Clinical utility of circulating PAPP-A measurement in patients with coronary artery disease

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Coronary artery disease (CAD) is currently a major health problem worldwide despite tremendous advances in its clinical management over the past decade. Many people who are apparently healthy die suddenly from the disease without receiving any treatment [1]. On the other hand, 2.1% to 3.8% of patients who present with myocardial infarctions are not diagnosed in the emergency department [2,3] and 7.1 to 15.7% of patients with acute coronary symptoms (ACS) suffer reinfarction, or die within 30 days of presentation [4]. Thus there is room for improvement regarding the available diagnostic and risk assessment approaches used in the management of coronary patients.

The search for new circulating protein markers that reflect the diverse pathophysiology of acute ischaemic heart disease has been given considerable attention [5]. Their measurement could provide an effective means of improving the clinical handling of coronary patients. Pregnancy associated plasma protein A (PAPP-A) is a screening marker for Down syndrome pregnancies. However, since PAPP-A was found to be implicated in ACS in 2001 [6], its role as either a diagnostic or prognostic marker for CAD has been an interesting area of research. The goal of this article is to discuss the clinical utility of circulating PAPP-A in patients with CAD.

Diagnostic aspects
PAPP-A is released into the circulation when coronary atherosclerotic plaque is disrupted and is thus a marker of plaque rupture [5]. The disrupted plaque exposes prothrombotic material to the blood that in turn causes coronary thrombosis. When the thrombus blocks coronary blood flow, clinical manifestations of ACS occur. PAPP-A is likely to be a sensitive marker for use in the early diagnosis of ACS, since the disruption of coronary plaque precedes the development of myocardial ischaemia and necrosis.

In a study in 2001 involving 17 patients with acute myocardial infarction (MI), 20 patients with unstable angina (UA), 19 patients with stable angina (SA) and 13 controls without atherosclerosis [6], it was demonstrated that serum PAPP-A concentrations were statistically higher in patients with MI, or UA than in patients with SA. It was found that at a cut-off value of 10 mIU/L, PAPP-A was able to identify ACS patients with a sensitivity of 89.2% and a specificity of 81.3%. The results thus indicate that PAPP-A can be used to diagnose patients with ACS. As no correlation was observed between PAPP-A and cardiac troponin I levels, PAPP-A may be useful in the diagnosis of ACS patients who are negative for troponins.

Release kinetics
In a recent study involving early and frequent blood sampling from patients with ST-elevation myocardial infarction (STEMI), it was shown that elevated PAPP-A on average peaked one hour after admission and then declined rapidly for three hours. The subsequent decline of slightly elevated PAPP-A was slow until the normal level was reached about twelve hours after admission [7]. Thus released PAPP-A can be detected early after the onset of symptoms and abnormal levels do not persist long in the blood of ACS patients.

Risk stratification
Risk stratification, based on factors such as age, lipid profile, cigarette smoking status and hypertension, has become an important part of CAD clinical management. Risk information can help identify patients who can benefit most from intensive drug treatment or an early invasive strategy.

Risk stratification in ACS
Clinical studies have been carried out to examine the role of PAPP-A as a prognostic marker of ACS in high-risk populations. One hundred and thirty-six consecutive hospitalised ACS patients who were negative for cardiac troponin I (cTnI) for up to 24 hours after admission were evaluated [8]. It was found, at a six-month follow-up, that elevated serum PAPP-A, at a cut-off level of 2.9 mIU/L, was an independent predictor of cardiovascular disease death, MI or revascularisation, with an adjusted risk ratio of 4.6 (95% CI, 1.8-11.8). The results were confirmed in a recent study, where elevated PAPP-A was found to identify patients at high risk of cardiac death or MI in 347 cardiac troponin T- (cTnT) negative ACS patients [9]. Follow-up was at six months. Thus, PAPP-A measurement is of great value in identifying high-risk ACS patients whose unstable clinical situation might otherwise remain unrecognised.

