Correlation of Signal-Averaged Electrocardiogram and Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in the Detection of Myocardial Fibrosis in Arrhythmogenic Right Ventricular Cardiomyopathy and other Myocardial Disorders

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DEDICATION

I would like to dedicate my thesis to my parents; my late father, Maliwa Arthur Mfolozi and mother Mabel Nomathamsanqa Mgidlana; my brothers, Malusi Mgidlana and Sipho Mfolozi whose unwavering support continues to form the essence of my being.

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DECLARATION

I, Msimelelo Mzwamadoda Mgidlana, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signature: Signed by candidate

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LIST OF ABBREVIATIONS AND ACRONYMS

2D	Two dimensional
ANOVA	Analysis of variance
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASD	Atrial septal defect
BSA	Body surface area
CMR	Cardiovascular magnetic resonance
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
fQRS	Filtered QRS
GFR	Glomerular filtration rate
HCM	Hypertrophic cardiomyopathy
IQR	Inter-quartile range
LAS40	Low amplitude signal duration under 40μV
LBBB	Left bundle brunch block
LGE	Late gadolinium enhancement
LV	Left ventricle/ventricular
LVEDd	Left ventricular end-diastolic diameter
LVEDV	Left ventricular end-diastolic volume
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PVC	Premature ventricular contraction(s)
RMS40	Root mean square in the last 40ms of the QRS
RV	Right ventricle/ventricular
RVEDd	Right ventricular end-diastolic diameter
RVEDV	Right ventricular end-diastolic volume
RVOT	Right ventricular outflow tract
SAECG	Signal-averaged electrocardiogram
SCD	Sudden cardiac death
SD	Standard deviation
SNR	Signal to noise ratio
VT	Ventricular tachycardia
VF	Ventricular fibrillation

Abstract

Background. The diagnosis of fibrotic scar tissue in arrhythmogenic right ventricular cardiomyopathy (ARVC) and other cardiomyopathies is crucial as it forms the substrate for ventricular tachycardia (VT) and fibrillation (VT). Signal-averaged electrocardiography (SAECG) abnormalities are frequent in ARVC and in other cardiomyopathy-related ventricular arrhythmias. The correlation between cardiovascular magnetic resonance (CMR) late gadolinium enhancement (LGE) and parameters of SAECG in ARVC is not known.

Method. Thirty-five patients [median age 32 years (IQR 25 – 46)] referred to the ARVC Registry at Groote Schuur Hospital were included in this retrospective study. SAECG was performed with high-amplification and filtered using bidirectional Butterworth filters between 40 and 250 Hz. A filtered averaged QRS (fQRS) was obtained and analysed for fQRS duration, low amplitude signal duration <40 mV (LAS40), and root-mean-square voltage in the last 40ms of the QRS (RMS40). LGE acquired at 5 to 20 minutes after intravenous administration of gadolinium (0.1mmol/kg to 0.2mmol/kg of body mass) was assessed. We evaluated the correlation between SAECG parameters and the presence of LGE.

Results. Sixteen patients had definite ARVC, 5 had possible ARVC, 4 had idiopathic VT/VF, 2 had Athlete's heart, 1 had dilated cardiomyopathy (DCM), 1 had hypertrophic cardiomyopathy (HCM), 1 had SVT and 1 had pericardial constriction. LGE was present in 13 (81%) ARVC patients, 2 (40%) with possible ARVC, 1 (50%) with athlete's heart and in all patients with DCM and HCM. Patients with idiopathic VT/VF, pericardial constriction and supraventricular tachycardias had no myocardial LGE on CMR. Comparing patients with LGE and those without LGE on CMR, there were no differences in fQRS, (114ms [102.3 – 119] versus 111ms [99.5 -130], p = 0.608); LAS40 (34.5ms [16.8 - 40.8] versus 31ms [27.5 – 45], p = 0.566) and a RMS40 (23.5 µV [14.3 – 47.5] versus 33 µV [18.5 – 43.5], p= 0.621), respectively. LGE was present in 6 (60%) patients who had VT at presentation, in 9 (56%) with VT at baseline or follow-up and in all (2) patients who survived cardiac arrest. Three one-way analyses of variance (fQRS vs LGE, LAS40 vs LGE and RMS40 vs. LGE) confirmed that there was no correlation between LGE technique on CMR and SAECG for the detection of myocardial fibrosis in ARVC and other myocardial disorders: for fQRS $F(1 , 33) = 1.47$, $p = 0.23$, $\eta^2 = 0.02$; for LAS40 $F(1 , 33) = 0.95$, $p = 0.34$, $\eta^2 = 0.02$ and for RMS40 $F(1 , 33) = 0.36$, $p = 0.85$, $\eta^2 = 0.02$.

Conclusion. In this study comparing assessment of myocardial fibrosis by LGE CMR and SAECG, there was no correlation between CMR and SAECG in detection of myocardial fibrosis in ARVC and other cardiovascular diseases.

Introduction, Literature Review and Study Rationale

INTRODUCTION

EPIDEMIOLOGY OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disorder characterised by fibrous or fibro-fatty replacement of myocardium in the inflow tract, outflow tract and/or apex of the right ventricle. The prevalence of ARVC in the general adult population is estimated to be approximately 1 in 2000 to 1 in 5000.[1] The disease affects men more frequently than women with an approximate ratio of 3:1. ARVC is a well-identified cause of sudden cardiac death (SCD) in young adults, accounting for approximately 11% overall of SCD cases.[2]

CLINICAL MANIFESTATIONS OF ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

The clinical presentation of ARVC is variable, ranging from lack of symptoms to palpitations, syncope, chest pain, dyspnoea and, rarely, to SCD. Palpitations and syncope may be the manifestations of ventricular arrhythmias. Ventricular arrhythmias range from frequent premature ventricular contractions (PVCs) to sustained ventricular tachycardia (VT); the frequency of which is dependent on the severity of the disease.[3] A non-sustained or sustained VT is the most common ventricular arrhythmia in ARVC and originates in the right ventricle (RV), and in particular, the RV outflow tract (RVOT), and therefore has left bundle branch block (LBBB) morphology.[3,4] Furthermore, PVCs can also arise from the RVOT in ARVC; in such cases it becomes paramount to differentiate ARVC from idiopathic RVOT tachycardia as the management and prognosis is different.[5]

In trying to address the dilemma of the clinical diagnosis of ARVC, an expert consensus group proposed diagnostic criteria in 1994 (Table 1).[6] These criteria were very specific to ARVC but lacked sensitivity in diagnosing milder or atypical presentations. They were later revised in 2010[6] and now incorporate advances made in both imaging and diagnostic technology and genetics. The revised criteria now include parameters from two-dimensional (2D) echocardiography, cardiovascular magnetic resonance (CMR) imaging, RV angiography, signal-averaged electrocardiogram (SAECG), 12 lead electrocardiogram (ECG) and endomyocardial biopsy (EMB).

