An inherited sudden cardiac arrest syndrome may be based on primary myocardial and autonomic nervous system abnormalities

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BACKGROUND A recently discovered sudden cardiac arrest (SCA) syndrome is linked to a risk haplotype that harbors the dipeptidyl-peptidase 6 (DPP6) gene as a plausible culprit.

OBJECTIVE Because DPP6 impacts both cardiomyocyte and neuronal function, we hypothesized that ventricular fibrillation (VF) in risk haplotype carriers arises from functional changes in both the heart and autonomic nervous system.

METHODS We studied 6 risk haplotype carriers with previous VF (symptomatic), 8 carriers without VF (asymptomatic), and 7 noncarriers (controls). We analyzed supine and standing heart rate variability, baroreflex sensitivity, pre-VF heart rate changes, and myocardial ^{123}I-*meta*-iodobenzylguanide (^{123}I-*m*IBG) scintigraphy.

RESULTS Carriers had longer interbeat intervals than controls (1.03 ± 0.11 seconds vs 0.81 ± 0.07 seconds; P <.001), lower low-frequency (LF) and higher high-frequency (HF) activity, and lower LF/HF ratio (0.68 ± 0.50 vs 2.11 ± 1.10; P = .013) in the supine position. Upon standing up, carriers had significantly larger decrease in interbeat interval and increase in LF than controls (standing-to-supine ratio: 0.78 ± 0.07 vs 0.90 ± 0.07; P = .002;

and 1.94 ± 1.03 vs 1.17 ± 0.34; P = .022, respectively), and nonsignificantly larger decrease in HF (0.62 ± 0.36 vs 0.97 ± 0.42; P = .065) and increase in LF/HF ratio (5.55 ± 6.79 vs 1.62 ± 1.24; P = .054). Sixteen of 17 VF episodes occurred at rest. Heart rate immediately before VF was 110 ± 25 bpm. Symptomatic carriers had less heterogeneous ^{123}I-*m*IBG distribution in the left ventricle than asymptomatic carriers (single-photon emission computed tomography score ≥3 in 7 asymptomatic and 1 symptomatic carrier; P = .008).

CONCLUSION It can be speculated that these data are consistent with more labile autonomic tone in carriers, suggesting that the primary abnormalities may reside in both the heart and the autonomic nervous system.

KEYWORDS Autonomic nervous system; Baroreflex sensitivity; Dipeptidyl-peptidase 6; ^{123}I-*m*IBG; Heart rate variability; Sudden cardiac arrest

Introduction

Sudden cardiac arrest (SCA) is mostly caused by cardiac arrhythmias (ventricular fibrillation [VF]) that may result from inherited cardiac ion channel dysfunction or cardiomyopa-

thies.[1] Ion channel properties may be disrupted by mutations in the encoding genes (inherited SCA syndromes)[2] and/or imbalances in neural control by the autonomic nervous system (ANS).[3] For instance, in long QT syndrome (LQTS), VF results from dysfunction of mutant cardiac ion channels (mostly voltage-gated K$^+$ channels) and their adverse responses to sympathetic stimulation.[4] Accordingly, the cornerstone of therapy in LQTS is β-adrenoceptor blocking drugs and, in selected cases, cardiac sympathetic denervation.[5] However, in LQTS, as in most other inherited SCA syndromes, the primary derangement resides in the heart rather than the ANS.

In another inherited SCA syndrome,[6] a risk haplotype in chromosome 7q36 harboring the dipeptidyl-peptidase 6 (DPP6) gene was identified as an underlying genetic variant.

https://doi.org/10.1016/j.hrthm.2021.10.026

Table 1 Characteristics of the study subjects

| | Controls (n = 7) | Carriers (n = 14) | P value | Carriers | | P value |
				Symptomatic (n = 6)	Asymptomatic (n = 8)	
Male sex	4	9	.75	4	5	.87
Age (y)	33.6 ± 5.8	39.2 ± 10.0	.19	38.2 ± 9.7	40.0 ± 10.9	.75
BMI (kg/m^2)	26.2 ± 4.4	28.7 ± 5.5	.31	27.0 ± 3.7	29.9 ± 6.5	.35
ICD	0	12	NA	6	6	NA
ICD shocks*	0	4	NA	4	0	NA
Symptoms						
Aborted VF	0	6	NA	6	0	NA
Syncope	0	2	NA	2	0	NA

Continuous data are given as mean ± SD and were tested with an unpaired Student t test. Binary variables are presented as absolute numbers and tested with the χ^2 test.

