A mathematical model of left ventricular contraction and its application in heart disease

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Abstract

Conflicting clinical data have led to a number of theories to explain both normal and abnormal cardiac function. The pathophysiology of heart failure is controversial although it is known to be related somehow to reduced cardiac performance. Following myocardial damage, a number of homeostatic mechanisms attempt to repair the physiological abnormalities by, for example, ventricular remodelling.

A simple new method for mathematically modelling left ventricular contraction is described and the potential implications in clinical practice are discussed. The modelling helps in the understanding of the relationship between left ventricular structure and function in health and disease. It improves comprehension of how myocardial fibre shortening may be translated into changes in whole organ physiology and supports the displacement pump hypothesis to describe left ventricular function.

The model can use either the area-length method or the hemi-cylinder-hemi-ellipsoidal volumetric shape to calculate both the internal and external left ventricular volumes. The model allows adjustment of left ventricular function, for example, left ventricular long- and short-axis shortening, and the effects of left ventricular hypertrophy on end-diastolic and end-systolic volume, stroke volume, systolic wall thickening and ejection fraction. A new definition of heart failure is proposed.

1 Introduction

1.1 Left ventricular structure and function

In fluid mechanics there are different types of pump described, for example displacement, centrifugal and kinetic. Most authors accept that the heart is probably a dynamic positive displacement pump but other theories include the proposal that the heart works as a perpetual vortex [1].

The heart comprises of three main but continuous layers of muscle bundles [2]. These are illustrated in Figure 1 (reproduced from Anderson [2]). At the endocardium and epicardium the fibres run relatively longitudinally from the base of the heart to loop around the apex and then return towards the base forming a helical structure. Circumferential fibres tend to run in the mid-wall of the left ventricle. The left ventricle ejects its stroke volume during systole by a combination of long- and short-axis shortening associated with twisting of the ventricle. In systole, myocardial shortening and thickening causes inward movement of the endocardium and a
reduction in left ventricular cavity volume. This results in an increase in pressure and expulsion of blood into the aorta (the pressure-propulsion hypothesis). During diastole there is myocardial fibre lengthening, ventricular wall thinning, untwisting and refilling of the ventricle.

It is generally agreed that the total heart volume does not change during the cardiac cycle and there is alternate emptying and filling of the left ventricle and atrium. A change in the total external volume in systole would require energy, physical interaction with the surrounding tissues and can be wasteful. There is only a small fall in the outer circumference of the mid-left ventricle with little change towards the apex [3–6]. As the long-axis of the ventricle shortens the wall thickens with an inward movement of the endocardium and significant endocardial short-axis shortening but a lesser degree of mid-wall circumferential shortening. Studies suggest that at rest long-axis shortening contributes to 75–82% of the stroke volume, suggesting that circumferential shortening is less important [4, 5].

1.2 Current concepts of the pathophysiology of heart failure

Heart failure has been characterised as due to ‘systolic’ dysfunction when the left ventricular ejection fraction is reduced to ≤50% or ‘diastolic’ dysfunction when the left ventricular ejection fraction is >50% [7]. This nomenclature implies that the mechanisms of heart failure are understood and heterogeneous. ‘Diastolic heart failure’ has been described as ‘non-systolic’ heart failure or heart failure with preserved (or normal) ejection fraction (HFpEF) and is associated with a relatively normal left ventricular end-diastolic volume. The term HFpEF is preferable as it does not assume the pathophysiology is wholly established.

Many individuals with HFpEF have a sub-normal ejection fraction [8]. Yip et al. showed that the mean left ventricular ejection fraction in HFpEF was 55% whereas in controls it was 68% [9]. Therefore, the term ‘heart failure with a normal ejection fraction’ is unsound. Often the term ‘heart failure with a normal or preserved function’ is used but this assumes that the ejection fraction equates to ventricular function. This does not appear to be true as explained below. A better term for ‘systolic’ heart failure without presumptions regarding the mechanism is heart failure with reduced ejection fraction (HFrEF). This phenotype typically has significant left ventricular remodelling or dilation.
It is important to note that, although the causes differ, the clinical features and neuro-humoral changes are indistinguishable between HFpEF and HFrEF, suggesting a mechanistic association. The processes involved on heart failure have been investigated for many decades but despite this the underlying pathophysiology remains poorly understood [10]. This has led some authorities to circumvent defining heart failure by using a collection of signs, symptoms and the results of investigations to describe the condition [11]. Heart failure is most commonly defined as the condition in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolising tissues or can do so only from an elevated filling pressure [11].

The Frank-Starling mechanism is the observation that the more the ventricle is filled with blood during diastole, the greater the volume of ejected blood will be during the resulting systolic contraction. This mechanism is exhausted in chronic heart failure and so elevated filling pressures cannot maintain stroke volume alone [12]. Further, patients may have normal filling pressures following treatment with diuretics yet still maintain a normal cardiac output. As there is no proven increase in demand of metabolising tissues (perhaps with the exception of thyrotoxicosis) this definition implies that a reduction in cardiac output is the cause of heart failure.

