Future developments in the MECKI score initiative

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Abstract
The Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) score is a validated prognostic score for heart failure with reduced ejection fraction which combines commonly available clinical and metabolic parameters with two cardiopulmonary exercise test derived prognostic measurements. It has been validated to predict prognosis and to aid clinical decision making and it has been shown to be superior in predicting mortality compared with other commonly used prognostic scores for heart failure. In the future it would be valuable to establish whether the score holds true also in other settings, and in particular in under-represented groups – the elderly, women, and people of different ethnic backgrounds – and in other heart failure syndromes. In future it may be extended to assess its value in the presence of a range of co-morbidities such as chronic obstructive pulmonary disease, pulmonary hypertension and frailty and cachexia as well as in other conditions such as hypertrophic cardiomyopathy, amyloid, asymptomatic left ventricular dysfunction and hypertension. It may also be a candidate end-point for adaptive trials designed to prove an improvement in the MECKI score as an approvable interim end-point whilst larger mortality and morbidity trials are still underway.

Keywords
Heart failure, exercise capacity, prognosis, MECKI score

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The MECKI score
The Metabolic Exercise combined with Cardiac and Kidney Indexes (MECKI) score is, as many articles in this issue attest, a useful prognostic score for heart failure and reduced ejection fraction, as it combines parameters derived from a cardiopulmonary exercise test with simple clinical and metabolic parameters which are very widely available. It has proven to be a very elegant and successful way of predicting prognosis and aiding clinical decision making in a variety of clinical settings and in different patient sub-groups including recovered heart failure with mid-range ejection fraction. In 6112 heart failure patients its prognostic accuracy was compared with other composite risk scores, the HF Survival Score and the Seattle Heart Failure Model score, in terms of their ability to predict the two- and four-year combined endpoints of cardiovascular death, urgent cardiac transplantation, or ventricular assist device implantation. The prognostic accuracy of the MECKI score was significantly superior to both alternative scores at both two years and four years. It has also been shown to be superior in predicting mortality compared with the MAGGIC score, notably after participation of heart failure with reduced ejection fraction (HFrEF) patients in a cardiac rehabilitation programme, although this particular cohort may have played to the advantage of the MECKI score because it was restricted to those with good quality peak oxygen consumption (VO₂) test results.

The MECKI score concept was originally proposed in 2013, with an initial derivation cohort of 2715 HFrEF from hospital centres with an interest throughout Italy. From 80 initially-considered parameters six were found to predict outcomes independently of each other: haemoglobin, sodium, kidney function evaluated...
by means of the Modification of Diet in Renal Disease equation, left ventricular ejection fraction by echocardiography, percentage of predicted peak oxygen consumption and the minute ventilation/carbon dioxide production (VE/VCO₂) relationship slope. The MECKI score was later successfully validated in a separate validation cohort. The MECKI score database is a collaborative venture of these Italian units which has continued to grow and has evaluated numerous prognostic features and has acted as a form of standardised assessment registry of contemporary HFrEF patients, albeit coming from expert units with standardised cardiopulmonary testing as a practice in their clinical evaluation of patients. For this reason it is perhaps not entirely representative of routine heart failure care in the community. In 2016 the group published a validation study in lower risk HFrEF subjects and showed maintenance of the prognostic accuracy of the MECKI score.7

Its utility has been shown by the fact that HFrEF patients assessed over three decades show a maintained prognostic value of the MECKI score despite overall prognosis improving, substantially, so that for the same absolute score a better prognosis is now predicted, but still differentiating between different prognostic groups, albeit with different operative thresholds in the modern era.8

Other uses of the MECKI score

The MECKI score has been shown to be able to differentiate between HFrEF patients able, or not able, to tolerate high dose sacubitril/valsartan dosing long term. This may well be true of other risk scores for HFrEF, as it is plausible they can all predict sickest, highest risk patients, because of advanced age, low blood pressure or poor renal function, or the presence and severity of other co-morbidities. Nonetheless it is an important finding for it shows the potential of the MECKI score to be used in routine practice in aiding clinical decision making, predicting which patients will likely tolerate certain drug therapies.

