

DOI: 10.16781/j.CN31-2187/R.20220221

· 论 著 ·

心血管反射试验与心率变异性诊断糖尿病心脏自主神经病变方法比较

张 珊¹, 徐梦珠², 樊月月¹, 项 颖³, 吴 坚^{4*}, 郝 娟⁴

1. 上海中医药大学市中西医结合临床医学院, 上海 201203

2. 郸城县第一人民医院, 郸城 276100

3. 上海中医药大学附属上海市中西医结合医院心电图室, 上海 200082

4. 上海中医药大学附属上海市中西医结合医院内分泌科, 上海 200082

[摘要] **目的** 探讨心血管反射试验(CART)及心率变异性(HRV)诊断糖尿病心脏自主神经病变(DCAN)的应用价值。**方法** 纳入2020年2月至12月于上海中医药大学附属上海市中西医结合医院住院治疗的2型糖尿病(T2DM)患者154例作为研究对象,所有患者均接受CART和24 h动态心电图检查并分析HRV指标,比较CART与HRV这2种方法诊断DCAN的差异。**结果** 154例T2DM患者中,采用CART诊断的DCAN组有101例、非DCAN组有53例,DCAN发病率为65.58%(101/154)。DCAN组与非DCAN组患者的年龄、病程、糖尿病周围神经病变发病率的差异均有统计学意义(P 均 <0.05),而性别、高血压、烟酒嗜好、BMI、腰臀比、糖化白蛋白、脑钠肽差异均无统计学意义(P 均 >0.05);DCAN组与非DCAN组患者的深呼吸心率差、立卧位心率变化、Valsalva动作指数、卧立位血压差差异均有统计学意义(P 均 <0.05);DCAN组与非DCAN组患者HRV指标所有正常R-R间期的标准差(SDNN)、每5 min正常R-R间期的标准差均值(SDANN)、相邻R-R间期差值均方根(RMSSD)、相差 >50 ms的相邻R-R间期占R-R间期总数的百分比(pNN50)、总功率(TP)、超低频(VLF)、低频(LF)、高频(HF)差异均有统计学意义(P 均 <0.05)。根据24 h动态心电图的HRV指标诊断DCAN发病率为59.74%(92/154),HRV与CART诊断的总符合率为61.68%, $Kappa$ 值为0.184,HRV诊断的DCAN的灵敏度及特异度分别为66.34%、52.83%。按CART评分将T2DM患者分为4个等级(无DCAN、亚临床DCAN、确诊DCAN、严重DCAN),DCAN病变程度与SDNN、SDANN、RMSSD、pNN50、TP、VLF、LF、HF均呈负相关($r=-0.252$ 、 -0.234 、 -0.260 、 -0.219 、 -0.315 、 -0.280 、 -0.316 、 -0.311 , P 均 <0.01)。CART诊断的DCAN组HRV指标相关性分析发现SDNN与SDANN相关性最强($r=0.977$, $P<0.001$),提示DCAN患者交感神经受损明显;LF与VLF($r=0.761$, $P<0.001$)、HF($r=0.829$, $P<0.001$)相关性均较强,提示心脏自主神经损伤累及交感和副交感神经。CART联合HRV诊断DCAN有134例、非DCAN有20例,DCAN发病率为87.01%(134/154),CART与HRV联合诊断DCAN的灵敏度为100.00%,特异度为37.74%。**结论** CART联合HRV在诊断DCAN时有较高的检出率,可对CART评分较低并处于DCAN早期的T2DM患者进一步行HRV分析以减少漏诊。

[关键词] 糖尿病心脏自主神经病变;心血管反射试验;心率变异性;诊断**[中图分类号]** R 587.25**[文献标志码]** A**[文章编号]** 2097-1338(2023)04-0446-08

Comparison of cardiovascular autonomic reflex test and heart rate variability in diagnosing diabetic cardiac autonomic neuropathy

ZHANG Shan¹, XU Meng-zhu², FAN Yue-yue¹, XIANG Ying³, WU Jian^{4*}, HAO Juan⁴

1. Clinical Faculty of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

2. The First People's Hospital of Tancheng County, Tancheng 276100, Shandong, China

3. Department of Electrocardiogram, Shanghai Traditional Chinese Medicine-Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200082, China

4. Department of Endocrinology, Shanghai Traditional Chinese Medicine-Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200082, China

[收稿日期] 2022-03-16**[接受日期]** 2022-12-22**[基金项目]** 上海市虹口区卫生健康委员会中医药科研课题(HKQ-ZYY-2020-09),虹口区“国医强优”三年行动计划:区域中医优势专科及提升项目(HGY-YSZK-2018-13)。Supported by Traditional Chinese Medicine Research Project of Shanghai Hongkou District Health Committee (HKQ-ZYY-2020-09) and Three-year Action Plan of “Guoyi Qiang You” in Hongkou District: Advantageous Specialty and Promotion Project of Regional Traditional Chinese Medicine (HGY-YSZK-2018-13).**[作者简介]** 张 珊,硕士生。E-mail: zhangshanandzs@163.com

