Differentiating hereditary arrhythmogenic right ventricular cardiomyopathy from cardiac sarcoidosis fulfilling 2010 ARVC Task Force Criteria

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Original Article

Differentiating Hereditary Arrhythmogenic Right Ventricular Cardiomyopathy from Cardiac Sarcoidosis Fulfilling 2010 ARVC Task Force Criteria

Short title: ARVC and Sarcoidosis

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Abstract

Background: Cardiac sarcoidosis (CS) may resemble the clinical presentation of arrhythmogenic right ventricular cardiomyopathy (ARVC).

Objective: goal of our study was identification of clinical variables to better discriminate between patients with genetically-determined ARVC and CS fulfilling definite ARVC 2010 TFC.

Methods: In this multicenter study, 10 patients with CS fulfilling definite 2010 ARVC TFC were age-and gender matched with 10 genetically-proven ARVC patients. A cardiac 18F-FDG PET-scan was required to be included in this study.

Results: The 2010 ARVC TFC did not reliably differentiate between the two diseases. CS patients presented with longer PR-intervals, advanced AVB, and a longer QRS-duration ($p < 0.001$; and $p=0.009$, respectively), while T wave inversions (TWI) in peripheral leads were more common in ARVC ($p=0.009$). CS patients presented with more extensive LV involvement and a lower LVEF, while ARVC patients had a larger RVOT ($p=0.044$). PET scan positivity was only present in CS patients (90% vs 0%).

Conclusion: The 2010 TFC do not reliably differentiate between CS patients fulfilling 2010 TFC and hereditary ARVC. A prolonged PR interval, advanced AVB, longer QRS duration, RV apical involvement, a reduced LVEF, and a positive 18F-FDG PET scan should raise the suspicion of CS, whereas larger RVOT dimensions and peripheral TWI favor the diagnosis of hereditary ARVC.

Keywords: cardiac sarcoidosis; arrhyhtmogenic right ventricular cardiomyopathy; international task force criteria; cardiomyopathy; genetic

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable cardiomyopathy characterized by fibro-fatty infiltration, predominantly of the right ventricle (RV)[1]. Pathogenic genetic variants encoding for proteins of the connexome are involved in its pathogenesis[2]. Diagnosis requires a multi-modality evaluation and is established by fulfillment of the Revised 2010 International Task Force Criteria (TFC)[3]. Although constituting the current diagnostic gold standard, previous studies suggest that the TFC are not very specific for ARVC, and that the TFC cannot reliably differentiate between hereditary ARVC and some of its phenocopies[4–8].

Sarcoidosis is a systematic inflammatory disease characterized by the formation of non-caseating granulomas. Whereas the lungs are involved in approximately 90% of patients, cardiac involvement (cardiac sarcoidosis, CS) has been reported in up to 40% of the cases. CS shares several clinical and morphological features with genetically-determined ARVC[9,10]. Previous studies have shown a considerable overlap between the two entities, which can render correct diagnosis very challenging[9,11–13].

Until now, only one study compared clinical characteristics between genetically-determined ARVC and CS fulfilling definite 2010 ARVC TFC[13]. The authors showed that PR interval prolongation and high-grade atrioventricular block (AVB) were exclusively associated with CS, and significant left ventricular (LV) dysfunction and myocardial delayed enhancement of the septum were more frequently seen in those with CS. However, neither the utility of cardiac 18F-fluordeoxyglucose positron emission tomography (18F-FDG PET), nor potential differences in regional myocardial disease distribution were systematically assessed.

The goal of our study was the identification of clinical variables discriminating between patients with genetically-determined ARVC and CS fulfilling definite ARVC 2010 TFC in order to provide

information to clinicians about when to suspect CS in patients fulfilling the 2010 ARVC TFC criteria.

METHODS

Three high-volume centers (University Hospitals Zurich and Lausanne, Switzerland; Centro Cardiologico Monzino, Milan, Italy) were screened for all patients with a diagnosis of CS that also fulfilled the diagnostic 2010 ARVC TFC, and complied with the additional inclusion criteria (CS cohort (CS-C)). A 1:1 gender and age match of the CS-C was performed with patients with a definite ARVC diagnosis, carrying a pathogenic/likely pathogenic variant associated with ARVC (ARVC cohort (ARVC-C)). The overall population of the three registries included 343 ARVC patients among which matching was performed. The current study complies with the Declaration of Helsinki.

Inclusion criteria in detail:

Patients were included in the CS-C when they met the following inclusion criteria:

- Diagnosis of CS according to the most recent 2016 Japanese Cardiac Sarcoid Guidelines[14]
- Availability of a cardiac 18F-FDG PET scan, transthoracic echocardiogram (TTE) and a 12-lead surface ECG
- Meeting a definite diagnosis according to the ARVC 2010 TFC

Patients were included in the ARVC-C when they met the following inclusion criteria:

- Diagnosis of definite ARVC according to the 2010 TFC
- Positive genetic testing for pathogenic (Class V) or likely pathogenic (Class IV) variants in genes associated with ARVC according to the 2015 ACMG criteria[15]
- Availability of a cardiac 18F-FDG PET scan, TTE and a 12-lead surface ECG

- Appropriate age and gender match for a patient from the CS-C group

Data collection and analysis

Demographics, genetic and clinical data including baseline 12-lead ECG, 24-h Holter ECG, TTE, cardiac magnetic resonance tomography (CMR), 18F-FDG PET) and histological data were collected, analyzed by experienced cardiologists and pathologists, and stored into a de-identified centralized database. Data from 12-lead ECG were extracted: QRS length was defined as the longest duration of all depolarization deflection measured in the lead with the maximal QRS duration among all 12 leads, while QRS fragmentation was defined as the presence of additional deflections/notches at the beginning of the QRS, on top of the R wave, or in the nadir of the S wave in either 1 right precordial lead or in >1 lead including all remaining leads, as in previous studies[16]; RVOT dimensions and fractional area change (FAC) by TTE were assessed as previously described[17].

Statistical Analysis

All statistical analyses were performed using Jamovi, The Jamovi project (2020; Version 1.2 [Computer Software] [https://www.jamovi.org]) and STATA v 14.0 (StataCorp, TX, USA). Continuous variables are presented as mean ± standard deviation or as median [inter-quartile range [IQR]] as appropriate. Categorical variables are presented as counts (%). Comparison between variables was performed using a Student's t-test, a Mann-Whitney U-test, a Chi-squared test, or Fisher's Exact test, as appropriate, using a pre-specified alpha of significance < 0.05. Optimal cut-off values were calculated using Receiver Operator Characteristic (ROC) curves.

RESULTS

Study Cohort

The CS-C comprised of 10 patients (age 46.4±10.7 years, 2 (20%) females). All patients underwent cardiac or extra-cardiac biopsy for histological analysis: non-caseating granuloma was found in all patients (n = 5 at cardiac histology; n = 5 at peri-bronchial lymph-node biopsy). The ARVC-C consisted of 10 age- and gender-matched patients (age 46.4±9.3 years; 2 (20%) females), all harboring a pathogenic/likely pathogenic genetic variant associated with ARVC: *PKP-2*: n=6 (60%); *DSG-2*: n=3 (30%); *LMNA*: n=1 (10%); a complete list of the genetic variants is provided in Supplementary Table 1). ARVC diagnostic score according to the 2010 TFC was similar between the two groups (CS-C 6.3±1.6 vs ARVC-C 6.8±1.8; p = 0.262).

