ORIGINAL ARTICLE

Clinical classification of rare cardiac arrhythmogenic and conduction disorders, and rare arrhythmias

Piotr Podolec[1,2]*, Adrian Baranchuk[3], Josep Brugada[4], Piotr Kukla[5], Jacek Lelakowski[6,7], Grzegorz Kopeć[1,2], Paweł Rubiś[1,2], Jakub Stępniewski[1,2], Jakub Podolec[8], Monika Komar[1,2], Lidia Tomkiewicz-Pająk[1,2], Paweł T. Matusik[2,6,7]*

1 Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
2 Centre for Rare Cardiovascular Diseases, John Paul II Hospital, Kraków, Poland
3 Cardiac Electrophysiology and Pacing, Kingston General Hospital, Division of Cardiology, Queen's University, Kingston, Ontario, Canada
4 Cardiovascular Institute, Hospital Clínic, Pediatric Arrhythmia Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain
5 Department of Cardiology and Internal Medicine, Specialist Hospital, Gorlice, Poland
6 Department of Electrocardiology, John Paul II Hospital, Kraków, Poland
7 Department of Electrocardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
8 Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College and John Paul II Hospital, Kraków, Poland

KEY WORDS

arrhythmia, arrhythmogenic disorder, conduction disorder, electrical disorder of the heart, rare disease

ABSTRACT

INTRODUCTION Rare cardiovascular diseases and disorders (RCDDs) constitute an important clinical problem, and their proper classification is crucial for expanding knowledge in the field of RCDDs.

OBJECTIVES The aim of this paper is to provide an updated classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias (RACDRAs).

METHODS We performed a search for RACDRAs using the Orphanet inventory of rare diseases, which includes diseases with a prevalence of no more than 5 per 10 000 in the general population. We supplemented this with a search of PubMed and Scopus databases according to a wider definition proposed by the European Parliament and the Council of the European Union.

RESULTS RACDRAs are categorized into 2 groups, primary electrical disorders of the heart and arrhythmias in specific clinical settings. The first group is further divided into subgroups of major clinical presentation: disorders predisposing to supraventricular tachyarrhythmias, ventricular tachyarrhythmias, bradyarrhythmias, and others. The second group includes iatrogenic arrhythmias or heart rhythm disturbances related to medical treatment, arrhythmias associated with metabolic disorders, and others. We provide a classification of RACDRAs and supplement them with respective RCDDs codes.

CONCLUSION The clinical classification of RACDRAs may form a basis to facilitate research and progress in clinical practice, both in diagnostic and therapeutic approaches.

Correspondence to:
Paweł T. Matusik, MD, PhD, Department of Electrocardiology, Institute of Cardiology, Jagiellonian University Medical College, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48 12 614 22 77, email: pawel.matusik@wp.eu
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* PP and PTM contributed equally to this work.

INTRODUCTION Rare cardiovascular diseases and disorders (RCDDs) constitute an important clinical problem, and their proper classification is crucial for expanding knowledge in the field of RCDDs. This classification provides an overview of RCDDs, which may also facilitate creation of databases and improved data gathering from various clinical centers.[1] The first clinical classification of RCDDs was published in 2013 in the *Journal of Rare Cardiovascular Diseases*.[2,3] We aimed to provide an updated classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias (RACDRAs) included in the recently revised RCDDs classification.[4] RACDRAs are often undervalued and clinical practice guidelines include many uncertainties in this field, including those associated with cardiovascular implantable electronic devices.[5-9] This updated classification will be valuable in planning further large-scale clinical studies, which may lead to improved care in patients with RACDRAs.

The definition of a rare disease as proposed by the European Parliament and the Council of the European Union, supported, as a guide, a threshold for rare disease prevalence of no more than 5 per 10 000 individuals in the general population (Regulation [EC] No 141/2000 of the European Parliament and of the Council on orphan medicinal products). This definition emphasized that in the case of rare diseases, the scale of the health problem is so small that it requires combined efforts to perform necessary analyses or effective interventions.[10] RCDDs and RACDRAs are in line with this definition. In addition, these disorders impact patient quality of life and/or mortality and insufficient knowledge about them may result in unfavorable clinical outcomes. Moreover, RACDRAs often require multidisciplinary management.

