Prognostic value of circulating pregnancy-associated plasma protein levels in patients with chronic stable angina

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Aims Unstable coronary atherosclerotic plaque can be present in patients with chronic stable coronary artery disease (CAD). Our objective was to assess whether measurement of plasma pregnancy-associated plasma protein (PAPP-A) level, a reflection of plaque instability, in patients with chronic stable CAD had an independent prognostic value on the subsequent incidence of death, acute coronary syndrome (ACS), and revascularization.

Methods and results Patients referred for coronary angiography were recruited. A cohort of 103 patients with stable symptoms for at least 6 weeks and with a coronary angiogram showing at least a 50% luminal diameter narrowing formed our study population. Median follow-up was 4.9 years. Mean age was 65 ± 10 years. In a multivariable model that included CAD traditional risk factors, ejection fraction, extent of coronary atherosclerosis, prior history of myocardial infarction, prior revascularization, discharge medications, and C-reactive protein, the plasma PAPP-A was found to be significantly associated with the endpoint of future death [adjusted hazard ratio (HR) 5.29; 95% CI 1.27–22.0; \( P = 0.023 \)] and with the endpoint of future death and ACS (adjusted HR 3.56; 95% CI 1.27–10.0; \( P = 0.015 \)), but not with the endpoint of future death and revascularization.

Conclusion Measurement of plasma PAPP-A level in patients with chronic stable CAD has an independent prognostic value on the occurrence of death and ACS.

KEYWORDS
Pregnancy-associated plasma protein; Stable coronary artery disease; Unstable atherosclerotic coronary plaque

Introduction

Atherosclerosis is considered a systemic chronic inflammatory disease.⁴ Release of matrix metalloproteinases by macrophages within a stable plaque has been implicated in its transformation to an unstable plaque.²–⁵ Plasma pregnancy-associated plasma protein (PAPP-A) is a zinc-binding metalloproteinase⁶ that has been found to be present more abundantly in unstable coronary plaques when compared with stable plaques.⁷ In patients presenting with an acute coronary syndrome (ACS), higher circulating PAPP-A levels have been found to be a strong independent predictor of cardiovascular events.⁸,⁹ Thus, it may be speculated that PAPP-A may be contributing to the transformation of a stable atherosclerotic plaque into an unstable one. Moreover, PAPP-A levels have been found in patients with stable angina to correlate with more complex stenosis¹⁰ and the coronary artery disease (CAD) extent¹¹ on angiography. However, a direct prognostic link between measurement of circulating PAPP-A level in patients with chronic stable angina and clinical outcome has not been demonstrated.

The mechanism by which stable plaques become unstable and may lead to ACS and ischaemic death is not fully understood. Moreover, the transition from stable to unstable plaques does not necessarily immediately translate to clinical symptoms.¹²,¹³ Current methods to identify such a plaque involve either invasive technology or costly imaging technics.¹⁴ A non-invasive test such as plasma PAPP-A level would be a very attractive alternative for detecting unstable plaque activity in patients with chronic stable angina. The hypothesis underlying the current study was that the process of transformation from stable to unstable plaque might be reflected in the circulation by an increase in the level of PAPP-A. Therefore, the aim of this study was

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to assess whether measurement of plasma PAPP-A level in patients with chronic stable angina has a prognostic value on the subsequent occurrence of death, ACS, and revascularization independent of known prognostic factors in such a patient population.

Methods
Patients and design

Informed consent was obtained from the patients. The research protocol was approved by the Mayo Clinic Institutional Review Board. Recruitment was done over 1 year between August 1998 and July 1999 in patients referred for a coronary angiogram with an initial intent to correlate PAPP-A levels with the cardiac presentation [i.e. myocardial infarction (MI) vs. unstable angina vs. stable angina]. Information regarding the patient characteristics was collected from the patients and was supplemented when necessary by review of the medical records. A total of 333 non-selected patients accepted to participate in the study.

Patients with chronic stable angina as well as asymptomatic patients with documented positive stress test were eligible for the current study. All patients enrolled in the study had to have a coronary angiogram at the time of the study showing at least one coronary artery diameter stenosis of ≥50%. Patients with a complex congenital heart disease or an inflammatory disease (i.e. current infection, vasculitis, or rheumatic disease) were excluded from the study.

