

Interrogating the Purkinje Network: A Multimodal Strategy for Ventricular Conduction System Research and Sudden Cardiac Death

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SUMMARY OF KEY RESEARCH FINDINGS

The ventricular conduction system delivers the rapid, coordinated activation on which every heartbeat depends. Paradoxically, the specialisation that synchronises contraction throughout life renders the Purkinje network disproportionately arrhythmogenic: it triggers and sustains idiopathic ventricular fibrillation, participates in post-infarction ventricular

tachycardia, and underlies polymorphic arrhythmia in inherited syndromes.¹⁻⁴ The work presented at the European Society of Cardiology (ESC) Congress 2026 addresses a more fundamental question: what can be measured in this complex network, by which means, and at what scale?⁵

Three converging axes are proposed: detect, define, and track phenotypic divergence of the Purkinje network at multiple scales. Cell-type-resolved transcriptomics of laser microdissected tissue has yielded stable Purkinje cell markers conserved in humans,⁶ and the same platform has characterised molecular and microstructural remodelling with age in sheep.⁵ The conclusion is methodological. Clinical characterisation rests on electrical mapping of Purkinje activity, which resolves the network sparsely. Such practice stands to be complemented by technologies better adapted to the network's distinguishing architectural, compositional, and functional properties. Better detection of and access to these properties would allow Purkinje-specific definitions, and features that diverge under stress are the most promising leads for clinical biomarkers.

WHAT CHALLENGE DOES THIS ADDRESS?

Direct electrophysiological measurement of Purkinje cells is long established: microelectrode recording resolves transmembrane behaviour directly in the network and the Purkinje-muscle junction directly,⁷ but is limited in the number of simultaneous recording sites. Difficulty arises in mapping electrical behaviour at high spatial resolution. Optical mapping of ventricles with endocardial imaging remains the most powerful integrated approach in large mammals,^{8,9} yet the voltage-sensitive signal from the thin, sparse Purkinje network is negligible against surrounding myocardium. The recorded signal is the

myocardial response to Purkinje activity, from which conduction velocity, retrograde activation, branch recruitment, and delay or block at the Purkinje-muscle junction remain difficult to separate. Electrical mapping is similarly constrained: clinical detection of Purkinje potentials has advanced,¹⁰ yet remains incomplete.

Structural interrogation trades field of view against specificity. Contrast-enhanced micro-CT resolves whole large-mammal hearts at the microscale but is preclinical, relying on poorly selective agents such as Lugol's iodine;¹¹ it may prefigure clinical photon-counting CT. Magnetisation transfer MRI provides endogenous contrast without staining, yet remains *ex vivo* and, limited by resolution and sensitivity, detects only the larger proximal network.^{12,13} False tendons may or may not contain Purkinje tissue, and a secure molecular identity allows changes in Purkinje cells to be tracked across stressors such as ageing, and across scales.

Molecular access is equally constrained. Purkinje cells are difficult to isolate intact, and although, readily identified in sheep, resemble cardiomyocytes in human tissue, undermining cell-type assignment.^{14,15} Expression studies have concentrated on established cardiac targets, confining discovery to what is already suspected.^{16,17} Unbiased profiling removes that ceiling; a secure identity permits phenotypic divergence to be tracked across stressors and scales.

RELEVANCE TO EUROPEAN PRACTICE

These limitations converge clinically: Purkinje-targeted ablation is effective when triggers can be mapped,^{10,18,19} but incomplete maps often result in treatment failure. Ablating all detectable Purkinje potentials to uncouple the network from critical arrhythmic pathways is increasingly adopted as a bail-out strategy. European centres have shown that Purkinje triggers and localised structural abnormality together govern the transition from ectopy to sustained ventricular fibrillation.^{20,21} Defining the Purkinje substrate molecularly

and structurally would benefit targeted therapy, offering detection routes that complement an incomplete electrogram picture. Label-free endoscopic optical coherence tomography illustrates this: it identifies a Purkinje-specific signature at micrometre resolution with automated 3D segmentation, and its catheter-scale probe provides a foundation for *in vivo* translation, albeit point-by-point over localised fields.²²

WHAT ARE THE NEXT STEPS FOR THE RESEARCH?

Structural definition in three dimensions is achievable *ex vivo*; functional definition remains far more limited. The priority is to contextualise sparse functional measurement with deeper molecular and structural insight. In the authors' view, progress will be convergent: *in vivo* validation of endoscopic optical coherence tomography via percutaneous access; extension of Purkinje cell markers to human cohorts, where accessible binding sites could support Purkinje-specific imaging or targeting; and more direct mapping of the intact network, whose electrical connection with the surrounding myocardium is poorly understood. Computational modelling binds these strands, integrating data across methods and scales to test mechanistic hypotheses that experiments alone cannot isolate.²³

Limitations remain substantial: large-mammal work is resource-intensive, human tissue is scarce, the human marker panel requires protein-level confirmation in larger cohorts, and the most informative methods remain *ex vivo*. Without methods adapted to this network's distinguishing features, its role in sudden cardiac death will remain descriptive rather than a basis for targeted therapy.

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