

Early Three-Dimensional Left Atrial and Right Ventricular Deformation changes during Immunotherapy and Targeted Cancer Therapy: A Prospective Cohort Study

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Abstract

Left atrial and right ventricular deformation have been studied less than left ventricular global longitudinal strain during cancer therapy, and three-dimensional measurements of both chambers have not been reported in a mixed-tumour cohort. Forty-five adults starting immunotherapy (n = 26) or targeted therapy (n = 19) underwent echocardiography and electrocardiography at baseline, 3 and 6 months. Three-dimensional left atrial reservoir, conduit and booster strain and right ventricular global longitudinal and free-wall strain were measured offline. From baseline to 6 months, right ventricular global longitudinal strain fell from 21.4% to 18.2%, free-wall strain from $25.3 \pm 3.8\%$ to $21.7 \pm 4.4\%$, and left atrial conduit strain from 20.0% to 15.0% (all $p < 0.001$). Reservoir strain fell modestly ($p = 0.005$) and booster strain did not change. No parameter changed between 3 and 6 months, and conventional right ventricular indices and chamber dimensions changed in parallel. New-onset arrhythmia occurred in 20 of 40 participants free of arrhythmia at baseline, most often sinus tachycardia, and no strain measure identified those in whom it occurred. In this uncontrolled cohort, right ventricular and left atrial conduit deformation declined within three months of therapy; without a comparison group these changes cannot be attributed to treatment.

Introduction

Immune checkpoint inhibitors and targeted agents have extended survival across many tumour types. In a meta-analysis of 63 randomised trials enrolling 32,518 patients, immune checkpoint inhibitor exposure was associated with an excess risk of six cardiovascular adverse events, including myocarditis, pericardial disease, heart failure and myocardial infarction¹. Fulminant myocarditis is uncommon but carries high mortality, and subclinical myocardial injury is more frequent and harder to detect².

Current surveillance rests on left ventricular ejection fraction and left ventricular global longitudinal strain. The 2022 European Society of Cardiology cardio-oncology guidelines define cancer therapy-related cardiac dysfunction using both measures and recommend strain imaging where it is available³. Ejection fraction changes late, and a relative fall in global longitudinal strain of more than 15% is now the accepted marker of mild dysfunction^{4,5}. Left ventricular deformation, however, describes one chamber. The left atrium and the right ventricle are exposed to the same circulating agents and to the same changes in loading, and both may be affected before the left ventricle.

Left atrial deformation separates into reservoir, conduit and contractile components, each of which reports a different phase of the cardiac cycle⁶. Reservoir strain relates more closely to invasively measured filling pressures than E/e' , left atrial volume index or tricuspid regurgitant velocity, and predicts pressure rises that occur only on exertion⁷. Reduced left atrial reservoir strain is associated with mortality and heart failure hospitalisation in heart failure with preserved ejection fraction⁸. In cancer populations, peak atrial longitudinal strain falls during anthracycline therapy alongside global

longitudinal strain, and larger falls occur in patients who go on to meet criteria for cardiac dysfunction^{9,10}.

The right ventricle has received less attention. In 30 patients with advanced melanoma studied before and approximately four weeks after starting checkpoint inhibitor therapy, right ventricular free-wall strain and right atrial contractile strain both deteriorated while tricuspid annular plane systolic excursion, fractional area change and pulmonary artery systolic pressure did not change¹¹. In 55 patients receiving immunotherapy, right ventricular global longitudinal strain and tricuspid annular plane systolic excursion both fell after treatment¹². Both studies derived strain from two-dimensional speckle tracking, with three-dimensional acquisition used only for left ventricular volumes in the second. Three-dimensional acquisition avoids the out-of-plane motion that biases two-dimensional longitudinal strain, and two-dimensional and three-dimensional values are not interchangeable¹³, but three-dimensional data from cancer cohorts are sparse.

Arrhythmia is a further consideration. Electrocardiographic abnormalities carry prognostic weight in checkpoint inhibitor myocarditis, where heart block and ventricular arrhythmias predict myocarditis-related death¹⁴. Whether serial change in atrial or right ventricular deformation identifies patients at risk of arrhythmia during therapy has not been tested.

This study measured three-dimensional left atrial and right ventricular strain at baseline, 3 months and 6 months in adults receiving immunotherapy or targeted therapy, and examined the relationship of these measures to conventional echocardiographic indices, left ventricular diastolic function and new-onset arrhythmia.

Methods

Study design and setting

This was a prospective observational cohort study at Kasturba Hospital, Manipal, a tertiary referral centre in southern India. The protocol was approved by the Institutional Ethics Committee of Kasturba Medical College and Kasturba Hospital, Manipal (IEC1:16/2024), and the study was registered with the Clinical Trials Registry of India (CTRI/2024/02/063271). Written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki, all methods were performed in accordance with the relevant guidelines and regulations, and this report was prepared with reference to the STROBE recommendations for cohort studies.

Study population

Adults aged 18 to 80 years with a histologically confirmed malignancy who were starting targeted therapy or immunotherapy were eligible. Baseline clinical data and at least one follow-up assessment were required for inclusion. Patients were excluded for pre-existing cardiovascular disease, moderate or

severe valvular heart disease, renal impairment, incomplete baseline data, loss to follow-up immediately after starting therapy, or a poor echocardiographic window.

Enrolment took place in the Departments of Cardiology and Medical Oncology. Baseline assessment recorded demographic and clinical characteristics, medical history, physical examination and a 12-lead electrocardiogram. Cardiovascular risk factors were recorded as present or absent. Cumulative drug dose was recorded in milligrams.

Echocardiography

Transthoracic echocardiography was performed on a Vivid S60 system with a [4Vc matrix-array probe] transducer (GE HealthCare, Horten, Norway). Electrocardiographically gated two-dimensional, Doppler and three-dimensional images were acquired according to prevailing recommendations, and images were analysed offline with EchoPAC version 206 (GE HealthCare). Readers were not blinded to visit order.

Left atrial datasets were acquired from apical views during breath-hold at 101 frames per second, and reservoir, conduit and booster strain were measured. Right ventricular datasets were acquired at 60 frames per second over three to four consecutive cardiac cycles, and global longitudinal and free-wall strain were measured (Fig. 1). Strain values are reported throughout as absolute magnitudes, so a lower value indicates less deformation; where values from other studies are quoted in the Discussion they retain the negative sign used in the source publication.

