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A dynamic mechanical framework unmask the ultrastructural and fluid-solid remodeling during myocardial infarction progression

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Abstract

Myocardial infarction (MI) triggers multiscale remodeling that changes the mechanical environment of the heart, but conventional stiffness measurements fail to capture the dynamic behavior of fluid-saturated tissue. Here, we developed a multiscale poro-viscoelastic framework to characterize MI-associated mechanical remodeling in murine myocardium. By combining power-law rheology with poro-elasticity theory, we resolved AFM creep responses into complementary markers of tissue state: the short-time power-law exponent (α_{short}), the long-time power-law exponent (α_{long}), the hydraulic permeability (D), the fluid–solid transition time (τ) and the elastic modulus (E). These mechanical signatures capture the delicate poro-viscoelastic alterations during MI: week-1 infarcts softened while the median D increased more than six-fold, consistent with edema and necrotic pore expansion. At week2, D fell below the control value and spatial heterogeneity was maximal, whereas week-4 scars were stiff, consolidated and characterized by persistently low D , a shortened fluid-like creep regime and a reduced long-time exponent. Integrating the poro-viscoelastic parameters improved cross-validated separation of early and chronic remodeling relative to stiffness alone, including an increase in AUC from 0.69 to 0.90 for control vs. week 1. These findings support dynamic fluid–solid mechanics as a quantitative framework for characterizing post-infarction remodeling and for defining mechanical benchmarks for cardiac regenerative biomaterials.

Keywords: Myocardial infarction (MI), Poro-viscoelasticity, Hydraulic permeability, Atomic Force Microscopy (AFM), Machine learning (ML)

1. Introduction

Myocardial infarction (MI) initiates a multiscale remodeling cascade that contributes to heart failure and mortality (Mechanic et al. 2023). Cardiomyocyte death and inflammatory infiltration are followed by fibroblast activation and collagen-rich scar formation (Frangogiannis 2014; Schoen 2008). This reconstruction changes the mechanical environment of the heart, whose function depends on coordinated force transmission and reversible deformation (Brazile et al. 2021). Clinical and experimental assessments commonly emphasize tissue stiffness, including elastography, magnetic resonance elastography, and cardiac magnetic resonance approaches (Frøysa et al. 2025; Jamthikar et al. 2025; Moeendarbary and Harris 2014). Stiffness is informative, but it represents only one state variable. The myocardium is also a fluid-saturated,

viscoelastic composite in which energy dissipation, fluid redistribution, and time-dependent relaxation influence tissue function (Avazmohammadi et al. 2019).

This limitation is particularly important during the early phase of remodeling. Edema, cytoskeletal disruption, and changes in interstitial fluid content may occur before substantial collagen deposition, yet they are difficult to interpret with single-phase elasticity models (Chang et al. 2023a; Emig et al. 2021; Lizardi et al. 2022). While emerging research suggests that myocardial viscoelasticity offers a promising avenue for early diagnosis (Chang et al. 2023b), current mechanical models frequently oversimplify the tissue as a homogeneous, impermeable solid. By employing single spring-damper or power-law systems that neglect the flow of interstitial fluid through the porous extracellular matrix (ECM) (Hang et al. 2021), these frameworks conflate solid matrix relaxation with hydraulic permeability. Consequently, they obscure the subtle biophysical fingerprints of early-stage MI—specifically the interplay between collagen cross-linking and water distribution (Beuve et al. 2021), hindering the development of precise diagnostic standards and mechanically matched regenerative therapies. To overcome this, a comprehensive analysis of the full poro-viscoelastic spectrum is required to detect and stage MI throughout its progression from acute inflammation to chronic scarring.

Bridging this gap requires a shift toward multiscale, poro-viscoelastic characterization. Non-invasive imaging provides information at the organ scale, but it does not directly resolve the nonlinear relationship between microscopic mechanics and tissue pathology (Chen et al. 2024; Kolawole et al. 2025). The onset of MI is molecular and cellular; therefore, detection demands nano- and micro-scale sensitivity. Atomic force microscopy (AFM) has emerged as a central approach in this domain, capable of resolving localized static and dynamic properties of cardiomyocytes and their surrounding tissue extracellular matrix (ECM) with micro- to nanoscale resolution (Chang et al. 2024a; Lou et al. 2023). Once fluid transport and viscoelastic parameters are included, however, interpretation becomes multidimensional. A reproducible constitutive framework is therefore required, together with a direct test of whether each parameter adds information beyond stiffness alone (Shao et al. 2024).

Here, we developed a multiscale poro-viscoelastic framework for characterizing MI-associated remodeling. Using AFM-based micro-rheology, we investigated the time-dependent creep behavior of myocardial tissue, capturing the transition in mechanical heterogeneity from the acute to the chronic stage. We established a composite analytical framework that unifies power-law rheology with poro-elasticity theory to decouple three key mechanical markers: the short-time power-law exponent (α_{short}), reflecting cytoskeleton-fluid interactions; the long-time exponent (α_{long}) associated with ECM cross-linking; and the hydraulic permeability (D), which quantifies effective pore size and fluid transport capacity. We find that MI progression is a spatiotemporal heterogeneous reorganization of tissue micromechanics. By integrating these features into a machine learning (ML) framework using a neural network classifier, we reveal that myocardial remodeling follows a unique biphasic evolution of fluid-solid interactions. Our results demonstrate that hydraulic permeability and spatial heterogeneity are significantly more sensitive indicators of early tissue disruption than conventional tissue stiffness alone during MI. The resulting framework links local fluid–solid mechanics to the temporal evolution of infarct tissue and provides

quantitative mechanical benchmarks for future studies of cardiac disease and regenerative biomaterials

2. Materials and Methods

2.1 Animal model of myocardial infarction

Myocardial infarction (MI) was induced in adult male mice (C57BL/6, 8-10 weeks; $n = 3$ per group) via permanent ligation of the left anterior descending (LAD) coronary artery. Anesthesia was maintained using isoflurane (1.5-2.0% in oxygen). Following a left thoracotomy, the LAD was ligated to induce ischemia. To investigate the temporal evolution of mechanical remodeling, animals were stratified into three post-injury stages: early-stage (week 1), mid-stage (week 2), and late-stage (week 4) (Talman and Ruskoaho 2016). A sham-operated cohort underwent identical thoracotomy without ligation. At defined endpoints, animals were euthanized, and hearts were rapidly excised for tissue processing. All procedures were approved by the Institutional Animal Care and Use Committee of Xi'an Jiaotong University.

2.2 Tissue preparation

Heart tissues were immediately embedded in Optimal Cutting Temperature (OCT) compound (Tissue-Tek, Sakura Finetek) and snap-frozen in isopentane chilled by liquid nitrogen to preserve tissue architecture and mechanical integrity. Samples were stored at -80°C until processing. Serial short-axis ventricular sections ($15\text{ }\mu\text{m}$ thickness) were obtained using a cryostat (Leica CM1950) at -20°C . Sections were mounted onto Poly-L-lysine coated slides (Superfrost Plus) and stored at -80°C . Adjacent sections were reserved for histological verification of infarct expansion and collagen deposition via Masson's trichrome staining prior to biomechanical characterization.

2.3 AFM-based microrheology and mechanical characterization

Local mechanical properties of the myocardial tissue were probed using an Atomic Force Microscope (AFM) (Nano-Observer One Plus, CS Instruments). To ensure the validity of the continuum contact mechanics assumption and minimize localized puncture damage, a colloidal probe was fabricated by attaching a $20\text{ }\mu\text{m}$ diameter silicon dioxide sphere (Fuhong Nanomaterials) to a tipless cantilever (NPO-10, Bruker). Prior to experimentation, the cantilever spring constant was calibrated using the thermal noise method ($k = 0.54\text{ N/m}$ for the control, week-2 and week-4 sessions and 0.41 N/m for the week-1 session). All measurements were conducted in a fluid cell at room temperature ($\sim 25^{\circ}\text{C}$) to maintain sample hydration.

