Industrial Health 2023, **61**, 455–461

Case Report

Brugada syndrome and job fitness: report of three cases

Stefano M. CANDURA[1, 2]*, Daniela VANOLI[1], Andrea MAZZANTI[3–5], Luca D'AMATO[1], Silvia G. PRIORI[3, 4] and Fabrizio SCAFA[2]

[1]Occupational Medicine Unit, Department of Public Health, Experimental and Forensic Sciences, University of Pavia, Italy
[2]Istituti Clinici Scientifici Maugeri IRCCS, Occupational Medicine Unit of Pavia Institute, Italy
[3]Istituti Clinici Scientifici Maugeri IRCCS, Molecular Cardiology of Pavia Institute, Italy
[4]Department of Molecular Medicine, University of Pavia, Italy
[5]Molecular Cardiology, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Spain

Received June 30, 2022 and accepted January 27, 2023
Published online in J-STAGE February 2, 2023
DOI https://doi.org/10.2486/indhealth.2022-0205

Abstract: Brugada syndrome (BrS) is an inherited arrhythmogenic disorder predisposing patients to a high risk of sudden cardiac death. Specific guidelines on the health surveillance of BrS workers are lacking. We report here three cases requiring assessment of specific job capacity, investigated with an interdisciplinary protocol including 24-h Holter electrocardiography with modified precordial leads, pharmacological test with ajmaline, molecular genetic analysis, electrophysiological study with ventricular stimulation, risk stratification, and occupational medicine evaluation: (1) a female 42-yr-old company manager with positive ajmaline test and *CACNA1C* gene mutation (judged fit for the job with limitations regarding work-related stress); (2) a male 44-yr-old welder with positive ajmaline test, *SCN5A* gene mutation, and associated OSAS (obstructive sleep apnea syndrome), who was advised to refrain from night shifts and driving company vehicles; (3) a male 45-yr-old electrical technician with inducible ventricular tachyarrhythmia, who was implanted with a biventricular cardioverter defibrillator, and therefore recommended to avoid exposure to electromagnetic fields and working at heights. We conclude that the collaboration between the cardiologist and the occupational physician allows defining the functional capabilities and the arrhythmogenic risk of BrS workers, to optimize job fitness assessment.

Key words: Arrhythmia, Syncope, Sudden cardiac death, Electrocardiography, Genetic analysis, Work fitness

Introduction

First described in 1992[1)], Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome, characterized by a peculiar electrocardiographic pattern, which predisposes patients to an increased risk of sudden cardiac death due to ventricular fibrillation in a structurally normal heart[2, 3)].

BrS mainly affects middle-aged patients. Its prevalence ranges between 1 in 5,000 to 1 in 2,000 in different populations, with the highest being in Southeast Asia, where the syndrome is endemic. The prevalence is 8–10 times higher in men compared to women, probably due to the

*To whom correspondence should be addressed.
E-mail: stefano.candura@icsmaugeri.it

influence of hormones and differences in transmembrane ion channel expression between genders[4, 5]. Both sporadic and familial cases of BrS have been reported, and pedigree analysis suggests an autosomal dominant pattern of inheritance. More than 20 genes have been associated with BrS, and the overall yield of genetic testing in BrS is approximately 30%. Loss-of-function mutations on *SCN5A*, encoding the α-subunit of the cardiac Na^+ channel $Na_V1.5$, account for most genotype-positive cases. In fewer cases, gain-of-function mutation on *CACN1AC* (encoding the α-1C subunit of the L-type voltage-dependent Ca^{2+} channel) are found[6, 7]. In nearly 70% of affected families the genetic cause is unknown and recent evidence suggests that a more complex polygenic mode of inheritance—including multiple variants acting in concert through different mechanisms—may explain some of the cases[8].

The diagnosis of BrS is made upon the documentation of ST-segment elevation with type 1 morphology ≥2 mm ("coved morphology") in one or more leads among the right precordial leads V_1 and/or V_2 positioned in the second, third, or fourth intercostal space. This pattern may be spontaneously evident, or it may be induced by a provocative pharmacological test with the administration of intravenous sodium channel blockers (such as ajmaline or flecainide)[5].

Typically, BrS manifests as an unexpected cardiac arrest, almost exclusively during states of vagal predominance, such as rest or sleep. The event may be triggered by fever, large meals, excessive alcohol consumption and cocaine[9]. Often, however, patients remain asymptomatic for life, and are diagnosed incidentally with a Brugada ECG pattern[3].