METHODS We performed a search for RACDRAs using the Orphanet inventory of rare diseases, which includes diseases that have a prevalence of no more than 5 per 10 000 individuals in the general population.[11] We supplemented this with a search of PubMed and Scopus databases according to a wider definition proposed by the European Parliament and the Council of the European Union. The following keywords were used to search PubMed and Scopus databases: "rare" OR "rarity" AND "arrhythmia" OR "arrhythmogenic" OR "cardiac conduction" OR "myocardial conduction" OR "heart conduction" AND "disorder" OR "disease" OR "syndrome." Initially, we have found over 3700 documents in PubMed and over 5100 documents in Scopus. This approach is in line with our methodology and appears to be more useful in clinical practice and should further improve research relating to RCDDs. An important limitation of the approach to rare diseases based only on the frequency of the disease is that their prevalence varies or is unknown depending on regions of the world. This limitation also applies to RACDRAs and is clearly illustrated by the differences in the prevalence of Brugada syndrome (BrS).[12,13]

In the updated classification, we aimed to minimize the repetition of diagnoses and to include more diseases and disorders. Therefore, the previous group of arrhythmias of atypical mechanism and electrocardiographic presentation was removed, and those diseases were moved into other appropriate subgroups. Because arrhythmic manifestations are varied and frequently more than one arrhythmia is present, a sample *International Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*) code was provided for each disease or condition to ensure clarity.[14] For diseases present in the Orphanet inventory of rare diseases (available at: http://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN), ORPHA numbers were added to enable search and direct comparison of the classified diseases and disorders in the Orphanet inventory (TABLES 1 and 2).

Clinical classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias RACDRAs constitute class VI of the clinical classification of RCDDs.[4] The principal group of RACDRAs is primary electrical disorders of the heart. This is further divided into subgroups by major clinical presentation: disorders associated with supraventricular tachyarrhythmias,[15] ventricular tachyarrhythmias,[16] bradyarrhythmias, and others (TABLE 1).[17,18-20] Moreover, common pathophysiology, choice of therapy, risk stratification, and clinical prognosis were considered in creating the subgroups.

Within the subgroup of rare disorders potentially associated with supraventricular tachyarrhythmias, several types of arrhythmogenic disorders were distinguished. These included: preexcitation syndromes (such as Mahaim syndrome[21] and enhanced atrioventricular nodal conduction, known previously as Lown–Ganong–Levine syndrome),[22] permanent form of junctional reciprocating tachycardia (Coumel tachycardia),[23] multifocal atrial tachycardia,[24] and His bundle tachycardia (junctional ectopic tachycardia).[25] Atrioventricular nodal reentrant tachycardia (AVNRT) prevalence is about 22.5 per 10 000 persons.[26] However, atypical forms of AVNRT, including fast-slow and slow-slow AVNRT, are rare and comprise about 6.4% of patients. It should be noted that some patients with AVNRT may not be reliably classified because of electrophysiological characteristics.[27] We also introduced double fire tachycardia (dual atrioventricular nodal nonreentrant tachycardia) into the group of disorders predisposing to supraventricular tachyarrhythmias.[28] There are sparse epidemiological data on specific supraventricular tachycardias.[29] However, considering the incidence of atrial flutter of 8.8 per 10 000 person-years in the general population,[30] it seems that atypical atrial flutter is rare (TABLE 1). Moreover, despite limited epidemiological evidence and possible underdiagnosis, we included sinoatrial reentry tachycardia into RACDRAs.[31] On the other hand, atrial tachycardia is the third most common specific supraventricular tachycardia and was not included in the RACDRAs.[32] Due to the relatively high prevalence of the Wolff–Parkinson–White syndrome and improvements in its treatment, it was excluded from the current classification.[33,34] However, familial forms of the Wolff–Parkinson–White syndrome[35] and AVNRT[36,37] seem to be rare and it appears to be appropriate to consider them as RACDRAs (RCDDs codes, VI-1A-1.0 and VI-1A-2.0, respectively). On the other hand, it is questionable whether familial forms of AF (ORPHA number 334)[38,39] or inappropriate sinus tachycardia[40] should be included in the current classification, because of their frequency, rare genetic testing, and potential underdiagnosing. Due to its high prevalence, we did not include interatrial block, which is a predictor of AF, into RACDRAs classification. In the Atherosclerosis Risk in Communities (ARIC)[41] study, performed in a population at a mean age of 54 years,

TABLE 1 Clinical classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias. Group 1. Primary electrical disorders of the heart, divided into subgroups (A–C and other).

