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Pablo Gonzalez-Martin

ELEM Biotech <https://orcid.org/0000-0002-1857-6556>

María Marín

ELEM Biotech

Aida Jimenez

ELEM Biotech

Jose M. Pozo

ELEM Biotech

Constantine Butakoff

ELEM Biotech

Alberto Zingaro

ELEM Biotech

Franca Morselli

University College London

Matthew Webber

University College London

Debbie Falconer

University College London

Fiona Chan

University College London

Swapnanil De

University College London

Christos Charalambous

University College London <https://orcid.org/0009-0000-3206-180X>

Lavinia Moro

University College London

Constantin-Cristian Topriceanu

University College London

Emma Martin

University College London

George Joy

3St Bartholomew's Hospital, Barts Health NHS Trust

Jonathan Bennett

University College London

Kanchani Makuloluwa

Frimley Health NHS Trust

Hunain Shiwani

University College London <https://orcid.org/0000-0002-0046-2884>

Rhodri H. Davies

Barts Health NHS Trust

Nishi Chaturvedi

University College London <https://orcid.org/0000-0002-6211-2775>

Michele Orini

King's College London <https://orcid.org/0000-0001-5773-0344>

James C. Moon

Institute of Cardiovascular Sciences, University College London

Pier D. Lambiase

University College London <https://orcid.org/0000-0002-9055-9267>

Alun D. Hughes

UCL <https://orcid.org/0000-0001-5432-5271>

Mariano Vazquez

ELEM Biotech

Oscar Camara

Physense, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona

Jazmín Aguado-Sierra*

jaguado@elem.bio

ELEM Biotech

Gabriella Captur*

UCL

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Mapping the healthy aging heart: a normative electrophysiological digital twin atlas for pathological remodeling assessment

Pablo Gonzalez-Martin^{1,2}, María Marín¹, Aida Jimenez^{1,2}, Jose M Pozo¹, Constantine Butakoff¹, Alberto Zingaro¹, Franca Morselli³, Matthew Webber³, Debbie Falconer³, Fiona Chan³, Swapnanil De³, Christos Charalambous³, Lavinia Moro³, Constantin-Cristian Topriceanu^{3,4,5}, Emma Martin³, George Joy⁶, Jonathan Bennett⁴, Kanchani Makuloluwa⁷, Hunain Shiwani⁴, Rhodri H Davies⁴, Nishi Chaturvedi⁴, Michele Orini⁸, James C Moon⁴, Pier D Lambiase⁴, Alun D Hughes³, Mariano Vazquez¹, Oscar Camara², Jazmín Aguado-Sierra^{1*†} and Gabriella Captur^{3†}

¹ ELEM Biotech, Barcelona, Spain

² Physense, BCN MedTech, Department of Engineering, Universitat Pompeu Fabra, Barcelona, Spain

³ Unit for Lifelong Health and Aging at UCL, University College London, London, United Kingdom

⁴ Institute of Cardiovascular Science, University College London, London, United Kingdom

⁵ Mayo Clinic, Rochester, United States of America

⁶ Cardiovascular Clinical and Academic Group, City St George's University of London, London, United Kingdom

⁷ Wexham Park Hospital, Frimley Health NHS Trust, Slough, United Kingdom

⁸ Biomedical Engineering Department, King's College London, London, United Kingdom

* Corresponding author: jaguado@elem.bio

† Joint last authors

Abstract

Distinguishing the intrinsic electrophysiological remodeling of healthy cardiac aging from early pathology is a prerequisite for preventive cardiology in older adults, yet no population-scale 3D normative reference exists. Leveraging the life-course design of the MyoFit46 birth cohort, community-dwelling adults aged 75+ born within the same week of 1946, we combined

cardiovascular magnetic resonance with 256-lead electrocardiographic imaging (ECGI) and a deterministic mapping framework to construct subject-specific digital twins (DTs) encoding myocardial conduction velocity, endocardial activation sequences, and regional repolarization heterogeneities. An aging repolarization layer was required in all 30 selected participants, demonstrating that standard adult cellular models do not reproduce the repolarization dynamics of healthy aging hearts and that explicit age-related ionic remodeling is systematically necessary. Population-level analysis revealed structured Purkinje-myocardial junction distributions consistent with classical anatomical landmarks, distinct apico-basal repolarization gradients, and sex-specific repolarization scaling reflecting age-related hormonal decline. The DTs replicated *in vivo* epicardial dynamics within established clinical ECGI uncertainties. As a proof-of-concept, the atlas was compared against an age-matched, non-fibrotic early-stage hypertensive group, identifying a directional shift toward action potential prolongation before overt structural disease. These findings establish the first normative electrophysiological DT atlas of the healthy aging heart for assessing pathological remodeling in older adults

Introduction

Global populations are aging at unprecedented rates, and the proportion of adults aged 65 years and older has reached historically high levels¹. This demographic transition has reshaped the concept of healthy aging, shifting the focus from the absence of disease toward the preservation of functional ability and well-being in later life². Importantly, although aging is the strongest risk factor for most chronic diseases of later life, its biological processes extend beyond the cumulative burden of lifelong risk exposures and overt pathology³. This distinction is particularly challenging in the cardiovascular system, as age-associated structural and electrophysiological remodeling may be present even in apparently healthy individuals and frequently overlaps with subclinical cardiovascular disease⁴. In the absence of a normative reference for the healthy aging heart, physiological remodeling risks being conflated with early

pathology, limiting both preventive cardiology and life-course risk stratification in older adults⁵. Distinguishing healthy-aging trajectories from early disease is therefore essential for preventive strategies in older adults.

During healthy aging, cardiac electrophysiology (EP) remodels at both cellular and tissue levels^{6,7}. At the cellular level, ionic channel remodeling prolongs the action potential^{8,9}, an effect compounded by declining estrogens¹⁰ and testosterone¹¹ that narrow sex differences in repolarization¹². Cardiomyocyte senescence further perturbs ionic homeostasis^{13,14}, though its regional distribution remains poorly characterized. At the tissue level, irreversible cardiomyocyte loss¹⁵ is compensated by survivor hypertrophy¹⁶, while reduced Cx43 expression¹⁷ and fibrosis-driven anisotropy are expected to slow and fragment conduction¹⁵. No framework has yet integrated these multiscale changes into a population-level normative reference of healthy cardiac EP. Digital twins (DTs), which translate multimodal clinical data into mechanistic models, provide a means to encode their functional electrophysiological signature at the tissue and organ scale.

DTs have emerged as a powerful framework for mechanistic cardiac phenotyping, providing a deterministic mathematical platform that integrates multimodal clinical data to replicate observed EP¹⁸. Electrophysiological DTs have been deployed for treatment planning^{19–21}, *in silico* clinical trials^{22–24}, and deep cardiac phenotyping at population scale^{25,26}. From a personalization perspective, these DTs are predominantly calibrated against 12-lead electrocardiogram^{27–30} given its clinical availability, though at the cost of limiting the spatial richness of the inferred parameters. Moreover, none of these studies have established a normative reference of the healthy aging heart from an age-matched, healthy cohort against which pathological remodeling could be assessed.

To address this gap, we leveraged the unique MyoFit46 cohort, a rigorously selected, community-dwelling population of healthy adults aged 75+ born within the same week of March 1946, alongside co-registered quasi-simultaneous cardiovascular magnetic resonance (CMR) and high-density electrocardiographic imaging (ECGI), to construct the first 3D

electrophysiological DT-based atlas of healthy cardiac aging. ECGI reconstructs epicardial potentials from hundreds of body-surface leads, providing richer spatial information than the standard electrocardiogram and resolving regional activation and repolarization map³¹ yet its quasi-simultaneous acquisition with CMR is rarely available, having never been achieved in a deeply phenotyped, age-matched healthy aging cohort. A deterministic, sequential mapping framework directly translated multimodal data into subject-specific DTs, including conduction velocity (CV), endocardial activation sequences, and regional repolarization heterogeneities, providing a high-resolution normative reference for the aging heart against which pathological remodeling can be systematically assessed.

Results

Results are organized in two parts. On the one hand, verification of the DT personalization pipeline against synthetic data to characterize its inherent uncertainties before application to human participants. Briefly, our deterministic pipeline infers subject-specific CV and activation sequence, defined by the location of the Purkinje-myocardial junction (PMJ) and their time of activation from ECGI data, and then personalizes ventricular repolarization in two steps: first, a baseline slow delayed rectifier potassium current conductance calibration by a scaling factor (g_{Ks}); second, an aging-specific repolarization calibration to account for regional action potential duration lengthening or shortening, above average healthy young values, using the rapid delayed rectifier potassium current conductance (g_{Kr}) as a surrogate of these changes. On the other hand, and constituting the primary contribution of this work, the pipeline was applied to a healthy aging cohort from the MyoFit46 study to construct a normative electrophysiological DT atlas of cardiac healthy aging. The atlas characterizes activation sequences, PMJ distributions, and both baseline and aging repolarization (AgR) heterogeneities across the ventricular epicardium. Finally, as a proof-of-concept, the healthy atlas is compared against an age-matched early-stage hypertensive (eHTN) aging group to demonstrate its capability as a normative reference for assessing early deviations from healthy aging EP.

Personalization pipeline verification

Pipeline verification was performed against six synthetic ground-truth DTs spanning the tested range of conduction velocities, activation strategies, and repolarization patterns. Across these benchmarks, endocardial activation times (ATs) were reconstructed with an activation time root mean square error (AT-RMSE) of 8.73 ± 1.35 ms for Durrer-based cases and 9.75 ± 0.98 ms for Purkinje-based ones, excluding septal and basal regions where ECGI lacks activation data. Verification tests identified the generation of supplementary PMJ (i.e., PMJ located on the borders of endocardial surface) to compensate for missing endocardial regions. Non-supplementary PMJ counts were comparable to their ground-truth counterparts in Durrer-based cases, with an average of ~ 9 PMJs against the 5 expected from Durrer et al. activation³². In Purkinje-based cases, the pipeline identified a subset of the denser ground-truth network, averaging ~ 54 against the 558 PMJs of the ground-truth activation sequence. Epicardial reconstruction yielded a mean AT-RMSE of 13.35 ± 9.67 ms, and a repolarization time root mean square error (RT-RMSE) of 16.99 ± 6.18 ms across all tests, with the largest repolarization errors observed in cases with the highest activation errors. CV estimation showed a sequence-dependent bias, with CV relative error of $-32.08 \pm 1.25\%$ for Durrer-based and $-8.50 \pm 3.78\%$ for Purkinje-based tests. Full verification results are provided in **Supplementary S1**.

Digital Twin Atlas of Healthy Aging

MyoFit46 healthy demographics

Table 1. MyoFit46 healthy cohort demographic. Variables are expressed as median and interquartile range. A Mann-Whitney U test with Benjamini-Hochberg correction was used for sex-group comparison (p_{adj}). AgR: aging repolarization; ARI90: time to 90% of epicardial activation-repolarization interval; AT90: time to 90% of epicardial activation; BMI: body mass index; BSA: body surface area; CMR: cardiac magnetic resonance; CV: conduction velocity; D-BP: diastolic blood pressure; Dr: fiber-direction diffusion coefficient; ECGI: electrocardiographic imaging; ECV: extracellular volume; EDVi: end-diastolic volume index; EF: ejection fraction; eGFR: estimated glomerular filtration rate; ESVi: end-systolic volume index; gKs: slow delayed rectifier potassium current conductance scaling factor; LA-EDVi: left atrial end-diastolic volume index; LGE: late

gadolinium enhancement; LVMI: left ventricle mass index; MPR: myocardial perfusion reserve; MWT: maximal wall thickness; PMJs: Purkinje-myocardial junctions; RR: R-R interval; RT90: time to 90% of epicardial repolarization; S-BP: systolic blood pressure; SVi: stroke volume index.