Further analysis of a group of 547 patients with confirmed ACS showed that elevated PAPP-A (>12.6 mIU/L) was of predictive value for an increased risk of cardiac death and non-fatal MI at 30 days (odds ratio: 2.84; 95% CI, 1.55 to 5.22) and at 6 months (odds ratio: 2.44; 95% CI, 1.43 to 4.15) [9]. A recent study on 62 consecutively hospitalised patients with STEMI reported that admission PAPP-A > 10 mIU/L was associated with increased 12-month risk of cardiovascular death or non-fatal MI [7].

There have also been some studies which evaluated the role of PAPP-A as a prognostic marker for ACS in relatively heterogeneous populations. Heeschen et al. studied a heterogeneous emergency room population of 644 patients with acute chest pain [9] and found that PAPP-A measured from blood samples collected at the time of arrival was a strong independent predictor of death or MI during 30 days of follow-up (odds ratio: 2.32; 95% CI, 1.32 to 4.26). However, in another study of 346 patients presenting to the Emergency Department with chest pain or other symptoms of possible ACS, it was shown that PAPP-A measured soon after ED presentation was a modest predictor of adverse events during a 30-day follow-up period [10].

Risk stratification in stable coronary artery disease
A study was carried out on 396 consecutive patients with chronic stable angina (CSA) [11]. It was found that serum PAPP-A concentrations were significantly (P=0.01) higher in patients with complex coronary stenoses (> 30% diameter reduction) than in patients without complex coronary stenoses (5.9 ± 1.6 versus 5.1 ± 1.4 mIU/L). With univariate analysis, it was further found that PAPP-A concentrations were correlated significantly (P < 0.001) with the number of complex stenoses. These results indicate that PAPP-A is likely to be a useful indicator of atherosclerotic plaque vulnerability in CSA patients.

In another study on 643 consecutive CSA patients, it was shown that patients with...
multi-vessel disease had significantly higher serum PAPP-A concentrations (6.45 ± 2.58 mIU/L) than those with single-vessel disease (5.49 ± 1.54 mIU/L, P < 0.01) or normal coronaries (4.62 ± 1.17 mIU/L, P < 0.01) [12]. At cut-off of 4.5 mIU/L, PAPP-A was shown to detect the presence of significant stenoses (≥ 50%) with a sensitivity of 45% and a specificity of 84%. Thus, PAPP-A appears to be a marker which can indicate the extent of CAD.

Assay diversity and implications

In pregnancy, circulating PAPP-A (more than 99%) exists as a disulfide-bound 500-kDa heterotetrameric 2:2 complex with the proform of eosinophil major basic protein (proMBP) [13, 14]. However, the circulating PAPP-A that accounts for the increase of concentrations observed in ACS patients is not complexed with proMBP [15]. This may have implications in clinical practice since antibodies used so far in immunoassays for the detection of PAPP-A in ACS are all raised by immunisation with PAPP-A isolated from serum in pregnancy. In fact, there have been conflicting reports on whether serum PAPP-A is a useful marker for ACS [8,9,10,16]. The inconsistency in different labs could be due to the use of different PAPP-A assays involving different antibodies [17].

Summary

Physical disruption of atherosclerotic plaque accounts for almost all acute coronary thromboses. PAPP-A is released from ruptured plaque(s) but does not appear to persist in the blood. PAPP-A is likely to be an early marker for the diagnosis of ACS. However, information on the early diagnostic value of PAPP-A in ACS is still limited. PAPP-A is a prognostic marker of adverse cardiac events in ACS patients, and its prognostic value is independent of cardiac troponins. In CSA patients, PAPP-A is an indicator of atherosclerotic plaque vulnerability and can be used to identify the extent of CAD. PAPP-A is thus useful in the clinical management of CAD patients. However, more studies are required to validate its clinical utility with well-established immunoassays [see this issue of CLI, page 33].

References


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