*通信作者(Corresponding author). Tel: 021-65415910, E-mail: 13661561759@126.com

[Abstract] Objective To investigate the value of cardiovascular autonomic reflex test (CART) and heart rate variability (HRV) for the diagnosis of diabetic cardiac autonomic neuropathy (DCAN). **Methods** A total of 154 hospitalized patients with type 2 diabetes mellitus (T2DM) in Shanghai Traditional Chinese Medicine-Integrated Hospital, Shanghai University of Traditional Chinese Medicine from Feb. to Dec. 2020 were enrolled. All patients underwent CART and 24-h Holter monitoring, and HRV indexes were analyzed. The differences in diagnostic value of DCAN between CART and HRV were analyzed. **Results** Among the 154 T2DM patients, 101 in the DCAN group and 53 in the non-DCAN group were diagnosed using CART. The incidence of DCAN was 65.58% (101/154). The differences in age, diabetes mellitus duration and incidence of diabetic peripheral neuropathy were statistically significant between DCAN and non-DCAN groups (all $P < 0.05$), while the differences in gender, hypertension, smoking or drinking habits, body mass index, waist-to-hip ratio, glycated albumin or brain natriuretic peptide were not statistically significant (all $P > 0.05$). There were significant differences in expiration/inspiration difference, 30/15 ratio, Valsalva test and blood pressure differences after postural change between the 2 groups (all $P < 0.05$). There were significant differences in HRV indexes (standard deviation of all normal N-N interval [SDNN], mean standard deviation of the normal N-N interval every 5 min [SDANN], root mean square of successive differences between adjacent N-N intervals [RMSSD], percentage of the number of pairs of adjacent N-N intervals differing by more than 50 ms [pNN50], total power [TP], very low frequency [VLF], low frequency [LF], and high frequency [HF]) (all $P < 0.05$). The incidence of DCAN was 59.74% (92/154) according to the HRV indexes of 24-h Holter. The total coincidence rate was 61.68% between HRV and CART, and $Kappa$ value was 0.184. The sensitivity and specificity of HRV in diagnosing DCAN were 66.34% and 52.83%, respectively. According to the CART score, T2DM patients were divided into 4 grades: non-, sub-clinical, confirmed and severe DCAN. The degree of DCAN was negatively correlated with SDNN, SDANN, RMSSD, pNN50, TP, VLF, LF, and HF ($r = -0.252, -0.234, -0.260, -0.219, -0.315, -0.280, -0.316$ and -0.311 , all $P < 0.01$). The correlation analysis of HRV indexes in the DCAN patients diagnosed by CART found that SDNN and SDANN had the strongest correlation ($r = 0.977, P < 0.001$), suggesting that sympathetic nerve damage was obvious; correlations between LF and VLF ($r = 0.761, P < 0.001$) and HF ($r = 0.829, P < 0.001$) were strong, suggesting that sympathetic and parasympathetic nerves were involved in cardiac autonomic damage. CART combined with HRV diagnosed 134 cases in the DCAN group and 20 cases in the non-DCAN group, and the incidence of DCAN was 87.01% (134/154). The sensitivity and specificity of CART combined with HRV in diagnosing DCAN were 100.00% and 37.74%, respectively. **Conclusion** CART combined with HRV has a higher detection rate in the diagnosis of DCAN. HRV analysis can be further performed on T2DM patients with low CART score at the early stage of DCAN to reduce the incidence of missed diagnosis.

[Key words] diabetic cardiac autonomic neuropathy; cardiovascular autonomic reflex test; heart rate variability; diagnosis

[Acad J Naval Med Univ, 2023, 44(4): 446-453]

糖尿病心脏自主神经病变 (diabetic cardiac autonomic neuropathy, DCAN) 属于糖尿病性神经病中弥漫性神经病分类中的一种自主神经病变, 是指支配心脏和血管的自主神经纤维受损, 累及交感与副交感神经失衡, 导致心率和血流动力学异常^[1-3], 临床上以静息性心动过速、不耐受运动、直立性低血压、心功能障碍及心肌病为特征^[4]。目前临床上对 DCAN 的诊断除依据症状、体征外, 还包括多种检测方法。Ewing 等^[5]采用心血管反射试验 (cardiovascular autonomic reflex test, CART) 评估糖尿病患者心脏自主神经功能, 并被美国糖尿病协会 (American Diabetes Association, ADA) 推荐用作诊断 DCAN 的金标准。CART 包括 5 个简单无创的检查方法, 即深呼吸心率差、卧立位心率变化、卧立位血压差、Valsalva 动作 (瓦氏动作) 及握

