Found in translation: metoprolol improves survival more than carvedilol in a mouse model of inherited dilated cardiomyopathy

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This editorial refers to 'Therapeutic effect of β-adrenoceptor blockers using a mouse model of dilated cardiomyopathy with a troponin mutation' by D.-Y. Zhan et al., pp. 64–71, this issue.

Over the past two decades, many mutations responsible for inherited forms of dilated cardiomyopathy (DCM) have been identified, providing important pathogenic insights. The first paradigm for explaining the role of genes in the mechanisms of ventricular dilation and dysfunction was elaborated after the identification of mutant proteins of the cytoskeleton that were implicated in defects of transmission of contractile force.1 In the year 2000, a mutation of a sarcomeric protein causally linked to DCM, a deletion (∆Lys210 or ∆K210) of the gene TNNT2 resulting in the loss of a lysine residue within a portion of the Ca2+-sensitive binding domain of troponin T (TnT), was described for the first time.2 Two years later, in isolated cardiac muscle fibres,3 it was demonstrated that the functional consequence of this mutation is a decrease in the Ca2+ sensitivity of cardiac muscle contraction, suggesting a deficiency of force generation by the sarcomere as the primary mechanism of this type of DCM. The idea was proposed that both mechanisms, cytoskeletal and sarcomeric, may be implicated in the origin of DCM. Either the reduction of contractile force or its transmission leads to ventricular dilation as a compensatory mechanism for the decrease in stroke volume.

In recent years, new evidence about clinical characteristics, prevalence, and risks of different mutations in patients with inherited DCM has been collected.4–7 TnT mutations (e.g. ∆Lys210) seem to be particularly prevalent in cases with early-onset ventricular dilatation and dysfunction, leading to severe heart failure (HF) with poor outcome and, not infrequently, with sudden cardiac death (SCD).

In the study reported by Zhan et al.,8 a knock-in mouse model with the deletion ∆K210-TNN2T that previously allowed for in vivo confirmation of the decreased myofilament Ca2+-sensitivity9 was employed to compare changes in cardiac structure and functional effects of three different β-blockers—atenolol, carvedilol, and metoprolol—at doses optimized to achieve comparable resting heart rates. Survival, remodelling, fibrosis, and left ventricular (LV) systolic function were improved by metoprolol administration, but not by carvedilol or atenolol.

More than 50 years after the discovery of propranolol, clinical and basic research on β-blockers still seems pertinent. Real life often shows that these agents, despite proven efficacy in indications such as chronic HF, often are under-utilized and that, at least in part, the ultimate mechanisms implicated in clinical effects are not well understood. In addition to selectivity in the blockade of the different adrenergic receptors (ARs) and beyond the classic effect known as ‘β-blockade’, many of the therapeutic peculiarities of β-blockers might rely on variable degrees of many other diverse effects. This pleiotropism is frequently invoked at the bedside, principally when differences in efficacy are difficult to explain.

Improvement in LV function and survival in patients with chronic HF has been demonstrated in large-scale randomized clinical trials (RCTs), both with metoprolol (selective β1-AR blockade) and carvedilol (combined β1-, β2-, and α1-AR blockade),10 in the Cardioliol or Metoprolol European Trial (COMET), carvedilol was superior to metoprolol in mortality reduction in chronic HF patients.11 However, it is not clear whether an equivalent degree of β-blockade was achieved with both agents and whether carvedilol and metoprol differ in more characteristics than they have in common with respect to their AR interactions, sympathetic agonism, lipophilicity, central nervous system (CNS) effects, antioxidant activity, and others. It was suggested that non-specific β-blockade of carvedilol, vasodilatation through α1-AR blockade, and antioxidant activity could confer benefit beyond β1-blockade alone. However, it is difficult to accept that a clinical trial may demonstrate the particular mechanisms that are involved in cardiac function or survival improvement, especially when heterogeneous aetio-pathogenic subgroups composed the final population to be studied.

At the bench, in the experimental model presented here,8 all three β-blockers employed had comparable significant
negative chronotropic and hypotensive effects on mutant mice, and phosphorylation of Ser-16 of phospholamban was also completely inhibited by each of the three agents. So, it can be assumed that these agents exert an equivalent level of sympathetic β-blockade at the myocardium.

It is also relevant that this mouse model of inherited DCM often develops SCD due to ventricular fibrillation. The ΔK210-TNNT2 mice exhibit a notably homogeneous prolongation in the QT interval that might be involved in the high incidence of ventricular fibrillation. The fact that metoprolol, but nor carvedilol or atenolol, was found to shorten the QT interval may have had an important influence on survival. In addition, metoprolol reduced fibrosis and probably activated the vagal nervous outflow, which was indirectly measured by determining the variability of the R-R interval. Although neither the β-blockade at CNS sites nor the vagal nervous activity is directly measured in this work, previous experimental data suggested that β-blockers with some degree of lipophilicity penetrate the blood–brain barrier and have effects on vagal activity, which may be of importance for prevention of ventricular fibrillation. However, it also has been shown that CNS effects of highly lipophilic metoprolol are quite attenuated when given systemically in comparison with intracerebroventricular administration. Another limitation of this hypothesis is that a greater dose of carvedilol, which is at least moderately lipophilic, has no impact on survival over lower doses. Also interesting is that in the same ΔK210-TNNT2 genetic model, propranolol, more than twice as lipophilic as metoprolol with important membrane-stabilizing effects and proven efficacy in reduction of ventricular arrhythmias generated mainly in the ischaemic context, has no impact on survival when tested by the authors of the current study.

Finally, as the authors correctly state, it is very difficult to directly compare the results from clinical and experimental studies. But it is also difficult to compare results from different animal models. Carvedilol and metoprolol, employed at equivalent doses in a genetic model characterized by sympathetic hyperactivity-induced HF, led to comparable cardiac remodelling and improvement of cardiac function and survival, and a plausible mechanistic explanation was also found for this equivalence. Models of disease in basic research as aetiologies in clinical studies are transcendental.

The use of gene-targeted animal models for therapeutic evaluation represents an opportunity to provide unique insights into the pathogenesis and mechanisms of different therapies for some rare human genetic diseases, such as TNNT2 mutations. Genetically modified mice are created more equal than human beings and, in addition, they express disease and develop outcomes in shorter periods of time. The possibility of in-depth analysis of animals accompanied by reductions in either follow up and sources of variability are clear advantages over human RCTs. Genetic models for treatment evaluation are probably closer to haute-couture than to the prêt a porter levels of evidence offered by RCT. However, like in clinical trials, problems arise when trying to export results, in this case from modified mice, to human individuals that present a heterogeneous reality. It is convenient to remember, too, that the ‘just one abnormal protein’ scheme is an excessive simplification even for single-gene diseases. On the contrary, RCTs suffer from their known limitations, including larger sample sizes, lack of benefit or even risks to some proportion of the participants, representation of the studied population (distribution of gender, ages, and aetiologies), and many others, but they still provide the best quality of evidence for the demonstration of differences in efficacy of therapies. Do not try to draw too many mechanistic conclusions from an RCT, and do not infer too much about efficacy in humans from a basic research study. Look at both sides of research, translate, and enjoy.

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References