

The South African Arrhythmogenic Right Ventricular Cardiomyopathy Registry: A brief review and a status report

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ABSTRACT Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), commonly an inherited condition affecting cell junctions, may present with sudden death or life-threatening arrhythmias. The pathogenesis, clinical presentation, diagnostic evaluation and treatment are reviewed. The South African ARVC Registry is described, giving the aims, organization and missions which include: establishment of a DNA/tissue bank, epidemiology, risk assessment and evaluation of therapy, imaging, pathological diagnosis and diagnostic validation. Results of analysis of the first 80 confirmed cases enrolled in the registry confirm its familial occurrence, high mortality and involvement of the left ventricle. A common finding is participation in sport. A new mutation has been discovered affecting the plakophilin gene. Physicians are invited to refer patients with confirmed or suspected ARVC for inclusion in the Registry. SAHeart 2008; 5:148-154

BACKGROUND

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a progressive disorder of the right ventricular myocardium, associated with ventricular arrhythmias, sudden death and heart failure. Despite

estimates of 1:2 500 to 1:5 000, its true prevalence is unknown, as some affected individuals may remain asymptomatic and others may be misdiagnosed. The importance of this unusual heart muscle disease is in its role as a major cause of sudden cardiac death in the young, especially athletes.^(1,2,3,19)

PATHOGENESIS

ARVC is familial in up to 50% of cases, with an autosomal dominant pattern of inheritance occurring in the majority. Rarer recessive modes of inheritance, however, do occur. One of these may be associated with abnormalities of skin (palmoplantar hyperkeratosis) and hair (wooly hair): the so-called Naxos disease.^(4,6,19)

The causative genes encode proteins of cell junctions (plakoglobin, plakophilin, desmoglein, desmocollin, desmoplakin), which mediate cell-cell interaction, allowing for both mechanical and electrical coupling of adjacent cells. Mechanical coupling is important for providing structural integrity and allowing synchronous contraction of myocardium, while electrical coupling, via gap junctions, allows for rapid spread of depolarizing electrical waves.^(4,6,19)

Mutations may lead to remodeling of the intercalated disks of cell junctions, resulting in loss of the structural integrity of the myocardium and myocyte death, with replacement by fibrosis and adipocytes. This dystrophy of the right ventricular myocardium with fibro-fatty replacement, which is the pathological hallmark of ARVC, serves as substrate for the development of life-threatening arrhythmias (Figure 1).^(4,6,19)

Since heritable penetrance of ARVC is incomplete and genetic mutations within families have been shown to display variable phenotypic expression, both environmental factors and other genetic modifiers have been implicated in its pathogenesis. Endurance sport and intense or prolonged physical activity have been consistently shown, in both humans and animal models of ARVC, to be a major modifier in terms of frequency and severity of symptoms, as well as an increased risk of death. Endurance sport in ARVC is associated with a 5-fold increase in the risk of sudden death in the young.^(6,16,19)

CLINICAL

The clinical picture is often described in four “classical” phases:⁽⁵⁾

1. **The concealed phase**, with either subtle or no structural changes, occurs in affected individuals, who despite being asymptomatic, remain at risk of sudden cardiac death (SCD) from an arrhythmia during episodes of extreme exertion. These individuals may be identified through family screening; however, in a significant proportion the diagnosis is first established at postmortem examination, the initial presentation having been SCD.
2. **The overt electrical phase** is characterized by effort-induced palpitations and syncope. The symptoms are due to ventricular arrhythmias of right ventricular (RV) origin, manifesting as multiple ventricular ectopic beats, sustained and non-sustained ventricular tachycardia (VT) with left bundle branch block (LBBB) morphology. Morphological and functional cardiac abnormalities are usually present at this stage, but often overlooked.
3. **Diffuse right ventricular dysfunction** occurs as a result of progressive loss of RV myocardium presenting with severe right-sided heart failure, with relatively preserved left ventricular function.
4. **Biventricular failure or dilated cardiomyopathy phase** in which both ventricles are equally affected; ARVC mimicking dilated cardiomyopathy. This may be severe enough to require cardiac transplantation.

