Prevention of heart failure: further insight from B-type natriuretic peptide

Introduction

Major advances have been made in the management of heart failure (HF) over recent years. Modern day pharmacotherapy and device-based therapy have brought about significant improvements in prognosis and a reduction in morbidity.[1,2] However, despite these advances the outlook still remains a concern.[3] It is generally accepted that an effective prevention strategy is better than waiting to treat the full clinical syndrome of HF when it develops. Accordingly, increasing attention has been focused on identifying those patients who are at risk for the development of heart failure and trying to implement meaningful interventions, such as treatment of asymptomatic left ventricular systolic dysfunction (LVSD), intensive risk factor modification and frequent clinical and echocardiographic review. Such an approach may delay or even prevent the development of this syndrome.

Preventative strategies for heart failure

Initial preventative strategies have focused on individuals with asymptomatic LVSD[4,5] since a feature of the natural history of this population is evolution over time to heart failure. This group is most easily identified in those surviving myocardial infarction. Studies to date, in particular the Survive and Ventricular Enlargement (SAVE) study and the Studies Of Left Ventricular Dysfunction (SOLVD) preventative arm, have demonstrated that treatment with angiotensin-converting enzyme (ACE) inhibitors can attenuate progressive ventricular remodelling and reduce the risk of development of heart failure.[4,5] More recently, the Carvedilol Post-Infarct Survival Control In Left Ventricular Dysfunction (CAPRICORN) trial has demonstrated the additional benefit of carvedilol in this setting.[6]

The demonstration that the onset of heart failure could be delayed or prevented in the survivors of myocardial infarction encouraged a broader search to identify those at risk. Other characteristics of this at-risk group include individuals with long-standing hypertension, valvular heart disease, diabetes and a history of coronary artery disease and arrhythmia. The Hypertension Optimal Treatment (HOT), UK Prospective Diabetes Study Group (UKPFD), Heart Outcomes Prevention Evaluation (HOPE) and EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) studies, for example, have shown that either more intensive risk factor modification or treatment with ACE inhibitors can delay or prevent the onset of heart failure in selected at-risk populations.[7-10] Furthermore, screening such populations with B-type natriuretic peptide (BNP) has been shown to be a very sensitive method of defining those with asymptomatic LVSD and thereby identifying individuals who would benefit from ACE inhibition and beta blockade.[11,12] In particular, this assay may be of most value to the general practitioner, allowing effective community screening of those in need of echocardiography, albeit with poor specificity.

BNP as an early screen for LVSD

With the increased use of BNP as a screening tool for asymptomatic LVSD, it became evident that another population was being defined: those with risk factors for heart failure, a high BNP level and echocardiographically-proven normal left ventricular systolic function. Initially, it was suggested that this represented a 'false positive' group in the screen for LVSD. However, more recently a hypothesis has evolved that this group may represent an earlier stage in the natural history of ventricular dysfunction. Doppler-echocardiographic data from our unit have shown that these individuals have evidence of diastolic dysfunction.[13] Furthermore, natural history data suggest that these individuals are at risk not only of developing heart failure but also of other cardiovascular events.[13,14] Our own preliminary experience indicates that asymptomatic individuals with an elevated BNP and preserved left ventricular systolic function are more than four times more likely to develop a cardiovascular event during a follow-up period of one year when compared with a matched group with normal BNP values.[13] The single most common clinical event was the development of heart failure.

More recently, Wang and colleagues demonstrated that BNP predicted the risk of death and cardiovascular events in an unselected population of 3,346 healthy individuals and that the information provided was incremental to that obtained from other routine risk factors.[14] Indeed, multivariate analysis demonstrated that elevated BNP conferred a hazard ratio of 3.07 for the development of new onset heart failure, 1.99 for stroke or TIA and 1.91 for new onset atrial fibrillation.

The usefulness of BNP in the management of heart failure is well established, particularly in screening for symptomatic

heart failure and asymptomatic LVSD, and in providing prognostic information for those with established heart failure.[15] In these circumstances BNP is thought to increase in response to volume overload, increased ventricular filling pressures and myocardial stretch, and it counteracts these stimuli through vasodilation and natriuresis. In asymptomatic, ambulatory individuals elevated BNP may still reflect a response to strain of a more subtle nature. BNP also increases in response to myocardial ischaemia, increased ventricular mass and vascular injury.[15-17]

BNP and fibrosis

What does BNP tell us in asymptomatic individuals with preserved systolic function? It is now well described that BNP possesses anti-fibrotic activity and it has been shown to inhibit aldosterone gene expression, a hormone known to stimulate collagen synthesis.[18-21] Experimental BNP knock-out models are characterised by progressive fibrosis, suggesting that this peptide plays an important role in regulation of fibrosis.[19] It is possible therefore that the elevation of BNP in otherwise asymptomatic individuals represents a normal physiological response to an early fibrotic process which could predispose individuals to cardiovascular events, such as arrhythmias and heart failure. Changes in myocardial collagen content have been associated with increased myocardial stiffness, diastolic dysfunction and increased arrhythmogenicity.[22] Supporting this hypothesis is the observation that screened individuals with preserved systolic function and a high BNP have Doppler evidence of early diastolic dysfunction, again consistent with a fibrotic process altering ventricular compliance.[13] Moreover, the development of heart failure in our pilot study was exclusively associated with preserved systolic function, again suggesting a problem with diastolic function.

The emerging data now indicate that elevated BNP levels identify an at-risk group for cardiovascular events. Based on these observations, it is important that research is directed at the cause of BNP stimulation in this at-risk population. If a predominant stimulus were identified, then it is reasonable to speculate that more effective preventative therapy rather than intensive risk-factor modification or treatment of LVSD with ACE inhibitors could evolve to prevent or stall the development of heart failure and cardiovascular events in general. In particular, confirming an early fibrotic process in the myocardium might expand the use of specific anti-fibrotic therapies. The recent re-emergence of the use of spironolactone in heart failure is likely based more on its potential to reduce the stimulus for fibrosis.[23-24] Eplerenone, a novel anti-aldosterone agent, has recently been shown to reduce the development of cardiovascular events in those experiencing post-infarction heart failure[25] and has been shown to have anti-fibrotic action in animal models.[26] It would be interesting if this concept of counteracting the stimulus to fibrosis found an even earlier application in individuals at risk for heart failure who had normal left ventricular systolic function and elevated BNP levels.

Conclusions

It is possible therefore that BNP is providing us with increasing insight into the pathogenesis of heart failure and possibly other cardiovascular diseases. We may be able now to identify earlier stages of the natural history of left ventricular dysfunction. As a result, prevention strategies for heart failure could be applied even earlier in the natural history of this syndrome. In this regard we require more detailed investigation of the processes responsible for stimulating BNP increase in the at-risk population. Further investigation of a possible accelerated fibrotic process in the myocardium would be of interest in view of the information linking BNP to fibrosis and onwards to clinical events.

Conflict of interest

None declared.

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