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Ischaemia-modified albumin in pulmonary hypertension

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Abstract

Background: Pulmonary hypertension (PH) may be associated with subendocardial ischaemia. We investigated whether ischaemia-modified albumin (IMA), an established marker of ischaemia, is elevated in stable patients with PH.

Methods: We studied 32 patients with PH and an equal number of age-matched normal volunteers. We assessed serum IMA levels with the albumin cobalt-binding test.

Results: Patients' mean ± SD (range) pulmonary arterial pressure was 56 ± 12 (33–73) mmHg and their exercise capacity was 394 ± 145 (121–688) m in the 6-min walk test. IMA was 92 ± 14 (69–115) U ml^{-1} in the patient group and 93 ± 9.4 (76–122) U ml^{-1} in the control group with no significant difference between the two ($p = 0.85$), although almost one-third of the patients had detectable troponin-I.

Conclusions: We conclude that IMA, a marker of ischaemia, does not differ in patients with advanced clinically stable PH compared with normal subjects.

Keywords: *Biomarkers; ischaemia modified albumin; pulmonary hypertension*

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure above 25 mmHg at rest in the setting of a normal pulmonary arterial wedge pressure of 15 mmHg or less (Badesh et al. 2009). The 6-min walk test, a measure of exercise capacity and the New York Heart Association (NYHA) functional classification, a measure of severity, both correlate with disease severity and prognosis and are used to follow the response to treatment (Hoeper et al. 2004).

An increasing number of biomarkers, however, have been described and may be of interest in diagnosis and therapy (Warwick et al. 2008). Disruption of the cardiac myocyte membrane, when cell necrosis occurs, causes release of cardiac troponins in the peripheral blood. Detectable troponin T has been documented in PH and has been linked to a poor prognosis (Torbicki et al. 2003). Severe right ventricular (RV) pressure overload may cause RV ischaemia without necrosis. It is not known, however, whether RV myocardial ischaemia adversely affects clinical outcome. The aim of the present study was to investigate whether ischaemia-modified albumin (IMA), a biomarker of ischaemia, which increases following percutaneous coronary intervention (Sinha et al. 2003, Quiles et al. 2003) and in relation to acute coronary syndromes (Christenson et al. 2001, Peacock et al. 2006), is also raised in advanced clinically stable, compensated patients with PH.

Methods

This is a case–control study and all study participants, patients and controls, gave written informed consent and the ethics committee of our institution approved the study protocol. We studied 32 patients with established PH all of whom are regularly followed up at the outpatient clinic of our hospital; all patients were clinically stable over at least the previous 3 months

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and the study took place between September 2007 and February 2009. Patients with significant anaemia (haemoglobin <11 g dl^{-1} and haematocrit <35%) or renal impairment (creatinine >1.8 mg dl^{-1}) and those with low albumin levels (albumin <3.5 g dl^{-1}) were excluded; IMA may be higher in anaemic patients (Cichota et al. 2008) and extremely low or high albumin levels may affect IMA. Patients with a recent history of acute coronary syndrome, cerebrovascular accident or acute peripheral arterial occlusion were also excluded from the study. Blood sampling was performed in the outpatients' clinic during regular follow-up visits. Blood samples were assayed for creatine kinase (CPK), the MB isoenzyme of creatine kinase (CPK-MB), cardiac troponin-I (Tn-I), total protein, albumin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), uric acid and IMA. All patients underwent evaluation of their functional class according to NYHA classification as well as the 6-min walk test.

Haemodynamic and echocardiographic assessments had been performed within the preceding 3 months in all patients. At right heart catheterization mean and systolic pulmonary arterial, mean atrial, pulmonary artery occlusion pressures and mixed venous saturation were obtained. Pulmonary vascular resistance and cardiac index were calculated based on Fick measurements. In addition, systemic pressure and saturation were recorded and systemic vascular resistance was calculated. On echocardiography an estimate of RV dimensions and function and degree of tricuspid regurgitation were recorded; RV dilatation was defined as mild (mid-RV diameter 3.4–3.7 cm), moderate (mid-RV diameter 3.8–4.1 cm) and severe (mid-RV diameter ≥4.2 cm) and RV function was defined as good (RV fractional area change ≥25%), moderate (RV fractional area change 18–24%) and poor (RV fractional area change ≤17%) (Lang et al. 2005). Our control group consisted of 32 healthy normal volunteers, age matched to our patients; there is evidence that gender has no significant effect on circulating IMA (Govender et al. 2008). In our control group we only assessed IMA serum levels.