However, stroke volume and cardiac output are not used to help in the diagnosis of heart failure despite the ability to make these measurements non-invasively. Patients with chronic heart failure in fact have a relatively normal stroke volume and cardiac output [13, 14]. A left ventricle that is unable to maintain cardiac output causes hypotension or shock rather than the heart failure syndrome.

Since no current definitions of heart failure are satisfactory, it is not surprising that the diagnosis of heart failure is difficult and treatment challenging. An erroneous diagnosis of heart failure is often made because the condition is ill-defined. Not only is this unfortunate for the individual but has also resulted in under-powering of heart failure trials that then become difficult to extrapolate to clinical practice.

Only in acute deterioration of heart failure is stroke volume reduced and cardiac output maintained by tachycardia. A reduction in stroke volume has also been demonstrated in HFpEF initially in some patients following admission with an acute deterioration [15].

It is unlikely that neuro-humoral activation has a sustained inotropic effect because of the down-regulation of β1-adrenergic receptors and uncoupling of β2-receptors to second messengers [16]. Further, cardiac output is maintained despite neuro-humoral antagonists used to treat heart failure. Therefore, in chronic heart failure the most important compensatory change is likely to be ventricular dilation or remodelling.

### 1.3 End-diastolic volume and remodelling in HFpEF

Left ventricular end-diastolic volume in HFpEF ranges from −19% to +17% of control groups (Figure 2). There is no consistent increase or decrease in end-diastolic volumes. This may partially reflect the severity, aetiology and patient selection in the different patient cohorts. Further, note the lack of correlation with end-diastolic volume and degree of left ventricular hypertrophy (Figure 2). What is clear is that some patients with HFpEF have an end-diastolic volume greater than controls. As will be demonstrated below most, if not all, patients also have greater than expected end-diastolic volumes, suggesting remodelling has taken place.

### 1.4 Left ventricular hypertrophy in HFpEF

Epidemiological studies suggest HFpEF is strongly associated with concentric left ventricular hypertrophy [17–19]. A left ventricular mass index of more than 122 g/m² in women and 149 g/m²...
in men is sufficient evidence for the diagnosis of HFpEF when tissue Doppler yields inconclusive results or when plasma levels of natriuretic peptides are elevated [7].

Observational clinical trials in HFpEF [13, 20–22] that have data corrected for body surface area are shown in Figure 2. Note how HFpEF patients in these trials have consistently increased left ventricular mass (15–40%) greater than normals.

This raises the possibility that left ventricular hypertrophy might be causally linked to the preservation of the ejection fraction in HFpEF.

1.5 Ejection fraction as a measure of systolic function

Ejection fraction has long been regarded as the principal measure of systolic function. It is important to consider that ejection fraction is merely a ratio of left ventricular stroke volume and end-diastolic volume and is only one of many indicators of systolic function. If resting stroke volume is relatively fixed at the lowest level that can allow tissue perfusion and maintain blood pressure then it is not surprising that stroke volume in heart failure remains relatively normal. The only way this can be achieved is by increasing end-diastolic volume. This is referred to as ‘adverse’ remodelling and has been thought of as an undesirable event to be avoided at all costs.

The ejection fraction in heart failure has a unimodal distribution showing that it is not a useful ‘rule out’ measurement [23]. Additional evidence that the ejection fraction is a sub-optimal measure of function include the following: there is poor concordance between the left ventricular ejection fraction and severity of heart failure symptoms in clinical practice [24] and the ejection fraction is a suboptimal predictor of mortality [25]. Furthermore, given a similar severity of symptoms, the prognosis is equally poor in both HFpEF and HFrEF [26, 27]. Therefore, ejection fraction cannot be regarded as the gold standard for measuring left ventricular performance.
1.6 Systolic Performance in HFpEF

It is commonly thought that individuals with a normal ejection fraction and heart failure have normal systolic performance and, therefore, that the heart failure must be due to isolated diastolic dysfunction. Recent echocardiographic methods using tissue Doppler or myocardial velocity imaging have shown that HFpEF is associated with significant systolic abnormalities. These abnormalities include an important decline in long-axis displacement, reduced systolic velocities of basal myocardial and mitral annular motion, and decrease of both longitudinal strain and strain rate [28–33].

In left ventricular hypertrophic conditions such as hypertension [34], hypertrophic cardiomyopathy [35], Fabry disease [36], diabetes [37], haemochromatosis [38], and amyloid [39], there are major systolic long-axis abnormalities.

Brain natriuretic peptide (BNP) is a biochemical marker which is used in the diagnosis of heart failure and closely correlated with severity and prognosis. There is a better correlation of BNP with long-axis systolic function than with ejection fraction in HFrEF patients [40]. This suggests that long-axis shortening may better reflect ventricular performance than ejection fraction.