Clinical Characteristics

No significant differences in symptoms were observed (Table 1). Presentation with ventricular arrhythmias was observed in 9 patients (90%; 8 patients with sustained ventricular tachycardia (VT) and one with non-sustained VT), and 7 patients (70%; 6 patients with sustained VT and one with ventricular fibrillation) of the CS-C and ARVC-C, respectively (p=0.61), all VT presenting with a left-bundle branch block morphology.

12-lead ECG findings

Subjects in the CS-C presented with a longer PR-interval and a maximum QRS-duration compared to those in the ARVC-C (250.4±45.4 vs. 160.3±21.1 ms, p <0.001; and 113.7±9.1 vs 89.1±3.1 ms, p=0.009, respectively) (Table 1). Two patients in the CS-C presented with a Mobitz type 2 and III° AVB, respectively. No differences were found regarding QRS fragmentation, and R- and S-wave amplitudes in V1. T wave inversions (TWI) across peripheral leads were rare in CS-C (median TWI in peripheral leads: 0 [0–1]), while they were common in the ARVC- C (median TWI in peripheral leads 2 [1–3]) (p=0.009). No significant differences in TWI in the precordial leads were observed (median TWI in precordial leads 3 [2–4] vs 3 [2–5], for CS-C vs ARVC-C, respectively; p=0.47).

Morpho-functional characteristics at imaging

LV impairment was more common in the CS-C, with an LV ejection fraction (LVEF) of 45.9%±3.4 vs 56.9%±1.4 (p=0.007) for the CS-C and ARVC-C, respectively (Table 2). RVOT dimensions in the parasternal short axis (PSAX) and long axis (PLAX), and FAC were 31.4±8.5 vs 37.6±3.2 mm (p=0.044), 32.3±8.9 vs 36.2±2.8 mm (p=0.205), and 29.3±10.3 vs 27.5±5.8 (p=0.636), respectively.

CMR was available in 7 CS-C (70%) and 8 ARVC-C (80%) patients. RVEF determined by CMR was 41.1±3.3 vs 45.8±4.0 (p=0.385), respectively, and late gadolinium enhancement (LGE) was detected in 7/7 (100%) and 6/8 (75%) patients, respectively (p=0.467).

Integrating TTE and CMR data, LV regional wall motion abnormalities (RWMA) were detected in 9 (90%) vs two (20%) patients in the CS-C and ARVC-C, respectively (p=0.005), with more regions being involved in the CS-C cohort (mean myocardial segments with dys-/akinesia: 2.2±1.1in CS-C vs 0.8±1.0 in ARVC-C; p = 0.009). RWMA were more frequently observed in the LV anterior wall and in the septal area of the CS-C (40% vs 0%, p=0.087; 50% vs 10%, respectively, p=0.141). RWMA of the RV were present in all patients. RWMA were more common in the RV apex of the CS-C (80% vs 20%, p=0.023), whereas the lateral subtricuspid region was less frequently affected in the CS-C (50% vs 100%, p=0.033). An RV thrombus at TTE was only detected in two (20%) patients in the CS-C, both located in the RV apex. Fibro-fatty tissue detected by CMR was present in 6/8 (75%) patients with ARVC, as compared to one patient (1/7, 14%; p=0.048) with CS (Table 2).

All patients underwent a cardiac 18F-FDG PET scan. Nine out of 10 patients (90%) in the CS-C presented with a positive 18-FDG PET; the tenth patient was under immunosuppressive therapy at the time of the negative PET scan. All the patients from the ARVC-C had a negative 18-FDG PET scan (p<0.001).

Assessment of 2010 TFC

Patients in the CS-C and ARVC-C both fulfilled the 2010 ARVC TFC to a similar extent (Table 3). No significant differences were found across the six different diagnostic categories between the two cohorts, apart from category VI (family history/genetics), as expected by the inclusion criteria.

Best criteria to discriminate between CS and ARVC

ROC curves were calculated for PR interval, QRS duration, and RVOT dimensions (Figure 1, Panel A–D). The best cut-off values to maximize correct CS vs ARVC diagnosis were: a PR interval ≥196 ms (sensitivity 100%; specificity 100%; AUC 1.00 [1.00–1.00]); QRS duration ≥96 ms (sensitivity 80%; specificity 70%; AUC 0.85 [0.69–1]); RVOT dimension measured in the PSAX ≥35 mm (sensitivity 100%; specificity 90%; AUC: 0.90 [0.71–1.00]; RVOT dimension measured in the PLAX ≥33 mm (sensitivity 100%; specificity 70%; AUC: 0.82 [0.61–1].

Discussion

In this study comparing patients with CS fulfilling definite 2010 ARVC TFC to genetically proven patients with definite ARVC, the main findings were as follows:

1. The 2010 ARVC TFC did not reliably differentiate between the two diseases
2. RVOT dilation ≥35mm and peripheral TWI favored the diagnosis of ARVC
3. CS often involved the RV apex and septum, whereas ARVC typically affected the subtricuspid region of the RV free wall
4. LVEF was generally lower in CS
5. A prolonged PR interval, advanced AVB, a longer QRS duration, and a positive 18-FDG PET favored a diagnosis of CS

ARVC and Phenocopies

The diagnosis of ARVC is established by applying the 2010 TFC. Although sensitive, the specificity of the 2010 TFC has been questioned[4,5,9]. CS represents one of the most common phenocopies of ARVC, and it is listed under the umbrella of the recently proposed "arrhythmogenic cardiomyopathy" definition[18]. *Vasaiwala et al* showed that about 15% of patients previously diagnosed with ARVC were re-classified as CS based on invasive findings [8]. However, differentiation between ARVC and CS has important consequences for therapy and genetic counseling[18–21]. Therefore, the goal of our study was the identification of clinical variables to better discriminate between patients with genetically-determined ARVC and CS fulfilling definite ARVC 2010 TFC.

2010 ARVC Task Force Criteria

The 2010 ARVC TFC did not reliably differentiate between the two diseases, with both cohorts showing similar ARVC TF scores. Among the parameters currently employed by the 2010 TFC, only RVOT dimension in the PSAX view reliably discriminated between both phenocopies (Figure 2). A cut-off ≥35 mm was associated with a diagnosis of ARVC. The 2010 TFC provide a cut-off of 36 mm (PSAX) in the presence of RV RWMA as a major criterion: the good agreement between this criterion and our cut-off indicates that this parameter is useful for discriminating both entities.

12-lead ECG

The number of leads with TWI and their distribution in the precordial leads were comparable between the two cohorts. The TWI criteria proposed by the 2010 TFC failed to correctly differentiate CS from ARVC. Interestingly, TWI in the peripheral leads were significantly more common in ARVC, as previously described[22]. Extending the ECG analysis, both PR-interval and QRS duration were significantly different in the two cohorts. CS patients presented with longer PR intervals and wider QRS complexes (Figure 3). Data regarding the PR interval and QRS duration were in line with findings reported by *Philips et al*[13] and a more recent study by *Hoogendorn et al*[23].