力试验^[5]。在 DCAN 早期, 由于支配心脏和血管的自主神经纤维损害, 导致心率变异性 (heart rate variability, HRV) 水平降低, 故可将 HRV 作为早期诊断 DCAN 的方法之一^[6-7]。本研究旨在探讨 CART 及 HRV 诊断 DCAN 的应用价值。

1 资料和方法

1.1 研究对象 选取 2020 年 2 月至 12 月于上海中医药大学附属上海市中西医结合医院住院治疗的 2 型糖尿病 (type 2 diabetes mellitus, T2DM) 患者 154 例作为研究对象, 纳入人群均符合《中国 2 型糖尿病防治指南 (2020 年版)》诊断标准^[8]。排除标准: (1) 糖尿病急性并发症 (酮症酸中毒、高渗状态) 患者; (2) 试验开始前 24 h 内及试验过程中摄入咖啡因、酒精等含有兴奋性成分食品的

患者; (3) 试验过程中剧烈运动影响最终试验结果的患者; (4) 处于脑梗死、脑出血、心肌梗死、感染、手术等所致应激状态者; (5) 经病史、体格检查、心电图、胸部X线片及实验室检查明确伴有严重心脏病(急性及陈旧性心肌梗死、心力衰竭、心肌病变、心绞痛、先天性心脏病、缺血性心脏病等)或安装人工心脏起搏装置、人工除颤器者; (6) 贫血或肝、肾及其他系统严重疾病者; (7) 眼底检查提示眼底增殖性病变或眼底出血; (8) 近1个月内服用过 β 受体阻滞剂、普罗帕酮、洋地黄类强心苷等影响HRV检测的药物; (9) 既往有精神系统疾病史,如癫痫或神经官能症,或近期服用抗抑郁、抗焦虑等治疗精神性药物,或依从性较差的患者; (10) 妊娠或哺乳期妇女。本研究获得上海中医药大学附属上海市中西医结合医院伦理委员会审批(2021-016-1),所有患者均签署知情同意书。

1.2 研究方法

1.2.1 一般资料收集 收集所有患者临床资料及实验室检查结果,记录患者性别、年龄、身高、体重、BMI、腰围、臀围、腰臀比、糖尿病病程、糖尿病性周围神经病变(diabetic peripheral neuropathy, DPN)、高血压、糖化白蛋白(glycated albumin, GA)、脑钠肽(brain natriuretic peptide, BNP)等。

1.2.2 DCAN诊断 (1) CART。由经过培训的2位专职人员共同进行测试。本研究记录的心电图均为II导联(走纸速度为25 mm/s)。因握力试验存在特异性差等问题,目前研究多不再将其纳入诊断标准,故本研究行除握力试验外的4项检测。受试者在测试前1 d和当天均不做剧烈运动,24 h内未曾大量饮酒、浓茶和咖啡。受试者检查前休息15 min,然后由专职人员用心电图仪进行测试。

深呼吸心率差(E/I difference)检测:受试者取平卧位,先训练患者学会深呼吸动作约6次/min,即吸气时间5 s、呼气时间5 s,用II导联心电图记录单次尽可能深吸气、深呼气时最短和最长R-R间期的改变,计算出深吸气与深呼气时每分钟心率之差即为本项试验结果。深呼吸心率差 ≥ 15 次/min为正常,11~14次/min为临界值, ≤ 10 次/min为异常。

卧立位心率变化(30/15 ratio)检测:受试者

在5 s内由安静平卧位迅速起立,并同时记录起立后II导联心电图上30次心搏,计算站立后第30次心搏附近最长R-R间期与第15次心搏附近最短R-R间期的比值即为本项试验结果。卧立位心率变化 ≥ 1.04 为正常,1.01~ <1.04 为临界值, ≤ 1.00 为异常。

卧立位血压差检测:受试者平卧位时应用血压计测量血压,当受试者从卧位到站立2 min内再次测量血压,计算站立后与卧位血压的收缩压差值为本项试验结果。其中收缩压的差值 ≤ 10 mmHg(1 mmHg=0.133 kPa)为正常,11~29 mmHg为临界值, ≥ 30 mmHg为异常。

Valsalva动作(瓦氏动作)检测:嘱受试者做Valsalva动作(深吸气后掩鼻闭口用力作呼气动作15 s),然后放松自然呼气10 s,同时记录心电图,计算在Valsalva动作后最长R-R间期与Valsalva动作后最短R-R间期的比值即为本项试验结果(Valsalva动作指数)。Valsalva动作指数 ≥ 1.21 为正常,1.11~1.20为临界值, ≤ 1.10 为异常。

