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Clinical Research

The Canadian Arrhythmogenic Right Ventricular Cardiomyopathy Registry: Rationale, Design, and Preliminary Recruitment

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ABSTRACT

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a complex and clinically heterogeneous arrhythmic condition. Incomplete penetrance and variable expressivity are particularly evident in ARVC, making clinical decision-making challenging.

Methods: Pediatric and adult cardiologists, geneticists, genetic counsellors, ethicists, nurses, and qualitative researchers are collaborating

RÉSUMÉ

Introduction : La cardiomyopathie arythmogène du ventricule droit (CAVD) est un trouble complexe et cliniquement hétérogène caractérisé par une irrégularité du rythme cardiaque. La pénétrance incomplète et l'expressivité variable sont particulièrement évidentes dans la CAVD, ce qui complique la prise de décisions sur le plan clinique.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial condition characterized by fibrofatty myocardial replacement and life-threatening ventricular arrhythmias; it presents with ventricular tachycardia, cardiac arrest, or sudden death.[1] The disease is diagnosed with a wide range of tests that focus on imaging the right ventricle and assessing for ambient arrhythmia or an abnormal electrical substrate. These factors are collated into a score that forms the ARVC task force criteria, known to be specific but not sensitive.[2] These criteria were revised in 2010, introducing a broader and more quantitative approach to diagnosis intended to enhance sensitivity without reducing specificity.[3] These criteria account for findings from genetic testing, confounded in part by the unknown significance of a positive genetic test result in the absence of a phenotype in a disease with variable penetrance and expressivity.[3-8]

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to create the Canadian ARVC registry using a web-based clinical database. Biological samples will be banked and systematic analysis will be performed to examine potentially causative mutations, variants, and biomarkers. Outcomes will include syncope, ventricular arrhythmias, defibrillator therapies, heart failure, and mortality.

Results: Preliminary recruitment has enrolled 365 participants (aged 42.7 ± 17.1 years; 50% women), including 129 probands and 236 family members. Previous cardiac arrest occurred in 28 (8%) participants, syncope occurred in 43 (12%) participants, and 46% of probands had a family history of sudden death. Overall yield of genetic testing was 36% for a disease-causing mutation and 20% for a variant of unknown significance. Target enrollment is 1000 affected patients and 500 unaffected family member controls over 7 years. The cross-sectional and longitudinal data collected in this manner will allow a robust assessment of the natural history and clinical course of genetic subtypes.

Conclusions: The Canadian ARVC Registry will create a population-based cohort of patients and their families to inform clinical decisions regarding patients with ARVC.

Méthodes : Des cardiologues, des pédocardiologues, des généticiens, des conseillers en génétique, des éthiciens, des infirmiers et des spécialistes en recherche qualitative travaillent conjointement à la création d'un registre canadien sur la CAVD à partir d'une base de données cliniques sur le Web. Des échantillons biologiques seront mis en réserve et feront l'objet d'une analyse systématique destinée à mettre en évidence de possibles mutations causales, variants et biomarqueurs. La syncope, l'arythmie ventriculaire, la défibrillation, l'insuffisance cardiaque et la mortalité figureront au nombre des issues cliniques.

Résultats : Au départ, 365 participants (âgés de 42,7 ± 17,1 ans; 50 % de sexe féminin), incluant 129 proposants et 236 membres de leur famille ont été recrutés. De ces 365 participants, 28 (8 %) avaient des antécédents d'arrêt cardiaque et 43 (12 %) avaient déjà fait une syncope, alors que 46 % des proposants avaient des antécédents familiaux de mort subite. De façon globale, les tests génétiques ont révélé que la maladie était causée par une mutation dans 36 % des cas et qu'un variant dont la portée était inconnue était présent dans 20 % des cas. On espère recruter 1000 personnes atteintes et 500 témoins non atteints parmi les membres de leur famille sur 7 ans. Grâce aux données transversales et longitudinales ainsi recueillies, il sera possible d'évaluer de façon robuste l'évolution naturelle et clinique des sous-types génétiques.

Conclusions : Le registre canadien sur la CAVD va rassembler une cohorte composée de patients et des membres de leur famille afin d'éclairer les décisions cliniques entourant ce trouble.

