

LETTERS TO THE EDITOR

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Keeping balance

The interesting manuscript of Bosman *et al.*¹ challenges the established 2010 arrhythmogenic right ventricular cardiomyopathy (ARVC) Task Force Criteria (TFC).² While I agree that the 2010 TFC ought to be improved, I am surprised by some aspects of this work.

First, I am surprised about the choice of the gold standard. Instead of using reproducible genetic, phenotypic and clinical criteria, Bosman *et al.* used expert consensus to diagnose or exclude ARVC. The [Supplementary Table 6](#) displays the challenge of making an ARVC diagnosis. Notably, 4 out of 10 'false positive' patients with the diagnosis ARVC according to 2010 TFC were diagnosed as 'at risk for ARVC' by the expert panel. And all as 'false negative' declared cases could be diagnosed as borderline or possible ARVC according to the 2010 TFC. Regrettably, the criteria for diagnosis of ARVC by the expert panel are not made available and can therefore not be reproduced.

Second, the control group did not consist of healthy controls but of patients in whom ARVC was suspected by referring physicians. Minor family criteria, autopsy diagnosis in a first-degree relative and signal-averaged electrocardiogram (SAECG) did not significantly vary between both groups and are therefore regarded as not useful by the authors. But not having the specifics of the control group plus the small number of patients with a positive minor family criteria limit the statistical power of the comparisons. Additionally, in the 2010 TFC, the SAECG had a sensitivity 74%, with a specificity of 92%.²

Third, the authors' statement that 'ECG and arrhythmia criteria alone can rule out ARVC with high sensitivity' is overconfident. In cases of early ARVC, ECG and arrhythmia criteria might be insufficient to diagnose the disease, while clinical and family history, magnetic resonance imaging and genetic diagnostic can give important hints to a timely, potentially life-saving diagnosis.^{3,4}

The 2010 TFC strive to balance over- and underdiagnosis.² Attempts to improve diagnostic criteria should maintain and improve this balance.

Conflict of interest: none declared.

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Keeping balance: Author's reply

We thank Dr Müssigbrodt¹ for his interest in our study and the complex question of arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis.² To continue the discussion in this reply, we elaborate on the elements that he found surprising and rectify inaccuracies in his statements.

His first concern regards our choice for an expert panel, instead of 'reproducible genetic, phenotypic, and clinical criteria'. However, unfortunately, such a 'gold-standard' test does not exist for diagnosing ARVC as none of the clinically available tests has sufficient sensitivity or specificity. Relying on genotype would exclude nearly half of cases that are 'gene-elusive'. Diagnosis must thus result from a composite reference standard: the 2010 Task Force Criteria (TFC).³ There are two recommended evidence-based options to validate composite reference standards; (i) an expert panel or (ii) latent classification learning algorithms,⁴ of which the latter is suboptimal for relative small cohort sizes in ARVC-research. The appealing strength of an expert panel is that the experts can use the totality of available evidence on an individualized basis, allowing a more comprehensive assessment with multiple shades of grey instead of a limited black-and-white approach from pre-defined criteria with fixed cut-off points.

Such expert panels have previously been proven to be valuable in the field of cardiology, for example, to validate the diagnostic value of B-type natriuretic peptide for heart failure.⁵

Secondly, Dr Müssigbrodt expressed concerns about our control group, a cohort of patients referred for evaluation of ARVC, instead of healthy individuals, and about the disappointing results of several criteria. We consider our control group a major strength of our analysis. In the real world, patients referred for ARVC evaluation have specific traits that resemble ARVC, making them much harder to discriminate. Most of the previously published diagnostic results of the 2010 TFC tests are based on comparison with healthy controls, leading to an overestimation of the true diagnostic accuracy. This explains why several tests, such as signal-averaged electrocardiogram (SAECG), showed lower values in our study. This did however not come as a surprise to us as the recently published expert consensus review of the 2010 TFC advocates for the elimination of SAECG based on 'non-specific findings and limited diagnostic accuracy'.⁶

The last point raised by Dr Müssigbrodt, that our statement 'ECG and arrhythmia criteria alone can rule out ARVC with high sensitivity' is 'overconfident', might be based on a misunderstanding. We fully agree with Dr Müssigbrodt's statement that ECG and arrhythmia criteria are insufficient to diagnose (i.e. 'rule-in') ARVC. Our study rather highlights the importance of the finding of a 100% sensitivity for 'ruling-out' ARVC, for example in relatives subject to frequent re-evaluations. As these are two different concepts not to be confused, we want to emphasize the importance of other tests such as cardiac magnetic resonance imaging (CMR) and genetics for diagnosing ARVC.