Variable	All (n=30)	Female (n=18)	Male (n=12)	<i>p</i> _{adj} -value
Demographics				
<i>Age (years)</i>	76.68 [76.33–77.44]	76.72 [75.99–77.36]	76.63 [76.47–77.50]	0.753
<i>Height (cm)</i>	162.95 [160.85–172.75]	161.80 [159.82–164.83]	172.50 [161.75–175.25]	0.158
<i>Weight (kg)</i>	66.20 [59.50–74.88]	64.55 [58.35–69.27]	71.25 [64.53–77.62]	0.158
<i>BSA (m²)</i>	1.72 [1.61–1.82]	1.68 [1.60–1.75]	1.81 [1.76–1.92]	0.098
<i>BMI (kg/m²)</i>	24.92 [21.74–26.75]	24.92 [20.75–26.75]	24.65 [22.32–26.67]	0.753
<i>S-BP (mmHg)</i>	123.00 [118.50–130.75]	123.00 [118.08–134.33]	123.50 [119.50–128.50]	0.897
<i>D-BP (mmHg)</i>	72.83 [66.08–78.16]	71.66 [64.50–77.42]	76.00 [68.66–79.33]	0.478
<i>eGFR (mL/min/1.73 m²)</i>	90.15 [77.03–95.45]	84.15 [72.00–91.50]	96.05 [92.72–101.30]	0.028
CMR parameters				
<i>EDVi (mL/m²)</i>	67.76 [61.72–74.26]	62.98 [61.17–70.62]	72.23 [66.04–76.48]	0.152
<i>ESVi (mL/m²)</i>	20.15 [17.23–24.17]	17.70 [15.83–20.66]	23.93 [20.63–27.23]	0.028
<i>SVi (mL/m²)</i>	48.69 [44.23–50.23]	48.69 [41.51–50.20]	48.43 [45.89–50.01]	0.647
<i>EF (%)</i>	70.06 [66.59–73.52]	72.46 [68.98–75.44]	66.93 [65.31–69.16]	0.048
<i>LVMI (g/m²)</i>	46.18 [41.26–50.26]	42.08 [39.80–47.56]	48.98 [46.20–53.06]	0.047
<i>MWT (mm)</i>	10.54 [9.53–11.29]	10.23 [9.25–11.05]	10.84 [10.25–11.32]	0.459
<i>LA-EDVi (mL/m²)</i>	6.44 [4.75–7.52]	6.30 [4.68–7.37]	6.55 [4.93–7.89]	0.647
<i>T1 (ms)</i>	1297.82 [1282.34–1319.39]	1303.72 [1291.73–1319.39]	1284.22 [1271.44–1314.19]	0.288
<i>MPR</i>	2.68 [2.06–3.20]	2.25 [1.69–2.71]	3.21 [2.92–4.04]	0.028
<i>Core LGE (%)</i>	0.00 [0.00–0.04]	0.00 [0.00–0.00]	0.00 [0.00–0.20]	0.753
<i>ECV (%)</i>	27.78 [24.93–28.98]	28.05 [26.95–29.12]	25.41 [24.68–26.70]	0.168

Variable	All (n=30)	Female (n=18)	Male (n=12)	$p_{\text{adj-value}}$
<i>ECGI parameters</i>				
<i>RR (ms)</i>	931.25 [855.50–993.88]	942.30 [857.32–988.10]	881.55 [850.62–995.95]	0.753
<i>CV (m/s)</i>	0.83 [0.73–0.94]	0.82 [0.77–1.01]	0.83 [0.71–0.87]	0.640
<i>AT90 (ms)</i>	50.20 [44.26–54.04]	48.79 [40.78–51.97]	53.75 [48.60–56.77]	0.168
<i>RT90 (ms)</i>	275.32 [232.17–320.89]	280.45 [232.17–319.59]	259.88 [232.00–320.69]	0.879
<i>ARI90 (ms)</i>	308.13 [275.97–338.91]	308.13 [275.97–338.82]	306.89 [278.74–341.18]	1.000
<i>In silico parametrization</i>				
D_f (cm ² /ms)	0.0020 [0.0015–0.0026]	0.0019 [0.0017–0.0031]	0.0020 [0.0014–0.0022]	0.640
g_{Ks}	2.59 [1.87–3.19]	3.08 [2.09–3.63]	2.21 [1.29–2.39]	0.039
AgR	1.02 [0.99–1.13]	1.06 [1.01–1.19]	1.00 [0.96–1.02]	0.039
PMJs	20.00 [15.00–44.50]	16.50 [12.00–37.75]	25.00 [16.75–50.50]	0.291

Table 1 summarizes the basic demographics and clinical characteristics of the MyoFit46 healthy cohort. Of the 505 available MyoFit46 participants, 30 fulfilled the inclusion/exclusion and modeling criteria, with late gadolinium enhancement (LGE) burden and hypertension being the two main exclusion drivers. A detailed flow diagram of participant selection can be found on **Supplementary material S2**. Sex-differences were found on estimated glomerular filtration rate, left ventricle (LV) indexed end-systolic volume, LV mass index, and myocardial perfusion reserve (**Table 1**). For the *in silico* parameters, females presented statistically higher mean g_{Ks} and AgR scale factors (**Table 1**). The remaining *in silico* EP parameters were not significantly different between sexes. The median *in silico* parameters obtained after personalization were a spatially constant fiber-direction diffusion coefficient (D_f) of 0.0020 cm²/ms and 20 PMJs per participant.

Healthy population replication

Figure 1 summarizes the agreement between ECGI-derived and simulated epicardial dynamics for both activation (**Figure 1a, c, e**) and repolarization (**Figure 1b, d, f**).

Regarding activation (**Figure 1a**), normalized cumulative activation curves showed close agreement between simulations and ECGI, with a stable interquartile range of timing errors throughout the activation. The ECGI data exhibited a slower activation rate during early phases but increased towards the end of the latest activated regions with respect to the DTs. Across the cohort, the global AT-RMSE was 12.31 ± 3.99 ms. Spatially, the ECGI showed earlier RV activation and delayed activation at the LV–RV insertion relative to the *in silico* results, while differences across the LV were spatially heterogeneous (**Figure 1c**). **Figure 1e** illustrates the spatially localized sources of errors in three DTs: (i) regions of late activation, where ECGI was faster than replicated DT activation, and (ii) regions where the spherical endocardial activation locations produce fast breakthroughs in the RV epicardium. These effects contribute to the overall error reported. Lastly, after matching the activation sequences, the ECGI-derived apparent CV was systematically faster than the simulated apparent CV, with a mean CV relative error of $-15.60\% \pm 4.82\%$, consistent with the sequence-dependent bias identified during verification tests (**Supplementary S1.2**).

In contrast, repolarization dynamics quantified in the ECGI (**Figure 1b**) showed an initial delay with respect to the DTs, followed by a gradual shift toward earlier times at the end of repolarization, approaching the mean DTs pattern. The mean global RT-RMSE was 15.14 ± 3.63 ms. Repolarization tended to occur later in the ECGI than in the *in silico* estimates, except at specific locations (the mid RV wall and the inferolateral LV wall), where it occurred earlier (**Figure 1d**). Subject-specific maps showed that simulated patterns remained qualitatively consistent with ECGI, preserving global gradients despite a systematic shift toward earlier repolarization in the basal regions (**Figure 1f**).

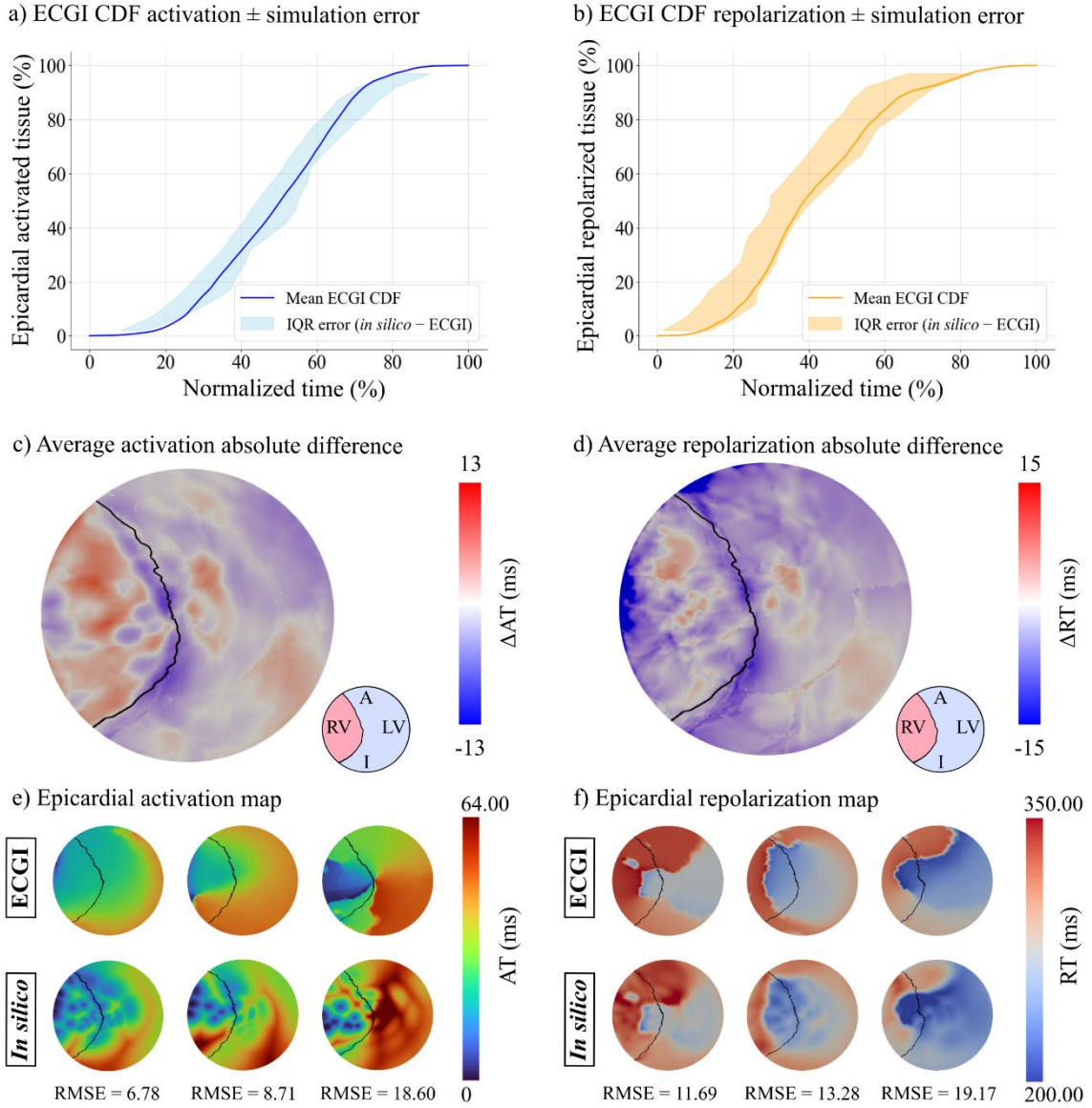


Figure 1. Replication of *in vivo* epicardial dynamics by personalized digital twins across the MyoFit46 cohort. Agreement between electrocardiographic imaging (ECGI)-derived and *in silico* epicardial activation (a, c, e) and repolarization (b, d, f) dynamics across the healthy MyoFit46 cohort. For both phases, panels are displayed from top to bottom: (a, b) the cumulative distribution function (CDF) of activated and repolarized tissue against normalized time are represented. The solid line represents the mean ECGI CDF, used as a temporal anchor, while the shaded region encodes the interquartile range of the paired percentile differences between *in silico* and ECGI CDFs; (c, d) a flattened epicardial representation of the mean healthy anatomy showing the point-to-point mean absolute error (*in silico* – ECGI) across the 30 participants, ΔAT for activation times (ATs) and ΔRT for repolarization times (RTs); and (e, f) three representative subjects, selected to span a range of characteristic root mean squared error (RMSE) values, comparing ECGI (top) and *in silico* (bottom) epicardial maps. The anatomical orientation of the flattened representation is indicated by the inset schematic, where right ventricle (RV) and left ventricle (LV) denote the right and left ventricles and A and I denote the anterior and inferior regions, respectively. The black curve delineates the LV–RV boundary.

Healthy aging atlas: activation sequences

Obtained activation sequences (i.e., PMJ location and time of activation) were mapped to the mean healthy anatomy (MHA) for population level analysis of the distribution of PMJs along the MyoFit46 healthy cohort. After exclusion of supplementary PMJs, 1034 PMJs remained among the 30 participants.

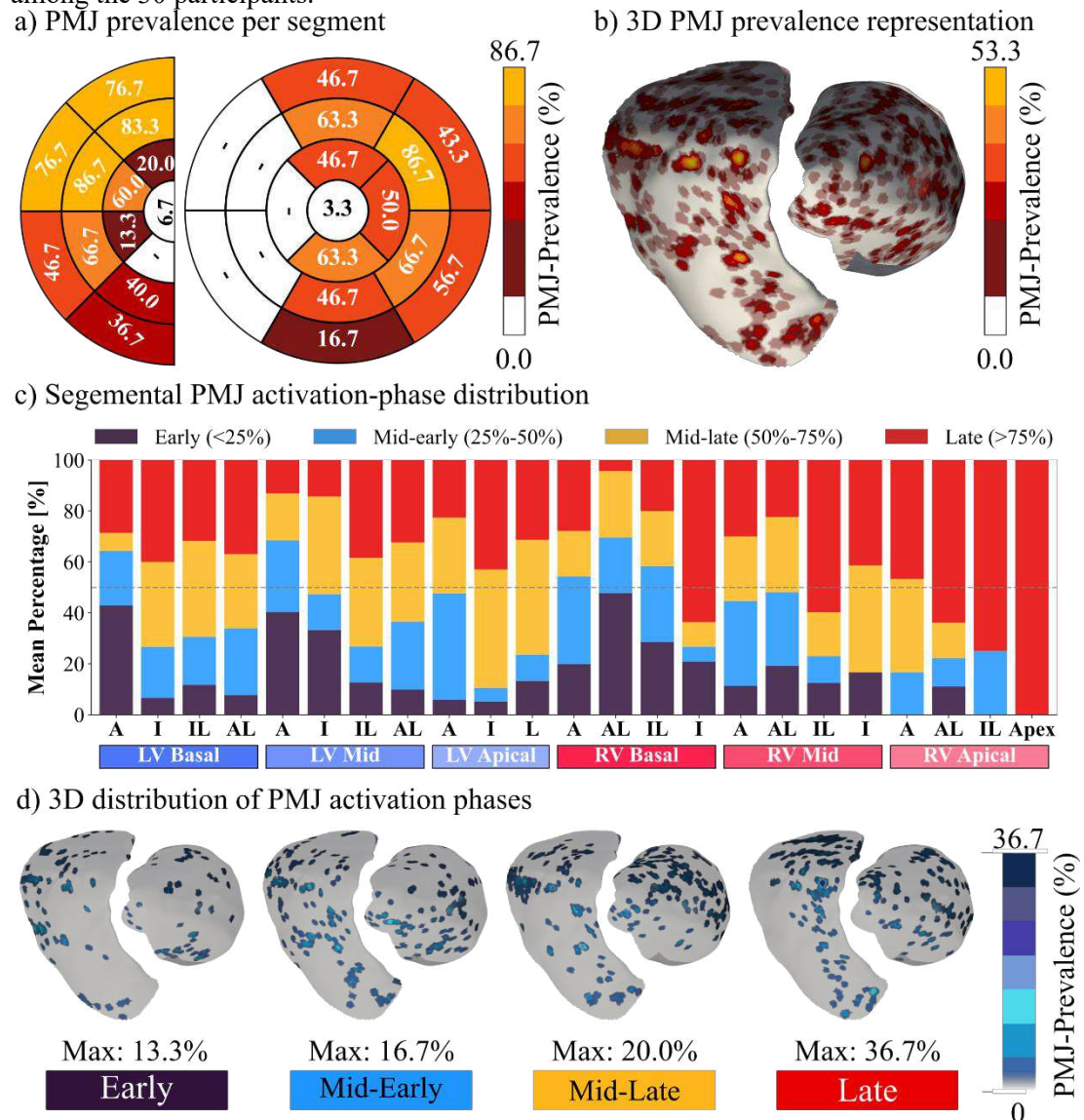


Figure 2. Spatial distribution, prevalence, and activation-phase dynamics of Purkinje-Myocardial