A PR-interval ≥196 ms was sensitive and specific for CS. Although single patient level data are not directly available, the PR intervals reported by *Philips et al* had an IQR of 198–260 ms, indicating high reproducibility with the cut-offs found in our study. Of note, regardless of a frequent involvement of the LV in patients with CS, all VT observed in the CS cohort presented a LBBB morphology, which may be related to low patient numbers, a mean LVEF >45%, and the selection of patients that all fulfilled 2010 TFC.; Yet, this finding suggests that VT morphology may not be of great help in differentiating between CS fulfilling 2010 TFC and genetic ARVC.

Assessment of Regional Wall Motion and Tissue characterization

We observed significant differences in RWMA between CS and ARVC, which may help in differentiating between the two conditions. CS patients presented with a more extensive LV involvement than ARVC patients, a significantly lower LVEF, and a higher number of segments being affected, which is in line with the two previous studies by *Philips et al*[13] and *Hoogendorn et al*[23]. There was a trend towards more frequent involvement of the LV anterior wall and septum in CS. Furthermore, although both cohorts presented with RV-RWMA, CS more frequently involved the apical region (Figure 3). Of note, RV thrombus was only found in CS, being confined to the RV apex. However, previous studies have reported the presence of RV thrombi in patients with ARVC as well, and our finding may be driven by the low numerosity of our sample[24]. ARVC was associated with more frequent involvement of the RV lateral subtricuspid region, typically showing aneurysms in that area. Fibro-fatty infiltration has been suggested as a pathologic hallmark of ARVC[25]. Among the 8 patients who underwent CMR in the ARVC cohort, 6 of them had fibro-fatty infiltration in various areas. Three EMB samples from the CS-C fulfilled a minor criterion according to the 2010 TFC, and one patient with CS even presented with septal and LV infero-lateral fibro-fatty infiltration in the absence of granuloma in these areas. EMB has been suggested as a diagnostic tie-breaker in complex cases[26]: however, it is of paramount importance to target the diseased area, e.g. by electroanatomical voltage mapping-guided myocardial biopsy[27,28].

Assessing of Myocardial Inflammation

A positive cardiac 18F-FDG PET scan was found to be helpful in differentiating between CS and ARVC. Nine out of 10 patients with CS had a positive PET scan of the LV, five of them presenting with RV involvement as well (Figure 4). We therefore suggest that 18F-FDG PET scan should be considered to exclude CS in patients fulfilling definite 2010 ARVC TFC, particularly if results of genetic testing are ambiguous. However, the specificity of a cardiac 18F-FDG PET scan has been recently questioned by *Protonotarios et al* showing that 7/16 patients with ARVC fulfilling 2010 TFC presented with a positive PET scan. Of note, 2/7 patients were later reclassified as CS, but the remaining five patients (of which two harbored a DSP variant) were considered to have ARVC, regardless of PET positivity. Hence, PET positivity may render CS more likely, but it is important to keep in mind that "hot inflammatory phases" of ARVC can lead to positive PET findings[29]. In addition, positivity at a 18F-FDG PET exam in patients with CS also depends on the phase of disease activity, with some chronic disease phases (so called "burned out" CS) potentially resulting negative at this advanced stage.

Limitations

Since both entities are rare and our inclusion criteria were stringent, patient numbers were low despite our multicenter approach. Only genetically-proven ARVC patients were included. However, no DSP variants were present in the final ARVC-C, and therefore our findings cannot be extrapolated to patients with DSP variants[11]. Given the low numerosity of the study, absolute values presented as cut-offs are in need of further validations and further refining from external and multicentered larger cohorts are needed.

Conclusions

The 2010 TFC do not reliably differentiate between CS patients fulfilling 2010 TFC and hereditary ARVC. A prolonged PR interval, advanced AVB, longer QRS duration, RV apical involvement, a reduced LVEF, and a positive 18F-FDG PET scan should raise the suspicion of CS, whereas larger RVOT dimensions and peripheral TWI favor the diagnosis of hereditary ARVC.

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Table 1 – Comparison of demographic and electrocardiographic characteristics of the two cohorts

	Cardiac Sarcoidosis (n=10)	**Arrhythmogenic Right Ventricular Cardiomyopathy (n=10)**	**p**
Age, mean±s.d.(years)	46.6±10.7	46.6±9.3	1.000
Male, n(%)	8 (80)	8(80)	1.000
ARVC 2010 TF score, mean±s.d.	6.3±1.6	6.8±1.8	0.262
Athletes, n(%)	2(20)	3(30)	0.600
VA at presentation, n(%)	9(90)	7(70)	0.582
Non-sustained VT, n(%)	1(10)	0	1.000
Sustained VT, n(%)	8(80)	6(60)	0.628
Ventricular fibrillation, n(%)	0	1(10)	1.000
Advanced AV block at presentation, n(%)	2(20)	0	
PR-interval, mean±s.d (ms)	250.4±45.4	160.3±21.1	**< 0.001**
QRS duration, mean±s.d (ms)	113.7±9.1	89.1±3.1	**0.009**
QRS fragmentation, n(%)	5(50)	3(30)	0.650
QRS fragmentation in peripheral leads, n(%)	4(40)	2(20)	0.628
QRS fragmentation in precordial leads, n(%)	5(50)	2(20)	0.350
R wave amplitude in V1, mean±s.d (mV)	0.16±0.04	0.18±0.04	0.58
S wave amplitude in V1, mean±s.d (mV)	0.65±0.13	0.58±0.09	0.32
No of TWI at 12-lead baseline ECG, median [IQR]	3 [2–4]	5 [4–7]	0.065
No of TWI in peripheral leads, median [IQR]	0 [0–1]	2 [1–3]	**0.009**
TWI in I, n(%)	0	2(20)	0.474
TWI in II, n(%)	0	3(30)	0.211
TWI in III, n(%)	4(40)	6(60)	0.656
TWI in aVF, n(%)	2(20)	5(50)	0.350
TWI in aVL, n(%)	0	3(30)	0.211
No of TWI in precordial leads, median [IQR]	3 [2–4]	3 [2–5]	0.468
TWI in V1, n(%)	8(80)	8(80)	1.000
TWI in V2, n(%)	7(70)	7(70)	1.000
TWI in V3, n(%)	7(70)	6(60)	1.000
TWI in V4, n(%)	3(30)	5(50)	1.000
TWI in V5, n(%)	1(10)	4(40)	0.300
TWI in V6, n(%)	1(10)	2(20)	1.000

AV: atrio-ventricular; IQR: interquartile range; TF: Task Force; TWI: T-wave inversion; VA: Ventricular arrhythmias; VT: ventricular tachycardia