In resource-limited settings, the diagnosis of ARVC is often a balancing act between available resources, patient clinical profile and the sensitivity and specificity of available diagnostic tools. In such settings it becomes imperative to explore data comparing different diagnostic modalities against each other.

CARDIOVASCULAR MAGNETIC RESONANCE IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY AND OTHER CARDIOMYOPATHIES

To appreciate the use of CMR in the diagnosis of ARVC it is imperative to first conceptualise how magnetic resonance (MR) functions and how this is applied in the context of ARVC diagnosis. Further, it is important to be cognisant of other cardiac pathologies that may mimic ARVC on the CMR; these warrant discussion as they may cause diagnostic dilemmas and are discussed later. CMR use in the diagnosis of cardiovascular diseases (CVD) can broadly be divided into structural (anatomical) and functional (physiology) assessment of the heart. The usefulness of CMR in specific diseases as advised by Consensus Report Panel on the Clinical Indications of CMR[7] is summarised by means of the following classification (Table 1).

Table 1: Clinical Indications for CMR	
Class	Indication
I	provides clinically relevant information and is usually appropriate; may be used as first line imaging technique; usually supported by substantial literature
II	provides clinically relevant information and is frequently useful; other techniques may provide similar information; supported by limited literature
III	provides clinically relevant information but is infrequently used because information from other imaging techniques is usually adequate
Inv	potentially useful, but still investigation. (ARVC is classified under Class I in the Consensus)

In particular reference to ARVC, CMR is helpful in determining whether 1) RV function is normal or abnormal; 2) to accurately calculate RV volumes and ejection fraction (EF); 3) to assess the presence of RV regional wall motion abnormalities, wall thinning or aneurysmal formation; 4) to assess the presence of RV fatty infiltration; 5) assess the presence of RV myocardial fibrosis using late gadolinium enhancement (LGE); 6) assess whether there is LV involvement.

With regards to cardiomyopathies in general, late gadolinium enhancement (LGE) refers to regions of scar, necrosis, and/or inflammation discriminated from normal tissue by prolonged retention of gadolinium-based contrast agents.[8] Recently, there has been growing interest in exploiting the role of myocardial fibrosis, an integral pathophysiologic component of dilated cardiomyopathy (DCM), as a biomarker for guiding patient management and determining prognosis.[9] Fibrosis can occur in 2 forms that can be detected by CMR:[10] (A) irreversible replacement fibrosis which corresponds to the presence of LGE and (B) diffuse interstitial

fibrosis which better corresponds to findings on T1-mapping. Furthermore, in cardiomyopathies due to ischaemic heart disease (IHD) Abdel-Aty *et al* found LGE accurately delineates infarction as defined by histology at various time points following injury.[11] In genetic cardiomyopathies like hypertrophic cardiomyopathy (HCM), CMR is more sensitive for the identification of more unusual sites of hypertrophy and for apical HCM than echocardiography.[12] In their study assessing the accuracy of LGE for predicting microscopic myocardial scarring in biopsied specimens of hypertrophic cardiomyopathy, Konno et al reported the LGE in the ventricular septum had an excellent sensitivity (100%) with a low specificity (40%) whilst the whole heart had 100% sensitivity and 27% specificity.[13] Between half and two-thirds of patients with HCM may have LGE with a characteristic pattern of patchy involvement, particularly at the LV/RV insertion sites and in those walls with the greatest hypertrophy.[9] In certain cases of ARVC, the RV free wall can be the site of LGE[14]; the difficulty of this definitive observation being (1) a thin RV wall, (2) discriminating from RV fat and (3) the technique requires significantly different inversion times compare with the LV.[15]

SIGNAL-AVERAGED ELECTROCARDIOGRAM IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

SAECG is a computerised technique for detecting subtle abnormalities in the surface ECG that are not visible to the naked eye. The SAECG is derived by computing the arithmetic mean of multiple ECG complexes. This process increases the signal-to-noise ratio (SNR) of cardiac potentials and enables the detection of much smaller (i.e. microvolt-level) signals than would otherwise be undiscernible from the surface ECG.[16] By detecting low-amplitude signals at the end of the QRS complex, referred to as ventricular late potentials, the SAECG allows for the diagnosis of delayed ventricular depolarisation which can be the result of myocardial scar tissue (fibrosis).[17] The use of SAECG in the detection of fibrosis in ARVC has therefore been studied extensively and the presence of ventricular late potentials is a minor task force criterion in the diagnosis of ARVC. The sensitivity and specificity of an abnormal SAECG in ARVC has

been reported as 57% and 95% respectively.[18] In 1991, a statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association and the American College of Cardiology on the Standards for Analysis of Ventricular Late Potentials Using High-Resolution or Signal-Averaged Electrocardiography proposed the use of following criteria in determining the presence of late ventricular potentials[19] (Table 2).

Table 2: Criteria for the presence of late ventricular potentials
• filtered QRS (fQRS) duration ≥ 114ms • low-amplitude (<40 μV) signal duration (LAS40) ≥ 38ms • root mean square voltage (RMS40) in the terminal 40ms of the fQRS ≤ 20μV

ARVC is a progressive disease and the difficulty in making the diagnosis at various stages further reiterate this notion. It is therefore no surprise there is no single gold-standard investigation.