对每项检查逐一评分,正常计0分,临界计1分,异常计2分,4项试验总分 ≥ 4 分即诊断为DCAN。

(2) HRV测定。采用迪姆软件(北京)有限公司DMS动态心电分析软件对154例受试者行24 h动态心电图检查,由心电图室专人进行分析得出长时程HRV结果。HRV包含时域指标与频域指标,其中时域指标包括所有正常R-R间期的标准差(standard deviation of all normal N-N interval, SDNN)、每5 min正常R-R间期的标准差均值(mean standard deviation of the normal N-N interval every 5 min, SDANN)、相邻R-R间期差值均方根(root mean square of successive differences between adjacent N-N intervals, RMSSD)、相差 >50 ms的相邻R-R间期占R-R间期总数的百分比(percentage of the number of pairs of adjacent N-N intervals differing by more than 50 ms, pNN50);频域指标包括总功率(total power, TP)、超低频功率(very low frequency, VLF)、低频功率(low frequency, LF)、高频功率(high frequency, HF)。

根据患者24 h动态心电图报告结果,异常参考值为SDNN <50 ms、SDANN <40 ms、RMSSD <15 ms、pNN50 $<0.75\%$ 、LF <300 ms²、HF <300 ms²[9-10]。

每项指标异常计1分,2项及以上指标异常即 $\geq$

2分则可诊断为DCAN。

(3) 联合试验。深呼吸心率差、卧立位心率变化、卧立位血压差、Valsalva动作指数、HF、LF，若这些指标存在3项及以上异常^[11]即可诊断为DCAN。

1.3 统计学处理 应用SPSS 25.0软件进行统计学分析。符合正态分布的计量资料用 $\bar{x}\pm s$ 表示，两组间比较采用独立样本 t 检验；符合偏态分布的计量资料用中位数（下四分位数，上四分位数）表示，两组间比较采用Mann-Whitney U 检验。计数资料用例数和百分数表示，两组间比较采用 χ^2 检验或秩和检验。相关性研究采用Pearson相关分析。

CART与HRV诊断一致性比较采用Kappa检验。均为双侧检验，检验水准（ α ）为0.05。

2 结 果

2.1 一般资料比较 154例T2DM患者中，采用CART诊断的DCAN组有101例、非DCAN组有53例，DCAN发病率为65.58%（101/154）。DCAN组与非DCAN组患者的年龄、T2DM病程、DPN的发病率差异均有统计学意义（ P 均 <0.05 ），而性别、高血压、烟酒嗜好、BMI、腰臀比、GA、BNP差异均无统计学意义（ P 均 >0.05 ）。见表1。

表 1 采用 CART 诊断的 DCAN 组与非 DCAN 组 T2DM 患者一般资料比较

Tab 1 Comparison of general data of T2DM patients in DCAN and non-DCAN groups diagnosed by CART				
Characteristic	Non-DCAN group $N=53$	DCAN group $N=101$	Statistic	P value
Gender, n (%)			$\chi^2=0.154$	0.695
Male	25 (47.17)	51 (50.50)		
Female	28 (52.83)	50 (49.50)		
Age, n (%)			$\chi^2=11.549$	0.009
<50 years	13 (24.53)	10 (9.90)		
50-59 years	13 (24.53)	15 (14.85)		
60-69 years	22 (41.51)	51 (50.50)		
≥ 70 years	5 (9.43)	25 (24.75)		
T2DM duration, n (%)			$\chi^2=20.659$	<0.001
<5 years	31 (58.49)	25 (24.75)		
5-10 years	7 (13.21)	18 (17.82)		
11-14 years	9 (16.98)	18 (17.82)		
≥ 15 years	6 (11.32)	40 (39.60)		
Hypertension, n (%)			$\chi^2=3.836$	0.050
No	36 (67.92)	52 (51.49)		
Yes	17 (32.08)	49 (48.51)		
Diabetic peripheral neuropathy, n (%)			$\chi^2=5.632$	0.018
No	23 (43.40)	25 (24.75)		
Yes	30 (56.60)	76 (75.25)		
Smoking and drinking habits, n (%)			$\chi^2=0.849$	0.357
No	35 (66.04)	59 (58.42)		
Yes	18 (33.96)	42 (41.58)		
Body mass index, n (%)			$\chi^2=0.565$	0.927
$<18.5\text{ kg}\cdot\text{m}^{-2}$	2 (3.77)	4 (3.96)		
$18.5\text{-}23.9\text{ kg}\cdot\text{m}^{-2}$	21 (39.62)	38 (37.62)		
$24\text{-}27.9\text{ kg}\cdot\text{m}^{-2}$	20 (37.74)	43 (42.57)		
$\geq 28.0\text{ kg}\cdot\text{m}^{-2}$	10 (18.87)	16 (15.84)		
Waist-to-hip ratio, $M(Q_L, Q_U)$	0.95 (0.91, 1.00)	0.94 (0.91, 1.00)	$Z=-0.179$	0.858
Glycated albumin/%, $\bar{x}\pm s$	24.30 ± 7.15	23.62 ± 7.62	$t=0.533$	0.595
Brain natriuretic peptide/(ng·L ⁻¹), $M(Q_L, Q_U)$	19 (14, 38)	26 (16, 47)	$Z=-1.908$	0.056

CART: Cardiovascular autonomic reflex test; T2DM: Type 2 diabetes mellitus; DCAN: Diabetic cardiac autonomic neuropathy; $M(Q_L, Q_U)$: Median (lower quartile, upper quartile).

