The measurement of plasma aldosterone in patients post-myocardial infarction

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This editorial refers to ‘Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction’† by B.R. Palmer et al., on page 2489

Aldosterone blockade, or more correctly mineralocorticoid receptor blockade (MRB), when administered between days 3 and 14 in patients with heart failure (HF) and left ventricular systolic dysfunction (LVSD) post-myocardial infarction (MI) has been shown to reduce all-cause mortality as well as hospitalizations for HF (EPHESUS).1 Of note, all-cause mortality was reduced by 31% at 30 days post-randomization.2 These benefits on mortality were seen in patients with an ST-segment elevation (STE) MI and in those with a non-ST-segment elevation (NST) MI, as well as in patients treated with ‘optimal’ medical therapy including an aspirin, statin, reperfusion, a diuretic, a β-adrenergic receptor blocker, and an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocking agent (ARB). This strategy has been adopted by both the European Society of Cardiology and the AHA/ACC guidelines.

Unfortunately, aldosterone levels were not routinely measured in EPHESUS, thereby precluding further detailed insight into the pathophysiological role of aldosterone and risk stratification. Fortunately, this void has been filled by Begui et al.3 who showed that patients with a STEMI in whom plasma aldosterone levels were measured on admission and were in the highest quartile had an increased risk of death compared with those in the lowest quartile. Palmer et al.4 provide further insight into the prognostic value of plasma aldosterone levels in patients with a STEMI or NSTEMI in the absence of clinical evidence of HF. They found that plasma aldosterone levels in the highest tertile (>141 pmol/L) measured early (24–96 h) after admission for an MI were an independent predictor of survival and hospitalizations for HF over a 5-year follow-up period post-MI after adjustment for established risk factors. It is important to point out that all values for plasma aldosterone were below the upper limit of the normal range for their laboratory (800 pmol/L) except for five patients (0.9%). The prognostic information provided by the measurement of plasma aldosterone was independently associated with the measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP), norepinephrine, and endothelin levels, and that patients above the medium level of both aldosterone and NT-proBNP had a mortality rate of ~40% compared with 25% in the remaining patients over the 5-year follow-up period. This information along with that provided by Begui et al.3 emphasizes the importance of aldosterone in the outcome of patients post-MI, both STEMI and NSTEMI, with or without clinical evidence of severe LVSD or HF, and raises the possibility that MRB might be effective in reducing mortality in patients post-MI independent of the severity of LVSD or clinical HF. At present one should, however, be cautious in adopting the exact values of plasma aldosterone noted by Begui et al.3 and Palmer et al.4 as predicting increased risk post-MI in clinical practice for deciding upon the need for a MRB since aldosterone levels may be affected by sodium intake, posture, concomitant medications, and other factors that may vary from patient to patient and from centre to centre. It will be necessary to have further confirmation as to the prognostic importance of plasma aldosterone levels post-MI and to standardize and quality control the measurement techniques and patient conditions so as to provide reliable threshold values upon which clinical decisions to administer an MRB to a patient post-MI may be made. To take optimum advantage of the prognostic information provided by Begui et al.3 and Palmer et al.4 and to identify those patients who might benefit most from an MRB, it may also be necessary to measure cortisol levels, since Guder et al.5 have recently shown that an increase in both cortisol and aldosterone levels predicts survival in patients with chronic HF. Both cortisol and aldosterone have been suggested to activate the mineralocorticoid receptor (MR) and their effects blocked by an MRB such as spironolactone or eplerenone.6 Activation of the MR has a number of deleterious effects aside from sodium retention and potassium loss. Activation of the MR results in an upregulation of ACE and the angiotensin type 1 receptor, an increase in calcium channel expression, a decrease in antioxidant reserve, a decrease in nitric oxide availability, apoptosis,
increased sympathetic nervous system activation, cytokine and growth factor activation, myocardial and vascular fibrosis and hypertrophy, ventricular dilatation, albuminuria, and renal dysfunction, all of which can be prevented by the administration of an MRB.7–9 An MRB when administered early post-experimental MI results in enhanced infarct neovascularization, improved infarct healing, and reduced left ventricular dilatation and dysfunction.10 Aldosterone acts synergistically with angiotensin II to amplify vascular injury, and it may be necessary to administer both an MRB and an angiotensin receptor blocker (ARB) or an ACE inhibitor to achieve optimal vascular protection.11

Hyashi et al.12 have shown that an MRB given on day 1 to patients with their first anterior STEMI for 1 month prevented ventricular remodelling and myocardial collagen formation in patients without severe LVSD or evidence of HF. These results, along with the finding that aldosterone levels are elevated relatively early post-MI and predict subsequent mortality,3,4 suggest that one should not delay administration of an MRB to patients at increased risk post-MI with or without evidence of severe LVSD or clinical evidence of HF, especially those with a history of hypertension,13 and that the reduction in mortality following the administration of eplerenone to patients in EPHEBUS5 probably underestimates the potential benefits of MRB on mortality post-MI since patients without LVSD and clinical HF, except for those high risk patients with diabetes mellitus who were included with LVSD regardless of evidence of HF, were not included and, as suggested by the results of Begui et al.3 and Palmer et al.4 might benefit from administration of an MRB. These speculations will, however, require further prospective evaluation in adequately designed randomized trials.

It is important to emphasize that if one is to consider the use of an MRB such as spironolactone or eplerenone in a patient post-MI then patients with a serum potassium $>$5.0 meq/L and/or an estimated glomerular filtration rate (GFR) $<$30 mL/min/1.73 m² should be excluded and potassium levels should be measured at baseline and serially, as recommended, with adjustment of the dose of the MRB accordingly.1 Many clinicians are, however, hesitant to administer an MRB to a patient post-MI and/or those with HF due the fear of inducing serious hyperkalaemia, as suggested by Jurlink et al.14 and others. A review of these reports suggests that in most instances the occurrence of serious hyperkalaemia and its consequences including renal failure and death are attributable to physician error in dosing, adhering to inclusion and exclusion criteria, and/or a failure to monitor serum potassium serially. A recent analysis of EPHEBUS15 suggests that when eplerenone is administered at an initial dose of 25 mg/day, to patients defined as above with baseline and serial measurements of potassium and adjustment of the dose of the MRB accordingly, there is a significant benefit on survival without serious consequences from hyperkalaemia. In $>$3000 patients administered eplerenone in EPHEBUS there was not a single death attributable to hyperkalaemia. However, if one is not willing to adhere to the recommended dosing, inclusion and exclusion criteria, to measure serum potassium serially, and adjust the dose of the MRB accordingly, there may be an increased risk of serious hyperkalaemia and its consequences, and the benefits for a further reduction in mortality post-MI promised by the information provided by Begui et al.3 and Palmer et al.4 may remain unrealized.

Conflict of interest: B.P. is a consultant for Pfizer.

References


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