To ensure a comprehensive assessment of tissue mechanics and to capture the spatial heterogeneity of the infarct zone, single point force spectroscopy measurements were performed at multiple discrete locations separated by more than $100\text{ }\mu\text{m}$ on each section. A relatively large spherical probe (diameter $20\text{ }\mu\text{m}$) was used so that each measurement reports the localized mechanical properties of the tissue at the micrometre scale, integrating over cells and matrix, rather than the properties of a single component such as an individual fiber or cell probed by a nanoscale tip. The contact radius at the trigger force is $2\text{-}4\text{ }\mu\text{m}$ and the indentation strain field extends over roughly ten micrometres, so locations $100\text{ }\mu\text{m}$ apart do not interact mechanically. Given the millimetre extent of the ventricular section, the distance between locations and the small volume sampled at each, the measurement at each location is regarded as a complete mechanical assessment of a distinct tissue region, equivalent to an independent sample, following the methodology of our previous studies of infarcted myocardium, fibrotic liver and

atherosclerotic plaque (Chang et al. 2023a, b, 2024a). This design assesses not only the average mechanical behavior of each group but also the mechanical heterogeneity within the infarct, which mean values alone would mask, and the separation between locations avoids mechanical similarity between neighboring measurements. Three mice per group was chosen in line with the principle of reduction (the 3Rs) in animal research, and the reliability of the group-level conclusions is examined by the sample-independence check described below and by the effect-size and robustness analyses. Sections were measured one animal at a time; the three measurement sessions per group identified from the acquisition record correspond to the individual animals, and a sample-independence check comparing the sections of each group is reported in Fig. S2 and Table S11.

Following strict quality control to exclude artifacts caused by surface debris or unstable contact, 85 datasets were retained for analysis (control: $n = 25$; week 1: $n = 15$; week 2: $n = 22$; week 4: $n = 23$). To assess stiffness while minimizing viscous drag, the probe was ramped into the tissue at $6 \mu\text{m/s}$ until a trigger threshold of 20 nN was reached; from first contact to the trigger force the loading lasted $0.26\text{--}0.41 \text{ s}$ (interquartile range across indentations). The indentation depth at the trigger force ranged from $\sim 0.15 \mu\text{m}$ in stiff scar tissue to $\sim 3.6 \mu\text{m}$ in the softest regions (group medians $0.3\text{--}2.0 \mu\text{m}$); rigid-substrate effects were therefore corrected explicitly, indentation by indentation, during analysis (Section 2.4). To quantify time-dependent deformation, a constant force clamp (target load: 20 nN) was applied and held for 100 s , allowing the tissue to undergo viscoelastic relaxation and fluid redistribution.

2.4 Data analysis

The instantaneous static elastic modulus (E) was quantified by analyzing the approach phase of the force-distance curves prior to the onset of creep. The actual indentation depth, h , was decoupled from the cantilever deflection, δ , and the piezo-actuator displacement, Z , according to the kinematic relationship $h = Z - \delta$. Using the calibrated spring constant k , the indentation force was determined via Hooke's Law ($F = k \cdot \delta$). To extract the elastic modulus, experimental data were fitted to the Hertzian contact model for a spherical indenter:

$$E = \frac{3F(1-\nu^2)}{4\sqrt{R}} h^{3/2} \quad (1)$$

where the radius of the spherical probe is R , ν is the Poisson's ratio. Because the contact radius is not negligible relative to the section thickness h_s ($\chi = a/h_s = 0.08\text{--}0.40$ across indentations; group medians $0.21, 0.29, 0.14$ and 0.12), apparent moduli were corrected for the rigid glass substrate indentation by indentation using the bonded-sample spherical-indentation correction, $E_{\text{corr}} = E_{\text{app}}/f(\chi)$, with $f(\chi) = 1 + 1.133\chi + 1.497\chi^2 + 1.469\chi^3 + 0.755\chi^4$. All moduli reported below are substrate-corrected (group means: control 3.76 kPa , week 1 1.08 kPa , week 2 16.5 kPa , week 4 21.9 kPa ; apparent values $4.75, 1.56, 18.98$ and 24.78 kPa), and the corrected modulus is used wherever E enters the poroelastic analysis.

Unlike traditional models that assume the myocardium is purely incompressible ($\nu = 0.5$), we incorporated poroelastic theory to account for interstitial fluid exudation during deformation. As fluid flows out of the porous matrix, the effective compressibility of the tissue changes. Consequently, the drained Poisson's ratio (ν) was derived from the creep trajectory through the ratio of the indentation depth at the onset of the hold, $h(0)$,

to the depth $h(\infty)$, reached when the pore pressure has equilibrated. Because the solid skeleton continues to creep as a power law and the total creep does not saturate, $h(\infty)$ is taken as $h(0)$ plus the amplitude of the saturating poroelastic term of the joint fit and the Poisson's ratio is expressed as follows (Selvadurai 2004):

$$h(\infty) = [2(1-\nu)]^{\frac{2}{3}} \cdot h(0) \quad (2)$$

To capture the viscoelastic relaxation spectrum, we analyzed the time-dependent creep compliance, $J(t)$, defined as the ratio of time-variant strain $\varepsilon(t)$ to the constant applied stress $\sigma(t)$:

$$J(t) = \frac{\varepsilon(t)}{\sigma_0} \quad (3)$$

In this study, all the force curves were obtained and analyzed by using the commercial software Igor Pro Version 16 from Asylum Research.

2.5 Poro-viscoelastic creep model and joint fitting

For each indentation, the creep displacement during the force clamp, $\Delta h(t) = h(t) - h(0)$, was fitted over the full hold (0.002–100 s) with a coupled model in which a saturating poroelastic term and a non-saturating power-law term act additively (Supplementary Note, Section 6): $\Delta h(t) = \Delta_p \cdot H_{\text{poro}}(T^*) + \Delta_v \cdot (t/\tau)^\alpha$, with $T^* = \sqrt[3]{(t/\tau)}$, H_{poro} the spherical-indentation master curve of Oyen (2008) with fixed constants $A = 0.928$, $T_0 = 0.772$ and $P = 2.0837$, and four fitted parameters (Δ_p , τ , Δ_v , α). Residuals were minimized in logarithmic time so that each decade carries equal weight, and each fit was started from six initial guesses to avoid local minima. The fluid–solid transition time $\tau = a^2/(2GD)$ yields the hydraulic permeability D from the contact radius $a = \sqrt[3]{Rh(0)}$ and the shear modulus $G = E_{\text{corr}}/[2(1+\nu_d)]$; $h(0)$ is the Hertz depth at the trigger force for the fitted modulus of each indentation, and the drained Poisson's ratio follows from Eq. (2) with $h(\infty) = h(0) + A \cdot \Delta_p$, the poroelastic plateau of the same fit, so that $h(0)$, ν_d , τ and D form one closed chain per indentation. The model treats the trigger force as a step load; the effect of the finite loading phase on τ and D is estimated by superposing the responses to the recorded load increments (Galli and Oyen 2009) in the Supplementary Note (Section 6, Table S6), and a model-free location of the transition, defined by the local creep exponent falling through 1/2 (Fabry et al. 2001), is given in Section 7 and Table S12 of the Supplementary Note. The short- and long-time power-law exponents were evaluated per indentation as the log–log slopes of the creep response over the fixed windows 0.01–0.1 s (α_{short}) and 10–100 s (α_{long}); the latter window lies beyond 20τ for every indentation and is therefore insensitive to the value of τ .

2.6 Supervised machine learning for MI staging

2.6.1 Dataset and feature engineering

To stratify MI progression based on micromechanical signatures, we constructed a supervised classification framework. The dataset comprised 85 individual measurements categorized into four histological stages: control ($n = 25$), week 1 ($n = 15$), week 2 ($n = 22$), and week 4 ($n = 23$). The input feature vector X consisted of five poro-viscoelastic parameters: elastic modulus (E), hydraulic permeability (D), short- and long-term power-law exponents (α_{short} , α_{long}), and drained Poisson's ratio (ν). To decouple the diagnostic contribution of traditional stiffness metrics from novel poro-viscoelastic markers, we evaluated three distinct input configurations: (i) stiffness only (E); (ii) poro-viscoelasticity only (D , α_{short} , α_{long} and ν); and (iii) the integrated multiparametric set. Prior to training, E and D underwent log10 transformation to

compress their dynamic range, the exponents and the Poisson's ratio, which are of order unity, were used untransformed, and all features were standardized to zero mean and unit variance on the training folds. The features are the substrate-corrected modulus and the joint-fit parameters of Sections 2.4 and 2.5.

2.6.2 Model architecture and training strategy

Classification was performed using a neural network ensemble implemented in PyTorch. To ensure robust performance estimation given the sample size, we employed a stratified 6-fold cross-validation scheme, preserving class prevalence across all partitions. Within each fold, we trained an ensemble of five independent Multilayer Perceptrons (MLPs) to mitigate the stochasticity of weight initialization. Each MLP featured a compact architecture designed to prevent overfitting: an input layer, two fully connected hidden layers (4 and 3 neurons, respectively) activated by Rectified Linear Units (ReLU), and a Softmax output layer. Models were optimized using the Adam algorithm (learning rate = 0.01) minimizing Categorical Cross-Entropy loss over a fixed duration of 1,000 epochs to ensure convergence. The final diagnostic prediction was derived by averaging the probability distributions of the ensemble estimators.

