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ORIGINAL ARTICLE

Myocardial perfusion defects in Bartter and Gitelman syndromes

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ABSTRACT

Background Normotensive hypokalaemic tubulopathies (Bartter and Gitelman syndromes (BS/GS)) are genetic diseases that are considered benign. However, QT prolongation, left ventricular dysfunction and reduction of cardiac index upon exercise leading to arrhythmias and sudden cardiac death have been reported in these patients. Hence, we aimed to verifying whether an isometric exercise could represent a useful tool for the identification of patients at risk for future cardiac events.

Patients and methods Myocardial function (MF) and perfusion, evaluated as myocardial blood flow (MBF) of 10 BS/GS patients and 10 healthy controls, were investigated at rest and during isometric exercise. MF and MBF were evaluated using quantitative two-dimensional and myocardial contrast echocardiography.

Results BS/GS patients had normal baseline MF and MBF. During exercise in BS/GS patients, corrected QT (QTc) was prolonged to peak value of 494 ± 9·1 ms ($P < 0·001$). In controls, MF increased from resting to peak exercise (left ventricular ejection fraction: 65 ± 4% to 78 ± 5%, $P < 0·003$) while in seven BS/GS patients (Group 1) it declined (64 ± 5% to 43 ± 9%, $P < 0·001$). Myocardial perfusion increased upon exercise in controls as shown by changes of its markers: β (a measure of myocardial flow velocity; 0·89 ± 0·12 vs. 0·99 ± 0·12, $P < 0·001$) and myocardial blood volume (14·4 ± 2 vs. 20·2 ± 0·25, $P < 0·001$), while in Group 1 BS/GS it decreased (0·87 ± 0·15 vs. 0·67 ± 0·15, $P < 0·001$; and 14·5 ± 1·9 vs. 8·3 ± 0·22, $P < 0·001$, respectively).

Conclusions Our results document for the first time that exercise induce coronary microvascular and myocardial defects in BS/GS patients. Therefore, this may challenge the idea that BS/GS are benign diseases. In addition, the diagnostic approach to these syndromes should include an in-depth cardiac assessment in order to identify patients at higher risk.

Keywords Bartter syndrome, Gitelman syndrome, left ventricular dysfunction, myocardial contrast echocardiography, sudden cardiac death.

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Introduction

Bartter and Gitelman syndromes (BS/GS) are normotensive hypokalaemic tubulopathies characterized by genetically determined functional defects of kidney transporters and ion channels, leading to a puzzling clinical picture including hypokalaemia, sodium depletion, coexistence of hypomagnesaemia and hypocalciuria (the association of these two latter features typical of Gitelman syndrome), activation of the renin–angiotensin–aldosterone system with increased plasma levels of angiotensin II, yet normo-hypotension, reduced peripheral resistance and hyporesponsiveness to pressor agents [1,2].

These tubulopathies are considered benign disorders and the diagnosis is generally incidental. However, prolonged QT interval on the electrocardiogram associated with severe hypokalaemia has been suggested to represent the underlying electrophysiological mechanism for dangerous arrhythmias that might even lead to sudden cardiac death [3–5]. The prevalence of these syndromes is difficult to evaluate because most of the patients remain asymptomatic; however, these syndromes could contribute to the significant proportion of unexplained sudden cardiac deaths in the general population. The recent report of BS/GS patients who experienced aborted sudden cardiac death is in keeping with this hypothesis [6]. In this clinical setting, it has been demonstrated that triggering factors are needed to precipitate malignant ventricular arrhythmias, which can occur during exercise; moreover, an exercise-induced left ventricular (LV) dysfunction was demonstrated in association with a corrected QT (QTc) prolongation during exercise [6]. Thus, hypokalaemia per