DIAGNOSTIC EVALUATION

A clinical diagnosis is achieved by demonstrating functional and structural alterations of the right ventricle, coupled with depolarization and repolarization abnormalities, arrhythmias with LBBB morphology (Figure 2) and fibro-fatty replacement on histology (Figure 1). ARVC is confirmed by a combination of 2 major, 1 major and 2 minor, or 4 minor criteria (Table 1).⁽⁴⁾ The main differential diagnoses include idiopathic right ventricular outflow tract tachycardia, myocarditis, dilated cardiomyopathy and sarcoidosis.^(4,5,19)

An ECG is essential in the evaluation of ARVC, providing both diagnostic and prognostic information. Abnormalities on ECG are detected in up to 90% of ARVC cases. Features include the presence of diffuse precordial T-wave inversions (beyond V2), an Epsilon wave in V1, widened localized QRS complex in leads V1-V3 (parietal block) and prolonged S-wave upstroke (≥ 55 ms) in V1-V3 (Figure 3).^(8,9,19)

T-wave inversion in leads V1-V3 in the absence of RBBB and coronary disease is a well-established electrocardiographic feature of ARVC and is a minor criterion (Table 1). An epsilon wave (defined as a discrete wave following the QRS complex in V1-V3) and parietal block are both major diagnostic criteria (Table 1). Late action potentials on signal averaged electrocardiogram (SAECG) recordings are the counterpart of the epsilon waves, demonstrating the presence of areas of slow conduction and late depolarization, and predict inducibility of ventricular tachycardia (VT) on electrophysiological study (EPS), as well as implantable cardioverter defibrillator (ICD) therapies.^(17,19) Prolonged

FIGURE 1: Typical histological features of ARVC

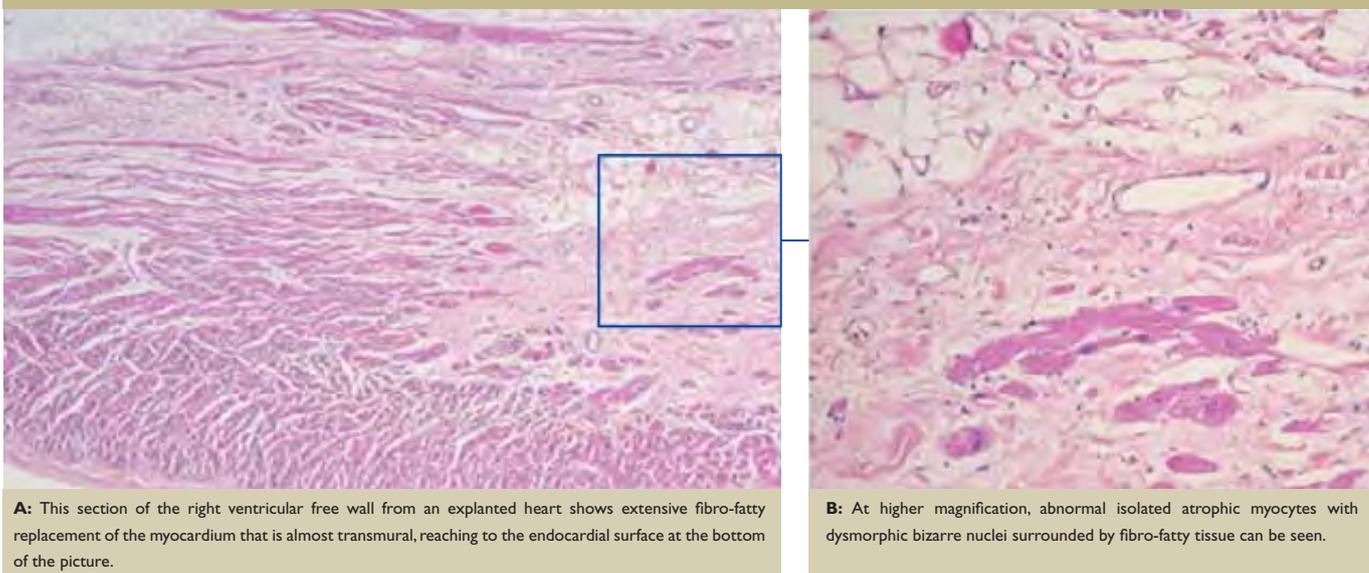
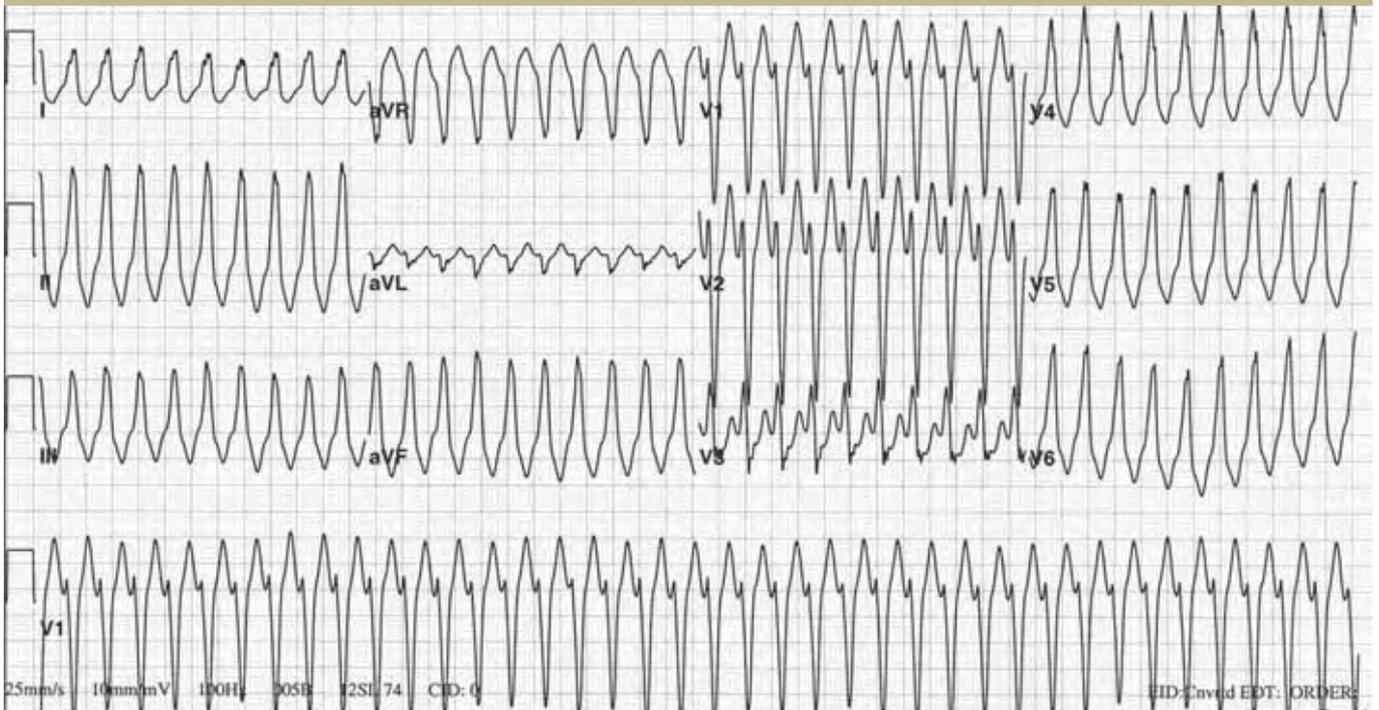