Additional evidence of systolic function abnormalities in hypertrophic left ventricular disease are supported by the finding of depressed longitudinal myocardial shortening in non-hypertensive [41] and hypertensive left ventricular hypertrophy in both echocardiographic [57] and magnetic resonance imaging studies [42] even in the absence of heart failure.

In addition to the many human studies discussed confirming overwhelming evidence of systolic abnormalities in HFpEF and hypertensive heart disease, there are numerous experimental small and large animal studies verifying reduced contractile function in hypertensive-hypertrophy ventricular disease [43–53].

The long-axis systolic abnormalities in HFpEF have been explained by suggesting

(a) the abnormalities are subtle, [54] which they are not,
(b) differentiating ‘regional’ from ‘global’ function, [55] which is erroneous. Tissue Doppler studies show that diastolic and systolic shortening velocities are reduced in all left ventricular segments in HFpEF. The presence of abnormalities in all parts of the myocardium indicates a widespread (i.e. global) abnormality,
(c) by distinguishing contractile from pump function, [56] which assumes the heart is not a displacement pump,
(d) citing a compensatory increase in circumferential function, [28] which is challenged by many reports [57–60]. Indeed, there is some evidence that mid-wall circumferential shortening is in fact reduced even though endocardial circumferential shortening is increased in hypertensive left ventricular hypertrophy [42]. This apparent paradox can only be explained by the presence of hypertrophy.

1.7 Diastolic function in heart failure

The documentation of diastolic dysfunction in HFrEF indicates that its mere presence in HFpEF does not prove it is the cause. Patients with HFrEF and HFpEF have similar degrees of diastolic dysfunction when assessed using tissue velocity imaging [61]. In fact, Bursi et al. showed that diastolic function is actually worse in HFrEF compared with HFpEF [62]. These findings probably represent reduced annular motion and/or elevated filling pressures and probably correspond to the severity of heart failure rather than the phenotype.
The end-diastolic pressure-volume relationships (EDPVR) have long been regarded as the method of choice for diagnosing HFpEF and assessing diastolic function as there is believed to be a shift in the curves upward and to the left in pure ‘diastolic’ heart failure.

Figure 3 (reproduced from Burkhoff [63]) shows the expected pressure-volume loops seen in normal controls and patients with heart failure and normal ejection fraction. However, Figure 4 shows the EDPVR of the HFpEF (HFNEF) patients can be shifted leftward (curve 3), rightward (curves 5 & 6) or are no different (curve 4) to the normal controls (1 & 2). This implies the heart failure seen in HFpEF is not due to isolated diastolic dysfunction [63, 64].

Furthermore, the interpretation of pressure-volume loops depends on the assumption that the left ventricular end-diastolic volumes are compared with the controls. However, as will be seen later, the predicted pre-compensatory (unremodelled) end-diastolic volumes are actually less than controls. Following remodelling and normalisation of stroke volume the end-diastolic volumes increase towards control values. Therefore, the reference volumes should be related to the predicted end-diastolic volume for that degree of hypertrophy rather than the normal control group. This explains the apparent incongruous findings in HFpEF and, potentially, invalidates a primary assumption of pressure-volume loops in the diagnosis of HFpEF.
1.8 Other determinants of left ventricular performance

The left ventricular volumes and geometry are influenced by multiple considerations such as body mass index, body fat, degree of fitness, gender, age, ethnicity, valvular disease, inotropic and chronotropic effects, neuro-humoral factors, inter- and intra-ventricular dyssynchrony, ventricular–ventricular interaction, filling pressure, blood pressure, ventricular compliance, ventricular torsion/rotation, ventricular ‘suction’, abnormal ventricular–arterial interaction, blood pressure, reflected waves and peripheral vascular resistance. This makes in vivo assessment difficult if not impossible. In addition, any perturbation of function in vivo is associated with both acute and chronic physiological responses which may conceal or confound any changes.

2 The hypotheses

2.1 Hypothesis 1

The heart failure syndrome is caused initially by a cardiac disorder resulting in a fall in stroke volume (pre-compensatory or non-remodelled stage) with subsequent compensatory ventricular dilation (post-compensatory or remodelled stage) to normalise net stroke volume in both HFrEF and HFpEF.

2.2 Hypothesis 2

The presence of an increased muscle mass in the non-dilated heart (i.e. concentric left ventricular hypertrophy) would explain the preserved ejection fraction and the relatively normal end-diastolic volumes seen in HFpEF through augmented radial thickening. More specifically, HFpEF may be caused by systolic dysfunction when concentric left ventricular hypertrophy is present.

3 Methods

3.1 Role of mathematical modelling

Current methods for modelling left ventricular contraction are complex and so difficult to employ. Therefore, there is a need for a simpler mathematical method.

