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EDITORIAL

New technologies, new therapies: toward personalized medicine in heart failure patients?

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This editorial refers to 'Myocardial gene expression profiles and cardiodepressant autoantibodies predict response of patients with dilated cardiomyopathy to immunoadsorption therapy'†, by S. Ameling *et al.*, on page 666

During the last decade, the therapeutic management of patients with left ventricular systolic dysfunction has improved. The major goals of the treatment are to reduce the mortality and the morbidity, to improve symptoms, and, if possible, to induce a reverse remodelling of the left ventricle.[1] There is indeed a direct link between survival and left ventricular ejection fraction (LVEF). Drugs such as beta-blockers[2,3] or, more recently, ivabradine,[4] or interventions such as resynchronization therapy[5] have been associated with a significant reverse remodelling in heart failure patients. However, the responses to these different treatments are highly variable. Some patients may undergo major reverse remodelling with a dramatic increase in LVEF (i.e. responders), while in others the LEVF remains unchanged (i.e. non-responders). Early identification of responders/non-responders may be associated with a better therapeutic management.

In patients with dilated cardiomyopathy (DCM), a possible physiopathological role for circulating autoantibodies against cardiac proteins has been suggested. Immunoadsorption (IA), by removing these circulating autoantibodies, could significantly improve symptoms and LVEF.[6–8] The long-term effects of IA have recently been published.[9] Other approaches aimed at neutralizing autoantibodies have also been reported.[10,11] However, these encouraging results on intermediate parameters were found in small series of patients, and currently no study has demonstrated a significant effect of IA on mortality or on morbidity. A double-blind multicentre study investigating the effect of IA on LVEF in 200 patients is still recruiting (ClinicalTrials.gov identifier: NCT00558584). Another international prospective and retrospective study will provide us with more information about the prevalence and the pathophysiological role of cardiac beta$_1$-adrenoceptor autoantibodies in different aetiologies of left ventricular systolic dysfunction (not only DCM but also myocarditis, post-myocardial infarction, and hypertensive cardiopathies).[12] The exact mechanisms of the beneficial effects of IA are not completely understood, but may be related either to the removal of depressant cardiac antibodies or to the modulation of the myocardial inflammation or the immune system. However, IA is an expensive and invasive method with a heterogeneous response, with a greater effect in patients with cardiodepressant autoantibodies.

Ameling and colleagues have now reported on the possibility of improving the selection of those patients likely to respond to IA.[13] Patients with DCM included in their study were well characterized and were receiving an optimal medical treatment for left ventricular systolic dysfunction. In their study population, 60% of the patients were responders to IA. Ameling *et al.* compared the genetic expression profiles in samples from endomyocardial biopsies of patients with DCM and of controls. These authors specifically analysed the genetic expression profile in responders and in non-responders to IA. They found that the combination of a genetic profile and the presence of autoantibodies in serum with negative inotropic effect, quantified *in vitro* in isolated cardiomyocytes, was the most powerful association of parameters for the selection of responders to IA. When combined with the negative inotropic effect of autoantibodies, four genes robustly discriminate responders from non-responders at baseline, with two up-regulated genes, RANBP1 and RGS10, involved in GTPase activity, and two down-regulated genes, UBE3B and USP22, components of the ubiquitin–proteasome system.

As acknowledged by the authors, these interesting results were obtained in a relatively small number of patients in a selected population with DCM and with circulating negative inotropic autoantibodies. A larger prospective study is required in order to validate their results. In fact, due to individual variability, the differences in expression of the four genes were not found to be statistically significant by quantitative real-time PCR. Furthermore, if these results could be confirmed, a study in a less selected

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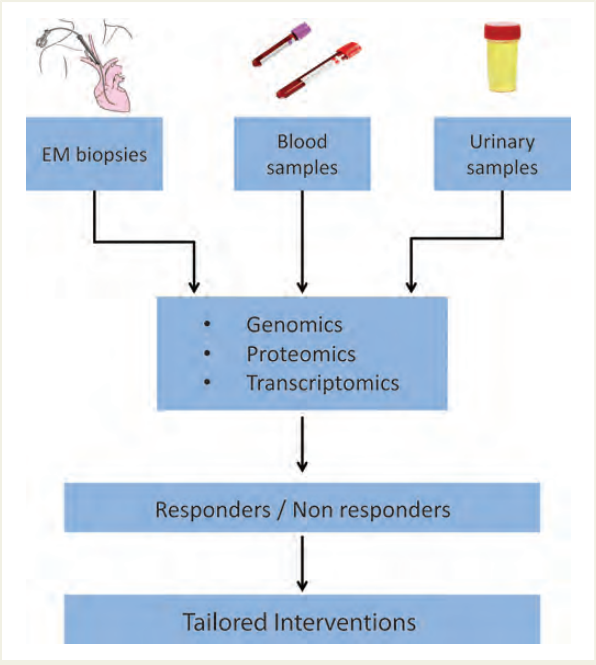

Figure 1 A hypothetical scheme for the selection of responders to heart failure treatments. EM, endomyocardial biopsies.

population would be required, including patients with coronary artery disease or inflammatory or toxic cardiomyopathies. In addition, the selection of responders relies on endomyocardial biopsies, an invasive method, which cannot be used easily in clinical practice. Further studies investigating the blood signature of responders/non-responders using white blood cells for transcriptomic analysis, performed in a few hours, could be of interest. Additional information on blood profiling could also be obtained from proteomic[14] or microRNA (miRNA) analyses.[15] Recent studies have indeed demonstrated correlations between gene expression in endomyocardial tissue and the concentration of proteins/miRNAs in blood samples.[16] Genomic analyses aimed at the identification of responders have also been reported.[17] Finally, in addition to blood samples, urinary samples may be useful for the profiling of heart failure patients.[18] It can be speculated that, in the not too distant future, these strategies will help us to select DCM patients who are responders not only to IA but also to other heart failure treatments for which a heterogeneous response is observed. This will set the stage for tailored interventions (*Figure 1*). The early identification of non-responder patients may improve their therapeutic management. A more aggressive treatment, such as cardiac transplantation or left ventricular assist device implantation, could be proposed to these selected populations.

In conclusion, Ameling and colleagues have provided us with new research directions that could have a significant impact for the management of patients with DCM. Results of these studies using new technologies improve our knowledge of the pathophysiology of cardiac diseases and may hold the key to a more personalized medicine in the future.

Conflict of interest: none declared.

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