FIGURE 2: An ECG recording of Ventricular Tachycardia (VT) in a patient with ARVC



This ECG shows a sustained wide QRS complex regular tachycardia at a heart rate of 240bpm with a “left bundle branch block-like” morphology and a QRS axis of 60°. This VT appears to be arising from the RV outflow region. The usual differential diagnosis of the underlying pathophysiology of this VT includes ARVC and the idiopathic RV outflow tract VT.

TABLE 1: Diagnostic Criteria for ARVC

Category	Major Criteria	Minor Criteria
Structural or Functional abnormalities	<ol style="list-style-type: none"> Severe dilatation and reduction of RV ejection fraction with mild or no LV involvement. Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulgings). Severe segmental dilatation of RV. 	<ol style="list-style-type: none"> Mild global RV dilatation and/or ejection fraction reduction with normal LV. Mild segmental dilatation of RV. Regional RV hypokinesia.
Tissue Characterization	Fibro-fatty replacement of myocardium on histology	
ECG Depolarization / Conduction abnormalities	<ol style="list-style-type: none"> Epsilon waves or Localized prolongation (>110 ms) of QRS complex in right precordial leads (V1-V3). 	Late potentials on SAECG
ECG Repolarization abnormalities		Inverted T waves in V1-V3 (above age 12 yrs, in absence of RBBB)
Arrhythmias		<ol style="list-style-type: none"> LBBB/VT on ECG or Holter monitoring or during exercise testing. Frequent PVCs (>1000/24 h on Holter)
Family History	Familial disease confirmed at autopsy or biopsy.	<ol style="list-style-type: none"> Family history of premature sudden death (<35 years of age) due to suspected ARVC. Family history (clinical diagnosis based on present criteria)