Rationale for this research

The incidence and clinical significance of LGE in cardiomyopathy patients, especially ARVC, with late potentials on SAECG has not been systemically evaluated. This study investigates the clinical utility of the LGE technique of CMR in relation to SAECG in the detection of myocardial fibrosis in ARVC patients and other cardiomyopathies. Such a comparison has never been performed before. Additional novelty of the study lies in the premise that a positive correlation of the 2 modalities would likely necessitate a modification or, at the least, a revision of the current Task Force Criteria[17] with the inclusion of the LGE on CMR as one of the diagnostic criteria thus further increasing the diagnostic sensitivity of CMR. The value proposition of assessing utility and accuracy of SAECG for assessment of myocardial fibrosis

is because CMR is expensive, not widely available, and the expertise for its performance and analysis lacking in many parts of sub-Saharan Africa.

Hypothesis

There is no correlation of the LGE technique in CMR and SAECG in the detection of myocardial fibrosis in ARVC.

STUDY AIMS AND OBJECTIVES

The aim of this study is to prove correlation between SAECG and LGE in the assessment of myocardial fibrosis

PRIMARY OBJECTIVES

Correlation of signal-averaged ECG and LGE CMR in assessment of myocardial fibrosis in patients referred with suspected ARVC

SECONDARY OBJECTIVES

Assess other cardiac parameters (including cardiac chamber size, function, wall thickness, strain and viability) using CMR, in patients referred with suspected ARVC.

METHODS

This was a retrospective sub-study based on selected patients incorporated into IMHOTEP (The African Cardiomyopathy and Myocarditis Registry Programme). IMHOTEP is a multi-centre, multi-national hospital-based prospective study of the clinical characteristics, causes, treatment and outcome of cardiomyopathies and myocarditis in children and adults from referral centres in Africa. Prevalent cases of the cohort study included are from the Groote Schuur Cardiomyopathy Clinic and South African ARVC Registry; whilst the incident cases are all newly diagnosed cardiomyopathy or myocarditis cases from Groote Schuur Hospital.

Study population

We conducted a retrospective study of patients referred to Groote Schuur Hospital Cardiac Clinic from 01 February 1996 – 31 May 2018 with suspected ARVC that had been evaluated for incorporation into IMHOTEP. Patients were included if they had undergone a complete cardiac examination including history, physical examination, 12 lead ECG, SAECG and gadolinium contrast-enhanced CMR. Patients were excluded from the study if they had (1) atrial fibrillation at the time of SAECG as variations in QRS complexes in atrial fibrillation affect validity of SAECG (2) a pacemaker at the time of SAECG as late potentials during a normal unpaced rhythm were being assessed and (3) an unfiltered QRS ≥ 110ms.

Data collection and measurements

Patient demographics, including age, sex, weight, height were obtained from the patients' clinic folders by IMHOTEP investigators at the time of referral and stored on the secure database (username and password protected), governed by the University of Cape Town. Anonymised data was provided to the sub-study investigators. Data collected included patients' history and symptoms were also be obtained and documented as dyspnoea (New

York Heart Association classification, NYHA 1-4), paroxysmal nocturnal dyspnoea, orthopnea, oedema, chest pain, palpitations and syncope. History of hypertension, type 2 diabetes mellitus, ischemic heart disease, hypercholesterolemia and rheumatic fever was recorded. Results of patients' investigations was obtained from the clinic folders and archives of the South African ARVC registry. These included ECGs, SAECGs, chest radiographs, echocardiograms and CMR. Laboratory results such as creatinine, haemoglobin were obtained from NHLS records, using the Labtrak and DISA systems. The data was independently reviewed by the ARVC diagnostic panel and was entered in to an Microsoft Excel Spreadsheet.

SAECG

The SAECG had been conducted using a General Electric (GE) MAC5500 (General Electric, Boston, Massachusetts, USA). The quantitative SAECG variables of the filtered QRS that were measured are: (1) total duration of fQRS, (2) duration of the low-amplitude signals (<40mV) in the terminal portion (LAS40) and (3) root-mean square voltage of the last 40ms (RMS40). Ventricular late potentials were considered positive when > 1 of the following criteria were fulfilled: (1) fQRS $\geq$ 114ms, (2) LAS40 $\geq$ 38ms and RMS40 $\leq$ 20µV, in the absence of a QRS duration of ≥110 ms on the standard ECG.

CMR

CMR had been performed using a 1.5T Siemens Symphony (VB 13, Siemens Healthcare, Erlangen, Germany) according to a standardised protocol. The following cardiac parameters were documented: (a) LV and RV volumes, mass and function, (b) Myocardial tissue characterisation using dual inversion recovery T2-weighted imaging and T1-weighted imaging, (c) Velocity-encoded 2-D phase contrast (flow) imaging, and (d) LGE imaging for viability and fibrosis assessment. LGE images acquired at 5 to 20 minutes after an intravenous

administration of gadolinium (0.1mmol/kg to 0.2mmol/kg of body mass) was reported when it was detected in more >1 imaging plane, using cross-plane localizers to confirm the position.

Statistical analysis

Data was analysed using statistical software (Version: 26.0.0.0 IBM Statistical Package for Social Sciences – SPSS, Armoyonk, NY, USA). Descriptive statistics were used to describe the study population. Categorical data has been reported as number and proportion. Chi-squared test of equal proportions was used to determine the difference between categorical data. Continuous variables were tested for normality using Shapiro-Wilks and a histogram for visualisation. Normally distributed data was reported as mean and standard deviation, and Independent t-test (2 samples) and Anova (more than 2 samples) were used to determine differences. Non-normally distributed data has been reported as median and interquartile range (IQR), and Wilcoxon sum rank (2 samples) and Kruskal-Wallis (more than 2 samples) were used to determine differences. Cox proportional hazard regression analysis was used to explore risk of adverse outcomes. Kaplan-Meier survival analysis was done to determine transplant-free survival. A composite primary outcome measure of death or cardiac transplantation was used. All statistical tests are two sided, at $\alpha = 0.05$.

Ethical considerations

HUMAN RESEARCH ETHICS COMMITTEE APPROVAL

Ethics approval was granted by the Faculty of Health Sciences Human Research Ethics Committee (HREC) with the REFERENCE: 787/2019.

INFORMED CONSENT

As the study was retrospective, no specific consent was obtained for this study, however, informed consent for inclusion into IMHOTEP (HREC 766/2014) or the ARVC Registry of South Africa (HREC 047/2003) had been previously obtained from all participants.

