·实验研究　Experimental research·

新型国产镍钛合金封堵器封堵犬左心耳实验研究

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【摘要】 **目的**　评估新型国产镍钛合金封堵器封堵犬左心耳的临床可行性和有效性。**方法**　选择清洁级健康成年杂种犬 14 只，采用自主研制的新型国产镍钛合金左心耳封堵器，经股静脉途径穿刺房间隔封堵左心耳。分别于术后即刻、1 个月、3 个月通过解剖、经食管超声心动图(TEE)检查等方法观察封堵效果。**结果**　14 只实验犬中 11 只成功植入封堵器(其中 2 例因术中封堵器大小不合适，回收后再次植入成功)，2 例房间隔穿刺时穿刺针误入心包引起心包积液而终止手术，1 例术后随访发现封堵器脱入左心室，无其它手术并发症。术后各时间点分别处死实验犬，术后 1 个月大体观察见封堵器表面覆盖稀疏细胞，其上有内皮细胞，未见血栓及赘生物。术后 3 个月 TEE 检查见封堵器形态、位置良好，左心耳被完全封堵，左心房内无血栓形成；大体解剖见封堵器表面完全被内皮细胞覆盖，肝、肾、脾脏无血栓栓塞或梗死灶。**结论**　新型国产镍钛合金封堵器经导管封堵左心耳完全可行，中期效果理想。

【关键词】 左心耳；封堵器；动物实验；犬

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A novel domestic nitinol occluder used for the occlusion of left atrial appendage: an experimental study in dogs

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【**Abstract**】 **Objective**　To assess the clinical feasibility and efficacy of a novel domestic nitinol occluder for the obstruction of left atrial appendage (LAA) in experimental dogs. **Methods**　A total of 14 clean level healthy mongrel dogs were selected for this study. A novel domestic nitinol LAA occluder was used to obstruct the LAA through puncturing atrial septum via femoral vein route in all experimental dogs. By using autopsy, transesophageal echocardiography (TEE) examination and other methods the experimental results were evaluated immediately after the procedure as well as at one and three months after the procedure. **Results**　Among the 14 dogs, LAA occluder was successfully implanted in 11 dogs, and in 2 of these 11 dogs the initially implanted occluder had to be retrieved as its size was not suitable and the implantation of suitable occluder had to be carried out. In two dogs, pericardial effusion occurred because during the performance of puncturing atrial septum the puncture needle wrongly entered into the pericardium, and the procedure had to be stopped. In one dog, follow-up examination revealed that the occluder dropped into the left ventricle. No other procedure-related complications were observed. After the operation, the experimental dogs were sacrificed at different points of time. One month after the operation, general observation showed that the sulface of occluder was covered by sparse endotherial cells and there was no thrombus and neoplasm on the sulface of the occluder. Three months after operation, the TEE examination showed that the shape and

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position of the occluder was in good condition, LAA cavity was completely obstructed, and no thrombosis was observed in left atrium. Gross anatomy showed that the surface of the occluder was completely covered with endothelial cells, and no thrombus or infarction was found in the liver, kidney and spleen. **Conclusion** It is completely feasible to use the novel domestic nitinol occluder to obstruct LAA through catheter, and the medium-term effect is satisfactory.(J Intervent Radiol, 2016, 25: 886-890)

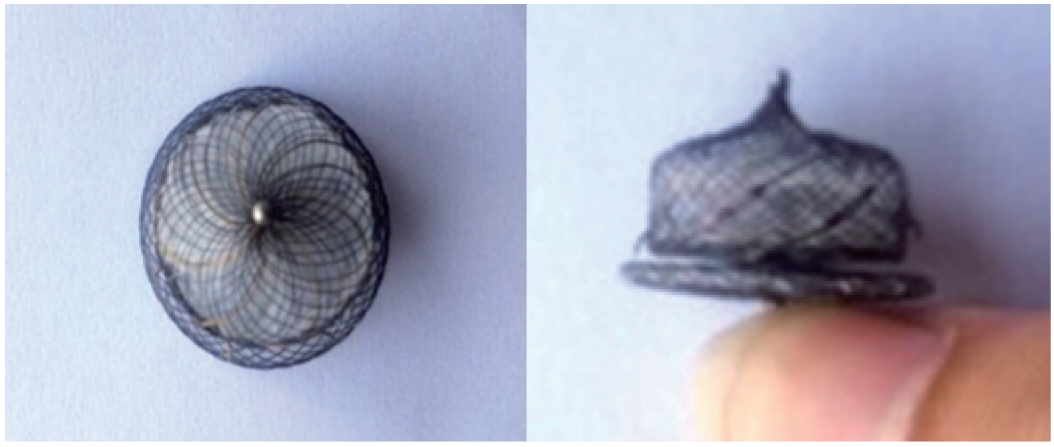
【**Key words**】 left atrial appendage; occluder; animal experiment; dog