Subgroup by major disorders and arrhythmias	RCDD code	*ICD-10* code[a]	ORPHA number[a]
A. Disorders predisposing to supraventricular tachyarrhythmias			
1. Associated with preexcitation	VI-1A-1	I45.6	–
1.1. Atrial tachyarrhythmia with short PR interval (enhanced atrioventricular nodal conduction)	VI-1A-1.1		844
1.2. Mahaim syndrome	VI-1A-1.2		–
1.0. Other	VI-1A-1.0		–
2. Atypical and/or familial AVNRT	VI-1A-2	I47.1	–
2.1 Slow-slow AVNRT	VI-1A-2.1		–
2.2 Fast-slow AVNRT	VI-1A-2.2		–
2.0 Other	VI-1A-2.0		–
3. Atypical atrial flutter	VI-1A-3	I48.4	–
4. Idiopathic neonatal atrial flutter	VI-1A-4	P29.1	45 452
5. Sinoatrial reentry tachycardia	VI-1A-5	I49.9	–
6. Multifocal atrial tachycardia	VI-1A-6	I47.1	3282
7. Permanent form of junctional reciprocating tachycardia	VI-1A-7	I47.1	–
8. His bundle tachycardia	VI-1A-8	I47.1	3283
9. Double fire tachycardia	VI-1A-9	I47.1	–
0. Other	VI-1A-0	–	–
B. Disorders predisposing to ventricular tachyarrhythmias			
1. Channelopathies	VI-1B-1	–	–
1.1 Brugada syndrome	VI-1B-1.1	I49.8	130
1.2 Familial long QT syndrome	VI-1B-1.2	I45.8	768
1.3 Familial short QT syndrome	VI-1B-1.3	I49.8	51 083
1.4 Catecholaminergic polymorphic ventricular tachycardia	VI-1B-1.4	I47.2	3286
1.5 Early repolarization syndrome	VI-1B-1.5	I49.8	–
2. Idiopathic ventricular fibrillation	VI-1B-2	I49.0	228 140[b]
3. Torsades de pointes syndrome with short coupling interval	VI-1B-3	I49.8	51 084
4. Ventricular flutter	VI-1B-4	I49.0	–
5. Idiopathic ventricular tachycardia	VI-1B-5	I47.2	–
6. Bundle branch reentry ventricular tachycardia	VI-1B-6	I47.2	–
7. Incessant infant ventricular tachycardia	VI-1B-7	I47.2	45 453
0. Other	VI-1B-0		–
C. Disorders predisposing to bradyarrhythmias			
1. Familial sick sinus syndrome	VI-1C-1	I49.5	166 282
2. Atrial standstill	VI-1C-2	I45.5	1344
3. Congenital heart block	VI-1C-3	I44.2	60 041
4. Familial progressive cardiac conduction defect	VI-1C-4	I45.8	871
0. Other	VI-1C-0	–	–
Other			
Other	VI-10	–	–

Please note that some RCDDs are not referenced in *ICD-10*. ORPHA numbers are provided from the Orphanet inventory of rare diseases; some RCDDs are not referenced in this inventory.

a Sample codes or numbers

b In the Orphanet list of rare diseases and synonyms: idiopathic ventricular fibrillation or familial paroxysmal ventricular fibrillation, non–Brugada type

Abbreviations: AVNRT, atrioventricular nodal reentrant tachycardia; *ICD-10*, *International Classification of Diseases, 10th Revision*; RCDDs, rare cardiovascular diseases and disorders

TABLE 2 Clinical classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias. Group 2. Arrhythmias in specific clinical settings, divided into subgroups (A, B, and other).

Subgroups by major disorders and arrhythmias	RCDD code	*ICD-10* code[a]	ORPHA number[a]
A. Iatrogenic or related to medical treatment			
1. Complication of pharmacotherapy	VI-2A-1	Z51.1	–
2. After surgical or invasive correction of heart diseases or disorders	VI-2A-2	Y83	–
3. After heart transplantation	VI-2A-3	Z94.1	–
4. After ablation of arrhythmias	VI-2A-4	–	–
5. After cardiovascular implantable electronic devices placement	VI-2A-5	Z95.0 Z95.8	–
0. Other	VI-2A-0	–	–
B. Metabolic disorders			
1. Fatty acid oxidation disorders	VI-2B-1	E71.3	157
0. Other	VI-2B-0	–	–
Other			
Other	VI-20	–	–

Please note that some RCDD are not referenced in *ICD-10*. ORPHA numbers are provided from the Orphanet inventory of rare diseases; some RCDD are not referenced in this inventory.

a Sample codes or number

Abbreviations: see TABLE 1

advanced interatrial block at baseline was observed in 0.5% of persons.

