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三维标测系统射频消融去肾交感神经术对高血压犬模型血压和心脏功能的影响

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[摘　要]　**目的：**研究三维标测系统指导下射频消融去肾交感神经术(renal sympathetic denervation，RSD)对高血压犬模型血压和心脏功能的影响。**方法：**10只合格的比格犬适应性喂养1周后随机分为手术组和假手术组(n=5)，均造成高血压模型犬，造模后手术组在CARTO三维标测系统指导下实施RSD术，假手术组仅行双肾动脉造影术。获取比格犬血压监测数据，术前(造模后12周)、术后2周行超声心动图检查，测定心脏功能指标，同时采集血清标本测定血管紧张素II(angiotensin II，AngII)、丙二醛(malondialdehyde，MDA)、一氧化氮(nitric oxide，NO)浓度。**结果：**两组比格犬造模前、造模后12周收缩压(systolic blood pressure，SBP)、舒张压(diastolic blood pressure，DBP)及平均动脉压(mean arterial pressure，MAP)比较无统计学意义(P>0.05)；与造模后12周比较，手术组术后2，4，8周SBP，DBP及MBP水平显著下降(P<0.05)；与假手术组比较，手术组术后2，4，8周时SBP，DBP及MAP水平显著降低(P<0.05)。术后手术组左室收缩末期内径(left ventricular end-systolic diameter，LVESD)、左室舒张末期内径(left ventricular end-diastolic diameter，LVEDD)、心输出量(cardiac output，CO)、心脏指数(cardiac index，CI)及左室射血分数(left ventricular ejection fraction，LVEF)显著改善，且LVESD，LVEDD明显低于假手术组，CO，CI，LVEF明显高于假手术组(P<0.05)。术后手术组血清AngII，MDA，NO水平显著改善，且AngII和MDA水平明显低于假手术组，NO水平明显高于假手术组(P<0.05)。**结论：**三维标测系统指导下RSD可有效降低高血压犬模型血压及改善心脏功能，可能与其抑制肾素血管紧张素系统、减轻氧化应激反应及改善血管内皮功能有关。

[关键词]　三维标测系统；射频消融去肾交感神经术；高血压犬模型；血压；心脏功能

Effect of three-dimensional mapping-guided radiofrequency ablation of renal sympathetic denervation on blood pressure and cardiac function in hypertensive canine models

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Abstract **Objective:** To investigate the effect of three-dimensional mapping-guided radiofrequency ablation of renal sympathetic denervation (RSD) on the blood pressure and cardiac function in hypertensive canine models. **Methods:** Ten qualified beagle dogs were randomly divided into the operation group and the sham operation group with 5 dogs in each group after 10 weeks of adaptive feeding. All of them were used for hypertensive canine models. The operation group was treated by RSD under the guidance of CARTO 3D mapping system after modeling while the sham operation group was given bilateral renal arteriography. The blood pressure monitoring data were obtained. Echocardiography was performed before operation (12 weeks after modeling) and 2 weeks after operation to determine the cardiac function parameters. Serum samples were collected to determine the levels of angiotensin II (AngII), malondialdehyde (MDA) and nitric oxide (NO). **Results:** There was no statistically significant difference in the systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial pressure (MAP) in the two groups before modeling and at 12 weeks after modeling (P>0.05). The SBP, DBP and MBP in the operation group at 2, 4 and 8 weeks after operation were significantly lower than those at 12 weeks after modeling (P<0.05), and those in the sham operation group (P<0.05). The left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), cardiac output (CO), cardiac index (CI) and left ventricular ejection fraction (LVEF) in the operation groups were significantly improved after operation. The LVESD and LVEDD were significantly smaller than those in the sham operation group, while CO, CI and LVEF were significantly larger than those in the sham operation group (P<0.05). The levels of serum AngII, MDA and NO in the operation group were significantly improved after operation, and the levels of AngII and MDA were significantly lower than those in the sham operation group while the level of NO was significantly higher than that in the sham operation group (P<0.05). **Conclusion:** The three-dimensional mapping system guided RSD can effectively decrease the blood pressure and improve the cardiac function in hypertensive canine models, which may be related to inhibiting the renin-angiotensin system, reducing oxidative stress response and improving endothelial function.