Table 1 SLC12A3 mutations identified in the patients with Gitelman's syndrome

Patient	Exon	Mutation at nucleotide	Homo–heterozygous	Predicted effect on protein
1	23	2736G---- > A	Homozygous	Arg904Gln
2	22	2579C---- > T	Heterozygous	Arg852Cys
	23	2736G---- > A	Heterozygous	Arg904Gln
3	15	1950G---- > A	Heterozygous	Arg642His or splice donor site truncated SLC12A3 protein
	18	2246G---- > A	Heterozygous	Gly741Arg
4	22	2579C---- > T	Heterozygous	Arg852Cys
	23	2736G---- > A	Homozygous	Arg904Gln
5	22	2579C---- > T	Heterozygous	Arg852Cys
	23	2736G---- > A	Heterozygous	Arg904Gln
6	21	2542G---- > T	Heterozygous	Asp848Tyr
	10	c.1196_1202dup 7 bp	Heterozygous	Ser402X
7	21	2542G---- > T	Heterozygous	Asp848Tyr
	10	c.1196_1202dup 7 bp	Heterozygous	Ser402X

se often is not sufficient to precipitate life-threatening arrhythmias but requires the presence of triggering factors. A systematic screening/treatment protocol for the recognition of such factors usually is not performed in these patients and a structurally normal heart has been described using standard cardiac evaluation [4–8]. By using diagnostic approaches adequate to the complexity of these syndromes, specific abnormalities of cardiac function, largely independent of hypokalaemia, have been described, including the inability to recruit myocardial contractility causing exercise-induced LV dysfunction [9,10]. Thus, cardiac manifestations in these syndromes may not be completely explained by the deficiency of potassium and magnesium. An important role in the induction of these cardiac manifestations could be played by the altered angiotensin II signalling pathway and nitric oxide system upregulation, which determine important derangements of vascular tone regulation in BS/GS that could reduce microvascular reserve and induce myocardial perfusion defects especially during exercise causing an acute LV overload [11–13].

No data are available on resting and exercise myocardial perfusion in BS/GS patients. In this study, we investigated the relationship between myocardial function and perfusion in BS/GS patients at rest and during isometric exercise by quantitative two-dimensional and myocardial contrast echocardiography. The goal of this study was to document, in these supposed benign syndromes, the hypothesized influence of physical exercise in the induction of coronary microvascular and myocardial dysfunction, which, if relevant, could identify patients at risk for future cardiac events.

Patients and methods

Patients

We recruited 10 patients (6 men and 4 women, aged 18–54 years) with either BS ($n = 1$) or GS ($n = 9$) from our cohort of Bartter and Gitelman syndrome patients; all have a full biochemical characterization with 7 having undergone full genetic analysis (Table 1) and 3 awaiting the results of the genetic screenings.

Ten normotensive healthy subjects (6 men and 4 women, aged 24–45 years) from the staff of the Department of Clinical and Experimental Medicine, University of Padova, were used as control group. The clinical and biochemical characteristics of the patients and controls are shown in Table 2.

None of the patients or controls were taking drugs for at least 2 weeks prior to the study. All subjects were on a normal Italian diet, which contains approximately 150 mmol of sodium per day. Informed consent was obtained from all the study participants.

Echocardiographic analysis

Studies were coded and read by two independent observers blinded to the patient's identity and experimental condition. LV volumes were calculated by an ellipsoid area-length method [14].

Left ventricular ejection fraction (LVEF) was derived as LVEDV – LVESV/LVEDV, where LVEDV is left ventricular end-diastolic volume, and LVESV is left ventricular end-systolic volume.

Inter- and intra-observer variability for LV area ($r = 0{\cdot}92$ and $r = 0{\cdot}96$, respectively) and for LV length ($r = 0{\cdot}94$ and $r = 0{\cdot}96$, respectively) was acceptable.

Table 2 Clinical and laboratory data of BS/GS patients and controls

	Sex	Blood pressure (mmol L^{-1})	Plasma electrolytes (mmol L^{-1})				Urinary electrolytes (mmol day^{-1})				Plasma renin activity (ng angiotensin I mL^{-1} h^{-1})	Aldosterone (nmol L^{-1})
			Na^+	K^+	Cl^-	Mg^{2+}	Na^+	K^+	Cl^-	Ca^{2+}		
Bartter's/Gitelman's patients ($n = 10$)	4 men/ 6 women	113·5/70·5 ± 5·8/1·6	139 ± 0·8	2·7 ± 0·3	98 ± 1·2	0·64 ± 0·1	213 ± 41·8	47·3 ± 17·7	229 ± 38·4	2·2 ± 0·5	9·3 ± 4·7	0·72 ± 0·1
Controls ($n = 10$)	6 men/ 4 women	128·5/82 ± 6·2/2·6	139 ± 1·0	4·1 ± 0·2	99 ± 0·97	0·99 ± 0·2	168 ± 16·5	52·8 ± 4·8	179·8 ± 19·6	4·5 ± 0·5	0·73 ± 0·11	0·18 ± 0·02