junctions (PMJs) across the healthy MyoFit46 cohort. (a) PMJ prevalence expressed as the percentage of participants with at least one PMJ within each segment, displayed separately for the left ventricle (LV) and right ventricle (RV) bull's-eye. Color scale ranges from white (low prevalence) to dark red (high prevalence). (b) Three-dimensional endocardial representation of the mean healthy anatomy (MHA) showing the spatial density of PMJ hotspots across the LV and RV, with color intensity reflecting local PMJ prevalence. (c) Mean percentage of activation-phase profiles of PMJs per anatomical segment. Activation times were normalized

from 0% (first PMJ activated) to 100% (last PMJ activated) for each participant to remove inter-subject temporal variability. Stacked bars illustrate the fraction of PMJs activated during four defined phases: Early (<25%, dark purple), Mid-early (25–50%, blue), Mid-late (50–75%, amber), and Late (>75%, red). Segments are grouped anatomically by region (LV Basal, LV Mid, LV Apical, RV Basal, RV Mid, RV Apical), with LV and RV walls aligned for direct comparison. (d) MHA endocardial surfaces showing the spatial distribution of PMJs stratified by activation phase, from Early (leftmost) to Late (rightmost). Color intensity reflects local PMJ density within each phase. A: anterior; AS: antero-septal; IS: inferoseptal; I: inferior; IL: inferolateral; AL: anterolateral; S: septal; L: lateral.

Figure 2 summarizes the spatial distribution, prevalence, and activation-phase dynamics of PMJs across the cohort. **Figure 2a, b** show PMJ prevalence per LV segments and the 13 supplementary RV segments and their 3D equivalent. The regions with the highest prevalences are the mid anterolateral wall of the LV and the mid anterolateral RV wall, with 86.66% of cases with at least one PMJs on those regions. From a chamber-based analysis, we observed that the LV PMJs were distributed throughout the chamber, whereas on the RV there was a clear difference between the anterior and inferior wall (see **Figure 2a**). In **Figure 2b**, we observed 6 regions that showed a prevalence of more than 35%: one on the LV mid inferolateral wall, three on the lateral RV wall distributed longitudinally and two on the mid and basal anterior RV wall.

Figure 2c shows the percentage of PMJ being activated per segment across four phases, defined by normalized activation time (i.e., Early (<25%), Mid-early (25–50%), Mid-late (50–75%), and Late (>75%)). The basal and mid-anterior regions of the LV, alongside the basal anterolateral region of the RV, exhibited the highest concentration of early activation, with over 60% of their PMJs firing during the early or mid-early phases. Then, there are regions with no clear phase dominance (i.e., neither late nor early phases have a percentage higher than 60%). These included the basal and mid anterior, mid anterolateral, and basal inferolateral regions of the RV, and the mid inferior and apical anterior regions of the LV. The remaining endocardial regions were predominantly activated during the late phases. **Figure 2d** shows in more detail how those early or late activated PMJs are distributed anatomically. Early-activated PMJ were mostly distributed across the LV anterior wall and the RV base, whereas late-activated PMJ were

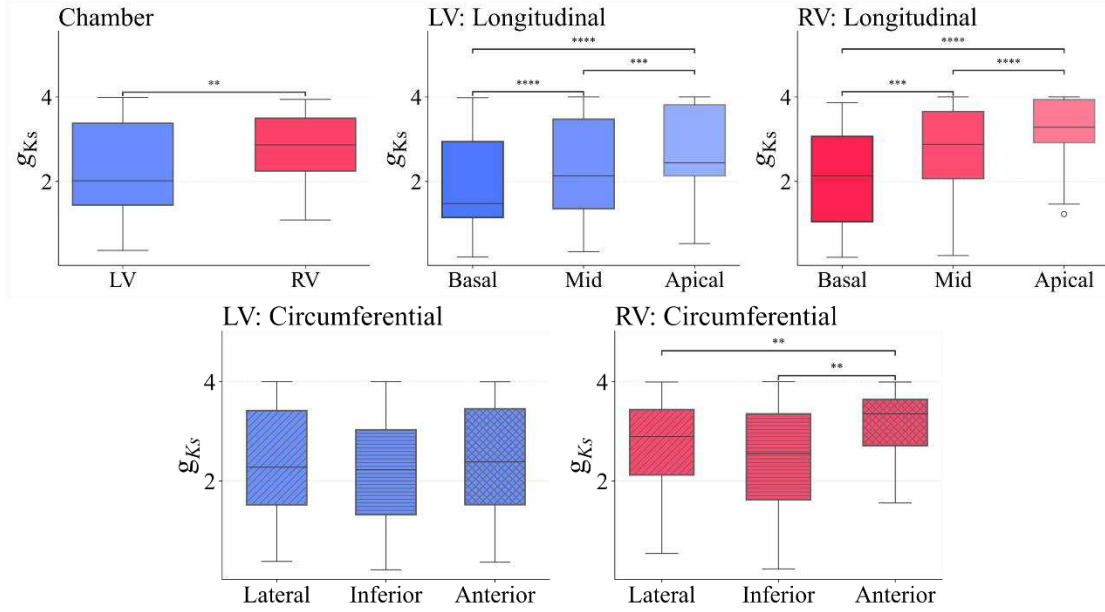
distributed homogeneously for the LV and apically located for the RV. Mid-early and mid-late PMJs showed a transition from a mostly lateral LV distribution, towards a more inferior distribution for the mid-late activated PMJs.

Healthy aging atlas: regional repolarization heterogeneities

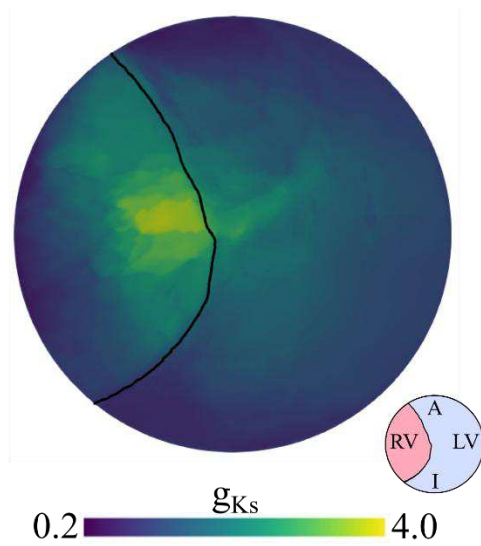
Baseline repolarization

The obtained baseline regional repolarization heterogeneities were mapped to the MHA of the MyoFit46 cohort for posterior analysis at multiple levels (**Figure 3**) using: (a) regional comparison and (b-c) in 3D representation using principal component analysis for the calculation of mean and modes of variation of the 3D g_{Ks} distribution. Overall, RV presented a higher g_{Ks} value than LV ($p=0.0026$, **Figure 3a**) with a clear g_{Ks} decay from the apex to the base in both chambers (**Figure 3a**). On the circumferential direction, there were only significant larger g_{Ks} values on the anterior wall than in the lateral and inferior walls (**Figure 3a**). **Figure 3b** recapitulates the apico-basal gradient described above, with higher g_{Ks} values at the RV apex decaying progressively toward the base. Principal component analysis of the spatially resolved g_{Ks} maps (**Figure 3c**) revealed that the first three modes of variation together explain 75% of inter-subject repolarization variability across the MyoFit46 cohort. Mode 1 defines the amplitude and direction of the longitudinal gradient. Modes 2 and 3 capture nearly orthogonal transverse gradients: mode 2 describes a g_{Ks} gradient from the RV anterolateral wall toward the LV inferolateral wall, while mode 3 describes the opposite orientation, from the RV inferolateral wall toward the LV anterolateral wall.

a) Regional g_{Ks} distribution



b) Mean spatial g_{Ks} distribution



c) Modes of variation in g_{Ks}

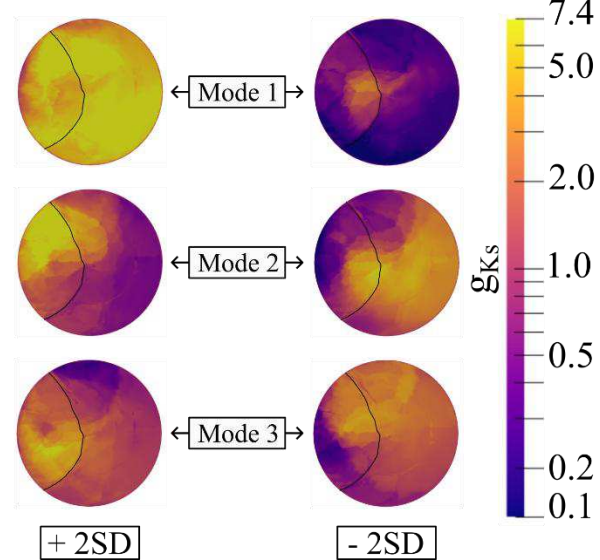


Figure 3. Baseline repolarization atlas: regional distribution and principal modes of variation of g_{Ks} across the healthy MyoFit46 cohort. (a) Boxplots of g_{Ks} scaling factors comparing inter-chamber (left ventricle (LV) vs. right ventricle (RV)), LV and RV longitudinal (Basal, Mid, Apical), and circumferential (Lateral, Inferior, Anterior) distributions. Statistical significance was assessed using the Mann-Whitney U test with Benjamini–Hochberg correction (* $p_{adj} < 0.05$, *** $p_{adj} < 0.001$). (b) Cohort-mean g_{Ks} map displayed on the flattened biventricular endocardial surface. The black curve delineates the LV–RV boundary. (c) Three leading principal modes of variation (Modes 1–3) derived from principal component analysis of the spatially resolved g_{Ks} maps across participants. For each mode, the positive (left) and negative (right) extremes (mean $\pm$ 2 standard deviations (SD)) are shown on the flattened biventricular surface, illustrating the dominant spatial patterns of inter-

subject variability. The anatomical orientation of the flattened epicardial representation is indicated by the inset schematic, where RV and LV denote right and left ventricles, respectively, and A and I denote anterior and inferior regions. g_{Ks} : slow delayed rectifier potassium current conductance scaling factor.

Aging repolarization

The median surface proportion of each compensation class per region is summarized in **Table 2**, while **Figure 4** illustrates the pointwise prevalence of each compensation class across the cohort. The neutral regulation ($AgR^=$) was the dominant spatial pattern, accounting for a median of 61.4% of epicardial surface covered by no AgR adjustment. The shortening ($AgR^\downarrow$) and prolongation ($AgR^\uparrow$) accounted for a median of 17.9% and 3.7% of the surface, respectively. Notably, $AgR^\downarrow$ regions were present in all 30 subjects, while $AgR^\uparrow$ regions were identified in 27 out of 30 subjects (90%), indicating that at least one form of active AgR regulation was present in every participant.

Table 2. Regional distribution of aging repolarization (AgR) classes across the healthy MyoFit46 cohort.

Median [interquartile range] epicardial surface percentage covered by $AgR^\downarrow$ (shortening), $AgR^=$ (neutral), and $AgR^\uparrow$ (prolongation) compensation per region across 30 subjects. Medians are computed independently per class and do not sum to 100%. Chamber comparisons were assessed using the Wilcoxon signed-rank test; longitudinal and circumferential comparisons using the Friedman omnibus test. Post-hoc analysis can be found in Supplementary S3. LV: left ventricle; RV: right ventricle.