The cornerstone of treatment is represented by the judicious use of an implantable cardioverter defibrillator (ICD), which is the only treatment shown to reduce the risk of sudden cardiac death. Risk stratification is critical, since the decision to implant an ICD, especially in a young patient, should be carefully weighed against the cost in terms of quality of life[10, 11].

According to the current guidelines of the European Society of Cardiology[9], ICD implantation is recommended in BrS patients who: (a) are survivors of an aborted cardiac arrest and/or (b) have documented spontaneous sustained ventricular tachycardia. Additionally, the implantation of an ICD should be considered in subjects with history of syncope in combination with a spontaneous type 1 ECG pattern, and it may be considered in patients who develop ventricular fibrillation during programmed ventricular stimulation with two or three extrastimuli at two sites (class IIb).

Although BrS can pose considerable difficulties to the occupational physician in formulating the judgment for job fitness[12, 13], no specific guidelines on the health surveillance of workers suffering from this arrhythmogenic disorder are available in the scientific literature. By presenting three illustrative cases, we propose here an interdisciplinary approach for the clinical and functional evaluation of BrS workers, aimed at continuing the occupational activity, by formulating appropriate prescriptions and limitations.

Subjects and Methods

We report three patients (one female and two males, all Caucasian) who required an interdisciplinary (cardiology and occupational medicine) specialist evaluation at our Institute, for suspected Brugada syndrome and assessment of specific work capacity.

A careful work history was collected, as well as family, physiological and pathological history. This step was followed by a complete physical examination. Subsequently, the diagnostic process included routine laboratory blood and urine analysis, baseline 12 leads electrocardiography, 24-h Holter electrocardiography with modified precordial leads (V_1–V_2 in second intercostal space, V_3–V_4 in third intercostal space, V_5–V_6 in fourth intercostal space, in the right and left parasternal position) (Fig. 1), and echocardiography. Cases 1 and 2 underwent provocative pharmacological test with ajmaline (1 mg/kg i.v. in 10 min, during continuous ECG recording with modified precordial leads). Patient 3, who presented a spontaneous type 1 pattern, underwent an electrophysiological study with programmed ventricular stimulation, to better stratify the arrhythmic risk.

In addition, DNA molecular genetic analysis was performed on all patients. The analysis regarded the coding regions, and part of the intronic regions, of the *SCN5A* and *CACNA1C* genes. The DNA was extracted from at least two different peripheral blood samples, amplified by PCR (polymerase chain reaction), and sequenced with the Sanger method. The analytical process included the analysis of a blank sample per analytical series, to verify the absence of contamination by exogenous DNA (negative control)[14].

After confirmation of BrS diagnosis and risk stratification, detailed indications about therapy, work resumption and follow-up were provided, and task limitations suggested. Recommendations were tailored to each single

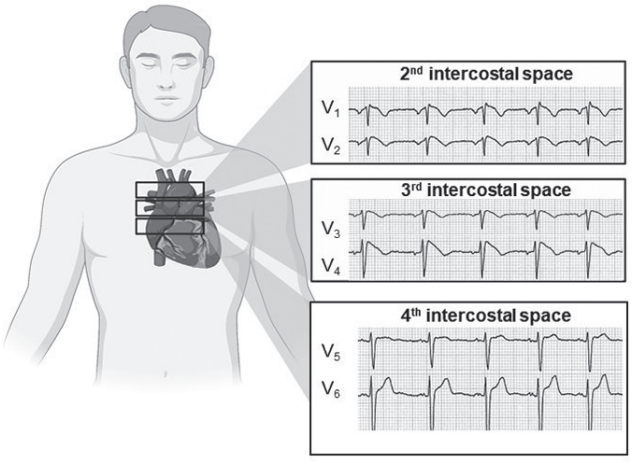

Fig. 1. Evidence of Brugada pattern type 1 in precordial leads during electrocardiogram (ECG) with modified precordial leads.

case, relating the patient's psychophysical conditions to the physical and mental requirements of his or her job.

Informed consent was obtained from each subject, and the ethics committee of ICS Maugeri IRCCS approved the utilization of the patients' clinical data (in anonymous form) for the present scientific report.

Results

Case #1

Female, 42-yr-old. Father with arterial hypertension and a previous acute myocardial infarction. Married with daughter and son (both delivered by caesarean section). One voluntary termination of pregnancy and two spontaneous abortions. At 38, surgical reduction of left-hand fracture. Nothing relevant in the remote cardiological history. After completing her studies (artistic high school degree), she started working at the age of 19, initially as a waitress, then as a designer at a municipal technical office.