Table 2 – Comparison of imaging findings between the two cohorts

	Cardiac Sarcoidosis (n=10)	**Arrhythmogenic Right Ventricular Cardiomyopathy (n=10)**	**p**
TTE, n (%)	10(100)	10(100)	1.000
LVEF, mean±s.d.	45.9±3.4	56.9±1.4	**0.007**
FAC, mean±s.d.	29.3±10.3	27.5±5.8	0.636
RVOT PSAX. mean±s.d.	31.4±8.5	37.6±3.2	**0.044**
RVOT PLAX, mean±s.d.	32.3±8.9	36.2±2.8	0.205
CMR, n (%)	7 (70)	8 (80)	1.000
RVEF, n(%)	41.1±3.3	45.8±4.0	0.385
LGE, n(%)	7(100)	6(75)	0.467
LV involvement, n(%)	5(71)	1(14)	0.103
Antero-lateral wall, n(%)	3(43)	1(14)	0.282
Infero-lateral wall, n(%)	1(14)	1(14)	1.000
Septum, n(%)	6(86)	4 (50)	0.282
Apex, n(%)	3(43)	0	0.077
RV involvement, n(%)	5(71)	5(63)	1.000
Fibro-fatty infiltration, n(%)	1(14)	6(75)	0.041
Regional Wall Motion Analysis			
LV dys/akinesia, n **(%)**	9(90)	2(20)	**0.005**
Anterior wall, n(%)	4(40)	0	0.087
Inferior wall, n(%)	3(30)	2(20)	1.000
Lateral wall, n(%)	4(40)	2(20)	0.628
Septum, n(%)	5(50)	1(10)	0.141
Apex, n(%)	6(60)	3(30)	0.370
No of areas with LV dys/akinesia, mean±s.d.	2.2±1.1	0.8±1.0	**0.009**
RV dys/akinesia, n(%)	10(100)	10(100)	1.000
Subtricuspid free wall, n(%)	5(50)	10(100)	**0.033**
Inferior wall, n(%)	7(70)	7(70)	1.000
RVOT, n(%)	5(50)	3(30)	0.650
Septum, n(%)	4(40)	0	0.087
Apex, n(%)	8(80)	2(20)	**0.023**
No of areas with RV dys/akinesia, mean±s.d.	2.1±0.9	1.8±1.0	0.492
Subtricuspid aneurysm, n(%)	2(20)	9(90)	**0.005**
RV Thrombus, n (%)	2 (20)	0	0.474
Cardiac 18F-FDG PET, n(%)	10(100)	10(100)	1.000
Positive, n(%)	9(90)	0	**<0.001**
RV positivity, n(%)	5(50)	0	**0.033**
LV positivity, n(%)	9(90)	0	**<0.001**
Septum, n(%)	*5(50)*	*0*	***0.033***
Apex, n(%)	*2(20)*	*0*	*0.474*
Antero-lateral LV, n(%)	*6(60)*	*0*	***0.011***
Infero-lateral LV, n(%)	*2(20)*	*0*	*0.474*

CMR: cardiac magnetic resonance tomography; FAC: fractional area change; LGE: late gadolinium enhancement; LV: left ventricle; LVEF: left ventricular ejection fraction; 18F-FDG PET: 18-fluordeoxyglucose positron emission tomography; PLAX: parasternal long axis; PSAX: parasternal

short axis; RV: right ventricle; RVEF: right ventricular ejection fraction; RVOT: right ventricular outflow tract; TTE: transthoracic echocardiography;

	Cardiac Sarcoidosis (n=10)	**Arrhythmogenic Right Ventricular Cardiomyopathy (n=10)**	**p**
No of Major Criteria	2 [2–3]	3 [2–4]	0.235
No of Minor Criteria	1 [1–2]	1 [0–1]	0.191
Category I			
Major, n(%)	9(90)	10(100)	1.000
Minor, n(%)	1(10)	0	1.000
Category II			
Major, n(%)	0	0	1.000
Minor, n(%)	4(40)	0	0.087
Category III			
Major, n(%)	5(50)	5(50)	1.000
Minor, n(%)	2(20)	2(20)	1.000
Category IV			
Major, n(%)	3(30)	3(30)	1.000
Minor, n(%)	4(40)	1(10)	0.303
Category V			

Table 3 – Comparison of 2010 Task Force diagnostic criteria positivity between the two cohorts

Major, n(%)	7(70)	2(20)	0.070
Minor, n(%)	2(20)	5(50)	0.350
Category VI			
Major, n(%)	0	10(100)	**< 0.001**
Minor, n(%)	2 (20)	0	0.474

Figure 1 – ROC Curves for the best electrocardiographic and echocardiographic parameters for discriminating cardiac sarcoidosis fulfilling the 2010 TFC from genetic ARVC

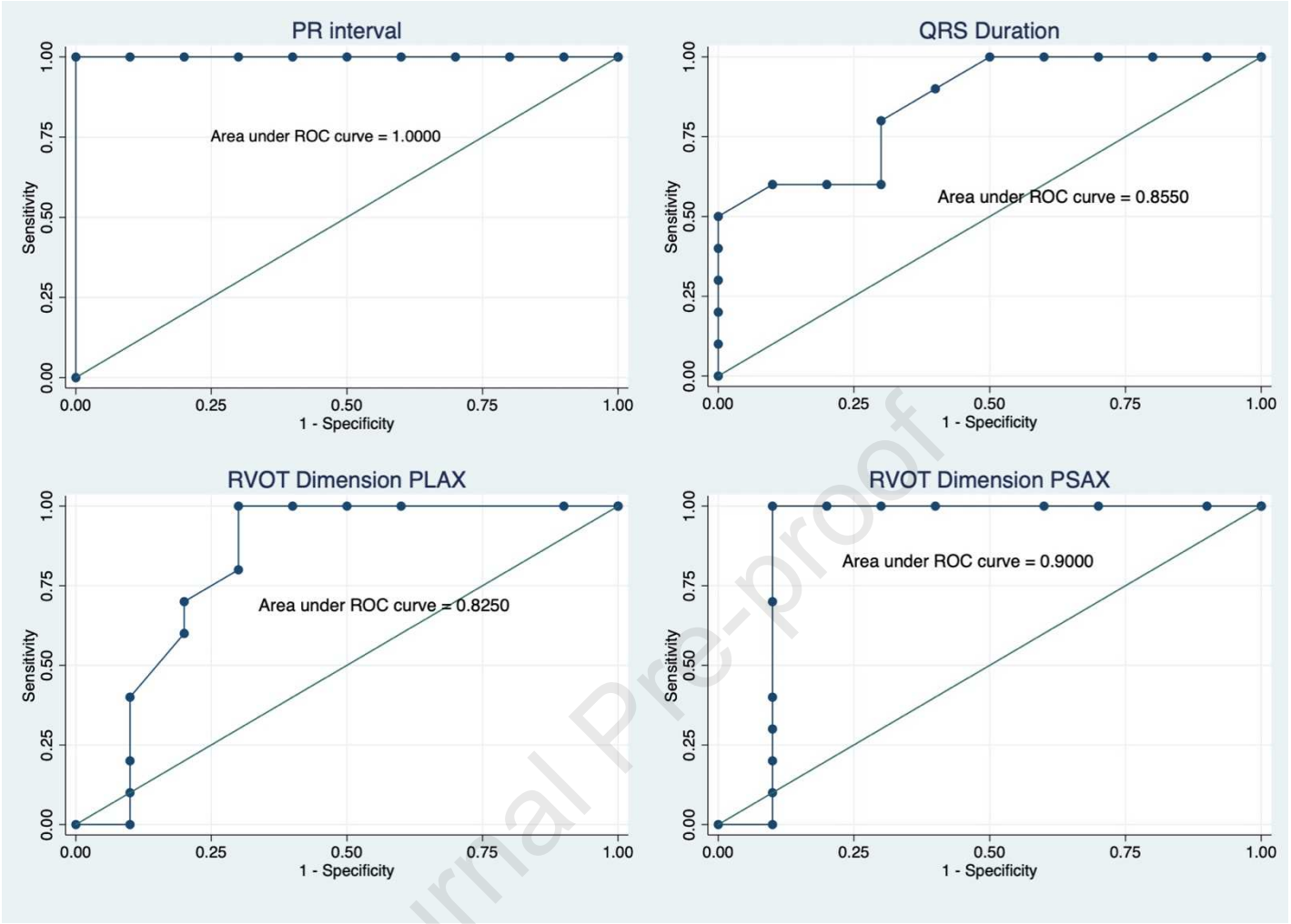


Figure 1 – ROC curves reporting diagnostic performance of values for PR interval, QRS duration, RVOT dimension in PSAX and PLAX, respectively.

