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Research Article

Global Longitudinal Strain and Heart Rate Variability, but Not Ejection Fraction, Independently Predict Peak Oxygen Uptake in Patients with Heart Disease

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Abstract: ***Introduction:*** Left ventricular ejection fraction (LVEF) is the parameter most often used to explain exercise limitation in heart disease, yet symptoms and functional capacity correlate poorly with it. We examined which physiological measures — autonomic, mechanical, or conventional — independently determine peak oxygen uptake (VO2 peak). **Methods:** In this prospective cross-sectional study, 130 medically stable patients aged 18–75 years with ischaemic heart disease, heart failure, or moderate-to-severe valvular heart disease underwent, within a 48-hour window, symptom-limited cardiopulmonary exercise testing (CPET) on a cycle ergometer using an individualised ramp protocol with breath-by-breath gas exchange analysis; 5-minute heart rate variability (HRV) analysis and baroreflex sensitivity (BRS) assessment; and two-dimensional speckle tracking echocardiography with blinded offline measurement of global longitudinal strain (GLS). Correlates of VO2 peak were examined by bivariate correlation and multivariable linear regression including age, sex, LVEF, and NYHA class. **Results**: Mean age was 56.4 ± 11.2 years; 82 (63.1%) were male. VO2 peak was reduced (16.8 ± 4.2 mL/kg/min) with an anaerobic threshold of 11.2 ± 3.1 mL/kg/min and a VE/VCO2 slope of 34.6 ± 6.8; a mean peak respiratory exchange ratio of 1.14 ± 0.06 confirmed maximal effort. Mean LVEF was preserved (52.4 ± 8.1%) while GLS was impaired (−15.8 ± 3.2%). GLS showed the strongest correlation with VO2 peak ($r = 0.51$, $p < 0.001$), followed by RMSSD ($r = 0.38$, $p < 0.001$) and BRS ($r = 0.36$, $p = 0.002$); the LF/HF ratio correlated with the VE/VCO2 slope ($r = 0.44$, $p < 0.001$). On multivariable regression, GLS ($\beta = 0.39$, $p < 0.001$), SDNN ($\beta = 0.27$, $p = 0.003$), and age ($\beta = -0.22$, $p = 0.01$) were independent predictors of VO2 peak, whereas LVEF was not ($\beta = 0.09$, $p = 0.18$). Patients with heart failure had the lowest VO2 peak (14.8 mL/kg/min; $p = 0.002$). **Conclusions:** Myocardial deformation and autonomic tone, but not ejection fraction, independently determined exercise capacity in patients with heart disease. Where CPET is unavailable, GLS and HRV may offer accessible surrogates of functional reserve.

Keywords: cardiopulmonary exercise testing; peak oxygen uptake; global longitudinal strain; heart rate variability; ventilatory efficiency; ejection fraction

INTRODUCTION

Exercise intolerance is the dominant symptom of most chronic cardiac disease and one of its strongest prognostic markers. Cardiopulmonary exercise testing (CPET) quantifies it objectively by measuring gas exchange during incremental exercise, integrating the cardiovascular, pulmonary, muscular, and metabolic responses to a physiological stress and identifying which system limits performance.[1,2] Peak oxygen uptake (VO_2 peak) predicts survival in heart failure and informs transplant candidacy, while the ventilatory efficiency slope (VE/VCO_2) adds independent prognostic information reflecting chemoreflex drive, pulmonary vascular involvement, and filling pressures.[3,4,5,6,7]

Yet in routine practice, exercise limitation is still most often attributed to, and monitored by, left ventricular ejection fraction. The correlation between resting haemodynamics and functional capacity is well known to be weak,[8,9] and the reasons are physiologically clear: ejection fraction is a load-dependent, geometrically derived ratio measured at rest, whereas exercise capacity depends on the ability to augment stroke volume, on chronotropic competence, on ventilatory control, and on peripheral oxygen extraction.[10,11]