The registry-like database of the MECKI score group has also assessed features such as the independent prognostic significance of atrial fibrillation, obesity, impaired renal function, beta-blocker use and dose and gender differences. It will continue to offer useful insights because of the elegance and importance of the prognostic parameters systematically obtained. The MECKI score data has allowed us to improve our knowledge on exercise physiology in heart failure patients.10,11

Future developments

Despite a good validation within the MECKI network, it is important to establish that the MECKI score also holds true in other settings, and other types of units, especially outside the cohort of Italian centres with an interest in cardiopulmonary exercise testing and cardiac rehabilitation. We understand that just such a validation in non-Italian settings in Europe is already underway. One very important aspect is to include under-represented groups – the elderly, women and people of different ethnic backgrounds – along with other pathophysiological patterns of heart failure, including heart failure with preserved ejection fraction and the varied aetiologies of heart failure. Given the central role of the cardiopulmonary exercise tests (CPXs) in the MECKI score, which arguably gives it its edge over other heart failure risk scores, it will be important to push the boundaries of CPX testing. One criticism of CPX is that it is complex, and hence more training in this standard methodology of heart failure assessment may be required, an initiative that several of the MECKI centres have been very active in already. Another criticism is that only a minority of heart failure patients are capable of full CPX evaluation. This may be in large part a misapprehension. In fact, many heart failure sufferers can perform low level exercise, during which valid cardiopulmonary data can be obtained, and it is in exactly such limited patients that some of the most clinically useful physiological data can be obtained. Even very limited patients can be asked to stand up and down from a chair or to leg raise in bed, during which exertions respiratory gas exchange can be measured and valid CPX data obtained. In such patients the peak VO₂ and VE/VCO₂ slopes can also often be derived. Features such as exercise induced oscillatory ventilation and periodic breathing during the day have been shown to be useful prognostic markers in heart failure and this could be a useful adjunct of the CPX methodology that the MECKI methodology includes. A standardised assessment of these parameters may be a useful extra element to be explored in future. This overlaps also with the pathophysiology of Cheyne Stokes respiration and central sleep apnoea, which may also be interesting new areas for the MECKI group to explore and add to their score in future. This has not been systematically assessed in any of the major heart failure scores systems to date.

Other co-morbidities

Several co-morbidities which are common in heart failure can potentially affect the CPX in terms of methodology, results and interpretation. These may be
important topics for the MECKI collaborative to address in future. Conditions such as heart failure with concomitant chronic obstructive pulmonary disease, to assess the respective pulmonary and cardiac components underlying the exercise limitation, will be important. Also, pulmonary hypertension is associated with abnormalities of ventilatory control and gas exchange and is a valid area of future MECKI-type investigation. Other common conditions associated with global cardiovascular limitation, but short of a full diagnostic picture of heart failure such as hypertrophic cardiomyopathy, amyloid, asymptomatic left ventricular dysfunction and even chronic hypertension could be valid areas for future research of the usefulness of a MECKI-type score, either as it is or adapted, but with the crucial addition of a cardiopulmonary exercise physiological assessment. Frailty, cachexia, and osteoporosis are both common conditions in severe heart failure where informed decision making is important and where the physiological approach of the MECKI score is likely to be useful. These could also be areas of future development of the role and refinement of the MECKI score.

Assessment of drug and device interventions

A very important area in the future may also be in the evaluation of drug and device responses. The heart failure community has been expert at proving therapies which reduce mortality and hospitalisation rates, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, ivabradine, sacubitril/valsartan, the sodium-glucose co-transporter-2 inhibitor class and selected devices – cardiac resynchronization therapy and, for secondary mitral regurgitation, percutaneous mitral regurgitation reduction via the Mitraclip. Few of these interventions have been established to improve functional capacity and if the MECKI score can be reliably be validated to predict improved major outcomes when it is improved, as well as showing improvements in objective exercise tolerance, it may be a useful end-point in an adaptive trial design programme for new therapies that may allow early approval whilst major outcomes trials are still underway. A series of more modestly sized trials, with MECKI score improvement as the primary end-point, perhaps usefully combined with a validated patient-reported outcomes score, may be an excellent way of bringing potentially effective new treatments to our heart failure patients at a fraction of the cost and much earlier than our present requirement to prove everything by large scale randomised controlled trials with mortality and hospitalisation as the only acceptable end-point.

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