BMI = body mass index; ICD = implantable cardioverter-defibrillator; NA = not applicable; VF = ventricular fibrillation.

*No. of patients who had received appropriate ICD shocks before inclusion.

DPP6 is a potential β-subunit of the cardiac transient outward K$^+$ current (I$_{to}$) encoded by Kv4.x-subunits. DPP6 modulates trafficking, kinetics, and pharmacology of Kv4.x-encoded channels.[7,8] Carriers of the risk haplotype have 20-fold increased DPP6 mRNA levels in the myocardium.[9] DPP6 overexpression may cause gain of function of Kv4, resulting in arrhythmia.[10] These findings suggest a role for DPP6 in the occurrence of VF. Yet, although previous studies of this SCA syndrome have focused on the heart, DPP6 is not exclusively expressed in cardiac tissue; it also plays an important role in various brain regions, such as the thalamus, hypothalamus, and hippocampus. In neuronal tissue, DPP6 is a putative β-subunit for neuronal A-type currents, encoded by Kv4.x-subunits, which increases the excitability of dendritic cells.[7] Moreover, DPP6 plays a role in hippocampal synaptic development and function,[11] a region involved in emotion and stress response, and coupled to ANS function. Because increased VF risk may be associated with both increased sympathetic tone (eg, in LQTS) and increased parasympathetic tone (eg, in Brugada syndrome, another inherited SCA syndrome),[12] abnormal ANS function may be a primary mechanism for VF occurrence in the DPP6-related SCA syndrome.

We hypothesized that risk haplotype carriers have imbalances in ANS function, and that these imbalances are associated with VF risk. There are many ways to study ANS function in relation to arrhythmogenic disorders.[13] We chose from this broad palette to analyze heart rate variability (HRV), baroreflex sensitivity (BRS), and heart rate changes immediately preceding VF (to study control of cardiac function by the ANS)[13] and ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) myocardial scintigraphy (to map norepinephrine release and reuptake within the heart). We performed these studies in symptomatic and asymptomatic risk haplotype carriers and in healthy family members who did not carry the risk haplotype. With these studies, we aimed to obtain further insights into the mechanisms by which the ANS modulates VF risk. Moreover, we sought to obtain novel tools to predict VF risk in carriers of the risk haplotype.

Methods
Design and setting
Three groups from 1 extended family recruited from the Cardiogenetics Department of Amsterdam UMC, were studied: (1) carriers of the risk haplotype with previous VF (symptomatic; n = 6); (2) age-/sex-matched carriers of the risk haplotype without previous VF (asymptomatic; n = 8); and (3) age-/sex-matched family members who did not carry the risk haplotype and had no cardiac history (controls; n = 7). The study protocol conformed to the ethical guidelines of

Table 2 Numbers and circumstances of VF episodes

Patient	Sex	Age (y)	Age at first VF episode (y)	No. of VF episodes before inclusion	VF during vagal condition	Circumstances of VF episodes*
1	M	32	30	1	Yes	Alcohol intake
2	F	38	34	3	Yes	Passenger in a car (1), sleep (2)
3	M	31	30	4	Yes	Alcohol intake (1), office (2), unknown (1)
4	M	38	33	5	Yes	Alcohol intake (2), fever (1), rest (2)
5	F	57	52	3	Yes	Sleep (3)
6	M	33	32	1	Yes	One hour after exercise

F = female; M = male.

*No. of ventricular fibrillation (VF) episodes during a described condition is given in parentheses.

Table 3 Heart rate variability and blood pressure measurements in carriers (symptomatic and asymptomatic combined) and controls