Two measures might capture these determinants better. Global longitudinal strain (GLS), derived from speckle tracking echocardiography, quantifies the shortening of subendocardial longitudinal fibres and detects contractile impairment while ejection fraction remains normal.[12,13,14] Because longitudinal shortening contributes substantially to stroke volume generation, impaired GLS would be expected to limit stroke volume augmentation during exercise and therefore oxygen delivery at peak. Separately, heart rate variability (HRV) and baroreflex sensitivity (BRS) index the autonomic regulation that governs the chronotropic and vasomotor response to exercise, and autonomic derangement predicts mortality in cardiac populations independently of ejection fraction.[15,16,17]

Whether these two measures explain exercise capacity better than ejection fraction — and whether they do so independently of each other — has not been examined comprehensively in a single cohort, particularly in low- and middle-income settings where CPET availability is limited and identifying accessible surrogates has practical value.[18] We therefore assessed autonomic function, myocardial deformation, and cardiopulmonary exercise performance concurrently in patients with established heart disease, with the aim of identifying the independent determinants of VO_2 peak.

MATERIALS AND METHODS

2.1 Study design and setting

This was a prospective, observational, cross-sectional study conducted over 18 months in the Department of Cardiology of a tertiary care teaching hospital in India, in collaboration with the Departments of Physiology and Radiology. The protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki (2013 revision) and Indian Council of Medical Research guidelines. All participants gave written informed consent.

2.2 Participants

Patients aged 18–75 years with established ischaemic heart disease (stable angina or prior myocardial infarction with documented coronary disease), heart failure (reduced, mildly reduced, or preserved ejection fraction, the last with echocardiographic evidence of diastolic dysfunction), or at least moderate valvular heart disease were eligible. Patients had to be medically stable, with no acute decompensation, cardiac hospitalisation, or medication change in the preceding two weeks, and willing and able to complete all three assessments.

Exclusion criteria were acute coronary syndrome or decompensated heart failure within two weeks; arrhythmias precluding valid HRV analysis (persistent or permanent atrial fibrillation, atrial flutter, ventricular ectopy > 10% of beats, complete heart block); any implanted pacemaker, defibrillator, or resynchronisation device; physical inability to perform cycle ergometry, including limiting orthopaedic, neuromuscular, or peripheral vascular disease; significant non-cardiac comorbidity independently impairing exercise performance (obstructive airway disease with $FEV_1/FVC < 70\%$, haemoglobin < 10 g/dL, uncontrolled thyroid disease, eGFR < 15 mL/min/1.73 m^2); known primary autonomic neuropathy with documented orthostatic hypotension; inadequate echocardiographic image quality; and pregnancy or lactation**.**

2.3 Sample size

Sample size was estimated for detection of a Pearson correlation of $r = 0.30$ between GLS and VO_2 peak with two-sided $\alpha = 0.05$ and 80% power using Fisher's Z transformation, yielding n = 85. Allowing for 15–20% attrition and to preserve power for subgroup analysis and multivariable modelling with up to four predictors, the target was set at 130 patients.

2.4 Assessment sequence

All three assessments were completed within a 48-hour window. Patients abstained from caffeine, nicotine, and strenuous activity for at least 12 hours before testing, and all testing was performed between 08:00 and 12:00 to limit circadian variation in autonomic tone.

2.5 Cardiopulmonary exercise testing

CPET was performed by trained personnel under cardiologist supervision with resuscitation equipment immediately available. Patients fasted for at least two hours beforehand and avoided vigorous exercise for 24 hours.

Testing used an electronically braked cycle ergometer with a metabolic cart capable of breath-by-breath gas analysis. Continuous 12-lead electrocardiography, non-invasive blood pressure every two minutes, and pulse oximetry were monitored throughout. An individualised ramp protocol was used, with work rate increasing continuously at 10–20 W/min, selected to produce an exercise duration of 8–12 minutes, preceded by three minutes of unloaded pedalling and followed by three minutes of active recovery. Testing was terminated for volitional fatigue, significant arrhythmia, ST depression > 2 mm, a fall in systolic pressure > 20 mmHg from peak, oxygen saturation < 85%, or patient request.

