Title: Improving diagnostic value of echocardiography in arrhythmogenic right ventricular cardiomyopathy using deformation imaging

Short title: Diagnostic value of deformation imaging in ARVC

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Improving diagnostic value of echocardiography in arrhythmogenic right ventricular cardiomyopathy using deformation imaging

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited cardiomyopathy diagnosed by a complex set of tests defined in the 2010 Task Force Criteria (TFC).[1] This includes echocardiography, which combines measures of right ventricular (RV) dilatation and function with subjective visual wall motion assessment to obtain diagnostic criteria. However, a recent clinical validation study of the TFC demonstrated that these echocardiographic criteria lack sensitivity for ARVC diagnosis. [2] Subtle wall motion abnormalities can be missed by visual assessment, hampering diagnosis. In contrast, echocardiographic deformation imaging is known for its high sensitivity for detection of wall motion abnormalities. The performance of deformation imaging within the TFC for ARVC diagnosis remains however unknown. We performed a head-to-head comparison of the diagnostic value of TFC visual wall motion assessment versus deformation imaging in a real-world cohort of consecutive patients evaluated for ARVC.

The study population was derived from a recently published study on TFC performance, which included 160 consecutive patients who were referred for ARVC evaluation at the UMC Utrecht, the Netherlands, between 2009-2011.[2] Of those, we included 59 patients who underwent an echocardiogram according to our current protocol[3] on a single vendor, allowing deformation analysis. The study was approved by the local ethics board.

In absence of a gold standard test for diagnosis of ARVC, the reference standard was diagnosis by consensus of 3 independent ARVC experts (JvdH/RH/AtR) who re-evaluated all available patient data, beyond the scope of the TFC, including a median follow-up of 5.9 years IQR[2.7-7.6 years] after the echocardiographic examination.[2]

All echocardiograms were performed with a Vivid 7 or E9 scanner and post-processed with EchoPac v.202 (GE Healthcare, Horten, Norway). The original clinical assessment of RV outflow tract dimensions, fractional area change and wall motion was used to determine conventional echocardiographic TFC.[1] In addition, RV deformation patterns of the subtricuspid area[3] were obtained by two experienced operators (FK/KT) blinded for clinical data. Deformation patterns were scored as either normal or abnormal, according to the presence of regional mechanical dysfunction (type II/III, as previously described in detail[3]). We evaluated the effect of replacing visual wall motion assessment with deformation imaging on the sensitivity, specificity and C-statistic of the echocardiographic TFC for ARVC diagnosis. *(Figure 1A)*

Of 59 patients (age 38±17 years, 49% male), the experts diagnosed 15 (25%) with ARVC. Conventional echocardiographic TFC, either minor or major, were observed in 10 (67%) patients. Using deformation imaging instead of visual wall motion assessment led to 5 (33%) additional detections of ARVC, whereas none were reclassified to normal. Consequently, deformation imaging increased sensitivity from 67% to 100%, while specificity decreased from 89% to 73%. The C-statistic increased from 0.78, 95%CI (0.64-0.91) to 0.86, 95%CI (0.80-0.93). *(Figure 1B)*

Of note, half (n=6/12) of the patients with "false positive" abnormal deformation patterns were at risk family members of ARVC patients. They all developed new TFC during follow-up and 4 of them later fulfilled criteria for a definite diagnosis. Therefore, it can be debated whether the deformation abnormalities in these patients were truly "false positive" or, more likely, reflective of a very early sign of disease in these patients.[3] Deformation imaging detected all patients who developed the diagnosis during follow-up, and including these patients resulted in an increased specificity (80%) and C-statistic (0.74, 95%CI [0.62-0.86] to 0.90, 95%CI [0.84-0.96]).

We showed that RV deformation is highly sensitive for diagnosing ARVC, and improves the diagnostic performance of echocardiographic TFC when replacing the visual wall motion assessment. When the original 1994 TFC were revised in 2010, hypokinesia was disregarded as a criterion and only akinesia/dyskinesia remained.[1] This was necessary to prevent overdiagnosing of the disease, but consequently led to a loss in sensitivity. As wall motion abnormalities are a prerequisite to fulfill a criterion, the diagnostic performance of echocardiography depends primarily on visual assessment of RV wall motion abnormalities, which is difficult and highly dependent on the observer's experience. Replacing visual assessment by deformation imaging offers a solution for this loss in sensitivity, while also being less subjective.

In the present study, all patients who were diagnosed with ARVC by the expert panel were detected by RV deformation abnormalities. The cohort size and absence of a true gold standard test for ARVC were limitations in our study design. Because deformation imaging is not able to reliably distinguish ARVC from other RV related disease as a stand-alone index, such diagnostic dilemmas should always be conducted in a clinical multi-modality approach like the TFC. Using deformation imaging instead of visual wall motion assessment improved the overall performance of echocardiographic TFC for diagnosing ARVC.

