Heart failure is characterised by a triad comprising cardiac abnormality, exercise limitation and neurohormonal activation. The 2% of the adult population who suffer with heart failure are known to derive both symptomatic and prognostic benefit from exercise and pharmacologic neurohormonal antagonism. The existence of heart failure has traditionally been considered in the context of ischaemic, hypertensive, valvular and myopathic disease but in this article we develop the argument that patients with congenital heart disease also manifest all the pathophysiological criteria that constitute the chronic heart failure syndrome. We discuss the inherent limitations to a purely anatomical approach to congenital heart disease, bring attention to the large and rapidly growing population of adults with this condition and conclude by calling for a therapeutic approach to congenital heart disease that is based on the heart failure paradigm.

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KEYWORDS
Congenital heart disease; Heart failure; Neurohormonal activation

Introduction

It has been suggested, and it is probably correct, that virtually any form of heart disease can lead to the development of heart failure.1 The logic behind this statement stems from the fact that regardless of the injury to the heart, be it by infarction, infection, toxin, genetic abnormality, hypertension or valve disease, a common syndrome can develop that is characterised by progressive exercise limitation and the activation of neurohormone, cytokine and natriuretic peptide systems. The presence of symptoms i.e. dyspnoea and fatigue, although common, may be redundant in this definition as there is no evidence to suggest that symptom onset represents a particular pathological event. Furthermore, treatments for heart failure also appear to be beneficial in the pre-symptomatic phase.2 It might be more helpful therefore to view heart failure as a continuum from asymptomatic ventricular dysfunction with modest neurohormonal activation to severe ventricular dysfunction with symptoms at rest and marked neurohormonal activation. The appropriateness or otherwise of the term ‘failure’ in describing this condition is a moot point not further debated here.

The size of the problem

The societal burden of symptomatic heart failure is considerable as it has been estimated that 0.5–2% of the adult population in the developed world is affected at any one time, the burden of disability is substantial and the prognosis poor.3 An equal number of people are thought to have asymptomatic left ventricular dysfunction4 and as populations age the prevalence of both symptomatic and asymptomatic left ventricular dysfunction will
increase yet further. Crucially, however, advances in the treatment of heart failure are paralleling these epidemiological trends. Contemporary, evidence-based therapy for heart failure involves pharmacological manipulation of neurohormonal pathways, an approach associated not only with substantial improvements in morbidity but with regard to angiotensin converting enzyme inhibitors (ACEis), beta-blockers and spironolactone, important survival advantages. In light of these findings there appears to be a moral imperative to treat all patients with heart failure with these agents when evidence suggests that they would benefit.

Coronary artery disease, the cardiomyopathies and hypertension have been identified as the aetiological factors attributable to the majority of cases of heart failure in the developed world and although the utilisation of neurohormone antagonists in these groups could be improved the overall awareness of the importance of neurohormone antagonism is exceedingly high. There is, however, a population of patients who, despite fulfilling the defining criterion for heart failure possibly better than any other group, i.e. that of having an important ‘abnormality of the heart’, have remained somewhat overlooked with regard to an appreciation of their heart failure and its treatment. When one also considers that the population in question may number over one million in Europe alone the existence of a significant deficiency in current cardiological practice begins to emerge. So who are these patients?

Adult congenital heart disease: an expanding population

Congenital heart disease, i.e. a ‘structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance’ has an incidence of around eight cases per 1000 live births. Although some defects are lethal during infancy or childhood and many are trivial or correct spontaneously, e.g. small septal defects and patent ducts, severe and moderately severe congenital heart disease that will necessitate expert cardiological care is found in around six per 1000 live births. Increasing numbers of affected infants survive into childhood and in turn to adulthood. In fact over 80% of infants born with congenital heart disease now reach 16 years of age, a testament to major improvements in surgical technique, post-operative care and medical management in recent years. In the United States today there are as many as one million adults with congenital heart disease with approximately equal prevalence in Europe. In addition the growth of this population is linear and the mortality rate, at least in the early adult years, relatively low. This nascent demographic phenomenon is creating major issues concerning the optimal management of adults with congenital heart disease.