Region	$AgR^\downarrow$ (%)	$AgR^\uparrow$ (%)	$AgR^=$ (%)
Global	17.9 [5.2–46.6]	3.7 [0.2–17.2]	61.4 [43.4–82.7]
Chamber			
LV	1.5 [0.2–21.5]	3.4 [0.2–18.0]	75.3 [48.8–89.5]
RV	31.5 [9.4–69.1]	2.0 [0.0–19.3]	60.6 [22.3–75.5]
<i>p</i> -value	<0.001	0.374	<0.01
Longitudinal LV			
LV Base	0.5 [0.0–6.2]	8.8 [0.2–32.2]	70.1 [52.2–92.6]
LV Mid	0.7 [0.0–12.6]	0.3 [0.0–14.3]	80.8 [53.0–92.7]

LV Apex	2.2 [0.0–54.9]	0.0 [0.0–0.3]	86.0 [38.5–99.8]
<i>p</i> -value	0.045	<0.001	0.190
<i>Longitudinal RV</i>			
RV Base	15.8 [1.2–35.9]	3.9 [0.1–46.9]	52.7 [29.5–76.4]
RV Mid	32.8 [7.9–80.1]	0.0 [0.0–7.1]	52.1 [14.1–84.6]
RV Apex	38.0 [0.1–95.0]	0.0 [0.0–0.0]	57.5 [2.4–99.5]
<i>p</i> -value	0.016	<0.001	0.873
<i>Circumferential LV</i>			
LV Lateral	1.0 [0.0–11.6]	0.9 [0.0–10.2]	88.2 [54.2–96.4]
LV Inferior	0.0 [0.0–6.7]	1.1 [0.0–26.7]	83.1 [42.0–99.1]
LV Anterior	4.2 [0.0–43.0]	2.0 [0.0–17.7]	64.2 [25.4–94.6]
<i>p</i> -value	<0.01	0.137	0.107
<i>Circumferential RV</i>			
RV Lateral	7.3 [0.0–59.9]	0.2 [0.0–13.1]	68.7 [23.2–90.9]
RV Inferior	41.4 [0.0–96.4]	0.0 [0.0–0.0]	54.8 [3.6–100.0]
RV Anterior	53.6 [10.6–72.8]	2.1 [0.1–17.4]	37.1 [19.1–78.1]
<i>p</i> -value	<0.01	<0.001	0.267

As illustrated in **Figure 4b**, AgR[−] was present throughout the epicardial surface with higher pointwise prevalence in the LV, reaching regions with prevalence higher than 80%. Consistently, the median surface percentage was significantly higher in the LV than in the RV (**Table 2**). Notably, in the mid, apical, lateral, and inferior LV regions exceeded 80% of epicardial surface coverage (**Table 2**). No significant longitudinal or circumferential gradients were identified in either chamber (**Table 2**).

The second most prevalent compensation class, AgR[↓] showed a markedly higher surface percentage in the RV compared to the LV (**Table 2**), representing the largest chamber-level difference observed across all three classes. As illustrated in **Figure 4c**, AgR[↓] was

predominantly concentrated toward the apex in both ventricles, with a particularly pronounced mid-apical accumulation in the RV. Consistently, the median surface percentage increased from base to apex in the RV and LV (more details in **Supplementary S3**). At the circumferential level, a significant gradient was identified in the LV (**Table 2**), driven by differences between the three defined segments for both ventricles (all $p_{\text{adj}} < 0.05$), except between RV inferior and anterior walls ($p_{\text{adj}} = 0.919$).

Lastly, $\text{AgR}^{\uparrow}$ was the least prevalent compensation class, with no significant difference in surface proportion between the LV and RV (**Table 2**). However, a consistent and significant base-to-apex gradient was identified in both ventricles (**Table 2**), with $\text{AgR}^{\uparrow}$ concentrated at the base and virtually absent at the apex. As illustrated in **Figure 4a**, this basal concentration was particularly evident in the RV lateral wall and the LV inferior and anterior walls. At the circumferential level, no significant gradient was identified in the LV (**Table 2**), whereas a significant circumferential gradient was found in the RV, driven by differences between the lateral and inferior walls ($p_{\text{adj}} < 0.001$) and between the inferior and anterior walls ($p_{\text{adj}} < 0.001$).

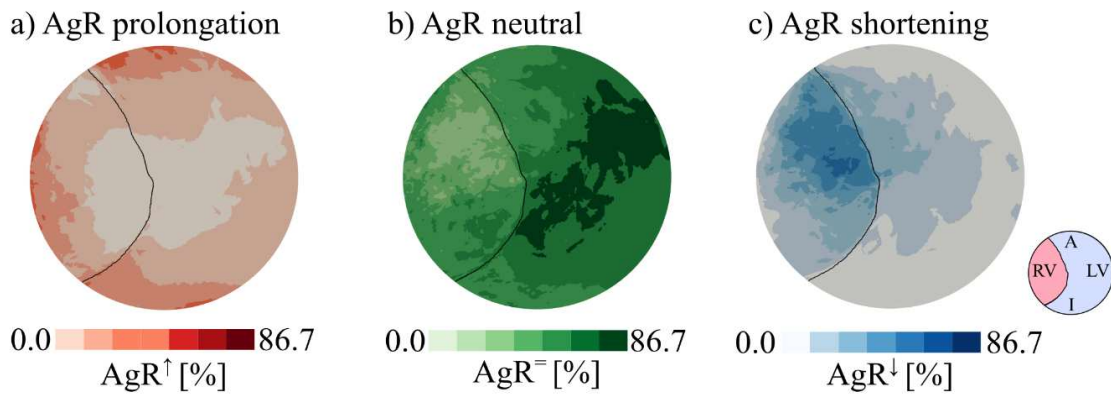


Figure 4. Aging repolarization (AgR) classes epicardial prevalence. Population-level prevalence maps of AgR compensation classes across the healthy MyoFit46 cohort. Each map displays the proportion of subjects exhibiting a given AgR compensation state at each epicardial point, ranging from 0 (no subject) to 100 ($n=30$). a) $\text{AgR}^{\uparrow}$ prolongation compensation prevalence. b) $\text{AgR}^{\pm}$ neutral prevalence (no compensation). c) $\text{AgR}^{\downarrow}$ shortening compensation prevalence. The black line indicates the LV-RV insertion. The anatomical orientation of the flattened epicardial representation is indicated by the inset schematic, where RV and LV denote right and left ventricles, respectively, and A and I denote anterior and inferior regions.

Atlas-Based eHTN cohort remodeling

A total of 47 participants (26 females) were selected from the 505 MyoFit46 participants for the eHTN cohort. The only significant clinical difference with the healthy cohort was in systolic and diastolic blood pressure ($p_{\text{adj}} < 0.001$), both higher in eHTN cohort. LV mass index trended higher in eHTN without reaching significance (46.18 vs. 49.75, $p_{\text{adj}} = 0.160$, healthy vs. eHTN). Same pattern was reported for time to 90% AT, RT and activation-repolarization intervals (ARIs) (AT: 50.20 vs. 53.38 ms, $p_{\text{adj}} = 0.160$; RT: 275.32 vs. 302.38 ms, $p_{\text{adj}} = 0.160$, and ARI: 308.13 vs. 336.72 ms, $p_{\text{adj}} = 0.160$, healthy vs. eHTN). AgR and g_{Ks} scaling factor showed sex differences, with larger values for the female eHTN subgroup (g_{Ks} : 2.89 vs. 1.34, $p_{\text{adj}} = 0.004$; AgR: 1.13 vs. 0.97 $p_{\text{adj}} = 0.004$). Complete demographics and clinical details are provided in **Supplementary S4-5**. eHTN personalized DTs achieved a comparable replication quality, with mean AT-RMSE and RT-RMSE of 12.5 ± 3.2 ms and 15.9 ± 3.6 ms, respectively. A comprehensive replication comparison of the eHTN cohort is provided in **Supplementary S6**.

Figure 5 summarizes the main atlas-based findings for the eHTN and healthy cohorts: (a) the mean 3D prevalence of PMJs on the eHTN cohort; (b) the mean g_{Ks} prevalence difference between eHTN and healthy atlases; and (c) the AgR classes prevalence differences. A complete atlas-like analysis of the eHTN cohort can be found on **Supplementary S7**. Regarding PMJs distribution, as can be observed in **Figure 5a**, the main PMJs hotspots identified on the healthy atlas are preserved on the eHTN subgroup, including a broader spectrum of PMJ locations. At segment-level, PMJ prevalence did not differ between cohorts (Wilcoxon signed-rank, $p = 0.62$; sign test 14-/12+, $p = 0.62$, true LV and RV apex and segments without PMJ discarded for the comparison, **Supplementary S8.1**). Phase-wise comparison across defined segments revealed a significant reduction of the Late-phase fraction in eHTN (median $\Delta = -7.89$ pp, Wilcoxon $p_{\text{adj}} = 0.021$), directionally consistent across 17 of 22 segments (sign test $p_{\text{adj}} = 0.068$, LV and RV true apex and segments with non PMJ excluded). The displaced mass redistributed predominantly toward the Mid-early phase (median $\Delta = +5.10$ pp), though not reaching significance after

correction ($p_{\text{adj}} = 0.098$). Early and Mid-late fractions were unchanged (See **Supplementary S8.2**).

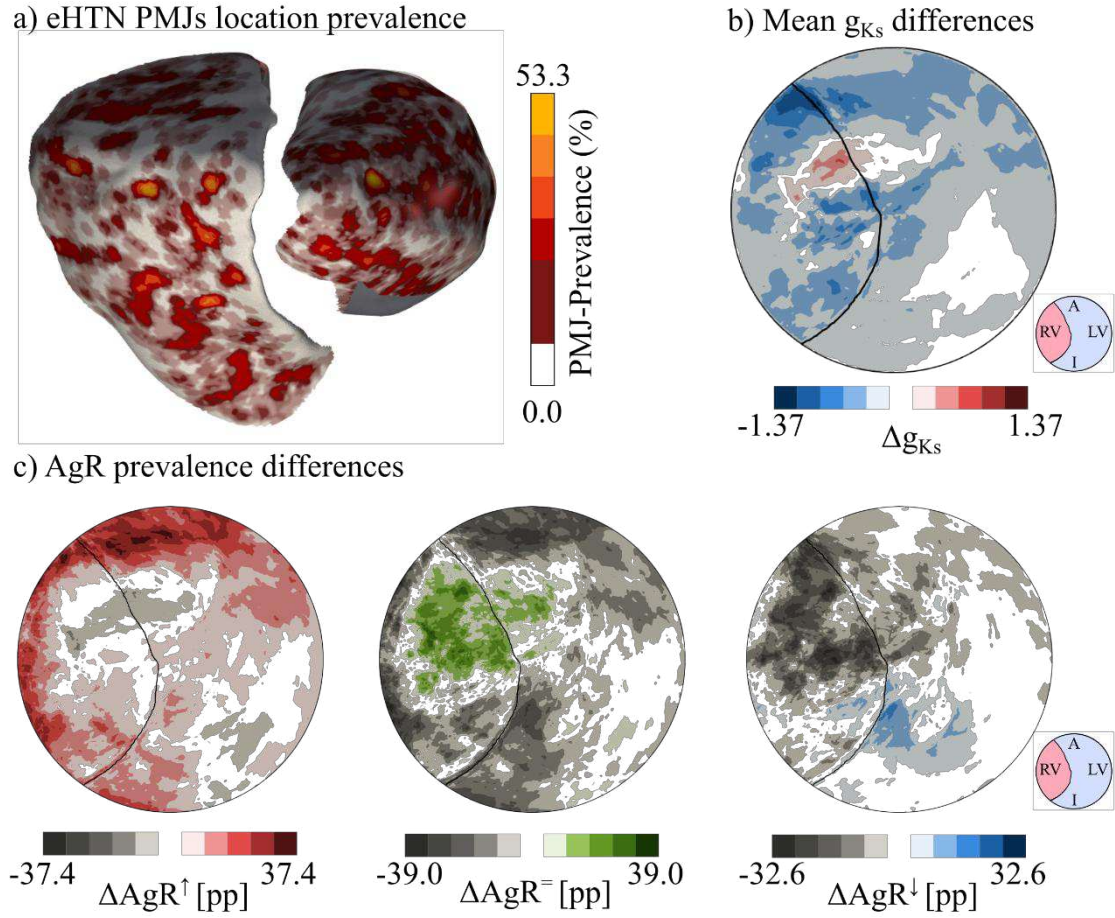


Figure 5. Atlas-based localization of early-stage hypertension (eHTN)-associated electrophysiological remodeling. (a) Three-dimensional endocardial representation of the joint mean anatomy showing the spatial density of Purkinje-myocardial junction (PMJ) hotspots across the left ventricle (LV) and right ventricle (RV) for eHTN cohort, with color intensity reflecting local PMJ prevalence. (b) Point-wise difference maps (eHTN minus healthy) of slow delayed rectifier potassium current conductance scaling factors (g_{Ks}), displayed on the flattened biventricular epicardial representation of the joint mean anatomy. Blue indicates lower g_{Ks} in the eHTN cohort and red indicates higher g_{Ks} . (c) Point-wise difference maps of aging repolarization (AgR) compensation class prevalence on the flattened biventricular epicardial representation of the joint mean anatomy, shown from left to right for $\text{AgR}^{\uparrow}$ prolongation (red), $\text{AgR}^{\text{=}}$ neutral (green), and $\text{AgR}^{\downarrow}$ shortening (blue). Positive values (colored) indicate higher prevalence in the eHTN cohort and negative values (greyscale) indicate lower prevalence relative to the healthy atlas; differences within ± 2 percentage points (pp) are rendered transparent to suppress noise-like variation. The black line indicates the LV-RV insertion. The

anatomical orientation of the flattened epicardial representation is indicated by the inset schematic, where RV and LV denote right and left ventricles, respectively, and A and I denote anterior and inferior regions.