Abbreviations: RV = right ventricle, LV = left ventricle, ARVD = arrhythmogenic right ventricular dysplasia, RBBB = right bundle branch block, LBBB = left bundle branch, VT = ventricular tachycardia, PVC = premature ventricular complex (Modified from McKenna et al.)⁽⁹⁾

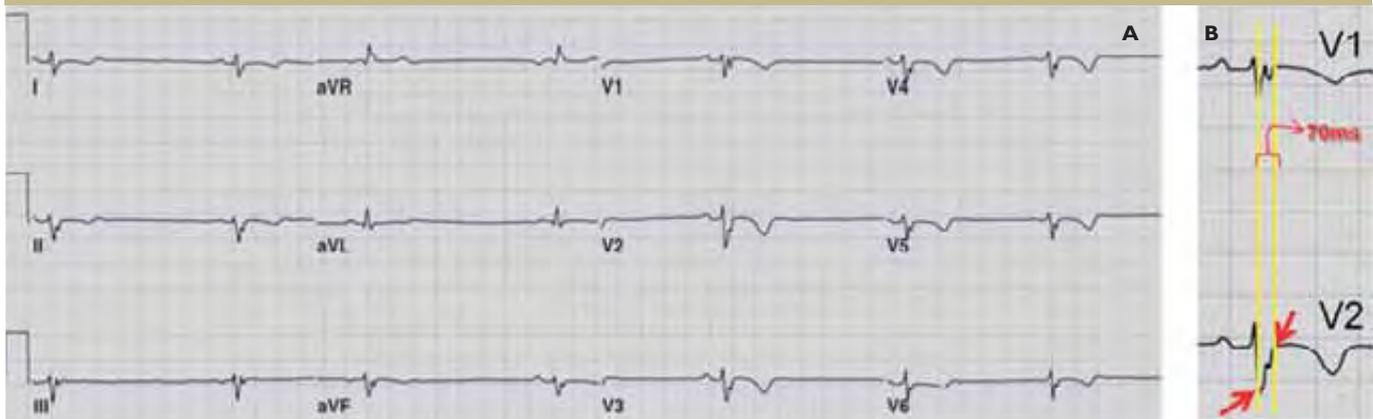
S-wave upstroke in V1-V3, the most prevalent electrocardiographic feature, is seen in 95% of the patients. It correlates with disease severity and the induction of ventricular tachycardia at EPS.^(9,19)

EPS should be considered in all individuals where ARVC is suspected or confirmed, as it has important diagnostic, prognostic and therapeutic utility. Inducibility of VT during EPS, correlates with prognosis, identifying individuals for ICD and/or radiofrequency ablation.^(4,14,15,19) Electroanatomic voltage mapping is able to detect areas of low voltage corresponding to myocardial atrophy with fibro-fatty replacement, enabling distinction between ARVC and idiopathic right ventricular outflow tract tachycardia. As the disease process is patchy, this mapping also allows for more directed targeting of endomyocardial biopsy.^(18,19)

RV angiography (RVA) is the imaging gold standard in ARVC and may demonstrate the classical features of localized aneurysms, prominent trabeculations of the RV and global dilation with decreased ejection fraction (Figure 4).^(19,21)

Echocardiography, despite being widely available and frequently performed, has a low sensitivity for the detection of ARVC due to the difficulty of imaging the RV. Despite these shortcomings, it remains useful as the first-line non-invasive imaging modality in assessing both presence of disease at primary evaluation in suspected ARVC and in

FIGURE 3: A resting 12-lead ECG in a patient with ARVC



A: The ECG shows typical abnormalities: The QRS morphology is abnormal with a delayed second component, most notable in V1. This is an Epsilon wave, which occurs in the right precordial leads, and may be upright or inverted, as it is here. Note also the inverted T waves in all the chest leads, which are abnormal if present beyond V1 after childhood. (The sinus bradycardia is due to beta-blockers.)