PLAX: parasternal long axis; PSAX: parasternal short axis; RVOT: right ventricular outflow tract

Figure 2

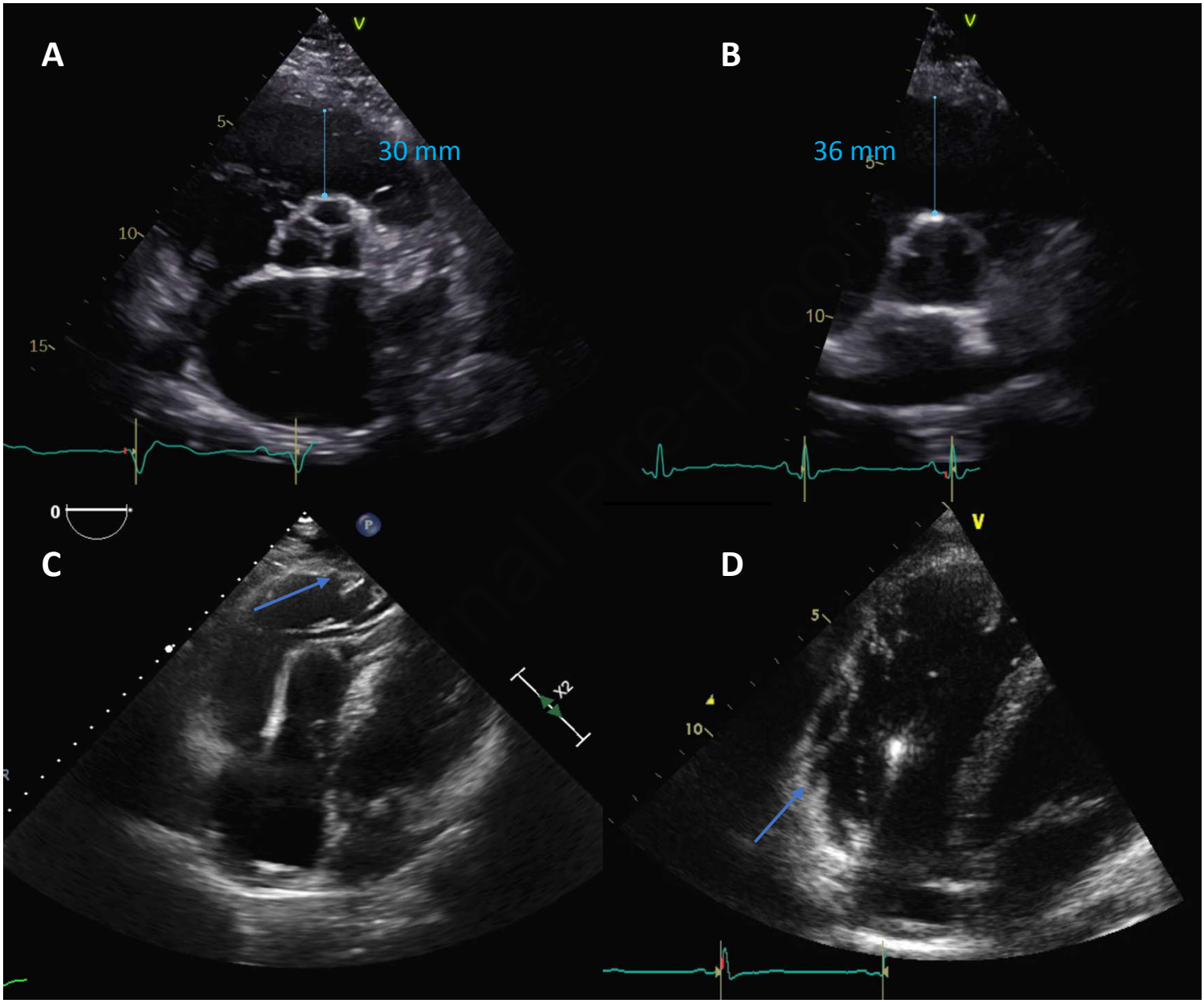


Figure 2: Transthoracic echocardiographic findings: A) RVOT dimension in PSAX view of a CS patient fulfilling the 2010 TFC; B) RVOT dimension in PSAX view of a genetic ARVC patient; C) Apical 4-chamber view focusing on the RV of a CS patient, showing apical involvement and an

aneurysm (arrow); D) 4-chamber view of a genetic ARVC patient, showing a subtricuspid aneurysm in loco typico (arrow)

