• 系統編號	RN9705-0521
• 計畫中文名稱	細胞支架和細胞內鈣子於 Propofol 造成血管擴張作用中可能扮演之角色研究(II)
• 計畫英文名稱	Roles of Cytoskeleton and Intracellular Calcium in Propofol-Induced Vasodilatation---An in vitro Study (II)
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC95-2314-B038-004
• 執行機構	台北醫學大學麻醉科
• 本期期間	9508 ~ 9607
• 報告頁數	8 頁
• 使用語言	中文
• 研究人員	陳大樑 Chen, Ta-Liang
• 中文關鍵字	內皮細胞; 細胞支架; 鈣離子; 共軛焦顯微鏡
• 英文關鍵字	Endothelial cell; Cytoskeleton; Calcium; Confocal microscopy; Propofol
• 中文摘要	Abstract2,6-雙異丙烷酚(2,6-diisopropylphenol)爲一油溶性製劑之靜脈麻醉劑，目前廣泛使用於麻醉誘導，以及持續性維持麻醉之用。臨床以 propofol 爲誘導藥物時，常導致病人平均動脈壓明顯的下降，周邊血管阻力降低並減少其心輸出量，此現象之確切機轉尚未完全釐清。本研究室過去使用酵素學及生化的方法，propofol 會與細胞色素 P450 的代謝功能產生競爭型之抑制交互作用，使 propofol 在臨床上與其他藥物共用時 (如 propranolol, fentanyl 或 succinylcholine)，產生如低血壓等副作用。至於 propofol 導致的低血壓、心跳減少的副作用，亦可從藥物效力學 (Pharmacodynamics) 的角度來探討，本實驗室過去在細胞株 Gm 7372a(牛主動脈內皮細胞株)的模式中，以共軛焦雷射掃瞄顯微鏡(Confocal laser scanning microscope)在螢光染色下，觀察活細胞內鈣離子的移動情形，證明在 10-5M 濃度的 propofol 存在下，會抑制 Bradykinin 刺激細胞內胞器中釋放鈣離子，進而推論 propofol 可以影響內皮細胞的功能；並且藉由內皮細胞粒線體的型態觀察與粒線體膜電位實驗證明，propofol 的存在的確會影響內皮細胞內粒線體的型態與功能，進而推論 propofol 導致血管舒張及血壓下降的可能機轉。本研究計劃的目的，即在探討「細胞支架」在 propofol 所造成的血管舒張現象機轉中，扮演何種角色？本計劃以人類臍帶靜脈內皮細胞(human umbilical vein endothelial cells; HUVECs)爲研究模式。實驗結果發現 propofol 會藉由抑制 F-actin 和 microtubule 的聚合作用，而造成細胞支架的重整，並透過影響細胞內鈣濃度，進而調控內皮細胞血管收縮或舒張因子的生合成。
• 英文摘要	Induction with 2,6-diisopropylphenol (propofol), might cause significant decreases in arterial blood pressure, systemic vascular resistance and cardiac output. The mechanisms for these adverse effects have not yet been thoroughly elucidated. Our previous studies from drug-metabolism point-of-view demonstrated that propofol exhibited competitive inhibition to the functional activities of hepatic and extrahepatic cytochrome

P450 drug-metabolizing enzymes. These interactions with other coadministered anesthetics might potentiate its clinical vasodilatory effects (pharmacokinetic aspect of drug-interaction). Another postulation for this suppression to cardiovascular function is that propofol may block the voltage-gated influx of extracellular Ca2+ and act as a Ca2+ channel blocker. Our recent data in bovine aortic endothelial model also showed that propofol could affect the intracellular Ca2+ concentration by inhibiting the intracellular Ca2+ mobilization or release from intracellular organelles (pharmacodynamic aspect of drug-interaction). In addition, the membrane potentials and mitochondrial morphology were also interrupted by the propofol that potentially would decrease the energy store of the endothelial cells. Pharmacokinetic or pharmacodynamic aspect, hepatocytes or endothelial cells, drug-metabolism or calcium mobilization, these cellular events are all intracellular trafficking related. Cytoskeleton is the major apparatus for generating tension and transmitting stresses within and among cells (intracellular or intercellular trafficking). The dynamic remodeling of the cytoskeleton causes the alterations in the mechanical force balance, which in turn causes events such as intracellular transport and reorganization. In this study, we found that propofol could modulate remodeling of F-actin and microtubule cytosketones and concentrations of intracellular. In parallel, propofol could regulate biosyntheses of endothelium-derived relaxing and contracted factors.