Keywords three-dimensional mapping system; radiofrequency ablation renal sympathetic denervation; hypertensive canine model; blood pressure; cardiac function

尽管目前可供高血压患者选择的降压药很多，如长效降压药物和复合制剂，但高血压病患者需长期终身用药，患者的经济负担大，且在接受规范药物降压治疗的患者中仍有约10%的患者血压不能达到靶目标，尤其以合并慢性肾脏疾病的肾性难治性高血压患者更为常见。尤其值得关注的是，通常顽固性高血压病患者足量联合地应用3种降压药物(包括利尿剂)后，血压仍难以降至目标水平，或至少需要同时应用4种降压药物才能使血压达标，并可能导致严重的靶器官损害，增加心脑血管意外风险[1-3]。因此，临床上一直在寻找能够简单、安全、有效地控制顽固性高血压的新的治疗手段。研究[4]表明：高血压的发病与肾有着十分密切的联系，肾交感神经过度激活是高血压发生和维持的关键因素，因此抑制交感神经的过度激活被认为是治疗顽固性高血压及其相关并发症的重要靶点。经导管射频消融去肾交感神经(catheter-based renal sympathetic denervation，RSD)治疗顽固性高血压取得了初步成就，但其引起的肾动脉狭窄、肾交感神经消融不彻底等并发症也时有报道[5]，寻求新的治疗方法来指导RSD有重要意义。基于此，本研究拟探索在CARTO三维标测系统指导下RSD的有效性。

1 材料与方法

1.1 实验动物

10~12月龄的合格比格犬10只，雌雄不限，体重9.5~12.0(10.92±1.45) kg。比格犬由南方医科大学实验动物中心提供，于实验前2周购进后进行单笼饲养，饲养环境适宜，温度(22±2) ℃，湿度40%~70%，适应性喂养1周后将10只比格犬随机分为手术组和假手术组，每组5只，均造成高血压模型犬，造模后手术组在CARTO三维标测系统指导

下实施RSD术，假手术组仅行双肾动脉造影。实验过程中对动物的处置符合中华人民共和国国家标准GB/T 16886.2-2011医疗器械生物学评价关于动物福利要求方法的相关规定。

1.2 高血压模型犬的建造

将比格犬麻醉成功后固定于试验台，对其颈部备皮，常规消毒铺巾，应用预先高温消毒的无菌器械操作，于颈部左侧做直线切口后分离颈动脉与迷走神经，以10 cm 5-0肠铬线固定于脱髓鞘后的迷走神经，并连接在周围组织上，与颈动脉形成交叉压迫，最终以颈动脉的规律性波动对迷走神经形成持续压迫造成高血压模型。

1.3 血压监测

采用智能无创动物血压仪(BP-10E型，北京软隆生物技术有限公司)测量所有高血压模型犬清醒状态下尾动脉血压。具体方法如下：比格犬置于固定架上，待其完全平静后将套袖放置于其尾根部，设置血压仪的参数，仪器自动读出收缩压(systolic blood pressure，SBP)、舒张压(diastolic blood pressure，DBP)及平均动脉压(mean arterial pressure，MAP)。取建模后2，4，6，12周为监测时间点，监测结果显示血压在6~12周处于稳定状态，且SBP>120 mmHg，DBP>75 mmHg (1 mmHg=0.133 kPa)认为造模成功。所有比格犬造模成功后进行后续实验，造模后12周开展CARTO三维标测系统指导下RSD术或双肾动脉造影术，分别选取术后第1，2，4，8周为监测时间点再次进行血压测定，记录血压水平。

1.4 手术方法

手术组实施三维标测系统指导下RSD术：以氯胺酮诱导麻醉，称体质量，备皮，以固定架将手术组比格犬仰卧固定后置于手术操作台，术中以丙泊酚维持麻醉并持续行心电监护和氧饱和度监测。左、右腹股沟中点外下方切开皮肤、钝性分离皮下组织及肌肉，暴露右侧股动脉及左股静脉，采用Seldinger法分别穿刺右股动脉与左股静脉。穿刺成功后于股动脉置入8F动脉鞘，股静脉置入6F防漏鞘管，经鞘管注射普通肝素100 U/kg。经股动脉鞘管插入6F猪尾巴导管至腹主动脉，外接高压注射器，采用碘海醇行选择性双肾动脉造影，然后拔出造影导管。连接普通电生理消融导管与体表电极。同时将CARTO三维标测系统与射频消融仪相并联，插入6F环状标测电极至腹主动脉，上、下来回移动电极导管，重建腹主动脉三维解剖图像。然后经动脉鞘导入7F消融电极导管至肾动脉，调整消融导管头端和电极导管方向，构建一侧肾动脉的三维几何模型。参考电极为经股静脉鞘插入环状标测电极至下腔静脉近肾静脉口处，在CARTO系统导航下引导7F消融导管在随机选择的一侧肾动脉主干内由远及近行螺旋状消融。能量设置为预设温度45 ℃，能量输出8 W，消融时间120 s。以相同方法构建对侧肾动脉三维几何模型，并取点标记，拔出射频消融导管后再次肾动脉造影。术后拔除鞘管，结扎股动静脉止血，最后缝合皮下组织及皮肤。假手术组行双肾动脉造影术，不进行肾动脉消融。本次实验结束后所有犬模型通过化学药物法实施安乐死。