心房颤动是临床最常见心律失常之一[1]。有研究显示 65 岁以上老年人群中 50%~60%有无症状性心房颤动[2-3]。非瓣膜性心房颤动使脑卒中风险增加 5 倍[1],而二尖瓣狭窄伴发心房颤动患者脑卒中风险增加 17 倍[4]。与心房颤动相关的血栓事件约 75%来自左心房血栓[5]。尸检、超声心动图及手术报告显示左心房血栓 91%发生于非瓣膜性心房颤动患者,57%发生于风湿病性心房颤动患者左心耳死腔样结构[6]。目前预防心房颤动引起脑卒中的主要方法是口服华法林, 一项 Meta 分析提示达到目标剂量的华法林能够使整体脑卒中风险降低 64%[7]。然而华法林应用率仍很低,因其有出血风险、需规律监测凝血酶原时间国际标准化比值(INR)、治疗窗窄、很易受食物及药物影响[4,8]。新型口服抗凝药物作为华法林替代药物正越来越广泛应用,但价格较昂贵,仍存在出血风险,且缺乏相应拮抗药物。左心耳封堵术是近年发展的新技术,适用于抗凝禁忌或不能耐受长期抗凝,且有栓塞高危因素患者。采用特制封堵器如经皮左心耳封堵(PLAATO)系统、Watchman 封堵器及 Amplatzer 封堵系统(ACP)闭塞左心耳,创伤小、操作简单、成功率高,已成为介入心脏病学研究热点。本研究旨在评价新型国产左心耳封堵器应用于动物经皮左心耳封堵术的可行性和有效性,为进一步临床应用提供实验依据。

1 材料与方法

1.1 实验动物与器材

实验动物为清洁级健康成年杂种犬(上海甲干生物科技有限公司提供)14 只, 体重 12~20 kg,雌雄不限。实验器材包括 8 F Swartz 房间隔穿刺系统、Brockenbrough 穿刺针(美国 St.Jude 医疗公司)、0.032 英寸导丝、左心房 2 圈半钢丝、6 F 防漏鞘管及猪尾导管、8~10 F 左心耳房间隔输送鞘管及扩张管、新型国产镍钛合金左心耳封堵器(上海普实医疗器械公司,图 1)、Lepu X 线数字减影血管造影系统(北京乐普医疗器械公司)、心电监测仪、IE33 S7-2 经食管超声心动图仪(荷兰 Philips 公司)以及盐酸赛拉嗪(速眠新Ⅱ)注射液(1.5 ml/支)、1%丙泊酚注射液、硫酸阿托品注射液(0.5 mg/支)、碘普罗胺或碘克沙醇注射液(100 ml/瓶)、青霉素钠粉针剂(80 万 U/支)。



注:根据心耳内盘片直径,有 14 mm、16 mm、18 mm、20 mm 等 4 种规格

图 1 新型国产左心耳封堵器正侧面观

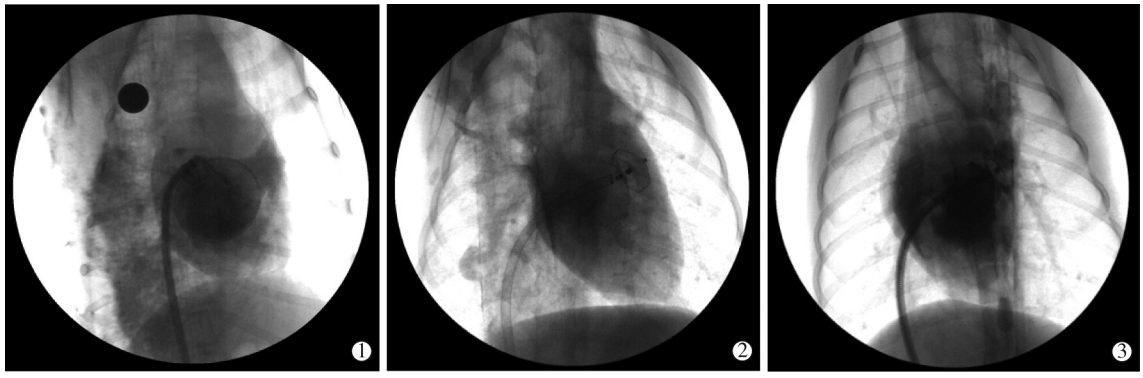
1.2 麻醉及术前准备

实验犬先后肌内注射硫酸阿托品(1 支)、盐酸赛拉嗪(0.08~0.1 ml/kg),麻醉起效后将实验犬固定于 V 字型手术台上,接心电图监护,备净双侧腹股

沟处皮毛;常规消毒、铺无菌巾单,穿刺右侧股静脉后置入 6 F 防漏鞘管, 术中根据实验犬麻醉深度给予 1%丙泊酚,以 4~12 mg·kg^{-1}·h^{-1} 速率持续输注或重复单次静脉注射 2~5 ml(20~50 mg);穿刺左侧股静脉后置入防漏鞘,接 0.9%氯化钠 500 ml+青霉素钠 240 万 U 静滴。

