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Clinical Benefits of the Classification of Cardiovascular Patients based on the Polymorphisms of Natriuretic Peptide Receptor Genes

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Abstract

Natriuretic peptides (NPs NP) are supposed to be important biomarkers as well as therapeutic medicines for cardiovascular diseases, however, there are still some controversies blocking the clinical application of NPs. Especially, natriuretic peptide receptors (NPRs) greatly interfere with the indicative efficiency, therapeutic effectiveness, clinical dosage, and medication time of NPs. Herein, we propose that the classification of cardiovascular patients will effectively promote the clinical utilization of NPs as either biomarkers or medicines. Generally, NPs bind to natriuretic peptide receptor A and B (NPRA and NPRB) to activate cellular signalings, but natriuretic peptide receptor C (NPRC) is mainly responsible for the clearance of NPs. So, it is expected that high NPs-sensitivity group includes individuals carrying the alleles that result in higher activity of NPRA and NPRB and lower activity of NPRC, while low NPs-sensitivity group is the opposite. Theoretically, the classification will improve the diagnostic accuracy of NPs for cardiovascular patients, and personalized administration of NPs-related medicines will benefit more individuals in order to achieve both of the maximum therapeutic efficacy and the minimum side effects.

Keywords: Cardiovascular diseases; Natriuretic peptide; Natriuretic peptide receptor genes; Diagnosis; Therapy

Introduction

World widely speaking, cardiovascular impairment becomes one leading medical problem of the aged people, and efficient therapeutic medicines are especially needed by millions of the elders suffering from cardiovascular diseases [1,2]. Natriuretic peptides (NPs) are considered as important biomarkers as well as therapeutic medicines for cardiac disease, heart failure, coronary disease, and hypertension, because of their multiple biological effects (such as diuresis, natriuresis, vasodilation, and so on), convenient detection, and low cost [3-5]. NPs can serve as quantitative biomarkers for predicting cardiovascular diseases, and the concentration of serum NPs is helpful for evaluating the therapeutic efficacy for cardiovascular diseases [4-8]. Moreover, some NPs-based medicines, such as Nesiritide, Ularitide, Carperitide, and CDNP, have been used to treat cardiovascular diseases in some countries [9-12].

However, there are still many difficulties interfering with the clinical application of NPs. For example, the diagnostic accuracy of NPs for cardiovascular diseases is not very stable, and the therapeutic efficacy of NPs-related medicines is variable owing to some uncertain factors in vivo [3,13]. Moreover, although prolonged medication time and higher dosage of NPs are necessary for achieving the expected therapeutic efficacy in some cardiovascular patients, these measures may result in severer side-effects in other patients [3,14]. Therefore, the optimization of the drug dose and the medication time of NPs are emergently needed in clinics. Prospectively, the genetic variability in the natriuretic peptide pathway is critical for improving the clinical efficacy of NPs as either diagnosis biomarkers or therapeutic medicines.

Classify Cardiovascular Patients based on the Polymorphisms of Natriuretic Peptide Receptor Genes

Atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) are three kinds of NPs [15,16]. Interestingly, it should be noted that the indicative and therapeutic efficacy of NPs are greatly dependent on the natriuretic peptide receptors (NPRs) in individuals [16,17]. Generally, the natriuretic peptide receptor A and B (NPRA and NPRB) are responsible for receiving the NP signalings, while the natriuretic peptide receptor C (NPRC) is responsible for the clearance of NPs [13,18-20]. NPRA, NPRB, and NPRC are encoded by the genes NPR1, NPR2, and NPR3, respectively, and the genetic variations of NPR1, NPR2, and NPR3 can result indifferent activity of NPRs and consequently influence the clinical efficacy of NPs in individuals [13,21].

The involvement of natriuretic peptide receptor genes in cardiovascular diseases

First, an eight nucleotides deletion in NPR1 gene is associated with the transcriptional activity of NPR1 gene and leads to the reduced activity of NPRA [21-24]. The single nucleotide polymorphism (SNP) G1023C of NPR1 alters the conformation and the activity of NPRA [21,25]. Several other variations in NPR1 gene influence not only the function of NPRA but also the concentration of ANP and BNP *in vivo*, significantly relevant to the pathogenesis of cardiovascular diseases [21,23,26-28]. Second, several SNPs in NPR2 significantly influence the concentration and the activity of NPRB, and NPR2 is an important candidate gene interfering with the therapeutic efficacy of NPs-related medicines [13]. The SNP C2077T of NPR2 gene is associated with the susceptibility and the severity of cardiovascular diseases [29]. Third, the SNP C–55A of NPR3 gene influences the activity of NPRC,

associating with the ANP concentration *in vivo* and the incidence of hypertension in individuals [21,30,31].

Therefore, the polymorphism of NPR genes regulate the nucleotide sequence, transcriptional efficiency, concentration, structure, and activity of NPRs in individuals, potentially influencing the concentration, clearance rate, and functional efficiency of NPs *in vivo*. Thus, cardiovascular patients with similar NPs concentration possibly show varied pathological characteristics when the NPR genes are differentiated among them, as a result the accuracy of NPs biomarkers are attenuated. Similarly, NPs-related medicines may have different therapeutic efficacy in cardiovascular patients with different NPR genotypes.