2.6.3 Performance evaluation

Diagnostic performance was quantified using aggregated confusion matrices to calculate global accuracy, precision, recall, and F1-score. For binary classification sub-tasks (e.g., Healthy vs. Infarcted), Receiver Operating Characteristic (ROC) curves were generated, and the Area Under the Curve (AUC) was computed to assess discriminatory power independent of decision thresholds.

2.6.4 Evaluation metrics for machine learning model

To quantitatively assess the diagnostic performance of the neural network in differentiating MI progression stages, we utilized a confusion matrix-based approach. For each classification boundary (e.g., healthy vs. infarcted), prediction outcomes were categorized into True Positives (TP), False Positives (FP), True Negatives (TN), and False Negatives (FN). Diagnostic reliability and clinical validity were evaluated using the following metrics:

Precision, or positive predictive value, characterizes the ratio of correctly identified positive instances to the total positive predictions, reflecting the model's reliability in flagging disease:

$$Precision = \frac{TP}{TP + FP} \quad (4)$$

Recall, or sensitivity, assesses the ratio of correctly identified positive cases to all actual positive cases, critical for minimizing missed diagnoses:

$$Recall = \frac{TP}{TP + FN} \quad (5)$$

F1 Score characterizes the harmonic mean of Precision and Recall, serving as a robust metric for global accuracy, particularly in scenarios with imbalanced class distributions:

$$F1 = 2 \times \frac{Precision \times Recall}{Precision + Recall} \quad (6)$$

Youden's Index is employed to evaluate the overall effectiveness of the biomarker and determine optimal diagnostic thresholds:

$$Youden = Sensitivity + Specificity - 1 \quad (7)$$

$$Specificity = \frac{TN}{TN + FP}$$

The Youden index ranges from 0 (no diagnostic value) to 1 (perfect classification). All evaluation metrics were computed on the independent test set derived from the 6-fold cross-validation scheme.

2.7 Statistical analysis

Data analysis and visualization were performed using Origin 2025 (OriginLab, Northampton, MA). Quantitative results are presented as mean $\pm$ standard deviation (SD) and, where indicated, as medians with interquartile ranges. Each indentation was treated as an independent mechanical assessment (Section 2.3). Between-group differences were assessed by Kruskal–Wallis ANOVA followed by Dunn’s pairwise comparisons, with the false discovery rate controlled at $q = 0.05$ by the two-stage step-up method of Benjamini, Krieger and Yekutieli; pairs that are discoveries at this level are marked in the figures (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; *n.s.*, not a discovery), and all pairwise p values are listed in Table S10. Effect sizes (fold change of group means and Cohen’s d) with bootstrap 95% confidence intervals are reported alongside (Table S3). As a check on the independence assumption, each parameter was compared between the three sections (one animal each) of the same group by Kruskal–Wallis ANOVA (Fig. S2, Table S11). Whether the long-time exponent carries information about infarction beyond stiffness was examined by comparing control and infarcted indentations within their common range of substrate-corrected modulus and by leave-one-out logistic classification of control versus infarcted indentations with E alone and with E plus α_{long} , summarized by the area under the receiver-operating curve (AUC) (Table S9).

3. Results

3.1 Static mechanical behavior of myocardial tissue

We first investigate the static mechanics of the infarction progression using AFM micro-rheology (Fig. 1). We revealed a distinct softening-then-stiffening trajectory in tissue stiffness (E) that reflects the underlying pathological remodeling (Fig. 1B, 1C and Table S1). In the acute phase of MI (week 1), the myocardium exhibited marked softening, with the mean elastic modulus dropping from ~ 3.8 kPa (control) to ~ 1.1 kPa (week 1). This was followed by a rapid, irreversible stiffening as the infarct matured into a fibrotic scar, rising to ~ 17 kPa by week 2 and peaking at ~ 22 kPa by week 4 (Fig. 1B). All between-group differences in E are significant except that between weeks 2 and 4 (Dunn’s test with BKY correction: control vs. week 1, $p = 0.03$; control vs. weeks 2 and 4, $p \leq 0.0002$; week 1 vs. weeks 2 and 4, $p < 10^{-7}$; week 2 vs. week 4, $p = 0.73$; Fig. 1B, Table S10). A sample-independence check across the animals of the control, week-1 and week-2 groups shows no systematic difference in E (Fig. S2, Table S11). However, mean stiffness values often mask the underlying structural disorder that can accompany disease progression (Leartrapun et al. 2024; Pirnat 2024). By analyzing the coefficient of variation (CV) as a metric of mechanical heterogeneity, we uncovered a transient homogenization of the tissue (CV, control: 0.78; week 1: 0.57; week 2: 0.94; week 4: 0.89) (Fig. 1B). During week 1, the heterogeneity decreased from 0.78 to 0.57, diverging from the behavior of the mean stiffness. One possible contribution, suggested by histology (Fig. 2A and 2B), is widespread tissue edema; our measurements do not directly quantify interstitial fluid content, and this interpretation remains a hypothesis. Conversely, in the mid- and late-stages of MI, the mechanical heterogeneity surged (CV

> 0.85) and remained elevated. This mechanical scatter corresponds to the dense, coarse collagen fiber bundles, marking the onset of irreversible structural instability (Fig. 2C and 2D).