To remove both confounding factors and the effects of any confusing or opposing physiological responses a mathematical model has been developed and recently published [65]. We described the early, pre-compensatory stage (or non-remodelled stage) of heart failure [65]. The model has been extended to assess the effect of ventricular remodelling following normalisation stroke volume to mimic the chronic phase of heart failure.

3.2 Basic model

The method employs one or other of two well-established three-dimensional internal ($I$) left ventricular geometric shapes using a combination of the area perpendicular to the long-axis at the level of the mitral valve and length ($L$) of long-axis to determine internal left ventricular volume (see Figure 5).

If one assumes that the external ($E$) left ventricular volume is a similar shape to the internal volume then total or external left ventricular volume can be calculated using the same formula.
Figure 5: Schematic diagram of the left ventricle used in the model to calculate internal ($I$) and external ($E$) volumes during diastole from the short-axis diameter/width ($IW_d$ & $EW_d$) and long-axis length ($IL_d$ & $EL_d$). The apex, base, endocardium and epicardium are labelled. The diastolic external and internal volumes are calculated and the myocardial volume obtained from the difference. The external short-axis width and length are reduced to simulate systole ($EW_s$ & $EL_s$, respectively) and the new external volume calculated. The internal end-systolic volume is calculated by subtracting the muscle volume from the external end-systolic volume.
The total myocardial volume is derived from the difference in total (external) left ventricular volume and the internal volume (Figure 5).

Two different formulae [66, 67] are available and each assumes a slightly different geometry of the left ventricle:

(a) Area-length method of Dodge

\[ V = \pi W^2 \cdot L/6 \]

where \( V \) = volume, \( W \) = width (i.e. short-axis diameter), \( L \) = long-axis length.

So

External volume in diastole = \( \pi EW_d^2 \cdot EL_d/6 \)

Internal volume = \( \pi IW_d^2 \cdot IL_d/6 \)

where \( I \) = internal, \( E \) = external, \( d \) = diastole

Myocardial volume = External volume - Internal volume

(b) Hemi-cylinder-hemi-ellipsoidal method

\[ V = 5\pi(W/2)^2 \cdot L/6 \]

3.3 Simulating systole

In order to simulate systole (s) the external short- and long-axis lengths are reduced and the new systolic external left ventricular volume recalculated (see Figure 5). The new systolic internal volume is calculated from the difference in external end-systolic volume and the muscle volume. It is assumed that there is no significant muscle compression and the muscle acts as a simple elastomer.

External volume in systole = \( \pi EW_s^2 \cdot EL_s/6 \)

Internal volume in systole = external volume in systole - muscle volume.

3.4 Physiological and pathophysiological changes

Adjustments for varying degrees of long- and short-axis dysfunction can then be mimicked by changing the long- and short-axis shortening. The degree of left ventricular hypertrophy can be adjusted by altering the difference between the end-diastolic internal (\( ID_d \)) and external diameters (\( ED_d \)).

Multiple measurement can then be derived including ejection fraction, stroke volume, endocardial/mid-wall/epicardial circumferential shortening, radial thickening, ventricular wall stress and other parameters.

4 Results

4.1 Results pre-compensation (un-remodelled or before remodelling)

The initial results of changing long-axis shortening and the effect of left ventricular hypertrophy on ventricular volumes have been described recently [65] using the area-length method of Dodge. We modelled an increase in left ventricular mass of between 13 and 35% of the control value. These results show that internal left ventricular hypertrophy resulted in augmentation of systolic wall thickening, a reduction in end-diastolic volume and an increased ejection fraction.
without a change in stroke volume. Abnormal long-axis function resulted in a reduction in stroke volume, ejection fraction and a small fall in end-systolic wall thickness (Figure 6).

We showed that the ejection fraction could remain >50% together with reduced long axis shortening and a reduced stroke volume if there was significant left ventricular hypertrophy.
present. This implied that HFpEF may be explained by the presence of left ventricular hypertrophy. The resulting amplified radial thickening in the setting of reduced long-axis shortening can explain the preservation of ejection fraction. We suggested that the reduced stroke volume in the pre-compensated state rather than diastolic dysfunction may be the cause of heart failure in both HFrEF and HFpEF.

4.2 Results post-compensation (following remodelling to normalise stroke volume)

As patients with chronic heart failure generally do not have reduced stroke volumes, the effect of left ventricular dilation or remodelling to normalise stroke volume on ejection fraction, end-diastolic volume and end-systolic wall thickness has been assessed.

This unpublished data used the hemi-cylinder-hemi-ellipsoidal method and has produced some interesting results (Figure 6). The previous findings using the Dodge formula in the pre-compensatory stage were also confirmed.