Out of the initial 333 patients enrolled, 27 patients had an acute MI, 110 had unstable angina, 86 patients had no significant CAD (<50% coronary artery diameter stenosis), leaving 110 eligible patients. Out of these 110 patients, one patient had a hypertrophic cardiomyopathy and six patients had significant inflammatory conditions. Consequently, the study consisted of a cohort of 103 patients who were followed prospectively for the occurrence of death, ACS, and revascularization. Eighty-four patients out of the total patient population enrolled had a measurement of their ejection fraction (EF) by echocardiography or cardiac catheterization.

The endpoints of the study included future death, the combined endpoint of the occurrence of future death and ACS, and the combined endpoint of death and revascularization.

Information on mortality was collected by the periodic review of the Social Security Death Index, which has been shown to be highly sensitive and specific. All-cause death was collected to reduce the possible biases and inaccuracies inherent to the recording of death certificates. Information regarding the occurrence of ACS and revascularization was collected by the periodic review of the Mayo Foundation medical records of the patients as well as available outside medical records. Cardiac revascularizations during follow-up either due to ACS or due to progressive symptoms of angina were included as endpoints. Patients were not asked to return for evaluation, specifically for research purposes. Follow-up on the occurrence of death was available for all patients, whereas follow-up on the occurrence of ACS and revascularization was available for 88 patients.

Definitions

Stable angina was defined as chronic stable effort or stress-induced angina relieved by rest or sublingual nitroglycerin of at least 6 weeks duration.

An ACS compromised unstable angina requiring hospitalization and MI. Unstable angina was defined as either: (i) symptoms of angina at rest with either ST-segment depression of at least 0.1 mV or T wave inversion in two or more contiguous electrocardiographic leads and a creatinine kinase MB fraction that was within normal limits; (ii) new onset exertional angina in the preceding 2 months (of at least Canadian Cardiovascular Society Class III); or (iii) acceleration of pre-existing angina over the preceding 2 months to at least Canadian Cardiovascular Society Class III.

Acute MI was defined as prolonged chest pain accompanied by ST-segment elevation or depression and confirmed by a finding that the creatinine kinase MB fraction was more than twice the upper limit of the normal range and by a troponin T level of >0.1 ng/mL.

CAD was defined angiographically as the presence of ≥50% luminal diameter narrowing by visual estimate. The atherosclerotic burden in the coronaries was assessed by using the modified Jenkins’ score that included branches in addition to proximal arteries.

Revascularization was defined as any non-planned percutaneous intervention or coronary artery bypass surgery (CABG) that occurred after index hospitalization discharge. Any revascularization that occurred during index hospitalization or prior to index hospitalization was accounted for in the statistical analysis on the occurrence of the endpoints of death, ACS, and revascularization during follow-up.

The definition of hyperlipidaemia was consistent with the most recent NCEP report. The body mass index was calculated by dividing the patient’s weight in kilograms by the square of the patient’s height in metres. Patients were considered to be hypertensive if their blood pressure was >140/90 mmHg or if they were being treated with antihypertensive medications. Active smokers were smokers who were still smoking within last 6 months of study enrolment.

Plasma protein assays

Fasting blood samples were collected from each patient just before coronary angiography. The blood was centrifuged immediately and the serum was then aliquoted and stored at −80°C. All tests were run within the next 3 months after collection.

PAPP-A levels were determined by means of a biotin-tyramide-amplified enzyme immunoassay, as previously described, with a limit of detection of 0.03 mIU/L and intra-assay and inter-assay coefficients of variation of 10 and 15%, respectively. PAPP-A polyclonal antibodies were used for capture and a combination of monoclonal antibodies was used for detection. The assay was calibrated against the World Health Organization’s international reference standard 78/610, which is the standard for pregnancy-associated proteins.

A highly sensitive latex-particle-enhanced immunoturbidimetric assay (Kamiya Biomedical, Seattle, WA, USA) was used to quantitate the level of C-reactive protein.

Statistical analysis

The statistical analysis was carried out independently by a statistician (R.J.L.). Continuous variables are summarized as either mean ± standard deviation or median (first and third quartiles). Nominal variables are presented as frequency (percentage). The Kaplan–Meier estimates are used to describe survival on follow-up. Patients who underwent percutaneous coronary intervention (PCI) or CABG during the index hospitalization begin follow-up after the revascularization, rather than the date of PAPP-A measurement. Group differences are compared using Student’s t-test, Pearson’s χ²-statistic, or the Mann–Whitney rank sum test.