	Supine position			Standing position			Standing-to-supine ratio		
	Control (n = 7)	Carriers (n = 14)	P value	Control (n = 7)	Carriers (n = 14)	P value	Control (n = 7)	Carriers (n = 14)	P value
Heart rate variability									
Mean IBI	0.81 ± 0.07	1.03 ± 0.11	<.001	0.74 ± 0.09	0.80 ± 0.11	.171	0.90 ± 0.07	0.78 ± 0.07	.002
SD-IBI	0.06 ± 0.02	0.06 ± 0.03	.993	0.06 ± 0.02	0.04 ± 0.02	.15	1.02 ± 0.24	0.88 ± 0.32	.330
Total power (ms²)	3687 ± 2773	4248 ± 4414	.764	3507 ± 2383	2184 ± 1836	.174	1.09 ± 0.46	0.87 ± 0.56	.398
VLF (ms²)	571 ± 352	696 ± 618	.627	693 ± 736	612 ± 468	.760	1.21 ± 0.69	1.34 ± 0.99	.766
LF norm (n.u.)	56.9 ± 16.5	31.3 ± 13.8	.001	63.6 ± 14.8	52.9 ± 20.4	.23	1.17 ± 0.34	1.94 ± 1.03	.022
HF norm (n.u.)	32.0 ± 13.5	57.3 17.9	.004	29.7 ± 15.1	33.8 ± 20.2	.64	0.97 ± 0.42	0.62 ± 0.36	.065
LF/HF	2.11 ± 1.10	0.68 ± 0.50	.013	2.98 ± 2.09	2.66 ± 2.58	.783	1.62 ± 1.24	5.55 ± 6.79	.054
BRS (ms/mm Hg)	12.55 ± 5.16	13.95 ± 8.00	.681	7.73 ± 3.12	6.68 ± 2.61	.425	0.64 ± 0.11	0.60 ± 0.35	.814
Blood pressure									
Mean systolic (mm Hg)	126 ± 17	125 ± 16	.885	127 ± 17	127 ± 13	.969	1.00 ± 0.05	1.02 ± 0.12	.704
SD	5.0 ± 1.4	4.5 ± 1.0	.369	6.4 ± 0.5	5.6 ± 1.9	.255	1.39 ± 0.38	1.29 ± 0.44	.615

Continuous data are given as mean ± SD and tested with an unpaired Student t test.
BRS = baroreflex sensitivity; HF = high frequency; IBI = Mean interbeat interval; LF = low frequency; n.u. = normalized unit; VLF = very low frequency.

the Declaration of Helsinki and was approved by the institutional Medical Ethics Committee. All subjects were aged >18 years and signed informed consent.

Analysis of HRV, BRS, and pre-VF heart rates

HRV measurement, performed in all subjects directly after the early planar [123]I-*m*IBG image was acquired, was conducted as described previously.[14] Heart rate and blood pressure were recorded for 20 minutes (10 minutes in supine position, followed by 10 minutes in standing position). These data were measured with the Nexfin Cardiovascular Monitor (BMEYE, Amsterdam, The Netherlands), a completely noninvasive blood pressure and cardiac output monitor based on finger arterial pulse contour analysis. During all measurements, patients held their hand at heart level. Data files were converted to beat-to-beat datafiles.

Mean interbeat interval (IBI) between the pulse waves and the standard deviation of all IBIs (SD-IBI) were measured. In power spectrum analysis, conducted using fast Fourier transform in MATLAB® (The MathWorks, Natick, MA), we analyzed very-low-frequency (VLF; 0.003–0.04 Hz), low-frequency (LF; 0.04–0.15 Hz), and high-frequency (HF; 0.15–0.4 Hz) bands. The LF band reflects a combination of sympathetic and parasympathetic activity. The HF band reflects an estimate of parasympathetic control. The LF/HF ratio is commonly used as a measure of sympathovagal balance. LF and HF were expressed as normalized units by division by the total variance (including the power in the VLF band). We also analyzed the gain from systolic blood pressure changes to heart period changes in the LF band (if coherence >0.5), a validated measure of BRS (ms/mm Hg).[15,16] Standing-to-supine ratios were calculated to quantify the increase in sympathetic drive upon standing.

To gain insight into the "autonomic state" preceding VF, implantable cardioverter-defibrillator (ICD) recordings in symptomatic patients were analyzed for heart rate before ICD shocks were delivered in the absence of β-adrenoceptor blockers or antiarrhythmic drugs.

[123]I-*m*IBG scintigraphy

[123]I-*m*IBG scintigraphy was performed in all study subjects to assess cardiac sympathetic activity. All subjects received 185 MBq (5 mCi; ±10%) of [123]I-*m*IBG (AdreView™, GE Healthcare, Eindhoven, Netherlands) intravenously after a 30-minute rest period in the supine position. At 15 minutes (early) and 4 hours (late) postinjection, 10-minute planar anterior thorax images were acquired. Only late imaging was followed by single-photon emission computed tomography (SPECT).