Following remodelling, when there is no left ventricular hypertrophy, significant ventricular dilation is necessary to correct the stroke volume. The presence of left ventricular hypertrophy causes the end-diastolic volume to fall compared with normal. In the presence of reduced long-axis shortening, the end-diastolic volume increases. Importantly, when both long-axis shortening and left ventricular hypertrophy are present remodelling results in the end-diastolic volume returning towards normal. This is the typical pattern seen in HFpEF in clinical trials and explains the apparent divergent results seen in Figure 4.

4.3 Summary of results

Figure 7 shows the scaled diagrams of left ventricular contraction. At the top of the figure is the control situation with relatively normal internal dimensions, an ejection fraction of 58% and stroke volume of 83 ml. On the left is the effect in a non-hypertrophic heart. Following acute damage, as may occur in acute fulminant myocarditis, there is a reduction in myocardial shortening which results in a fall in ejection fraction and stroke volume. This would normally be compensated for by a tachycardia resulting in normalisation of cardiac output and the syndrome of acute heart failure. If the tachycardia were insufficient to improve the cardiac output then the patient would have a low cardiac output and develop a shock/hypotensive syndrome. Should the patient survive and go on to the chronic phase then renal under-perfusion would lead to an increase in intra-vascular volume, an increase in right heart filling pressures, a mismatch between right and left ventricular stroke volumes, a rise in left ventricular end-diastolic pressure and finally a significant increase in end-diastolic volume, a normalisation of stroke volume with an associated reduction in ejection fraction. Some patients with dilated cardiomyopathy have a more gradual onset of dysfunction and will never suffer from acute heart failure. In this case the left ventricle will gradually dilate (remodel) in parallel with the fall in myocardial shortening to normalise the stroke volume.

The situation in pathological hypertrophic left ventricular disease, such as amyloid or hypertrophic-hypertensive left ventricular disease, is different and is shown on the right in Figure 7. Cardiac hypertrophy is relatively slow to develop so that one does not see a similar acute dysfunction phase as is observed in (non-hypertrophic) acute myocarditis. Therefore, patients will gradually remodel as the hypertrophic process progresses concurrently with the myocardial dysfunction as demonstrated with the solid arrow. The uncompensated stage is the hypothetical predicted situation following hypertrophy but in the absence of any remodelling (shown with the dashed arrow). Although this will not be seen in clinical practice it does not diminish its importance as a reference point prior to remodelling.
Figure 7: Schematic illustration to scale showing the normal situation (upper part) with normal long-axis displacement (1.6 cm). The effects of reduced myocardial shortening (long-axis displacement 0.5 cm) without left ventricular hypertrophy (on left) versus moderate (+35% increase in mass) left ventricular hypertrophy (on right) before (middle) and after compensatory dilation (lower) to normalise stroke volume are shown. The dashed arrow represents predicted hypothetical changes probably not occurring in vivo. Also shown are the intra-ventricular volumes (ml) in systole and diastole, stroke volume (ml) and ejection fraction (shown within the cylinders).
5 Conclusions

5.1 Interpretation

A simple and yet flexible mathematical model has been described that can determine the effect of left ventricular contraction. The model assumes the heart is a positive displacement pump with a known geometric shape. It removes the confounding effects of other known as well as non-predictable physiological and pathological responses. The model can determine the effect of left ventricular hypertrophy and myocardial shortening and other physiological changes on stroke volume, ejection fraction, end-systolic wall thickness and end-diastolic volume.

The study has determined that, in the absence of remodelling, stroke volume can be predicted to fall following reduced myocardial shortening. This effect is independent of the presence of left ventricular hypertrophy. The changes necessary to normalise stroke volume through ventricular dilation were calculated. Remodelling without hypertrophy results in a high end-diastolic volume and low ejection fraction (typical features of HFrEF). Following remodelling, left ventricular hypertrophy resulted in a near-normal end-diastolic volume and preserved ejection fraction (as seen in HFpEF).

These findings are consistent with the hypothesis that heart failure is caused initially by a reduced stroke volume compensated by tachycardia (i.e. acute HF). This is followed by gradual remodelling (i.e. compensated by dilation) to normalise stroke volume in both phenotypes. HFpEF can be explained fully by reduced systolic myocardial shortening due to a fall in contractility in presence of concentric left ventricular hypertrophy rather than isolated diastolic dysfunction. A central observation is that the amount of ventricular dilation is highly dependent on the degree of left ventricular hypertrophy. These findings are validated by published observational data.

5.2 Advantages of the model

The model allows the assessment of changes in shape, size and shortening without confounding effects of body size etc. It also removes the physiological or pathological responses which could modify the consequences of these changes. A similar clinical or in vivo experimental study would be impossible to perform because of all the many homeostatic changes.

Additional modifications to the model can be made such as measuring the effect of changes in mid-wall circumferential shortening or the effect of thinner apical wall and differing shaped ventricles (e.g. sphericity). The model has allowed the facility to determine the outcome of modification in long-axis, short-axis as well as the degree of left ventricular hypertrophy on ejection fraction, stroke volume, wall stress etc. whilst keeping other factors constant and avoiding problems of interpretation following physiological feedback or secondary pathological mechanisms.

