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**RESEARCH LETTER**

# Arrhythmogenic substrate elimination for safe testosterone therapy in symptomatic Brugada syndrome patients

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**Background** Brugada Syndrome (BrS) is a cardiogenetic disease known for its association with sudden cardiac death (SCD) in individuals with structurally normal hearts. The prevalence of BrS is higher in males, who also face a greater risk of SCD. Its higher prevalence and worse outcome in male subjects may be due to testosterone effects on ion channels expression and function. The influence of testosterone on cardiac action potentials, both genomically and non-genomically, underscores its potential role in unmasking the syndrome and triggering life-threatening arrhythmias. Notably, testosterone replacement therapy (TRT), used for hypogonadism and gender reassignment, has been linked to BrS unmasking. The role of epicardial ablation in symptomatic BrS patients where hormonal therapy cannot be discontinued is unknown.

**Methods and results** In this study we describe the first two cases of substrate mapping and ablation in BrS patients experiencing arrhythmic events while on TRT. In both cases, high-density epicardial mapping revealed abnormal areas of prolonged and fragmented electrograms in the right ventricular (RV) outflow tract and anterior wall. These abnormalities were completely abolished by radiofrequency ablation (RFA). After ablation, both patients showed a persistent normalization of the ECG and were free from ventricular arrhythmias at follow-up, despite ongoing TRT.

**Conclusion** RFA can be considered as a therapeutic option in symptomatic BrS patients with a high-risk profile who cannot discontinue TRT, being essential for restoring their normal physiology or preserving their sexual identity. As testosterone use is increasing, further studies are warranted to define a standardized diagnostic and therapeutic strategy in this specific subset of BrS patients.



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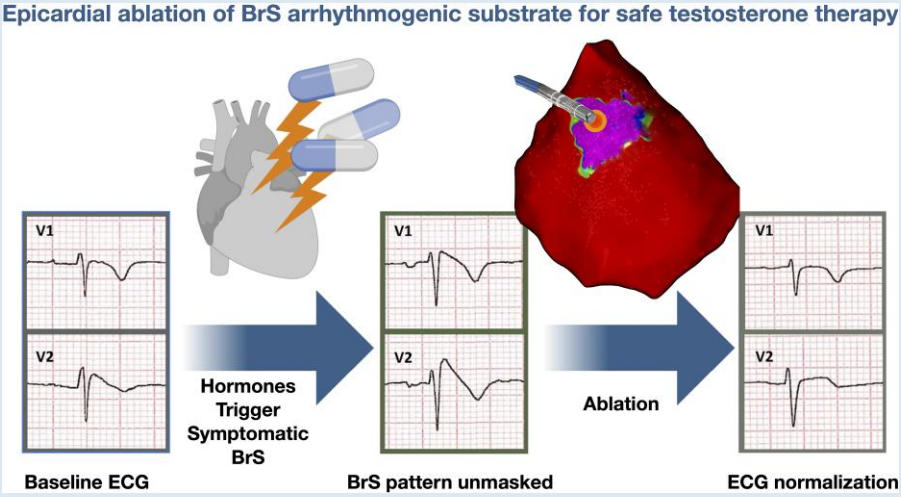
## Graphical Abstract




**Keywords** Brugada syndrome • Testosterone therapy • Radiofrequency ablation

Brugada syndrome (BrS) is a cardiogenetic disease representing one of the leading causes of sudden cardiac death (SCD) in patients with structurally normal hearts. Its manifestations are the result of the combined effects of various genetic, hormonal, and environmental factors.[1,2] *SCN5A* pathogenic variants represent the most common genetic trait; however, gender-related differences have been demonstrated to affect the phenotypic expression of the disease.[3] The prevalence of BrS exhibits a higher incidence in male patients as compared to females, with a 5.5-fold increased risk of SCD.[4] This gender disparity, along with the more severe clinical outcomes observed in males, may be attributed to the influence of sex hormones.[5] Notably, higher levels of testosterone have been consistently observed in male patients with BrS than in control subjects,[6] and disappearance of the typical Brugada electrocardiogram (ECG) pattern has been described in men after surgical castration.[7]

Testosterone is thought to modulate cardiomyocytes' action potential by genomic and non-genomic pathways. In predisposed individuals, exposure to exogenous androgens may critically interfere with ion channels' function, unmasking the syndrome and triggering life-threatening arrhythmias.[8]

Testosterone replacement therapy (TRT) is currently used for the treatment of hypogonadism and to obtain adequate hormonal plasmatic concentrations in the female-to-male sex reassignment. While the role of TRT in unmasking BrS has been reported,[8] there are no data regarding the epicardial substrate of the disease in this specific subset of patients. Moreover, the role of substrate modification in patients with BrS under testosterone therapy has never been investigated.