When genetically identified, the disease is predominantly caused by defects in genes encoding cell-cell adhesion proteins of the intercalated disk, particularly desmosomal proteins.[9] Additional common molecular themes include the inhibition of certain intracellular signalling pathways potentially contributing to fibrofatty replacement and gap junction remodelling early in the disease.

Genetic testing has been reported to identify the underlying mutation in 40%-60% of clearly affected patients.[10-12] Genetic testing often detects a variant of unknown significance (VUS) in patients with manifest or borderline evidence of ARVC, further confounding test interpretation and family screening. Genetic testing has demonstrated that family members often harbor the culprit mutation or VUS, with little evidence of disease from clinical testing. Given the risk of life-threatening arrhythmia as a first presentation of disease expression, early enhanced detection of ventricular arrhythmia would help identify patients with manifest ARVC. Our inability to define the clinical ramifications related to each mutation is hampered by a lack of data. The Canadian ARVC registry has been created to address this deficit.

Methods

Study overview and objectives

The registry will identify patients that fulfill 2010 task force criteria (TFC) for definite or probable ARVC as well as their affected and unaffected first-degree relatives.[3] This prospectively followed cohort will include both prevalent and incident cases in an established national network of inherited arrhythmia clinics,[13] with active cascade screening. Patients will undergo standard clinical testing to determine TFC, including clinical genetic testing and biobanking for future sample analysis. Annual follow-up will include outcome ascertainment and periodic repeated phenotyping.

The primary objectives of the Canadian ARVC registry are:

1. To determine the natural history of ARVC, including risk of symptomatic arrhythmias and sudden death
2. To understand risk factors for sudden death/appropriate implantable cardioverter device (ICD) use in ARVC, including test characteristics and performance and their relationship to outcomes
3. To establish a phenotype/genotype correlation, including comparison of patients with disease-causing mutations, VUS, and TFC-positive, gene-negative patients.

Secondary objectives include the following:

1. To identify the genes or mechanisms of disease in patients for whom these are not yet identified
2. To describe the decisional needs of patients and family members considering genetic screening for ARVC and primary and secondary prevention therapeutic decision-making.

Patient population

Determining robust data on the natural history of any disease requires an unbiased ascertainment strategy. Bias is inherent in all aspects of the diagnosis of ARVC, resulting in part from the fact that the diagnostic criteria are descriptive, do not apply to children, and have been derived from severely affected probands. By default, this excludes those who died before presentation and those who did not come to

presentation. These biases also relate to the requirement for tertiary-level testing, with low-access populations likely to be missed or misclassified. The single-provider Canadian health care model combined with lessons learned from major founder population knowledge translation strategies will be primary tools in mitigating ascertainment bias. The majority of those referring participants to the registry will be cardiology specialists, although the team responsible for building and maintaining the registry includes molecular geneticists, nurses, genetic counsellors, and ethicists.

Patients will be identified from centres that form the Canadian Genetics Heart Rhythm Network of Inherited Heart Rhythm Clinics.[14] Those patients who fulfill the inclusion criteria (Table 1) will be invited to consent to participate. Patients who meet the TFC and are subsequently diagnosed with ARVC "phenocopies," such as sarcoidosis, myocarditis, and mimic cardiomyopathies, such as phospholamban cardiomyopathy,[15,16] will be included in the registry. Patients with idiopathic right ventricular outflow tract tachycardia or premature ventricular contractions will not be enrolled unless they fulfill the TFC for at least probable ARVC.

Data elements and collection

After informed consent, patients will undergo baseline data collection (Supplemental Table S1). For those patients with earlier testing, records will be obtained and any previous testing noted for purposes of defining incident vs prevalent events. Family members will undergo screening, and genetic counselling will be provided to the patient and family. Family histories will include a standard 3-generation pedigree, with a goal to expand to ensure that all second-degree relatives are both identified and offered screening. The web-based database is in compliance with national Canadian privacy guidelines and is hosted on the University of British Columbia server. Online tools available to all study and nonstudy participants include electronic and paper-based family awareness correspondence provided to the affected individual to enhance cascade screening of family members.

