Aldosterone Blockade in Patients With Acute Myocardial Infarction

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Aldosterone blockade (AB) has found increasing use in patients with severe heart failure due to systolic left ventricular dysfunction based on the results of the Randomized Aldactone Evaluation Study (RALES).\(^1\) The role of AB in patients with acute myocardial infarction has been uncertain, however. This situation is about to change with the availability of the results of the Eplerenone Post acute myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS)\(^2\) and the results of the study by Hayashi et al\(^3\) in this issue of Circulation.

See p 2559

The EPHESUS study\(^2\) of over 6600 patients with acute myocardial infarction complicated by evidence of systolic left ventricular dysfunction (left ventricular ejection fraction \(\leq 40\%\)) and signs of heart failure showed that the selective AB with eplerenone, when administered at a dose of up to 50 mg daily (mean dose 42 mg daily) between days 3 and 14 after infarction (mean 7.3 days) in addition to standard therapy which could include reperfusion, aspirin, statins, angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB), and a \(\beta\)-blocker, resulted in a 15% reduction in total mortality \((P=0.008)\) and a 17% reduction in cardiovascular mortality \((P=0.005)\), mainly due to a 21% reduction in sudden cardiac death \((P=0.03)\). There was also a 13% \((P=0.002)\) reduction in the co-primary endpoint of cardiovascular mortality/cardiovascular hospitalization (including hospitalization for non-fatal myocardial infarction, non-fatal stroke, heart failure, and ventricular arrhythmias). The reduction in cardiovascular hospitalizations was mainly attributable to a 15% \((P=0.03)\) reduction in patients hospitalized for heart failure and a 23% \((P=0.002)\) reduction in episodes of hospitalization for heart failure. There was also an 8% \((P=0.02)\) reduction in total mortality/total hospitalizations. These beneficial effects were associated with a 1.6% \((P=0.002)\) excess incidence in serious hypokalemia \((K\geq 6.0 \text{ mEq/L})\) but a 4.9% \((P=0.001)\) decrease in the incidence of hypokalemia \((K\leq 3.5 \text{ mEq/L})\). In contrast to the previous experience with the use of spironolactone, there was no increase in the incidence of gynecomastia, breast pain, or impotence in males or menstrual irregularities in females.

Of interest was the finding that the reduction in mortality associated with AB, especially sudden cardiac death, seemed to occur relatively early after AB and was sustained over the mean 16-month follow-up period. At the time EPHESUS was planned, there was little experience with the use of AB during the early hours after infarction. Given the uncertainty at that time as to the effectiveness of AB in patients with acute myocardial infarction, the necessity of both starting an ACE-I/ARB, \(\beta\)-blocker, aspirin, and a statins and of assuring the most timely and effective means of reperfusion, and the potential for hypotension when adding an AB to standard therapy, it was decided to delay the administration of AB until patients were hemodynamically stable between day 3 to 14 after myocardial infarction. Given the beneficial results of AB in EPHESUS\(^2\) along with the results of Hayashi et al\(^3\), one can now consider evaluating the administration of AB during the early hours after infarction. Hayashi et al\(^3\) have shown that patients with a first anterior myocardial infarction treated with an ACE-I with or without a \(\beta\)-blocker, when randomized immediately after successful coronary reperfusion after infarction to AB with canrenoate 200 mg IV followed by oral spironolactone at a dose of 25 mg daily for 1 month, had a significant improvement in left ventricular remodeling. Left ventricular ejection fraction significantly improved and left ventricular end-diastolic volume was reduced. They also found a significant reduction in the extraction of aldosterone across the heart with a concomitant reduction in myocardial collagen formation, as evidenced by a reduction in circulating procollagen type III amino terminal peptide levels. This beneficial effect was achieved without any compromise of systemic blood pressure. The results of EPHESUS and Hayashi et al\(^3\) are complimentary and suggest the need for further exploration of AB in the early hours after myocardial infarction.