B: A sensitive measurement in ARVC that may be positive even before Epsilon waves can be discerned, is the duration of the S wave upstroke >55ms. In this patient, the measurement from the nadir of the S wave to termination of the QRS or when the S wave upstroke reaches baseline is 70ms, which is abnormal.

family screening and also, by means of serial examinations, progression during the follow-up of affected patients. Both functional and structural abnormalities can be evaluated, the detection of which may avoid the need for invasive RVA or costly cardiac magnetic resonance imaging (CMRI).^(10,19)

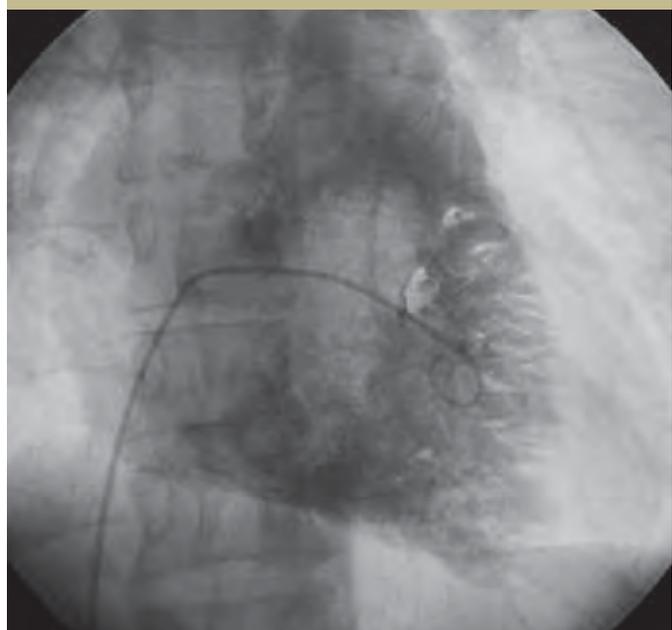
CMRI has become integral to the evaluation of ARVC because it is non-invasive, with increased sensitivity over echocardiography. Accurate measurements of both RV and LV size, volume and ejection fraction are obtained. Wall motion abnormalities with akinesia, dyskinesia and aneurysms diagnostic of ARVC are readily appreciated, as well as

evidence of fibrosis and fatty infiltration (Figure 5). However, the contraindication of CMRI in the presence of ICDs, high inter-observer variability coupled with a lack of standardized protocols producing variable results have resulted in CMRI disappointingly not living up to its initial expectations as the definitive mode of investigation. This is of particular importance in the South African context with its lack of expertise in the field of CMRI. In the case of the diagnosis of ARVC, it

TABLE 2: Points to Remember about ARVC

Symptoms
Fainting episodes, especially with exercise
Episodes of transient or persistent palpitations; may be associated with lightheadedness
Diagnostic Clues
Family History
Unexplained sudden death in young or middle aged family member(s)
ECG findings
T-wave inversions beyond lead V1
Epsilon waves in leads V1-V3
Ventricular premature beats with left bundle branch configuration
Abnormal electrical potentials in high-resolution (signal-averaged) ECG
Echocardiography
Dilated RV with aneurysms
Treatment
Antiarrhythmic medications
ICD
Radiofrequency ablation
Heart transplant

FIGURE 4: Right Ventricular angiographic features of ARVC



This RV angiogram would be best appreciated in "movie" mode as it shows hypokinesia of the entire anterior wall and apex. Other typical abnormalities can be noted here: along the anterior wall prominent trabeculations, which may have a "stack of coins" appearance, and localized aneurysms closer to the RV outflow region.

FIGURE 5: Cardiac Magnetic Resonance Imaging in ARVC



This MRI 4-chamber view of a patient with advanced ARVC shows some of the typical features: dilated right ventricle (RV), dilated right atrium (RA), multiple aneurysms of the RV free wall. The left ventricle (LV) is displaced posteriorly, in this patient, by the massive RV. The LV size is preserved.

has been shown that the sensitivity and specificity of CMRI are directly related to the experience of the radiologist in the reading of ARVC cases.^(11,12,19) Multidetector Cardiac CT has shown promise as an alternative imaging modality with the added benefit of coronary anatomy evaluation.⁽¹³⁾

TREATMENT

Treatment of ARVC is directed toward preventing life-threatening ventricular arrhythmias. This is achieved by sports avoidance and a combination of anti-arrhythmic drugs, radiofrequency ablation and ICDs.^(5,14,15,19)

All forms of intense physical activity and endurance sport should be prohibited; competitive sport is also to be avoided. These activities are associated with an unacceptably high risk of death and avoidance has been shown to be associated with a reduction in SCD among participants. An exercise test may be of benefit in identifying individuals at risk for developing exercise-induced arrhythmias but, as it is unable to mimic the competitive sport situation with its probable associated catecholamine rise and sympathetic effects, its sensitivity is low.^(16,22)

Beta-blockers are the most commonly used drugs. Alternative agents include sotalol and amiodarone.