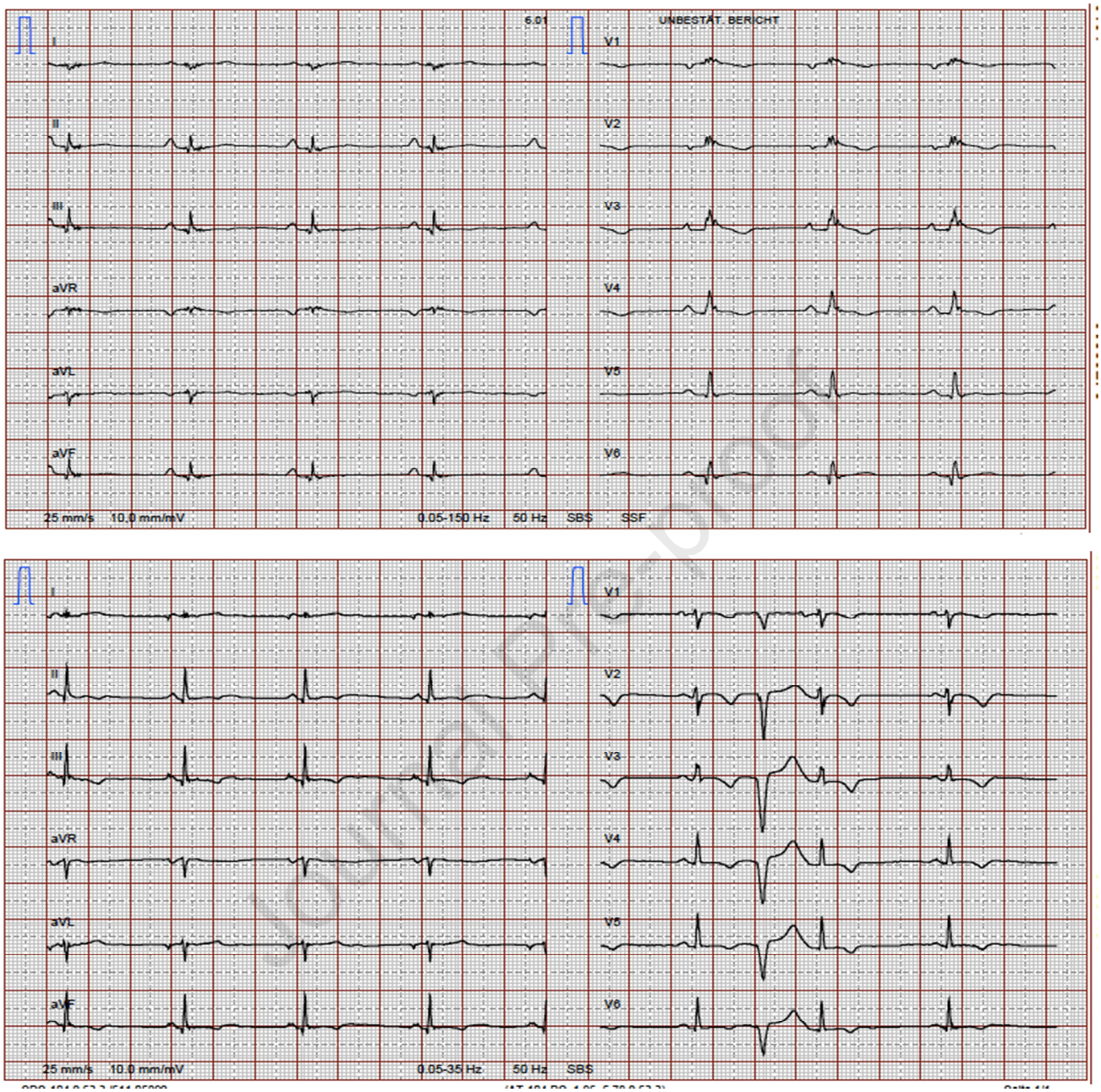


Figure 3

Figure 3: Upper tracing: 12-lead ECG from a patient with CS showing a prolonged PR interval (≥ optimal cut-off 196 ms) and a wide, fragmented QRS complex (≥ optimal cut-off 96 ms). T wave inversions in precordial leads (V1-V4) can be observed, fulfilling a major 2010 TF repolarization criterion.
Lower tracing: 12-lead ECG from a patient with ARVC, showing a normal PR interval and QRS duration, and T wave inversions in precordial (V1-V6) leads, fulfilling a major 2010 TF repolarization criterion, and additionally T wave inversions in the inferior (II, III, aVF) leads.

