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Commentary

Understanding and Managing Brugada Syndrome Today

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DESCRIPTION

Since its first description by the Brugada brothers in 1992, Brugada syndrome has posed significant challenges due to its unpredictable propensity for sustained ventricular fibrillation, leading to typical symptoms such as syncope, aborted cardiac arrest, and sudden cardiac death. Survivors of cardiac arrest remain at the highest risk of recurrent sustained ventricular fibrillation without prodromes as observed prior to the initial event. Lack of independent predictors of such events still represents a significant limitation for preventive strategies. Consequently, Implantable Cardioverter-Defibrillator (ICD) implantation remains the mainstay treatment option, although it does not prevent sustained Ventricular Fibrillation (VF). Long-term ICD complications, particularly in young patients with prolonged life expectancies, raise significant concerns.

A pressing concern in managing this life-threatening electrical disease is the scarcity of alternatives to ICD therapy and the absence of independent prognostic predictors beyond survivors of cardiac arrest. Recent research has illuminated previously undisclosed pathophysiological and therapeutic aspects, prompting a reassessment of prognostic paradigms and allowing the introduction of innovative therapeutic and potentially curative modalities.

Our recent prospective pilot studies, conducted from 2011 to 2024 and involving over 1300 high-risk Brugada Syndrome (BrS) patients with different clinical presentations, focused on identifying, quantifying, and ablating BrS substrates at Policlinico San Donato in San Donato Milanese, Italy [1-4]. These studies revealed significant correlations between substrate extent, coved ST-segment elevation [1], VF inducibility [2], SCN5A genetic variants [3], and long-term outcomes both before and after epicardial ablation [4].

Employing a standardized mapping/ablation protocol involving ajmaline infusion to delineate the complete epicardial substrate area, we identified substrate extent exceeding a 9 cm^2 threshold as a significant risk predictor for sustained VF in a substantial cohort of symptomatic BrS population with ICD implantation [4]. Complete substrate elimination, confirmed by ajmaline infusion, yielded striking long-term efficacy and safety, ensuring sustained normalization of Electrocardiogram (ECG) pattern and nearly complete freedom from VF events compared to a control group treated with ICD implantation without ablation.

Previous studies have explored various facets for risk stratification, focusing on typical clinical manifestations, family history, ECG patterns, electrophysiological findings and genetic aspects, overlooking a crucial gap in our understanding of the syndrome's pathophysiology and underlying mechanisms. The discovery of variable abnormal epicardial areas in highly symptomatic patients with BrS has thus emerged as pivotal, addressing this gap and, more recently, unveiling substrate extent's prognostic significance, with remarkable therapeutic implications [4]. Despite the seemingly low numerical risk of sudden cardiac death across the entire BrS population, it remains considerable, particularly given the youthfulness and extended life expectancy of affected patients. Additionally, sudden cardiac death often occurs unexpectedly in previously asymptomatic individuals or several years post-initial near-fatal presentations, underscoring the necessity for ICD implantation and indefinite systematic follow-up periods.

The identification of substrate extent as the primary risk determinant of sustained VF in BrS advocates for early ablation tailored to individual risk profiles to optimize outcomes, thereby curtailing the need for ICD implantations, particularly in primary prevention of sudden death. This approach assumes pivotal significance in tackling diverse clinical presentations and therapeutic complexities ensuring interventions are custom-tailored to optimize long-term outcomes. Our pilot studies underscore the urgent imperative to reevaluate existing norms, address lingering queries, and embrace emergent paradigms to facilitate more informed clinical decision-making, advocating for global cooperation in the interest of scientific advancement and public welfare.

We aim to disseminate our insights globally, advocating for early ablation in expert BrS centers to avoid repeat ablations [5], particularly for very young patients presenting with extensive substrates and heightened susceptibility to premature sudden cardiac death. We anticipate that these new findings will address

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lingering queries and engender a global dialogue in this critical domain of clinical research.

The burgeoning recognition of substrate extent's pivotal role underscores its significance as a key determinant of type 1 ECG pattern, VF inducibility, and favorable long-term outcomes beyond cardiac arrest survivors [4]. Regardless of clinical presentations, we can speculate that patients with substrates exceeding 9 cm^2 might also derive substantial benefits from early ablation, akin to patients with typical BrS-related symptoms beyond survivors of cardiac arrest, potentially expanding the therapeutic purview.

Our extensive experience in invasive substrate mapping/ablation has underscored the urgency of non-invasively quantifying substrate extent, heralding a significant breakthrough in the field. The development of non-invasive methodologies to assess substrate extent holds transformative potential, empowering clinicians with a comprehensive understanding of the underlying mechanisms and facilitating precise patient selection for early ablation. This innovative methodological approach, currently underway in our lab, holds promise for its wider applicability in the near future.

While these strides represent notable progress in understanding and preventing ventricular fibrillation in Brugada syndrome, it's imperative to acknowledge that there is still much work to be done. Continued research and clinical efforts are essential to refine our comprehension and enhance patient outcomes, equipping clinicians with the requisite tools and strategies to ultimately improve the lives of those affected by this condition.

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