Within the subgroup of disorders potentially associated with ventricular tachyarrhythmias, several examples of inherited arrhythmogenic disorders were listed. These included channelopathies: BrS, familial long QT syndrome, familial short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia.[42-49] Moreover, idiopathic ventricular fibrillation and torsades de pointes syndrome with a short coupling interval are also included as major disorders.[50,51] We also included incessant infant ventricular tachycardia in the subgroup of disorders predisposing to ventricular tachyarrhythmias, considering that this clinical entity seems to have a heterogeneous pathogenesis, including histiocytoid cardiomyopathy and cardiac rhabdomyomas.[52-54] Moreover, we included early repolarization syndrome (malignant early repolarization syndrome), ventricular flutter, idiopathic ventricular tachycardia and bundle branch reentry ventricular tachycardia in this subgroup.[55-58]

The subgroup of rare disorders associated with bradyarrhythmias includes familial sick sinus syndrome,[59] atrial standstill,[60,61] congenital heart block,[54] and familial progressive cardiac conduction defect. It should be emphasized that in patients with rare arrhythmias, other coexisting heart rhythm disturbances may be observed, but in the clinical classification, it is proposed to indicate the most significant arrhythmia or that which poses the greatest threat to the patient (major clinical presentation or risk). As an example, patients with BrS, who are prone to ventricular tachycardia or fibrillation, may suffer from concomitant atrioventricular conduction abnormalities, atrial fibrillation, or atrial flutter.[13,43] Importantly, primary arrhythmias may either be inherited or acquired and may coincide with each other.[48,62] Such coincidence increases the difficulty of patient management.

Arrhythmias are one of the most frequent manifestations of heart disease and may be associated with increased risk of comorbidities and death.[63] Cardiac arrhythmias are relatively frequent in the course of RCDDs and may be secondary to virtually all RCDDs.[64-69] Due to this fact, the RACDRAs class was moved into class number VI, and in the updated RCDDs classification, presumably causative or coexistent rare cardiovascular disease classes are now listed before RACDRAs. However, as mentioned previously, we did not distinguish a group of arrhythmias secondary to or coexistent with RCDDs because the introduction of such a group could lead to misclassification of the diseases and disorders and influence future data on epidemiology and morbidity.[4] Another reason for this is that a patient may have more than one RCDDs. In the interest of epidemiological accuracy, we propose that patients with 2 or more RCDDs should be classified using 2 or more RCDDs codes. Such patients will probably have increased diagnostic and therapeutic difficulties when compared with those with a single RCDD. It should be noted that arrhythmogenic right ventricular cardiomyopathy (ORPHA number 247), which predisposes patients to ventricular arrhythmias, is classified in class III of the clinical classification of RCDDs—rare diseases of the heart (cardiomyopathies).[70] Importantly, arrhythmias may also result from, or coexist with congenital heart defects. In this group of arrhythmias, atrial septal defect with atrioventricular conduction defects (ORPHA number 1479, atrial septal defect--atrioventricular conduction defects syndrome) should be mentioned. This disorder may be associated with both atrioventricular block and atrial fibrillation.[71]

In the updated classification we introduced more iatrogenic causes of arrhythmias into the last proposed group, arrhythmias in specific clinical settings, as shown in TABLE 2.[8,19,72-77] This is in light of observed complications of pharmacotherapy and more common invasive cardiovascular treatments.[78,79] Furthermore, another goal was to increase awareness among physicians about possible rare complications of these treatments. This group of rare heart rhythm disturbances and/or arrhythmias in rare clinical settings highlights the need to consider challenges associated with rare and/or specific concomitant clinical conditions.[80] Moreover, we do not possess detailed data on the prevalence, prevention, and management of such conditions.[5,6,81,82] We introduced an example of fatty acid oxidation disorders in the subgroup of metabolic disorders because in these clinical entities potentially lethal

arrhythmias may occur as the first symptom without associated cardiomyopathy.[83] This highlights the fact that metabolic alterations may affect cardiac electrophysiology.[84]

Limitations of the classification of rare arrhythmogenic and conduction disorders, and rare arrhythmias It should be noted that this updated classification has potential limitations and may still require revision. We are open to comments and suggestions to further improve it in the future. Physicians or researchers who believe that any other disease or disorder should be included into RACDRAs are encouraged to write to the corresponding author of the classification, including the reasons for inclusion and the prevalence of a disorder or disease in the general population.

Conclusion The updated clinical classification of RACDRAs may be used to facilitate further research and progress in clinical practice, both for diagnostic and therapeutic purposes.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT PP and PTM conceived the concept of the update of the RACDRA classification and contributed to the design of the paper. PP, PK, JL, GK, PR, JS, JP, MK, LT-P, and PTM were involved in the collection and/or assembly of RCDD data and/or data analysis and interpretation. PTM wrote the paper. AB and JB critically reviewed the paper and contributed to data analysis and interpretation. JL provided funding of the publication fee. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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NOTE For references 51–84, see Supplementary material at www.mp.pl/paim.

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