Conventional measurements followed the chamber quantification recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging¹⁵. These included left atrial anteroposterior and superoinferior diameters, left atrial volume index, right atrial area and volume, tricuspid annular diameter, right ventricular basal, mid-cavity and longitudinal end-diastolic diameters, and right ventricular outflow tract proximal and distal diameters. Right ventricular systolic function was assessed by fractional area change, tricuspid annular plane systolic excursion, tissue Doppler S' velocity and the myocardial performance index. Right ventricular systolic pressure was estimated from peak tricuspid regurgitant velocity using the modified Bernoulli equation with an added right atrial pressure derived from inferior vena caval diameter and collapsibility. Right ventricular to pulmonary artery coupling was expressed as the ratio of tricuspid annular plane systolic excursion to right ventricular systolic pressure. Left ventricular diastolic function was graded from 0 to 3 according to the joint American Society of Echocardiography and European Association of Cardiovascular Imaging update¹⁶.

Follow-up and outcome definitions

Participants were reassessed at 3 and 6 months after starting therapy with the same imaging protocol and a repeat 12-lead electrocardiogram. Reminder telephone calls preceded each visit. Additional outcome data came from hospital discharge summaries and structured telephone interviews.

Electrocardiograms were reported for sinus bradycardia, sinus tachycardia, ventricular premature complexes, right and left bundle branch block, and left and right ventricular hypertrophy. Arrhythmia at any visit was recorded as present or absent. New-onset arrhythmia was defined as arrhythmia recorded at 3 or 6 months in a participant with no arrhythmia at baseline. A secondary composite of conduction and ventricular abnormality comprised new ventricular premature complexes, right bundle branch block or left bundle branch block.

Endpoints

The primary endpoint was change in three-dimensional left atrial reservoir, conduit and booster strain and in three-dimensional right ventricular global longitudinal and free-wall strain across the three visits. Secondary endpoints were the association of strain with conventional echocardiographic indices, the relationship between strain and left ventricular diastolic dysfunction grade, the incidence of electrocardiographic abnormality and new-onset arrhythmia, and the association between serial strain change and new-onset arrhythmia.

Statistical analysis

Analyses were performed in Python 3.10 using pandas 2.3.3, SciPy 1.15.3 and statsmodels 0.14.6. Distributional assumptions were tested before analysis: the Shapiro-Wilk test was applied to every longitudinal variable at each visit and to the within-participant six-month difference. A variable was analysed parametrically only when normality was not rejected at all three visits and for the difference score. Under this rule 3 of 32 longitudinal variables qualified for parametric analysis.

Continuous variables are summarised as mean $\pm$ standard deviation when normally distributed and as median (interquartile range) otherwise. Categorical variables are given as counts and percentages. Change across the three visits was tested with one-way repeated-measures analysis of variance or the Friedman test. Three pairwise comparisons were then performed for every parameter with paired t tests or Wilcoxon signed-rank tests and Bonferroni correction, including parameters with a non-significant omnibus test so that the corresponding effect sizes could be reported. Paired effect size is reported as Cohen d for repeated measures, calculated as the mean difference divided by the standard deviation of the differences.

Correlations used the Pearson coefficient when both variables met the normality criterion and the Spearman coefficient otherwise. Strain was compared across diastolic dysfunction grades with the Kruskal-Wallis test and a Spearman test for monotonic trend. Change in binary electrocardiographic findings across visits was tested with the Cochran Q test. Two-group comparisons used the Mann-Whitney U test with the rank-biserial correlation as effect size. Discrimination for new-onset arrhythmia was assessed by the area under the receiver operating characteristic curve with 2,000-replicate bootstrap confidence intervals.

Random-intercept linear mixed-effects models with time in months as a fixed effect were fitted as a sensitivity analysis for the primary endpoint, unadjusted and adjusted for age, sex and therapy type. Multivariable linear regression modelled six-month strain change against age, sex, therapy type, hypertension, diabetes, cumulative dose and the baseline value of the parameter.

Because the analysis addressed several endpoints and a large number of exploratory comparisons, the Benjamini-Hochberg false discovery rate procedure was applied across variables within each analysis family and q values are reported alongside p values. Tests were two-sided with alpha of 0.05. Findings from the pre-specified primary and secondary endpoints are presented as confirmatory; subgroup and regression analyses are exploratory.

Results

Cohort characteristics and data completeness

Forty-five participants completed baseline and both follow-up assessments. Mean age was 55.5 ± 12.2 years (range 28 to 81) and 21 participants (46.7%) were men. Twenty-six (57.8%) received immunotherapy and 19 (42.2%) received targeted therapy, drawn from six drug classes across 23 tumour types. Median cumulative dose was 300 mg (200 to 400). Hypertension was present in 21 participants (46.7%), diabetes in 11 (24.4%), alcohol use in 14 (31.1%) and smoking in 11 (24.4%). Baseline characteristics are given in Table 1.

Table 1
Baseline characteristics of the study cohort (n = 45).

Characteristic	Value
Age, years, mean $\pm$ SD	55.5 $\pm$ 12.2
Age range, years	28 to 81
Male sex, n (%)	21 (46.7)
Immunotherapy, n (%)	26 (57.8)
Targeted therapy, n (%)	19 (42.2)
Hypertension, n (%)	21 (46.7)
Diabetes mellitus, n (%)	11 (24.4)
Alcohol use, n (%)	14 (31.1)
Smoking, n (%)	11 (24.4)
Cumulative dose, mg, median (IQR)	300 (200 to 400)
Drug classes represented, n	6
Tumour types represented, n	23
Normal diastolic function at baseline, n (%)	22 (48.9)
Grade 1 diastolic dysfunction at baseline, n (%)	21 (46.7)
Grade 2 diastolic dysfunction at baseline, n (%)	2 (4.4)
Arrhythmia at baseline, n (%)	5 (11.1)
IQR, interquartile range; SD, standard deviation.	

Complete three-dimensional strain data at all three visits were obtained in all 45 participants for all five strain parameters. Two data points were missing across the entire dataset, both inferior vena caval measurements at the 3-month visit in one participant, giving completeness of 99.97% across the 6,165 cells formed by 45 participants and 137 recorded variables. No imputation was performed. Complete strain data in every participant at every visit is a high yield for volumetric atrial and right ventricular deformation analysis, and reflects the exclusion at enrolment of patients with a poor echocardiographic window.