At age 26, hired by a computer technology company. After working as programmer and data analyser, at 33 she was promoted to project manager. The activity was carried out exclusively in the office, full time, spending many hours at the video display terminal. She reported stressful working conditions due to high workload and responsibility, and to the necessity of commuting (for a total of four hours a day).

During the year preceding our evaluation, the patient experienced two pre-syncopal episodes (nausea, sweating, feeling of fainting) during febrile events. On the second occasion, an electrocardiogram (ECG) recorded in the emergency room documented a coved 1.5 mm elevation of the ST segment in V_1: this finding suggested the possible diagnosis of BrS.

At the time of our consultation, the patient was asymptomatic. Nothing relevant on physical examination. Blood and urine laboratory data, baseline ECG, and echocardiography were normal. Holter electrocardiography with modified precordial leads showed a non-diagnostic coved elevation of the ST segment in second intercoastal space V_1–V_2. Thus, provocative pharmacological testing with ajmaline (at the cumulative dose of 40 mg) was performed, unmasking a type I tracing diagnostic for BrS. Molecular genetic analysis revealed the *p.Gly490Arg* variant in the *CACNA1C* gene[7].

Since the patient had shown a diagnostic ECG pattern only during the drug test, she was classified as at low arrhythmic risk. In consideration of the reported symptoms, a loop recorder was installed for a more accurate monitoring of the heart rhythm.

Regarding work capacity, we judged the patient suitable to maintain the role of project manager, avoiding excessive stress and not extending her stay in the office beyond the pre-established working hours. Moreover, we recommended not to go to work in case of malaise or fever, and to evaluate the possibility of smart working from home.

Case #2

Male, 44-yr-old. Family history of diabetes mellitus and ischemic heart disease. Previous smoker. Several previous surgeries (left orchiectomy for testicular torsion, reduction of clavicle fracture, laparoscopic Nissen fundoplication for gastroesophageal reflux disease, appendectomy, right inguinal hernioplasty). Previous diagnosis of OSAS (obstructive sleep apnea syndrome) at another medical centre (no documentation available). He always worked, from the age of 18, as a welder and fitter of industrial components in iron and steel, with occasional handling of heavy loads (≥25 kg).

Two years before our evaluation, occasional ECG findings suspected for BrS (trace not available for review). At the time of our consultation, the patient reported daytime sleepiness (Epworth sleepiness scale score: 13/24) but no cardiological symptoms. Physical examination revealed grade 1 obesity (body mass index: 30.1) and scars from previous surgery. Blood and urine laboratory data, echocardiography, baseline and (modified precordial leads) Holter ECG were normal. The provocative ajmaline test induced a type 1 Brugada pattern at the cumulative dose of 50 mg. Molecular genetic analysis revealed the *Val-1353Met* mutation in the *SCN5A* gene. Similarly to patient

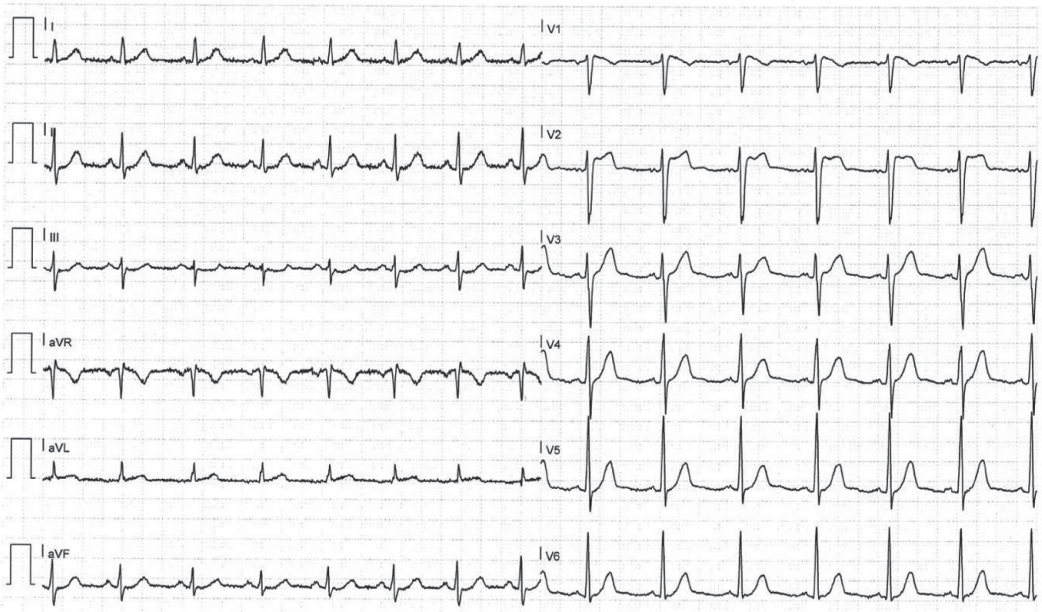

Fig. 2. Baseline electrocardiogram (ECG) of case 3, showing ST segment elevation (with morphology suggestive for Brugada syndrome) in V_1 and V_2.