Radiofrequency ablation (RFA) may be used as the sole treatment modality in selected cases where the VT originates from a focal area amenable to ablation; however, it is mostly combined with anti-

arrhythmic agents or an ICD. It is indicated particularly for drug failure and break-through arrhythmias or frequent ICD shock therapy. Although effective in the short term, RFA is not curative and is associated with a high recurrence of VT of 40% at 3 years, probably due to the progressive nature of the disease.⁽¹⁴⁾

Major risk factors for adverse prognosis are: young age, family history of juvenile sudden death, QRS dispersion ≥ 40 ms, T-wave inversion, left ventricular involvement, cardiac failure, ventricular tachycardia, syncope and previous cardiac arrest. Sports avoidance, ICDs and heart transplant (in severe heart failure) are life-saving interventions.^(14,15,16,19)

SA ARVC REGISTRY

International registries have been established in order to address issues relating to pathogenesis, prognosis and treatment. Much of our understanding of ARVC emanates from this.^(5,6,7,9,11,12,14,19,20) To this end, the SA ARVC registry, under the steering of the Working Group on Registries of the Cardiac Arrhythmia Society of Southern Africa (CASSA) was established. The coordinating centre is based in the Cardiac Clinic, Groote Schuur Hospital, Cape Town. Ethics approval had been obtained from the Research Ethics Committee of the University of Cape Town Faculty of Health Sciences.

Prospective enrolment has taken place since January 2004. Physicians refer suspected cases to the registry coordinator. After the diagnosis has been confirmed by the diagnostic panel, patients are invited, with consent, to partake in the registry. Written informed consent is obtained for blood samples for DNA analysis and for release to the registry and storage of any biopsy material obtained previously during diagnostic work-up by the treating physician. Additional written consent is obtained for any further investigations which may be performed to confirm the diagnosis of ARVC, to determine the extent or severity of the disease or for prognostication purposes.

The functional organization of the registry has been formalized (see the organogram in Figure 6). The registry has six major missions: DNA/Tissue bank, epidemiology, risk assessment and evaluation of therapy, imaging, pathological diagnosis and diagnostic validation.

DNA / Tissue banking

Blood samples for DNA analysis are obtained from all confirmed cases and family members to determine gene loci and to identify specific abnormal genes.

This will enable genotype-phenotype correlation and facilitate family screening for identified mutations.

Epidemiology

The screening for and the detection of familial occurrence by means of ECG, SAECG, Holter 24-hour ECG recording, exercise stress test, echocardiography, CMRI and genetic screening of known mutations will expand the limited epidemiological database of this condition in southern Africa. The pathology reports of explanted hearts obtained at cardiac transplantation, will be reviewed for features consistent with ARVC. Anatomical and forensic pathologists across South Africa will be encouraged to forward identified potential cases for review.

Risk stratification and evaluation of therapies

The main aim is to identify prognostic factors and evaluate long-term efficacy of current pharmacological and non-drug therapy.

Imaging

In addition to evaluating the diagnostic and prognostic value of existing imaging modalities and techniques, new MRI protocols, such as those utilizing cine Displacement Encoding with Stimulated Echoes (cine DENSE) for quantifying regional myocardial strain based on phase contrast images optimized for RV, are being developed using the registry patients to enhance earlier disease detection.

Pathology registry and tissue bank

A cardiac pathology registry has been set up to collect either heart specimens or endomyocardial biopsies. Protocols have been developed for processing and analysis of these specimens including immunohistochemistry, histochemistry, electron microscopy and myocyte culture. Insight will be gained into the etiopathogenesis of the disease and the diagnostic value of endomyocardial biopsy in the workup of suspected cases of ARVC.