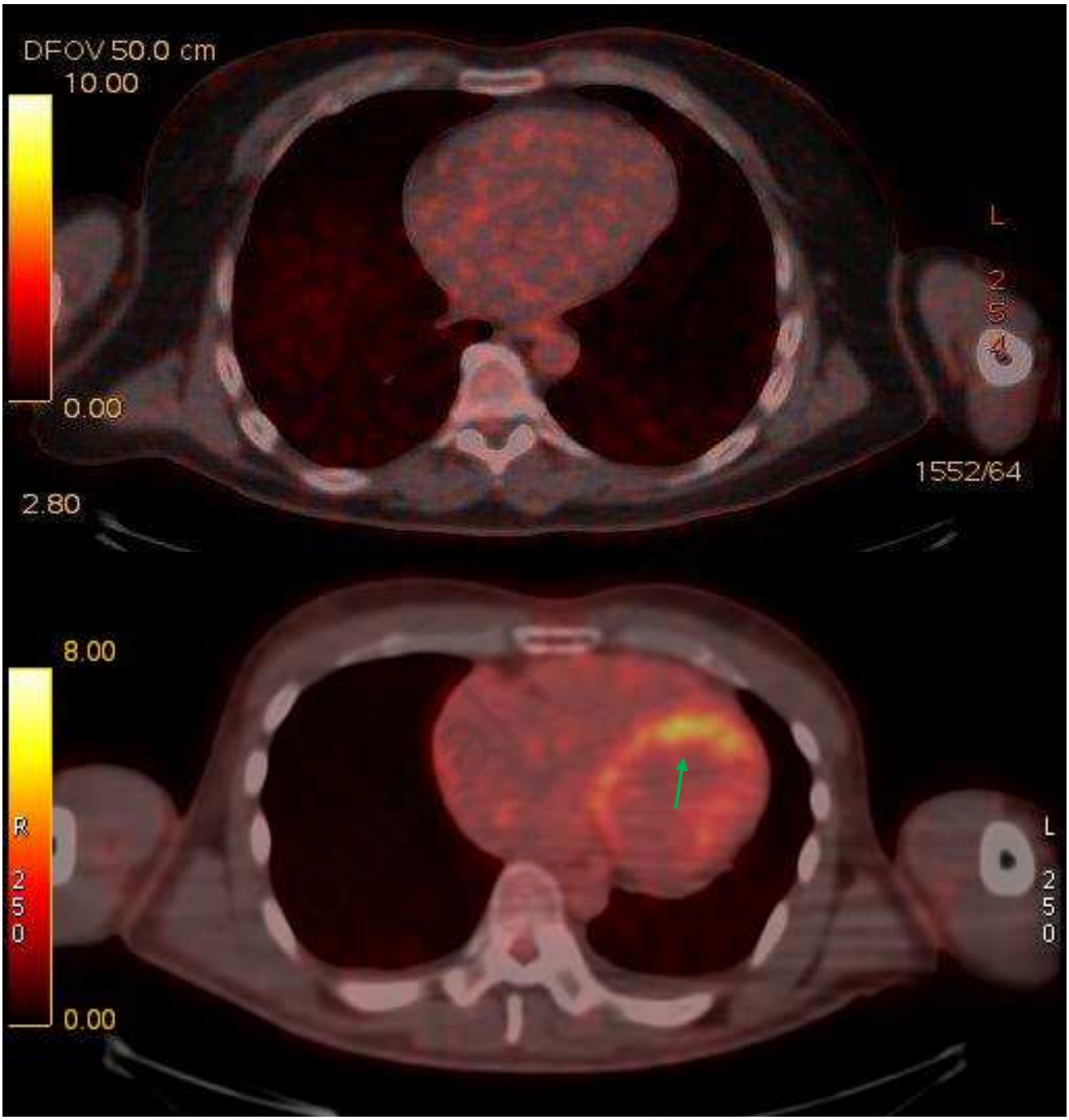
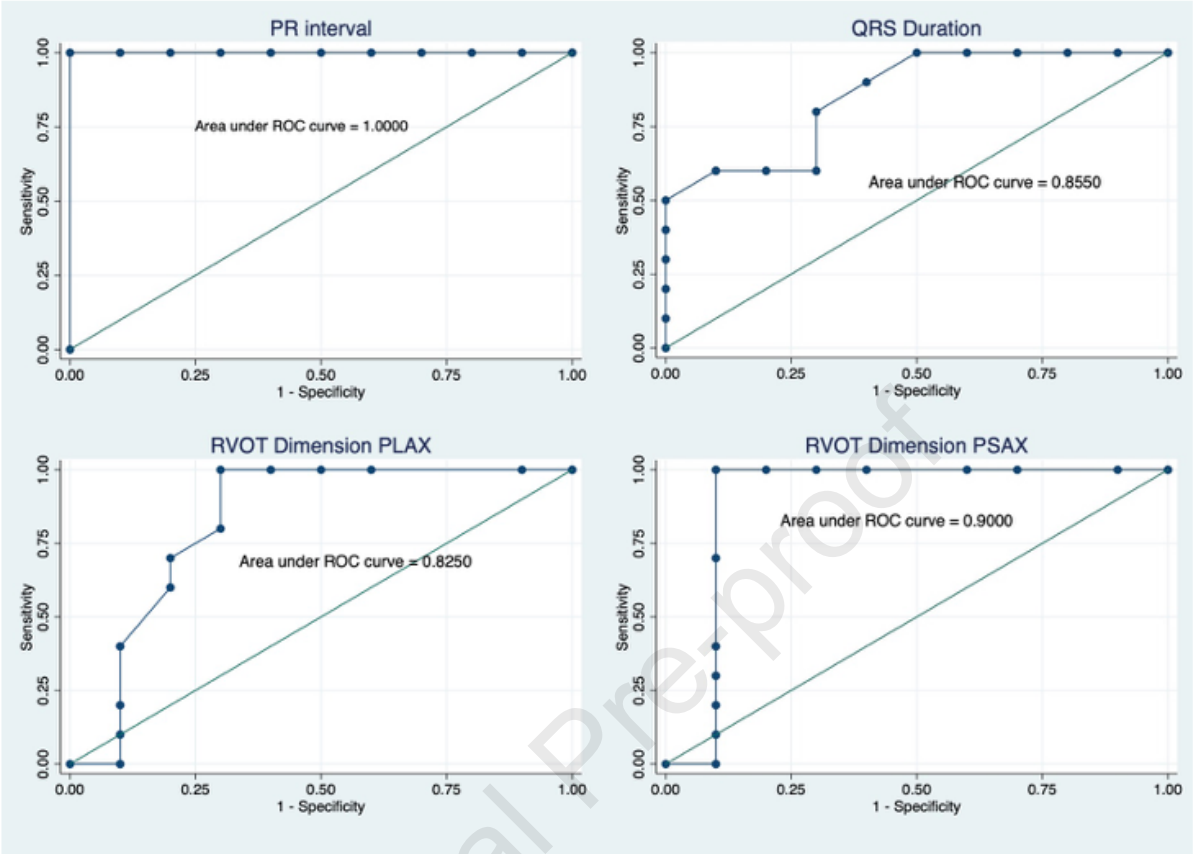
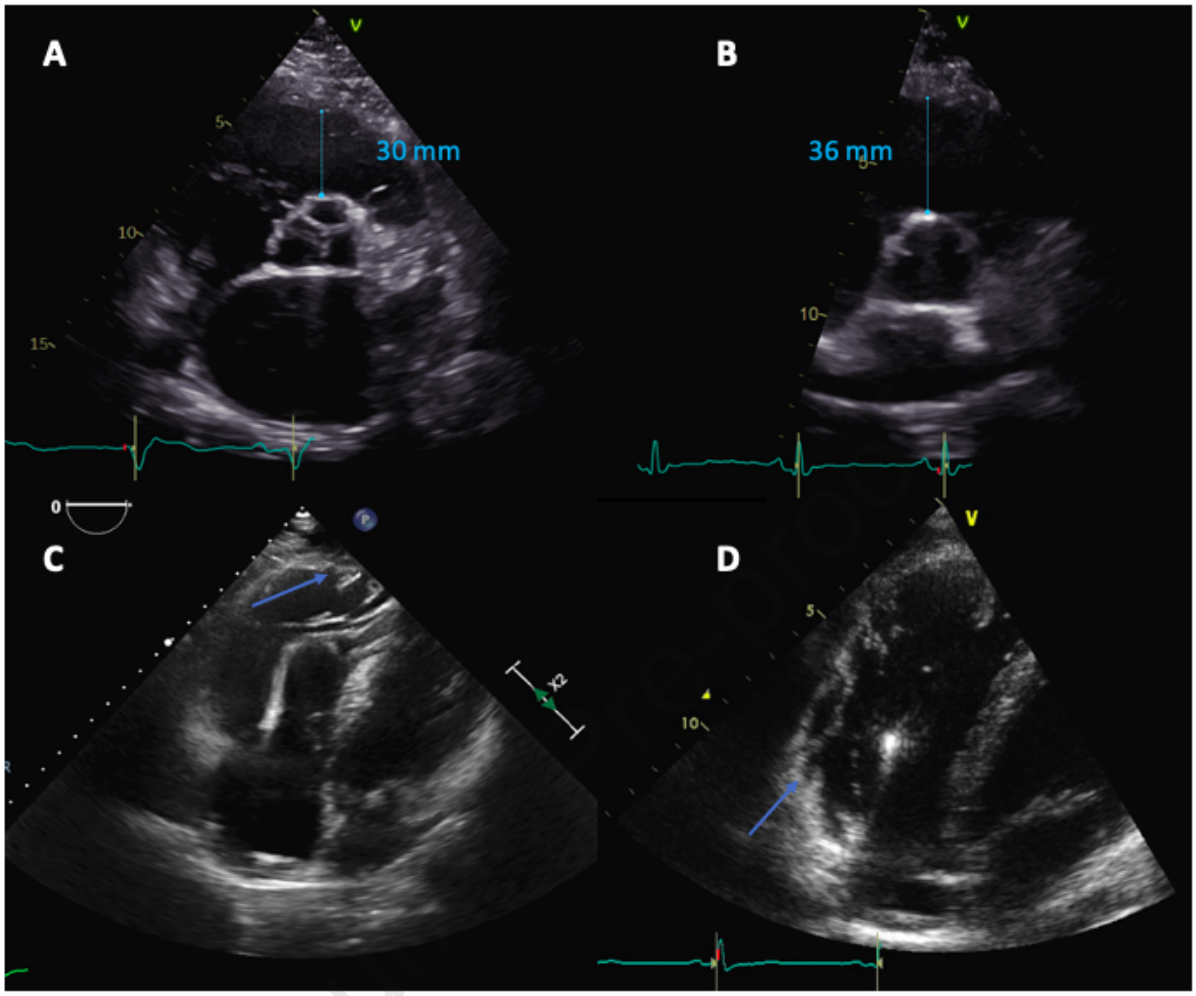


Figure 4

Figure 4: Upper Panel: 18-FDG PET of a genetic ARVC patient, showing no hypermetabolic activity at the myocardial level. Lower Panel: 18-FDG PET of a CS patient fulfilling the 2010 TFC, showing areas of hypermetabolic activity in the septal and anterior area of the LV (arrow).