Patients will be approached to donate a biobank blood sample that may be stored in any of 3 locations: the central biobank at the Population Health Research Institute (Hamilton Ontario, Canada), the clinical testing laboratory's research biobank, or the host institution. Genetic testing will be performed initially through routine clinical testing. DNA banked for purposes of this registry will be analyzed for further mutations or variants, or both, and the results will be included in the registry. In all cases, the genetic results will be reviewed by 2 independent subcommittee members and assigned a status of likely disease causing, VUS, or no known pathology in accordance with the current American College of Medical Genetics and Genomics guidelines.[17] Discrepancies will be resolved by consensus involving a third panel member, along with accessing current in silico tools, publicly accessible data sets, and ongoing databases such as www.arvcdatabase.info. Comprehensive family assessment will aim to reduce the extent of VUS assignment based on the process of segregation analysis.[17]

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
2010 revised TFC-positive patients[3]	Known condition that mimics ARVC, eg, sarcoidosis (biopsy proven or with lung involvement)
2010 revised TFC borderline patients[3]	Dilated cardiomyopathy not compatible with an ARVC variant
Patients with no TFC criteria for ARVC but with a disease-causing ARVC pathogenic mutation*	Hypertrophic cardiomyopathy not compatible with an ARVC variant
Variants of unknown significance carriers with $\geq$ 1 minor TFC criteria	Known inherited condition that predisposes to sudden cardiac death, eg, LQTS, CPVT, and Brugada syndrome
Age $\geq$ 2 y	Age $<$ 2 y
First-degree relatives of 2010 revised TFC-positive or TFC-borderline patients[3]	Life expectancy $<$ 1 y
Able and willing to provide informed consent or has a parent/guardian able and willing to provide informed consent	Unable or unwilling to provide informed consent, or both

ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; TFC, task force criteria.

*A DNA alteration associated with ARVC that alters (or is expected to alter) the encoded protein in a significant way, is unobserved or rare in a large control population, and either alters (or is predicted to alter) the structure or function of the protein by computational (in silico) predictions or functional validation in a biological model system (or both) or has demonstrated linkage to the disease phenotype in a conclusive pedigree. Mutation carriers by definition have a single major TFC.[3]

Study operations

The study team will include the steering committee, which is composed of all contributing site investigators. Ownership of data and biobank samples is under the jurisdiction of the steering committee, chaired by the principal investigator (A.D.K.). Details are outlined in a study governance document that includes outlined processes for accessing data and samples, proposal of studies and substudies, the first major analyses agreed on, a publication policy, and ethical handling of biobanked samples.

Outcomes

Follow-up will occur annually, and the presence of cardiovascular symptoms and events relevant to ARVC (syncope, palpitations, cardiac arrest, ICD implantation, ICD therapy, sudden death, and heart failure) will be noted. Clinical follow-up data will be collected according to standard local practice. Patients will undergo repeated clinical testing according to the local institution's standard practice, with a recommendation to reassess TFC every 3 years. A resting electrocardiogram, a signal-averaged electrocardiogram, and 24-hour Holter monitoring will be recommended annually.

Preliminary data and analysis

In the participants currently enrolled, categorical variables between enrollment groups were compared using a χ^2 test with the Fisher exact test for cells with 5 or less participants. Continuous variables were analyzed using analysis of variance. Statistical analysis was performed using R statistical software (The R Project for Statistical Computing, Vienna, Austria), which is embedded in the online database. All participating sites' institutional ethics review boards approved the registry.

All participants provided written informed consent, with separate consent for biobanking. Participants were typically approached to provide consent to disclose their personal health information to family members and to use electronic communication to enhance cascade screening. The protocol is registered at www.ClinicalTrials.gov (NCT01804699).

Results

The registry has enrolled 365 patients since its inception in 2013 (Table 2). This includes a balanced blend of probands (n = 129) and affected family members (n = 126), unaffected family members (n = 110), and ICD recipients and nonrecipients (64% of probands, 34% overall). Of 236 family members enrolled, cardiac symptoms were present in 21%, predominantly palpitations. One hundred thirty-two family members underwent genetic testing on the basis of findings in the family proband, with positive findings in 87 (66%) of them. The projected enrollment is 1500 study participants over the first 7 years, which will include 1000 affected individuals and 500 unaffected first-degree relatives. The latter will be included to enhance gene discovery and form a de facto control group for comparative testing. Only those who are gene negative and those with normal clinical testing results in the absence of a culprit genetic factor in the proband will be considered controls.

In the first 236 family members, 110 individuals did not have clinical evidence of ARVC (2 or more minor or 1 or more major TFC). In patients enrolled to date, the inclusion of "gene negative" in the definition of unaffected reduced the clinically unaffected number of potential control participants from 110 to 34.