An experienced nuclear medicine technologist, blinded to the subject's group status, processed the planar images to determine the early (15 minutes postinjection) and late (4 hours postinjection) heart (H)/mediastinal (M) ratios (HERMES Medical Solutions, Stockholm, Sweden). Early H/M indicates myocardial norepinephrine transporter uptake function, whereas late H/M gives a measure of overall
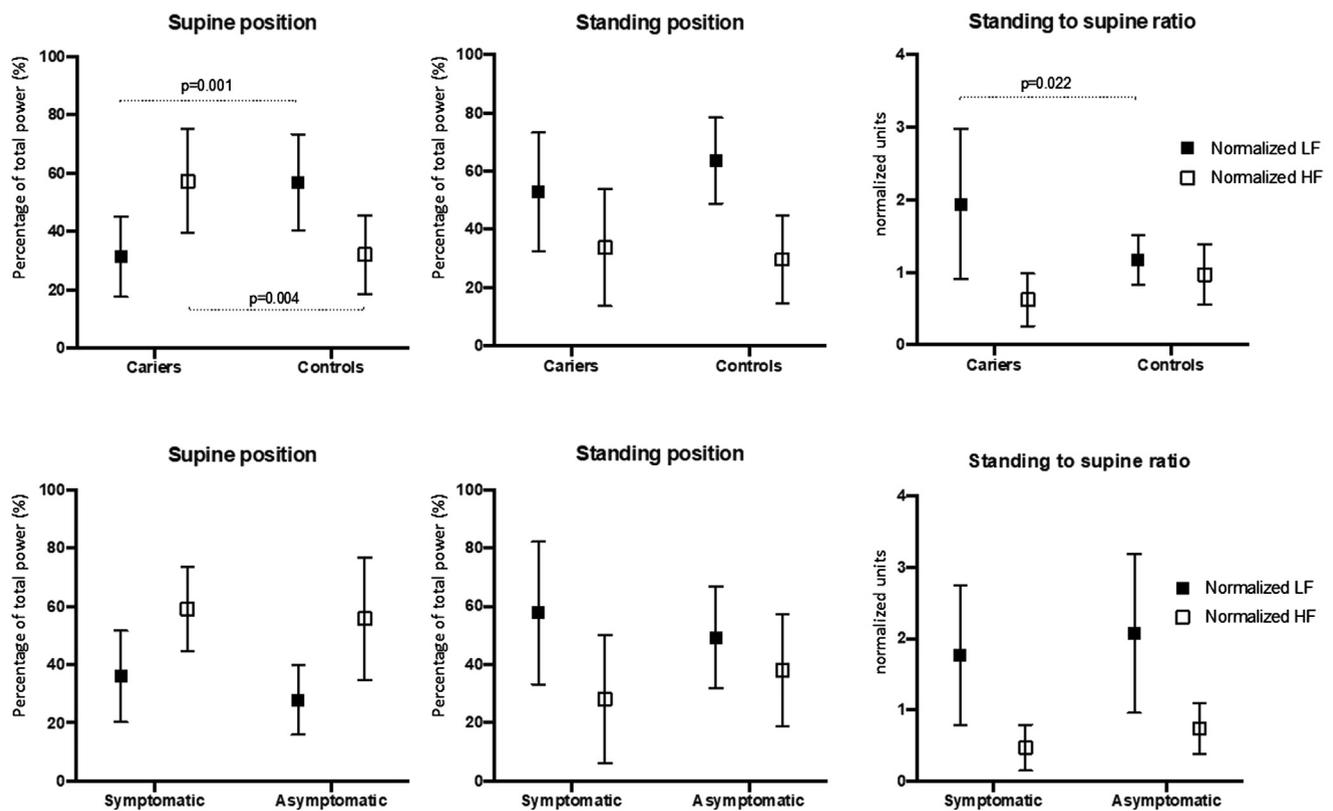
Figure 1 Heart rate variability. **Top left:** In the supine position, the normalized LF *(closed squares)* is significantly lower in carriers than controls (*P* = .001). The normalized HF *(open squares)* is significantly higher in carriers than controls (*P* = .004). **Top middle:** During active standing, there were no significant differences in LF or HF between carriers and controls. **Top right:** Only the standing-to-supine ratios of normalized LF were higher in carriers than controls (*P* = .022). **Bottom row:** There were no significant differences in normalized LF, normalized HF, or standing-to-supine ratios between symptomatic and asymptomatic carriers. HF = high frequency; LF = low frequency.

neuronal function including information from uptake to release through the storage mechanism.[17] In addition, myocardial washout, which indicates sympathetic drive, was calculated as given in Equation 1:

$$\left\{ \frac{(\text{early H/M} - \text{late H/M})}{\text{early H/M}} \right\} * 100\% \qquad (1)$$

