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# Left ventricular ejection fraction is determined by both global myocardial strain and wall thickness

David H. MacIver [a,b,c,*], Ismail Adeniran [a], Henggui Zhang [a]

[a] Biological Physics Group, School of Physics & Astronomy, University of Manchester, Manchester, UK
[b] Department of Cardiology, Taunton & Somerset Hospital, Musgrove Park, Taunton, UK
[c] Medical Education, University of Bristol, Senate House, Tyndall Avenue, Bristol BS8 1TH, UK

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ABSTRACT

*Objectives:* The purpose of this study was to determine the mathematical relationship between left ventricular ejection fraction and global myocardial strain. A reduction in myocardial strain would be expected to cause a fall in ejection fraction. However, there is abundant evidence that abnormalities of myocardial strain can occur with a normal ejection fraction. Explanations such as a compensatory increase in radial or circumferential strain are not supported by clinical studies. We set out to determine the biomechanical relationship between ejection fraction, wall thickness and global myocardial strain.

*Methods:* The study used an established abstract model of left ventricular contraction to examine the effect of global myocardial strain and wall thickness on ejection fraction. Equations for the relationship between ejection fraction, wall thickness and myocardial strain were obtained using curve fitting methods.

*Results:* The mathematical relationship between ejection fraction, ventricular wall thickness and myocardial strain was derived as follows: $\varphi = e^{(0.14\mathrm{Ln}(\varepsilon) + 0.06)\omega + (0.9\mathrm{Ln}(\varepsilon) + 1.2)}$, where $\varphi$ is ejection fraction (%), $\omega$ is wall thickness (cm) and $\varepsilon$ is myocardial strain (−%).

*Conclusion:* The findings of this study explain the coexistence of reduced global myocardial strain and normal ejection fraction seen in clinical observational studies. Our understanding of the pathophysiological processes in heart failure and associated conditions is substantially enhanced. These results provide a much better insight into the biophysical inter-relationship between myocardial strain and ejection fraction. This improved understanding provides an essential foundation for the design and interpretation of future clinical mechanistic and prognostic studies.



## 1. Introduction

The terms global left ventricular function and ejection fraction are usually used synonymously. Ejection fraction is measured by assessing changes in the *lumen* of the ventricle. In contrast, myocardial muscle function is evaluated using displacement, velocity or deformation of the *wall* of the ventricle. These quantities may be measured using mitral annular displacement, tissue Doppler velocities, Doppler or speckle tracking derived myocardial strain and strain rate.

A reduction in myocardial systolic strain might be expected to result in a fall in ejection fraction; however this is often not the case in hypertrophic left ventricular diseases and heart failure with a normal ejection fraction (HFNEF) (Table 1) [1–5]. Systolic myocardial abnormalities such as long-axis displacement, systolic velocities of basal myocardial and mitral annular motion and strain rate are often observed in HFNEF [4–8]. Similar abnormalities of myocardial strain occur in patient groups with thick walled ventricles such as hypertension and aortic stenosis (Tables 1 and 2). In addition, abnormalities of global strain occur in hypertrophic cardiomyopathy with the lowest values in the segments with the most hypertrophy [3]. Furthermore, abnormalities of midwall and longitudinal fractional shortening in the presence of a normal ejection fraction have been described in hypertensive hypertrophic left ventricular disease (Table 2) [9–14]. Of note, as wall thickness increases in hypertensive left ventricular disease, midwall fractional shortening decreases [15]. Depressed midwall fractional shortening also occurs in cardiac amyloid despite a preserved ejection fraction [16].

How can the presence of widespread myocardial abnormalities and a normal ejection fraction be reconciled? One viewpoint is that myocardial function (strain) and global function (ejection fraction) are distinct entities. For example, some authorities see the muscular pump and haemodynamic compression pump as intrinsically different [17]. However, the mechanical or physical reasons as to how this might arise are unexplained. Another possibility is that longitudinal strain may be reduced and a compensatory increase in circumferential strain or shortening

* Corresponding author at: Department of Cardiology, Taunton & Somerset Hospital, Musgrove Park, Taunton TA1 5DA, UK. Tel.: +44 1823 342130; fax: +44 1823 342709.
*E-mail address:* david.maciver@tst.nhs.uk (D.H. MacIver).

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**Table 1**
Left ventricular strain in hypertrophic left ventricular diseases.
The table shows either trend or significant reduction in average myocardial strain in various cohorts with an increased left ventricular wall thickness despite a preserved ejection fraction. Note the lower (less negative) longitudinal and circumferential strains and lower (less positive) radial strains despite unchanged ejection fractions. HFREF is shown for comparison.

| Cohort | Longitudinal strain (%) | | Circumferential strain (%) | | Radial strain (%) | | EF (%) | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Patient | Control | Patient | Control | Patient | Control | Patient | |
| cLVH | −22.9 | −17.9** | −23.7 | −20.4** | +74.4 | +62.7** | 77 | 70* | [1] |
| AS | −20.3 | −14.6** | −19.5 | −15.2** | +38.9 | +33.9$^{ns}$ | 62 | 61$^{ns}$ | [2] |
| HBP | −20.3 | −17.2** | −19.5 | −17.0$^{ns}$ | +38.9 | +34.4$^{ns}$ | 62 | 61$^{ns}$ | [2] |
| HCM | −20.3 | −15.1** | −19.6 | −16.8** | +36.8 | +25.2** | 67 | 69$^{ns}$ | [3] |
| HFNEF | −19.0 | −12.0* | −20.0 | −15.0$^{ns}$ | +47.0 | +28.0* | 64 | 63$^{ns}$ | [4] |
| | −20.0 | −14.6* | −27.1 | −22.9* | NA | NA | 61 | 59$^{ns}$ | [5] |
| | −20.9 | −18.9* | NA | NA | +49.2 | +41.8* | 62 | 61$^{ns}$ | [6] |
| | −20.9 | −15.9** | −26.4 | −20.8$^{ns}$ | +44.5 | +32.9** | 68 | 61$^{ns}$ | [7] |
| HFREF | −19.0 | −4.0* | −20.0 | −7.0* | +47.0 | +14.0* | 64 | 24* | [4] |
| | −20.9 | −9.6** | −26.4 | −9.5** | +44.3 | +18.0** | 68 | 31* | [7] |