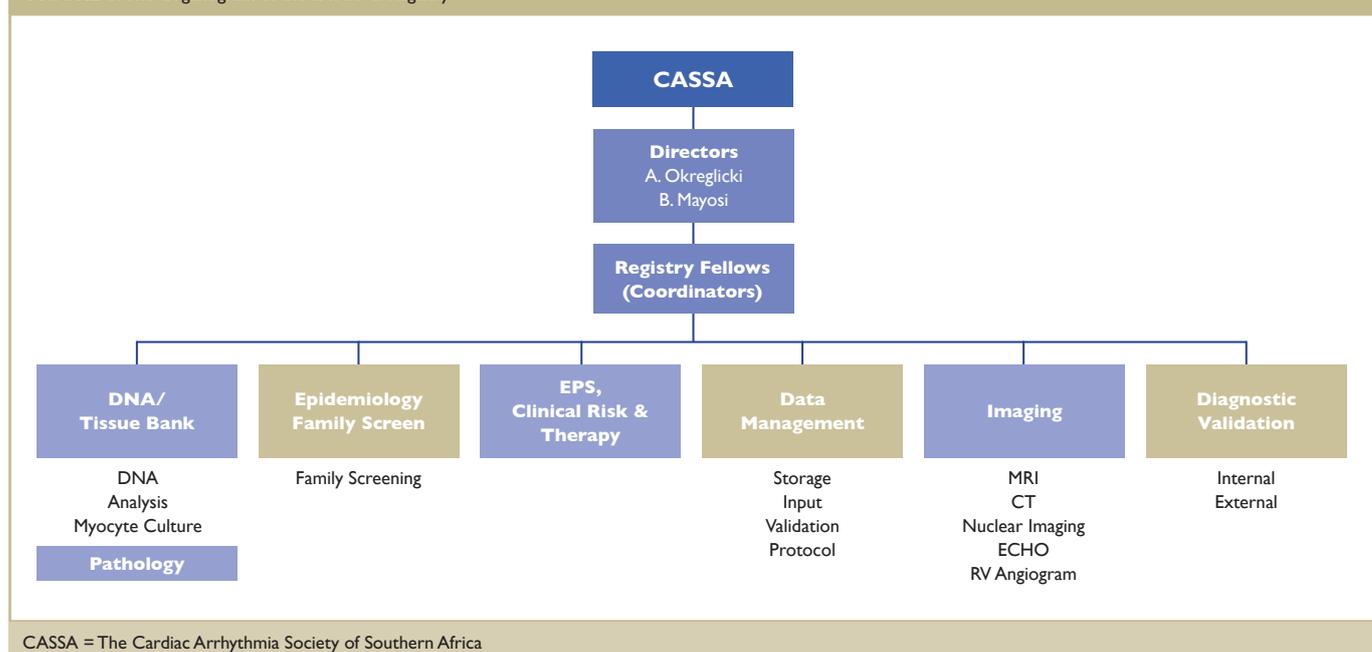
RESULTS AND REGISTRY DATA

To date, 80 confirmed cases of ARVC, 70 being probands, have been enrolled in the registry of whom 54/80 (68%) were males. The median age at diagnosis was 27.5 years (range 11-74 years), 23/80 (29%) of whom were 20 years or younger: ARVC has been diagnosed in all racial groups.

With regard to inheritance, 48/80 (60%) had either a family member with confirmed ARVC or a history of SCD or sudden unexplained death. LV involvement in ARVC, a measure of the extent of the disease, was present in 35/80 (44%), 4 of whom subsequently had heart transplants with another awaiting transplantation. Other relevant therapy data reveal that ICDs were implanted in 30/80 (38%).

Assessment of potential risk factors shows that 40/80 (50%) participated in some form of organized sport; 4/80 (5%) were survivors of SCD which occurred whilst participating in sporting activity.

FIGURE 6: The Organogram of the SA ARVC Registry



Follow-up data are available for 66/80 (83%) of whom 14/66 (21%) have died.

A novel genetic mutation in the plakophilin gene was discovered in one family that presented with early progressive disease proceeding to cardiac transplantation in 2 siblings.

DISCUSSION

This registry represents the largest cohort of ARVC patients from the African continent. The results confirm the clustering of ARVC in families, the significant role of endurance sport and the high mortality of ARVC.^(4,6,16,19)

Despite the short existence of the registry and minimal financial support, considerable strides have been made with respect to recruitment, data collection and novel findings. In this regard it compares favourably with the output of other international registries.⁽²⁰⁾

There remains a call for cardiologists and physicians across South Africa to be vigilant in identifying affected individuals and to be diligent in referring all suspected or confirmed cases of ARVC to the registry in order for it to achieve its goals.

Contact details for referral of confirmed and suspected cases of ARVC: arvc.sa@uct.ac.za

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