Regional differences in ^{123}I-*m*IBG uptake were assessed using a 17-segment bull's-eye model. Two experienced nuclear medicine physicians, both blinded to the subject's group status, scored each segment on a scale from 0–4, where 0 = normal ^{123}I-*m*IBG uptake, and 4 = no ^{123}I-*m*IBG uptake. The SPECT score was calculated as the sum of individual SPECT segment scores. Heterogeneous myocardial ^{123}I-*m*IBG uptake was defined as reduced tracer uptake (segment score >0) in at least 3 adjacent segments (SPECT score ≥3). A total SPECT score of 1–2 was considered homogeneous ^{123}I-*m*IBG uptake.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 for Mac (SPSS, Inc., Chicago, IL). Results are given as mean ± SD. Data normality was determined using the Kolmogorov-Smirnov test. Logarithmic transformation was performed on non-normally distributed data to obtain normal distribution. Testing for significant differences between groups (carriers vs controls and symptomatic vs asymptomatic patients) was performed with the Student *t* test, χ^2 test, or Fisher exact test as appropriate. *P* <.05 was considered significant.

Results
Clinical characteristics

We studied 14 carriers of the risk haplotype (9 men and 5 women; age 39.2 ± 10.0 years; range 28–62 years; median 36 years) (Table 1). The 6 symptomatic carriers experienced 17 VF episodes before this study. Sixteen VF episodes occurred at rest (unknown circumstances surrounding 1 VF episode), including 4 after mild alcohol use (Table 2). All symptomatic carriers had an ICD; 4 previously had appropriate ICD shocks (54 appropriate shocks for 11 VF episodes). Although VF risk in carriers is age dependent (increasing with advancing age), the ages of the symptomatic and asymptomatic carriers did not differ.[9] The noncarrier control group comprised 7 relatives of the carriers (4 men; age 33.6 ± 5.8 years). In all subjects, HRV and ^{123}I-*m*IBG scintigraphy were studied in the absence of β-adrenoceptor blocking or antiarrhythmic medication.

Table 4 Heart rate variability and blood pressure measures in symptomatic and asymptomatic carriers

	Supine position			Standing position			Standing-to-supine ratio		
	Symptomatic (n = 6)	Asymptomatic (n = 8)	P value	Symptomatic (n = 6)	Asymptomatic (n = 8)	P value	Symptomatic (n = 6)	Asymptomatic (n = 8)	P value
Heart rate variability									
Mean IBI	1.07 ± 0.11	1.0 ± 0.10	.322	0.83 ± 0.13	0.79 ± 0.10	.479	0.78 ± 0.10	0.78 ± 0.06	.959
SD-IBI	0.07 ± 0.03	0.05 ± 0.03	.417	0.06 ± 0.02	0.04 ± 0.01	.022	0.95 ± 0.33	0.83 ± 0.32	.504
Total power (ms^2)	5238 ± 5,493	3505 ± 3,629	.290	3286 ± 2,138	1358 ± 1,083	.017	1.00 ± 0.59	0.78 ± 0.56	.499
VLF (ms^2)	694 ± 431	697 ± 760	.444	927 ± 461	376 ± 327	.013	1.64 ± 1.16	1.11 ± 0.85	.341
LF norm (n.u.)	36.0 ± 15.7	27.9 ± 12.0	.294	57.7 ± 24.5	49.3 ± 17.5	.467	1.77 ± 0.98	2.07 ± 1.11	.609
HF norm (n.u.)	59.2 ± 14.5	55.8 ± 21.0	.740	28.09 ± 22.07	38.01 ± 19.07	.385	0.47 ± 0.32	0.74 ± 0.36	.166
LF/HF	0.73 ± 0.60	0.64 ± 0.46	.774	3.86 ± 3.46	1.76 ± 1.28	.205	7.27 ± 9.17	4.26 ± 4.59	.433
BRS (ms/mm Hg)	16.20 ± 8.78	12.26 ± 7.49	.382	8.04 ± 2.31	5.65 ± 2.45	.479	0.60 ± 0.33	0.60 ± 0.39	.986
Blood pressure									
Mean systolic (mm Hg)	131 ± 15	121 ± 16	.295	128 ± 18	126 ± 9	.745	0.98 ± 0.06	1.05 ± 0.14	.296
SD	4.3 ± 1.4	4.6 ± 0.7	.641	6.5 ± 2.7	4.8 ± 0.7	.188	1.57 ± 0.50	1.08 ± 0.25	.064

Continuous data are presented as mean ± SD and tested with an unpaired Student t test.
Abbreviations as in Table 3.