5.3 Limitations of the model

The main limitation of the model is that it is based on certain geometric assumptions although these do appear to correlate with direct observation and have been well validated in the clinical setting [66, 67]. Furthermore, using either the hemi-cylinder-hemi-ellipsoidal or the area-length method gave similar results.

The model presupposes that the shapes of both the external and internal left ventricular walls are similar and remain the same in systole and diastole. Moreover, it was assumed that internal concentric hypertrophy occurs in the pre-compensation (unremodelled) state. This appears
to be appropriate as the model resulted in a constant stroke volume that was independent of
the amount of left ventricular hypertrophy. This was employed because maintaining a normal
stroke volume was felt to be the most likely physiological response following the development
of hypertrophy.

The simulation presupposes that there is no loss in myocardial muscle volume (that it is
non-compressible) during contraction. This appears reasonable as the myocardium comprises
mainly of water; however, there may be a small loss due to vascular compression.

Although the calculation of ventricular volumes may be approximate, the concepts proposed
are likely to be sound. A normalisation of stroke volume in the post-compensation stage was
used rather than a partially corrected stroke volume to simulate the study findings; it may be
assumed that the resting stroke volume in normal controls is likely to be near the lowest level
that physiologically maintains sufficient tissue (including renal) perfusion.

The model will produce some examples that may not occur in clinical practice such as
pathological hypertrophy with normal long-axis function. With these exceptions, the model
results approximate satisfactorily well to those found in clinical practice.

5.4 Correlation of model predictions with observational studies

The model predicts that reduced long-axis shortening results in a decreased stroke volume in
the pre-compensation stage in heart failure. Acute myocardial damage, say following acute
myocarditis or a myocardial infarction, results in a reduced stroke volume and normalisation of
cardiac output is brought about by a tachycardia. This is regularly seen in HFrEF and may be
occasionally seen in acute exacerbations of HFpEF [13].

In chronic heart failure due to systolic dysfunction, the ejection fraction is reduced (HFrEF)
and ventricular dilation (remodelling) results in a high end-diastolic volume with normalisation
of stroke volume. The data presented predicts that HFpEF would be more frequent with increasing
concentric left ventricular hypertrophy and HFrEF would occur in the absence of hypertrophy.

HFpEF is thought by many to be due to diastolic dysfunction. The end-diastolic volume is
usually relatively normal and so it has been assumed that ventricular remodelling has not taken
place. Moreover, it is often thought that ejection fraction equates to ventricular performance;
however, there is overwhelming evidence of major systolic dysfunction in human and animal
studies both in HFpEF and in hypertensive heart disease as outlined above.

The germane finding of the model in both phenotypes of heart failure is the predicted
reduced stroke volume in the pre-compensation stage. The study also shows the effect on left
ventricular end-diastolic volume with the predicted volumes being significantly greater when
there is no left ventricular hypertrophy and lower left ventricular end-diastolic volumes when
there is hypertrophy present despite remodelling occurring in both phenotypes. This is compat-
ible with the typical findings in HFrEF and HFpEF and is supported by a substantial body of
data (also see Figure 2).

The finding of an increase in ejection fraction with hypertrophy demonstrated by the model
is supported by an observational study in hypertension which confirmed a higher ejection frac-
tion (69% vs. 63%) in patients with hypertensive left ventricular hypertrophy than in controls
despite having reduced long-axis shortening (1.8 vs. 2.1 cm) [68].

5.5 Implications in heart failure

This study suggests that the development of concentric left ventricular hypertrophy, occurring
concurrently or before the perturbation causing contractile dysfunction may be the cardinal
feature that determines whether HFrEF or HFpEF develops. This would be entirely consistent with observational studies showing a strong association of left ventricular hypertrophy with HFpEF.

The term ‘global’ function when referring to ejection fraction and ‘regional’ when referring to myocardial velocities is flawed. Heart failure can occur when the ejection fraction is preserved if sufficient left ventricular hypertrophy takes place to result in increased radial thickening to maintain ejection fraction but not stroke volume in the presence of reduced long-axis systolic shortening. The model shows how patients with HFpEF can have significant reductions in long-axis shortening and reduced stroke volume yet maintain their ejection fraction in the presence of hypertrophy. In fact the maintained radial function seen in HFpEF is explained by the additional radial thickening and augmented inward endocardial displacement secondary to left ventricular hypertrophy rather than by increased contractility itself.