OTHER ETHICAL CONSIDERATIONS

All patient data was anonymised and an alpha numeric nomenclature identification number was used for each participant in respect of confidentiality. No personal/identifying details were utilised in the analysis. Data and analysis records were kept in a secure computer and via an online storage facility that required login details and a password only known to the researchers.

Safety

CMR is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionising radiation. Participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the CMR magnet would have been excluded from clinical studies. All participants entering the scanner room had been screened for such objects. Gadolinium contrast is widely used for clinical indications in CMR and is safe. Occasionally it may cause a mild headache, nausea, itching and very rarely (< 1 in 1000) a more severe allergic reaction. It is cleared within hours by the body. Gadolinium has been associated with nephrogenic systemic fibrosis in patients with severe renal dysfunction; hence, all patients with glomerular filtration rate (GFR) < 30 ml/min (stage 3-5 renal disease) were not included in this study.

RESULTS

Enrolment and diagnosis

In this sub-study, we looked at a total of 162 patients with suspected ARVC who were referred to the ARVC Registry for evaluation at Groote Schuur Hospital Cardiac Clinic from 01 February 1996 – 31 May 2018. Of the 162 patients referred, 40 patients had had both SAECG and LGE CMR performed (Figure 1). Of the 40 patients, only 35 had a valid SAECG (unfiltered QRS <110ms) and thus were eligible for the study.

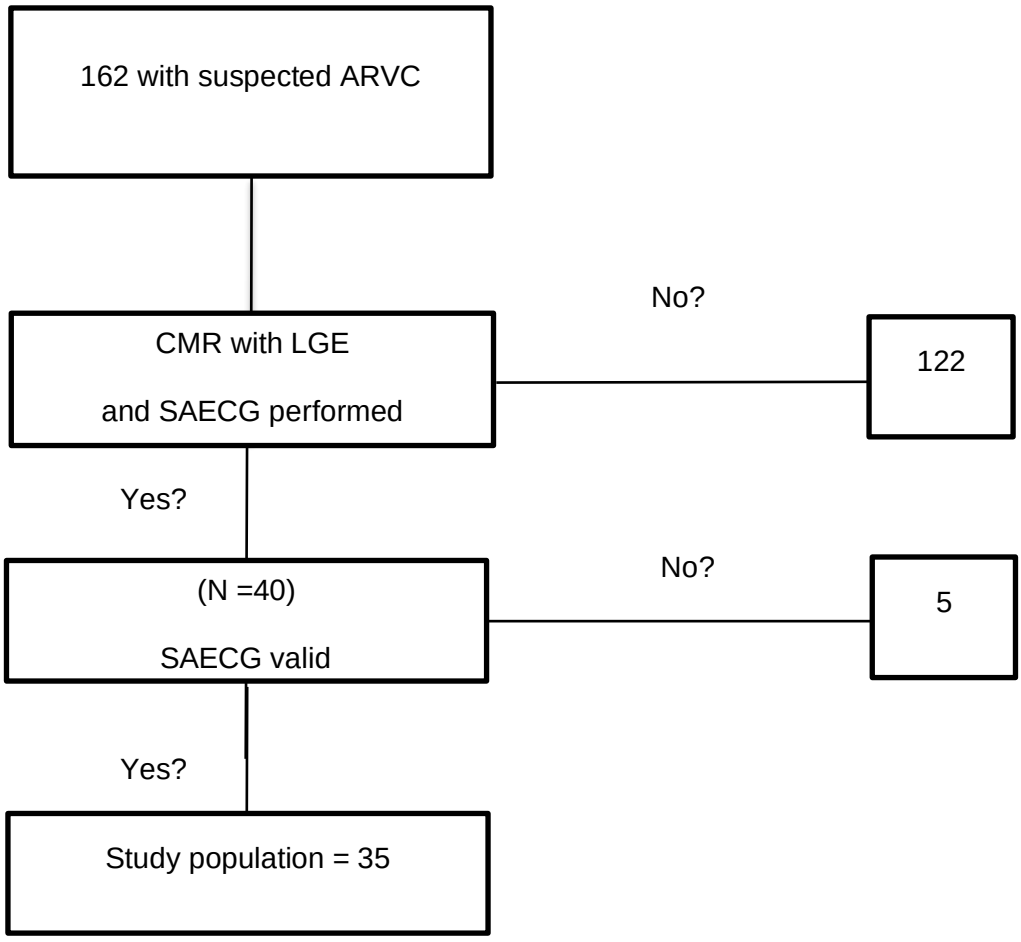

Figure 1: Study population

Demographics and baseline clinical characteristics

Table 4 outlines the baseline characteristics for 35 patients included in the study, comparing those with (n = 17) and without (n = 18) LGE on CMR. The most prevalent condition was ARVC (45.7%) fulfilling either definite (34.4%) or borderline (11.4%) criteria. Possible early ARVC was considered in 14.3% of cases, however due to insufficient TFC a diagnosis of ARVC could not be confirmed. Alternative cardiac diagnoses were made in the remaining cases; idiopathic RVOT VT/VF (11.4%), athlete's heart (5.7%), DCM (2.9%), HCM (2.9%), supraventricular tachycardia – SVT (2.9%) and pericardial constriction (2.9%). There was notable diagnostic variation between the groups; those with evidence of myocardial disease were more likely to have LGE, whereas LGE was not observed in patients with primary arrhythmias (Idiopathic VT/VF or SVT).

The median age of presentation was 32 years (IQR 25- 46) with a male predominance (65.7%). Patients of mixed ancestry and Caucasians constituted 45.7% and 34.3% respectively, with 14.3% and 5.7% of the cohort represented by Black African and patients of South-East Asian descent. There were no statically significant differences in demographic profiles between the LGE negative and LGE positive groups.

All patients were symptomatic at presentation. The most prevalent presenting compliant was palpitations (77%), followed by pre-syncope (42.9%), chest pain (40%), syncope (37.1%) and dyspnoea (9%). Twenty-eight percent had VT at presentation whilst a small number presented having survived cardiac arrest (5.7%). Four patients underwent cardiac radiofrequency ablation for incessant arrhythmias.