As the first study validating the 2010 TFC as a whole in a real-world population, our results highlight the potential for improvements in ARVC diagnostic criteria. We, like Dr Müssigbrodt, advocate that new diagnostic criteria should maintain a balance between over- and underdiagnoses, and be based on evidence-based approaches.

Conflict of interest: none declared.

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Sympathetic hyperactivity after coronary artery bypass graft surgery: an important player in the development of postoperative atrial fibrillation?

In their elegant study ‘C-reactive protein after coronary artery bypass graft surgery and its relationship with postoperative atrial fibrillation’, Olesen *et al.*¹ demonstrated that, in an adjusted analysis, increased postoperative C-reactive protein (CRP) levels after coronary artery bypass graft (CABG) surgery were associated with the development of postoperative atrial fibrillation (POAF). The study population was divided into quartiles based on CRP levels. Patients in the highest CRP group were older and more often men compared with those in the lowest CRP group. In the lowest and highest CRP groups, 24.5% and 35.1% developed POAF, respectively ($P < 0.0001$). In the adjusted analysis, the highest CRP levels were associated with greater odds of developing POAF (odds ratio 1.31; 95% confidence interval 1.12–1.54).¹

In reviewing participants’ baseline characteristics, we noticed that the prevalence of conditions

that are commonly characterized by substantially elevated sympathetic drive including hypertension (52.5 vs. 45.1%), heart failure (20.3 vs. 16.4%), diabetes (23.2 vs. 20.2%), and renal disease (9.2 vs. 2.6%) was significantly more common in patients in the high CRP group. Furthermore, more patients in the top CRP group were on calcium channel blockers (CCB) compared to patients in the lowest CRP group (34.2 vs. 25.9%), whereas fewer patients in the high CRP group were on β -blockers (50.6 vs. 54.5) compared to the subjects in the lowest CRP quartile.

Taken together, the higher prevalence of conditions of sympathetic overdrive paired with a higher percentage of patients on CCBs, known to exaggerate sympathetic drive, and less frequent use of β -blockers in the high CRP group may have created a sympathetically driven environment that promotes the onset of POAF.

The omission of body weight as a potential confounder is a limitation in the current analysis. Donnellan *et al.*² recently reported an association between increased epicardial fat volume (EFV) and higher rates of atrial fibrillation (AF) recurrence after ablation therapy. Bariatric surgery-induced weight-loss was associated with both reductions in EFV and lower AF recurrence. Hence, increased body mass index represents another important factor associated with high CRP levels³ which was neglected in the authors’ model. This may, in part, explain the surprising finding that diabetes did not emerge as a risk factor for POAF in the current analysis. Of note, increased CRP levels are common in type 2 diabetes,⁴ and closely associated with AF severity.⁵

It may also be relevant to note that in their multivariable-adjusted analysis the authors did not include glucose-lowering drugs, which can have either a stimulating effect (insulin, sulphonylureas, dipeptidyl peptidase-4 inhibitors, and thiazolidinediones), a neutral effect (α -glucosidase inhibitors and glucagon-like peptide-1 receptor agonists) or an inhibitory effect (sodium-glucose co-transporter-2 inhibitors and metformin) on the activation of the renin-angiotensin-aldosterone system and sympathetic nervous system both of which are implicated in cardiac remodelling and development of POAF.

Such factors above may have influenced the outcomes of the current analysis, and a repeat multivariable-adjusted analysis may reveal a different risk ratio for the development of POAF post-CABG stratified by CRP levels.

Conflicts of interest: M.G.K., S.C., L.G.A., and R.C. declare that they have no conflict of interest. M.P.S. is supported by an NHMRC Research Fellowship and has received consulting fees, and/

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Sympathetic hyperactivity after coronary artery bypass graft surgery: an important player in the development of postoperative atrial fibrillation? Authors’ reply

We would like to thank Dr Kiuchi and colleagues for their interest in our study¹ and we appreciate