1.5 观察指标

1)获取比格犬造模前、造模后12周(术前)、术后1，2，4，8周SBP、DBP及MAP监测数据。2)心脏功能评估：术前(造模后12周)、术后2周行超声心动图检查，测定所有比格犬左室收缩末期内径(left ventricular end-systolic diameter，LVESD)、左室舒张末期内径(left ventricular end-diastolic diameter，LVEDD)、心输出量(cardiac output，CO)、心脏指数(cardiac index，CI)及左室射血分数(left ventricular ejection fraction，LVEF)。3)血清指标测定：术前(造模后12周)、术后2周采集所有比格犬大隐静脉血4 mL于促凝管，低温离心机离心处理15 min后存于−80 ℃冰箱保存待测；采用放射免疫法、TBA法、硝酸还原酶法分别测定血清血管紧张素II(angiotensin II，AngII)、丙二醛(malondialdehyde，MDA)、一氧化氮(nitric oxide，NO)浓度。

1.6 统计学处理

采用SPSS19.0软件进行数据分析。计量资料以均数±标准差($\bar{x}\pm s$)表示，同一组术前、术后比较采用配对t值检验，组间对比进行独立t值检验，以$P<0.05$为差异有统计学意义。

2 结果

2.1 两组比格犬术前、术后血压水平比较

两组比格犬造模前、造模后12周(术前)SBP，DBP及MBP比较差异均无统计学意义($P>0.05$)；造

模后12周SBP，DBP及MBP与造模前比较均显著升高(P<0.05)；与造模后12周比较，手术组术后2，4，8周SBP，DBP及MBP水平显著下降，假手术组仅术后2周明显下降(P<0.05)；手术组术后2，4，8周SBP，DBP及MAP水平显著低于假手术组(P<0.05，图1)。

2.2 两组比格犬术前、术后心脏功能比较

两组比格犬术前LVESD，LVEDD，CO，CI，LVEF比较差异无统计学意义(P>0.05)；术后手术组LVESD，LVEDD，CO，CI，LVEF显著改善，且LVESD，LVEDD明显低于假手术组，CO，CI，LVEF明显高于假手术组(P<0.05)；假手术组术后上述心脏功能指标未见显著改善(P>0.05；表1，图2)。

2.3 两组比格犬术前、术后血清指标比较

两组比格犬术前血清AngII，MDA，NO比较差异无统计学意义(P>0.05)；术后手术组血清AngII，MDA，NO水平显著改善，且术后AngII，MDA水平明显低于假手术组，NO水平明显高于假手术组(P<0.05)；假手术组术后上述血清指标均未见显著改善(P>0.05，表2)。

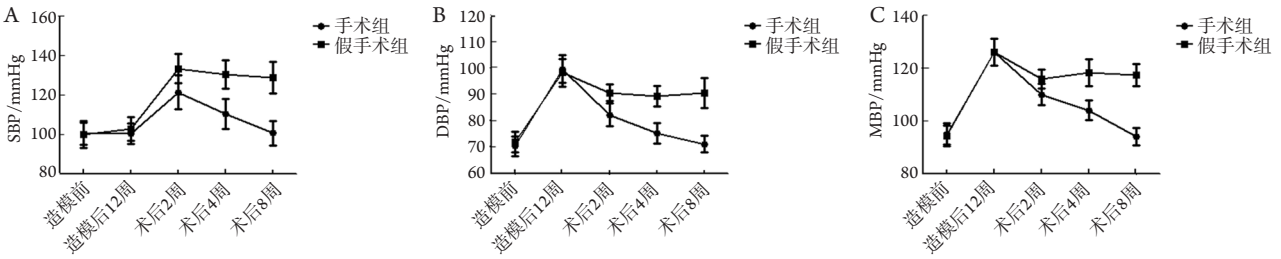

图1 两组SBP(A)，DBP(B)和MAP(C)水平比较

Figure 1 Comparison of SBP (A), DBP (B) and MAP (C) levels between the two groups

表1 两组比格犬术前、术后心脏功能比较(n=5，$\bar{x} \pm s$)

Table 1 Comparison of cardiac function of beagle dogs before and after operation between the two groups (n=5, $\bar{x} \pm s$)