Since January 2016, two out of nine patients referred to our department because of a Brugada ECG pattern during TRT experienced BrS-related symptoms. Data were collected in an institutional review board–approved database.

The first patient (*Figure 1*, left panel) was a 26-year-old man with iatrogenic hypopituitarism, following radiation therapy of a suprasellar germinoma. After 3 years of continuative TRT, he experienced an out-of-hospital cardiac arrest. The ECG after recovery showed a BrS ECG pattern. He underwent implantable cardioverter defibrillator (ICD) implantation. Notably, the ECG recorded 3 years before TRT showed minor, non-diagnostic abnormalities.

The second patient (*Figure 1*, right panel) was a 21-year-old transgender male on TRT. After 1 year of TRT, he suffered an episode of malignant syncope without prodromes while driving. His ECG after the event showed a type 1 BrS ECG pattern. The electrophysiological study (EPS) was positive for ventricular fibrillation (VF) induction. The patient refused to discontinue androgens and underwent ICD implantation. The ECG 2 years before TRT showed a suspicious and less prominent Brugada pattern.

Both patients initially received quinidine, which was discontinued due to intolerance. A mapping and ablation procedure was then proposed as an alternative treatment strategy, considering the need for TRT.

In both cases, high-density epicardial mapping revealed abnormal areas of prolonged and fragmented electrograms in the right ventricular (RV) outflow tract and anterior wall. These abnormalities were completely abolished by radiofrequency ablation (RFA). After ablation, both patients showed a persistent normalization of the ECG and were free from ventricular arrhythmias at follow-up (respectively, 14 and 7 months) despite ongoing TRT (*Figure 1*; Supplementary material online, *Figure S1*). Both patients tested negative for *SCN5A* variants.

These findings highlight the preponderant role of testosterone in influencing symptom status and its pro-arrhythmic effect in BrS patients, even without a definite genetic background. In fact, these patients showed an aggressive phenotype without *SCN5A* variants, whose presence correlates with a severe arrhythmic risk.[9]

Moreover, epicardial mapping confirmed the presence of a specific arrhythmogenic substrate also on TRT, providing evidence that these patients were indeed affected by BrS, whose expression was unmasked and exacerbated by testosterone administration. Therefore, the observed ECG should not be considered a mere phenocopy.

As in this case, catheter ablation aiming at substrate modification showed its beneficial effect in phenotype expression as occurring in other high-risk cohorts.[10–12] Despite the inherent difficulties in directly comparing ECGs taken by different technicians at different time intervals, the consistent abolition of the BrS ECG pattern after ablation, while on TRT without discontinuation, indicates a direct beneficial effect on the arrhythmogenic substrate.