2.2 DCAN组与非DCAN组CART得分比较 CART诊断的DCAN组与非DCAN组T2DM患者的深呼吸心率差、卧立位心率变化、Valsalva动作指数、

卧立位血压差间差异均有统计学意义（ P 均 <0.05 ，表2）。

表 2 CART 各项试验评分评价 DCAN 结果

Tab 2 DCAN results evaluated by each CART index score

Group	E/I difference			30/15 ratio			Valsalva test			BP differences after postural change		
	0	1	2	0	1	2	0	1	2	0	1	2
DCAN $N=101$	0	9	92	10	12	79	15	30	56	85	10	6
Non-DCAN $N=53$	11	20	22	19	18	16	41	11	1	51	2	0
Z value	-6.831			-5.746			-7.959			-2.245		
P value	<0.001			<0.001			<0.001			0.025		

CART: Cardiovascular autonomic reflex test; DCAN: Diabetic cardiac autonomic neuropathy; E/I difference: Difference in heart rate during deep expiration and deep inspiration; 30/15 ratio: The subjects stood up quickly from the quiet flat position within 5 s, and at the same time recorded 30 beats on the lead II electrocardiogram after standing up, and calculated the ratio of the longest N-N interval near the 30th heart beat and the shortest N-N interval near the 15th heart beat after standing up; BP: Blood pressure.

2.3 DCAN 组与非 DCAN 组 HRV 指标比较 CART 标 SDNN、SDANN、RMSSD、pNN50、TP、VLF、LF、HF 差异均有统计学意义 (P 均<0.01, 表 3)。

表 3 采用 CART 诊断的 DCAN 组与非 DCAN 组 T2DM 患者 HRV 指标比较

Tab 3 Comparison of HRV indexes of T2DM patients in DCAN and non-DCAN groups diagnosed by CART

Index	Non-DCAN group $n=53$	DCAN group $n=101$	Statistic	P value
SDNN/ms, $M(Q_L, Q_U)$	105 (89, 131)	93 (75, 112)	$Z=-3.098$	0.002
SDANN/ms, $\bar{x}\pm s$	83.94 ± 28.16	97.98 ± 30.39	$t=-2.86$	0.005
RMSSD/ms, $M(Q_L, Q_U)$	22 (19, 27)	19 (14, 24)	$Z=-2.979$	0.003
pNN50/%, $M(Q_L, Q_U)$	3 (1, 6)	1 (0, 4)	$Z=-2.613$	0.009
TP/ms ² , $M(Q_L, Q_U)$	1 723.0 (1 202.7, 2 311.1)	1 223.4 (756.1, 1 610.2)	$Z=-3.805$	<0.001
VLF/ms ² , $M(Q_L, Q_U)$	1 235.9 (925.2, 1 622.8)	877.7 (567.5, 1 278.0)	$Z=-3.409$	0.001
LF/ms ² , $M(Q_L, Q_U)$	304.3 (163.7, 397.3)	165.7 (98.6, 241.5)	$Z=-4.046$	<0.001
HF/ms ² , $M(Q_L, Q_U)$	128.5 (75.0, 191.9)	62.3 (38.7, 135.8)	$Z=-3.64$	<0.001

CART: Cardiovascular autonomic reflex test; DCAN: Diabetic cardiac autonomic neuropathy; T2DM: Type 2 diabetes mellitus; HRV: Heart rate variability; SDNN: Standard deviation of all normal N-N interval; SDANN: Mean standard deviation of the normal N-N interval every 5 min; RMSSD: Root mean square of successive differences between adjacent N-N intervals; pNN50: Percentage of the number of pairs of adjacent N-N intervals differing by more than 50 ms; TP: Total power; VLF: Very low frequency; LF: Low frequency; HF: High frequency; $M(Q_L, Q_U)$: Median (lower quartile, upper quartile).

2.4 DCAN 病变程度与 HRV 指标的相关性 按照 CART 得分对 154 例 T2DM 患者进行分组, 0~1 分为无 DCAN, 2~3 分为亚临床 DCAN, 4~6 分确诊 DCAN, 7~8 分为严重 DCAN。其中无 DCAN 组 21 例 (13.64%), 亚临床 DCAN 组 32 例 (20.78%), 确诊 DCAN 组 85 例 (55.19%), 严重 DCAN 组 16 例 (10.39%)。分析 DCAN 不同病变程度与 HRV 各指标的相关性, 结果显示 DCAN 病变程度与 SDNN、SDANN、RMSSD、pNN50、TP、VLF、LF、HF 均呈负相关 ($r=-0.252$ 、 -0.234 、 -0.260 、 -0.219 、 -0.315 、 -0.280 、 -0.316 、 -0.311 , P 均<0.01)。