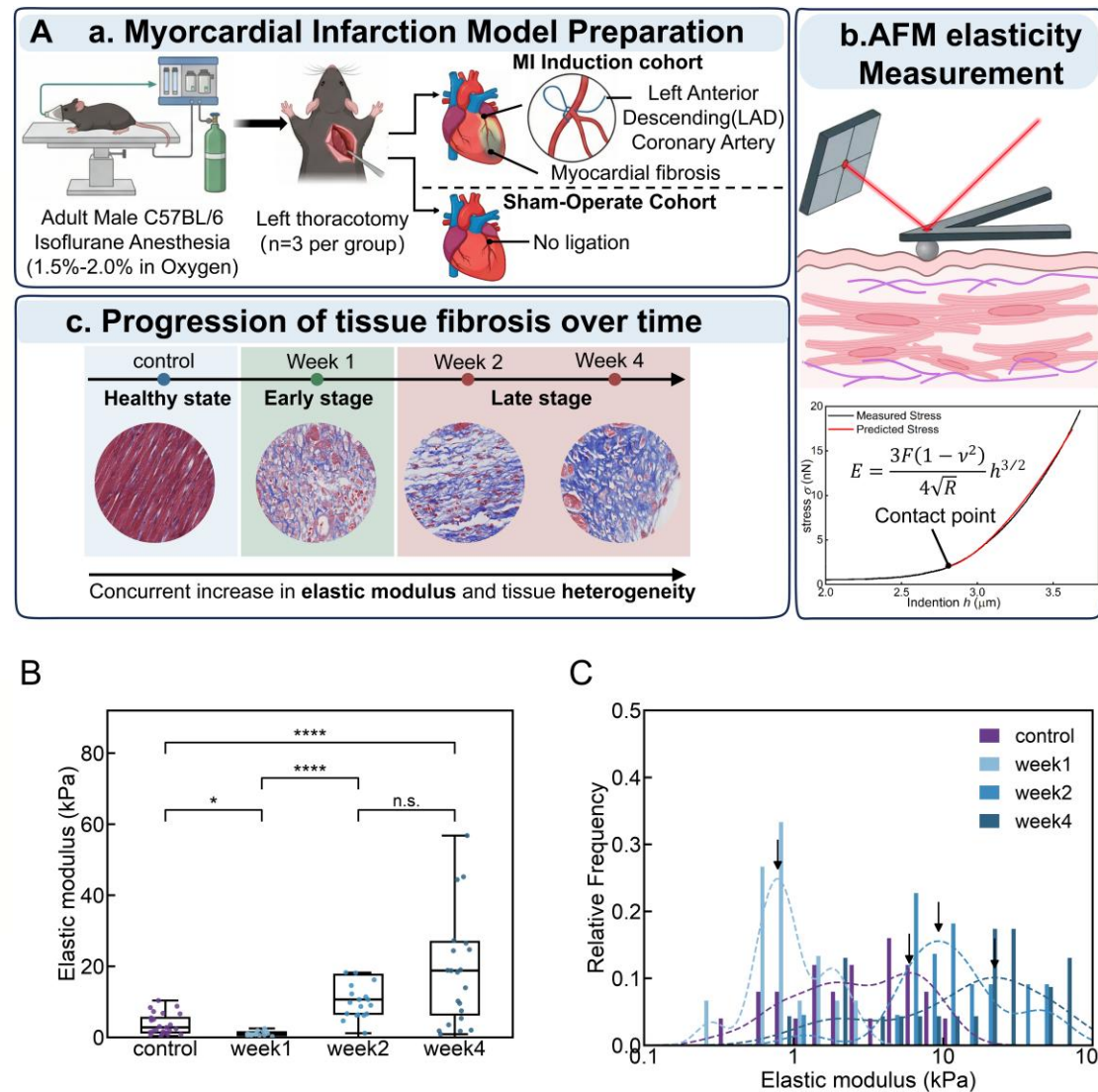


Fig. 1 AFM-based characterization of myocardial remodeling. (A) MI animal model/MI progression and ultrastructure/AFM-based mechanical characterization. The process of establishing a mouse model of myocardial infarction (MI), as well as the complete experimental protocol for evaluating biomechanical properties elastic modulus of myocardial tissue at different pathological stages using micro-rheology techniques based on AFM. (B) Substrate-corrected tissue stiffness during myocardial infarction progression (boxes, median and interquartile range; whiskers, $1.5 \times$ interquartile range). (C) Distributions and frequency histograms of the substrate-corrected elastic modulus at each time point. Kruskal–Wallis ANOVA followed by Dunn’s pairwise test with the two-stage step-up false-discovery-rate procedure of Benjamini, Krieger and Yekutieli ($q = 0.05$): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; n.s., not a discovery at $q = 0.05$. N = 25, 15, 22 and 23 indentations from 3 animals per group

While static stiffness provides a snapshot of damage, the heart is fundamentally a viscoelastic composite dependent on energy dissipation and time-dependent relaxation for function (Frangogiannis and Kovacic 2020). Relying solely on E neglects the critical contributions of fluid redistribution and cytoskeletal damping. To bridge this gap, we analyzed the time-dependent creep compliance, $J(t)$, which quantifies the tissue's

capacity for reversible deformation (Table S1). The temporal evolution of $J(t)$ revealed a monotonic collapse in tissue deformability, distinct from the biphasic stiffness trend. Average compliance dropped by nearly 70% from the healthy state (control = $5.21 \pm 1.55 \times 10^{-4} \text{ Pa}^{-1}$) to the end-stage (week4 = $1.72 \pm 0.98 \times 10^{-4} \text{ Pa}^{-1}$) (Table S1). This systemic rigidification restricts macromolecular rearrangement, consistent with the dense collagen accumulation observed in late-stage histology (Fig. 2D) (Chang et al. 2024b; Li et al. 2025). Week2 and late-stage MI tissues exhibited broad, unimodal distributions, reflecting the fragmented mechanics of the native extracellular matrix (ECM). By Week 4, however, the distribution did not merely shift; it deformed, developing a pronounced heavy tail skewed toward low-compliance values. This distributional skew, where the CV of compliance nearly doubled from 0.30 to 0.57 (Table S1), signals the emergence of focal fibrosis.

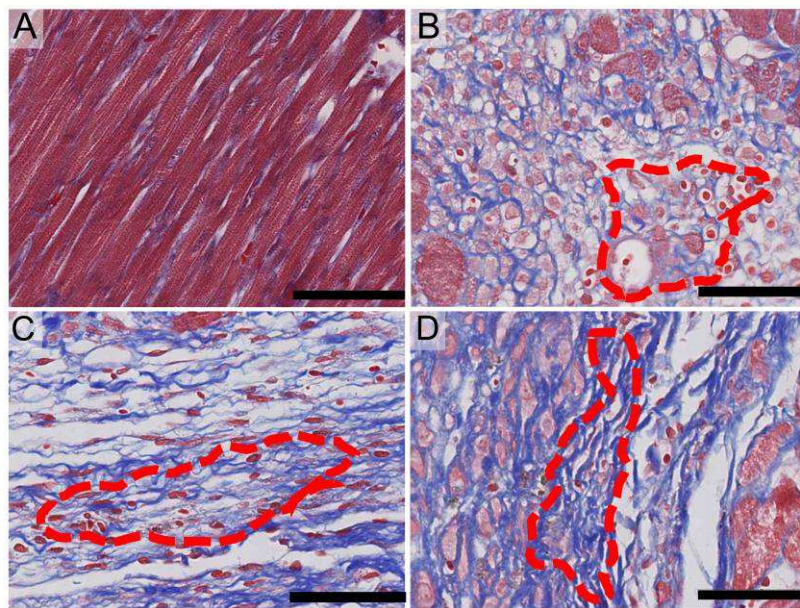


Fig. 2 Histological images of myocardial infarction pathological progression (Masson's Trichrome staining). Evolution from Dense and healthy tissue in (A) control group to disorganized collagen network in (B) week 1, loose and wavy collagen fibers in (C) week 2, and dense, mature protein fibers in (D) week 4 after MI. Scale bar = 50 μm for all the images

3.2 Two-stage power-law rheology

To decode the dynamic mechanics of myocardial remodeling, we analyzed the creep response $J(t)$. Across all tissues, regardless of pathological state, the response exhibits two regimes: a steep short-time rise followed by a shallow long-time power law (Fig. 3A), consistent with our previous observations in myocardium and other soft tissues (Chang et al. 2023b; Hang et al. 2021). The two regimes are separated by the fluid–solid transition time τ of each indentation (Section 2.5): for $t < \tau$ pressurized interstitial fluid drains from the contact region and the tissue creeps like a fluid, whereas for $t > \tau$ the response is governed by the slow power-law rearrangement of the solid collagen–cytoskeletal matrix (Fig. 4).

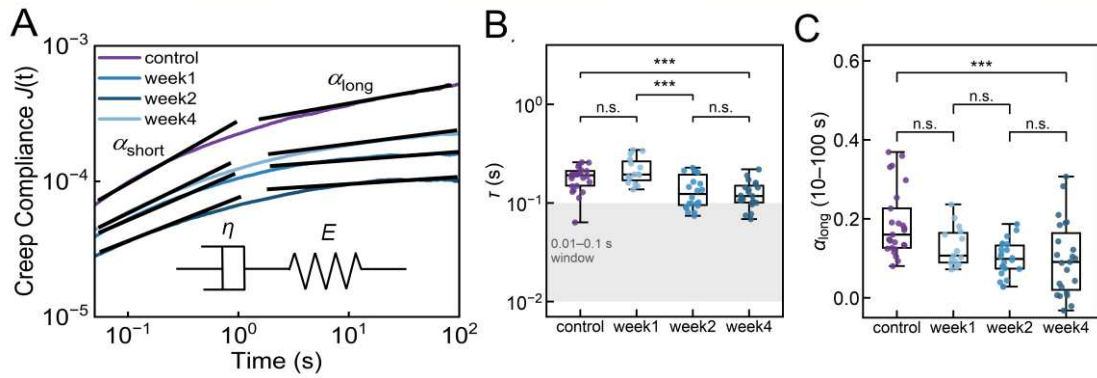


Fig. 3 Two-stage power-law rheology across the progression of MI. (A) Representative compliance–time curves for the four groups on a double-logarithmic scale, showing a steep short-time regime followed by a shallow long-time power law. (B) Per-indentation fluid–solid transition time $\tau = a^2/(2GD)$ from the joint fit for each group (log scale; boxes, median and interquartile range; whiskers, $1.5 \times$ interquartile range); the shaded band marks the 0.01–0.1 s window used for α_{short} . (C) Long-time exponent α_{long} evaluated over 10–100 s. Kruskal–Wallis ANOVA followed by Dunn's pairwise test with the two-stage step-up false-discovery-rate procedure of Benjamini, Krieger and Yekutieli ($q = 0.05$): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; n.s., not a discovery at $q = 0.05$. $N = 25, 15, 22$ and 23 indentations from 3 animals per group

Fitting the coupled model to every indentation yields τ confined to 0.06–0.43 s, with group medians of 0.19 s (control), 0.20 s (week 1), 0.12 s (week 2) and 0.12 s (week 4) (Fig. 3B, Table S3); τ is significantly shorter in weeks 2 and 4 than in control and week-1 tissue ($p \leq 0.007$), whereas control and week 1, and weeks 2 and 4, do not differ (Table S10). The short-time exponent α_{short} , evaluated in the fixed 0.01–0.1 s window that lies within the fluid-dominated regime (the window ends at 0.5–0.85 τ , group medians), follows the same pattern: it remained at 0.65 ± 0.12 in week-1 tissue, comparable to control (0.62 ± 0.08), and dropped to 0.48 ± 0.09 and 0.48 ± 0.10 in weeks 2 and 4 (Table S2; Dunn's test, $p < 10^{-4}$ for weeks 2 and 4 versus control and week 1; control vs. week 1, $p = 0.79$). The short-time exponent thus tracks the earlier onset of solid-like creep in the maturing scar, consistent with cytoskeletal condensation and collagen deposition shortening the drainage-dominated interval, whereas the fluid-rich, edematous tissue of the acute phase retains the fluid-like short-time response of healthy myocardium.