Analysis of HRV, BRS, and pre-VF heart rate changes

Carriers had longer mean IBI than controls (Table 3). In line with this finding, the power spectral HRV data in the supine position showed that carriers had lower normalized LF activity, higher normalized HF activity, and lower mean LF/HF ratio (Figure 1). During active standing, no significant between-group differences in mean IBI, normalized LF, normalized HF, or LF/HF ratio occurred (Figure 1). Analysis of standing-to-supine ratios revealed that the sympathetic trigger of standing up elicited a stronger decrease in mean IBI, a stronger increase in normalized sLF (P = .022), and a larger (although not statistically significant) decrease in normalized HF in carriers compared to controls. Consequently, carriers had a larger increase in LF/HF ratio than controls, although this difference just failed to reach statistical significance (P = .054). There were no statistically significant differences in HRV parameters between symptomatic and asymptomatic carriers (Table 4 and Figure 1).

In 1 symptomatic carrier (31-year-old man), the heart rate accelerated suddenly after 9 minutes of measurement in the supine position. This patient became anxious, fearing his ICD would deliver a shock, as he recognized this feeling from a previous period that occurred immediately before an ICD shock. After his heart rate had started to return to normal, the measurement was continued according to protocol. The recording showed that his sudden acceleration in heart rate was attended by small decreases in blood pressure, stroke volume, and maximal dP/dt of the pulse wave, all suggestive of parasympathetic withdrawal rather than sympathetic activation (Figure 2).

Of the ICD shocks before this study, ICD recordings could be retrieved from 3 patients, yielding 7 analyzable VF episodes. Mean recorded time before VF onset was 7.4 ± 1.0 seconds, and mean heart rate immediately before VF was 110 ± 25 bpm (range 80–162).

[123]I-mIBG scintigraphy

Planar image analysis revealed no statistically significant differences between carriers and controls in early H/M, late H/M, or washout (Table 5). Quantitative segmental analysis of the SPECT images showed no differences in SPECT score between carriers and controls (Figure 3, left). However, symptomatic carriers had less spatially heterogeneous ^{123}I-mIBG distribution in the left ventricle compared to asymptomatic carriers. Heterogeneous ^{123}I-mIBG SPECT (SPECT score ≥3) occurred in 7 of 8 asymptomatic carriers, and in 1 of 6 symptomatic carriers (P = .008) (Figure 3, right).

Discussion

Clinical analysis revealed that, although VF in risk haplotype carriers seemed to occur under conditions of increased parasympathetic tone (rest, sleep, after mild alcohol use), heart rates immediately preceding VF also can be elevated, consistent with a sudden swing from a parasympathetic state to a sympathetic state. One symptomatic carrier exhibited such a swing during HRV recording, when heart rate suddenly
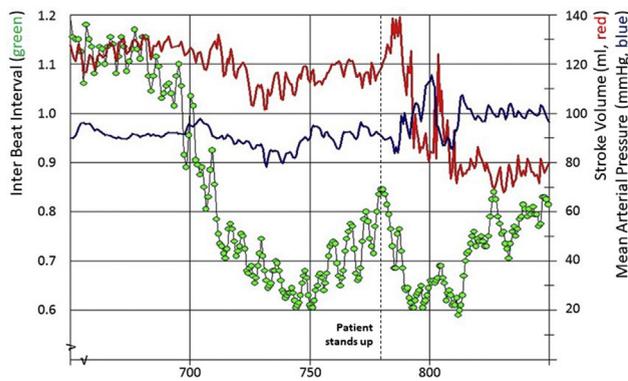
Figure 2 Sudden drop in interbeat interval in supine position with attendant changes in stroke volume and mean arterial pressure in a patient just before standing up.