The finding by Hayashi et al\(^3\), which suggest an early effect of AB on ventricular remodeling and collagen formation, as well as previous experimental and clinical studies showing an effect of AB on ventricular remodeling and collagen formation\(^4\)\(^\text{--}12\) without any interference in myocardial scar healing,\(^13\) may explain the beneficial effects of AB in EPHESUS, on a reduction in hospitalizations for heart failure. The effect of AB on ventricular remodeling and collagen formation might also in part explain the effectiveness of AB in EPHESUS on sudden cardiac death, in that myocardial stretch is associated with activation of various neurohormones, including angiotensin II and endothelin. A reduction in ventricular remodel-
ing and collagen formation would also improve the homogeneity of ventricular conduction and hence reduce the likelihood for ventricular arrhythmias. Other mechanisms, however, may also be of importance. The finding that the transcardiac extraction of aldosterone is reduced by AB in patients with acute myocardial infarction would might effect intracellular potassium content and therefore the tendency for ventricular arrhythmias. Studies by Guidieri have shown that mineralocorticoid receptor activation decreases tissue potassium and potentiates the tendency for catecholamine-induced ventricular arrhythmias. Studies in patients with chronic heart failure have shown that AB improves myocardial norepinephrine uptake, resulting in decreased circulating catecholamine levels and shortening of QT dispersion. More recently, experimental studies of myocardial damage and heart failure have suggested that release of cytokines such as tumor necrosis factor-α may result in an increase in reactive oxygen species (ROS) and prostaglandin E₂, which can cross the blood brain barrier and activate central mineralocorticoid receptors, which in turn results in an increase in central sympathetic drive. Aldosterone-blocking agents may therefore play an important role in improving myocardial norepinephrine uptake and decreasing central sympathetic drive. Aldosterone-blocking agents have also been shown to improve heart rate variability, which is associated with an improvement in nitric oxide availability and a decrease in ROS, which might also play an important role in sudden cardiac death.

Regardless of the precise mechanisms, the demonstrations in EPHESUS and in the study by Hayashi et al of the effectiveness of AB during the early phase of acute myocardial infarction suggest that AB will be an important addition to the current therapy of patients with acute myocardial infarction. Clearly, the risk/benefit of early (day 1) AB after infarction will need to be explored in large-scale prospective randomized studies. Further studies will also be required to determine whether AB should be restricted to patients with early evidence of systolic left ventricular dysfunction or be used as are ACE-I and ß-blockers in all patients with myocardial infarction, regardless of left ventricular ejection fraction, unless contraindicated or not tolerated. The fact that mean left ventricular ejection fraction in the study by Hayashi et al was 46% at baseline suggests that severe systolic left ventricular dysfunction is not necessary for AB to be beneficial. One might also consider administration of an AB before reperfusion and percutaneous revascularization because experimental studies have suggested that AB may prevent restenosis. AB should also be considered regardless of reperfusion status because in EPHESUS, it was effective both in patients who underwent coronary reperfusion by thrombolysis or percutaneous techniques and in patients who were not reperfused. The duration of AB after myocardial infarction is also uncertain. If AB initiated during the early hours after infarction prevents ventricular remodeling when given over a period of approximately 1 month, is long-term therapy necessary? The answer to this question in patients with persistent left ventricular dysfunction after infarction is likely yes in view of the results of RALES. The question as to whether there is any advantage of eplerenone in comparison with spironolactone is also of importance, if for no other reason than cost-effectiveness. Should prolonged administration prove necessary to maintain the effects of AB on ventricular remodeling and therefore morbidity/mortality, the absence of side effects such as gynecomastia and breast pain in males and menstrual irregularities in females would favor selective AB with eplerenone. There are clearly a number of questions that need to be answered by further clinical research before we can take full advantage of AB for patients with acute myocardial infarction.

Basic research is often the stimulus for clinical investigation and clinical practice. However, in this instance, clinical investigation into the role of AB in patients with acute myocardial infarction will hopefully stimulate further basic research into the mechanisms responsible for the benefits of AB, and thereby lead to further clinical application of this important strategy to other cardiovascular conditions.

References


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