Table 4. Baseline and demographic parameters

Participant characteristics	**All n = 35**	**LGE – n = 17**	**LGE+ n = 18**	***p*-value**
Diagnosis				
ARVC (definite/borderline)	12/4 (34.3/11.4)	3/- (17.6)	9/4 (50/22.2)	0.024
Possible ARVC (%)	5 (14.3)	3 (17.6)	2 (11.1)	
DCM (%)	1 (2.9)	-	1 (5.6)	
HCM (%)	1 (2.9)	-	1 (5.6)	
Athlete's heart (%)	2 (5.7)	1 (5.9)	1 (5.6)	
Idiopathic VT/VF (%)	4 (11.4)	4 (23.5)	-	
Pericardial constriction (%)	1 (2.9)	1 (5.9)	-	
Supraventricular tachycardia (%)	1 (2.9)	1 (5.9)	-	
Age of onset in years*				
Mean (±SD)	34.3 ±13.3	32.2 ±11.7	36.2 ±14.7	0.389
Median (IQR)	32.0 (25 – 46)	30 (22.5 – 42.0)	33.5 (25 – 49.5)	-
Male sex, n (%)	23 (65.7)	9 (52.9)	14 (77.8)	0.122
Ethnicity				
Caucasian (%)	12 (34.3)	5 (29.4)	7 (38.9)	0.918
Black African (%)	5 (14.3)	3 (17.6)	2 (11.1)	
Mixed ancestry (%)	16 (45.7)	8 (47.1)	8 (44.4)	
South-East Asian descent (%)	2 (5.7)	1 (5.9)	1 (5.6)	
Symptoms				
Palpitation (%)	27 (77.1)	13 (76.5)	14 (77.8)	0.927
Pre-syncope (%)	15 (42.9)	6 (35.3)	9 (50)	0.380
Syncope (%)	13 (37.1)	7 (41.2)	6 (33.3)	0.631
Chest pain (%)	14 (40)	7 (41.2)	7 (38.9)	0.890
Dyspnoea (%)	9 (25.7)	3 (17.6)	6 (33.3)	0.289
Clinical events				
VT at presentation (%)	10 (28.6)	4 (23.5)	6 (33.3)	0.521
VT at baseline or follow-up (%)	16 (45.7)	7 (41.2)	9 (50)	0.600
Survived cardiac arrest (SCD) (%)	2 (5.7)	-	2 (11.1)	0.157
Previous ablation (%)	4 (11.4)	1 (5.8)	3 (16.7)	
ICD implantation (%)	15 (42.9)	7 (41.2)	8 (44.4)	0.845

*Shapiro Wilks, p 0.289

Baseline investigations

There was no significant difference in the presence of a sinus rhythm between those with and without LGE on CMR. The unfiltered QRS tended to be longer in patients with LGE on CMR compared to those without LGE (95.9 ±9.9 vs 88.1 ±10.3; p = 0.967), but did not reach statistical significance. Late potentials also tended to be more prevalent in patients with LGE on CMR compared to those without (61.1% vs 35.3% p = 0.127), but without statistical significance (Table 5).

Further analysis of the late potential parameters, though not significant, revealed RMS40 and fQRS had greater differences between the LGE positive and LGE negative groups (15% and 14.7%, respectively) than HFLA < 40μV (9.4%, p =0.555). The median fQRS duration in those with LGE was prolonged, 114ms (IQR 102.3 – 119) compared to 111ms (IQR 99.5 -130) in those without with a p = 0.608 highlighting no statistically significant difference. Even though the median RMS40 was lower 23.5 μV (IQR 14.3 – 47.5) in the group with LGE when compared to 33 μV (IQR 18.5 – 43.5) in the group without, the p value is 0.358 and therefore this observed difference was not significant. (Table 5).

Table 5. Standard ECG and SAECG

	All n = 35	**LGE – n = 17**	**LGE+ n = 18**	***p*-value**
ECG data				
Sinus rhythm (%)	33 (94.3)	16 (94.1)	17 (94.4)	0.967
Heart rate (%)	74.5 ±13.7	75.5 ±10.5	73.6 ±16.4	
Unfiltered QRS duration, mean ±SD	92.1 ±10.7	88.1 ±10.3	95.9 ±9.9	0.028
SAECG				
Positive for late potentials (%)	17 (48.6)	6 (35.3)	11 (61.1)	0.127
Filtered QRS ≥ 114ms (%)	15 (42.9)	6 (35.3)	9 (50)	0.380
Terminal QRS ≥ 38ms (%)	12 (34.3)	5 (29.4)	7 (38.9)	0.555
RMS ≤ 20μV (%)	13 (37.1)	5 (29.4)	8 (44.4)	0.358
Filtered QRS duration (ms)*				
Mean ±SD	112.1 ±18.5	114.9 ±19.0	109.3 ±18.1	0.608
Duration of terminal QRS < 40μV (ms)				
Mean ±SD	33.5 ±15.2	35 ±13	32 ±17.2	0.566
RMS voltage of terminal 40ms (μV)*				
Mean ±SD	34.1 ±24.6	34.7 ±22.3	34.33.6 ±27.3	0.621

Three one-way analyses of variance (fQRS vs LGE, LAS40 vs LGE and RMS40 vs LGE) were conducted to evaluate the null hypothesis that there is no correlation of the LGE technique in CMR and SAECG in the detection of myocardial fibrosis in the cohort (n = 35). In the fQRS analysis, the independent variable; LGE, included two groups: positive (108.2ms [90.2 – 126.2], n = 17) and negative (115.7ms [97 – 134.5], n = 18); p=0.127. The assumption of normality was evaluated using histograms (see Figure 2) and found tenable for both groups. The assumption of longevity of variances was tested and found tenable using Levene's Test $F(1, 33) = 0.559$, $p = 0.460$. The ANOVA was not significant $F(1 , 33) = 1.47$, $p = 0.23$, $\eta^2 = 0.02$. In the LAS40 analysis, LGE groups were: positive (30.9ms [13.9 – 48], n = 17) and negative (36ms [22.8 – 49], n = 18). The assumption of normality was evaluated using histograms (see Figure 2) and found tenable for both groups. The assumption of longevity of variances was tested and also found tenable using Levene's Test $F(1, 33) = 1.126$, $p = 0.296$. The ANOVA for LAS40 was also not significant $F(1 , 33) = 0.95$, $p = 0.34$, $\eta^2 = 0.02$. In the RMS40 analysis, LGE groups were: positive (34.9 µV [7.4 – 62.5], n = 17) and negative (33.3µV [11 – 55.7], n = 18). The assumption of normality was evaluated using histograms (see Figure 2) and found tenable for both groups. The assumption of longevity of variances was tested and also found tenable using Levene's Test $F(1, 33) = 0.639$, $p = 0.430$. The ANOVA for RMS40 was not significant $F(1 , 33) = 0.36$, $p = 0.85$, $\eta^2 = 0.02$. Figure 3 shows SAECG with positive parameters for myocardial fibrosis.