Cox proportional hazards models were used to estimate unadjusted and partial hazards ratios (HRs) for follow-up events. Our sole interest is the estimated effect of PAPP-A. Thus, effects of other risk factors (covariates) are not presented. The covariates were age, body mass index, EF, modified Jenkins’ score to assess the extent of atherosclerosis, C-reactive protein, prior MI, prior bypass surgery, revascularization at index hospitalization, statin use at discharge, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use at discharge. For each of the five continuous variables, another variable was defined to create a three-knot spline basis. The covariate space (16 columns) was
then reduced using principal components. The smallest set of principal components that explained 90% of the total variance was used for covariance adjustment. PAPP-A was log-transformed (base 2) so that estimates reflect the relative effect of a doubling of the PAPP-A value. Likelihood ratio tests were used to test the significance of the PAPP-A effect and the combined covariate effect. A likelihood ratio test was used to test the significance of non-linearity (four-knot spline vs. linear trend) in the PAPP-A effect. The proportional hazards assumption appeared valid for all analyses. In patients with missing EF, the value was imputed with the sample median to include all subjects in the model.

Results

Patients and in-hospital revascularization

There were 103 patients with stable CAD enrolled in the study; 73 (71%) were males. The average age was 65.4 (±9.6) years. Table 1 shows the clinical characteristics of the patients in the highest quartile of PAPP-A levels (group 1 with PAPP-A >4.8 mIU/L) vs. the rest of the population (group 2 with PAPP-A ≤4.8 mIU/L). Patients in group 1 were older and were more likely to be hypertensive when compared with group 2 patients. Patients in group 2 were more likely to undergo revascularization at index hospitalization when compared with group 1 patients.

During index hospitalization, a total of 56 patients had coronary revascularization: 29 patients had a PCI, 24 patients had a CABG, and three patients had both procedures with bypass surgery following an unsuccessful or complicated angioplasty. Out of the 47 patients who did not have revascularization during index hospitalization, 16 patients were older and were more likely to be hypertensive when compared with group 2 patients. Patients in group 2 were more likely to undergo revascularization at index hospitalization when compared with group 1 patients.

Table 1 Baseline characteristics of the patients in the highest quartile of PAPP-A levels (PAPP-A >4.8 mIU/L) vs. the rest of the population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient comparisons</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 PAPP-A &gt;4.8 mIU/L (n = 28)</td>
<td>Group 2 PAPP-A ≤4.8 mIU/L (n = 75)</td>
</tr>
<tr>
<td>Age</td>
<td>69.5 ± 6.6</td>
<td>63.9 ± 10.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>21 (75)</td>
<td>52 (69)</td>
</tr>
<tr>
<td>Body mass index, median (Q1, Q3)</td>
<td>28.5 (24.9, 35.4)</td>
<td>27.5 (24.5, 29.4)</td>
</tr>
<tr>
<td>Symptons, n (%)</td>
<td>9 (32)</td>
<td>31 (41)</td>
</tr>
<tr>
<td>No angina</td>
<td>19 (68)</td>
<td>44 (59)</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Jenkins’ score, median (Q1, Q3)</td>
<td>14.0 (11.0, 20.0)</td>
<td>12.0 (9.0, 17.0)</td>
</tr>
<tr>
<td>EF, median (Q1, Q3)</td>
<td>59.0 (40.0, 63.0)</td>
<td>57.0 (44.0, 63.0)</td>
</tr>
<tr>
<td>C-reactive protein, median (Q1, Q3) mg/L</td>
<td>2.0 (0.8, 6.1)</td>
<td>2.0 (0.9, 4.1)</td>
</tr>
<tr>
<td>Creatinine, median (Q1, Q3) mg/dL</td>
<td>1.2 (1.0, 1.4)</td>
<td>1.2 (1.1, 1.3)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (82)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (32)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>20 (71)</td>
<td>56 (75)</td>
</tr>
<tr>
<td>Active tobacco (within last 6 months), n (%)</td>
<td>0 (0)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>15 (54)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>In-hospital revascularization, n (%)</td>
<td>10 (36)</td>
<td>46 (61)</td>
</tr>
<tr>
<td>Statins at discharge, n (%)</td>
<td>16 (59)</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Aspirin at discharge, n (%)</td>
<td>27 (96)</td>
<td>63 (84)</td>
</tr>
<tr>
<td>Beta-blocker at discharge, n (%)</td>
<td>19 (68)</td>
<td>49 (65)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at discharge, n (%)</td>
<td>11 (39)</td>
<td>25 (33)</td>
</tr>
</tbody>
</table>