References

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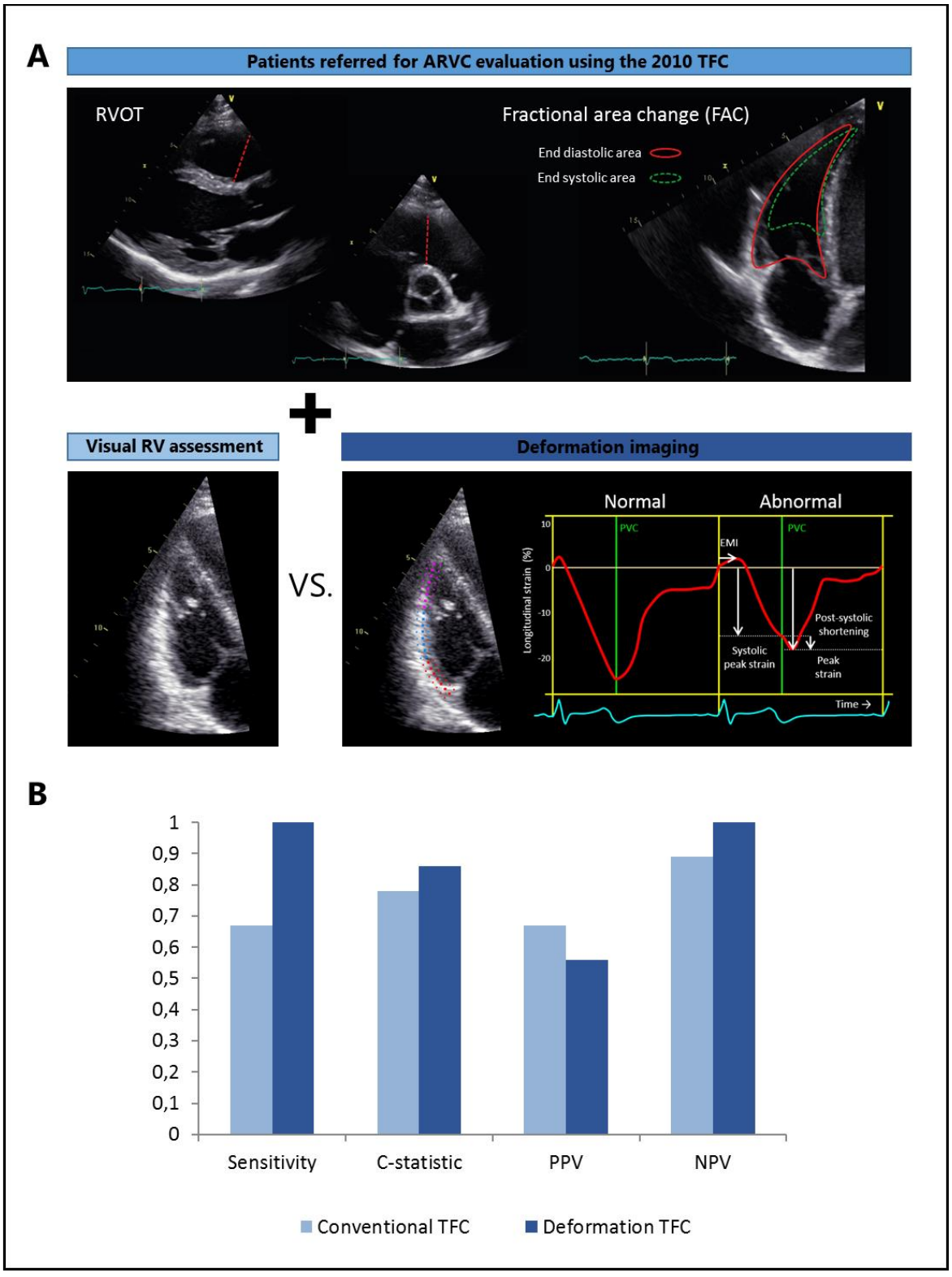
Figure legend

Figure 1. (A) ARVC evaluation according to the echocardiographic 2010 TFC by using visual wall motion assessment vs. deformation imaging. An RV-focused 4-chamber view was used to classify local deformation patterns as normal or abnormal [3] **(B)** Diagnostic performance of echocardiographic TFC when using conventional visual assessment compared to deformation imaging.

Figure


A
Patients referred for ARVC evaluation using the 2010 TFC
RVOT
Fractional area change (FAC)
End diastolic area
End systolic area
Visual RV assessment
Deformation imaging
VS.
Normal
Abnormal
PVC
PVC
EMI
Longitudinal strain (%)
Post-systolic shortening
Systolic peak strain
Peak strain
Time →
B
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
Sensitivity
C-statistic
PPV
NPV
Conventional TFC
Deformation TFC