Figure 5b highlights the g_{Ks} regional differences between the mean eHTN map and the healthy one, where blue denotes reduction from healthy to eHTN and red increment. From those differences can be identified a reduction of g_{Ks} values particularly on the RV. However, no previously defined region reached statistical significance with respect to healthy values (all $p_{adj} > 0.05$, **Supplementary 8.3**), and a sign test on the regional median differences was not significant (11 of 15 regions reduced, $p = 0.119$). Lastly, **Figure 5c** illustrates the AgR prevalences classes difference between the eHTN and healthy cohorts. Increase in prevalence of each class is defined by colored regions, while downgrade by grayscale. Comparison of AgR class prevalences revealed a general increment of $AgR^{\uparrow}$, with 12 out of 15 ventricular regions, previously defined in **Table 2**, showing prevalence increment (sign test, $p_{adj} = 0.0015$), as consequence $AgR^{\downarrow}$ prevalence was reduced in 11 out of 15 regions ($p_{adj} = 0.086$). Regionally, $AgR^{\uparrow}$ prevalence is mostly accumulated on the basal regions of the RV and inferior and anterior LV walls (**Figure 5c**), expanding the prevalence pattern reported in the healthy cohort (**Figure 4a**), transferred from the $AgR^=$ class. In contrast, $AgR^{\downarrow}$ is mostly reduced on the RV (**Figure 5c**) and transferred to the $AgR^=$ class (**Figure 5c**). No statistically significant difference was observed between the distribution of proportions of AgR per ventricular region between healthy and eHTN cohorts (all $p_{adj} > 0.05$, **Supplementary S8.4**)

Discussion

This study presents the first population-scale 3D EP atlas of healthy cardiac aging, providing a normative reference for ventricular conduction properties, endocardial activation sequences, and regional repolarization heterogeneities in a rigorously selected cohort of community-dwelling adults aged 75+. Its central finding is that healthy cardiac aging at age 75+ produces electrophysiologically structured, spatially consistent remodeling that is computationally

distinct from the assumptions embedded in standard adult cellular models. Three findings support this conclusion: every participant required an aging-specific repolarization adjustment; the population-level PMJ distributions were structured and extended classical anatomical descriptions to a living older cohort; and the repolarization heterogeneities were spatially coherent, concentrating where the baseline repolarization burden was highest. Grounded in the unique MyoFit46 birth-cohort design and a deterministic CMR-ECGI mapping framework that directly translates multimodal clinical data into subject-specific DTs, the atlas provides a principled baseline against which early-stage remodeling in eHTN participants was assessed as an atlas-based application.

Of the 505 MyoFit46 participants, only 30 met the inclusion/exclusion criteria for the healthy reference subgroup, with LGE burden and hypertension as the two main exclusion drivers. This attrition itself reflects how rare a clinically healthy phenotype is at age 75+. Even so, the atlas revealed that the AgR layer was required in every one of the 30 participants, demonstrating that standard adult cellular models do not adequately reproduce the repolarization dynamics of healthy aging hearts and that explicit age-related ionic remodeling is systematically necessary in this population. This confirms that the electrophysiological remodeling associated with aging, including accumulation of senescent cells¹⁴ and Ca^{2+} pathway dysregulation⁸, induced repolarization dynamics distinct from those captured by the young adult O'Hara-Rudy healthy cardiomyocyte model^{33,34}. Critically, standard adult cellular formulations may systematically underestimate or mischaracterize repolarization-dependent outcomes in this age group during *in silico* cardiac safety pharmacology, as recently demonstrated for age-related hormonal decline in drug trial frameworks³⁵.

The AgR requirement having been established, the next question is where age-related remodeling accumulates and how it relates to the underlying repolarization landscape. Spatially, the AgR layer did not introduce independent remodeling patterns but rather reinforced and extended the heterogeneities already encoded in the baseline g_{Ks} . The baseline layer captured the dominant pattern: an apex-to-base gradient with higher values at the apex progressively

decaying toward the base in both the LV and RV, pattern previously observed on healthy young individuals^{36,37}. In addition, the principal component analysis revealed secondary transverse gradients from the RV anterolateral to the LV inferolateral walls, a pattern not previously reported to our knowledge, suggesting a level of repolarization complexity only accessible through the 3D atlas approach, but not strictly related to aging. The AgR layer specifically encoded: $\text{AgR}^{\downarrow}$ concentrated at the RV apex where g_{Ks} was highest, and $\text{AgR}^{\uparrow}$ concentrated at the base where g_{Ks} was lowest. This additive behavior suggested that age-related remodeling accumulates preferentially in regions already carrying the highest repolarization burden. The LV lateral wall was the region least affected by age-related repolarization remodeling. Together, these spatial findings demonstrate that healthy cardiac aging produces structured, anatomically consistent repolarization heterogeneities rather than diffuse or random remodeling, with implications for how age-related substrates are spatially represented on the aging heart.

These spatially structured repolarization heterogeneities were not uniform across the cohort. Beyond the spatial patterning of age-related remodeling, the atlas revealed significant sex differences in both repolarization layers, with g_{Ks} and AgR scaling factors both significantly higher in females than males. This pattern is consistent with sex-specific ion channel expression in the cellular model, with longer action potential durations in females³⁴. However, age-related decline in sex hormones attenuates these differences in elderly cohorts³⁸, reducing the shortening and lengthening effects of testosterone and estrogen on action potential duration¹². As a result, the larger scaling adjustments required in females reflect not only an intrinsic sex difference in repolarization but also the compounding effects of age-related hormonal changes, highlighting a potential life-course interaction with implications for sex-stratified risk assessment in older adults³⁹.

The atlas characterized the most prevalent activation sequences in this healthy aging population, revealing consistent population-level PMJ distributions that closely aligned with the classical *ex vivo* mapping of Durrer et al.³². LV initial activation predominantly originated in the basal anterior regions, corresponding to Durrer's high anterior para-septal area, which extends toward

the anterior papillary muscle, and propagated toward the inferior and lateral walls, where the majority of late-activated LV PMJs were located. A concentrated PMJ hotspot emerged on the mid inferior wall in over 35% of participants, anatomically corresponding to the posterior papillary muscle insertions and lying near Durrer's posterior para-septal area. Beyond these primary hotspots, the remaining LV PMJs were broadly distributed, reflecting the dense nature of the left Purkinje Network. In contrast, the RV displayed a distinct base-to-apex activation sequence driven by five highly structured PMJ hotspots — three clustered along the lateral wall and two on the mid-inferolateral and mid-anterolateral walls — consistent with the structural insertions of the moderator band into the RV free wall⁴⁰. These RV findings expand upon Durrer's initial observation of early RV activation near the anterior papillary muscle³², providing a more granular, population-level map of *in vivo* RV free-wall insertions. Together, the PMJ atlas provides the first population-scale *in vivo* map of healthy aging activation sequences, extending classical *ex vivo* anatomical descriptions to a living older age cohort, although septal and basal coverage remains inherently limited by the ECGI inverse solution.

As a proof-of-concept, the framework was applied to an age-matched eHTN subgroup from within the MyoFit46 cohort, capturing participants at an early disease stage, meeting guideline criteria for a diagnosis of hypertension but without overt target organ damage. This eHTN subgroup allows us to show the atlas' ability to identify subclinical, function-level electrostructural remodeling at the early stages of hypertensive heart disease. The *in vivo* replication by the DTs and the generated structural scaffold of the atlas was preserved between cohorts. Cohort characteristics —except blood pressure measurements—PMJ distributions across segments and the apico-basal g_{Ks} gradient did not differ significantly from the healthy reference. Despite the absence of structural remodeling in the eHTN group, a global transition from $AgR^{\downarrow}$ toward $AgR^{\uparrow}$ was found, indicating a directional shift toward action potential prolongation that has previously been linked to hypertensive remodeling^{41,42}. Additionally, this atlas-based comparison further localized that remodeling to the basal regions, most pronounced in the RV. These regions may correspond to sites more susceptible to arrhythmogenic events⁴³ and, given

the established link between higher life-course blood pressure and myocardial fibrosis in this cohort⁴⁴ potentially to early fibrotic remodeling. Additionally, a redistribution of PMJ activation from late toward mid-early was observed, indicating an earlier-weighted activation pattern; although PMJ remodeling and altered activation have been reported in murine hypertensive pressure overload⁴⁵ the specific mechanistic correlate of this redistribution remains to be established.

Beyond this study, the atlas provides a non-invasive framework to differentiate age-related changes from early pathological remodeling, relevant for preventive cardiology in older adults. Its encoded statistical distributions also position it as a generative resource for synthetic aging populations, enabling virtual cohorts for *in silico* cardiac safety pharmacology and clinical trials, and as an informed prior for DT personalization, reducing the parameter search space to guide pacing-site selection or ablation strategies in the elderly.

The scientific findings described above rest on the fidelity with which the personalization pipeline reproduced *in vivo* EP across the cohort. Applied to the 30 healthy MyoFit46 participants, the pipeline replicated *in vivo* epicardial dynamics with AT-RMSE and RT-RMSE below the clinical uncertainties reported for ECGI against invasive electroanatomical mapping (i.e., 24 ms for AT and 51ms for RT)⁴⁶. LV replication showed higher fidelity than the RV, with the largest discrepancies at basal and RV–LV insertion regions, which are prone to ECGI reconstruction artefacts⁴⁷ and coincide with the blind spots identified during *in silico* verification. The slower RV activation reflects the pipeline's homogeneous CV assumption, which can produce local errors in a cohort with regionally heterogeneous aging-related conduction^{15,17}. A consistent cohort-wide CV underestimation was also observed, reflecting the sequence-dependent nature of apparent CV measured from epicardial ECGI data⁴⁸.

Several limitations qualify these findings beyond the methodological constraints already discussed. While 30 subject-specific DTs represent a significant computational cohort, a larger multi-ethnic sample will be needed to make these findings fully generalizable across

populations. A sex-balanced younger healthy CMR-ECGI cohort would also allow these findings to be quantified directly against a younger baseline, reinforcing their age-specificity. Regarding the ECGI inverse solution, inherent constraints in spatiotemporal resolution and blind spots in the interventricular septum and deep intramural layers limit activation and repolarization coverage in these regions, with any local depolarization errors potentially absorbed into the estimated repolarization factors. Regarding repolarization, the personalization targeted only g_{Ks} and AgR scaling; other ion channel conductances known to contribute to repolarization dynamics were not modelled, and transmural homogeneity of repolarization properties was assumed throughout. Importantly, the AgR scaling factor represents a computational surrogate for the net ionic remodeling required to reproduce the observed repolarization dynamics — it should not be interpreted as a direct tissue-level identification of g_{Kr} remodeling. Finally, as with any ECGI-based personalization strategy, the estimated electrophysiological parameters represent a plausible solution consistent with the observed surface data rather than a unique ground-truth characterization of each individual's EP.

Expanding this study to the full MyoFit46 cohort ($n=505$) would provide a more comprehensive portrait of the 75-year-old human heart, with greater statistical power to resolve population-level heterogeneity and sex-specific aging trajectories, and is expected to incorporate additional clinical data such as extracellular volume measurements and quantitative stress perfusion that could further refine myocardial tissue characterization. Building on this expanded normative reference and on the proof-of-concept comparison against an age-matched eHTN cohort presented here, future studies will scale the proposed personalization pipeline to broader clinical populations and life-course trajectories to quantitatively distinguish healthy aging repolarization from early pathological remodeling. Finally, future iterations of the pipeline should optimize the assessment of septal and basal regions and include enhanced cellular- and tissue-level characterization to achieve a more faithful representation of individual participants.

This work establishes the first 3D normative electrophysiological DT atlas of healthy cardiac aging. Using the MyoFit46 birth cohort alongside quasi-simultaneous CMR-ECGI and a direct

sequential mapping framework, we reconstructed subject-specific conduction properties, activation sequences, and regional repolarization heterogeneities across community-dwelling adults aged 75+. Population-level analysis revealed structured PMJ distributions consistent with classical anatomical landmarks, distinct apico-basal repolarization gradients, and spatially consistent AgR patterns that accumulate preferentially in regions of highest repolarization burden. Every participant required AgR personalization, confirming that healthy aging hearts are not well described by standard adult cellular computational models, with direct consequences for *in silico* DTs of older adults. Together with the first population-scale maps of activation and repolarization heterogeneity in a healthy elderly cohort, these findings establish a quantitative normative reference for the aging heart. Applied to an age-matched eHTN cohort, the atlas localized coherent subclinical electrophysiological deviations in the absence of structural remodeling, demonstrating its capability to assess pathological trajectories in older adults.

Methods

The proposed methodology encompasses three main components: (i) the MyoFit46 study population and the selection criteria for the healthy aging and eHTN cohorts; (ii) the DT personalization pipeline, including the integration of multimodal clinical data and the modeling of electrophysiological properties; and (iii) the pipeline verification and statistical methods used for atlas generation.