Limitations of surgery for congenital heart disease

Surgery is of course the cornerstone of treatment for the majority of patients with congenital heart disease, where the abiding aim is to restore cardiac anatomy to as near normal as possible, from as early an age as possible. But surgery alone may not completely resolve the anatomical problem. Firstly, several patterns of complex congenital heart disease are not amenable to surgical repair, e.g. single ventricular hearts and many cases of complex pulmonary atresia. In such cases palliative approaches are mandated and gross distortions of cardiac anatomy persist.

Secondly few patients escape the attentions of a surgeon on a second or subsequent occasion. Many palliations and repairs of complex lesions require an approach of two or more stages and further surgery is often needed due to the natural history of the condition and the development of complications many years down the line. Pulmonary regurgitation is an emerging problem for patients with tetralogy of Fallot (ToF) for example and pulmonary valve replacement several decades from definitive repair an increasing necessity.

Finally although surgical repair may appear to restore apparently normal architecture it is likely that subtle and persistent abnormalities of cardiac or extra-cardiac structure and function persist. Natriuretic peptide systems are activated two decades after routine closure of lesions as simple as atrial septal defects for instance, telling us that neurohormonal activation can occur even in the setting of near-normal hearts. These findings raise the possibility of more profound neurohormonal abnormalities following the repair of complex congenital heart disease where atrio-ventricular relationships and integrity are restored but structural abnormalities clearly endure. To illustrate this point, the patient with repaired ToF, even if asymptomatic, is likely to have marked abnormality of septal motion (where the defect has been patched), have a degree of pulmonary regurgitation (following resection and patching of the right ventricular outflow tract) and have impaired right ventricular function consequent on the pre-surgical...
disease, the effects of cardiopulmonary bypass and the post-surgical abnormalities mentioned above.

Evidence for a 'heart failure' approach to congenital heart disease

There appears, therefore, to be good reason for supposing that adults with congenital heart disease might have heart failure as conventionally defined. But, rather than developing heart failure as a result of suffering myocyte loss (myocardial infarction) or by dint of intrinsic abnormalities in myocardial components (inherited cardiomyopathies), heart failure in congenital heart disease according to this model would be sculpted, perhaps over many years, by persistent abnormalities in cardiac pressure, volume, tension and flow. Surgery has enormous potential to improve these dynamics but abnormalities will persist and should in complex ways relate to the 'degree' of heart failure, i.e. to reproducible measures of exercise limitation and neurohormonal activation.

All very well in theory perhaps, but this begs the question, what can we learn from the literature about heart failure in patients with congenital heart disease? In fact until recently, there has been, somewhat surprisingly, little attention paid to this aspect of the condition. Most reports concerning neurohormonal activation in congenital heart disease have been confined to small numbers of paediatric patients, have focussed on specific types of cardiac lesions, have been limited to the assessment of a single neurohormone system and have often been undertaken in the setting of overt decompensated heart failure. Much less is known about neurohormonal activation in adults with a broad spectrum of congenital heart disease. Reports have, in the main, considered natriuretic peptide activation in specific anatomical groups and data concerning activation of the renin–angiotensin–aldosterone and sympatho-adrenergic axes have been lacking.

More is known about that other cardinal feature of the heart failure syndrome, exercise limitation. It has been appreciated for some time that adults with cyanotic heart disease have important limitations in their oxygen uptake during exercise as do adult patients with Fontan physiology (diversion of systemic venous return from right atrium or vena cava to pulmonary artery in a univentricular heart). It is only more recently, however, that an objective limitation to exercise capacity has been noted to be a feature of congenital heart disease per se rather than to specific anatomical patterns; one centre having reported depressed maximal oxygen uptake in adults with a closed atrial septal defect, surgically corrected transposition of the great arteries, congenitally corrected transposition of the great arteries, repaired ToF, Ebsteins's anomaly and those with Fontan physiology. All six groups had a mean peak VO$_2$ of <22 ml/kg/min and was as low as 16 ml/kg/min in the Fontan group, a figure comparable to that of patients with ischaemic or dilated cardiomyopathy in New York Heart Association (NYHA) functional class III. That such varying abnormalities of cardiac anatomy can produce similar deficiencies in maximal oxygen uptake supports the notion that exercise capacity in these patients is largely dependent on extra-cardiac factors. Again this appears typical of the heart failure syndrome as currently perceived, where limitations to exercise capacity have been related to abnormalities of skeletal muscle consequent on cardiac pathology rather than to measures of central haemodynamics.