The table reports data as mean ± standard deviation of BS/GS patients and control subjects. Blood samples were obtained in supine position for at least 1 h. Normal values for plasma renin activity and plasma aldosterone in our laboratory are 0·2–2·8 ng angiotensin I mL^{-1} h^{-1} and 0·08–0·29 nmol L^{-1}, respectively. Normal values for plasma Na^+, K^+, Cl^-, Mg^{2+} are 136–145, 3·5–5, 96–108, 0·65–1·05 mmol L^{-1}, respectively. Normal values for urinary Na^+, K^+, Cl^- and Ca^{2+} excretion are 40–220, 25–125, 110–250 and 2·5–7·5 mmol day^{-1}, respectively.

Isometric exercise (hand-grip)

Maximal voluntary contraction was determined by mean of a dynamometer. Then, isometric exercise was performed for 3 min at 40% maximal voluntary contraction. During the exercise, arterial blood pressure was measured every 30 s by an oscillometric method, and heart rate and electrocardiographic tracings were monitored continuously.

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) studies were performed in apical four- and two-chamber views using intermittent harmonic imaging with a phased-array system (Sonos 5500) interfaced to an S3 transducer that transmits ultrasound at a mean frequency of 1·6 MHz and receives it at 3·2 MHz. The transmit power was set at maximum, and compression was set at 50 dB. Mechanical index was 1·4. Gain settings were optimized at the beginning of each study and subsequently held constant. Continuous venous infusion of a contrast agent (Levovist, Bayer AG, Leverkusen, Germany) was performed with an infusion pump (Medrad Pulsar, Indianola, PA, USA). An intensity-dose curve from the LV cavity was plotted to obtain the dose at which the relation was linear. This dose was used in the contrast echocardiographic studies. In each patient, to avoid significant changes in the concentration of contrast in LV cavity before and after the meal, only studies with similar values of peak LV cavity contrast intensity were analysed. We accepted a range of ratios of peak contrast intensity in the resting state to peak contrast intensity in the exercise state from 0·9 to 1·1. Absence of any change in myocardial video intensity over five successive frames by visual assessment indicated the steady state. Once steady state was achieved, repeated imaging was obtained with sequential ECG triggering at end systole. The pulsing interval was gated to the ECG and progressively increased from 80 ms to 10 s. Up to 12 images acquired at each pulsing interval were recorded on an optical disk for quantitative analysis. Background-subtracted myocardial signal intensity was plotted over the increasing pulsing intervals and fit to an exponential function as described by Wei *et al*. [15] to determine the slope of the ascending curve of myocardial contrast intensity (β), which provides a measure of myocardial flow velocity, and the myocardial plateau intensity, which correlates to capillary cross-sectional area and, hence, to myocardial blood volume (MBV). The product (β × MBV) represents a dimensionless index of MBF [16].

Digitized studies were coded and read by two independent observers blinded to patient identity and the order of the study. An index of mean global myocardial perfusion was calculated by adding the values of regional MBF and dividing this value by the number of analysed LV segments. In this study, the degree of inter-observer and intra-observer correlations for measurements of MBV ($r = 0·94$, $r = 0·96$, respectively) and β ($r = 0·95$, $r = 0·96$, respectively) was acceptable.

Statistical analysis

Results are expressed as mean ± standard deviation for normally distributed variables (ejection fraction, end-diastolic and end-systolic volume indexes, myocardial perfusion indexes, age, blood pressure, heart rate, blood chemical variables). Comparisons between control subjects and BS/GS patients were made with the unpaired *t*-test. The change in parameters of MCE (β, MBV, MBF) from the rest to peak exercise state were performed with repeated-measures analysis of variance, followed by Fisher's protected least significant difference test. Correlations between MCE and LV function parameters were determined by a linear least-squares method.