1, the subject was classified at low arrhythmic risk, and a loop recorder was implanted to monitor for the occurrence of asymptomatic arrhythmias.

The diagnosis of OSAS was confirmed by polysomnography (16 phasic episodes of desaturation during six complete sleep cycles; hourly desaturation index: 2.6). The patient was enrolled in a weight reduction program and adapted to non-invasive nocturnal ventilation with CPAP (continuous positive airway pressure).

He was confirmed fit for the job of assembler and welder. However, given the concomitance of OSAS, we recommended abstaining from driving company vehicles and from night shifts.

Case #3

Male, 45-yr-old. No family history of sudden cardiac death or major arrhythmic events. Nothing relevant in the physiological anamnesis. Tonsillectomy at the age of 3. He always worked, from the age of 19, as a technician in an electronics company.

During a health surveillance visit, occasional ECG findings were considered suspect for BrS (Fig. 2). Asymptomatic at the time of consultation. Nothing relevant on physical examination. Blood and urine laboratory data, and echocardiography were normal. Although molecular genetic analysis resulted negative, baseline and Holter electrocardiography with modified precordial leads disclosed a type 1 tracing clearly diagnostic for BrS in upper intercoastal spaces (Fig. 3).

The electrophysiological study, performed to stratify better the patient's arrhythmic risk, demonstrated the presence of inducible ventricular fibrillation during programmed electrical stimulation. After in-depth discussion with the patient on the benefit/risk ratio, a bicameral ICD was implanted. He was subsequently declared fit for his job, with the recommendations to avoid exposure to electromagnetic fields and not to work at heights.

Discussion

Previous experience from our research group demonstrated the usefulness of the interactive approach between the cardiologist and the occupational medicine specialist to facilitate work resumption after invasive cardiac treatments, adapting work tasks to new psychophysical capabilities. Following this strategy, patients can return to work early, satisfactorily, and with minimal risks[15, 16]. The three reported cases indicate that the same approach can be useful for assessing job fitness in workers with BrS, a problematic issue for which specific guidelines are lacking.

The protocol described here primarily contemplates diagnostic confirmation. This is possible through an accurate electrocardiographic study and molecular analysis. The