Serial change in three-dimensional strain

Representative acquisitions of the right ventricular linear dimensions and of right ventricular and left atrial strain are shown in Fig. 1. Right ventricular global longitudinal strain fell from 21.4% (19.2 to 22.8) at baseline to 17.8% (15.9 to 21.9) at 3 months and 18.2% (15.3 to 21.0) at 6 months (Friedman χ^2 = 37.73, p < 0.001). Right ventricular free-wall strain, the only strain parameter meeting the normality

criterion, fell from $25.3 \pm 3.8\%$ to $22.2 \pm 4.8\%$ and $21.7 \pm 4.4\%$ ($F = 13.84$, $p < 0.001$). Left atrial conduit strain fell from 20.0% (16.0 to 26.0) to 15.0% (12.0 to 20.0) and 15.0% (12.0 to 19.0) ($\chi^2 = 35.54$, $p < 0.001$). Left atrial reservoir strain fell from 34.0% (30.0 to 39.0) to 31.0% (26.0 to 33.0) and 30.0% (27.0 to 33.0) ($\chi^2 = 10.78$, $p = 0.005$). Left atrial booster strain was 14.0% (11.0 to 19.0) at every visit ($\chi^2 = 0.15$, $p = 0.927$). All omnibus results other than booster strain remained significant after false discovery rate correction (Table 2, Fig. 2, Supplementary Fig. S1 online).

Table 2
Serial change in three-dimensional left atrial and right ventricular strain (n = 45).

Parameter	Baseline	3 months	6 months	Statistic	p	q
LA reservoir strain, %	34.0 (30.0–39.0)	31.0 (26.0–33.0)	30.0 (27.0–33.0)	$\chi^2 = 10.78$	0.005	0.006
LA conduit strain, %	20.0 (16.0–26.0)	15.0 (12.0–20.0)	15.0 (12.0–19.0)	$\chi^2 = 35.54$	< 0.001	< 0.001
LA booster strain, %	14.0 (11.0–19.0)	14.0 (11.0–19.0)	14.0 (11.0–19.0)	$\chi^2 = 0.15$	0.927	0.927
RV global longitudinal strain, %	21.4 (19.2–22.8)	17.8 (15.9–21.9)	18.2 (15.3–21.0)	$\chi^2 = 37.73$	< 0.001	< 0.001
RV free-wall strain, %	25.3 ± 3.8	22.2 ± 4.8	21.7 ± 4.4	$F = 13.84$	< 0.001	< 0.001
Values are median (interquartile range) except right ventricular free-wall strain, which met the normality criterion and is shown as mean $\pm$ standard deviation. Strain is reported as absolute magnitude; lower values indicate less deformation. χ^2 , Friedman test statistic; F, repeated-measures analysis of variance; q, Benjamini-Hochberg adjusted p value across the five parameters. LA, left atrial; RV, right ventricular.						

Pairwise comparisons located the change in the first three months. Baseline to 3-month falls were significant for left atrial conduit strain (mean change -4.42 percentage points, Cohen $d = 0.74$, $p < 0.001$), right ventricular global longitudinal strain (-2.65 , $d = 0.76$, $p < 0.001$) and right ventricular free-wall strain (-3.13 , $d = 0.60$, $p < 0.001$). Corresponding baseline to 6-month falls were -5.33 ($d = 0.81$), -3.23 ($d = 0.77$) and -3.59 ($d = 0.72$), all $p < 0.001$. Left atrial reservoir strain fell by 3.29 points at 6 months ($d = 0.37$, $p = 0.043$). No comparison between 3 and 6 months reached significance for any parameter (all corrected $p \geq 0.316$). Expressed as the median of the within-participant relative change from baseline, falls at 6 months were 30.0% for conduit strain, 19.4% for right ventricular global longitudinal strain, 16.0% for free-wall strain and 8.6% for reservoir strain. These differ from the ratio of the group medians in Table 2 because relative change was computed for each participant before taking the median.

Random-intercept mixed-effects models reproduced these results. Estimated monthly change was -0.89 percentage points for conduit strain (95% CI -1.24 to -0.53), -0.60 for free-wall strain (-0.85 to -0.35), -0.54 for right ventricular global longitudinal strain (-0.72 to -0.36) and -0.55 for reservoir strain

(– 0.96 to – 0.13), all $p \leq 0.010$, with no significant slope for booster strain (+ 0.20, – 0.20 to 0.60, $p = 0.322$). Adjustment for age, sex and therapy type left the slopes unchanged, as expected for time-invariant covariates in a balanced design.

Applying the 15% relative decline threshold used for left ventricular global longitudinal strain, 30 participants (66.7%) met this threshold for conduit strain at 6 months, 23 (51.1%) for right ventricular global longitudinal strain, 23 (51.1%) for free-wall strain, 19 (42.2%) for reservoir strain and 17 (37.8%) for booster strain (Table 3). The last figure reflects individual variability rather than a group-level change: booster strain fell by at least 15% in 17 participants and rose by a comparable amount in others, leaving the cohort median identical at every visit.

Table 3
Pairwise comparisons, effect sizes and proportion meeting a 15% relative decline threshold.

Parameter	Δ BL to 3 mo	p	d	Δ BL to 6 mo	p	d	Δ 3 to 6 mo	p	$\geq 15\%$ decline at 6 mo, n (%)
LA reservoir	–2.62	0.051	–0.38	–3.29	0.043	–0.37	–0.67	1.000	19 (42.2)
LA conduit	–4.42	< 0.001	–0.74	–5.33	< 0.001	–0.81	–0.91	1.000	30 (66.7)
LA booster	+ 1.33	1.000	+ 0.20	+ 1.20	1.000	+ 0.16	–0.13	1.000	17 (37.8)
RV global longitudinal	–2.65	< 0.001	–0.76	–3.23	< 0.001	–0.77	–0.58	0.316	23 (51.1)
RV free-wall	–3.13	< 0.001	–0.60	–3.59	< 0.001	–0.72	–0.46	1.000	23 (51.1)
Δ is the mean change in percentage points; negative values denote a fall in strain magnitude. p values are Bonferroni-corrected across the three comparisons within each parameter. d is Cohen d for repeated measures. BL, baseline; LA, left atrial; mo, months; RV, right ventricular.									