组别	LVESD/mm	LVEDD/mm	CO/(L·min^{-1})	CI/(L·min^{-1}·g^{-1})	LVEF/%
手术组					
术前	14.26 ± 2.64	32.56 ± 5.86	1.71 ± 0.33	0.13 ± 0.03	43.49 ± 4.51
术后	9.98 ± 1.23*&	26.39 ± 3.14*&	3.70 ± 0.54*&	0.30 ± 0.05*&	60.46 ± 6.48*&
假手术组					
术前	14.03 ± 2.39	32.25 ± 5.92	1.75 ± 0.40	0.13 ± 0.04	44.10 ± 4.88
术后	13.87 ± 1.96	31.39 ± 4.06	1.79 ± 0.42	0.014 ± 0.06	46.08 ± 5.79

与术前比较，*P<0.05；与假手术组比较，&P<0.05。

Compared with before operation, *P<0.05; compared with the sham operation group, &P<0.05.

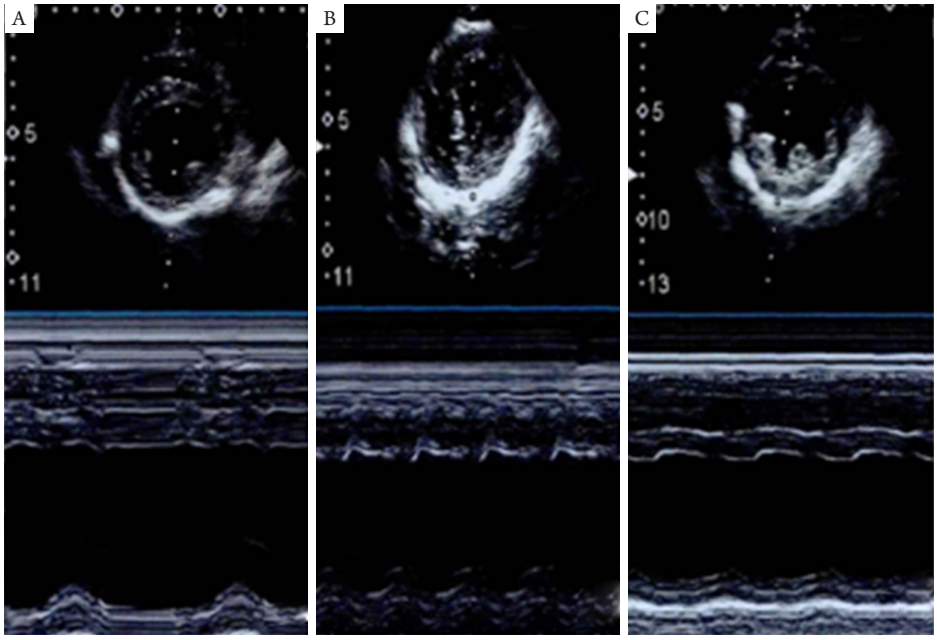

图2 超声心动图示例

Figure 2 Echocardiogram example

(A)造模前(术前)正常超声心动图；(B)手术组术后2周超声心动图，室间隔厚度与左室后壁厚度与正常相比差异不明显；(C)假手术组术后2周超声心动图，室间隔厚度与左室后壁厚度明显增加。

(A) Normal echocardiography before modeling (preoperation); (B) Echocardiogram, interventricular septum thickness and left ventricular posterior wall thickness in operation group were not significantly different from normal two weeks after operation; (C) Echocardiogram, interventricular septum thickness and left ventricular posterior wall thickness increased significantly in sham-operated group 2 weeks after operation.

表2 两组比格犬术前、术后血清指标比较(n=5，$\bar{x} \pm s$)

Table 2 Comparison of serum indexes of beagle dogs before and after operation between the two groups (n=5, $\bar{x} \pm s$)

组别	AngII/(ng·mL^{-1})	MDA/(nmol·mL^{-1})	NO/(μmol·L^{-1})
手术组			
术前	120.50 ± 17.97	15.79 ± 1.89	52.33 ± 5.80
术后	74.36 ± 9.34*&	7.32 ± 1.21*&	79.54 ± 6.79*&
假手术组			
术前	121.43 ± 16.34	15.56 ± 2.07	52.44 ± 5.75
术后	119.47 ± 14.91	15.27 ± 2.20	51.43 ± 5.60

与术前比较，*P<0.05；与假手术组比较，&P<0.05。

Compared with before operation, *P<0.05; compared with the sham operation group, &P<0.05.