18-FDG PET: 18-fluordeoxyglucose positron emission tomography

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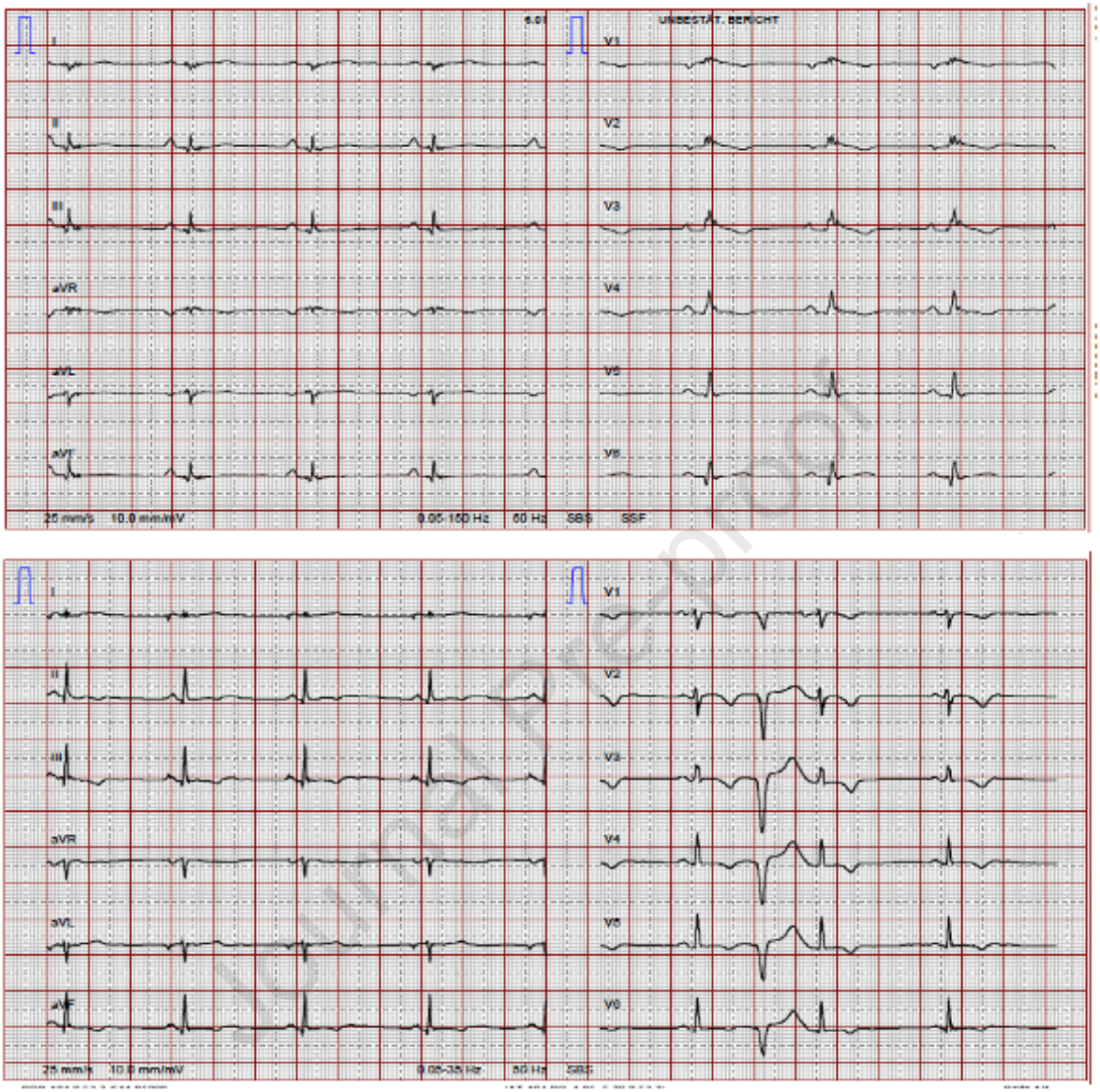
30 mm
B
36 mm
C
D


UNBESTÄT. BERICHT
I
II
III
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aVL
aVF
V1
V2
V3
V4
V5
V6
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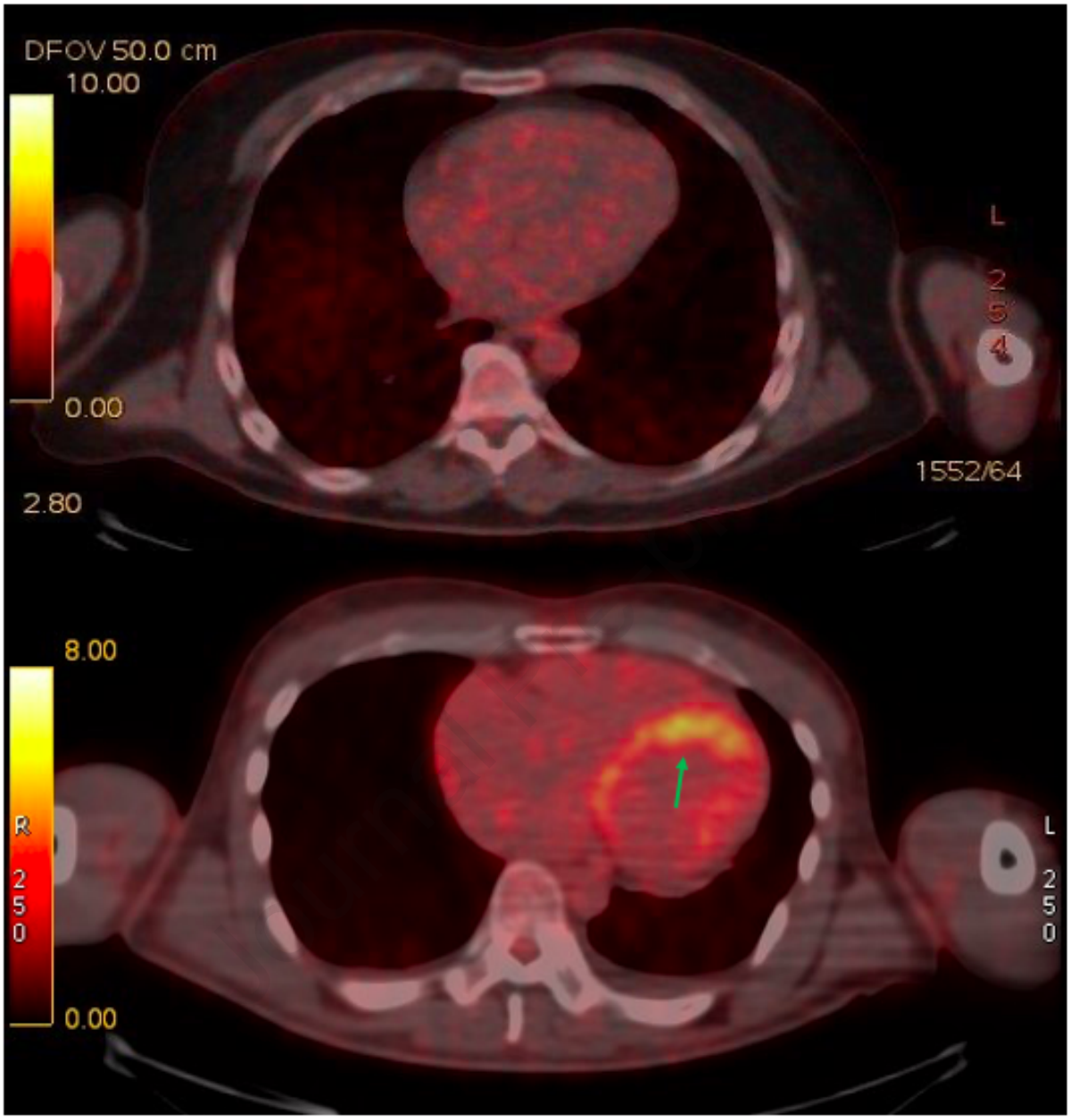
25 mm/s 10.0 mm/mV 0.05-35 Hz 50 Hz SBS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2.80
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1552/64
8.00
R
250
0.00
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250