Conventional echocardiographic indices

Every conventional index of right ventricular systolic function deteriorated. Tricuspid annular plane systolic excursion fell from 20.1 ± 2.6 mm to 16.9 ± 2.8 mm ($F = 23.18$, $p < 0.001$), fractional area change from 45% (40 to 50) to 34% (32 to 43) ($p < 0.001$), and tissue Doppler S' velocity from 0.13 m/s (0.12 to 0.14) to 0.11 m/s (0.10 to 0.13) ($p < 0.001$). The myocardial performance index rose from 0.40 (0.36 to 0.46) to 0.50 (0.42 to 0.55) ($p < 0.001$). Right ventricular systolic pressure rose from 23 mmHg (21 to 26) to 30 mmHg (26 to 33) and tricuspid regurgitant velocity from 2.40 m/s (2.00 to 2.50) to 2.70 m/s (2.50 to 2.80), both $p < 0.001$. Right ventricular to pulmonary artery coupling fell from 0.84 (0.74 to 0.96) to 0.56 (0.44 to 0.64) ($p < 0.001$).

Right ventricular chamber dimensions changed in a segment-specific manner. The longitudinal end-diastolic dimension increased from 66 mm (61 to 70) at baseline to 71 mm (67 to 75) at 6 months (Friedman $\chi^2 = 15.08$, $p < 0.001$; baseline to 6 months + 5.0 mm, Bonferroni-corrected $p = 0.005$), and the right ventricular outflow tract proximal diameter increased from 24 mm (23 to 27) to 27 mm (25 to 30) ($\chi^2 = 12.92$, $p = 0.002$). The basal end-diastolic diameter showed a borderline omnibus change from 27.4 ± 3.1 mm to 28.6 ± 3.9 mm ($F = 3.30$, $p = 0.041$, $q = 0.062$), with no pairwise comparison significant after Bonferroni correction, while the mid-cavity diameter, 23 mm (20 to 25) at baseline and unchanged thereafter ($p = 0.678$), and the outflow tract distal diameter ($p = 0.351$) did not change.

On the left side, left atrial volume index rose from 22 mL/m² (19 to 27) to 29 mL/m² (28 to 35) ($p < 0.001$), e' fell from 0.10 m/s (0.08 to 0.11) to 0.07 m/s (0.06 to 0.10) ($p < 0.001$) and E/e' rose from 7.27 (6.15 to 8.57) to 8.57 (7.50 to 11.43) ($p < 0.001$). Heart rate rose from 81.0 ± 13.1 to 88.5 ± 17.4 beats per minute ($p = 0.025$). Mitral E velocity, right atrial area and volume, and tricuspid annular diameter did not change (Supplementary Table S1 online).

Relationship between strain and conventional indices

Of 405 strain-by-index correlations tested across the three visits, 24 were significant with a coefficient of at least 0.40 in absolute value. The complete matrix is provided as Supplementary Table S2 online and selected correlations are given in Supplementary Table S3. Right ventricular free-wall strain correlated with tissue Doppler S' velocity ($\rho = 0.71$ at 3 months, $q < 0.001$) and with tricuspid annular plane systolic excursion ($r = 0.62$, $q < 0.001$). Right ventricular global longitudinal strain correlated with S' ($\rho = 0.61$ at 3 months and 0.59 at 6 months), with tricuspid annular plane systolic excursion ($\rho = 0.58$ at both visits) and with fractional area change ($\rho = 0.55$ at 6 months).

Left atrial strain tracked indices of left ventricular relaxation rather than atrial size. Reservoir strain correlated with e' at 6 months ($\rho = 0.58$, $q = 0.001$) and conduit strain with e' ($\rho = 0.53$, $q = 0.004$) and inversely with E/e' ($\rho = -0.44$, $q = 0.041$). Correlations between left atrial strain and left atrial volume index were weak at every visit (absolute $\rho \leq 0.13$ at 6 months) (Fig. 3).

Diastolic function

Left ventricular diastolic function deteriorated across the study. Participants with normal diastolic function fell from 22 (48.9%) at baseline to 8 (17.8%) at 3 months and 7 (15.6%) at 6 months, while grade 2 or higher dysfunction rose from 2 (4.4%) to 4 (8.9%) and 14 (31.1%) (Friedman $p < 0.001$; Fig. 4). At participant level, 16 of the 22 with normal function at baseline had a higher grade at 6 months, one participant improved from grade 1 to normal, and 23 of all 45 participants (51.1%) moved to a higher grade. Left atrial reservoir strain declined across worsening grades at baseline (Spearman $\rho = -0.30$, p for trend 0.044) and booster strain differed across grades at 3 months (Kruskal-Wallis $H = 8.60$, $p = 0.014$). Right ventricular strain showed no consistent relationship with left ventricular diastolic grade at any visit.

Electrocardiographic abnormality and arrhythmia

Any arrhythmia was recorded in 5 participants (11.1%) at baseline, 14 (31.1%) at 3 months and 17 (37.8%) at 6 months (Cochran $Q = 10.17$, $p = 0.006$). Among the 40 participants free of arrhythmia at baseline, 20 developed new-onset arrhythmia, a cumulative six-month incidence of 50.0%. Sinus tachycardia rose from 2 participants (4.4%) to 9 (20.0%) and 14 (31.1%) ($Q = 11.47$, $p = 0.003$), with new-onset in 17 of 43 at-risk participants (39.5%). Of the 20 participants with new-onset arrhythmia, 16 had sinus tachycardia recorded at follow-up and in 14 it was the only new finding. The composite of new ventricular premature complexes or bundle branch block occurred in 7 of 45 participants (15.6%), none of whom had any of these findings at baseline. Electrocardiographic left ventricular hypertrophy was absent at baseline and present in 10 participants (22.2%) at 3 months and 8 (17.8%) at 6 months ($Q = 16.80$, $p < 0.001$). Right ventricular hypertrophy was not recorded at any visit (Supplementary Table S4 online, Fig. 4).

Strain and new-onset arrhythmia

This analysis was restricted to the 40 participants free of arrhythmia at baseline, since those with prevalent arrhythmia could not by definition develop new-onset arrhythmia. Twenty developed new-onset arrhythmia and 20 did not. Median six-month change in right ventricular free-wall strain was -5.10 percentage points (-7.48 to -2.57) in those who developed arrhythmia and -3.75 (-7.02 to -0.52) in those who did not ($p = 0.351$), and median change in right ventricular global longitudinal strain was -4.00 (-6.75 to -1.03) against -3.10 (-5.60 to -0.85) ($p = 0.588$). Rank-biserial effect sizes across all 25 comparisons of strain value and strain change ranged from -0.39 to $+0.32$ (Fig. 5).