The poor relationship seen between ejection fraction and symptoms in clinical practice may be explained by the lack of association between the ejection fraction and stroke volume demonstrated by the model. The main association is with long-axis shortening and stroke volume in the pre-compensation stage. Assuming a worse stroke volume indicates a more severe heart failure syndrome then these findings would imply that measures of long-axis function should be even better predictors of morbidity and mortality than ejection fraction. Certainly, long-axis function is good at assessing prognosis [69–72]. The preserved ejection fraction seen in HFpEF reflects the relative normal end-diastolic volumes and reduced stroke volume observed in the pre-compensation stage. ‘Global’ left ventricular performance is impaired as evident by the reduced stroke volume and long-axis dysfunction. The reduced stroke volume in the pre-compensatory stage may be brought about by either reduced contractile performance, restricted filling secondary to poor compliance or, in all probability, a combination of both. The preserved ejection fraction in HFpEF gives the false impression of normal systolic myocardial function and, in effect, conceals the adaptive changes that normalise the reduced stroke volume.

As stroke volume is usually not reduced in chronic heart failure, it is understandable that ejection fraction became a commonly used alternative measure of ventricular function. However, the teleological argument is that it does not matter to the organs what the ejection fraction is. As far as tissue perfusion is concerned, the ejection fraction is irrelevant; it is the net stroke volume, rather than ejection fraction, that is most pertinent in enabling tissue perfusion. Since it is long-axis shortening that mainly determines the stroke volume it probably also determines the severity of the heart failure syndrome. Furthermore, it may be speculated that although stroke volume may be normal or near normal at rest there may be blunting of the expected increase in stroke volume with exercise. This might explain why most treated and euvolaemic patients only have symptoms on exertion.

It is likely that in normal individuals the resting stroke volume is maintained near the minimum necessary to allow adequate tissue perfusion. Any greater stroke volume would be both physiologically unnecessary and inefficient. The increase in stroke volume seen in some studies [13] in heart failure may be the result of valvular regurgitation where the gross stroke volume is increased but the net stroke volume, the ejected stroke volume and tissue perfusion, is normal. If the compensatory increase in net stroke volume were inadequate, it would lead to hypotension or shock rather than the syndrome of heart failure. Presumably, some patients with Class IV heart failure are also in this category.

The mechanism by which end-diastolic volume increases is unknown. It may be speculated that an elevated end-diastolic pressure may arise from increased blood volume secondary to reduced tissue/renal perfusion, neuro-humoral activation, fluid retention and a right ventricular stroke volume transiently greater than the left ventricular stroke volume. It is suggested that
the mechanisms involved in chronic heart failure would be as follows: myocardial injury or disease, reduced stroke volume, reduced renal perfusion, fluid retention, increased blood volume, increased right ventricular filling pressures, mismatch between right and left ventricular stroke volumes, increased left ventricular end-diastolic pressure, increased left ventricular volumes and finally normalisation of stroke volume. In heart failure, the stroke volume returns towards normal by increasing the left ventricular end-diastolic volume. This would predict that additional left ventricular dilation (remodelling) would occur only if systolic function deteriorates further. It is likely that intra-vascular volume expansion occurs until left ventricular dilation causes a normalisation of stroke volume.

Only cases of severe hypertrophic disease (such as amyloid) at one end of the spectrum and dilated cardiomyopathy at the other with moderate hypertensive-hypertrophic disease in between have been modelled. More complex situations, such as a combination of hypertensive and ischaemic heart disease, have not been specifically modelled. However, this may explain some of the intermediate cases when markedly reduced long-axis shortening and moderate hypertrophy result in only a mildly reduced ejection fraction. It has been proposed that HFrEF and HFpEF are either two separate disorders or part of a continuum [7]. This study would suggest potentially three different phenotypes of myocardial (i.e. excluding valvular etc.) heart failure. Firstly, pure HFrEF as seen in non-hypertensive, young dilated cardiomyopathy patients at one end of a spectrum, secondly, pure HFpEF of hypertensive-hypertrophic disease or amyloid at the other. A third more complex group would have a combination of hypertension with left ventricular hypertrophy and myocardial infarction. This third group may be the most common and would explain the disparity in ejection fraction and symptom severity commonly seen following a myocardial infarction. Each type would not only have a continuum of the amount of hypertrophy but also a spectrum of severity from mild to severe. Furthermore, the third type would have a proportional impact of each cause. This would satisfactorily explain both the apparent continuum and the unimodal distribution of ejection fraction in heart failure as well as the morphological difference in the diverse cohorts.

Further, this study would predict that the presence of reduced ejection fraction confirms systolic dysfunction but conversely the presence of a normal ejection fraction does not rule out significant systolic dysfunction. Left ventricular dysfunction accordingly becomes easier to understand. If the left ventricle is dilated with reduced ejection fraction both systolic and diastolic function are likely to be equally impaired. If the ejection fraction is normal then the systolic and diastolic function may be either normal or abnormal. This study would predict that measures of systolic and diastolic function are likely to be closely related and that consequently either diastolic dysfunction or long-axis systolic function can be measured to support the diagnosis of HFpEF. Measuring endocardial circumferential shortening or radial thickening may be misleading particularly in the presence of concentric hypertrophy because of augmented thickening.