PAPP-A and C-reactive protein levels

Median (25th and 75th percentiles) PAPP-A was 4.0 mIU/L (3.3, 4.9). The PAPP-A values ranged from 1.99 to 10.30 mIU/L. Median (25th and 75th percentiles) C-reactive protein was 2 mg/L. The C-reactive protein values ranged from 0.26 to 17.9 mg/L. There was no significant correlation between PAPP-A and C-reactive protein values (r = 0.05; P = 0.59).

Outcomes

The median follow-up time for the occurrence of death, ACS, and revascularization was 4.9 years (inter-quartile range 1.1–5.9 years). There was no statistically significant difference in the PAPP-A levels between patients who had
complete follow-up for the occurrence of ACS and revascularization (85%) and patients who did not (4.29 ± 1.49 vs. 4.22 ± 1.32; P = 0.87). There were 15 deaths. Nine patients suffered MI. Five patients had unstable angina requiring hospitalization. Twelve patients had percutaneous intervention, four had CABG, and five had both revascularizations after index hospitalization. Out of these 21 revascularizations, 10 were done in the setting of an ACS and 11 in the setting of progressive anginal symptoms with no ACS.

PAPP-A as a predictor of adverse outcomes

Univariate analysis

Univariate analysis plasma PAPP-A level (log-transformed) was associated with the endpoints of death (HR for doubling of PAPP-A 5.57; 95% CI 1.94–16.0; P = 0.002) and of future death and ACS (HR 5.37; 95% CI 2.45–11.8; P < 0.001), but not with death and revascularization (HR 1.68; 95% CI 0.86–3.28; P = 0.13).

Figure 1 shows the survival rates using PAPP-A quartiles. At 6 years of follow-up, patients in the highest quartile had a cumulative mortality of 29%, whereas the cumulative mortality for the rest of the patients was 9% (P = 0.014). Although the plot seems to indicate that the PAPP-A effect is mainly observed in the highest quartile, formal statistical tests (tests for non-linearity) indicated that the data did not contain significant evidence of a threshold effect.

Figure 2 shows the survival free of ACS rates according to PAPP-A quartiles. After 1 year, the rate of death or ACS was 16% in the highest PAPP-A quartile, but was 2% in the lower three quartiles (P < 0.001). Although the plot seems to indicate that the PAPP-A effect is mainly observed in the highest quartile, formal statistical tests (tests for non-linearity) indicated that the data did not contain significant evidence of a threshold effect.

Multivariable analysis

After adjusting for age, the coronary atherosclerotic burden, EF, body mass index, prior MI, prior CABG, diabetes mellitus, revascularization at index hospitalization, C-reactive protein, statin use at discharge, and angiotensin-converting enzyme inhibitors or angiotensin receptor blocker use at discharge, plasma PAPP-A was found to be significantly associated with the endpoint of future death (adjusted HR 5.29; 95% CI 1.27–22.0; P = 0.023) and with the endpoint of future death and ACS (adjusted HR 3.56; 95% CI 1.27–10.0; P = 0.015), but not with death and revascularization. Results of the multivariable analysis are summarized in Table 2.

Discussion

This study demonstrates that in patients with chronic stable CAD, plasma PAPP-A level has a significant prognostic value on all-cause mortality and on the occurrence of ACS. Circulating PAPP-A prognostic values were independent of traditional coronary artery atherosclerotic risk factors, extent of coronary atherosclerosis, and EF. Plasma PAPP-A levels did not predict future revascularization.

Our study is the first to find a prognostic link between measurement of plasma PAPP-A levels and future death and ACS in patients with stable CAD. The strongest prognostic link that we present is between measurement of plasma PAPP-A levels and future death. The strength of this association comes from the complete follow-up that was available on a non-selected group of patients for a relatively long period. Data were collected on all-cause mortality to reduce the possible biases and inaccuracies inherent to the recording of death certificates. The data collection on future ACS and revascularization included the majority of the patients for a relatively long period of follow-up, thus avoiding significant bias favouring follow-up of the sickest patients. In fact, there was no difference in PAPP-A levels between patients who had complete follow-up on future ACS and revascularization and patients who did not.