Measured variables were VO_2 peak (highest 30-second averaged oxygen uptake, the primary functional outcome); anaerobic threshold, determined by the V-slope method and confirmed by ventilatory equivalents; the VE/VCO_2 slope below the respiratory compensation point; oxygen pulse (VO_2/heart rate) as a non-invasive surrogate of stroke volume; peak work rate and exercise duration; and chronotropic response including heart rate recovery at one minute. Effort adequacy was confirmed by a peak respiratory exchange ratio ≥ 1.10. Data were analysed offline using standardised algorithms, with interpretation following joint ATS/ACCP recommendations.[2,19]

2.6 Autonomic function testing

After at least 10 minutes of supine rest in a quiet room at 22–24°C, a digital 12-lead electrocardiogram was recorded at ≥ 1000 Hz sampling. A 5-minute artefact-free segment was analysed after visual inspection and manual editing of ectopic beats. Time-domain (SDNN, RMSSD, pNN50) and frequency-domain (LF, HF, LF/HF ratio, total power) indices were derived by Fast Fourier Transform following Task Force standards.[15] LF and HF are reported in normalised units.

BRS was assessed by the spontaneous sequence method using beat-to-beat finger plethysmography (sequences of

≥ 3 beats with concordant change in systolic pressure ≥ 1 mmHg/beat and R-R interval ≥ 6 ms/beat, expressed as the regression slope of ΔR-R on ΔSBP) and by the Valsalva manoeuvre (40 mmHg for 15 seconds, with BRS derived from the phase IV overshoot); patients with severe aortic stenosis or active ischaemia did not undergo Valsalva. The mean of available methods was used.

2.7 Echocardiography and deformation imaging

Transthoracic echocardiography was performed by a single trained operator using a commercially available system with a 3.5–5 MHz transducer. Apical four-chamber, two-chamber, and long-axis views were acquired at 50–90 frames per second with three consecutive cycles stored during breath-hold. Studies with fewer than 14 of 16 trackable segments were excluded.

Offline speckle tracking analysis was performed with vendor-independent software by an independent analyst blinded to clinical data and CPET results, on de-identified loops. GLS was the average peak systolic longitudinal strain across 16 segments; values less negative than −16% were regarded as impaired.[12] Strain rate, circumferential and radial strain, left atrial strain, biplane Simpson's LVEF, and conventional diastolic indices were also recorded.[20] Reproducibility was assessed in 20 randomly selected studies by intra- and inter-observer re-analysis, expressed as intraclass correlation coefficients, coefficients of variation, and Bland–Altman limits of agreement.

2.8 Statistical analysis

Analyses used IBM SPSS Statistics v26.0 and R v4.2.0, with two-tailed $p < 0.05$ considered significant. Normality was assessed by Shapiro–Wilk and Kolmogorov–Smirnov tests with graphical inspection. Continuous data are presented as mean ± SD or median (IQR); categorical data as counts and percentages.

Bivariate associations used Pearson's r or Spearman's ρ as appropriate, interpreted as weak (< 0.3), moderate (0.3–0.5), strong (0.5–0.7), and very strong (> 0.7). Because longitudinal strain is conventionally negative, correlation and regression analyses used the absolute magnitude of GLS; positive coefficients therefore indicate that greater (better) longitudinal deformation is associated with higher VO_2 peak. Group comparisons used the independent-samples t-test or Mann–Whitney U test, and one-way ANOVA with Tukey's HSD or Kruskal–Wallis with Dunn's correction across three groups; categorical comparisons used chi-square or Fisher's exact test.

Independent predictors of VO_2 peak were identified by multivariable linear regression with hierarchical entry, including variables significant at $p < 0.10$ on univariate analysis together with the clinically mandated covariates age, sex, LVEF, and NYHA class. Standardised β coefficients are reported. Model assumptions were verified through residual plots, variance inflation factors (VIF < 5, excluding significant multicollinearity), and Cook's distance for influential observations.

RESULTS

3.1 Baseline characteristics

One hundred and thirty patients completed all assessments (Table 1). Mean age was 56.4 ± 11.2 years and 82 (63.1%) were male, with a mean BMI of 27.8 ± 3.9 kg/m^2. Hypertension was present in 78 (60.0%), diabetes mellitus in 52 (40.0%), and dyslipidaemia in 61 (46.9%). Sixty-eight patients (52.3%) were in NYHA class II and 42 (32.3%) in class III. Ischaemic heart disease accounted for 58 patients (44.6%), heart failure for 47 (36.2%), and valvular disease for 25 (19.2%).