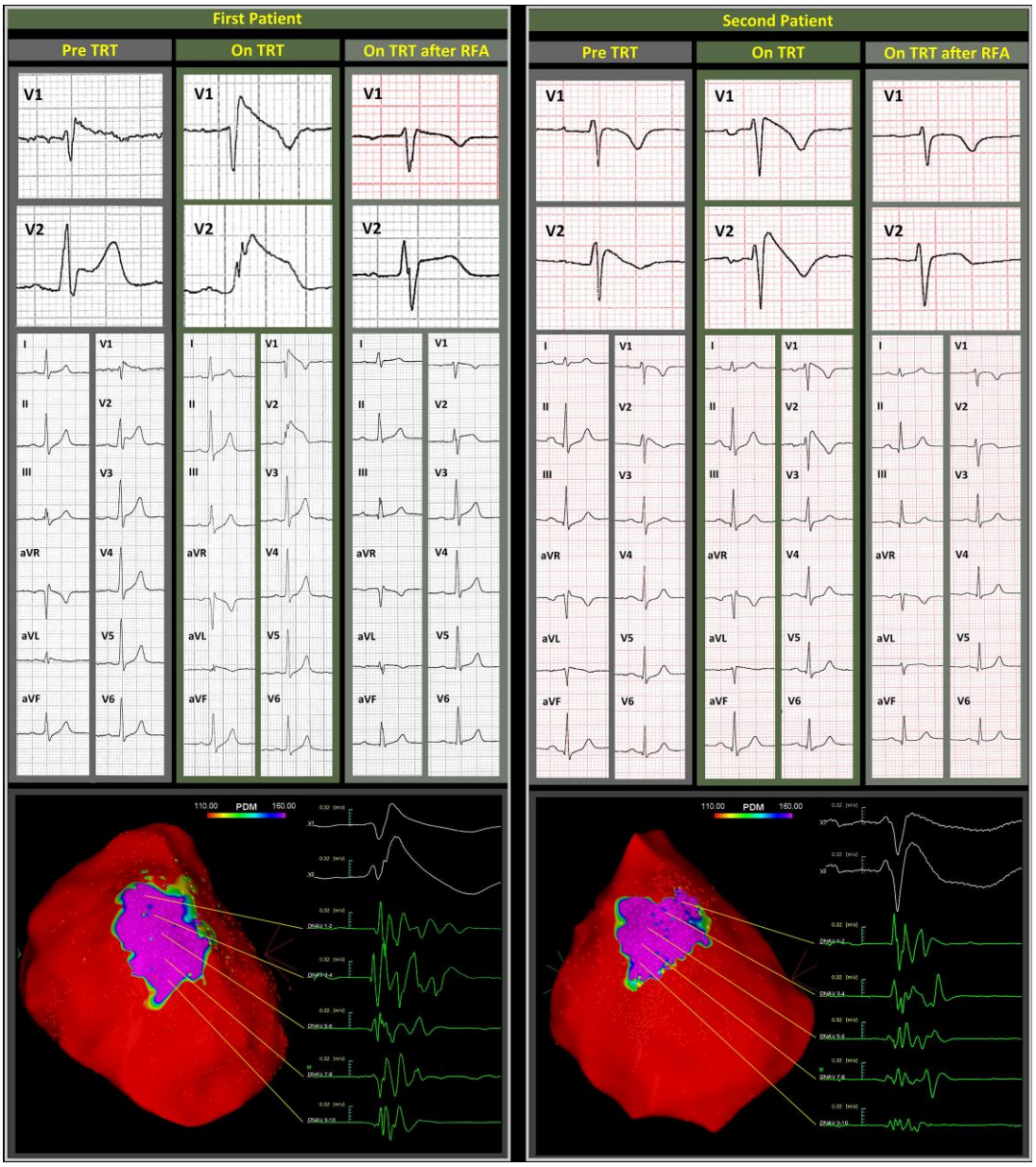



**Figure 1** Electrocardiogram and epicardial mapping of two symptomatic patients with BrS on TRT. Both patients showed a type 1 Brugada ECG pattern while on TRT. Epicardial mapping showed extensive areas of abnormal electrograms on the right ventricular outflow tract in both patients. After ablation, both patients showed ECG pattern normalization and were free from ventricular arrhythmias at follow-up despite the ongoing TRT. BrS, Brugada syndrome; ECG, electrocardiogram; PDM, potential duration map; RFA, radiofrequency ablation; TRT, testosterone replacement therapy.

Although it might be unusual to consider RFA after the first symptomatic event, there are several factors in these particular scenarios that have led to this alternative approach: (i) intolerance to quinidine therapy, requiring withdrawal; (ii) impossibility to discontinue TRT, which showed deleterious effects; and (iii) high-risk profile characterized by type 1 BrS ECG in both patients, cardiac arrest in one and syncope with inducible VF at EPS in the other.

This finding might support ablation treatment as an alternative therapeutic approach in symptomatic BrS patients, when hormonal therapy discontinuation is not a feasible option, being essential for restoring their normal physiology or preserving their sexual identity.

Consistent with our findings, previous studies have reported the reversibility of testosterone's adverse effects in BrS patients through surgical castration.[7] Different from Matsuo *et al.*, who focused on asymptomatic BrS subjects compared to the present case series, our investigation describes the phenotype modification resulting from local substrate ablation, despite ongoing exposure to testosterone. Of note, while the detrimental effects of hormones were mitigated in Matsuo *et al.*'s study by reducing androgen hormone levels, our study specifically targeted and removed the arrhythmogenic substrate, which may be influenced by testosterone. From different perspectives, both observations align and support the notion of a potential functional effect.

Furthermore, as testosterone is widely available and its prescription steadily increasing over the years,[13] these observations may have a profound clinical impact on the diagnosis of BrS and the prevention of its rare but potentially lethal complications. Further studies on the arrhythmic risk of patients with BrS on TRT are warranted to possibly define a population-oriented screening process and a standardized therapeutic strategy.

# Supplementary material

Supplementary material is available at *Europace* online.

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**Conflict of interest:** None declared.

## Data availability

The data collected for the present study are available from the corresponding author, G.C., upon reasonable request.

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