accelerated in a manner consistent with vagal withdrawal. These observations led to the notion that carriership is associated with more labile autonomic tone, that is, stronger fluctuation between parasympathetic and sympathetic status. This notion is supported by HRV analysis, which showed that carriers had higher parasympathetic tone at baseline (higher IBI, lower LF, higher HF, lower mean LF/HF in supine position) but stronger response to sympathetic stimulation (more decrease in IBI and HF, more increase in LF and LF/HF ratio in response to standing up), than controls. Using ^{123}I-mIBG scintigraphy, we found no evidence that increased sympathetic responsiveness in carriers was due to higher cardiac sympathetic activity, as early H/M, late H/M, and washout did not differ between carriers and controls. This finding suggests that increased (para)sympathetic responsiveness in carriers is due to extracardiac factors (eg, efferent signaling pathways of the ANS). This notion is consistent with the finding that DPP6, the putative causative gene, is expressed in neurons and plays an important functional role there (eg, by modulating gating function of neuronal ion channels).[18] ^{123}I-mIBG scintigraphy revealed that symptomatic carriers are distinguishable from nonsymptomatic carriers by a more spatially homogeneous distribution of ^{123}I-mIBG uptake. This observation goes against the generally accepted concept that more heterogeneity in functional properties (eg, autonomic activity) increases

arrhythmia risk. We fully subscribe to this concept and certainly would not propose the opposite (more heterogeneity in functional properties *reducing* arrhythmia risk). In an effort to better understand our observation, we can only provide a speculative explanation, as follows. Our finding could reflect the clinical observation that VF in carriers seems to be often initiated by premature beats originating from specific areas within the heart.[19] Such specific arrhythmogenic areas in the heart were also found in other inherited SCA syndromes. For instance, in Brugada syndrome,[20] the right ventricular outflow tract and free wall are focal points for arrhythmia, and ablation of these areas drastically reduces VF incidence. In DPP6 haplotype carriers, it is conceivable that, while sympathetic signaling in symptomatic carriers, similar to controls, is spread evenly throughout the heart (as indicated by SPECT ^{123}I-mIBG scintigraphy), asymptomatic carriers may be protected from VF occurrence by the fact that they happen to have reduced sympathetic signaling (which is critical for arrhythmia onset) in regions where premature beats in carriers trigger VF. Whatever the reason for localized reduced sympathetic signaling in these carriers, this scintigraphic parameter may have clinical relevance, as it may be used to distinguish carriers with increased VF risk from carriers without. Such a distinction is crucial for risk stratification and may have important therapeutic consequences. At present, ICD implantation is considered the only viable therapy option in carriers, because predictors of VF occurrence are lacking at present, and carriers with increased VF risk cannot be distinguished from carriers without elevated risk.[6] Consequently, carriers without increased VF risk receive unnecessary ICD implantation and derive no benefit from it, but they are exposed to possible harm from the potentially serious adverse effects of the ICD.[21]

The study of heart rate and blood pressure variability (Tables 3 and 4) gave some unexpected results. Because BRS and IBI are normally correlated (higher BRS at longer IBI), one would have expected carriers to have higher BRS values than controls because their supine IBIs were considerably longer. BRS by Fourier analysis is computed as the square root of interval power over systolic pressure power in the LF band (ms/mm Hg) (see Methods). The LF numbers for systolic variances (average 13.3 and 6.8 mm

Table 5 ^{123}I-mIBG scintigraphy

	Controls (n = 7)	Carriers (n = 14)	P value	Carriers		P value
				Symptomatic (n = 6)	Asymptomatic (n = 8)	
^{123}I-mIBG						
Early H/M	2.73 ± 0.28	2.61 ± 0.46	.55	2.56 ± 0.35	2.65 ± 0.55	.76
Late H/M	3.08 ± 0.70	2.74 ± 0.59	.25	2.68 ± 0.27	2.78 ± 0.77	.77
Washout (%)	−12.2 ± 16.2	−4.9 ± 12.3	.26	−5.7 ± 14.6	−4.2 ± 11.3	.83
^{123}I-mIBG SPECT						
Median score	2 (0–5)	3 (0–7)	.25	1 (0–3)	4 (2–7)	.13
Heterogeneous SPECT (%)	3	8	.66	1	7	.03

Continuous data are given as mean ± SD or median (range) and tested with an unpaired Student t test. Categorical variables are given as absolute numbers and tested with the Fisher exact test.

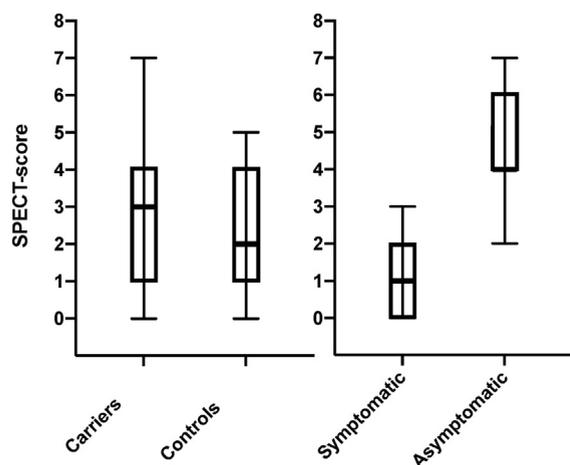H/M = heart/mediastinal ratio; SPECT = single-photon emission computed tomography.