MyoFit46 Study Population

MyoFit46 (www.myofit46.com; <https://www.clinicaltrials.gov>; Unique identifier: NCT05455125) is the cardiovascular sub-study of the Medical Research Council National Survey of Health and Development –a prospective, longitudinal birth cohort study. Originally 5,362 participants (53% females) born the same week of March 1946 in England, Scotland and Wales were included^{49,50}. Over the last decade, multiple data collection waves have tracked

early-life exposures, cardiometabolic risk factors, and the emergence of multimorbidity through continuous medical and social follow-up^{51,52}. As part of the latest data collection wave at age 75+, a subset of 505 individuals was recruited for the MyoFit46 sub-study to investigate how life-course trajectories impact cardiovascular health and longevity.

Clinical data acquisition and processing

Participants of the MyoFit46 study underwent detailed clinical phenotyping, including 3 Tesla single-magnet quantitative stress perfusion contrast CMR (Siemens Prisma) combined with 256-lead high-resolution ECGI using a bespoke CMR-ECGI vest engineered at University College London⁵³. For CMR dataset collection protocols, we refer the readers to the following publications^{44,50}.

ECGI data were processed using the methodology described by Webber et al.⁵⁰, with previously reported validation and reproducibility of the full analytical pipeline⁵³. Briefly, body surface potentials were signal-averaged and combined with subject-specific heart–torso geometries derived from CMR to solve the inverse problem of electrocardiography. Epicardial potentials were reconstructed on a subject-specific mesh using a previously validated regularized inverse solution framework^{54–56}, yielding unipolar epicardial electrograms and corresponding activation and repolarization maps. AT was defined as the interval from earliest epicardial activation to the maximum negative derivative of the QRS complex in each unipolar epicardial electrograms. RT was identified as the point of maximum derivative of the T wave, and ARI was calculated as RT minus AT.

MyoFit46 was approved by the London Queen Square Research Ethics Committee (reference: 19/LO/1774; Integrated Research Application System reference: 254776). All participants provided written informed consent to take part in the study, and for their data to be stored electronically in accordance with the 2018 Data Protection Act.

Healthy aging group selection

While the broader MyoFit46 cohort encompasses a wide range of lifestyles and health states, the present study aims to characterize healthy cardiac aging. Therefore, a specific healthy aging subgroup was selected based on rigorous inclusion and exclusion criteria. Selected participants were required to be in sinus rhythm with no known cardiovascular disease, preserved LV ejection fraction ($\geq 55\%$), minimal fibrosis (LGE burden $< 2\%$ of total LV mass), normal systemic pressure, and free of major metabolic and respiratory comorbidities. Individuals with cardiac implantable electronic devices, renal failure, or high-grade atrioventricular blocks were deemed ineligible. Full criteria are detailed in **Supplementary S9**.

Early-stage hypertensive aging group selection

As a proof-of-concept, an eHTN aging group was selected from within the MyoFit46 cohort following the same inclusion and exclusion criteria as for the healthy aging group, with the sole exception of the systemic blood pressure criteria. For inclusion, participants were required to have a documented history of hypertension, elevated systolic or diastolic arterial blood pressure reading, or be receiving antihypertensive drug therapy. The resultant eHTN group thus captures early-stage hypertension without overt target organ damage (minimal if any detectable hypertrophy, LGE $< 2\%$ of LV mass and preserved LV ejection fraction). This carefully selected subgroup enables us to study the early electrophysiological sequelae of hypertension, free of confounding from structural cardiomyopathy.

Digital Twin Personalization pipeline

This subsection details the pipeline developed to translate multimodal clinical data into subject-specific electrophysiological DTs. The following segments describe: the integration of anatomical and tissue-characterization data from cine and LGE-CMR; the processing of ECGI-derived maps; and the mechanistic modeling approach used to personalize myocardial CV, activation sequences, and regional repolarization heterogeneities. A schematic overview of the complete personalization workflow is presented in **Figure 6**.

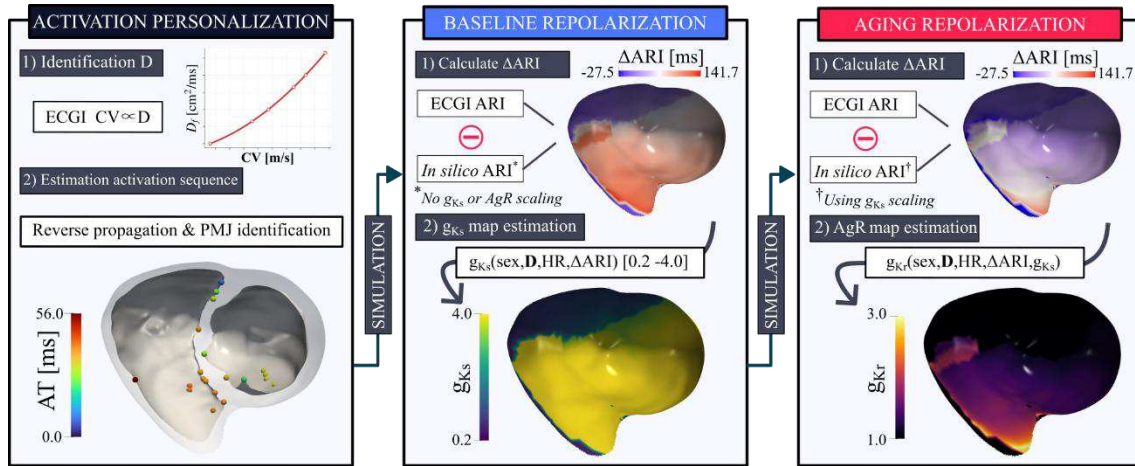


Figure 6. Comprehensive pipeline for digital twin personalization. The workflow comprises three sequential stages: (Left) Activation Personalization: estimation of the electrical diffusion tensor (D) from electrocardiographic imaging (ECGI)-derived conduction velocity (CV) and identification of the subject-specific activation sequence via reverse propagation and Purkinje-Myocardial junction (PMJ) detection. (Center) Baseline Repolarization: estimation of regional g_{Ks} scaling factors from discrepancies between simulated and ECGI-derived activation-repolarization intervals (ARIs). (Right) Aging Repolarization (AgR): additional adjustment applied to regions where g_{Ks} reached its physiological bounds, encoding the direction of action potential duration adaptation required. All stages incorporate subject-specific sex, D , and heart rate. AT: activation time; g_{Ks} : slow delayed rectifier potassium current conductance scaling factor.

Multimodal clinical data integration

Subject-specific anatomy was reconstructed from manual segmentation of the LV and RV endocardial and epicardial borders on end-diastolic cine CMR short- and long-axis images. Segmentations were performed using 3D Slicer (version 5.6.1)⁵⁷ by one trained reader (MW, CMR Level III) and subsequently validated by a separate experienced cardiac imaging expert (GC, CMR Level III). The obtained masks were processed and, when necessary, realigned via rigid transformation to generate a contour-based representation of the participants' biventricular anatomy. Lastly, we applied a mesh morphing algorithm⁵⁸, based on B-spline deformations, to adapt a reference biventricular model to the subject-specific contours by minimizing surface-to-surface distance.

LGE data were acquired using a free-breathing, motion-corrected balanced steady-state free precession sequence with phase-sensitive inversion-recovery to acquire a left ventricular short-axis stack. Following acquisition, the LGE images were analyzed by a single reader blinded to clinical data using ADAS3D (ADAS3D Medical, Barcelona, Spain version 2.12) and segmented using the 3 standard deviation method⁵⁹; as a result, a 3D representation of the subject-specific LGE burden was obtained. Then, we applied the mesh morphing algorithm to adapt reconstructed 3D LGE burden to previously reconstructed end-diastolic heart.

Lastly, ECGI AT maps were processed using a spatiotemporal post-processing step based on the combination of local activation-time gradient thresholds with amplitude-weighted timing of candidate negative deflections to enforce physiologically coherent activation patterns, reducing the artificial ECGI lines of block caused by the inverse ECGI solution^{60,61}. Once filtered, as was done with the LGE, ECGI epicardial data was registered, using the mesh morphing algorithm, to the end-diastolic anatomy reconstructed from the cine-CMR. A schematic overview of this integration workflow is provided in **Supplementary S10**.

Electrophysiological modeling

Cardiac electrophysiological modeling framework follow the strategy described by Gonzalez-Martin et al,⁶² using the monodomain formulation⁶³ for the tissue level propagation and the O'Hara–Rudy as the cellular model³³. We employed the modified version of the O'Hara–Rudy formulation proposed by Passini et al.⁶⁴ with ion-channels conductance adjusted according to Dutta et al.⁶⁵. In addition, sex-specific ion-channel expression patterns were incorporated based on participants' sex, following the modifications described by Yang and Clancy³⁴. At the tissue level, transmural myocyte heterogeneity was represented by dividing the ventricular wall into three layers of equal thickness—endocardial (33%), mid-myocardial (33%), and epicardial (33%)—each assigned distinct electrophysiological and cellular properties^{33,66}. Finally, myocardial fiber orientation was prescribed using the rule-based method described by Doste et al.⁶⁷. Propagation properties were personalized by estimating subject-specific myocardial

apparent CV from ECGI-derived activation maps (see Section 2.2.2.1). These estimates were used to adjust the electrical diffusion tensor (**D**) of the monodomain model, with diffusion aligned to the myocardial fiber direction (D_f) and a three-fold reduction prescribed in the transverse directions.

The personalization of these electrophysiological properties proceeds through three sequential stages, as illustrated in **Figure 6**: (i) estimation of subject-specific **D** from ECGI-derived CV; (ii) determination of the activation sequence through ECGI epicardial activation time map processing; and (iii) characterization of regional repolarization heterogeneities through calibration of potassium channel conductances. Each stage is detailed below.

Estimation of apparent conduction velocity

Local apparent CVs were derived from the ECGI epicardial activation map using the inverse-gradient approach⁶⁸. To avoid artefacts related to inverse reconstruction uncertainty, spatial regularization and contiguous breakthroughs, CV values were filtered to exclude physiologically implausible measurements (i.e., below 0.05 m/s or above 2.5 m/s)⁶⁹. Because CV is an emergent property rather than an explicit parameter in the monodomain formulation, the median apparent CV was translated into the tissue's **D**. This translation was performed using a pre-established second-order polynomial relationship derived from benchmark simulations (detailed in **Supplementary Material S11**). To reduce sensitivity to local noise and reconstruction variability, a homogeneous myocardial CV was assumed, except in dense scar regions identified by LGE, which were modelled as non-conductive tissue ($D_f=0$)⁷⁰.

Estimation of electrical activation sequence

Subject-specific activation sequence estimation was derived from the ECGI epicardial activation map. The procedure comprises two main steps: (i) estimation of the endocardial activation map; and (ii) identification of PMJ locations and their corresponding time of activation. A schematic can be found in **Figure 7**.

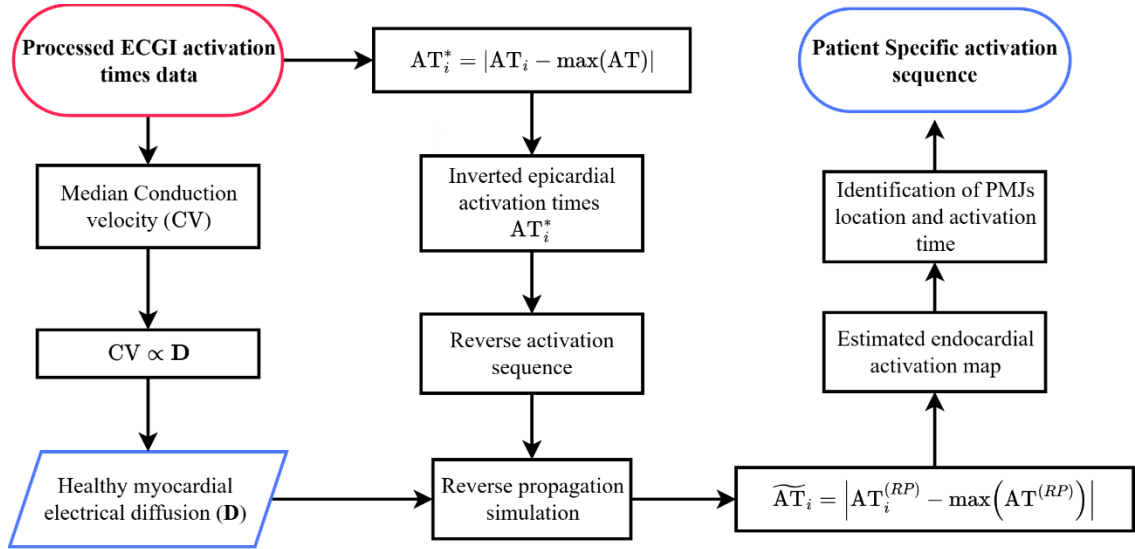


Figure 7. Flow diagram illustrating the estimation of subject-specific myocardial electrical diffusion (D) and the electrical activation sequence. Processed electrocardiographic imaging (ECGI)-activation times data (red oval) drives two parallel estimation streams. Down the left column, the median apparent conduction velocity (CV) is extracted and translated, via pre-established correlation, into the subject-specific D (blue parallelogram). Moving rightward, the epicardial activation times (ATs) are mathematically inverted (AT_i^*) and used as the input sequence for a reverse propagation (RP) simulation (i.e., from epicardium to endocardium). This simulation, which incorporates the previously estimated D , generates a reverse activation pattern ($AT^{(RP)}$) that is inverted a second time ($\widetilde{AT}_i$) to approximate the endocardial activation map. Finally, Purkinje-Myocardial junctions (PMJs) are identified from this estimated endocardial map to output the final subject-specific activation sequence (blue oval).