For all statistical analyses, we used SPSS version 10·1 for Windows (SPSS Inc., Chicago, IL, USA). A value of $P < 0{\cdot}05$ by the two-tailed test was considered statistically significant.

Results

Baseline LV function and myocardial perfusion

All BS/GS patients had a normal baseline LVEF and were classified into two groups on the basis of LV response to hand-grip: Group 1 ($n = 7$: 6 Gitelman syndrome and 1 Bartter syndrome patients) included patients with an abnormal response to exercise (decline > 0·05 U which is equal to decline > 0·5% in LVEF); Group 2 ($n = 3$, Gitelman syndrome patients) included patients with a normal response (increase or no changes in LVEF). Measurements of LV end-diastolic volume index (LVEDVI) (60 ± 9 mL m^{-2}, range 53–71) and LVEF (65 ± 4%, range 55–72) in the controls were used to determine mean and 95% confidence limits of normal values. In BS/GS patients, baseline LVEDVI and LVEF did not differ from controls indicating that patients of both groups had normal LVEDVI and LVEF values.

Myocardial contrast echocardiographic studies showed that both baseline β (a measure of myocardial flow velocity) (0·89 ± 0·12 vs. Group 1: 0·87 ± 0·15 vs. Group 2: 0·88 ± 0·10, P = NS) and MBV (14·4 ± 2·0 vs. Group 1: 14. 5 ± 1·9 and vs. Group 2: 14·5 ± 2·0, P = NS) did not differ between control subjects and BS/GS patients. As a consequence, baseline MBF was normal in all BS/GS patients.

Changes in QTc interval during exercise

QT interval was measured from the beginning of the QRS complex to the end of the T wave. It reflects the duration of depolarization (electric systole). Because the duration of QT interval varies with cycle length, it was corrected for heart rate using a linear regression model [17].

At rest, an electrocardiogram showed sinus rhythm in all patients with a PR interval of 161 ± 0·9 ms, and a QTc interval of 420 ± 4 ms.

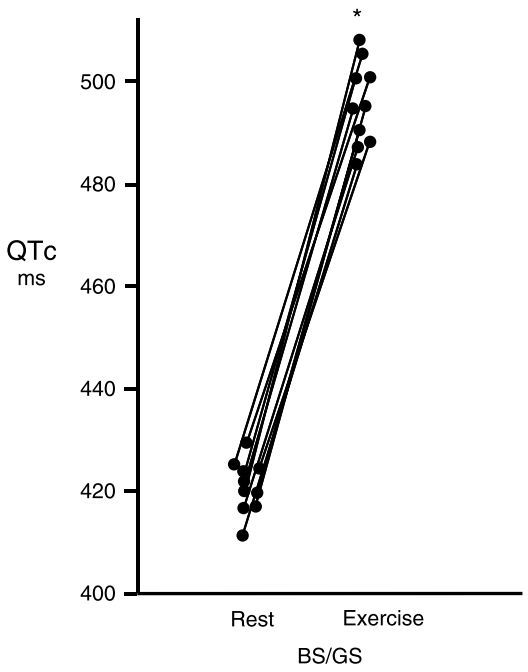

Figure 1 Exercise-induced paradoxical QTc prolongation in study patients (*$P < 0{\cdot}001$).

Potassium level, measured just before the beginning of exercise, was 2·9 ± 0·3 mmol L^{-1}. During exercise, QTc interval prolonged to a peak value of 494 ± 9·1 ms ($P < 0{\cdot}001$) (Table 3, Fig. 1).

