Genes and acquired disease: beta-adrenoceptor polymorphisms and heart failure

The selfish gene has little interest in the welfare of its host after reproduction[1]. This teleological concept, albeit simplistic in the present context, may partly explain why the neuroendocrine compensatory mechanisms that have evolved for congestive cardiac failure, a condition affecting mostly older patients, are fundamentally flawed. One of these misguided compensatory responses is chronic activation of the sympathetic nervous system. This not only causes down-regulation of beta-receptors and their uncoupling from signal transduction pathways (the latter resulting from up-regulation of beta-adrenoceptor kinases and increased activity of the G-inhibitory protein G\textsubscript{i}[2]; the former from a reduction in the half-life of beta-receptor mRNA[3]) but is directly cardiotoxic (due possibly to adrenoceptor-mediated increases in intracellular calcium and altered macromolecular synthesis[4]). The extent of these changes correlates with the degree of adrenergic stimulation. The clinical consequences are a loss of exercise tolerance, progression of left ventricular dysfunction and an increased prevalence of arrhythmia and sudden death. The documented functional and survival benefits of long-term therapy with beta-adrenergic receptor antagonists are final proof positive that nature does not always know best[5,6].

Given the importance of this system in the pathogenesis of chronic congestive heart failure, it might be predicted that mutations or polymorphisms of beta-adrenoceptor genes would modulate survival. Several polymorphisms of the beta\textsubscript{2} receptor have been identified. The most impaired variant of these is due to a threonine to isoleucine (Ile) switch at amino acid 164 in the 4th transmembrane domain of the receptor. This receptor demonstrates a small decrease in binding affinity for catecholamines, a substantial decrease in basal and stimulated adenyl cyclase activities due to defective coupling of the receptor to the stimulatory G protein and impaired agonist promoted sequestration[7]. In a study of 259 patients with ischaemic or dilated cardiomyopathy the 1 year survival free from death or cardiac transplantation of Ile-64 patients was 42% compared with 76% for patients with the wild type beta\textsubscript{2} receptor[8]. This finding seems counterintuitive since it might be hypothesized that the more active receptor would be associated with the worst outcome. However, beta\textsubscript{1} and beta\textsubscript{2} receptors may have different roles in heart failure. Beta\textsubscript{2} receptors constitute just 20% of the myocardial beta receptors in the normal heart and are not downregulated to the same extent as beta\textsubscript{1} receptors in heart failure[9–11]. In adult rat ventricular myocytes beta\textsubscript{1} receptor stimulation increases apoptosis whereas beta\textsubscript{2} receptor stimulation inhibits it[12]. The clinical effects of beta-receptor antagonism have been tested for beta\textsubscript{1} selective or non-selective agents; the effects of selective beta\textsubscript{2} antagonism have not been studied.

The study by Borjesson et al.[13] published in this issue is of particular interest since it examines the effect on survival of a polymorphism of the beta\textsubscript{1} receptor, a substitution of serine for glycine at position 49 (Ser49Gly). The survival analysis was performed on a cohort of 184 patients with heart failure identified as part of an epidemiological study of idiopathic dilated cardiomyopathy. It should be pointed out that, as acknowledged in the text, because of the methodology of the study, a significant proportion of these may have been ischaemic in aetiology. This is borne out by the demographics of the cohort in which the mean age was 10–15 years higher than most dilated cardiomyopathy cohorts, in spite of an upper age limit for the epidemiological study of 65 years, and by the finding of coronary artery disease in 15% of the small proportion of the total number who underwent coronary angiography. The study should therefore be regarded as relevant to cardiac failure of mixed aetiology rather than being exclusive to dilated cardiomyopathy. The Ser49Gly variant was common, being present in 33% of patients, and a similar prevalence was found in control subjects. Survival (free from death or cardiac transplantation) was significantly better among
Ser49Gly patients than among those with the wild type (77% vs 54%). Following Cox regression analysis controlling for relevant variables including age, ejection fraction, heart rate and serum sodium, the survival difference was no longer significant (confidence intervals for relative risk 0.99–4.16), but the findings are nonetheless provocative.

Of particular interest is the survival curve in relation both to the presence of the Ser49Gly variant and beta-blocker treatment. The Ser49Gly variant was associated with improved survival both in patients receiving and those not receiving therapy. Survival was greatest in Ser49Gly patients receiving beta-blockers and lowest in wild type patients not receiving therapy. What is striking is that survival was similar in untreated Ser49Gly patients and treated wild type patients. This reinforces the suggestion that the Ser49Gly variant may be conceptualized as a form of ‘inborn’ beta-blockade which is protective in cardiac failure.