1.3 房间隔穿刺及左心耳封堵器植入

沿右侧股静脉鞘送入 0.032 英寸导丝至右心房,退出鞘管,沿导丝送入 8 F Swartz 房间隔穿刺鞘至右心房,透视下调整穿刺鞘方向使其长轴充分舒展,鞘管头端指向上方,回撤导丝至穿刺鞘内再出导丝,将导丝送至上腔静脉,按照王胜强等[9]报道的穿刺方法作房间隔穿刺; 穿刺成功后沿穿刺针尾端推注少量对比剂迅速在左心房弥散,采用张志钢等[10]报道的经皮左心耳封堵途径固定穿刺针,推送鞘管超出穿刺针 2~3 mm,撤出穿刺针,确认无心脏压塞后注入普通肝素(80~100 U/kg),经扩张鞘送入左心房钢丝至左心房内,确认钢丝在左心房弯曲 2~3 圈后,透视下固定扩张鞘及钢丝,推送 Swartz 外鞘至左心房内,退出扩张鞘;沿左心房钢丝送入猪尾导管至左心耳内,沿猪尾导管将 Swartz 外鞘送至左心耳内,在右前斜 30°、右前斜 30°+头位 10°~20°、右前斜 30°+足位 10°~20°作左心房造影, 选择左心耳颈部显影最清晰体位测量颈部直径(参照钢球,直径 14 mm),在颈部实测值基础上选择直径大 2 mm 心耳内盘片直径封堵器,释放后造影显示无残余分流(图 2),随后心电监护 1 h,透视观察心影无增大、无心脏压塞迹象后,予以双侧股静脉穿刺点 8 字形缝合并压迫 20~30 min, 确保局部无渗出及血肿后包扎。



①右前斜 30°+头位 10°造影清晰示左心耳颈部;②选择合适封堵器植入;③封堵器释放后造影示无残余分流

图 2 左心耳封堵器植入 DSA 影像

1.4 术后随访

术后随访实验犬 5~7 d,给予青霉素钠 80 万 U(2 次/d)肌内注射,依诺肝素(20 mg/12 h)皮下注射,每天口服阿司匹林 50 mg、氯吡格雷 25 mg 直至随访结束。