Table 1. Baseline demographic and clinical characteristics (n = 130)

Variable	Mean ± SD or n (%)
Age (years)	56.4 ± 11.2
Male	82 (63.1)
Female	48 (36.9)
Body mass index (kg/m^2)	27.8 ± 3.9
Hypertension	78 (60.0)
Diabetes mellitus	52 (40.0)
Dyslipidaemia	61 (46.9)
NYHA class II	68 (52.3)
NYHA class III	42 (32.3)
Ischaemic heart disease	58 (44.6)
Heart failure	47 (36.2)
Valvular heart disease	25 (19.2)

3.2 Cardiopulmonary exercise performance

CPET results are presented in Table 2. VO_2 peak was 16.8 ± 4.2 mL/kg/min, substantially below age- and sex-predicted norms and within the range associated with impaired prognosis in chronic heart failure.[3,5] The anaerobic threshold occurred at 11.2 ± 3.1 mL/kg/min. Mean VE/VCO_2 slope was 34.6 ± 6.8, at the threshold conventionally regarded as marking ventilatory inefficiency. Oxygen pulse was 9.1 ± 2.3 mL/beat. A mean peak respiratory exchange ratio of 1.14 ± 0.06 confirmed that maximal or near-maximal effort was achieved, supporting the validity of the peak measurements.

Table 2. Cardiopulmonary exercise testing parameters (n = 130)

Parameter	Mean ± SD
VO_2 peak (mL/kg/min)	16.8 ± 4.2
Anaerobic threshold (mL/kg/min)	11.2 ± 3.1
VE/VCO_2 slope	34.6 ± 6.8
Oxygen pulse (mL/beat)	9.1 ± 2.3
Peak respiratory exchange ratio	1.14 ± 0.06

3.3 Autonomic and echocardiographic findings

Autonomic assessment showed reduced overall variability (SDNN 82.6 ± 24.3 ms) and vagal modulation (RMSSD 21.4 ± 10.8 ms), with sympathetic predominance (LF 61.2 ± 12.5 nu, HF 29.6 ± 9.4 nu, LF/HF 2.3 ± 0.8) and depressed baroreflex sensitivity (5.8 ± 2.1 ms/mmHg). On echocardiography, mean LVEF was preserved at 52.4 ± 8.1%, while GLS was impaired at −15.8 ± 3.2% and global longitudinal strain rate was $-0.89 \pm 0.21\ s^{-1}$ (Table 3). The cohort therefore exhibited markedly reduced exercise capacity in the presence of an ejection fraction that would conventionally be reported as normal.

Table 3. Autonomic and echocardiographic parameters (n = 130)

Parameter	Mean ± SD
SDNN (ms)	82.6 ± 24.3
RMSSD (ms)	21.4 ± 10.8
LF/HF ratio	2.3 ± 0.8
Baroreflex sensitivity (ms/mmHg)	5.8 ± 2.1
LVEF (%)	52.4 ± 8.1
Global longitudinal strain (%)	−15.8 ± 3.2
Global longitudinal strain rate (s^{-1})	−0.89 ± 0.21

3.4 Correlates of exercise capacity

Bivariate correlations are shown in Table 4. GLS demonstrated the strongest association with VO_2 peak ($r = 0.51$, $p < 0.001$), indicating that patients with better preserved longitudinal deformation achieved higher peak oxygen uptake. Autonomic indices were also significantly associated with functional capacity: RMSSD correlated with VO_2 peak ($r = 0.38$, $p < 0.001$), as did baroreflex sensitivity ($r = 0.36$, $p = 0.002$). The LF/HF ratio correlated positively with the VE/VCO_2 slope ($r = 0.44$, $p < 0.001$), linking sympathetic predominance to ventilatory inefficiency. SDNN correlated with GLS magnitude ($r = 0.42$, $p < 0.001$).