This is not to say that specific treatments for heart failure have been entirely overlooked in adults with congenital heart disease. ACEIs and other neurohormonal antagonists are utilised but there has been little hard evidence on which to base this and there are scarce data on patterns of use. Experience from the clinic and ward (our own and that of others) suggest that, historically, diuretics and ACEIs have been reserved for patients with fluid retention and significant exercise limitation, so called 'congestive' heart failure, or for those with gross abnormalities of systemic ventricular function. We have been able to identify only three reports describing the impact of antagonism of the renin–angiotensin–aldosterone axis in adults with congenital heart disease. One described a cross-over study of seven patients with systemic right ventricular physiology (surgically corrected transposition of the great arteries) given the angiotensin receptor blocker losartan, and there have been two retrospective analyses of the effects of ACEIs in 10 and 14 patients with cyanotic heart disease and systemic right ventricular physiology, respectively. All three studies reported favourable effects in some patients although the size of the studies and aspects of their design hinder statistical authority and the drawing of firm conclusions. Outpatients with mild symptoms and relatively preserved cardiac function, who constitute the majority of patients with congenital heart disease, and who could be considered to typify the conventionally defined patient with stable 'chronic' heart failure, have on the whole been overlooked in this regard. As for beta-blockers, this class of drug tends to be used for the control of...
supra-ventricular arrhythmias or hypertension in the treatment of congenital heart disease rather than to counter pathophysiological sympathetic activation. There are no reported trials of beta-blocker use in adults with congenital heart disease for the specific treatment of heart failure although there are data from the paediatric literature on the use of these agents in children with severe congestive disease.37–39

From the formulation of this thesis, and by taking the clinical evaluation of heart failure as a model, we sought to determine whether neurohormonal activation is common to adults with congenital heart disease of all types. If confirmed we thought it important to establish whether neurohormonal activation in such patients relates to common measures of disease severity such as functional class, exercise capacity and measures of ventricular function (as is typical in chronic heart failure) or whether specific patterns of cardiac anatomy are more important discriminants. Results from this study have recently been published.40 We were able to demonstrate that, taken as a whole and compared to healthy age-matched study participants, adults with congenital heart disease had activation of natriuretic peptide, sympathoadrenergic, renin–aldosterone and endothelin pathways. Activation of each neurohormonal system increased in a step-wise manner across NYHA functional class and plasma levels of natriuretic peptides, norepinephrine and endothelin-1 were elevated even in those patients without symptoms (NYHA class I). A similar pattern of activation was observed when an analysis was made according to the severity of systemic ventricular dysfunction of the patient cohort. In marked contrast to these findings differences in neurohormonal activation were not found amongst the four main anatomical groups that comprised the patient cohort (ToF, systemic right ventricular physiology, single ventricle physiology and a miscellaneous group). Other generic measures of heart failure severity, such as cardio-thoracic ratio, left and right atrial volumes and QRS width also correlated well with the degree of neurohormonal activation as well as to NYHA class and systemic ventricular function. Again by contrast anatomical group did not discriminate between these measures.

This is not to say that the type or severity of anatomical abnormality is unimportant in this respect, the central tenet to this thesis is that it is. It is highly likely that some congenital lesions will lead to greater degrees of exercise limitation and neurohormonal activation than others. In our cohort for example, those with cyanotic heart disease had worse peak oxygen consumption and higher plasma levels of several neurohormones than matched patients with acyanotic disease (unpublished data) and patients with Fontan circulation appear to have particularly poor exercise capacity.30,31 Lesion specific differences may therefore be important and certainly require further evaluation. But the theme that unites much of the work in this field is that a wide variety of cardiac lesions result in the same pathological manifestations even if some may at first appear relatively trivial.

Adults with congenital heart disease have by definition an abnormality of the heart. Given that, if looked for, many will have neurohormonal activation40 and objective evidence of exercise limitation then they should also be considered to have ‘heart failure’. Many will also manifest symptoms of their disease but this is not a prerequisite for the diagnosis of heart failure to be made or its standard treatments to be used to good effect. As there appear to be no major pathophysiological thresholds in the evolution of congenital heart disease from childhood into adulthood it would not seem unreasonable to extrapolate this concept to much younger patients. Similarities in the degree of exercise limitation and neurohormonal activation of adults with congenital heart disease and patients with heart failure due to other causes are illustrated in Fig. 1.