Figure 2: Tests of Homogeneity of Variances

		Levene Statistic	df1	df2	Sig.
fQRS	Based on Mean	.559	1	33	.460
	Based on Median	.242	1	33	.626
	Based on Median and adjusted df	.242	1	32.652	.626
	Based on trimmed mean	.496	1	33	.486
LAS40	Based on Mean	1.126	1	33	.296
	Based on Median	1.199	1	33	.281
	Based on Median and adjusted df	1.199	1	32.598	.282
	Based on trimmed mean	1.283	1	33	.266
RMS40	Based on Mean	.639	1	33	.430
	Based on Median	.267	1	33	.609
	Based on Median and adjusted df	.267	1	28.711	.609
	Based on trimmed mean	.489	1	33	.489

Overall, the LVEF and LVEDV index measurements were normally distributed with means of 60% ± 10.8% and 89mL/m^2 ± 17.5mL/m^2 respectively (Table 6). There was a notable difference of the mean LVEF in patients without LGE compared to those with LGE (64.5 ± 8.7 vs 55.7 ± 11%, p = 0.014) and of the mean LVEDV index (82.5m ± 14.7 vs. 95.3 ± 18.1 mL/m^2,

p = 0.028). The overall median RVEF and RVEDV index measurements were 53.5% (IQR 41.6 - 60.3) and 96.4mL/m^2 (84.9 – 122.6), respectively. An observed difference in the median RVEF of patients with and without LGE [47.7 (IQR 30.4 – 56.1) vs. 56.2% (IQR 48.1 – 63.3), p = 0.025) was noted and the median RVEDV index [116.2 (IQR 89.2 – 154.6) vs. 87.8 (IQR 78.8 – 101.2) mL/m^2, p = 0.003] is statistically significant. The LV mass index measurements followed a normal distribution with a mean of 64.2 ± 14.5 g/m^2 and a significant difference in the LV mass index noted between those with and without LGE (72.5 ± 13.3 vs. 55.4 ± 10.2 g/m^2, p < 0.001). LV maximal and minimal wall thickness had a mean of 10.3 ± 2mm and 6.89 ± 1.3 mm, retrospectively with no differences between the group with and without LGE. CMR LV regional wall motion abnormalities were detected in 4 patients of which 3 had LGE and 1 with no LGE. CMR RV regional wall motion abnormalities were observed in 9 patients of which 7 had LGE and the remaining 2 without LGE. (Figure 4)

