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REVIEW ARTICLE

Natriuretic peptides in aortic stenosis

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Abstract Aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries. Diagnosis, risk stratification and monitoring are usually based on clinical and echocardiographic parameters. Complementary methods are needed to improve management and outcome, particularly in patients with severe asymptomatic AS, whose management remains controversial. Natriuretic peptides (NPs) have established value as biomarkers in heart failure, coronary heart disease and pulmonary hypertension. This review discusses the usefulness and prognostic value of natriuretic peptides in AS. B-type natriuretic peptide (BNP) and its prohormone (NT-proBNP) correlate with disease severity, development of symptoms and prognosis, but before they can be routinely used in clinical practice, additional prospective studies are needed.

PALAVRAS-CHAVE
Estenose aortica;
Peptideos natriuréticos;
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Peptídeos natriuréticos na estenose aórtica

Resumo A estenose aórtica (EA) é a doença valvular mais prevalente em países desenvolvidos. O diagnóstico, a estratificação do risco e a monitorização são habitualmente baseados em parâmetros clínicos e ecocardiográficos. São necessários métodos complementares para melhorar a gestão e os resultados, particularmente nos doentes com EA grave assintomática, cuja abordagem permanece controversa. Os peptídeos natriuréticos (PN) demonstraram utilidade como biomarcadores na insuficiência cardíaca, cardiopatia isquémica e hipertensão pulmonar. Esta revisão pretende discutir a utilidade e valor prognóstico dos PN na AS. O Peptídeo natriurético do tipo B (BNP) e a sua prohormona (NT-proBNP) correlacionam-se com a gravidade da

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doença, desenvolvimento de sintomas e prognóstico, mas antes do seu uso por rotina na prática clínica, são necessários estudos prospetivos adicionais.

Introduction

Aortic stenosis (AS) is the most common of all valvular heart diseases in the developed world and its prevalence may double in the next 20 years as populations age.[1] The management of AS usually involves monitoring for clinical symptoms and functional deterioration generally assessed by transthoracic echocardiography. The current treatment of choice in symptomatic AS is aortic valve replacement (AVR), but the optimal timing for surgery in asymptomatic patients remains controversial.[2–4] A watchful waiting strategy is both safe and viable, but the risk of sudden death is not negligible, reaching almost 5% per year,[5] and the association between symptom status and AS severity may not always be linear.

Biomarkers are defined as biological molecules that can be identified in a particular disease and can additionally assess the severity and prognosis or monitor the response to treatment of that disease state.[6] In valvular disease, a strong biomarker will be very useful, potentially avoiding the need for costly imaging studies and providing support to clinical management decisions, particularly the optimal timing for intervention in asymptomatic AS. Natriuretic peptides (NPs) are endogenous cardiac hormones that have shown utility as biomarkers in heart failure,[7,8] ischemic heart disease[9,10] and pulmonary hypertension.[11] This review examines the role of NPs as potential biomarkers in the management of AS, with particular emphasis on asymptomatic severe AS.

Natriuretic peptides

The NP system consists of three main peptides: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Their complex physiology will not be discussed here in detail as it has been extensively reviewed elsewhere.[12,13] BNP and ANP exist as prohormones that are cleaved into inactive N-terminal fragments (N-terminal proBNP [NT-proBNP], N-terminal proANP [NT-proANP]) and biologically active hormones (BNP, ANP) before release into the circulation (Figure 1). The N-terminal fragments are more stable *in vivo* and are often used as surrogate markers for the biologically active hormone. The predominant cardiac source of ANP is the atria, while the ventricles are the main cardiac source of BNP, although both can be synthesized in either chamber. The stimulus for ANP and BNP release is primarily myocyte stretch, but endothelin-1, nitric oxide, and angiotensin II may all have a role. ANP concentrations are more closely related to left atrial (LA) pressure and BNP to left ventricular (LV) pressure. CNP is structurally distinct from ANP and BNP; it is

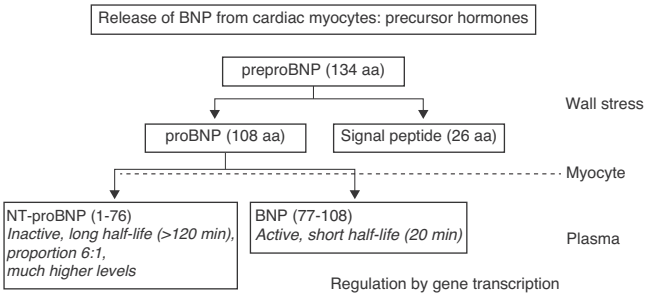

Figure 1 Release of BNP into the circulation from cardiac myocytes via precursor hormones. aa: amino acids. Adapted from Bergler-Klein.[15]

expressed to a much greater extent in the central nervous system and vascular tissues than in the heart, acting as a potent vasorelaxant and inhibitor of vascular smooth muscle proliferation and endothelial cell migration. Three natriuretic peptide receptors (NPRs) have been identified: NPR-A and NPR-B, which mediate their biological action, and NPR-C, which is a clearance receptor. NPs' cardiovascular and renal actions include natriuresis, increase in glomerular filtration, systemic vasodilation, inhibition of renin release, reduction of left ventricular remodeling, and reduction of venous and wedge pressures. Additionally, NPs, their processing enzymes, and their receptors are expressed in the cardiac valves themselves.[14]

Natriuretic peptides in aortic stenosis

On the basis of currently available evidence, the need for better risk stratification of asymptomatic patients with moderate to severe AS is widely accepted, and biomarkers may play an important role here. The ideal biomarker should be easily and reliably measured, reflect disease severity, increase with disease progression, and discriminate between patients in whom symptoms will or will not develop in the short to medium term. In comparison with controls, AS has been strongly associated with increased NP levels.[16,17] In AS, pressure overload induces significant expression of BNP and NT-proBNP.[18,19] ANP levels have also been demonstrated to be raised in proportion to LV end-systolic wall stress in patients with AS.[20]

Severity of aortic stenosis

Several studies have shown a correlation between plasma NP levels and severity of AS.[16,21–24] This is the case for both BNP and NT-proBNP. Although there is a correlation between