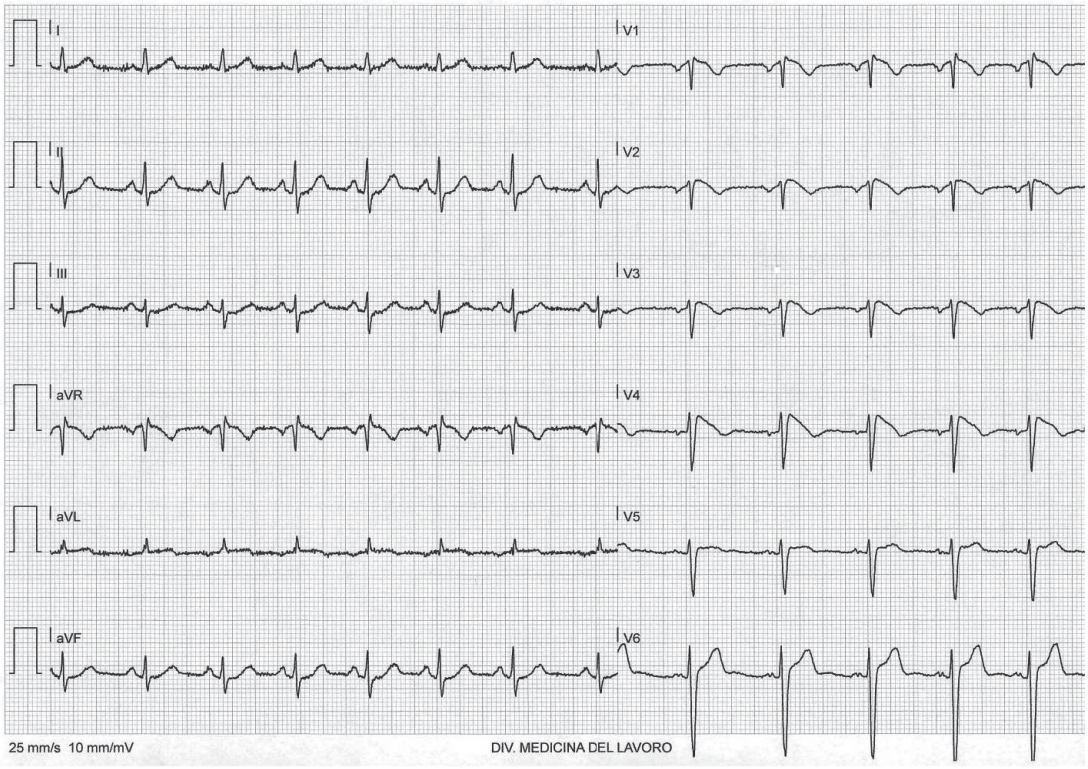

Fig. 3. Baseline electrocardiogram (ECG) of case 3 with modified precordial leads, showing ST segment elevation with coved morphology (type 1 tracing, diagnostic for Brugada syndrome) in V_1–V_4.

assessment performed at our Institute comprises a baseline ECG, and an ECG with modified leads, to increase the sensitivity for detecting the type 1 pattern[17]. In patients in whom spontaneous type 1 pattern is not evident at ECG, we use a 24-h Holter ECG with modified leads. When Holter ECG with modified leads is not clearly diagnostic (as in patients 1 and 2), provocative pharmacological testing using ajmaline is performed. Additionally, echocardiography is performed to exclude other cardiac conditions and obtain a baseline evaluation of general cardiac function, which ought to be taken into due consideration for the purposes of work capability assessment.

Differential diagnosis is rather broad and requires an expert cardiologist. For example, arrhythmogenic ventricular cardiomyopathy (ACM), another inherited disease[18], and early repolarization[19], both frequent in young males, should be excluded.

Once the diagnosis of BrS is established, an accurate risk stratification must be made. Cases 1 and 2 resulted at low arrhythmic risk, as they were both asymptomatic and showed a drug-induced BrS pattern. In both, a loop recorder was installed for monitoring of the heart rhythm. The third patient, although asymptomatic, received an ICD because of the induction of ventricular fibrillation during programmed electrical stimulation.

The interdisciplinary protocol is completed by occupational medicine evaluation, aimed at providing indications on job fitness. In this regard, the first aspect to be considered concerns physical exertion and the manual handling of loads. Importantly, workers with ICD (such as patient 3) should avoid tasks that require excessive extension and effort of the arms, as any overload or unusual/violent movement of the left upper limb could damage the device and alter its functionality.

Furthermore, although modern ICDs guarantee protection from the interference produced by most electronic equipment, they are still sensitive to strong electromagnetic fields, making it necessary to formulate restrictions regarding tasks carried out in the vicinity of large industrial generators and radar sources, or sources related to the use of certain tools, such as chainsaws, arc welders or pneumatic hammers[20].

Night work deserves particular attention (see case 2, further complicated by the concomitance of OSAS), not because there is a particular correlation between the syndrome and the circadian rhythm, but because staff

reduction during night shifts reduces the possibility of prompt rescue by a colleague. The same problem concerns tasks carried out in confined spaces, for the possible poor visibility of the victim, and for the possible difficulty in accessing the area.

The increase in body temperature is one of the main arrhythmogenic factors in Brugada syndrome[3, 10]. Thus, workers affected by the disorder should not go to work in case of fever or malaise (case 1 is emblematic from this point of view). For the same reason, it is advisable to limit exposure to high temperatures, both outdoor or in proximity of ovens or other heath sources.

Lastly, two tasks that should be avoided are working at heights and driving company vehicles. In the first eventuality (as in case 3), the limitation safeguards the worker's safety. In the second (see case 2), the limitation not only protects the worker from trauma, but also third parties.

Conclusion

The three reported cases indicate that patients with Brugada syndrome may come to the attention of the occupational physician. In this circumstance, the collaboration with an expert cardiologist allows to define the functional capabilities and the arrhythmogenic risk, and to formulate the judgment for job fitness. Specific scientific guidelines on health surveillance of workers suffering from this disease are needed.

Acknowledgment

We thank Christine Broughton for linguistic revision.