2.5 DCAN 组 HRV 指标相关性分析 相关性分析结果提示, 在采用 CART 诊断的 DCAN 患者中, SDNN 与 SDANN 相关性最强 ($r=0.977$, $P<0.001$), 提示 DCAN 患者交感神经受损明显; LF 与 VLF

($r=0.761$, $P<0.001$)、HF ($r=0.829$, $P<0.001$) 相关性均较强, 提示心脏自主神经损伤累及交感和副交感神经。

2.6 HRV 及 CART 联合 HRV 诊断 DCAN 结果 以 CART 诊断结果 (DCAN 组有 101 例、非 DCAN 组有 53 例) 为金标准, 根据 24 h 动态心电图的 HRV 指标诊断 DCAN 组有 92 例、非 DCAN 组有 62 例, HRV 与 CART 的诊断总符合率为 61.68% (95/154), 但相关性并不强, $Kappa$ 值为 0.184, HRV 诊断 DCAN 的灵敏度及特异度分别为 66.34%、52.83%。见表 4。

CART 联合 HRV 诊断 DCAN 组有 134 例, 非 DCAN 组有 20 例, 联合试验与 CART 的诊断总符合率为 78.57% (121/154), $Kappa$ 值为 0.443, CART 联合 HRV 诊断 DCAN 的灵敏度为 100.00%, 特异度为 37.74%。见表 5。

表 4 HRV 诊断 DCAN 结果
Tab 4 DCAN results diagnosed by HRV

HRV	CART <i>n</i>		Total <i>n</i>	<i>Kappa</i>	<i>P</i> value	Sensitivity ^a /%	Specificity ^a /%
	Positive	Negative					
Positive	67	25	92	0.184	0.021	66.34	52.83
Negative	34	28	62				
Total	101	53	154				

^a: The CART diagnosing results as gold standard. HRV: Heart rate variability; DCAN: Diabetic cardiac autonomic neuropathy; CART: Cardiovascular autonomic reflex test.

表 5 CART 联合 HRV 诊断 DCAN 结果
Tab 5 DCAN results diagnosed by CART combined with HRV

Combined	CART <i>n</i>		Total <i>n</i>	<i>Kappa</i>	<i>P</i> value	Sensitivity ^a /%	Specificity ^a /%
	Positive	Negative					
Positive	101	33	134	0.443	<0.01	100.00	37.74
Negative	0	20	20				
Total	101	53	154				

^a: The CART diagnosing results as gold standard. CART: Cardiovascular autonomic reflex test; HRV: Heart rate variability; DCAN: Diabetic cardiac autonomic neuropathy.

3 讨 论

DCAN是糖尿病常见的慢性并发症之一，是心脑血管死亡率增加的一个独立危险因素。有研究表明，DCAN患者死亡风险为非DCAN患者的1.48~4.38倍^[12]。较早的DCCT（糖尿病控制与并发症试验）研究发现DCAN发病率约为2.5%，并随病程增加不断升高，甚至可高达90%^[13]。因此，DCAN的早期诊断对糖尿病患者的临床判断和预后具有重要意义。ADA、中国T2DM防治指南都明确建议在所有初发T2DM及病程>5年的1型糖尿病患者中进行DCAN筛查^[8,14]，从而进一步提高其诊治率。ADA神经病变独立声明和多伦多共识均推荐以CART作为DCAN的临床诊断标准，自1985年Ewing等^[5]提出CART至今，此项检查已作为DCAN诊断标准被广泛应用于临床试验研究^[1,15-16]，故本研究采用CART作为诊断DCAN的金标准。

目前，CART和HRV均是指南推荐的方法，但它们各有优缺点。CART费时少且无需仪器设备，但该方法操作烦琐，受操作者及患者主观因素影响较大。有研究表明握力试验的特异度和灵敏度较低，并且与其他CART的结果没有关联，加之临床操作不便，在糖尿病患者的心血管自主神经病变测试期间，握力试验不应再用于评估交感神经功能障碍^[17-19]，因此本研究未做此项检测。此外，CART

在操作过程中有诸多局限性，如严重糖尿病视网膜病变（diabetic retinopathy，DR）患者进行Valsalva动作时可能会加重病情造成失明等严重后果，部分患者因憋气不足15s而不能完成操作，体位性低血压患者进行卧立位血压试验时可能会出现一过性晕厥、恶心呕吐等不适。同时CART还受多种疾病及药物影响，也可能会影响最终试验结果。通过使用24h动态心电图的HRV检测可反映交感神经与迷走神经的平衡状态，定量分析自主神经功能及反映HRV时间节律，具有操作简便、指标客观的特点，但同时也受年龄、性别、心率、室性早搏、运动、药物等影响，其测量方法因操作烦琐也未实现标准化，临床应用受到一定的限制。CART中深呼吸心率差、卧立位心率变化、Valsalva动作指数主要反映心脏副交感神经功能，而卧立位血压差主要反映交感神经功能。HRV时域指标SDNN、SDANN反映交感和副交感神经调节功能，pNN50、RMSSD是副交感神经的调节指标；频域指标LF/HF用于评估自主神经系统均衡关系，受交感与副交感神经系统的双重调节，HF反映副交感神经张力，LF反映交感神经张力^[4]。

