醫用不銹鋼材質表面氧化物膜之特質及其在體內之反應與血栓影響以及塗藥功能分析

The Role of Surface Oxide Properties of Implantable Stainless Steel in Tissue and It's Effect on Thrombogenic Potential as well as Drug-Coating Analysis

中文摘要

316 L 不銹鋼是生醫材料中，被廣泛使用於人體外固定或植入於體內的金屬，且爲治療心臟冠狀動脈硬化狹窄的支架的最主要材質。然而醫用金屬使用於人體內，必須符合下列特性：(一)足夠的強度以維持固定。(二)在生物體組織中能抗腐蝕，以維持金屬的穩定性。(三)良好的生物相容性;不會產生毒性，不會排斥或過敏。若放於心臟血管中則要能抗血栓。影響這些特性的因素包括有表面結構(texture)、表面能量(energy)、電荷(charge)、及化學組成(chemical composition)等。但金屬材質的化學特性使其無法完全克服其自身所衍生的問題，特別是腐蝕與血栓的部分。於是學者乃著手於材質之改造、或金屬表面處理方法的改良、或在金屬表面加上聚合物塗層。文獻中已知金屬的化學性質及電化學反應取決於金屬的最外層氧化物膜，此氧化物膜與腐蝕及血栓有非常重要的關係。因此了解外層氧化物膜的特性及反應，甚至改良，就成爲金屬生醫材質改造的重要課題。

在本論文的系列研究證實，316 L 不銹鋼在體內會進行腐蝕造成金屬疲勞及毀損。原因來自於 316 L 不銹鋼製作過程的表面缺損、或內含雜物、或臨床操作時的金屬傷害。腐蝕過程中釋放的鎳離子則會造成白血球的吞噬及局部發炎。在對血管細胞傷害的研究中，發現血管平滑肌細胞會受到 316 L 不銹鋼腐蝕後之懸浮液或腐蝕之沉澱物抑制細胞生長甚至死亡，其傷害程度與時間及濃度相關。但若 316 L 不銹鋼的表面鈍化處理良好，如將其表面氧化物改變成爲”無晶型氧化物”，可增強其抗腐蝕及抗血栓之能力。無晶型氧化物在電子顯微鏡檢視下顯示其氧化物粒子小至 0.3 奈米，均勻且完整，其組成以鉻之氧化物爲主，鍵結以氫氧鍵居多。無晶型氧化物在電化學上有穩定而低的開路電位及穩定而負值的開路電流，故有較良好的抗腐蝕性。同時無晶型表面氧化物層具有較大的時間常數，時間常數愈高愈不易血栓。在生物體內的血栓試驗中處理成無晶型氧化物的 316 L 不銹鋼線圈也明顯優於如電拋光法及熱處理法等其他表面處理方式。316 L 不銹鋼血管支架扮演著治療嚴重冠狀動脈心臟病的重要角色，也改善了氣球擴張術的再狹窄率，但仍有 20-30%的半年內再狹窄率。爲了改善此缺陷，於是在支架表面做藥物塗層，以釋放出抑制細胞增生的藥物的”塗藥支架”在臨床上也明顯降低再狹窄率至 10%以下。藥物塗層支架之成功取決於有效藥物的

選擇之外，負責攜帶及釋放藥物的支架表面負載平台更是重要。目前藥物攜帶方式大多用聚合物做成支架表面塗層，以做爲藥物負載的平台。而 316 L 不銹鋼無晶型氧化物以肝素藥物塗層證實無晶型氧化物爲一個良好的藥物攜帶平台，其原因可能來自於奈米級的氧化物鑲嵌，深而低的表面負電荷，及無晶型表面氧化物的豐富的氫氧基(OH-)。

無晶型氧化物 316 L 不銹鋼有良好之物理化學特質，抗腐蝕、抗血栓又可做爲攜帶藥物的平台，非常適合用於心血管治療之用途。未來的研究中我們將以 316 L 不銹鋼的無晶型氧化物塗藥技術，測試其在攜帶目前已使用於血管支架的藥物如 Sirolimus 及 Paclitaxel 上是否比現行聚合物塗藥法具優勢。另外也將選擇具有抑制細胞生長作用的中草藥例如厚朴(magnolol)、單參酚酸 B (Salvianolic acid B)等做爲塗藥支架之藥物，研究是否也有很好的塗藥與釋出之效果，以及分析其對生物體血管細胞的影響，特別是在抑制新內膜增生以及發炎反應的影響，並探討此影響的作用機轉及相關之訊息傳遞。期望能提供塗藥支架的改良並使冠狀動脈心臟病及血管狹窄的治療更進一步。

英文摘要

316L stainless steel is a popular medical material, and extensively employed in modern clinical practice, especially the usage for endovascular stents. However, There are some important properties for implantable metallic biomaterials , including: (1) good strength to face the tissue compression or cyclic force, (2) corrosion resistance to stabilize electrochemistry in tissue, (3) good biocompatibility, no allergy, cytotoxicity, and no carcinogenicity, (4) thromboresistance for intravascular implants. For most metals used in cardiovascular devices, these properties are strongly related to the nature and processing of the materials including surface texture, surface energy, surface charge and chemical composition. So the surface treatment of endovascular metals should be paid attention particularly.

This series studies demonstrate that corrosion would really occur when 316L stainless steel was exposed to bio-tissue. Corrosion mostly occurred over mechanical damage of metal or since surface inclusion . The corrosion products such as Ni would activate macrophage and are proinflammatory. In smooth muscle cell culture, both corrosion supernatant and corrosion precipitate inhibited cell growth and the cytotoxicity is related to concentration of Ni.

Most metals and alloys form a protective oxide film on the surface, which will retard the further dissolution of the metal ions into the environment. If surface oxide of 316L stainless steel were successfully passivated to amorphous oxide by a special procedure. The oxide particles would become tiny (0.3 nm diameter) and is mainly Chromium Hydroxyl group oxide. Open circuit potential would be negative, time

constant would be high and the thomboresistance much better than 316L stainless steel treated with thermal oxidation or electropolishing .

Coronary stent mostly composited with 316L stainless steel is the standard treatment of coronary artery disease, but has 20-30 % restenosis rate. Recent studies demonstrated striking reductions in the development of restenosis to about 8 % with drug-coated stents (such as paclitaxel-eluting stent and Sirolimus-coated stent). Both the two marketed drug eluting stents use polymer to coat drug. But we demonstrate that Amorphous oxide has ability to coat and release heparin and is a good non-polymer platform of drug eluting.

We conclude that 316L stainless steel will corrode and have cytotoxicity in tissue. 316L amorphous oxide surface film can change this character and has anti-corrosion, anti-thrombogenicity properties and is a good platform for drug coating. In the future, mechanism of corrosion toxicity and mechanism of drug coating ability of amorphous oxide should be studied. Some other drugs will be tried to coat on amorphous oxide stent and exam the ability of neointimal hyperplasia reduction.