Table 4. Correlations between autonomic, mechanical, and cardiopulmonary parameters

Variables compared	Correlation (r)	p value
GLS vs VO_2 peak	0.51	< 0.001
LF/HF ratio vs VE/VCO_2 slope	0.44	< 0.001
SDNN vs GLS	0.42	< 0.001
RMSSD vs VO_2 peak	0.38	< 0.001
BRS vs VO_2 peak	0.36	0.002

Correlations involving GLS use the absolute magnitude of strain; a positive coefficient denotes association between better longitudinal function and the comparator.

3.5 Independent predictors of peak oxygen uptake

On multivariable linear regression (Table 5), GLS was the strongest independent predictor of VO_2 peak ($\beta = 0.39$, $p < 0.001$), followed by SDNN ($\beta = 0.27$, $p = 0.003$) and age ($\beta = -0.22$, $p = 0.01$). LVEF did not retain independent predictive value ($\beta = 0.09$, $p = 0.18$). Variance inflation factors were below 5 for all retained variables, excluding significant multicollinearity between GLS and LVEF.

Table 5. Multivariable linear regression: independent predictors of VO_2 peak

Variable	Standardised β	p value
Global longitudinal strain	0.39	< 0.001
SDNN	0.27	0.003
Age	−0.22	0.01
LVEF	0.09	0.18 (NS)

Model additionally adjusted for sex and NYHA class. NS = not significant.

3.6 Comparison across disease categories

Functional, mechanical, and autonomic impairment differed significantly by diagnosis (Table 6). Patients with heart failure had the lowest VO_2 peak (14.8 mL/kg/min), most impaired GLS (−14.2%), and lowest SDNN (70.5 ms), compared with ischaemic (17.9 mL/kg/min; −16.4%; 86.2 ms) and valvular (18.2 mL/kg/min; −17.1%; 88.1 ms) subgroups, with p = 0.002, 0.001, and 0.004 respectively. The rank ordering of subgroups was identical across all three domains.

Table 6. Comparison of functional, mechanical, and autonomic parameters across disease categories

Parameter	Ischaemic (n = 58)	Heart failure (n = 47)	Valvular (n = 25)	p value
VO_2 peak (mL/kg/min)	17.9	14.8	18.2	0.002
Global longitudinal strain (%)	−16.4	−14.2	−17.1	0.001
SDNN (ms)	86.2	70.5	88.1	0.004

DISCUSSION

The central finding of this study is that in patients with established heart disease, exercise capacity was determined by myocardial deformation and autonomic tone, and not by ejection fraction. In a multivariable model that deliberately retained LVEF as a clinically mandated covariate, GLS and SDNN emerged as independent predictors of VO_2 peak while LVEF did not.

4.1 The magnitude of functional impairment

Mean VO_2 peak of 16.8 mL/kg/min represents substantially reduced cardiorespiratory fitness, falling well below age-predicted values and within the band associated with adverse prognosis in heart failure populations.[3,5,21] The mean VE/VCO_2 slope of 34.6 sits at the threshold above which ventilatory inefficiency is conventionally recognised and prognostic risk begins to rise.[6,7,22] That this degree of impairment was present in a cohort whose mean LVEF was 52.4% underlines the limited information ejection fraction conveys about how a patient actually functions. The mean peak respiratory exchange ratio of 1.14 is important methodologically: submaximal effort is the commonest reason for uninterpretable CPET data, and its exclusion here strengthens confidence in the peak values.[2,19]

4.2 Deformation as a determinant of functional reserve

GLS showed the strongest bivariate correlation with VO_2 peak (r = 0.51) and the largest standardised coefficient in the multivariable model. The physiological interpretation is straightforward. Longitudinal shortening of subendocardial fibres, together with the associated atrioventricular plane descent, contributes materially to stroke volume generation.[12,23] When longitudinal function is impaired, the capacity to augment stroke volume during incremental exercise is constrained, and since oxygen delivery at peak is the product of cardiac output and arteriovenous oxygen difference, peak oxygen uptake falls accordingly. GLS thus indexes mechanical reserve in a way that a resting volumetric ratio cannot: two patients with identical ejection fractions may differ substantially in longitudinal function and therefore in their ability to increase output under load. This interpretation is consistent with the observation that oxygen pulse — a non-invasive surrogate of stroke volume — was also depressed in our cohort at 9.1 mL/beat.