One of the 25 comparisons was nominally significant: baseline left atrial reservoir strain was lower in participants who subsequently developed arrhythmia, at 31.5% (27.8 to 35.5) against 37.0% (31.0 to 41.2) ($p = 0.037$, rank-biserial $r = -0.39$). The corresponding area under the receiver operating characteristic curve was 0.69 (bootstrap 95% CI 0.53 to 0.86). This result did not survive false discovery rate correction ($q = 0.416$), and one nominally significant result is the number expected by chance among 25 tests. Across all strain parameters and visits, areas under the curve ranged from 0.37 to 0.69, and every other bootstrap confidence interval included 0.50. Univariable and adjusted logistic regression using baseline strain or six-month strain change as the predictor produced no significant odds ratio for any parameter.

Exploratory analyses

Comparisons between therapy groups, between sexes and by hypertension or diabetes status produced 10 to 21 nominally significant results out of 128 comparisons in each analysis. Three survived false discovery rate correction, all right atrial dimensions at 3 months that were larger in men ($q = 0.039$ for right atrial area, volume and superior-inferior dimension); these measurements were not indexed to body surface area. In multivariable regression, older age predicted greater six-month decline in left atrial conduit strain (beta -0.32 per year, 95% CI -0.50 to -0.15 , $p < 0.001$) and reservoir strain (beta -0.20 , -0.39 to -0.001 , $p = 0.049$). Baseline value of each parameter predicted its own change in all five models,

which is expected from regression to the mean and is not interpreted further. Neither therapy type nor cumulative dose predicted change in any strain parameter.

Discussion

In this cohort of 45 adults receiving immunotherapy or targeted therapy, three-dimensional right ventricular global longitudinal and free-wall strain and left atrial conduit strain declined significantly over six months, with moderate to large paired effect sizes. Left atrial reservoir strain declined less markedly. Left atrial booster strain did not change. Most of the change occurred by three months, and no strain parameter changed significantly between 3 and 6 months. Diastolic dysfunction and arrhythmia both increased, but strain change did not distinguish participants who developed arrhythmia from those who did not.

The right ventricular findings are consistent with the two published series that examined this chamber during checkpoint inhibitor therapy. Pohl and colleagues found that free-wall strain fell from $-25.5 \pm 6.4\%$ to $-22.4 \pm 4.3\%$ approximately four weeks after starting therapy in 30 patients with melanoma, while tricuspid annular plane systolic excursion, fractional area change and pulmonary artery systolic pressure were unchanged¹¹. Xu and colleagues reported a fall in right ventricular global longitudinal strain from $-18.5 \pm 4.7\%$ to $-15.0 \pm 3.9\%$ in 55 patients receiving immunotherapy¹². The magnitude of change here, 3.2 percentage points for global longitudinal strain and 3.6 for free-wall strain, is similar.

Where the present cohort differs is in the behaviour of the conventional indices. Tricuspid annular plane systolic excursion fell by 3.2 mm, fractional area change by 11 percentage points and right ventricular to pulmonary artery coupling by a third, whereas Pohl and colleagues found no change in conventional measures at four weeks; Xu and colleagues did record a fall in tricuspid annular plane systolic excursion, so the divergence is with the earlier and shorter of the two studies. Follow-up duration may account for it, since deformation abnormalities that precede conventional changes at one month could be accompanied by them at six. Right ventricular systolic pressure also rose by 7 mmHg, and the right ventricular longitudinal end-diastolic dimension and proximal outflow tract diameter increased over the same interval while the mid-cavity diameter was unchanged, a pattern compatible with early chamber dilatation under rising load. Right ventricular longitudinal deformation is load-dependent as well as contractility-dependent, and right ventricular strain-curve morphology relates to disease severity and outcome in pulmonary arterial hypertension¹⁷. The fall in strain in this cohort therefore cannot be attributed to intrinsic myocardial injury alone. Right ventricular to pulmonary artery coupling, which incorporates both load and function, fell in parallel.

The atrial findings separate by component. Conduit strain, the passive phase during which blood traverses the atrium from pulmonary veins to ventricle, fell by a median of 30% and had the largest effect size of any parameter measured. Reservoir strain fell modestly. Booster strain, the active contractile phase, was unchanged at every visit.

This pattern is consistent with impaired ventricular relaxation and is less readily explained by intrinsic atrial myopathy. Conduit function depends on the rate and extent of left ventricular relaxation, whereas booster function reflects atrial contractility⁶. Concurrent observations in this cohort are compatible with that interpretation: e' fell, E/e' rose, and 16 of the 22 participants with normal diastolic function at baseline had a higher grade at 6 months. Left atrial reservoir and conduit strain correlated with e' at 6 months (ρ 0.58 and 0.53) and conduit strain correlated inversely with E/e' (ρ - 0.44), while correlations with left atrial volume index remained weak. Left atrial deformation and left atrial size therefore carried different information here, in keeping with work relating reservoir strain to invasively measured filling pressure⁷ and to diastolic dysfunction in populations with preserved ejection fraction¹⁸.

Published cardio-oncology data on atrial strain come largely from anthracycline-treated breast cancer cohorts and report peak atrial longitudinal strain, which corresponds to reservoir strain, without separating conduit and contractile components^{9,10}. The component-specific pattern seen here suggests that reporting all three phases may add information, and that conduit strain in particular deserves examination in larger cohorts.

No strain parameter changed significantly between 3 and 6 months. If most deformation change occurs within the first three months and then plateaus, the interval over which change is detectable would lie early in treatment, which bears on the timing of surveillance imaging. This cohort cannot determine when the inflection occurs, since no measurement was made between baseline and three months. Pohl and colleagues recorded a change at four weeks, which suggests the interval may be shorter still¹¹. An alternative explanation for the plateau is a survivorship or treatment-modification effect: participants with the largest early falls may have had therapy interrupted or dose reduced, attenuating later change. Treatment modification data were not collected, so this cannot be excluded.

New-onset arrhythmia occurred in half of participants who were arrhythmia-free at baseline. Interpretation depends on composition. Sixteen of these 20 participants had sinus tachycardia at follow-up, and in 14 it was the only new finding. Sinus tachycardia during cancer therapy has many causes other than myocardial injury, including anaemia, deconditioning, fever, pain, volume depletion and the infusion itself. The composite of conduction abnormality and ventricular ectopy, which is more specific for myocardial or conduction system involvement, occurred in 7 of 45 participants (15.6%), none of whom had any of these findings at baseline. Without a comparison group the relationship of either figure to therapy cannot be established.