The absence of association between plasma PAPP-A levels and revascularization can be explained on the basis of several facts. The decision to have revascularization is often complex and based on multiple factors including the presence or the absence of angina, patients’ general medical condition, and very importantly, the suitability of the coronary tree for revascularization. In fact, several cases of advanced atherosclerosis were treated medically at index presentation based on a coronary anatomy not readily amenable to revascularization.

A role for increased PAPP-A as a marker for cardiovascular events continues to emerge. In patients who died suddenly of cardiac causes, expression of PAPP-A in plaque cells and extracellular matrix of ruptured and eroded unstable plaques were higher than in stable plaque, and plasma PAPP-A was equally higher in patients presenting with an
ACS when compared with stable patients. In patients presenting with chest pain and a negative troponin level, plasma PAPP-A was found to be a strong independent predictor of cardiovascular death, MI, and revascularization. In patients presenting with an ACS, plasma PAPP-A was found to reliably identify high-risk patients and to have additive prognostic power to markers of ischaemia and inflammation. These reports have strongly argued in favour of the prognostic importance of plasma PAPP-A in patients presenting with a suspected ACS. In asymptomatic hyperlipidaemic patients with no known CAD, elevated plasma PAPP-A levels were associated with increased echogenicity of carotid atherosclerotic plaques detected by ultrasound and enhanced inflammatory state as reflected by elevated C-reactive protein. The current study extends these previous observations and demonstrates for the first time the prognostic value of measuring plasma PAPP-A in patients with chronic stable CAD.

One of the most important prognostic factors for patients with chronic stable CAD is the extent of coronary atherosclerosis. In our study, even after correcting for the extent of atherosclerosis, the prognostic value of plasma PAPP-A in patients with stable CAD was still significant. This observation is in accord with the concept that most ACS are due to coronary atheroma disruption of the fibrous cap or erosion of the intima-triggering acute thrombosis at sites of non-critical stenoses of the coronary arteries. This concept forms the basis of the concept of the ‘vulnerable’ plaque or patient and has fuelled significant research towards identification and possibly treating these plaques prior to the occurrence of an ACS. Moreover, vulnerable plaques are detected not only in patients with ACS, but also in patients with stable CAD, although less frequently. The detection of ‘vulnerable’ plaques currently involves an invasive strategy using coronary angiography, intravascular ultrasound, angiography or thermography, or costly non-invasive imaging modalities with multiple shortcomings. Consequently, the identification of a non-invasive marker with the ability to risk stratify patients with stable coronary disease on the basis of plaque vulnerability would be extremely valuable.

**Limitations**

One the limitations of the current study lies in its design as a prospective observational study of a relatively small number of patients referred to a tertiary medical centre. This might limit the generalization of its conclusions. However, our study may contribute to future clinical practice and could potentially save significantly, if resources were to be streamlined according to the potential risk group that a patient belongs to as determined by a relatively cheap and non-invasive test.

Outcome data based on hospital and outside records may be problematic. Nonetheless, data were available on a majority of the patients (85%). The length of follow-up was a strong point of the study with a median follow-up time of 4.9 years. Accordingly, this allowed data collection on the majority of the patients. In fact, a significant portion of our patients is local to the area and our clinic represents a major medical source to these patients. Even patients who might have been referred for an initial evaluation are likely to come back for a second time if enough follow-up time is allowed (as it was the case in our study). Most importantly, there was no statistically significant difference in the PAPP-A levels between patients who had follow-up and patients who did not.

Older age and other known cardiovascular comorbidities in the group with higher PAPP-A levels could have had potentially a confounding effect on the association between higher PAPP-A levels and future cardiovascular events. In our patient population, patients with a higher PAPP-A levels were significantly older and were more likely to be hypertensive when compared with patients with a lower PAPP-A value. As far as other known cardiovascular risk factors, there was no statistical difference favouring the group of patients with a lower PAPP-A value. In spite of that, we have taken into account all known traditional cardiovascular risk factors and corrected for them. Consequently, we have tried to account for any possible confounding effect that risk factors might have played. After correcting for age and known risk factors, PAPP-A was still a good predictor and marker of future cardiovascular events. Whether PAPP-A is playing an aetiological effect is difficult to prove and requires more extensive research at a more basic level.