The long-time exponent, evaluated over 10–100 s and therefore beyond 20τ for every indentation, is $\alpha_{\text{long}} = 0.19 \pm 0.09$ (control), 0.13 ± 0.05 (week 1), 0.10 ± 0.04 (week 2) and 0.10 ± 0.09 (week 4) (Fig. 3C, Table S2). It is thus lower after infarction than in control tissue (Cohen's $d = -0.79, -1.27$ and -0.99 for weeks 1, 2 and 4; Dunn's test, $p = 0.0002$ for weeks 2 and 4 and $p = 0.04$ for week 1, the last not a discovery at $q = 0.05$; Tables S3 and S10), consistent with a denser, more cross-linked collagen network, but it does not separate the three infarct stages from one another. α_{long} is only weakly coupled to local stiffness (pooled Spearman $\rho = -0.31$ against E) and remains lower in infarcted than in control tissue at matched stiffness, so that adding it to E improves the leave-one-out separation of control from infarcted indentations (Table S9): the long-time exponent carries information about infarction that stiffness does not. Approximately 40% of the creep accumulated during the hold is carried by the poroelastic term (group medians 39–44%), in line with rapid pore-pressure equilibration followed by slow solid rearrangement.

3.3 A composite constitutive framework for multiscale poro-viscoelasticity

To bridge the gap between microscopic fluid dynamics and tissue mechanics, we developed a composite constitutive framework (details in Supplementary Note). Unlike classical viscoelastic models that reduce the heart to a homogeneous continuum (Angeli et al. 2025; Rienks et al. 2014), our approach explicitly accounts for the biphasic nature of the myocardium: a porous, elastic solid matrix saturated with mobile interstitial fluid. We quantify the tissue's fluid transport capacity via the Hydraulic Permeability (D), describing the ease of pressure-driven interstitial fluid transport through the porous myocardial matrix under load. The fluid dynamics are governed by Darcy's Law, which relates the interstitial fluid velocity vector (v_i) to the local pore pressure gradient (p,i): $v_i = -D p,i$, where D is the hydraulic permeability of the fluid-saturated matrix (units $\text{m}^4 \text{N}^{-1} \text{s}^{-1}$), following the biphasic-theory convention of Mow and co-workers. To extract D from the indentation creep data we use the poroelastic master curve for spherical indentation (Oyen 2008), formulated in the normalized time $T^* = \sqrt{(2GDt)/a}$, and fit it jointly with the long-time power law (Section 2.5); the fluid–solid transition time $\tau = a^2/(2GD)$ is the time at which $T^* = 1$, where G is the shear modulus and the contact radius. When $t < \tau$, the system is dominated by poroelastic fluid exudation and rapid pressure equilibration; for $t > \tau$, the response is governed by the slow power-law rearrangement of the solid collagen–cytoskeletal matrix.

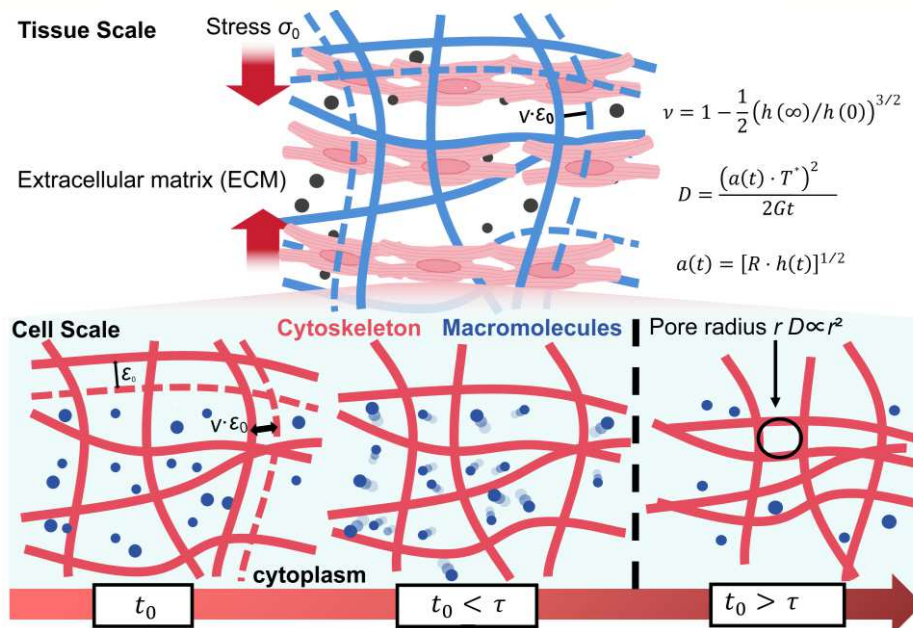


Fig. 4 Schematic of the poroelastic response of myocardial tissue. The hierarchy spans protein fibers, cytoskeletal elements, and tissue-scale fluid-filled pores. Multiscale hierarchical schematic of myocardial tissue creep experiments, from protein fibers (blue lines) to cytoskeletal elements (red lines) within the tissue. Red dashed lines indicate the displacement destinations of the cytoskeleton after transient stress application. For $t < \tau$, pressurized interstitial fluid drains from the contact region and the tissue exhibits liquid-like mechanical behavior. As the experiment progresses, cellular deformation slows and the cytoskeleton stabilizes, leading the tissue to display solid-like mechanical characteristics

This coupled description accounts for the rapid initial deformation observed in our experiments, where about 40% of the creep accumulated during the hold occurs within the first second, and for the slow solid relaxation that follows. Fitting the two contributions jointly is essential: fitted alone, the poroelastic master curve is degenerate because the long-time response does not saturate, so that widely different values of D

give nearly identical residuals. The influence of the finite loading phase and of the alternative, purely phenomenological description of the short-time regime is examined in the Supplementary Note (Section 6) and considered in the Discussion (Section 4).

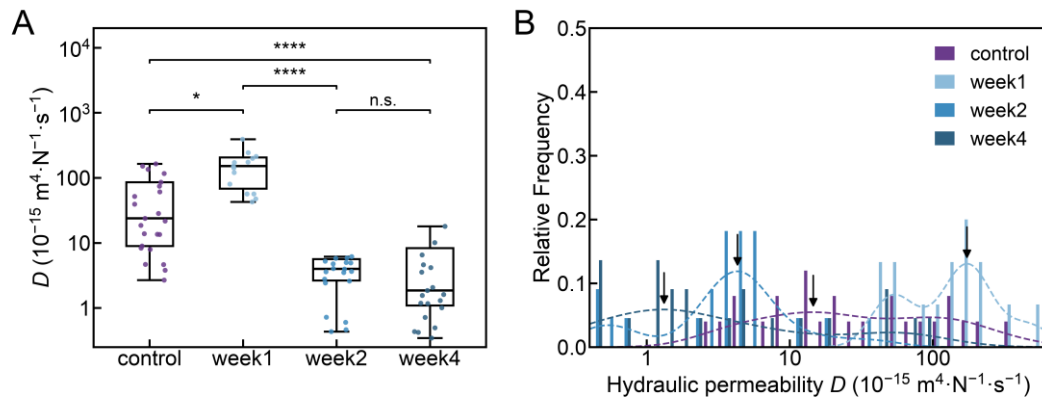


Fig. 5 Hydraulic permeability of murine myocardial tissue. (A) Box and whisker plots of the hydraulic permeability D from the joint fit (log scale; boxes, median and interquartile range; whiskers, $1.5 \times$ interquartile range); D is an apparent value for 15- μm cryosections bonded to glass, and only between-group comparisons are interpreted. Kruskal–Wallis ANOVA followed by Dunn’s pairwise test with the two-stage step-up false-discovery-rate procedure of Benjamini, Krieger and Yekutieli ($q = 0.05$): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; n.s., not a discovery at $q = 0.05$. $N = 25, 15, 22$ and 23 indentations from 3 animals per group. (B) Relative-frequency histograms of $\log D$ for each group with kernel-density estimates (dashed lines); arrows mark the density peaks