There are a number of limitations to this study, including the small number of patients and the retrospective nature of the analysis. In particular, in contrast with the situation regarding the Ile-64 variant of the beta receptor, the functional consequences of the Ser49Gly polymorphism are as yet unknown and studies thereof are in progress. In addition, it is not stated how many of the patients were homozygous for Ser49Gly and, probably because of the small numbers involved, there is no comparison between homozygotes and heterozygotes to determine whether there is evidence of a gene–dose effect. Therefore the true significance of these findings needs to be established both by elucidation of the biological mechanisms of the observed differences, and further clinical studies carried out prospectively on larger populations. These tantalizing initial findings of Börjesson et al.[13] should provide ample encouragement for such endeavours.

What of the clinical significance of these results? Major clinical implications are not immediately apparent since wild type and Ser49Gly patients benefited equally from beta-blocking therapy. However, in view of the relatively small numbers of patients studied, the limitations of retrospective subgroup analyses and the lack of knowledge of the molecular biological effects of the polymorphism, the possibility that there is a differential response to beta-blockade cannot be excluded. This may have implications for dose-ranging or selection of beta-blocker subtype. Knowledge of the survival implications of a particular genotype could also influence clinical decision making such as timing of referral for cardiac transplantation. However, the influence of beta-adrenoceptor genotype on survival in any individual will be determined by a host of additional genetic factors as well as environmental influences. The overall influence of any single polymorphism is likely to be small. Emerging DNA chip technology will allow the analysis of enormous numbers of genes to be performed quickly and cheaply[14]. It may ultimately be possible, notwithstanding the clinical, ethical and legal issues involved, to determine a composite risk assessment based on the aggregate effects of a large number of relevant mutations and polymorphisms. This will depend on the accurate collection of relevant clinical data, a task which is likely to prove considerably more difficult than the genetic analysis itself[15], and one to which the work of Börjesson and colleagues reported in this issue makes an interesting and useful contribution.

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References
Semicarbazide-sensitive amine oxidase and mortality in chronic heart failure

See page 1859 for the article to which this Editorial refers

A 5-year follow-up clinical investigation, as reported in this issue, has shown that mortality in patients with chronic heart failure is significantly increased in the subgroup of patients with higher serum semicarbazide-sensitive amine oxidase (SSAO) activity than in those with low SSAO activity[1]. This intriguing finding not only suggests that serum SSAO could become an independent prognostic marker for chronic heart failure, but it also raises the interesting notion of a potential involvement of SSAO-catalyzed deamination in the pathogenic process related to the morbidity and mortality of patients suffering with cardiovascular disorders.

SSAO is an enzyme, or group of enzymes, residing predominantly in the plasma membrane of endothelial, vascular smooth muscle and adipose cells[2]. The enzyme contains copper and 6-hydroxydopa quinone (TOPA) as cofactors. Therefore, hydrazine compounds, such as semicarbazide, are generally potent at inhibiting SSAO activity. This is distinctly different from the well-known monoamine oxidases, which are mitochondrial flavine-containing enzymes. SSAO was initially found capable of deaminating benzylamine and was thus called benzylamine oxidase. However, benzylamine is not present endogenously. Methylamine and aminoacetone have now been established as the endogenous substrates for SSAO. This discovery has stimulated vigorous research of the enzyme.

The physiological function of SSAO was initially thought to be simply to detoxify xenobiotic amines. Recently, SSAO-mediated deamination has been shown to be co-localized with GLUT-4 transporter in adipocytes. The hydrogen peroxide generated from SSAO-mediated deamination was found to be involved in the regulation of glucose transport[3]. It was also suggested that SSAO might play a role in connective tissue matrix development and maintenance and specifically the development of normal elastin in vascular smooth muscle cells[4]. Interestingly, totally independent research has revealed that the primary structure of a protein called VAP-1 (vascular adhesion protein-1) is identical to that of SSAO[5]. VAP-1 is also capable of deaminating amines. VAP-1, which contains polysialic acid, induces cell adhesion and regulates lymphocyte trafficking. It would be intriguing to know whether or not the dual functions of this protein act in a concerted fashion. VAP-1 level is up-regulated during certain types of chronic inflammation[6]. Formaldehyde is a well-known potent inflammatory agent, and yet it is a deaminated product of methylamine as catalyzed by SSAO.

The first observation of the association of SSAO with damage to the heart followed from studies of a cardiovascular toxin, allylamine. Allylamine is an industrial chemical and is known to cause extensive and progressive vascular and myocardial lesions in several mammalian species. Allylamine (CH₂=CHCH₂NH₂) is actually converted by vascular SSAO to acrolein (CH₂=CHCHO), an extremely toxic agent[7]. This vascular toxicity of allylamine could, therefore, be completely prevented by selective SSAO inhibitors as shown in experimental animals.

Unlike allylamine, methylamine and aminoacetone are present endogenously. Deamination of methylamine and aminoacetone leads to the production of...