Figure 3   [123]I-*m*IBG single-photon emission computed tomography (SPECT). **Left:** There were no differences in SPECT score between carriers and controls. **Right:** Symptomatic carriers more often had a more homogeneous distribution of [123]I-*m*IBG on SPECT.

Hg[2] in controls and carriers, respectively) tally with the HRV-LF variances of 2098 and 1330 ms^2 ending up in the computed almost equal BRSs. In view of the large standard deviations and the number of comparisons, we consider only the dominance of parasympathetic control in the supine position a result that distinguishes carriers from controls, as proven by the lower heart rates and lower LF/HF.

Therefore, our study seems to indicate that DPP6 haplotype carriers have a higher vagal outflow at rest, which can suddenly, without apparent cause, drop. Thus, compared to LQTS patients, these patients are not *per se* characterized by an absolute higher sympathetic activity but more by a relative higher parasympathetic activity.[22,23]

We can only speculate about the mechanisms that underlie the increased vulnerability to VF of risk haplotype carriers. In the heart, the putative increase in DPP6 activity would result in increased I_{to}. This current is present in atrial and ventricular cardiomyocytes, and it causes initial (phase 1) repolarization of the action potential,[24] thereby setting the initial plateau potential of phase 2 and modulating inward and outward currents during phase 2, in particular, the voltage-gated L-type calcium current I_{Ca-L}. In this way, I_{to} controls action potential duration and amplitude. I_{to} is carried by a voltage-gated transmembrane ion channel consisting of 4 Kv4.3 α-subunits.[25] Cell surface expression and channel properties are influenced by several accessory subunits, including DPP6[7,8] (in addition to KChIP2,[26] Kvβ,[27] and MinK or MinK-related peptide[28]). Kv4 α-subunit expression on the cell surface increases when coexpressed with DPP6.[7] DPP6 also modifies I_{to} gating properties.[7,8,18] Of note, I_{to} density and properties are modulated by α-adrenergic and β-adrenergic stimulation through G-protein–coupled pathways.[29] This regulation links I_{to} to control by the ANS. One possible mechanism by which net increase in I_{to} may facilitate VF occurrence is through its effect in counteracting I_{Ca-L} activation, resulting in action potential abbreviation and increased susceptibility to reentrant excitation, analogous to the mechanism proposed to underlie arrhythmia occurrence in Brugada syndrome.[30] Accordingly, the I_{to} blocker quinidine prevents VF in risk haplotype carriers. Although DPP6 and I_{to} also impact neuronal excitability, the mechanisms by which abnormal (increased) function of DPP6 in neurons (eg, of the ANS) may elicit cardiac arrhythmia is less clear.

Study limitations

A study limitation is the small size of the study population. To compound this difficulty, inclusion of symptomatic carriers (ie, those who survived VF) is extremely difficult as the survival rate after out-of-hospital VF is low (~20%).[31] Moreover, potential study subjects cannot be included if they use β-adrenoceptor or antiarrhythmic drugs, as these drugs impact on HRV and [123]I-*m*IBG scintigraphy. Yet, these drugs (quinidine) are often prescribed to these individuals to prevent VF recurrence. Another limitation is that, although analysis of QT variability or other indicators of heterogeneity of repolarization might give valuable information (in particular, information on sympathetic control possibly superior to information gained from HRV analysis[32]), we could not conduct such analyses because data needed for these analyses were not systematically collected. Despite these limitations, we believe that this study is of significant novelty value because it provides indications that an inherited SCA syndrome is based on primary derangements in 2 organ systems (heart and ANS) that conspire to increase VF risk.

Conclusion

Although speculative in part, this study provides clinical functional suggestions that the primary pathophysiological basis of an inherited SCA syndrome may lie in combined disruptions in the heart and the ANS. This novel insight suggests that studies aimed at discovering genes underlying inherited SCA syndromes should focus on genes that are expressed both in the heart and in neurons.[33] Moreover, our findings suggest that [123]I-*m*IBG scintigraphy may be used for risk stratification and identification of risk haplotype carriers with elevated VF risk in whom ICD implantation should be considered.

Acknowledgment

References

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