Next, we study the alterations in D to characterize the structural transition from early-stage acute destruction to late-stage chronic reconstruction. The distribution of D within each group is broad (coefficient of variation 0.8–1.8), so we report medians with interquartile ranges. In healthy myocardium the median D was $24 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ (interquartile range 9–86) (Fig. 5A, B; Table S2). Following infarction (week 1), D rose to $152 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ (68–207), a 6.4-fold increase of the median (fold change of means 2.7, bootstrap 95% CI 1.4–5.3; Table S3). This increase coincides with the acute inflammatory phase, in which cardiomyocyte necrosis and clearance of cellular debris create transient micro-cavities (Fig. 2B) that enlarge the effective pore size and reduce tortuosity. As the tissue entered the reparative phase (week 2), the trend reversed sharply: D fell to $4.0 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ (2.6–5.7), one sixth of the control median, consistent with activated fibroblasts depositing dense collagen that progressively fills the interstitial voids (Fig. 2C). By the chronic stage (week 4), D reached $1.9 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ (1.1–8.3), more than an order of magnitude below control, with a long upper tail contributed by residual soft regions within the scar; the mature fibrotic scar behaves as a hydraulically restrictive environment (Fig. 2D). All pairwise differences in D are significant except that between weeks 2 and 4 ($p \leq 0.02$ and $p = 0.81$, respectively; Fig. 5A, Table S10). Because the drainage boundary of a 15 μm cryosection bonded to glass differs from intact tissue, all D values are effective, apparent permeabilities of the present section geometry, and only between-group comparisons are interpreted.

3.4 Machine learning classification of MI progression

To translate these complex micromechanical biophysical signatures into a potential proof-of-concept classification framework, we integrated the five markers (D , α_{short} , α_{long} , E and Poisson’s ratio ν) into a neural network classifier with a Softmax output

layer (Yaman et al. 2024; Rhyou et al. 2025) (Fig. 6). This architecture was specifically designed to decode the latent, non-linear relationships defining the transition between MI stages.

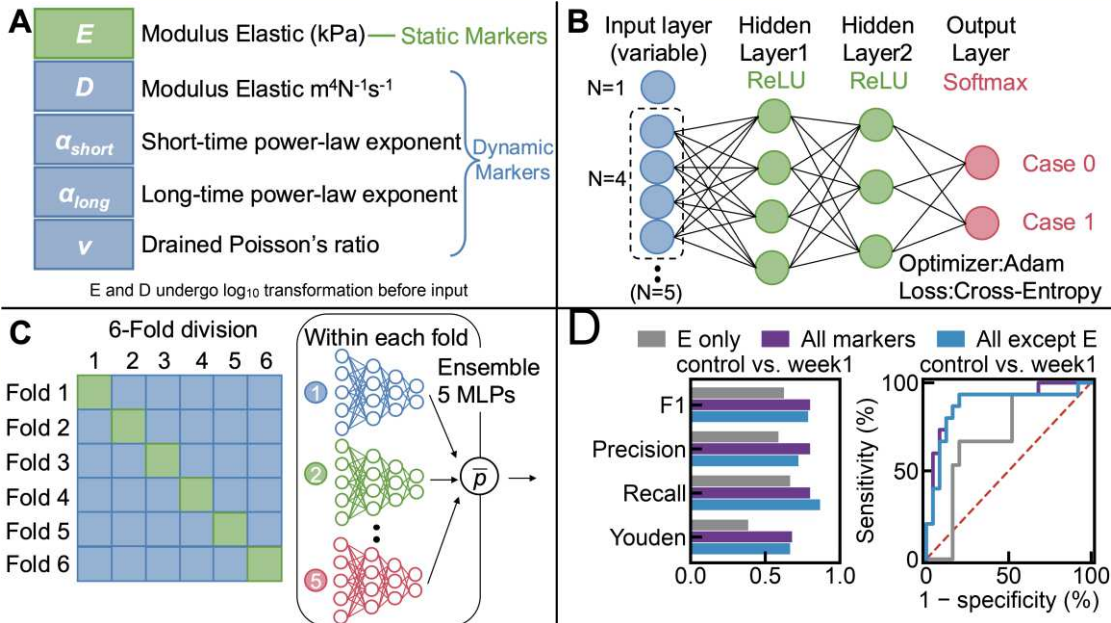


Fig. 6 Neural network-based machine learning models for MI staging. A framework for dataset partition, model training and independent validation. (A) Feature engineering and input markers. (B) Single MLP architecture. (C) Training and ensembling scheme. (D) Key evaluation indexes (F1, precision, recall and Youden's index) and ROC curves for control vs. week 1 with E only (grey), all markers (purple) and all markers except E (blue)

Receiver operating characteristic (ROC) analysis confirmed that the multiparametric integration yields exploratory proof-of-concept classification potential (Fig. 7A, B). The classifier achieved high discriminatory fidelity across all progression boundaries, particularly in distinguishing healthy myocardium from the acute and the chronic infarct. Specifically, the area under the curve (AUC) for distinguishing control vs. week 1 (the acute phase) reached 0.90, and control vs. week 4 (chronic scar) reached 0.91, compared with 0.69 and 0.73 for stiffness alone. The model also resolved the difficult discrimination between mid-stage and late-stage fibrosis (week 2 vs. week 4, AUC = 0.89 against 0.58 for stiffness alone; Fig. S3). Over five different cross-validation partitions the AUC of the full-marker model ranged from 0.84 to 0.94 (control vs. week 1) and from 0.84 to 0.93 (week 2 vs. week 4), so the advantage over stiffness alone does not depend on the particular partition.