Whether the coronary arterial tree was the major source of PAPP-A at the time of blood collection or a significant contribution comes from other vascular source is difficult to prove. Most importantly, all our patients were clinically stable with no evidence of cerebrovascular or peripheral vascular events at the time of blood collection. No data were collected on future cerebrovascular or peripheral vascular events. Further research on the value of PAPP-A in predicting peripheral vascular events might be of potential value.

Our definition of MI might have missed some cases of non-ST-elevation MI and most likely categorized them as unstable angina. However, our analysis of endpoints has taken both into account under the category of ACS. It is unlikely, although based on the clinical presentation, that these cases could have been mis-categorized as stable patients and included initially as eligible stable angina patients to be enrolled in the study.

Another potential limitation lies in the test itself and the inability of plasma PAPP-A in the current study to identify specific vulnerable plaques for which localized treatment can be done. However, to date, no established local intervention to such vulnerable plaques is clinically available and most measures aiming at stabilizing such plaques remain systemically applied.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HRb</th>
<th>95% CI</th>
<th>p-valuesc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5.29</td>
<td>1.27, 22.1</td>
<td>0.023</td>
</tr>
<tr>
<td>Death + ACS</td>
<td>3.56</td>
<td>1.27, 10.0</td>
<td>0.015</td>
</tr>
<tr>
<td>Death + revascularization</td>
<td>1.06</td>
<td>0.47, 2.38</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*Age, C-reactive protein, EF, body mass index, modified Jenkins’ score, prior MI, prior coronary bypass surgery, revascularization prior to discharge, diabetes, angina, statin use at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use at discharge (collapsed into nine principal components).

bPAPP-A was log2-transformed. Thus, the HR represents the relative effect for a doubling in the value of PAPP-A.

p-Values of likelihood ratio test.
Finally, we did not explore any correlation of the PAPP-A levels with a direct assessment of the presence and the number of vulnerable plaques in this current study. However, it might be speculated that the levels of plasma PAPP-A correlate with the number and the activity of unstable plaques, which contribute to the development of cardiovascular events.

Conclusions

In our patient population with chronic stable CAD, plasma PAPP-A measurement had an independent prognostic value on the occurrence of death and ACS. The value of measuring plasma PAPP-A should be further studied prospectively in a larger patient population with chronic stable CAD to ascertain its prognostic value. This test might potentially replace other more expensive and labour intensive tests used in the prognostication of patients with chronic stable coronary atherosclerosis.

Acknowledgement

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Conflict of interest: none.

References

Clinical vignette

Dysphagia associated with an aneurysm decades after Blalock–Taussig anastomosis

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A 55-year-old female patient presented with dysphagia and weight loss. The history revealed a diagnosis of Fallot tetralogy (TOF) with right aortic arch. The patient had an original left Blalock–Taussig anastomosis (BTA) performed at the age of 4 and reparative surgery with ligation of the BTA, ventricular septal defect closure, and comissurotomy of the pulmonary valve at the age of 43.

During the routine follow-up on chest X-ray, an enlargement of the upper left mediastinum was seen (Panel A). A computed tomography scan demonstrated a mass extending from left anterior into the posterior mediastinum with proximity to the esophagus posteriorly (Panels B–D), suggesting a partly thrombosed aneurysm.

At repeat operation, the diagnosis was confirmed, and a complete resection of the thrombosed aneurysm with patch closure of the left subclavian artery take-off from the brachiocephalic trunk was performed successfully. The post-operative recovery was uneventful.

The BTA, first performed in 1944, was the earliest of the palliative shunts and has allowed generations of blue babies’ long-term survival. This type of operation is associated with a considerable morbidity due to numerous complications (e.g. kinking, occlusion, cardiac failure, pulmonary vascular disease). Aneurysmal degeneration or formation of a pseudoaneurysm is a quite uncommon complication after BTA. Such aneurysms have been found at the systemic end of a ligated shunt and may be related to a large shunt flow and long duration. Moreover, recent findings indicate that marked histological abnormalities exist in the aortic wall in patients with TOF, which may facilitate aneurysm formation.

This report highlights the importance of regular follow-up of adult patients with congenital cardiac defects, even decades after surgery, as these patients are not cured.

Chest X-ray and CT scan images of the aneurysm.
Panel A. Chest X-ray demonstrating left upper mediastinal enlargement.
Panel B. Coronary section of the aneurysm.
Panel C. In the sagittal view, the close contact with oesophagus can be appreciated.
Panel D. The transverse section demonstrates the broad origin of the aneurysm. Asterisk indicates aneurysm.