Mini Review

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Novel biomarkers in acute heart failure: MR-pro-adrenomedullin

Abstract: First isolated from human pheochromocytoma cells, adrenomedullin (ADM) is a peptide hormone with natriuretic, vasodilatory, and hypotensive effects mediated by cyclic adenosine monophosphate (cAMP), nitric oxide, and renal prostaglandin systems. ADM expression occurs in many tissues and organ systems, including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal, and endocrine tissues where it acts as a circulating hormone and a local autocrine and paracrine hormone. ADM plasma concentrations are increased in hypertension, chronic renal disease, and heart failure. As ADM is unstable in vitro, it is necessary to measure its mid-regional pro-hormone fragment, the levels of which correspond to ADM concentration (MR-proADM). The prognostic potential of MR-proADM was recently demonstrated in the Biomarkers in Acute Heart Failure (BACH) trial. In this trial of 568 acute heart failure patients, MR-proADM was superior to both brain natriuretic peptide (BNP) and NT-proBNP in predicting mortality within 14 days. MR-proADM also provided significant additive incremental predictive value for 90-day mortality when added to BNP and NT-proBNP.

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Adrenomedullin (ADM), a 52-amino acid ringed peptide with C-terminal amidation, was first isolated from human pheochromocytoma cells.Physiologically, this hormone has natriuretic, vasodilatory, and hypotensive effects that are mediated by the cyclic adenosine monophosphate (cAMP), nitric oxide, and renal prostaglandin systems. ADM expression can be found in many tissues and organ systems, including cardiovascular, renal, pulmonary, cerebrovascular, gastrointestinal, and endocrine tissues where it functions as a circulating hormone as well as a local autocrine and paracrine effector. ADM is a hemodynamically active vasodilatory peptide with potent hypotensive effects [1]. It also demonstrates acute inotropic, vasodilatory, diuretic, and natriuretic effects, and it inhibits aldosterone production. Chronically, ADM also has anti hypertrophic, anti-apoptotic, antifibrotic, antioxidant, and angiogenesis effects.

ADM also may have utility as a disease maker. Elevated measurements have been described in hypertension, chronic renal disease, and heart failure [1]. Its concentrations are elevated in chronic heart failure [2], and it is increased in proportion to disease severity [3, 4]. However, because of its very limited in vitro stability, accurate ADM measurement was until recently difficult, thus a complete understanding of its potential as a diagnostic and therapeutic was hindered.

Fortunately, a new immunoassay technique has been developed. This measures the concentration of the inactive stable protein fragment that is released into the systemic circulation during ADM synthesis. Called MR-proADM, it is the stable fragment of pro-adrenomedullin that is manufactured in a one to one ratio with active ADM. In this manner measurement of MR-proADM serum levels accurately reflect that of ADM [5] and have allowed the production of functional clinical assays to determine ADM concentrations [5–8].

By this marker assay strategy, large prospective studies have evaluated the importance of ADM in Emergency Department patients. The recently published Biomarkers in Acute Heart Failure (BACH) trial [9] evaluated the clinical utility of ADM. This multicenter international study prospectively enrolled 1641 patients presenting to an emergency department (ED) with a complaint of acute dyspnea. Of these, 568 (34.6%) were diagnosed with acute heart failure. The final gold standard diagnoses for this investigation were determined by
two cardiologists reviewing all available data at 90 days post ED visit.

Overall, there were 130 deaths during the 90-day follow-up period (survival rate 92.1%, 95% CI 90.7%–93.3%). Patients who died had higher median MR-proADM than survivors, 1.57 (1.02–3.21) versus 0.84 nmol/L (0.55–1.35), p<0.0001, respectively, with higher quartiles being associated with higher mortality (see Figure 1). Of the AHF subgroup, there were 65 deaths (90-day survival rate 88.6%, 95% CI 85.6%–90.9%). In this HF cohort, those who died had a higher median MR-proADM compared to those who died, 2.07 (1.19–3.64) versus 1.34 nmol/L (0.96–3.76), respectively, p<0.0001. Ultimately, MR-proADM predicts 90-day mortality in all ED patients presenting with dyspnea, including those with acute heart failure, and this information was independent of natriuretic peptide concentrations.

To further evaluate the utility of MR-proADM in a period relevant to emergency physicians, the 14-day death rate was examined [10]. As expected, this represented a smaller cohort (n=21, 3.5%). The value of 14-day mortality prediction is unique to the emergency department because of its potential to identify patients for whom immediate intervention or intensive care unit (ICU) admission would have some expectation as to the ability change outcomes. Although of significant clinical relevance, short-term mortality prediction is rarely reported as a biomarker endpoint, with the norm to report 30- and 90-day mortality. Accurate clinical decision making in the emergency department requires knowledge of potential outcomes in a much shorter time frame than 90 days. By identifying patients at short-term mortality risk, emergent hospitalization and aggressive intervention may potentially decrease the mortality rate.

To define the value of biomarker performance, mortality prediction outcome data is presented by the C-statistic (the area under the receiver operator characteristic curve) (see Figure 2). Overall, a C-statistic of 0.487 and 0.585 (p>0.05) for brain natriuretic peptide (BNP) and NT-proBNP, respectively, suggests essentially no value for short-term mortality prediction. In fact, in the overall cohort, neither BNP nor NT-proBNP provided any added value in addition to MR-proADM for the longer 90-day follow-up [10].

In contradistinction to natriuretic peptides, MR-proADM, and copeptin (C terminal pro-arginine vasopressin; CTproAVP) demonstrated excellent 14-day mortality prediction (C-statistic=0.714, 0.723 and 0.777, respectively, all p<0.05). Finally, the best 14-day mortality prediction at ED presentation for acute heart failure was found to be the combination of MR-proADM and copeptin (C-statistic=0.779, p<0.00001). Besides troponin [11], no commonly available prognostic marker accurately predicts acute heart failure short-term mortality.

It is important to recognize that ADM has unique capability to identify patients at high risk of short-term mortality and that this information is not readily apparent to the treating clinician. If physicians could identify a cohort at high risk of short-term death, it would be
reasonable to assume that they would administer more aggressive care as compared to those patients at low risk of short-term death. Unfortunately, that was not the case. When initial treatment was compared between the cohort who ultimately suffered a 14-day mortality versus survivors, the groups received identical treatment, defined as oxygen, diuretics, vasodilators, or inotropes (all \( p > 0.05 \)). Furthermore, while only 7% of survivors were admitted from the ED to the ICU, 74% of patients who suffered a 14-day death were admitted to a non-ICU setting. The fact that nearly three quarters of patients at high risk for death did not receive maximum treatment suggests that physicians could not identify mortality risk based solely on clinical grounds, and that measuring MR-proADM could potentially identify patients in need of more aggressive therapy.

Finally, while an elevated ADM is associated with increased short-term mortality risk, a low level does equate to low risk. Mortality is not the only outcome of importance and presenting symptoms must be considered. It should also be considered that MR-proADM is a non-specific hemodynamic marker. Regardless of the presence of acute heart failure, a high level is indicative that a serious underlying illness exists and appropriate intervention considered. Ultimately, ADM may be similar to troponin in that it is a marker that predicts short-term death, the findings of which may supersede the overall clinical impression.

Conflict of interest statement

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References