• 計畫中文名稱	以倍頻光學顯微鏡觀察心房細胞外間質排列亂度與心房顫動之相關		
• 計畫英文名稱	Assessment of the Relation between Entropy of Atrial Extracellular Matrix and Atrial Fibrillation by Harmonics Optical Microscopy		
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• 英文關鍵字	Extracellular matrix； atrial fibrillation； harmonics optic microscopy；entropy		

• 中文摘要

心房細胞外間質(extracellular matrix)膠原纖維的增加，會使得心房細胞的間隙加大，導致電氣訊號傳遞的延滯，因而增加心房顫動發生的機會。因此心房顫動和心房細胞外間質的改變有相當大的關係。這些心房顫動病人血中，代表細胞外間質的第一型膠原蛋白、第三型膠原蛋白、細胞外黏附蛋白(fibronectin protein)及膠原蛋白代謝產物也會增加。這些血清標記在心房顫動病人臨床治療及追蹤的意義上，一直有許多的研究在進行; 但至今沒有研究是直接分析這些血清標記和心房細胞外膠原纖維在三度空間中排列亂度(entropy)的相關性。目前倍頻式光學顯微鏡(harmonics optical microscopy)，這種對組織無破壞性的觀察技術在生物實驗上的應用逐漸增加，藉由三倍頻譜波可直接觀察心房細胞的型態及在三度空間中排列的改變；而藉由二倍頻譜波可觀察膠原蛋白形變與在三度空間中的排列的改變。我們更可以同時使用三倍頻和二倍頻譜波，來直接觀察膠原蛋白和心房細胞相互之間的排列關係。本團隊與台大光電研究所孫啟光教授、中央大學數據分析方法研究中心黃鍔院士共同合作；可以直接觀察心房細胞與細胞外膠原纖維在三度空間中排列的改變；更可以將這些三度空間中排列的變化以亂度來量化與分析。第一年研究，我們計畫將開心手術中取出的病患心房組織以倍頻式光學顯微鏡直接觀察，將記錄並比較正常心律和心房顫動病人心房組織中膠原蛋白在三度空間中排列的差異；同時以西方點墨法及螢光組織染色法測量這些病人第一型膠原蛋白, 第三型膠原蛋白,細胞外黏附蛋白與膠原蛋白代謝產物的血清濃度。藉此，以比較 1)這些纖維化血清標記和心房外間質纖維排列亂度的相關性；2)正常心律病人和心房顫動病人的心房組織中膠原蛋白排列亂度的差異。第二年起則以快速心房搏動刺激方式來製造心房顫動的豬隻後,取出不同部位的心房組織(右心耳、右心房上方、右心房下方連接下腔大靜脈與三尖瓣的島狀部位(isthmus)、心房中隔、左心耳、左心房與肺靜脈交界)以倍頻式光學顯微鏡直接觀察,藉此，以比較 1)正常心律時不同心房部位是否有膠原蛋白三度空間排列亂度的差異；2)正常心律和心房顫動豬隻不同心房部位膠原蛋白三度空間排列亂度的差異。第三年起則給予正常心律與心房顫動的豬隻 statin 類藥物及血管張力素抑制劑藥物三個月後；取出不同部位的心房組織(右心耳、右心房上方、右心房下方連接下腔大靜脈與三尖瓣的島狀部位、心房中隔、左心耳、左心房與肺靜脈交界)以倍頻式光學顯微鏡直接觀察藥物治療有無改變心房組織膠原蛋白三度空間排列的亂度。

• 英文摘要

Atrial fibrillation is associated with fibrosis and atrial remodeling. Enhanced expression of extracellular matrix (ECM) proteins in atrium will cause atrial cells separation by fibrotic depositions, which may increase the incidence of atrial fibrillation. Besides, elevated circulating level of collagen I, collagen III, fibronectin protein and collagen type I degradation marker in atrial fibrillation patient had been found for years. Studies were done for potential clinical use of these serum markers for diagnostic and prognostic propose in atrial fibrillation patient, but no studies about the relation of these markers and collagen fiber alignment in atrium were done. Harmonics-based optical microscopy has been widely applied in biomedical researches. Third-harmonic-generation can provide morphologic information including the distribution of atrial cells and second harmonic generation can provide distribution of collagen fibers. By utilizing second-harmonic-generation and third-harmonic-generation, we can observe collagen fiber alignment directly. Its noninvasiveness to the studied materials makes it a potential in vivo examination tool in the future. In this case-control study, we will exam the atrium tissue taken from patient receiving open heart surgery by harmonic optical microscopy. The collagen alignment and quantify in patient with sinus rhythm and atrial fibrillation will be compared. Besides, we will check their serum collagen I, collagen III, fibronectin protein and collagen type I degradation marker level by quantitative western blotting techniques and immunohistochemical methods. From the second year we will induce sustained atrial fibrillation by rapid pacing in Yorkshire-Landrace pigs. Then the different part of atrial tissue will be examed by harmonic optical microscopy to see if there is geographically distribution difference of collagen alignment in different atrial tissue. In the third year we will give these normal sinus rhythm and atrial fibrillation pigs statin or angiotension converting enzyme inhibitor for 3 months, and check the atrial tissue by harmonic optical microscopy to see if these medication change the collagen alignment.