To approximate subject -specific endocardial activation, we implemented a reverse-propagation strategy as a pragmatic modeling approach for sequence inference. This approach exploits the approximate spatial reversibility of wavefront propagation in a medium with relatively homogeneous conduction properties: by inverting the epicardial activation times from the ECGI and propagating it backward through the myocardium — incorporating fiber orientation and subject-specific CV— the resulting map provides a first-order surrogate of endocardial activation times. While anisotropy and boundary effects preclude exact reversibility, the feasibility of this assumption was assessed through dedicated verification tests. The resulting activation-time map, after the reverse-propagation simulation, was inverted a second time so

that the latest-activated regions became the earliest, yielding an approximation of the endocardial activation pattern.

Following the estimation of the endocardial activation map, we applied the methodology proposed by Barber et al.⁷¹ to identify self-activated regions from electroanatomical mapping or estimated endocardial maps, in this case applied to our estimated endocardial activation maps. Owing to limited electrophysiological detail in the septal region (that is inherent to all epicardial ECGI maps), this area was excluded from the activation sequence estimation.

Estimation of repolarization regional heterogeneities

Regional repolarization heterogeneities were estimated via a two-step process. In the first stage, repolarization properties were tuned by modulating the local expression of the slow delayed rectifier potassium current, represented by a scaling factor (g_{Ks}). As previously reported in the literature²⁹, this conductance was selected due to its spatial heterogeneity across the myocardium⁷², making it the most suitable conductance parameter for capturing regional repolarization differences. To prevent physiologically unrealistic conductances, this scaling was constrained between 0.2-fold and 4.0-fold of the baseline value consistent with and moderately extending the inter-subject variability in g_{Ks} derived from gene expression data in healthy human ventricles^{30,73,74}. Following an initial simulation, using the personalized **D** and activation sequence, local discrepancies between the *in silico* and ECGI-derived ARIs were measured. These differences were translated into epicardial g_{Ks} scaling factors using a pre-established relationship that accounts for the participant's sex, heart rate, and **D** as detailed in

Supplementary Material S12.

Because extreme ARIs were observed in the *in vivo* ECGI data, an additional AgR layer was introduced to capture the pronounced electrophysiological remodeling associated with aging^{9,12,14}. This second calibration step was exclusively applied to regions where the g_{Ks} scaling factor had reached its predefined boundary constraints, as these regions could not be further adjusted through the baseline personalization alone. In those regions, a local scaling factor was applied to g_{Kr} as an effective computational surrogate to achieve the required action potential

duration calibration⁷⁵. Importantly, this g_{Kr} scaling does not imply an underlying tissue-level change in this current specifically; rather, it serves as a surrogate for the net ionic remodeling needed to reproduce the observed AgR dynamics in regions where the baseline personalization had reached its physiological limits. The direction of this calibration defines the AgR class of each region: $AgR^{\downarrow}$ where action potential duration shortening was required (i.e., $g_{Kr} > 1$), $AgR^{\pm}$ where no further modification was needed (i.e., $g_{Kr} = 1$), and $AgR^{\uparrow}$ where action potential duration prolongation was required (i.e., $g_{Kr} < 1$). This second calibration followed the same methodology as g_{Ks} , utilizing the discrepancies from a second simulation that already incorporated the personalized g_{Ks} adjustments. Finally, the optimized epicardial g_{Ks} and g_{Kr} distributions were propagated through the ventricular wall assuming a homogeneous transmural gradient. A description of this pipeline is provided in **Figure 6**.

Computational framework

Electrophysiological DTs were solved using the supercomputer MareNostrum V (Barcelona Supercomputing Center, Barcelona, Spain) with the simulation engine Alya⁷⁶. Alya is a high-performance finite element software developed at the Barcelona Supercomputing Center and ELEM Biotech S.L., designed to solve complex coupled multiphysics and multiscale problems.

Pipeline verification

Pipeline accuracy was assessed through six synthetic benchmark tests using forward-simulated DTs with prescribed CV, activation sequences, and repolarization properties as ground truth. Tests spanned three CV values covering the interquartile range of ECGI-derived measurements, two activation strategies (Durrer-based³² and Purkinje-based PMJs²⁴, and two repolarization patterns for both g_{Ks} and g_{Kr} (apex-to-base gradient³⁷ and a Voronoi distribution). Detailed test specifications and evaluation metrics are provided in **Supplementary S13**.

Healthy population replication and characterization

Following verification, the personalization pipeline was applied to the selected healthy MyoFit46 participants. Replication accuracy was assessed across three aspects consistent with the verification framework: apparent CV and epicardial activation and repolarization maps replication. Agreement between *in silico* and ECGI-derived epicardial dynamics was quantified using pointwise AT-RMSE and RT-RMSE and further characterized through normalized CDFs of AT and RT, which describe the temporal distribution of epicardial activation and recovery across the cohort.

To support population-level DTs characterization, reconstructed anatomies were used to build a statistical shape model. Because all subject-specific biventricular meshes were generated by morphing a common reference template, point-to-point correspondence was inherently preserved across the cohort. The anatomies were rigidly aligned using Generalized Procrustes analysis, and the resulting average coordinate representation, referred to as the MHA, was used to construct a spatial atlas by mapping both the regional repolarization properties and the activation sequence (i.e., PMJs locations and time of activation). This common framework enabled population-level analyses of regional repolarization heterogeneities variability and the identification of prevalent PMJ locations. Regional repolarization heterogeneities, mapped onto the MHA, were initially analyzed at a higher level using segment-based distributions: whole ventricles (LV, RV), longitudinal levels (basal, mid, apical) and circumferential regions (lateral, inferior, anterior) within each chamber. Subsequently, principal component analysis was applied to characterize dominant spatial modes of inter-subject variability. To characterize the spatial distribution of the AgR layer, each epicardial point was assigned to its AgR class ($\text{AgR}^\uparrow$, $\text{AgR}^\downarrow$, $\text{AgR}^\ominus$) as defined above, based on the direction of action potential duration adaptation encoded by the estimated g_{Kr} . These classes were analyzed in terms of prevalence on the cohort. Similarly, activation sequences were analyzed in terms of the prevalence of PMJs per segment, as well as on the MHA using spatial kernel density estimation. When analyzing PMJs time of activation we normalized the activation times from 0 to 100% scale to remove the variability in

activation time, where 0% represents the first PMJ activated from each participant and 100% the last PMJ activated. In addition, we have defined four groups representing the early activation (<25% relative activation), mid-early (25-50%), mid late (50-75%) and late activation (>75%).

For visualization of the characterization, we used the standard American Heart Association 17-segment model for the LV, extended with 13 supplementary RV segments, 4 segments each at the basal, mid, and apical rings, plus a true RV apex. In addition, we employed a 2D flattened representation of the joined LV and RV epicardium following the strategy described by Soto-Iglesias et al.⁷⁷.

Identification of eHTN trajectories

As a proof-of-concept application, the same personalization and characterization framework was applied to an age-matched eHTN subgroup of the MyoFit46 cohort to localize where hypertension-associated remodeling departs from the healthy aging baseline. To enable point-to-point comparison, healthy and eHTN anatomies were jointly aligned through Generalized Procrustes analysis, yielding a joint mean anatomical representation onto which PMJ locations and activation times, g_{Ks} scale factors, and AgR classes were mapped as described above. For each of these outputs, group-level distributions within the eHTN subgroup were computed following the procedure used for the healthy cohort, and point-wise difference maps (eHTN minus healthy) were derived on the new mean anatomy to localize inter-group divergences. Between cohort regional comparisons were performed using the same regions defined on the healthy atlas. The true LV and RV apical segments were excluded from the analysis.

Statistical analysis

Statistical analyses were performed in Python (version 3.14) using SciPy and statsmodel libraries (v1.17.1 and v0.14, respectively). Continuous variables are reported as median [interquartile range]. Comparisons between two independent groups used the Mann–Whitney U test. Within-subject comparisons of regional g_{Ks} and AgR values used the Wilcoxon signed-rank test for paired two-group comparisons and the Friedman test as omnibus for three-group

comparisons, followed by post-hoc pairwise Wilcoxon signed-rank tests when the omnibus yielded $p < 0.05$. The Benjamini–Hochberg false discovery rate procedure was applied within each analytical family: all variables of each demographics table, and all post-hoc pairwise comparisons within each regional analysis. To assess the global directional consistencies, a sign test (two-sided binomial test against $p = 0.5$) was applied. A p -value < 0.05 was considered statistically significant.

Data availability

National Survey of Health and Development data are available from <https://nshd.mrc.ac.uk/>. For MyoFit46 collaborations, please access <http://www.myofit46.com/>. For data queries, please contact mrclha.swiftinfo@ucl.ac.uk. ELEM Biotech owns the commercial rights to Alya, the computational finite element solver employed in this study. The methodology can be replicated using any finite element solver given all the models' information provided in this paper. The data generated and analyzed during this study are proprietary to ELEM Biotech and cannot be publicly shared due to commercial confidentiality. However, access to the data may be considered on a case-by-case basis. Requests for access can be directed to ELEM Biotech compliance department (compliance@elem.bio) and will be subject to a data use agreement ensuring compliance with relevant regulations and restrictions.

References

1. Affairs, U. N. D. of E. and S. *World Population Ageing 2023: Challenges and Opportunities of Population Ageing in the Least Developed Countries*. (United Nations, 2024). doi:10.18356/9789213586747.
2. Beard, J. R. *et al.* The World report on ageing and health: a policy framework for healthy ageing. *The Lancet* **387**, 2145–2154 (2016).
3. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. Hallmarks of aging: An expanding universe. *Cell* **186**, 243–278 (2023).

4. Triposkiadis, F., Xanthopoulos, A. & Butler, J. Cardiovascular Aging and Heart Failure. *JACC* **74**, 804–813 (2019).
5. Fleg, J. L. & Strait, J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. *Heart Fail Rev* **17**, 545–554 (2012).
6. Dai, D.-F., Chen, T., Johnson, S. C., Szeto, H. & Rabinovitch, P. S. Cardiac Aging: From Molecular Mechanisms to Significance in Human Health and Disease. *Antioxidants & Redox Signaling* **16**, 1492–1526 (2012).
7. Nakou, E. *et al.* Healthy aging and myocardium: A complicated process with various effects in cardiac structure and physiology. *International Journal of Cardiology* **209**, 167–175 (2016).
8. Fares, E. & Howlett, S. E. Effect of age on cardiac excitation-contraction coupling. *Clin Exp Pharmacol Physiol* **37**, 1–7 (2010).
9. Mirza, M., Strunets, A., Shen, W.-K. & Jahangir, A. Mechanisms of Arrhythmias and Conduction Disorders in Older Adults. *Clin Geriatr Med* **28**, 555–573 (2012).
10. Sedlak, T., Shufelt, C., Iribarren, C. & Merz, C. N. B. Sex Hormones and the QT Interval: A Review. *Journal of Women's Health* **21**, 933–941 (2012).
11. Decaroli, M. C. & Rochira, V. Aging and sex hormones in males. *Virulence* **8**, 545–570 (2017).
12. Pham, T. V. & Rosen, M. R. Sex, hormones, and repolarization. *Cardiovasc Res* **53**, 740–751 (2002).
13. Anversa, P. *et al.* Myocardial aging. *Basic Research in Cardiology* **100**, 482–493 (2005).
14. Lazzarini, E. *et al.* Stress-induced premature senescence is associated with a prolonged QT interval and recapitulates features of cardiac aging. *Theranostics* **12**, 5237–5257 (2022).
15. Boyle, A. J. *et al.* Cardiomyopathy of aging in the mammalian heart is characterized by myocardial hypertrophy, fibrosis and a predisposition towards cardiomyocyte apoptosis and autophagy. *Experimental Gerontology* **46**, 549–559 (2011).

16. Polak, S. & Fijorek, K. Inter-individual Variability in the Pre-clinical Drug Cardiotoxic Safety Assessment—Analysis of the Age–Cardiomyocytes Electric Capacitance Dependence. *Journal of Cardiovascular Translational Research* **5**, 321–332 (2012).
17. Stein, M. *et al.* Dominant arrhythmia vulnerability of the right ventricle in senescent mice. *Heart Rhythm* **5**, 438–448 (2008).
18. European Commission, E. C. European Virtual Human Twins (VHT) Initiative. <https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins> (2025).
19. Azzolin, L. *et al.* Personalized ablation vs. conventional ablation strategies to terminate atrial fibrillation and prevent recurrence. *Europace* **25**, 211–222 (2023).
20. Koopsen, T. *et al.* Virtual pacing of a patient’s digital twin to predict left ventricular reverse remodelling after cardiac resynchronization therapy. *Europace* **26**, euae009 (2024).
21. Waight, M. C. *et al.* Heart Digital Twins Predict Features of Invasive Reentrant Circuits and Ablation Lesions in Scar-Dependent Ventricular Tachycardia. *Circ Arrhythm Electrophysiol* **18**, e013660 (2025).
22. Pappalardo, F., Russo, G., Tshinanu, F. M. & Viceconti, M. In silico clinical trials: concepts and early adoptions. *Brief Bioinform* **20**, 1699–1708 (2019).
23. Rodero, C. *et al.* A systematic review of cardiac in-silico clinical trials. *Prog. Biomed. Eng.* **5**, 032004 (2023).
24. Gonzalez-Martin, P. *et al.* Electromechanical evaluation of conduction system pacing techniques in a patient-specific virtual cohort: an in silico clinical trial. <https://www.authorea.com/users/1023656/articles/1383560-electromechanical-evaluation-of-conduction-system-pacing-techniques-in-a-patient-specific-virtual-cohort-an-in-silico-clinical-trial> (2026).
25. Salvador, M. *et al.* Digital twinning of cardiac electrophysiology for congenital heart disease. *J R Soc Interface* **21**, 20230729 (2024).
26. Qian, S. *et al.* Developing cardiac digital twin populations powered by machine learning provides electrophysiological insights in conduction and repolarization. *Nat Cardiovasc Res* **4**, 624–636 (2025).