Figure 3: SAECG with fQRS>114ms, LAS40>38ms and RMS<20 µV

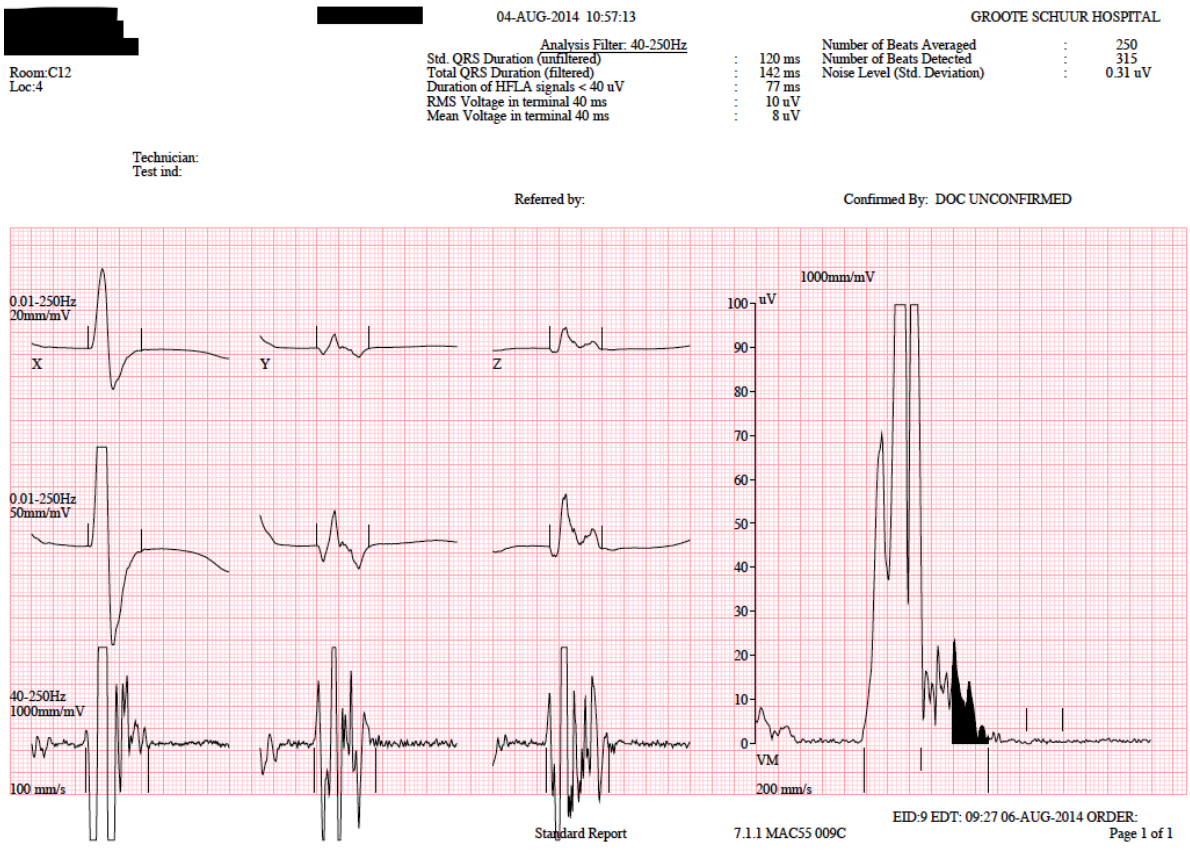

Figure 4: CMR image of a 15-year old male with ARVC

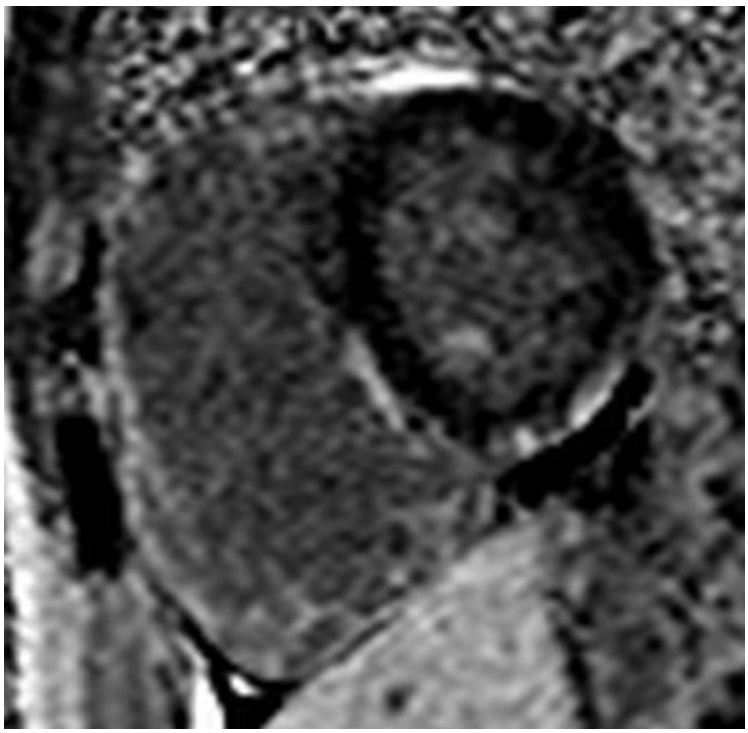

Image courtesy of IMHOTEP Study

Short axis image showing diffuse late gadolinium enhancement of the right ventricular free wall and patchy enhancement of the right ventricular septum. Patching enhancement of the left ventricular septum and left ventricular walls also demonstrated.

Table 6. CMR findings

	All n = 35	**LGE – n = 17**	**LGE+ n = 18**	***p*-value**
CMR findings				
LVEF (%)				
Mean ±SD	**60 ±10.8**	**64.5±8.7**	**55.7±11.1**	**0.014**
Median (IQR)	59.1(53.2 - 62.1)	62.7(60.2–70.4)	57.3(50.1 – 59.2)	-
LVEDD/BSA (mL/m^2)				
Mean ±SD	**89.1 ±17.5**	**82.5±14.7**	**95.32±18.1**	**0.028**
Median (IQR)	88.8(74.6 –100.6)	84.7(67.9–91.8)	97(83.93 – 108.5)	-
RVEF (%)*				
Mean ±SD	**49.8 ±14.3**	**55.8±8.6**	**44±16.4**	-
Median (IQR)	53.5 (41.6 - 60.3)	56.2(48.1-63.3)	47.7(30.4 – 56.1)	**0.025**
RVEDD/BSA (mL/m^2) *				
Mean ±SD	**107.2±33.3**	**90.2±17.3**	**123.3±37.2**	-
Median (IQR)	96.4(84.9 - 122.6)	87.8(78.8-101.2)	116.2(89.2-154.6)	**0.003**
LV mass/BSA (g/m^2)				
Mean ±SD	**64.2 ±14.5**	**55.4±10.2**	**72.5±13.3**	**< 0.001**
Median (IQR)	62.1(53.3 – 75.7)	54.2(47.7 - 60.8)	73.4(62.5 – 78)	-
LV maximal wall thickness (mm)				
Mean ±SD	**10.3 ± 2**	**9.7±1.6**	**10.8±2.2**	**0.081**
Median (IQR)	10 (9 – 11)	10(8.5 – 10)	11(9 – 13)	-
LV minimal wall thickness (mm)				
Mean ±SD	**6.89 ±1.3**	**6.9±1**	**6.8±1.6**	**0.810**
Median (IQR)	7 (6 – 8)	7(6 - 8)	7 (5.8 – 8)	-
LV RWMA, n (%)	4 (11.4)	1 (5.9)	3 (16.7)	0.316
RV RWMA, n (%)	9 (25.7)	2 (11.8)	7 (38.9)	0.067

*Non-parametric data – confirmed using visualization of the histogram and Shapiro-Wilk test for normality < 0.05

LVEF – Left Ventricular Ejection Fraction

LVEDD – Left Ventricular End-Diastolic Diameter

BSA – Body Surface Area

RVEF – Right Ventricular Ejection Fraction

RVEDD – Right Ventricular End-Diastolic Diameter

RWMA – Regional Wall Motion Abnormality

DISCUSSION AND CONCLUSION

Discussion

LGE CMR and SAECG are complementary investigations providing similar information in the detection and evaluation of fibrofatty change in ARVC and other cardiomyopathies. Whilst SAECG is a relatively cheap and ubiquitous investigation modality, CMR is a scarce resource in the South African context. Comparing the SAECG parameters (fQRS, LAS40, RMS40) with LGE in patients with definitive ARVC and other cardiomyopathies such as HCM and DCM we found no correlation. Our study therefore does not support a modification or revision of the current Task Force Criteria[6] to include LGE as one of the diagnostic criteria as a means of further increasing the diagnostic sensitivity of CMR.