The term ‘left ventricular function’ when referring to ejection fraction should probably be avoided as it is imprecise and confusing. As patients with ‘systolic’ heart failure have significant diastolic dysfunction and HFpEF patients have significant systolic dysfunction the use of heart failure with reduced ejection fraction is more precise. The term ‘diastolic heart failure’ oversimplifies the pathophysiology and the phrase ‘heart failure with normal ejection fraction’ is inconsistent as many patients have a subnormal ejection fraction. At present, the term ‘heart failure with preserved ejection fraction’ is preferred.

The isolated diastolic dysfunction hypothesis has been accepted as fact by some authors and has formed the basis of research and clinical trials for more than two decades. The diastolic dysfunction premise may appear outwardly plausible but the mechanisms of heart failure remain
contentious. Any erroneous theory would have serious consequences. The misunderstanding in HFrEF appears to arise from the belief that ejection fraction is a suitable surrogate for systolic function.

In hypertensive-hypertrophic myocardial disease and HFrEF, myocardial dysfunction occurs gradually and concurrently with concentric left ventricular hypertrophy; the reduced stroke and end-diastolic volumes are compensated simultaneously so that only the post-compensated state is seen in practice. A sudden further small fall in contractility for any reason, such as arrhythmia or ischaemia, could explain the acute exacerbations observed in HFrEF.

Accordingly, all the apparent paradoxes of heart failure can be explained: important systolic dysfunction and yet preserved ejection fraction in HFrEF, the remodelling in HFrEF yet ‘normal’ end-diastolic volume, the maintained cardiac output in chronic heart failure, ‘regional’ vs. ‘global’ function and the poor correlation of symptoms with ejection fraction. The disparate results of pressure-volume loops are also elucidated as they have assumed that the control end-diastolic volume is equivalent to the un-remodelled situation. Remodelling can be seen as a positive adaptive physiological process to correct a reduction in stroke volume. Thus a controversial unifying hypothesis of chronic heart failure is proposed as a syndrome where reduced net resting stroke volume is normalised through remodelling in both phenotypes. The isolated diastolic dysfunction hypothesis is redundant.

5.6 Implications for repair and redesign

Left ventricular remodelling has been thought of as an adverse event in heart failure and so methods to repair and prevent the dilation have been proposed. These techniques include ventricular reduction surgery (Batista operation), to reduce the left ventricular end-diastolic volume and the use of an epicardial mesh (CorCap®, HeartNet®) to restrain the heart and prevent ventricular dilation. It would be predicted from this work that both these procedures would result in a reduction in stroke volume with additional neuro-humoral activation associated with an improvement in ejection fraction but not myocardial function. It comes as little surprise therefore that these methods have had disappointing outcomes. This may have been predicted before patients had been subjected to these procedures if a better comprehension of the pathophysiology of heart failure had been available.

A greater understanding of the mechanisms of both normal and abnormal left ventricular function will help the development and redesign of artificial hearts and ventricular assist devices. It will also facilitate understanding of ventricular dysfunction and so allow a better assessment of left ventricular performance than ejection fraction. An improved appreciation of myocardial function will enhance the design and evaluation of the effects of drugs and stem cell research to aid repair of myocardium and help our patients.

5.7 Summary

The mathematical modelling demonstrated supports the view that the heart is a positive displacement pump. Ockham’s razor would suggest a unifying theory would be preferable to describe the pathophysiology of heart failure with preserved and reduced ejection fraction than the current heterogeneous mechanisms proposed.

A tenable hypothesis for both HFrEF and HFrEF is that reduced stroke volume in the pre- or un-remodelled state is the initial event. Compensatory mechanism, such as intra-vascular volume expansion, occurs which leads to ventricular dilation and results in a normalisation of stroke volume.
One of the essential conclusions is that, in the presence of reduced myocardial shortening, a normal ejection fraction can occur when concentric hypertrophy is present and equally reduced ejection fraction occurs in the absence of hypertrophy. Therefore, the model predicts that to diagnose HFpEF concentric hypertrophy must be present.

The study demonstrates the mechanism by which patients could have significant contractile dysfunction yet have a normal ejection fraction. Conversely, if a reduced ejection fraction is present it does suggest significant systolic dysfunction. The model explains the paradox of heart failure with reduced long-axis function and a normal ejection fraction by demonstrating the disparity between the ejection fraction and stroke volume. It is suggested that the terms ‘ejection fraction’ and ‘function’ are not interchangeable and therefore, should not be used synonymously. The term ‘left ventricular function’ should be abandoned as it causes misunderstanding.

The mathematical model supports a new paradigm of chronic heart failure. Specifically, heart failure secondary to myocardial disease is a syndrome where reduced net resting stroke volume is normalised through left ventricular remodelling.

References


A Mathematical Model of Left Ventricular Contraction and Its Application in Heart Disease