Preliminary recruitment included 129 probands and 236 family members. A small number of pediatric patients were enrolled, with several pediatric centres recently agreeing to contribute patients. Previous cardiac arrest occurred in 28 (8%) and syncope occurred in 43 (12%) patients; a family history of sudden death in 46% of these patients. The overall yield of genetic testing was 36% for a disease-causing mutation and 10% for a VUS. Of note, clinics enrolling patients typically review genetic testing results during routine follow-up, with a particular focus on VUSs, updating their classification using www.arvcdatabase.info and other public data sets.

Table 2. ARVC population characteristics

Parameter	Proband (n = 129)	Symptomatic family member (n = 50)	Asymptomatic family member (n = 186)	All (N = 365)
Age at enrollment (y)	46 ± 17.4	39.7 ± 16.1	42.3 ± 16.9	42.7 ± 17.1
Female sex	54 (42%)	37 (74%)	92 (49%)	183 (50%)
Symptoms				
Syncope	33 (26%)	10 (20%)	0 (0%)	43 (12%)
Cardiac arrest	28 (22%)	0 (0%)	0 (0%)	28 (8%)
Presyncope	38 (29%)	7 (14%)	0 (0%)	45 (12%)
Palpitations	72 (56%)	36 (72%)	0 (0%)	108 (30%)
Chest pain	24 (19%)	8 (16%)	0 (0%)	32 (9%)
Other	30 (23%)	4 (8%)	0 (0%)	34 (9%)
Testing				
Electrocardiographic TWI V_2	27%	14%	6%	15%
Electrocardiographic TWI V_2/V_3	29%	14%	5%	14%
Electrocardiographic RBBB	14%	8%	5%	9%
SAECG positive	43%	18%	20%	28%
SAECG borderline	10%	4%	10%	9%
Echocardiographic minor TFC	7%	6%	2%	4%
Echocardiographic major TFC	13%	24%	10%	13%
Minor TFC by MRI	26%	18%	12%	18%
Major TFC by MRI	33%	24%	16%	23%
LVEF (%)	55.5 ± 11.2	57.4 ± 7.3	59.9 ± 8.5	57.9 ± 9.6
RVEF (%)	40.1 ± 12.3	51.2 ± 9.7	53.5 ± 9.4	48.6 ± 12.2
Genetic test results				
Disease-causing mutation (major TFC)	34%	46%	34%	36%
VUS	21%	6%	4%	10%
Diagnosis				
Unaffected/normal	0 (0%)	18 (36%)	92 (49%)	110 (30%)
ARVC	128 (99%)	31 (62%)	90 (48%)	249 (68%)
Dilated cardiomyopathy	1 (0.8%)*	1 (2%)	4 (2%)	6 (1.6%)
Affected (TFC probable or definite)	129	32	94	255
Unaffected (TFC negative, 1-2 minor or 1 major criterion)	0	18	92	110
Treatment				
β-Blocker	53%	18%	10%	26%
Sotalol	12%	6%	0.5%	5%
Amiodarone	18%	2%	0%	7%
ICD	64%	32%	13%	34%

ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; RBBB, right bundle branch block (includes both complete and incomplete); RVEF, right ventricular ejection fraction; SAECG, signal-averaged electrocardiogram; TFC, task force criteria; TWI, T wave inversion; VUS, variant of uncertain significance.

*Patient fulfilled the TFC and was subsequently diagnosed with phospholamban cardiomyopathy.

Of the 236 family members, 110 were considered unaffected based on either genetic or clinical testing, or both (45.1%). Medical treatment and ICD implantation were common in probands but minimal in family members, particularly in the realm of β-blocker use. In contrast to other specialty referral reports, disease severity was relatively mild, with only 8% of patients having a previous cardiac arrest (including sustained ventricular tachycardia), and only one third of patients undergoing ICD implantation.