Changes in LV function during exercise

In control subjects, LVEF significantly increased at peak exercise from resting value (65 ± 4 vs. 78 ± 5%, $P < 0{\cdot}003$) (Fig. 2), and the individual response to hand-grip was characterized by a > 0·05 U increase in all but two subjects, who showed no significant changes. In seven BS/GS patients (Group 1), an LV dysfunction induced by exercise occurred (> 0·05 U (> 0·5%) decline in LVEF: from 64 ± 5 to 43 ± 9, $P < 0{\cdot}001$); the remaining three patients (Group 2) had a normal LV response to hand-grip (two had a significant increase whereas one showed no change in LVEF). As a consequence, peak exercise LVEF in Group 1 patients was significantly lower than that of controls (43 ± 9 vs. 78 ± 5, $P < 0{\cdot}001$), while no difference was detected in Group 2 (77 ± 5, P = NS) in comparison to controls (Table 3, Fig. 2).

Heart rate increased at peak hand-grip in both groups of patients with BS and GS and controls without significant differences (Group 1: 96 beats min^{-1}; and Group 2: 94 beats min^{-1} vs. 95 beats min^{-1}), while peak exercise systolic blood pressure was significantly lower in both groups of patients in comparison to controls (165 ± 15 mmHg vs. Group 1: 140 ± 19 mmHg and Group 2: 142 ± 15 mmHg; $P < 0{\cdot}01$) (Table 3).

Table 3 Baseline and peak exercise variables in controls and Bartter's and Gitelman's syndrome (BS/GS) patients

	Controls ($n = 10$)	BS/GS Group 1 ($n = 7$)	BS/GS Group 2 ($n = 3$)
Baseline			
HR (beats min^{-1})	65 ± 12	67 ± 10	68 ± 9
SBP (mmHg)	120 ± 5	115 ± 7	114 ± 9
DBP (mL m^{-2})	70 ± 7	68 ± 10	67 ± 9
LVEDVI (mL m^{-2})	60 ± 9	62 ± 12	60 ± 10
LVESVI (mL m^{-2})	24 ± 5	25 ± 4	26 ± 8
LVEF (%)	65 ± 4	64 ± 5	65 ± 5
β	0·89 ± 0·12	0·87 ± 0·15	0·88 ± 0·10
MBV	14·4 ± 2	14·5 ± 1·9	14·5 ± 2
MBF	5·29 ± 0·14	5·32 ± 0·10	5·30 ± 0·12
Peak exercise			
HR (beats min^{-1})	95 ± 15	96 ± 15	69 ± 19
SBP (mmHg)	165 ± 15	140 ± 19¶	142 ± 15§
DBP (mL m^{-2})	80 ± 15	78 ± 14	77 ± 19
LVEDVI (mL m^{-2})	65 ± 9	79 ± 12	69 ± 10
LVESVI (mL m^{-2})	14 ± 5	45 ± 7†‡§	15·8
LVEF (%)	78 ± 5*	43 ± 9†‡§	77 ± 5
β	0·99 ± 0·12	0·67 ± 0·15†‡§	0·98 ± 0·10
MBV	20·4 ± 2·2	12·5 ± 1·5†‡§	19·8 ± 2
MBF	20·2 ± 0·25	8·3 ± 0·22†‡§	19·9 ± 0·32
MBF reserve (exercise MBF/resting MBF)	3·85 ± 0·19	1·56 ± 0·15†‡§	3·75 ± 0·22

Data are expressed as mean ± standard deviation. Controls at rest vs. exercise.* $P < 0·003$. Group 1 at rest vs. exercise and vs. controls. † $P < 0·001$. Group 1 exercise vs. control exercise. ‡ $P < 0·001$. Group 1 vs. Group 2. § $P < 0·001$. Group 1 and 2 vs. Controls. ¶ $P < 0·01$. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; MBV, myocardial blood volume, β, mean microbubble velocity; MBF, myocardial blood flow.