Different NPs-sensitivity gradients of cardiovascular patients

The above analysis indicates that analyzing the NPR genotypes may improve the clinical efficacy of NPs-based diagnosis and therapeutics for cardiovascular diseases. Briefly, we propose that it is necessary to classify the cardiovascular patients into different NP-sensitivity groups, from low NP-sensitivity to high NP-sensitivity, based on the polymorphisms of NPR genes. It has been shown that the activity of NPs is dependent on their binding to NPRA and NPRB, and that the clearance of NPs is promoted by NPRC [13,18-20], so it is expected that higher activity of NPRA and NPRB and lower activity of NPRC may lead to higher sensitivity to NPs, while lower activity of NPRA and NPRB and higher activity of NPRC may lead to lower sensitivity to NPs.

Henceforth, individuals can be divided into high NPs-sensitivity group and low NPs-sensitivity group. Theoretically, high NPs-sensitivity group includes individuals carrying the NPR alleles that result in higher activity of NPRA and NPRB as well as lower activity of NPRC, potentially leading to higher sensitivity to NPs *in vivo*. Whereas, low NPs-sensitivity group includes individuals carrying the NPR alleles that result in lower activity of NPRA and NPRB as well as higher activity of NPRC. Then, personalized medications and differentiated therapeutic procedures may benefit more cardiovascular patients aiming to improve the predictive efficacy and to achieve better therapeutic efficacy and fewer side effects.

The current difficulties hindering the classification

The methodologies that are suitable for detecting the polymorphisms of NPR genes include primer designing, PCR amplification, electrophoresis, DNA sequencing, and so on. However, the research focusing on the polymorphisms of NPR genes is still inadequate for guiding the clinical utilization. One main difficulty is that most of the known studies only investigated a single sequence variant and sometimes obtained negative results [18,28,29,32,33]. It should be noted that the effect of a single sequence variant might be very limited, but the combined and systematic analysis may be necessary for obtaining more significant outcomes [21,34]. Another frequent difficulty disturbing the effectiveness of the analysis is that many studies employed a relatively small patient sample size, which may be not enough to give a convinced determination of some polymorphism sites, especially those sites of rare frequency [21]. So, it is expected that the international collaboration of researchers are required to investigate the synergistic effects of the polymorphic sites of NPR genes in sufficient amounts of individuals. This may greatly improve the understanding of the potential gene–gene interactions associating with the susceptibility to cardiovascular diseases and the pharmacogenetic response to NPs-based medicines. Besides, it is also suggested that analyzing rare polymorphism sites in some susceptible families is of great importance to explain the negative results as described previously.

Discussion

In brief, as concisely shown in Figure 1, the classification may improve the diagnostic accuracy of NPs for cardiovascular diseases. Although NPs are supposed to be efficient biomarkers for predicting cardiovascular diseases, individuals in low NPs-sensitivity group may have severer pathologies than those in high NPs-sensitivity group when the concentration of NPs is identical among them. Similarly, cardiovascular patients with similar pathologies may have significantly varied NPs levels *in vivo* between high NPs-sensitivity group and low NPs-sensitivity group. As a result, these problems may inevitably disrupt the diagnostic accuracy of NPs. Therefore, more attention should be paid to the clinical diagnosis of individuals in low NPs-sensitivity group, and other more suitable diagnostic methodologies rather than NPs biomarkers should be applied to the early diagnosis of their susceptibility to cardiovascular diseases.

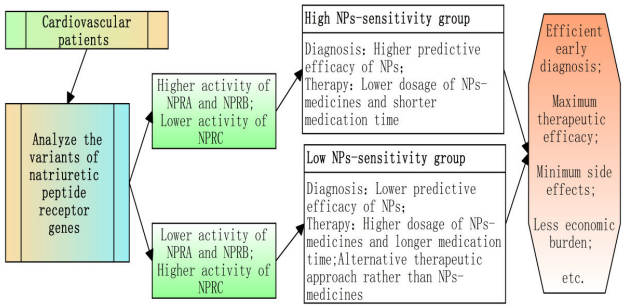

Figure 1: Schematic representation for the proposed classification of cardiovascular patients based on natriuretic peptide receptor genes and its clinical implications

The classification may be helpful for screening cardiovascular patients who are sensitive to NPs-related medicines. For patients in high NPs-sensitivity group, NPs-related medicines can be very robust; however, for those in low NPs-sensitivity group, NPs-related medicines may be ineffective, delay the therapy, and cause unnecessary economic burden. Consequently, it is better to administrate NPs-based medicines to patients in high NPs-sensitivity group at the earliest stage, while alternative medical approaches rather than NPs-based medicines should be applied to individuals in low NPs-sensitivity group. Further, in order to achieve maximum therapeutic efficacy as well as minimum side effects, individuals in low NPs-sensitivity group need higher dose of NPs-based medicines and longer medication time, while those in high NPs-sensitivity group need lower dose and shorter medication time.

Besides, because abnormal metabolism of NPs contributes to the development of cardiovascular diseases in a large number of individuals, the classification has great implications in the early prevention of cardiovascular diseases. In other words, the early screening of individuals who are very susceptible to cardiovascular diseases and the subsequent prevention measures are very important to decrease the severity and mortality of cardiovascular patients. For

this aim, analyzing the genetic variations of NPRs will certainly contribute to the early prevention of cardiovascular diseases [18,21,30].

Conclusion

Because NPR genes play important roles in the diagnosis and therapy of cardiovascular diseases, the classification of cardiovascular patients based on the polymorphisms of NPR genes will have multiple clinical benefits, which makes it possible to administrate personalized medical approaches for cardiovascular patients with different NPR genotypes. The classification may improve the diagnostic efficiency of NPs, screen individuals sensitive to NPs-based therapy, and guide the clinical administration of NPs-related medicines. In summary, on the basis of the argument that prevention is better than cure in geriatric medicine [35], the classification will especially contribute to the early diagnosis of cardiovascular diseases and the administration of NPs-related medicines.

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