References

1) Brugada P, Brugada J (1992) Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol **20**, 1391–6.
2) Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R (2018) Present status of Brugada syndrome: JACC state-of-the-art review. J Am Coll Cardiol **72**, 1046–59.
3) Korlipara H, Korlipara G, Pentyala S (2021) Brugada syndrome. Acta Cardiol **76**, 805–24.
4) Postema PG (2012) About Brugada syndrome and its prevalence. Europace **14**, 925–8.
5) Polovina MM, Vukicevic M, Banko B, Lip GYH, Potpara TS (2017) Brugada syndrome: a general cardiologist's perspective. Eur J Intern Med **44**, 19–27.
6) Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP, Heart Rhythm Society (HRS) European Heart Rhythm Association (EHRA) (2011) HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace **13**, 1077–109.
7) Novelli V, Memmi M, Malovini A, Mazzanti A, Liu N, Yanfei R, Bongianino R, Denegri M, Monteforte N, Bloise R, Morini M, Napolitano C (2022) Role of CACNA1C in Brugada syndrome: prevalence and phenotype of probands referred for genetic testing. Heart Rhythm **19**, 798–806.
8) Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, Guicheney P, Fressart V, Leenhardt A, Antzelevitch C, Bartkowiak S, Borggrefe M, Schimpf R, Schulze-Bahr E, Zumhagen S, Behr ER, Bastiaenen R, Tfelt-Hansen J, Olesen MS, Kääb S, Beckmann BM, Weeke P, Watanabe H, Endo N, Minamino T, Horie M, Ohno S, Hasegawa K, Makita N, Nogami A, Shimizu W, Aiba T, Froguel P, Balkau B, Lantieri O, Torchio M, Wiese C, Weber D, Wolswinkel R, Coronel R, Boukens BJ, Bézieau S, Charpentier E, Chatel S, Despres A, Gros F, Kyndt F, Lecointe S, Lindenbaum P, Portero V, Violleau J, Gessler M, Tan HL, Roden DM, Christoffels VM, Le Marec H, Wilde AA, Probst V, Schott JJ, Dina C, Redon R (2013) Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet **45**, 1044–9.
9) Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M, ESC Scientific Document Group (2022) 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J **43**, 3997–4126.
10) Gourraud JB, Barc J, Thollet A, Le Marec H, Probst V (2017) Brugada syndrome: diagnosis, risk stratification and management. Arch Cardiovasc Dis **110**, 188–95.
11) Cerrone M (2018) Controversies in Brugada syndrome. Trends Cardiovasc Med **28**, 284–92.
12) Martini A, Signorini S, Jannone V, Riservato R, Fantini S (2007) [Brugada syndrome and work place: two case report]. G Ital Med Lav Ergon **29**, 170–3 (in Italian).
13) Dobler D, Huber SW, Maire R (2010) Brugada syndrome and fitness to fly: risk stratification in two pilot applicants. Aviat Space Environ Med **81**, 789–92.
14) Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K Rehm HL, ACMG Laboratory Quality

Assurance Committee (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med **17**, 405–24.

15) Scafa F, Calsamiglia G, Tonini S, Lumelli D, Lanfranco A, Gentile E, Berzolari FG, Candura SM (2012) Return to work after coronary angioplasty or heart surgery: a 5-year experience with the "CardioWork" protocol. J Occup Environ Med **54**, 1545–9.
16) Scafa F, Calsamiglia G, Cadei P, Pettenuzzo E, Forni G, Candura SM (2018) [Health and work after invasive heart procedures, rehabilitation and occupational evaluation]. Med Lav **109**, 219–24 (in Italian).
17) Nagase S, Hiramatsu S, Morita H, Nishii N, Murakami M, Nakamura K, Kusano KF, Ito H, Ohe T (2010) Electroanatomical correlation of repolarization abnormalities in Brugada syndrome: detection of type 1 electrocardiogram in the right ventricular outflow tract. J Am Coll Cardiol **56**, 2143–5.
18) Zhang L, Liu L, Kowey PR, Fontaine GH (2014) The electrocardiographic manifestations of arrhythmogenic right ventricular dysplasia. Curr Cardiol Rev **10**, 237–45.
19) Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen JT, Wellens H, Yan GX (2015) The early repolarization pattern: a consensus paper. J Am Coll Cardiol **66**, 470–7.
20) Souques M, Magne I, Lambrozo J (2011) Implantable cardioverter defibrillator and 50-Hz electric and magnetic fields exposure in the workplace. Int Arch Occup Environ Health **84**, 1–6.