Changes in myocardial perfusion during exercise

During isometric exercise, β values (a measure of myocardial flow velocity derived from the time-intensity curve) significantly increased from resting values in controls (0·89 ± 0·12 vs. 0·99 ± 0·12, $P < 0·001$), while they significantly decreased in BS/GS patients of Group 1 (0·87 ± 0·15 vs. 0·67 ± 0·15, $P < 0·001$) and remained unchanged in those of Group 2 (0·88 ± 0·12 vs. 0·98 ± 0·15, P = NS). In controls, MBV increased during exercise (14·4 ± 2 vs. 20·2 ± 0·25, $P < 0·001$) while in Group 1 BS/GS patients, MBV decreased from baseline to peak hand-grip (14·5 ± 1·9 vs. 8·3 ± 0·22, $P < 0·001$). Patients of Group 1 also had exercise MBV and MBF significantly lower than controls ($P < 0·001$) (Table 3). On the contrary, in patients of Group 2, MBV increased during the acute overload imposed by hand-grip (14·5 ± 2 vs. 19·8 ± 0·32, $P < 0·01$), with no difference compared to controls. Exercise MBV and MBF were significantly higher in Group 2 compared with Group 1 ($P < 0·001$). Thus, the capacity to increase MBF during LV acute overload as expressed by the ratio exercise-MBF/baseline-MBF was significantly reduced in BS/GS patients with LV dysfunction induced by exercise (Table 3).

Discussion

This study demonstrates that the majority of our BS/GS patients show a reduced capacity to adapt LV function in response to an acute overload imposed by isometric exercise, despite the fact that LV function and dimensions are normal at rest. Myocardial

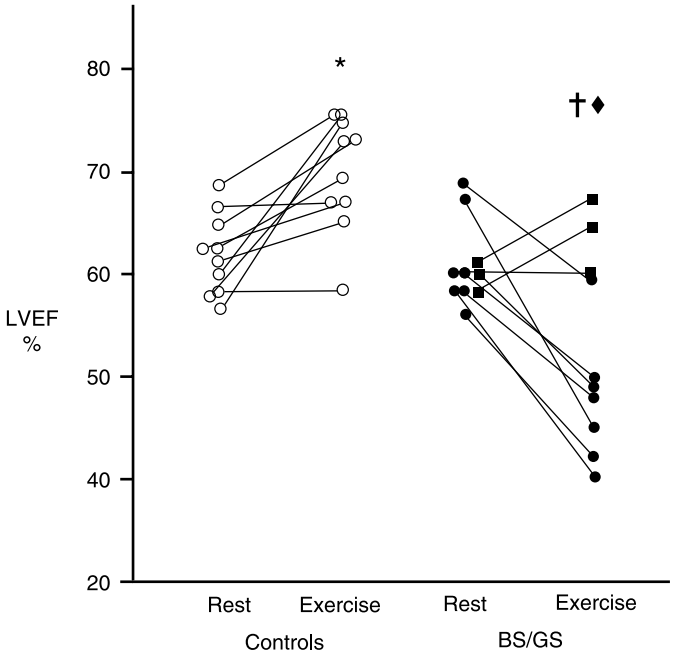

Figure 2 Changes in left vetricular function induced by exercise in controls (○) ($n = 10$) and Group 1 (●) ($n = 7$) and Group 2 (■) ($n = 3$) Bartter's and Gitelman's syndrome (BS/GS) patients. *$P < 0{\cdot}001$: Controls rest vs. exercise; †$P < 0{\cdot}001$: BS/GS Group 1 vs. Controls; ◆$P < 0{\cdot}001$: BS/GS Group 1 rest vs. exercise.

perfusion defects are not present in these patents at rest but a reduced microvascular reserve can be demonstrated with exercise. The inadequate increase in myocardial MBF during exercise demonstrated by MCE is due to a reduction of myocardial flow velocity, related to coronary epicardial vessel resistance (as shown by the reduced β values) and of the myocardial plateau intensity (which correlates to capillary cross-sectional area and, hence, to myocardial blood volume). In addition, the altered intracellular calcium-mediated signalling for vasopressors joined to the upregulation of nitric oxide system associated to an increased nitric oxide production, characteristic of these patients, cause maximal vasodilation (even at basal condition) and reduced driving pressure [11–13,18,19]. From a hypothetical point of view, the increased nitric oxide production in our patients, in fact, might attenuate the β1/β2 adrenergic increase in inotropy and chronotropy and reinforce the pre- and post-synaptic vagal control of cardiac contraction, just as an 'endogenous beta blocker' [20].