No strain measure discriminated participants who developed arrhythmia after correction for multiple comparisons. Lower baseline left atrial reservoir strain in those who later developed arrhythmia reached nominal significance (p = 0.037, area under the curve 0.69) but did not survive false discovery rate correction across the 25 comparisons, and a single nominal result among 25 tests is what chance alone produces. The observation is reported for completeness and would require prospective testing in an independent cohort before it could be regarded as a signal. Two considerations qualify the overall null result. With 20 events and 20 non-events, the analysis had approximately 80% power to detect only a

large between-group difference (Cohen d of about 0.90), so a moderate association could have been missed. Separately, the outcome as defined is dominated by sinus tachycardia and is therefore an imprecise marker of arrhythmic cardiotoxicity; the more specific composite yielded too few events to analyse. Both a larger sample and a more specific endpoint would be needed to test this relationship adequately.

The 2022 European Society of Cardiology guidelines define cancer therapy-related cardiac dysfunction primarily by left ventricular measures³. Expert consensus has identified surveillance strategy and the choice of imaging marker as areas where evidence remains incomplete^{19,20}. The present data indicate that left atrial conduit and right ventricular deformation change measurably during immunotherapy and targeted therapy, alongside changes in loading and in diastolic function. Whether these changes precede left ventricular abnormality, and whether they predict later clinical events, is not addressed by this study.

This study has limitations. There was no control group. All observed change occurred during therapy, and the design does not permit attribution to the therapy itself. Cancer progression, deconditioning, anaemia, volume status, concomitant medication and the natural course of the underlying malignancy were not measured and could each produce the observed pattern. The findings are described as change during therapy throughout.

Left ventricular ejection fraction and left ventricular global longitudinal strain were not measured. The comparison of greatest clinical interest, whether left atrial and right ventricular deformation change earlier than the established left ventricular markers, therefore cannot be made from these data. Cancer therapy-related cardiac dysfunction as defined in current guidelines could not be adjudicated, and participants could not be classified by that criterion.

Inter-observer and intra-observer reproducibility were not assessed. Three-dimensional atrial and right ventricular deformation analysis is technically demanding and depends on image quality and endocardial tracing, and reproducibility data would be needed to establish measurement precision in this laboratory. Left atrial and right ventricular datasets were acquired at different frame rates (101 and 60 frames per second), which is appropriate to each chamber but means the two are not matched for temporal resolution. Two-dimensional and three-dimensional strain values are not interchangeable¹³, so the numerical values here are not directly comparable with the two-dimensional literature; that evidence derives from fetal echocardiography, and comparable adult data specific to right ventricular free-wall strain are lacking.

The sample of 45 participants is small for subgroup analysis and for predicting a binary outcome, and no a priori sample size calculation was performed. Six drug classes and 23 tumour types were represented, so agent-specific and tumour-specific effects could not be examined. Cumulative dose was recorded in milligrams and pooled across pharmacologically distinct agents, so it is not on a common scale; the absence of a dose-response relationship should be read with that in mind. Right atrial and right ventricular dimensions were not indexed to body surface area, which confounds the sex comparison.

Readers were not blinded to visit order, which is a potential source of bias in a study whose principal finding is a serial decline.

Arrhythmia was ascertained by 12-lead electrocardiography at scheduled visits, so paroxysmal events between visits were not captured and the incidence reported here is a lower bound for some arrhythmia types. Two electrocardiographic patterns warrant caution. Left ventricular hypertrophy by voltage criteria was absent at baseline, present in 10 participants at 3 months and in 8 at 6 months; de novo voltage criteria arising and partly resolving over this interval is more likely to reflect variation in body habitus, electrode placement or fluid status than true hypertrophy. Bundle branch block was recorded in a pattern that included two participants in whom it was present at 3 months and absent at 6 months, and three in whom right and left bundle branch block were both recorded. Electrocardiograms were reported clinically rather than by blinded core-laboratory adjudication, and these findings should be interpreted with that in mind.

Right ventricular to pulmonary artery coupling values at the 6-month visit could not be reproduced from the recorded tricuspid annular plane systolic excursion and right ventricular systolic pressure in 10 of 45 participants, although they were exactly reproducible at baseline and 3 months. Follow-up extended to six months. Whether the plateau observed after three months persists, reverses or progresses beyond this period is unknown.

Conclusions

Three-dimensional right ventricular global longitudinal strain, right ventricular free-wall strain and left atrial conduit strain declined during the first six months of immunotherapy or targeted therapy, with most of the change occurring by three months. Left atrial booster strain was preserved, and the component-specific atrial pattern was accompanied by falling e' , rising E/e' and worsening diastolic dysfunction grade, consistent with impaired ventricular relaxation. Conventional right ventricular indices, right ventricular dimensions and pulmonary pressures changed in parallel. New-onset arrhythmia occurred in half of those free of arrhythmia at baseline, most often sinus tachycardia, and no strain parameter identified the participants in whom it occurred. Studies with a comparison group, concurrent left ventricular strain, earlier imaging and a specific arrhythmia endpoint are needed to establish whether these deformation changes have prognostic value.

Declarations

Data availability

The data supporting the findings of this study are available from the corresponding author on reasonable request, subject to institutional data sharing policy and ethics committee approval.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Corresponding Author.

Supplementary Information is available for this paper.