本研究发现，CART诊断的DCAN组与非DCAN组CART和HRV检测结果的差异均有统计学意义（*P*<0.05），DCAN组与非DCAN组在年龄、性别、DPN方面存在差异，DCAN组较非DCAN

组年龄更大、病程更长、DPN患病率更高。诸多研究表明年龄与病程均是DCAN的独立危险因素^[1],随着患者年龄增大、病程增加,长期的高血糖代谢环境使得机体发生多元醇代谢通路激活、糖基化终末产物增多、氧化应激增加、蛋白质及脂质代谢紊乱等,从而引起自主神经的神经元活性、胞膜通透性、细胞内皮功能及线粒体改变,表现为神经元损害和死亡^[20]。糖尿病微血管病变(diabetic microangiopathy, DMAP)包括DPN、DR、糖尿病肾病(diabetic nephropathy, DN)和糖尿病自主神经病变(diabetic autonomic neuropathy, DAN)。多项研究表明,DCAN与DPN、DR、DN有显著相关性,DPN、DN、DR可作为DCAN的预测因素,因神经病变损伤机制相似,DPN患者常伴有自主神经病变^[11,21-24]。本研究按CART评分将154例T2DM患者为无、亚临床、确诊、严重DCAN 4个等级,结果提示病变程度与SDNN、SDANN、RMSSD、pNN50、TP、VLF、LF、HF均呈负相关(P 均 <0.01),说明随着CART评分增加,DCAN病情进一步发展,HRV水平下降明显。此外,通过研究发现SDNN与SDANN相关性最强($r=0.977$, $P<0.001$),提示DCAN患者的交感神经受损明显,LF与VLF、HF相关性均较强($r=0.761$ 、 0.829 , P 均 <0.001),说明发生DCAN时交感神经与副交感神经均受损。这一结果与既往研究结果^[25]一致。

本研究以CART诊断结果为金标准,使用HRV诊断DCAN的发病率为59.74%(92/154),HRV与CART诊断的总符合率不高[61.78%(95/154)],HRV诊断DCAN的灵敏度(66.34%)及特异度(52.85%)均较低,说明HRV在临床应用时不能替代CART。CART联合HRV在诊断DCAN时的检出率为87.01%(134/154),增大了阳性检出率,提示可对CART评分较低、处于DCAN早期的T2DM患者进一步行HRV分析以减少漏诊。此外,本研究中SDNN与SDANN相关性最强,LF与VLF、HF相关性也较强。因此,在后期研究中可着重将SDNN、SDANN、LF、VLF、HF指标与CART联合,探究是否可更早发现DCAN。

[参考文献]

[1] POP-BUSUI R, BOULTON A J M, FELDMAN E L,

BRIL V, FREEMAN R, MALIK R A, et al. Diabetic neuropathy: a position statement by the American Diabetes Association[J]. *Diabetes Care*, 2017, 40: 136-154.

[2] AGASHE S, PETAK S. Cardiac autonomic neuropathy in diabetes mellitus[J]. *Methodist Debaque Cardiovasc J*, 2018, 14: 251-256.

[3] SPALLONE V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet[J]. *Diabetes Metab J*, 2019, 43: 3-30.

[4] 廖二元,袁凌青.内分泌代谢病学[M].4版.北京:人民卫生出版社,2019:1599-1605.

[5] EWING D J, MARTYN C N, YOUNG R J, CLARKE B F. The value of cardiovascular autonomic function tests: 10 years experience in diabetes[J]. *Diabetes Care*, 1985, 8: 491-498.

[6] DIMITROPOULOS G, TAHRANI A A, STEVENS M J. Cardiac autonomic neuropathy in patients with diabetes mellitus[J]. *World J Diabetes*, 2014, 5: 17-39.

[7] PHURPA M, FERDOUSI S. Short-term heart rate variability: a technique to detect subclinical cardiac autonomic neuropathy in type 2 diabetes mellitus[J]. *Mymensingh Med J*, 2021, 30: 447-452.

[8] 中华医学会糖尿病学分会.中国2型糖尿病防治指南(2020年版)[J].*中华糖尿病杂志*,2021,13:315-409.

[9] LIN X P, CHEN C N, LIU Y S, PENG Y, CHEN Z G, HUANG H S, et al. Peripheral nerve conduction and sympathetic skin response are reliable methods to detect diabetic cardiac autonomic neuropathy[J/OL]. *Front Endocrinol (Lausanne)*, 2021, 12: 709114. DOI:10.3389/fendo.2021.709114.