3 讨论

研究[6-7]表明：肾交感神经过度激活是高血压发生和维持的关键因素。肾交感神经分为传出纤维和传入纤维，其中传出纤维过度激活产生和分泌过多的去甲肾上腺素，使肾血管收缩肾血流减少，进而激活肾素-血管紧张素-醛固酮系统，导致血管收缩、水钠重吸收增多，而传入纤维的过度激活，可激活中枢交感神经系统，使全身交感神经活性亢进，从而引起肾、心和血管等靶器

官的结构和功能改变，导致高血压、充血性心力衰竭等。因此，理论上肾去交感神经可降低肾脏局部和全身的交感神经活性，抑制交感神经的过度激活被认为是治疗顽固性高血压及其相关并发症的重要靶点，而肾交感神经纤维进出肾绝大部分经肾动脉主干外膜，这一解剖特点决定了RSD可选择性消融肾交感神经纤维。Investigators等[8]最早采用RSD治疗顽固性高血压取得了初步成就，该研究在澳大利亚和欧洲的5个中心共纳入50例顽固性高血压患者，其中5例患者解剖原因未行RSD治疗，剩余进行RSD手术治疗的患者血压较前得到良好的控制，这为顽固性高血压的治疗提供了一条新思路。随后2010年一项多中心、前瞻性、随机对照的研究[9]发现：106例顽固性高血压患者中，RSD手术组对比多药联合治疗组出现更显著的降压效果，进一步初步证实了该技术治疗顽固性高血压的有效性和安全性。然而，虽然随后几年，RSD手术的有效性与安全性逐步得到认可，但仍有学者[10]认为消融方法不当可能导致未能完全去除肾交感神经，尤其是Bhatt等[11]、Epstein等[12]均认为RSD手术较为安全，但其难以达到预期的主要临床终点。为此，有必要寻求新的治疗方法来指导RSD。国外有文献[13]显示：通过EnSite-NavX建立肾动脉三维立体模型指导RSD治疗顽固性高血压安全有效，且可显著减少X线曝光时间与造影剂用量。谭洪文等[14]的基础报道亦支持此观点。但目前国内关于三维标测系统在RSD手术中的应用报道仍较少见。

本研究应用CARTO三维标测系统引导盐水灌注导管RSD治疗高血压模型犬(手术组)，以行双肾动脉造影术为对照(假手术组)。结果显示两组比格犬造模前、造模后12周SBP，DBP及MBP比较均无明显差异，与造模后12周比较，手术组术后2，4，8周SBP，DBP及MBP水平显著下降；且与假手术组比较，手术组术后2，4，8周SBP，DBP及MAP水平显著低。同时，术后手术组LVESD，LVEDD，CO，CI，LVEF显著改善，且LVESD，LVEDD明显低于假手术组，CO，CI，LVEF明显高于假手术组，而假手术组术后上述心脏功能指标未见显著改善。证实三维标测系统指导下RSD可有效降低高血压犬模型血压及改善心脏功能，与刘莉等[15]的报道相符。王彬等[16]的研究建立肥胖型高血压家兔模型后实施RSD处理，与对照组比较，肥胖+RSD组的血压无显著差异，与肥胖组比较，肥胖+RSD组的血压显著降低，且肥胖+RSD组血浆去甲肾上腺素、精氨酸血管加压素、AngII和醛固酮较肥胖组明显下降；由此认为RSD可降低肥胖型高血压动物的血压，与降低血浆甲肾上腺素、精氨酸血管加压素、AngII和醛固酮水平具有一定相关性。为了进一步分析三维标测系统指导下RSD降低高血压犬模型血压及改善心脏功能的可能机制，本研究采集所有比格犬血清标本，检测血清AngII，MDA，NO浓度。发现术后手术组血清AngII，MDA，NO水平显著改善，且术后AngII，MDA水平明显低于假手术组，NO水平明显高于假手术组，而假手术组术后上述血清指标均未见显著改善。其中AngII可通过激活突触前AngII 1型受体，促进儿茶酚胺类物质释放来实现间接增强交感神经活性，导致血压升高；且AngII是激活肾素血管紧张素系统中最重要的生物活性分子，其水平与交感神经活性密切相关[17]。而血清MDA的增加及NO的降低往往可分别反映氧化应激的激活及血管内皮功能的受损[18]。因此，上述结果显示三维标测系统指导下RSD可有效改善高血压犬模型血清AngII，MDA，NO浓度，由此推测其降低高血压犬模型血压及改善心脏功能的机制可能与抑制肾素血管紧张素系统、减轻氧化应激反应及改善血管内皮功能有关，但其仍需进一步深入探究与论证。

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