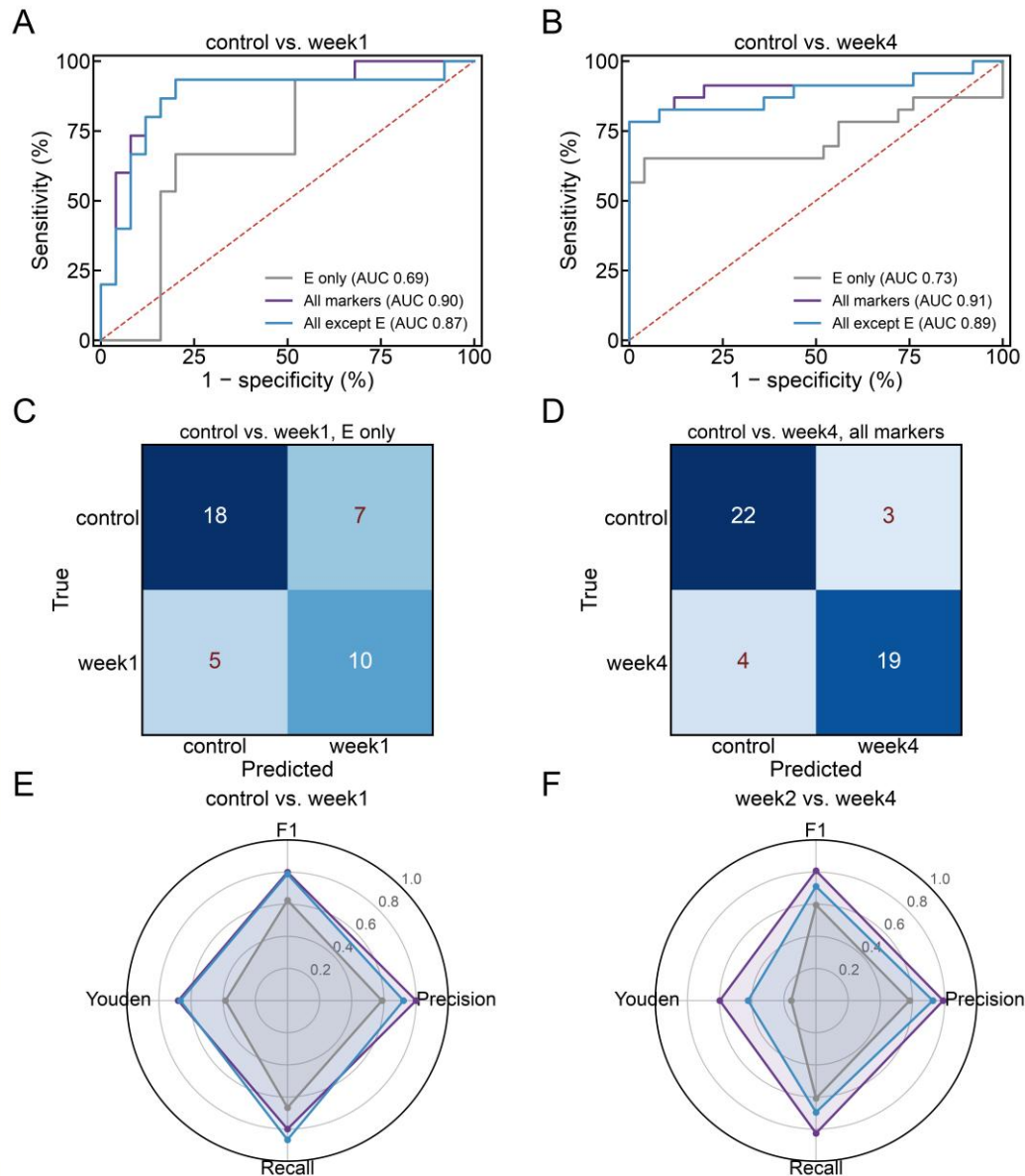


Fig. 7 Classification performance of poro-viscoelastic features. (A, B) ROC curves of *E* only (grey), all markers (D , α_{short} , α_{long} , *E* and ν ; purple) and all markers except *E* (blue) for (A) control vs. week 1 and (B) control vs. week 4; the AUC of each model is given in the legend. Confusion matrices (rows, true class; columns, predicted class) for (C) the stiffness-only model, control vs. week 1, and (D) the all-marker model, control vs. week 4. (E, F) Radar charts of *F1*, precision, recall and Youden's index for the three feature sets (same colours) for (E) control vs. week 1 and (F) week 2 vs. week 4. Metrics are pooled over the six cross-validation folds ($N = 25, 15, 22$ and 23 locations)

To further quantify performance on specific classification tasks, we examined representative confusion matrices (Fig. 7C, D). For the early task (control vs. week 1), the stiffness-only model correctly classified 18 of 25 control locations and 10 of 15 week-1 locations, misclassifying a third of the acute infarcts and more than a quarter of the healthy tissue (Fig. 7C), whereas the full-marker model classified 22 of 25 and 12 of 15 correctly (Fig. S4A). For the chronic task (control vs. week 4), the full multiparametric model correctly classified 22 of 25 control and 19 of 23 week-4 locations (Fig. 7D). Consistent with the ROC analysis (Fig. 7A, B), incorporating the poro-viscoelastic markers improves discrimination over stiffness alone, raising the AUC for the acute-phase task from 0.69 to 0.90. These results indicate that tissue

stiffness alone is inadequate for capturing the heterogeneous characteristics of the transitional phase, and that the poro-viscoelastic parameter set provides richer and more robust discriminative features than traditional stiffness metrics. Next, we systematically evaluated the performance of the integrated neural network across multiple binary classification tasks (summarized in Fig. 7E, F and in Figs. S3–S5). The model demonstrated robust discriminative capability for MI staging, particularly in the critical separation of healthy tissue from early-stage infarction (control vs. week 1). In this task, the full-marker classifier achieved an *F1* score of 0.80, with precision and recall both of 0.80 and a Youden index of 0.68, against 0.62, 0.59, 0.67 and 0.39 for stiffness alone.

4. Discussion

This study demonstrates that myocardial remodeling after myocardial infarction is expressed as a coordinated reorganization of stiffness, time-dependent relaxation and fluid transport, rather than as a monotonic change in elastic modulus. The AFM measurements captured the softening-to-stiffening trajectory in stiffness *E*, but the poro-viscoelastic parameters resolved additional stage-dependent features that were not apparent from *E* alone. The median *D* increased from $24 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ in control tissue to $152 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ at week 1, then declined to 4.0×10^{-15} and $1.9 \times 10^{-15} \text{ m}^4 \text{ N}^{-1} \text{ s}^{-1}$ at weeks 2 and 4, respectively. Over the same interval, τ shortened and the short- and long-time power-law exponents changed, consistent with a shift from an acute, fluid-rich and mechanically compliant state toward a hydraulically restrictive, consolidated scar. Taken together, the data suggest that post-infarction mechanical remodeling is defined not only by the mean level of stiffness but also by the temporal organization and spatial heterogeneity of the tissue response. The early increase in apparent permeability is consistent with altered fluid spaces and loss of structural support, whereas the later reduction in *D* and α_{long} accompanies the stiffening and collagen-rich organization of the scar. These mechanistic links remain interpretations rather than direct measurements of pore geometry, collagen turnover or fluid content, and the poroelastic assignment of the short-time response is model dependent. We therefore discuss the three stage-specific regimes as a mechanistically informed interpretation of the measurements, while reserving claims about clinical staging for future studies with animal-level validation, orthogonal histology and in vivo measurements.

Based on the distinct poro-viscoelastic signatures, we describe three biophysical phases of MI progression (Fig. 8): an acute high-permeability phase, a reparative hydraulic-blockade phase, and a chronic consolidated-composite phase. The mechanisms proposed for each phase are interpretations consistent with the measured parameters and with histology; they were not tested directly in this study. From healthy to week 1, the clearance of necrotic cardiomyocytes creates micro-cavitations, while inflammatory edema expands the interstitial space (Mayorca-Guiliani et al. 2025; Rienks et al. 2014; Wen et al. 2025). According to Poiseuille-based hydraulic scaling, permeability is proportional to the square of the hydraulic pore radius ($D \propto r^2$) (Barr 2001). The necrotic expansion of pore connectivity, together with the loss of solid support that softens the tissue, is therefore consistent with the observed 6.4-fold rise of the median permeability. Physically, the tissue behaves as a "leaky sponge": soft, highly permeable, and mechanically unstable due to the loss of solid ECM support. The transition to week 2 represents a mechanical inversion. As fibroblasts activate, the disordered deposition of nascent collagen distorts diffusion pathways and increases tortuosity (Hynes 2009; Mayorca-Guiliani et al. 2025; McKleroy et al. 2013). Such densification would create

a hydraulic blockade; the median permeability indeed falls to one sixth of the control value while stiffness rises 4.4-fold. This stage is mechanically chaotic, characterized by high spatial heterogeneity, as fluid-filled voids are occluded by focal scars (Lindsey and Zamilpa 2012). By week 4, the substrate-corrected elastic modulus (E) rises to ~ 6 times that of healthy tissue, while the median D falls below one tenth of the control value and α_{long} remains below control. This is consistent with the transition to a fibrotic state (Ghatak et al. 2015; McKleroy et al. 2013; Stern et al. 2006), in which dense, cross-linked collagen bundles eliminate free fluid volume. The tissue evolves into a consolidated composite: a globally stiffened matrix punctuated by distinct, highly rigid scar domains.

Parameters(mean)	Control	Week 1	Week 2	Week 4
E (substrate-corrected) kPa	3.76	1.08	16.52	21.90
α_{long}	0.19	0.13	0.10	0.10
D (median) $\text{m}^4\text{N}^{-1}\text{s}^{-1} \times 10^{-15}$	23.9	151.7	4.0	1.9
ν	0.34	0.42	0.33	0.35

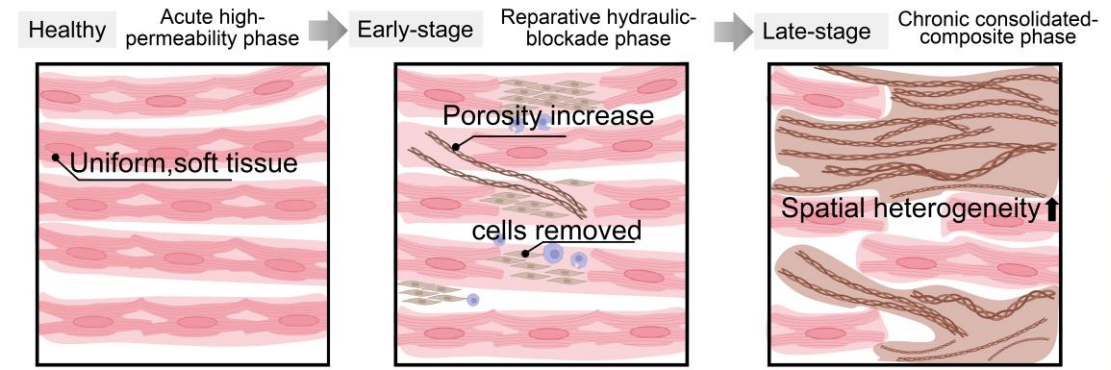


Fig. 8 Stage-dependent parameters and a schematic interpretation of myocardial remodeling. Initially, pink, wavy, smooth, and dense tissue with uniform mechanical properties (healthy). In the early-to-mid pathological stage, cardiomyocytes undergo disintegration first. Macrophages (blue) initiate clearance, and granulation tissue begins to form, increasing tissue porosity and the sparsest state of myocardial tissue. In the late disease stage, extensive fibrous scar tissue replaces the original healthy myocardial tissue, and the tissue as a whole becomes dense again. Table: group means of the substrate-corrected elastic modulus E (kPa), the long-time exponent α_{long} (10–100 s) and the drained Poisson's ratio ν , and group medians of the hydraulic permeability D ($\text{m}^4 \text{N}^{-1} \text{s}^{-1} \times 10^{-15}$)