cLVH, concentric left ventricular hypertrophy. AS, aortic stenosis. HBP, high blood pressure. HCM, hypertrophic cardiomyopathy. HFNEF, heart failure with a preserved ejection fraction. HFREF, heart failure with reduced ejection fraction. EF, ejection fraction. *significant, ns, non-significant. NA, data not available.

maintains the ejection fraction. However, observational data (Tables 1 and 2) does not support this viewpoint. The final option is that there is another factor influencing the ejection fraction [8]. Previously, we have shown that increasing left ventricular wall thickness increases the ejection fraction independently of all other variables [18].

Studies have shown the importance of left ventricular ejection fraction in predicting prognosis [19]. For example, following myocardial infarction there is a reciprocal relationship between ejection fraction and mortality [20–22]. However, increasing left ventricular wall thickness or concentric hypertrophy is also associated with a higher mortality in the presence of a preserved ejection fraction [23–28]. The greater the left ventricular mass the greater the risk [24]. An increase in left ventricular wall thickness may be a consequence of either myocyte hypertrophy, such as that occurs in hypertension and hypertrophic cardiomyopathy or 'pseudohypertrophy' as in infiltrative disorders such as cardiac amyloidosis.

These findings indicate that myocardial wall thickness and ejection fraction are independent risk factors for mortality [29]. This observation may explain why heart failure with a reduced ejection fraction has the same mortality as HFNEF when presenting symptoms are similar [30,31]. These data would also explain why measures of myocardial mechanics such as global longitudinal and circumferential strain are better markers of mortality and morbidity than ejection fraction [32–34].

A combination of longitudinal and circumferential shortening of 20% results in a radial wall thickening of approximately 56% [35]. This wall thickening results in an inward displacement of the endocardium (absolute wall thickening) and, when combined with movement of the mitral annulus (and a minor outer contour change), causes a reduction in left ventricular cavity volume generating the stroke volume (Fig. 1). Previous modelling has shown that ejection fraction in normal and thick walled ventricles, is predominantly determined by *absolute* wall thickening (change in wall thickness) rather than *relative* wall thickening (radial strain) [36]. Furthermore, *absolute* wall thickening is determined by both end-diastolic wall thickness and radial strain [36]. The contribution of midwall circumferential shortening has a greater impact on stroke volume and ejection fraction (67%) than longitudinal shortening (33%); importantly these values do not change with increasing concentric hypertrophy [37].

Normal tissue perfusion is viewed as a fundamental physiological requirement with potent feedback mechanisms designed to maintain the net stroke volume [38–40]. In heart failure syndromes due to myocardial diseases, a reduced myocardial strain is compensated for by concentric or eccentric remodelling which preserves the normal stroke volume [39,40]. Contrary to a commonly held view, most patients with heart failure have a normal resting stroke volume [8], although an inadequate increase in stroke volume with exertion is commonly observed [39,40]. Only a minority of individuals, usually with severely reduced ejection fractions and hypotension, have a low stroke volume at rest [41]. This cohort may be related to insufficient time for the compensatory mechanism to fully occur or because of functional limits to these processes.

Biomechanical theoretical studies are used to gain a greater comprehension of physical processes of complex biological systems. Abstract modelling may improve understanding of myocardial mechanics and the relationship between measures of myocardial strain and ejection fraction. Such modelling complements existing investigational *in vitro*, experimental and observational methods and often has a number of distinct advantages. For example it enables the exclusion of confounding factors *e.g.*, body size, valvular disease, inotropic effects, heart rate, rhythm, filling pressures, blood pressure, ventricular–arterial interaction, reflected waves and peripheral vascular resistance. More importantly, modelling is particularly helpful in studying complex systems where multiple, and often linked, processes are taking place as well as studying the specific effects of certain physiological changes or

**Table 2**
Left ventricular shortening in hypertension.
The table shows reduced midwall fractional shortening in hypertensive hypertrophic left ventricular disease despite a normal (or increased) ejection fraction. Note longitudinal shortening is also decreased.

| Cohort | Longitudinal fractional shortening (%) | | Midwall fractional shortening (%) | | Endocardial fractional shortening (%) | | EF (%) | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Patient | Control | Patient | Control | Patient | Control | Patient | |
| HBP | NA | NA | 21.4 | 16.7* | NA | NA | 64.2 | 64.7$^{ns}$ | [9] |
| HBP | NA | NA | 21.0 | 16.0* | 35 | 35$^{ns}$ | 65 | 66$^{ns}$ | [10] |
| HBP | NA | NA | 19 | 16* | 37 | 35$^{ns}$ | 67 | 64$^{ns}$ | [11] |
| HBP | 21 | 18* | 21 | 18* | 37 | 42* | 63 | 69* | [12] |
| HBP | NA | NA | 17.6 | 15.6* | 38.2 | 36.6* | NA | NA | [15] |

HBP, high blood pressure. EF, ejection fraction. NA, data not available. *significant, ns, non-significant.