Discussion

We describe the methodology used to develop a multidisciplinary collaboration to study patients with ARVC in Canada. Beginning with pilot data in 2004, a Canadian network was established to evaluate familial causes of sudden death.[18] This has focused on unexplained cardiac arrest with latent inherited arrhythmic causes and investigation of family members of victims of sudden cardiac death. The **C**ardiac **A**rrest **S**urvivors with **P**reserved **E**jection Fraction **R**egistry (CASPER) involves 14 centres across Canada with broad representation.[13,18] Each of these centres has a site investigator with a focused interest in inherited arrhythmias and enrolls patients in this national registry. The CASPER study provides the background for the current development of a national ARVC registry.[13]

Existing ARVC registries have provided a wealth of information regarding the nature of the disease but have suffered from several limitations. Previous registries have reflected large specialty referral centres without population-based representation of case detection and management. Major centres such as those in Amsterdam and at Johns Hopkins University in the United States have published extensively in the field,[7,8] but they typically compile cases that are self-referred or externally referred, with inherent referral bias and outcome ascertainment. The Canadian registry will include representation from all geographic regions of Canada, where this type of specialty care provision is largely restricted to large centres. This precedent led to capture of $>$ 90% of cases in a national ICD registry and the CASPER registry.[13,19]

Patients in other studies are derived from a heterogeneous health care delivery system limiting comprehensive family-based management. Canada is uniquely positioned to systematically offer care to families because of the universal nature of the health care delivery system. Canada is a multiethnic country with pockets of homogeneity. This allows for approaches that focus on the general heterogeneous Canadian population, a strength with respect to generalizability. These results can be compared with Canadian homogeneous founder populations, including the Hutterite population with a *DSC2* Q554X mutation and the nondesmosomal S358L mutation in *TMEM43*.[11,20-22] Several founder populations may allow for more focused studies of ARVC gene modifiers.

Anticipated outcomes

ARVC is a variable disease with multiple clinical manifestations at different ages. Determining risk based on genotype phenotype correlation and natural history data is required for the establishment of risk stratification to guide therapy for effective clinical practice. This registry will provide an opportunity to (1) group subjects with the same mutation across Canada, (2) better ascertain relatives, (3) enable more accurate determination of the variable natural histories, and (4) enable the assessment of other variants that may modify the phenotype, particularly any behaviours that increase the risk for sudden cardiac death. The utility of test modalities currently perceived as essential (eg, magnetic resonance imaging) will be testable with this registry. We will also evaluate the role of exercise in accelerating the phenotype in ARVC, looking at lifetime exercise and ARVC severity. Patient-centred outcome measures, including patient preferences and decision-making, will also be analyzed (Supplemental Table S2). Lastly, the validity of the 2010 TFC will be evaluated over time. A proposed more nuanced patient classification of affected status is outlined in Table 3, which will be adopted incremental to tracking the TFC status.

Conclusions

ARVC is the most challenging inherited arrhythmia syndrome in the cardiogenetics realm, stemming from a lack of systematic unbiased natural history data. This is amplified by immense clinical and genetic variability, driving uncertainty in the diagnostic and therapeutic realm. The Canadian ARVC registry was created to better understand the nature of ARVC as well as a clear need to develop enhanced detection and prevention strategies.

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Table 3. ARVC Registry proposed patient categories

Patient type	Phenotype*	Genotype†
Affected: mutation/variant positive‡ (TFC $\geq$ 3)	+	+
Affected: variant of uncertain significance§ (TFC $\geq$ 3)	+	+/−
Affected: gene negative (TFC $\geq$ 3)	+	−
Affected: genetic testing unavailable or pending	+	?
Susceptible: mutation/variant positive‡ no phenotype (TFC* score $\leq$ 2)	+	−
Unaffected: negative for family mutation and no phenotype	−	−
Unaffected: no phenotype and positive for variant of uncertain significance		+/−
Unaffected: genetic testing unavailable or pending	−	?
Borderline: TFC* 1 or 2 with proband gene negative	−	Not applicable
Borderline: gene negative for family mutation/variant but phenotype borderline TFC* 1 or 2	+	−
Borderline: genetic testing unavailable or pending	+/−	?

ARVC, arrhythmogenic right ventricular cardiomyopathy; TFC, task force criteria.

* TFC 2010 ARVC Task Force Criteria: score = 1 for minor criterion, 2 for major criterion. Disease-causing gene carrier is a major criterion. Possible ARVC = TFC 2, probable ARVC = TFC 3, definite ARVC = TFC $\geq$ 4.

† Genetic classification: pathogenic, likely pathogenic, variant of uncertain significance (VUS), (benign excluded).

‡ Mutation/variant pathogenic and likely pathogenic considered positive.

§ VUS, considered uncertain.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2016.04.004.