27. Gillette, K. *et al.* A Framework for the generation of digital twins of cardiac electrophysiology from clinical 12-leads ECGs. *Medical Image Analysis* **71**, 102080 (2021).
28. Pezzuto, S. *et al.* Reconstruction of three-dimensional biventricular activation based on the 12-lead electrocardiogram via patient-specific modelling. *Europace* **23**, 640–647 (2021).
29. Camps, J. *et al.* Digital twinning of the human ventricular activation sequence to Clinical 12-lead ECGs and magnetic resonance imaging using realistic Purkinje networks for in silico clinical trials. *Med Image Anal* **94**, 103108 (2024).
30. Cicci, L. *et al.* Personalising cardiac electrophysiology models from CT and ECG for 3D activation imaging and tissue characterisation. Preprint at <https://doi.org/10.21203/rs.3.rs-8873590/v1> (2026).
31. Rudy, Y. Noninvasive Electrocardiographic Imaging of Arrhythmogenic Substrates in Humans. *Circulation Research* **112**, 863–874 (2013).
32. Durrer, D. *et al.* Total Excitation of the Isolated Human Heart. *Circulation* **41**, 899–912 (1970).
33. O'Hara, T., Virág, L., Varró, A. & Rudy, Y. Simulation of the Undiseased Human Cardiac Ventricular Action Potential: Model Formulation and Experimental Validation. *PLOS Computational Biology* **7**, e1002061 (2011).
34. Yang, P.-C. & Clancy, C. E. In silico Prediction of Sex-Based Differences in Human Susceptibility to Cardiac Ventricular Tachyarrhythmias. *Front. Physiol.* **3**, (2012).
35. Dominguez-Gomez, P. *et al.* Replicating clinical placebo effects in computational trials: Bridging the gap between in silico and clinical studies. *The Journal of Precision Medicine: Health and Disease* **3**, 100011 (2025).
36. Ramanathan, C., Jia, P., Ghanem, R., Ryu, K. & Rudy, Y. Activation and repolarization of the normal human heart under complete physiological conditions. *Proceedings of the National Academy of Sciences* **103**, 6309–6314 (2006).
37. Szentadrassy, N. *et al.* Apico–basal inhomogeneity in distribution of ion channels in canine and human ventricular myocardium. *Cardiovasc Res* **65**, 851–860 (2005).

38. Rabkin, S. W., Cheng, X.-B. J. & Thompson, D. J. Detailed analysis of the impact of age on the QT interval. *J Geriatr Cardiol* **13**, 740–748 (2016).
39. Liu, Y. & Li, C. Sex differences in cardiovascular disease risk and the role of biological aging pace. *Eur. J. Prev. Cardiol.* zwaf726 (2025) doi:10.1093/eurjpc/zwaf726.
40. González-Casal David *et al.* The Right Ventricular Moderator Band. *JACC: Case Reports* **29**, 102647 (2024).
41. Cerbai, E., Barbieri, M., Li, Q. & Mugelli, A. Ionic basis of action potential prolongation of hypertrophied cardiac myocytes isolated from hypertensive rats of different ages. *Cardiovascular Research* **28**, 1180–1187 (1994).
42. Klimas, J., Kruzliak, P. & Rabkin, S. W. Modulation of the QT interval duration in hypertension with antihypertensive treatment. *Hypertens Res* **38**, 447–454 (2015).
43. Prenner, S. B., Shah, S. J., Goldberger, J. J. & Sauer, A. J. Repolarization Heterogeneity: Beyond the QT Interval. *Journal of the American Heart Association* **5**, e003607 (2016).
44. Topriceanu, C.-C. *et al.* Higher Life-Course Blood Pressure Associates With Reduced Myocardial Perfusion in Older Age: Insights From MyoFit46. *Circulation: Cardiovascular Imaging* **19**, e019105 (2026).
45. Harris, B. S. *et al.* Remodeling of the peripheral cardiac conduction system in response to pressure overload. *American Journal of Physiology-Heart and Circulatory Physiology* **302**, H1712–H1725 (2012).
46. Graham, A. J. *et al.* Simultaneous Comparison of Electrocardiographic Imaging and Epicardial Contact Mapping in Structural Heart Disease. *Circulation: Arrhythmia and Electrophysiology* **12**, e007120 (2019).
47. Duchateau, J. *et al.* Performance and limitations of noninvasive cardiac activation mapping. *Heart Rhythm* **16**, 435–442 (2019).
48. Vigmond, E. J., Massé, S., Roney, C. H., Bayer, J. D. & Nanthakumar, K. The Accuracy of Cardiac Surface Conduction Velocity Measurements. *JACC: Clinical Electrophysiology* **11**, 694–705 (2025).

49. The Lancet Healthy Longevity, null. The Lancet Healthy Longevity: looking to the future. *Lancet Healthy Longev* **7**, 100821 (2026).
50. Webber, M. *et al.* Study protocol: MyoFit46—the cardiac sub-study of the MRC National Survey of Health and Development. *BMC Cardiovasc Disord* **22**, 140 (2022).
51. Kuh, D. *et al.* Cohort Profile: Updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. *Int J Epidemiol* **40**, e1–e9 (2011).
52. Kuh, D. *et al.* The MRC National Survey of Health and Development reaches age 70: maintaining participation at older ages in a birth cohort study. *Eur J Epidemiol* **31**, 1135–1147 (2016).
53. Webber, M. *et al.* Technical development and feasibility of a reusable vest to integrate cardiovascular magnetic resonance with electrocardiographic imaging. *Journal of Cardiovascular Magnetic Resonance* **25**, 73 (2023).
54. Oster, H. S., Taccardi, B., Lux, R. L., Ershler, P. R. & Rudy, Y. Noninvasive Electrocardiographic Imaging. *Circulation* **96**, 1012–1024 (1997).
55. Ramanathan, C., Ghanem, R. N., Jia, P., Ryu, K. & Rudy, Y. Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. *Nat Med* **10**, 422–428 (2004).
56. Wang, Y. *et al.* Noninvasive Electroanatomic Mapping of Human Ventricular Arrhythmias with Electrocardiographic Imaging. *Science Translational Medicine* **3**, 98ra84–98ra84 (2011).
57. Kikinis, R., Pieper, S. D. & Vosburgh, K. G. 3D Slicer: A Platform for Subject-Specific Image Analysis, Visualization, and Clinical Support. in *Intraoperative Imaging and Image-Guided Therapy* (ed. Jolesz, F. A.) 277–289 (Springer, New York, NY, 2014). doi:10.1007/978-1-4614-7657-3_19.
58. Sederberg, T. W. & Parry, S. R. Free-form deformation of solid geometric models. in *Proceedings of the 13th annual conference on Computer graphics and interactive*

- techniques* 151–160 (Association for Computing Machinery, New York, NY, USA, 1986).
doi:10.1145/15922.15903.
59. Flett, A. S. *et al.* Evaluation of Techniques for the Quantification of Myocardial Scar of Differing Etiology Using Cardiac Magnetic Resonance. *JACC: Cardiovascular Imaging* **4**, 150–156 (2011).
 60. Schaufelberger, M. *et al.* Comparison of Activation Times Estimation for Potential-Based ECG Imaging. *Comput Cardiol (2010)* **46**, 10.22489/cinc.2019.379 (2019).
 61. Vermoortele, D. *et al.* Electric Field-Based Spatial Analysis of Noncontact Unipolar Electrograms to Map Regional Activation-Repolarization Intervals. *JACC: Clinical Electrophysiology* **9**, 1217–1231 (2023).
 62. Gonzalez-Martin, P. *et al.* Ventricular anatomical complexity and sex differences impact predictions from electrophysiological computational models. *PLOS ONE* **18**, e0263639 (2023).
 63. Franzone, P. C., Pavarino, L. F. & Scacchi, S. *Mathematical Cardiac Electrophysiology*. (Springer, 2014).
 64. Passini, E. *et al.* Mechanisms of pro-arrhythmic abnormalities in ventricular repolarisation and anti-arrhythmic therapies in human hypertrophic cardiomyopathy. *J Mol Cell Cardiol* **96**, 72–81 (2016).
 65. Dutta, S. *et al.* Optimization of an In silico Cardiac Cell Model for Proarrhythmia Risk Assessment. *Front. Physiol.* **8**, (2017).
 66. Campbell, S. G. *et al.* Effect of transmurally heterogeneous myocyte excitation–contraction coupling on canine left ventricular electromechanics. *Experimental Physiology* **94**, 541–552 (2009).
 67. Doste, R. *et al.* A rule-based method to model myocardial fiber orientation in cardiac biventricular geometries with outflow tracts. *Int J Numer Method Biomed Eng* **35**, e3185 (2019).
 68. Barnette, A. R. *et al.* Estimation of 3-D conduction velocity vector fields from cardiac mapping data. *IEEE Transactions on Biomedical Engineering* **47**, 1027–1035 (2000).

69. Aronis, K. N. *et al.* Accurate Conduction Velocity Maps and their Association with Scar Distribution on Magnetic Resonance Imaging in Patients with Post-Infarction Ventricular Tachycardias. *Circ Arrhythm Electrophysiol* **13**, e007792 (2020).
70. Casoni, E. *et al.* Electromechanical computational modeling of heart failure provides extensive analysis of cardiac pathophysiological features. *Biomech Model Mechanobiol* **25**, 15 (2026).
71. Barber, F. *et al.* Estimation of Personalized Minimal Purkinje Systems From Human Electro-Anatomical Maps. *IEEE Trans Med Imaging* **40**, 2182–2194 (2021).
72. Antzelevitch, C. & Fish, J. Electrical heterogeneity within the ventricular wall. *Basic Res Cardiol* **96**, 517–527 (2001).
73. Gaborit, N. *et al.* Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. *Journal of Molecular and Cellular Cardiology* **49**, 639–646 (2010).
74. Ambrosi, C. M., Yamada, K. A., Nerbonne, J. M. & Efimov, I. R. Gender Differences in Electrophysiological Gene Expression in Failing and Non-Failing Human Hearts. *PLOS ONE* **8**, e54635 (2013).
75. Altomare, C. *et al.* IKr Impact on Repolarization and Its Variability Assessed by Dynamic Clamp. *Circulation: Arrhythmia and Electrophysiology* **8**, 1265–1275 (2015).
76. Vázquez, M. *et al.* Alya: Multiphysics engineering simulation toward exascale. *Journal of Computational Science* **14**, 15–27 (2016).
77. Soto-Iglesias, D. *et al.* Integration of electro-anatomical and imaging data of the left ventricle: An evaluation framework. *Medical Image Analysis* **32**, 131–144 (2016).

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Author contributions

P.G.M. conceived the study, designed the methodology, developed the software, performed the validation and formal analysis, conducted the investigation, curated the data, prepared the visualizations, and wrote the original draft. M.M. contributed to the methodology and software development, performed validation and formal analysis, prepared visualizations, and contributed to the original draft. A.J., F.M., M.W., D.F., F.C., S.D., C.C., L.M., C.C.T., E.M., G.J., J.B., K.M., H.S., R.H.D., N.C., J.C.M. and P.D.L. provided resources and clinical data curation, including segmentations, ECGI and CMR processing. J.M.P. and C.B. participated in the methodology design and developed the mesh morphing software. A.Z. participated in the methodology development and reviewed the original draft. M.O. developed the software for ECGI processing from raw data and provided the analyzed ECGI data. A.D.H. administered the project and acquired funding. M.V. contributed to the software development, provided resources, administered the project, and acquired funding. O.C. conceived the study, conducted the investigation, and contributed to writing and revising the manuscript. J.A.S. conceived the study, developed software, conducted the investigation, provided resources, supervised the work, administered the project, and contributed to writing and revising the manuscript. G.C. conceived the study, conducted the investigation, provided resources, curated data, supervised the work, administered the project, acquired funding, and contributed to writing and revising the manuscript. J.A.S. and G.C. contributed equally as joint senior authors and supervised the work. All authors read and approved the final manuscript.

Competing Interests

P.G.M, M.M, JM. P, A. Z, C. B, J.A.S are ELEM Biotech employees. M.V is ELEM Biotech co-founder and chief technical officer. J.C.M who is the chief executive officer of MyCardium AI and has served on advisory boards for Genzyme and Sanofi. N.C. receives funds from AstraZeneca to serve on clinical trial data safety and monitoring committees. RD has received payments and has shares in MyCardium AI. There are no conflicts of interest for any other authors.

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