The acute surge in hydraulic permeability (D) acts as a sentinel event, signaling structural integrity loss and pore expansion well before the onset of irreversible fibrosis. In contrast to static stiffness, which acts as a lagging indicator of established scarring, this early poro-elastic shift opens a critical diagnostic window to identify subjects at risk of adverse remodeling in the immediate post-infarction period. Furthermore, the sensitivity of D to spatial heterogeneity enables the precise mapping of the border zone, where the interface between the rigid scar and salvageable myocardium. By resolving these subtle micro-mechanical boundaries, our framework offers a robust metric to help evaluate therapeutic response in future studies. These findings establish hydraulic permeability not merely as a parameter of pore size, but as a potential exploratory proof-of-concept classification biophysical marker for assessing the MI-associated remodeling. The heavy tail represents the formation of isolated, mechanically rigid islands of dense collagen (Eslami and Darvishi 2025; Silver et al. 2001), which possess viscoelastic moduli orders of magnitude higher than the surrounding cardiomyocytes.

We speculate that this resulting mechanical discontinuity has profound functional implications. The myocardium evolves from a coherent syncytium into a heterogeneous composite of compliant muscle embedded with rigid fibrotic foci. Such localized stress concentrations are known to impair coordinated contraction (Moeendarbary et al. 2013). Crucially, this heterogeneity acts as a potent substrate for arrhythmogenesis; abrupt spatial transitions in stiffness can perturb mechano-electrical coupling, potentially creating conduction blocks and re-entrant circuits (Auerbach et al. 2011; Babu-Narayan et al. 2016). Thus, we conclude that the progression of MI is defined not merely by global stiffening, but by the catastrophic loss of viscoelastic and microstructural coherence.

Our findings demonstrate that the mechanical parameters proposed in this study constitute a highly sensitive, high-dimensional signature of infarction progression. Just as magnetocardiography and 3D deformation imaging have expanded the functional toolkit (Li et al. 2024; Tao et al. 2025), our framework unveils a latent biophysical layer, the dynamic evolution of fluid–solid interactions, that traditional stiffness metrics overlook (Wang et al. 2024). By decoding these signatures, we establish an exploratory proof-of-concept classification approach for MI staging. The ability to distinguish between the fluid-dominated acute phase and the matrix-locked chronic phase bridges the gap between microscopic tissue mechanics and future clinical decision-making, offering a proof-of-concept classification standard for assessing MI-associated remodeling. Crucially, our comparative analysis reveals that configurations employing the full poro-viscoelastic markers (D , α_{long} , α_{short} , E , ν) consistently outperform those relying solely on static stiffness (E). This advantage holds across all evaluation metrics, indicating that the improvement is intrinsic to the physics-informed feature set rather than a statistical artifact, and that the fluid-transport and time-dependent parameters (D , α_{long} , α_{short}) unlock a diagnostic dimension that stiffness alone cannot access. Disease progression is a dynamic, continuous process that is far more complex than a static binary diagnosis; ignoring the viscoelastic and poroelastic nature of the tissue yields metrics that lack the universality required for reliable clinical testing. By capturing the spatiotemporal variations in poro-viscoelasticity, our framework aligns with the true mechanical complexity of the myocardium and offers a rigorous standard for distinguishing the subtle gradations of disease progression. These poro-viscoelastic markers also provide quantitative design constraints for cardiac biomaterials. A material intended for the acute infarct niche should not be matched only to elastic modulus; it should also account for elevated permeability, edema-driven fluid transport and low structural coherence. Conversely, materials designed for chronic scars must operate within a stiff, low-permeability, transport-restricted matrix. Thus, the present framework establishes stage-specific mechanical target windows for regenerative patches, injectable matrices and mechanically informed diagnostic platforms after MI.

Several limitations should be noted. First, the study used three mice per group, in line with the principle of reduction in animal research and with our previous studies (Chang et al. 2023a, b), and 85 retained indentation datasets, each treated as an independent assessment of a distinct tissue region. A comparison between the sections of each group shows no systematic section effect in control, week-1 and week-2 tissue for E , τ , D and α_{long} (Fig. S2, Table S11). Larger cohorts would reduce random variation and increase statistical power, and might also reveal additional biological variability. We consider it more important that future studies examine more animals at finer time resolution over the progression of infarction, so as to capture the mechanical heterogeneity and

gradients of the healing infarct and to develop more reliable diagnostic models that can improve the efficiency of non-invasive approaches such as magnetic resonance elastography and shear wave elastography. Second, measurements were obtained from ex vivo cryosections bonded to glass at room temperature; the drainage boundary differs from intact myocardium, so D is an apparent, geometry-dependent permeability, and in vivo loading, perfusion and neurohumoral environments are not reproduced. Third, the poroelastic assignment of the short-time regime is a model choice: a phenomenological two-power-law description fits most curves at least as well, and the finite loading phase, which is comparable to τ , shifts the fitted τ by a factor of 2–6 in an approximate superposition estimate (Supplementary Note, Section 6); the ranking of the groups is preserved in either description. Finally, the proposed biophysical phases are murine time points, not clinical MI stages; because of the limited cohort, this study did not correlate quantitative histological metrics with the mechanical parameters at the level of individual indentations, and longitudinal in vivo measurements, larger cohorts and orthogonal histological quantification (e.g., collagen volume fraction) will be required before diagnostic claims can be made.

5. Conclusion

This study establishes a multiscale poro-viscoelastic framework for characterizing the mechanical remodeling of infarcted myocardium. By fitting AFM creep responses with a coupled poroelastic–power-law model, we resolved the mechanical state of each tissue location into complementary descriptors: the substrate-corrected elastic modulus E , the hydraulic permeability D , the fluid–solid transition time τ , the short- and long-time power-law exponents α_{short} and α_{long} , and the drained Poisson’s ratio ν . Across the four groups these descriptors trace a consistent biphasic evolution of fluid–solid interactions. In the acute phase the infarct softens, becomes transiently more homogeneous and its permeability rises more than six-fold, consistent with edema and the micro-cavities left by necrotic clearance. In the reparative and chronic phases stiffness increases up to six-fold, permeability falls by more than an order of magnitude, the fluid-like regime of creep shortens and the long-time exponent declines, indicating a dense, cross-linked and hydraulically restrictive scar with pronounced spatial heterogeneity. The time-dependent parameters carry information that stiffness alone does not: the long-time exponent distinguishes infarcted from control tissue at matched stiffness, and integrating the poro-viscoelastic markers into a neural network classifier improved the cross-validated separation of the stages relative to stiffness alone, including the difficult early separation of control from week-1 tissue. These results support dynamic fluid–solid mechanics as a quantitative framework for staging post-infarction remodeling and provide stage-specific mechanical target windows for regenerative patches, injectable matrices and mechanically informed diagnostic platforms after myocardial infarction.

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Author contribution Luo-Jian Peng: Conceptualization, Methodology (AFM and computational modeling), Investigation, Formal analysis, Data curation, Validation, Writing – original draft, Writing – review & editing. Xian-Jun Wu: Software (machine learning implementation), Methodology, Investigation, Data curation. Zhuo

Chang: Conceptualization, Validation, Project administration, Funding acquisition,
Writing – review & editing. **Guang-Kui Xu**: Conceptualization, Methodology,
Investigation, Supervision, Validation, Project administration, Funding acquisition,
Writing – original draft, Writing – review & editing.

Data Availability The indentation creep curves analyzed in this study and the scripts
used for the joint fit are available from the corresponding authors on reasonable
request; summary data are provided in the paper and its Supplementary Information
files.

Declarations

Conflict of interest The authors declare that they have no known competing financial
interests or personal relationships that could have appeared to influence the work
reported in this paper.

Supplementary materials

Supplementary materials associated with this article can be found, in the online version,

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