Implications of classifying congenital heart disease as a heart failure syndrome

What is the usefulness of this new categorisation? First and most obviously neurohormones are an important therapeutic target in patients with heart failure. Plasma neurohormone levels are of prognostic importance in this condition42 and neurohormonal activation appears to beget further neurohormonal activation by perpetuating a decline in cardiac function.45 The antagonism of neurohormonal systems appears to retard this process and consequently improves symptoms and increases survival rates.6–13 The prognostic significance of neurohormonal activation in the context of congenital heart disease ought to be ascertained although a case could be made for commencing neurohormonal antagonism, by analogy to work already published in other heart failure syndromes, even in the absence of this data. Longitudinal studies are clearly required to gauge the impact of neurohormonal antagonism on morbidity and mortality in these previously untested groups.
On the other hand some might argue that per annum mortality rates are so low in patients with congenital heart disease, 14% over 32 years in one large series of patients with ToF, that any benefit would be marginal and numbers needed treat too large to justify blanket use of drug therapy. This at first seems a reasonable position when one considers that 12-month placebo group mortality rates have been 11–13% in series where neurohormonal antagonism has shown prognostic benefit in mild to moderate heart failure. It should be remembered, however, that the majority of mortality data for congenital heart disease is collected from patients under 40 years of age whereas the mean age of patients recruited to the heart failure trials cited here was 63 years. It is also worth bearing in mind that of patients with ToF, a condition with a relatively less malignant course, around 20% have symptoms of heart failure by the end of their fourth decade of life. There is a clear need therefore for longer follow up data for patients with congenital heart disease but before these are available, age-corrected mortality data or life expectancy might be better denominators when comparisons are being made with other heart failure cohorts. As well as a target for treatment, the extent of neurohormonal activation may be useful as a guide to treatment and the relative success thereof. Plasma aminoterminal brain natriuretic peptide-guided treatment has been shown to reduce total cardiovascular events and delay time to first event versus clinically guided treatment in patients with heart failure of predominantly ischaemic aetiology. There is no such experience in congenital heart disease although neurohormone levels are known to fall, occasionally to normal, following reparative surgery. Additionally amongst patients with ToF followed up in our centre those who had undergone palliative surgery had greater neurohormonal activation than those who had...
undergone repair.\textsuperscript{40} We are not aware of any published data describing either the predictive power of pre-operative neurohormone levels on surgical outcome or the relationship of post-operative levels on short-term morbidity or mortality, although an appreciation of both may reveal important lessons.

Finally, although currently more esoteric, the study of cardiac remodelling following surgery or an appreciation of central changes in pressure, volume, stress and flow as patients age may allow unique insights into the particular factors that shape neurohormonal activation and exercise physiology in congenital heart disease. Such understanding could also have relevance to other heart failure syndromes\textsuperscript{30} and help in the refinement of existing treatments and the development of new therapeutic approaches, particularly as remodelling is increasingly seen as an important therapeutic target.\textsuperscript{51}

Putting theory into practice

It is almost certain that the prevalence of clinically important heart failure in patients with congenital heart disease is under-appreciated, indeed the population prevalence of congenital heart disease per se may be a surprise to some. The degree of heart failure in patients with congenital heart disease as in other aetiologies could be defined in terms of the extent of exercise limitation and neurohormonal activation but only if these measures are found to have prognostic significance. In keeping with current heart failure management exercise training and neurohormonal antagonism could then be considered in patients with congenital heart disease and should be assessed in appropriate randomised placebo controlled trials wherever possible. As a final point, many patients with congenital heart disease also exhibit prolongation of the QRS width and as in heart failure\textsuperscript{21} this appears to relate to mortality in certain cohorts.\textsuperscript{52}

The existence of ventricular activation abnormalities should therefore also be considered, with the aim of extending cardiac resynchronisation therapy to selected patients with congenital heart disease, an exciting new therapy showing benefits for patients with ischaemic and non-ischaemic cardiomyopathy manifesting conduction abnormalities.\textsuperscript{53}

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References