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Figures

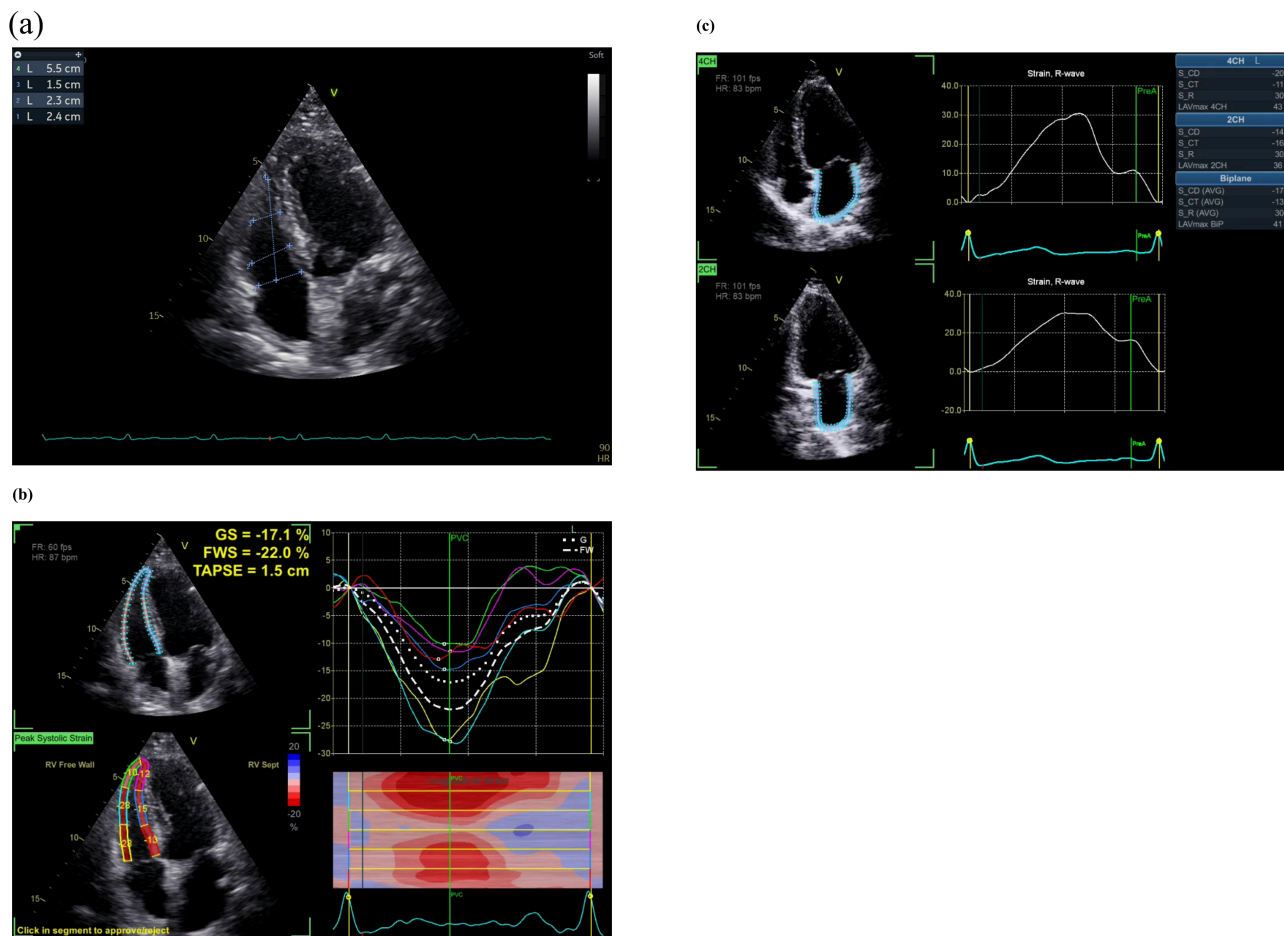


Figure 1

Representative echocardiographic acquisitions. (a) Apical four-chamber view showing end-diastolic measurement of the right ventricular basal, mid-cavity and longitudinal diameters together with the right ventricular outflow tract proximal diameter. (b) Speckle-tracking analysis of the right ventricle in the right ventricle-focused apical four-chamber view showing measurement of right ventricular global longitudinal strain and free-wall strain, with segmental strain curves and the corresponding colour-coded anatomical M-mode. (c) Speckle-tracking analysis of the left atrium from the apical four- and two-chamber views showing reservoir, conduit and contractile (booster) strain, with endocardial tracing and the corresponding strain curves. Strain values in (b) and (c) are displayed with the negative sign generated by the analysis software; strain is reported in the text as absolute magnitude.

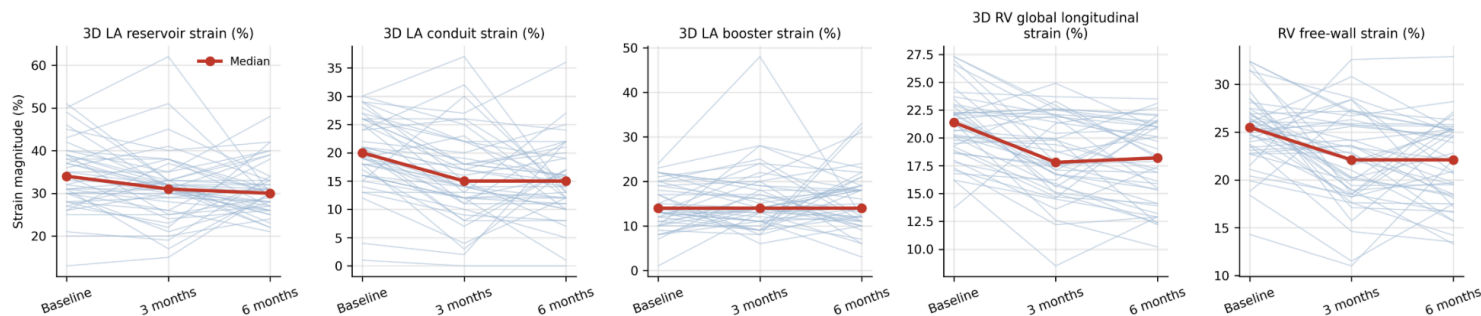


Figure 2

Individual and median trajectories of three-dimensional left atrial and right ventricular strain across baseline, 3 months and 6 months. Light lines show individual participants and the heavy line shows the cohort median. Strain is plotted as absolute magnitude, so downward movement indicates less deformation. Left atrial conduit, right ventricular global longitudinal and right ventricular free-wall strain fall between baseline and 3 months and then plateau. Left atrial booster strain is unchanged throughout.