These three mechanisms (inadequate increase in myocardial blood flow, nitric oxide-induced maximal vasodilation and reduced driving pressure) are factors limiting a further increase in myocardial perfusion during increased metabolic requests. Moreover, myocardial perfusion abnormalities induced by exercise may cause a defective myocardial contractile recruitment with subsequent incapacity to match the acute LV overload and reduced cardiac index. Myocardial perfusion abnormalities and reduced cardiac index are strongly interrelated and may aggravate each other in a vicious cycle, thus representing the basis for the paradoxical prolongation in QT interval demonstrated during exercise in these patients. These results support the role of microvascular dysfunction and myocardial perfusion abnormalities as triggering factors precipitating malignant ventricular arrhythmias in the context of chronic hypokalaemia usually present in BS/GS patients. Thus, hypokalaemia predisposes to ventricular arrhythmias, but per se is often not sufficient to cause a critical prolongation in QT interval and malignant ventricular arrhythmias. The multifactorial pathogenesis of ventricular arrhythmias predisposing BS/GS patients to cardiac sudden death reflects both the complexity of abnormalities in ion channels function typical of the disease and the abnormalities of intracellular signalling leading to the altered vascular tone regulation demonstrated in these syndromes [11–13].

In a previous report, we described an aborted cardiac sudden death during strenuous exercise (body building) that was coincident with an episode of sustained ventricular tachycardia [6]. In this case, the severe hypokalaemia on admission, however, was associated with values of QTc of 413 ms that are not held sufficient to induce dangerous ventricular arrhythmias. In this patient, LV dysfunction during exercise could have determined a reduction in cardiac index and the association of a high level of LV work load and reduced cardiac index could have caused myocardial hypoperfusion sufficient to further prolong QTc and/or induce myocardial ischaemia during the episode of aborted cardiac sudden death. The combination of these factors may easily explain the appearance of a severe electrical instability.

The demonstration of myocardial perfusion abnormalities in BS/GS patients is of clinical relevance because similar defects have been indicated as predictors of an increased risk of cardiovascular mortality in patients with various diseases [21–27]. Therefore, in patients with BS/GS, it would appear that serious consideration should be given to the need for an appropriate assessment of cardiac performance during exercise. Non-invasive imaging might be of particular value in this regard. Myocardial perfusion imaging using single-photon emission tomography (SPECT), Rubidium-82 positron emission tomography (^{82} Rb PET), and MCE have been used as means to identify high-risk subjects among patients with different diseases, and have shown good prognostic value [21–27].

Data in BS/GS patients are not yet available on a larger scale also in consideration of the rare nature of the diseases but the present findings strongly support the necessity for an update of the guidelines in the evaluation of these patients. A questionnaire-based inquiry performed among European

paediatric nephrologists with a large experience with normotensive hypokalaemic tubulopathies, the only available in the literature, raised the current opinion that inherited normotensive hypokalaemic tubulopathies do not predispose per se to dangerous cardiac arrhythmias which, on the other hand, may be acutely precipitated by treatments with drugs prolonging QT interval, diarrhoea or vomiting, which further worsen hypokalaemia, and perhaps by intense physical activities such as competitive sports. Most of the nephrologists interviewed, however, felt that further investigations were important to assess the true hazard of dangerous arrhythmias in these patients, recommending the need to develop practical guidelines for a cardiac work-up and management of children and adolescents with normotensive hypokalaemic tubulopathies [28]. Given the findings of our study, the same need also appears to adult patients with these syndromes. A systematic screening protocol should therefore be developed based on an adequate cardiac assessment including resting and, at least for adult patients, exercise LV function evaluation and QTc interval dynamic changes during daily life. In the presence of a documented exercise-induced LV dysfunction, precautions are mandatory in order to limit physical activity and to avoid situations causing excessive potassium loss.

In conclusion, these results provide the first evidence for coronary microvascular dysfunction and myocardial defects that may expose the patients with BS/GS to the risk of cardiac sudden death despite the absence of clinical symptoms and the apparently normal heart at rest. General practitioners and specialists (cardiologists and nephrologists) should therefore pay attention to the possible dramatic cardiac consequences of these diseases that are generally considered benign. The evidence we have provided makes it mandatory the introduction of new protocols for cardiac surveillance and adequate cardiac diagnostic procedures in these high-risk patients.

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