcoils with or without thrombogenic coatings. Invest Radiol. 1998; 33: 407-10.

[3] Iomhair MM, Lavelle SM. The antithrombotic effect of some Eurobiomat project test polymers in vivo. Technol Health Care. 1996; 4: 385-8.

[4] Klotzsch C, Nahser HC, Henkes H, et al. Detection of microemboli distal to cerebral aneurysms before and after therapeutic embolization. Am J Neuroradiol. 1998; 19: 1315-8.

[5] Byrne JV, Hope JK, Hubbard N, et al. The nature of thrombosis induced by platinum and tungsten coils in saccular aneurysms. Am J Neuroradiol. 1997; 18: 29-33.

[6] Herrmann R, Schmidmaier G, Markl B, et al. Antithrombogenic coating of stents using a biodegradable drug delivery technology. Thromb Haemost. 1999; 82: 51-7.

[7] Tanigawa N, Sawada S, Kobayashi M. Reaction of the aortic wall to six metallic stent materials. Acad Radiol. 1995; 2: 379-84

[8] Kanagaraja S, Lundström I, Nygren H, et al. Platelet binding and protein adsorption to titanium and gold after short time exposure to heparinized plasma and whole blood. Biomaterials. 1996; 17: 2225-32.

[9] Eriksson C, Nygren H. The initial reactions of graphite and gold with blood. J Biomed Mater Res. 1997; 37: 130-6.

[10] Tweden KS, Cameron JD, Razzouk AJ, et al. Silver modification of polyethylene terephthalate textiles for antimicrobial protection. ASAIO J. 1997; 43: M485-81.

[11] Hemmerlein JB, Treretola SO, Kraus MA, et al. In vitro cytotoxicity of silver impregnated collagen cuffs designed to decrease infection in tunneled catheters. Radiology. 1997; 204: 363-7

[12] Bambauer R, Mestres P, Pirrung KJ, et al. Scanning electron microscopic investigation of catheters for blood access. Artif Organs. 1994; 18: 272-5.

[13] Stegmeier K, Pill J, Muller-Beckmann B, et al. The pharmacological profile of the thromboxane A2 antagonists BM 13.177. A new anti-platelet and anti-thrombotic drug. Thromb Res. 1984; 35: 379-95.

[14] Monnink SHJ, Boven AJ van, Peels HO, et al. Silicon-carbide coated stents have low platelet and leukocyte adhesion during platelet activation. J Investig Med. 1999; 47: 304-10.

[15] Seeger JM, Ingegno MD, Bigatan E, et al. Hydrophilic surface modification of metallic endoluminal stents. J Vasc Surg. 1995; 22: 327-36.

[16] Fontaine AB, Koelling K, Clay J, et al. Decreased platelet adherence of polymer-coated tantalum stents. J Vasc Interv Radiol. 1994; 5: 567-72.

[17] Scott NA, Robinson KA, Nunes GL, et al. Comparison of the thrombogenicity of stainless steel and tantalum coronary stents. Am Heart J. 1995; 129: 866-72.

[18] Hamm CW, Beytien C, Sievert H, et al. Multicenter evaluation of the Strecker tantalum stent for acute coronary occlusion after angioplasty. Am Heart J. 1995; 129: 423-9.

[19] Park SW, Park SJ, Hong MK, et al. Coronary stenting (Cordis) without anticoagulation. Am J Cardiol. 1997; 79: 901-4.

[20] Fontaine AB, Koelling K, Passos SD, et al. Polymeric surface modifications of tantalum stents. J Endovasc Surg. 1996; 3: 276-83.

[21] Nan H, Ping Y, Xuan C, et al. Blood compatibility of amorphous titanium oxide films synthesized by ion beam enhanced deposition. Biomaterials. 1998; 19: 771-6.

[22] Aswad MA, Sandager GP, Pais SO, et al. Early duplex scan evaluation of four vena cava interruption devices. J Vasc Surg. 1996; 24: 809-18.

[23] Dion I, Roques X, More N, et al. Ex vivo leucocyte adhesion and protein adsorption on TiN. Biomaterials. 1993; 14: 712-9.

[24] Dion I, Baquey C, Havlik P, et al. A new model to test platelet adhesion under dynamic conditions. Application to the evaluation of a titanium nitride coating. Int J Artif Organs. 1993; 16: 545-50.

[25] Mitamura Y, Hosooka K, Matsumoto T, et al. Development of a ceramic heart valve. J Biomater Appl. 1989; 4: 33-55.

[26] Prince MR, Salzman EW, Schoen FJ, et al. Local intravascular effects of the nitinol wire blood clot filter. Invest Radiol. 1988; 23: 294-300.

[27] Sheth S, Litvack F, Dev V, et al. Subacute thrombosis and vascular injury resulting from slotted-tube nitinol and stainless steel stents in a rabbit carotid artery model. Circulation. 1996; 94: 1733-40.

[28] McPherson TB, Shim HS, Park K. Grafting of PEO to glass, nitinol, and pyrolytic carbon surfaces by gamma irradiation. J Biomed Mater Res 1997; 38: 289-302.

[29] Makkar RR, Eigler NL, Kaul S, et al. Effects of clopidrogel, aspirin and combined therapy in a porcine ex vivo model of high shear induced stent thrombosis. Eur Heart J. 1998; 19: 1538-46.

[30] Yun YH, Turitto VT, Daigle KP, et al. Initial hemocompatibility studies of titanium and zirconium alloys: prekallikrein activation, fibrinogen adsorption, and their correlation with surface electrochemical properties. J Biomed Mater Res. 1996; 32: 77-85.

[31] Takami Y, Yamane S, Makinouchi K, et al. Evaluation of platelet adhesion and activation on materials for an implantable centrifugal blood pump. Artif Organs. 1998; 22: 753-8.

[32] Goodman SL, Tweden KS, Albrecht RM. Platelet interaction with pyrolytic carbon heart-valves. J Biomed Mater Res. 1996; 32: 249-58.

[33] Bolz A, Schaldach M. Artificial heart valves: improved blood compatibility by PECVD a-SiC:H coating. Artif Organs. 1990; 14: 260-9.

[34] Oeveren W van. Reduced deposition of blood formed elements and fibrin onto amorphous silicon carbide stainless steel. Progr Biomed Res. 1999; 1(4): 78-83.

[35] Heublein B, Özbek C, Pethig K. Silicon carbide-coated stents: clinical experience in coronary lesions with increased thrombotic risk. J Endovasc Surg. 1998; 5: 32-6.

[36] Miller DD, Karim MA, Edwards WD, et al. Relationship of vascular thrombosis and inflammatory leukocyte infiltration to neointimal growth following porcine coronary artery stent placement. Atherosclerosis. 1996; 124: 145-55.