We found patients presented at a younger age and were more likely to be male in keeping with known epidemiology as ARVC patients accounted for nearly fifty percent of the entire cohort. We found all patients were symptomatic at presentation; palpitations being the most prevalent symptom (77%), followed by pre-syncope (42.9%), chest pain (40%), syncope (37.1%) and dyspnoea (9%) with no significant statistical difference between those with and without LGE on CMR ($p = 0.289$). We found 28% had VT at presentation but unfortunately the morphology of the VT had not been characterised, 5.7% presented having survived cardiac arrest, 46% had documented VT on enrolment or follow-up and 43% had an ICD inserted subsequent to their initial presentation. Although VT and SCD were more frequently reported in LGE positive patients compared to LGE negative patients, the differences between the groups were not statistically significant (VT, 50% versus 41.2%, p 0.521; SCD, 11.1% versus 0%, $p = 0.157$); a significant finding was expected as the frequency of VT is dependent on the severity of the disease[3].

In comparing the SAECG to LGE CMR, we found the unfiltered QRS tended to be longer in patients with LGE compared to those without LGE (95.9 ±9.9 vs 88.1 ±10.3), this finding however was not statistically significant. Late potentials were more prevalent in patients with LGE on CMR compared to those without (61.1% vs 35.3% p = 0.127). Kamath et al examined the diagnostic and clinical value of the SAECG in a population of 87 genotyped ARVC probands diagnosed as affected or borderline by Task Force Criteria without the SAECG criterion against 103 controls and found that using 1 of 3 SAECG criteria contributed to increased sensitivity and specificity for the diagnosis of ARVC.[20] Further analysis of the late potential parameters revealed RMS40 and fQRS duration had the greatest difference between the two groups (15% and 14.7%, respectively vs. 9.4% for HFLA < 40μV; p = 0.555). The median fQRS duration in those with LGE was prolonged, 114ms (IQR 102.3 – 119) compared to 111ms (IQR 99.5 -130) in those without. The median RMS40 was lower 23.5 μV (IQR 14.3 – 47.5) in the group with LGE when compared to 33 μV (IQR 18.5 – 43.5) in the other. A one-way analysis of variance conducted for each of the SAECG parameters found the correlation to LGE not statistically significant.

Various studies have compared SAECG against other Task Force modalities in the diagnosis of ARVC with varying results. A study by Park et al correlating 2D echocardiography and SAECG in 33 ARVC patients found that the RVOT was the most frequently involved segment in ARVC and there was no significant correlation between parameters of the SAECG and 2D echocardiography for the entire patient population.[21] Another study correlating SAECG with left and right endo-myocardial biopsy in 38 patients with VT and no clinical evidence of structural heart disease concluded the presence of late QRS potentials on the SAECG is useful in identifying patients with VT without clinically apparent heart disease who, despite normal function, have a moderate increase in myocardial fibrosis on biopsy.[22]

We found the CMR measurements of LVEF and LVEDV index means to be within normal range when compared to the findings of Hudsmith et al who obtained LV and RV

measurements in 108 healthy volunteers[23]. The vast majority of patients in the cohort had definite ARVC and thus it was expected that there would be a significant difference of LVEF and LVEDV index means as the LV is affected in 75% cases of ARVC especially in phenotypes with early and predominant LV involvement[24]. The RVEF and RVEDV index means were expected and found to be lower than those of healthy volunteers as RV dilatation and dysfunction are the hallmarks of ARVC diagnosis but this result was confounded by the small population size as evident in the wide confidence interval. The lower values did not, however, meet the 2010 ARVC Revised TFC for diagnosis of ARVC. The difference in the medians of the RVEDV index of patients with and without LGE was significant suggesting correlation between a high RVEDV index and LGE. The LGE patterns of the RV were not assessed further to delineate different patterns of ARVC. Although our study showed no correlation between SAECG and LGE in predicting myocardial scar tissue related ventricular arrhythmias and in the diagnosis of ARVC; a meta-analysis of 9 studies involving 1488 patients with non-ischemic cardiomyopathy followed on average for 30 months noted LGE presence in 38% of patients and was associated with an odds ratio of 3.3 for mortality and 5.3 for sudden cardiac death (SCD) or aborted SCD.[25] Tandri et al evaluated the role of LGE CMR for non-invasive detection of fibrosis in ARVC and found CMR to have an excellent correlation with histopathology and predicted inducible VT on programmed electrical stimulation.[14]

Our study has several limitations. The study included a small sample of patients and thus caution must be exercised in extrapolating the findings to a larger cohort of patients. It is also imperative to mention the base for IMHOTEP ARVC Registry is a tertiary institution, Groote Schuur Hospital where patients with a clinical suspicion of cardiomyopathy are referred to by other institutions. Referral bias may have, therefore, influenced features of the study population.

CONCLUSION

Whilst SAECG is a known and reliable non-invasive study method in detecting myocardial fibrosis we have not shown its correlation to the presence of CMR LGE alone. This finding suggests fragmented electrical activity might appear with no significant relation to fibrofatty changes, necrosis and/or inflammation in the myocardium. However, further larger studies that quantify LGE extent are warranted to definitively elucidate the correlation to SAECG.

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ANNEXURES

Table 1. Comparison of Original and Revised Task Force Criteria

Original Task Force Criteria	Revised Task Force Criteria
I. Global or regional dysfunction and structural alterations*	
Major	
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the RV	**By 2D echo:** • Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) — *or* fractional area change ≤33% **By MRI:** • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) — *or* RV ejection fraction ≤40% **By RV angiography:** • Regional RV akinesia, dyskinesia, or aneurysm
Minor	
• Mild global RV dilatation and/or ejection fraction reduction with normal LV • Mild segmental dilatation of the RV • Regional RV hypokinesia	**By 2D echo:** • Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): — PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) — PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) — *or* fractional area change >33% to ≤40% **By MRI:** • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) — *or* RV ejection fraction >40% to ≤45%
II. Tissue characterization of wall	
Major	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	
	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	
	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	
• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)	• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block

(*Continued*)

ANNEXURE

Table 1. Continued

Original Task Force Criteria	Revised Task Force Criteria
IV. Depolarization/conduction abnormalities	
Major	
• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)
Minor	
• Late potentials (SAECG)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
V. Arrhythmias	
Major	
	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	
• Left bundle-branch block–type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) • Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
Major	
• Familial disease confirmed at necropsy or surgery	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	
• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D • Familial history (clinical diagnosis based on present criteria)	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.