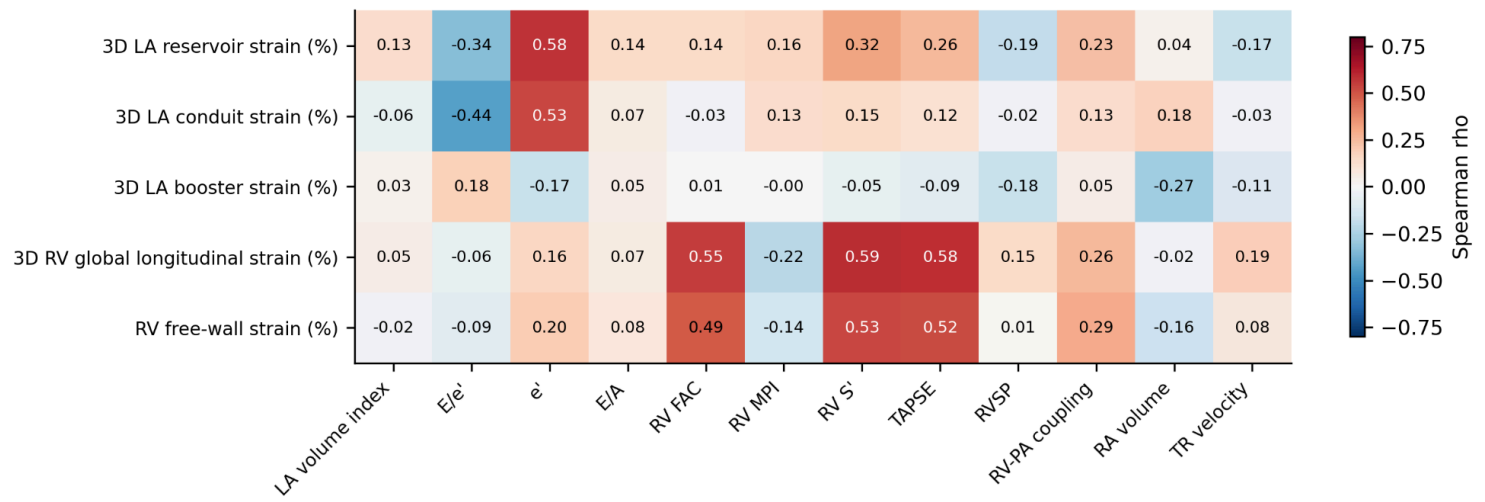


Figure 3

Spearman correlation between three-dimensional strain parameters and conventional echocardiographic indices at 6 months. Right ventricular strain measures correlate with conventional indices of right ventricular systolic function, and left atrial reservoir and conduit strain correlate with e' and inversely with E/e'. Correlations between left atrial strain and left atrial volume index are weak.

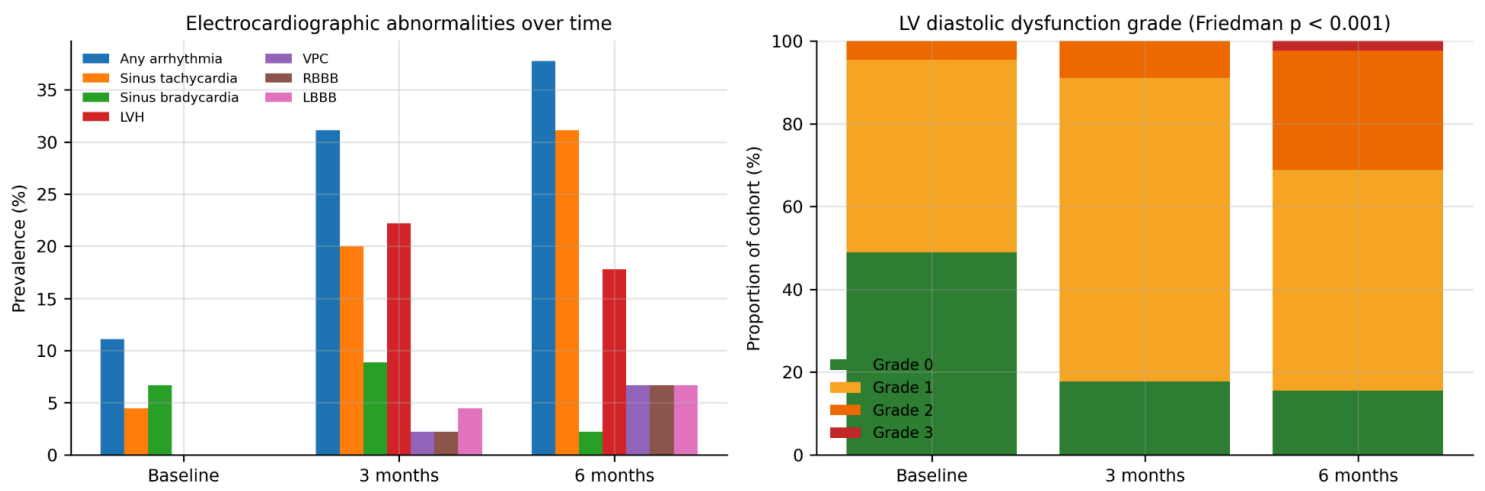


Figure 4

Electrocardiographic abnormalities and left ventricular diastolic function across follow-up. Left panel: prevalence of each electrocardiographic finding at baseline, 3 months and 6 months, expressed as a

percentage of the 45 participants; right ventricular hypertrophy was not recorded at any visit and is therefore absent from the plot. Right panel: distribution of left ventricular diastolic dysfunction grade at each visit as a proportion of the cohort. Corresponding counts and Cochran Q statistics are given in Supplementary Table S4.

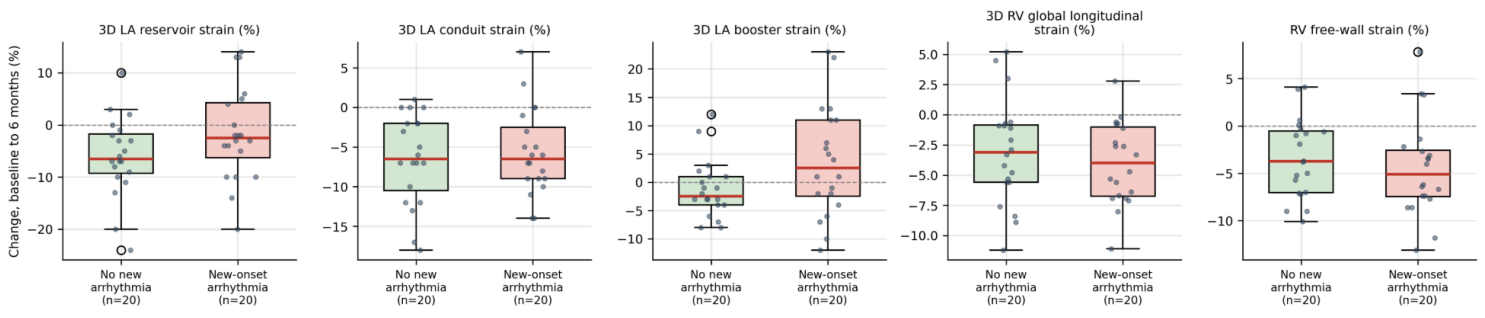


Figure 5

Six-month change in each strain parameter among the 40 participants free of arrhythmia at baseline, in those who developed new-onset arrhythmia (n = 20) and those who did not (n = 20). The dashed line marks no change. No comparison of six-month change reached statistical significance.

Supplementary Files

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