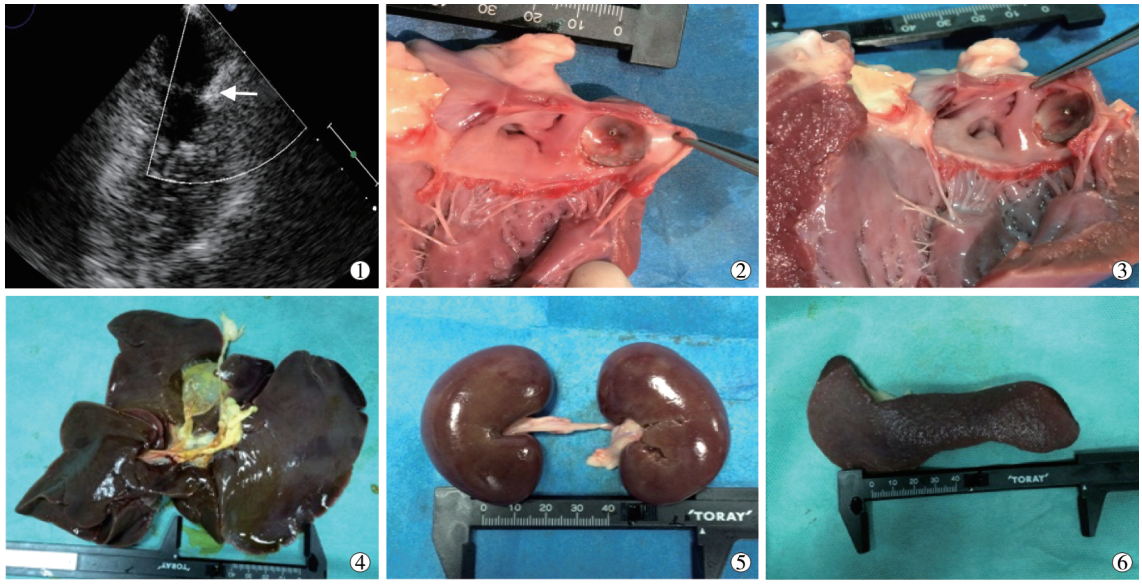
2 结果

14 只实验犬中 11 只成功植入封堵器(其中 2 只因术中封堵器大小不合适, 回收后再次植入成功),2 只房间隔穿刺时穿刺针误入心包引起心包积液而终止手术,1 只术后随访发现封堵器脱入左心室致动物死亡。无其它手术并发症。手术时间 90~120 min,X 线曝光时间 25~35 min。按实验节点处死实验犬,术后 1 个月大体观察显示封堵器表面覆盖稀疏内皮细胞,未见血栓及赘生物。术后 3 个月经食管超声心动图(TEE)检查显示封堵器形态、位置良好,左心耳被完全封堵,左心房内无血栓形成;大体解剖可见封堵器表面完全被内皮细胞覆盖,左上、下肺静脉及二尖瓣未受影响,肝、肾、脾脏无栓塞或梗死灶(图 3)。

3 讨论

经皮左心耳封堵术适用于抗凝治疗有禁忌、接受抗凝治疗仍发生栓塞事件或不能耐受抗凝治疗患者[11]。2012 年欧洲心脏病学会(ESC)和 2014 年美国心脏病学院(ACC)/美国心脏协会(AHA)/美国心律协会(HRS)将经皮左心耳封堵术列为治疗心房颤动有高危脑卒中和长期口服抗凝治疗有禁忌患者的Ⅱb 类推荐手段[12-13]。目前临床上应用的多为进口左心耳封堵器,价格高昂,因此尽快研制出适合国情的左心耳封堵器显得尤为重要。

我院在既往左心耳封堵器研究[14]基础上,与上海普实医疗器械科技有限公司合作研制出新型左心耳封堵器。该封堵器与 ACP 封堵器类似,具有操



①TEE 检查示封堵器形态、位置良好，左心耳被完全封堵，左心房内无血栓形成；②大体解剖示封堵器表面完全内皮化；③左上、下肺静脉及二尖瓣未受影响；④⑤⑥肝、肾、脾脏无栓塞或梗死灶

图 3　术后 3 个月 TEE 和大体解剖检查图像

作简便、回收容易、能最大程度减少左心耳残腔的特点，不同点在于左心耳内盘片采用圆锥形柱状，可以较好地适应各种形态左心耳；双排倒刺，多方位植入倒刺，倒刺长度为 1~2 mm；释放后位置不佳可予回收，且输送系统管径为 12 F，相对较细。本实验采用与人左心耳形态相似的犬作为动物模型，封堵途径亦是通过外周静脉穿刺房间隔。本实验即刻封堵成功率达 78.6%，主要并发症为穿刺房间隔失败导致的心脏压塞，这与操作者熟练程度及犬心脏变异较大有关；封堵器型号选择一般比左心耳颈部直径大 2 mm，这样既能保证封堵器在左心耳腔内不会脱落，也不影响左心耳周围组织结构；封堵术后 3 个月 TEE 及解剖学检查提示封堵器位置良好，表面内皮化好，无血栓及赘生物，生物相容性好。

关于左心耳封堵术后抗凝策略文献报道不一。有研究报道为避免术后封堵器上血栓形成，术后常规给予阿司匹林(100 mg/d)+华法林(INR 目标值 2.0~3.0)，直至 45 d 后 TEE 检查提示封堵器位置良好，周围无或仅有很少残余分流(<5 mm)可停用华法林，随之加用氯吡格雷(75 mg/d)，直至术后 6 个月[15]；也有一些中心甚至建议术后 3~6 个月停用阿司匹林，但缺乏长期随访数据。Viles-Gonzalez 等[16]报道残余分流<5 mm 患者封堵术后发生脑卒中/短暂性脑缺血发作概率与无残余分流患者相比，无明显差异；如果 TEE 证实残余分流>5 mm，继续予以华法林 3 个月后再次 TEE 检查分流量仍无明显改变提示封堵失败，患者仍需长期口服抗凝药；如果分流量减少至<5 mm，可改用阿司匹林+氯吡格雷抗血小板治疗[17]。对口服华法林有绝对或相对禁忌证患者，ASAP 研究[18]推荐方案是封堵术后 6 个月口服阿司匹林+氯吡格雷，随后单独口服阿司匹林；如果术后 TEE 检测封堵器表面有血栓形成，需再次给予 4~8 周低分子肝素或口服抗凝药并复查 TEE[17]。

本实验采用国产新型镍钛合金左心耳封堵器完成左心耳封堵术，结果提示该封堵器封堵犬左心耳确实简便易行，封堵效果确切、并发症较少、生物相容性好。本研究不足之处在于实验例数较少，长期效果还有待于进一步随访观察。我院正在扩大实验样本量，以期获得更加全面的远期实验数据，为下一步临床应用提供依据。

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