4.3 Autonomic determinants and ventilatory inefficiency

SDNN retained independent predictive value for VO_2 peak after adjustment, and RMSSD and BRS both correlated significantly with it. Autonomic regulation governs the chronotropic response, the redistribution of blood flow to exercising muscle, and venous return, so its impairment limits exercise capacity through mechanisms distinct from those indexed by GLS. This distinctness is what makes the two variables independently informative in the same model.

The correlation between LF/HF ratio and VE/VCO_2 slope (r = 0.44) is of separate interest. Ventilatory inefficiency in cardiac disease is attributed to increased dead space ventilation, heightened chemoreflex and ergoreflex sensitivity, and pulmonary vascular abnormality.[11,24,25] Sympathetic predominance plausibly links these: enhanced peripheral chemosensitivity and muscle ergoreceptor overactivity both drive ventilation and both accompany sympathetic activation in heart failure.[24,25] Our data are consistent with, though cannot establish, this pathway. The LF/HF ratio should nonetheless be interpreted cautiously as a descriptive index rather than a direct measure of sympathovagal balance.

4.4 The limits of ejection fraction

That LVEF did not retain significance (β = 0.09, p = 0.18) is the study's most clinically pointed result. It is not that ejection fraction is unrelated to functional capacity,

but rather that its contribution is subsumed by measures that capture the same underlying mechanics with greater sensitivity, together with a neural dimension that ejection fraction does not address at all. This parallels the established observation that CPET-derived variables outperform resting LVEF in prognostication.[4,21,26,27] Practically, it argues against using an ejection fraction within the normal range to reassure a symptomatic patient, and in favour of measuring what actually limits them.

4.5 Subgroup differences

The heart failure subgroup was most impaired in all three domains, and the ordering of subgroups was identical for functional, mechanical, and autonomic indices. This coherence supports the view that these are correlated manifestations of a common disease process rather than independent phenomena. The relative preservation of function in the valvular subgroup should be interpreted with caution given its small size (n = 25) and the heterogeneity of lesions it contains.

4.6 Clinical implications

CPET remains the reference standard for functional assessment, but its cost, space, and expertise requirements place it beyond the reach of most secondary-level centres in India and comparable settings.[18] Our findings suggest a pragmatic alternative: GLS and SDNN together account for a meaningful proportion of the variance in VO_2 peak and are obtainable from equipment already present in most echocardiography laboratories and from a 5-minute electrocardiographic recording. These measures should not be presented as replacements for CPET, which provides information about ventilatory efficiency, chronotropic response, and effort adequacy that neither can supply. They may, however, serve to identify which patients most need referral for full cardiopulmonary testing, and to provide interim functional information where such referral is not feasible.

4.7 Limitations

This single-centre cross-sectional study cannot establish causality or prognostic value; longitudinal follow-up would be required to determine whether GLS and HRV predict events, not merely current capacity. The sample, while adequate for the primary analysis, limits subgroup power, particularly for the valvular group. Beta-blocker therapy, near-universal in this population, affects both HRV and the chronotropic response to exercise and was not stratified in the present analysis; this is likely to have attenuated rather than inflated the autonomic associations. Cycle ergometry typically yields VO_2 peak values 5–10% lower than treadmill testing, so absolute values should be compared with modality-matched norms. Inter-vendor variability in strain software limits direct transfer of absolute GLS thresholds between platforms, although a single vendor-independent package and a single blinded analyst were used throughout. Finally, exclusion of patients with atrial fibrillation and implanted devices — necessary for valid HRV analysis — selects against a higher-risk segment of the heart failure population and limits generalisability to that group.

CONCLUSION

In patients with established heart disease, peak oxygen uptake was independently determined by global longitudinal strain and heart rate variability, while left ventricular ejection fraction retained no independent predictive value. Exercise capacity was substantially reduced despite a preserved mean ejection fraction, and impairment across functional, mechanical, and autonomic domains was greatest in patients with heart failure. These findings support integrating deformation imaging and autonomic assessment into the evaluation of exercise intolerance, and suggest that where cardiopulmonary exercise testing is unavailable, these accessible measures may provide useful information about functional reserve. Prospective outcome studies are required to establish whether a composite of mechanical and autonomic indices improves risk stratification over existing approaches.

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