[10] ZHANG Z Y, MA Y J, FU L J, LI L P, LIU J, PENG H F, et al. Combination of composite autonomic symptom score 31 and heart rate variability for diagnosis of cardiovascular autonomic neuropathy in people with type 2 diabetes[J/OL]. *J Diabetes Res*, 2020, 2020: 5316769. DOI: 10.1155/2020/5316769.

[11] PAVY-LETRAON A, BREFEL-COURBON C, DUPOUY J, ORY-MAGNE F, RASCOL O, SENARD J M. Combined cardiovascular and sweating autonomic testing to differentiate multiple system atrophy from Parkinson's disease[J]. *Neurophysiol Clinique*, 2018, 48: 103-110.

[12] LACIGOVA S, BROZOVA J, CECUROVA D, TOMESOVA J, KRCMA M, RUSAVY Z. The influence of cardiovascular autonomic neuropathy on mortality in type 1 diabetic patients; 10-year follow-up[J]. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*, 2016, 160: 111-117.

[13] The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on

- measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT)[J]. *Diabetologia*, 1998, 41: 416-423.
- [14] American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes-2019*[J]. *Diabetes Care*, 2019, 42 (Suppl 1): S103-S123.
- [15] SPALLONE V, ZIEGLER D, FREEMAN R, BERNARDI L, FRONTONI S, POP-BUSUI R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management[J]. *Diabetes Metab Res Rev*, 2011, 27: 639-653.
- [16] POP-BUSUI R, BACKLUND J Y C, BEBU I, BRAFFETT B H, LORENZI G, WHITE N H, et al. Utility of using electrocardiogram measures of heart rate variability as a measure of cardiovascular autonomic neuropathy in type 1 diabetes patients[J]. *J Diabetes Investig*, 2022, 13: 125-133.
- [17] POSADA-QUINTERO H F, FLORIAN J P, ORJUELA-CañÓN A D, ALJAMA-CORRALES T, CHARLESTON-VILLALOBOS S, CHON K H. Power spectral density analysis of electrodermal activity for sympathetic function assessment[J]. *Ann Biomed Eng*, 2016, 44: 3124-3135.
- [18] KEMPLER M, HAJDÚ N, PUTZ Z, ISTENES I, VÁGI O, BÉKEFFY M, et al. Diabetic cardiovascular autonomic neuropathy, the handgrip test and ambulatory blood pressure monitoring parameters: are there any diagnostic implications?[J/OL]. *J Clin Med*, 2020, 9: 3322. DOI: 10.3390/jcm9103322.
- [19] BELLAVERE F, RAGAZZI E, CHILELLI N C, LAPOLLA A, BAX G. Autonomic testing: which value for each cardiovascular test? An observational study[J]. *Acta Diabetol*, 2019, 56: 39-43.
- [20] DIDANGELOS T, VEVES A. Treatment of diabetic cardiovascular autonomic, peripheral and painful neuropathy. Focus on the treatment of cardiovascular autonomic neuropathy with ACE inhibitors[J]. *Curr Vasc Pharmacol*, 2020, 18: 158-171.
- [21] PAFILI K, TRYPSIANIS G, PAPAZOGLU D, MALTEZOS E, PAPANAS N. Correlation of cardiac autonomic neuropathy with small and large peripheral nerve function in type 2 diabetes mellitus[J/OL]. *Diabetes Res Clin Pract*, 2019, 156: 107844. DOI: 10.1016/j.diabres.2019.107844.
- [22] YEN C Y, CHEN C S, LIAO K M, FANG I M. Cardiac autonomic neuropathy predicts diabetic retinopathy progression in Asian population with type 2 diabetes mellitus[J]. *Graefes Arch Clin Exp Ophthalmol*, 2022, 260: 2491-2499.
- [23] RAJ R, MISHRA R, JHA N, JOSHI V, CORREA R, KERN P A. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review[J/OL]. *BMJ Open Diabetes Res Care*, 2022, 10: e002573. DOI: 10.1136/bmjdr-2021-002573.
- [24] HAQ T, AHMED T, LATIF Z A, SAYEED M A, ASHRAFUZZAMAN S M. Cardiac autonomic neuropathy in patients with type 2 diabetes mellitus having peripheral neuropathy: a cross-sectional study[J]. *Diabetes Metab Syndr*, 2019, 13: 1523-1528.
- [25] AKINLADE O M, OWOYELE B V, SOLADOYE O A. Heart rate variability indices, biomarkers, and cardiac nerve density: independent surrogate markers for diagnosis of diabetic cardiac autonomic neuropathy in type 2 diabetes mellitus animal model[J]. *Int J Health Sci (Qassim)*, 2020, 14: 24-30.

[本文编辑] 商素芳