Serum IMA was measured with the albumin cobalt-binding test on an Integra 800 analyzer (Roche, Basel, Switzerland), which is an indirect method of IMA measurement. Cobalt not bound to the N-terminus of albumin is detected using dithiothreitol as a colometric indicator. Blood samples were collected in serum separator tubes, centrifuged at 3000 rounds per min for 10 min and stored at −70°C for 1 month. All samples were tested in one session in triplicates and were thawed only once. The variability in IMA measurements in our laboratory was calculated in 15 patients as follows: three times consecutively for each sample at day 1, once at day 2 and once at day 3. The same-day variability was estimated with Cronbach's alpha and was 0.97 and the between-days variability was 0.95. Reference normal values for cardiac enzymes and NT-proBNP were as follows: CPK <190 mU ml^{-1}, CPK-MB <3.6 ng ml^{-1}, Tn-I <0.01 ng ml^{-1} and NT-proBNP <125 pg ml^{-1}.

We used the Mann–Whitney test for comparison of IMA levels between the patients and the controls as well as between patients according to their NT-proBNP and Tn-I levels. Statistical calculations were performed in SPSS version 14 (SPSS Inc., Chicago, IL, USA).

Results

Our patients were aged 50 ± 16 years (Table 1). According to the most recent classification, the underlying pathology was idiopathic arterial PH in 12 patients, scleroderma-associated PH in one patient, congenital heart disease associated with PH in six patients (five atrial septal defects and one patent ductus artery), portal hypertension-associated PH in three patients, thalassaemia-associated PH in two patients, in three PH associated with chronic obstructive pulmonary disease, in four PH due to chronic thromboembolic disease and in one PH associated with sarcoidosis (Simonneau et al. 2009). Regarding treatment, 18 patients were on bosentan, 11 were on sildenafil (10 of whom were also on bosentan), three on intravenous epoprostenol (these patients were on triple therapy), eight on calcium-channel blockers, six on digitalis, four on beta-blockers, 24 on diuretics and 24 on coumadin derivatives. Our normal subjects were aged 50 ± 15 years, of whom 20 were male and 12 female.

The patients' mean ± SD (range) IMA was 92 ± 14 (69–115) U ml^{-1} and the controls' was 93 ± 9.4 (76–122) U ml^{-1} with no significant difference between the two ($p = 0.85$). The patients' total protein and albumin were well within normal limits (7.2 ± 0.7 and 4.1 ± 0.3 g dl^{-1}, respectively). Indices of myocardial necrosis in the patient group were as follows: CPK was 57.5 ± 37.9 mU ml^{-1}, CPK-MB was 0.6 ± 0.5 ng ml^{-1} and Tn-I was 0.018 ± 0.02 ng ml^{-1}; nine patients in the overall group had detectable Tn-I (≥0.01 ng ml^{-1}). NT-proBNP was elevated at 1581 ± 2861 (18–12 549) pg ml^{-1}; only six patients had NT-proBNP in the normal range. Uric acid was 7.6 ± 1.9 mg dl^{-1}; eight patients had uric acid levels >8.4 mg dl^{-1}. When we compared IMA levels in troponin-positive and -negative patients, we found no significant difference ($p = 0.67$); likewise, no significant difference in IMA was observed in patients with elevated NT-proBNP compared with those with normal NT-proBNP ($p = 0.82$).

Discussion

We assessed IMA in clinically stable patients with advanced PH of various aetiologies and found that it does

not differ compared with age-matched normal subjects; almost one-third of these patients had detectable Tn-I.

PH may be associated with low systemic blood pressure and this may decrease the coronary perfusion gradient, leading to myocardial ischaemia. In addition, increased RV intramural pressure may disturb RV myocardial perfusion. In one study, 14% of patients with PH were troponin T positive and these had higher heart rates, lower mixed venous saturation, higher NT-proBNP, walked less in the 6-min walk test and had worse survival at 24 months (Torbicki et al. 2003). In accordance to this study, we also found that 28% of our patients had detectable Tn-I; IMA levels, however, did not differ in relation to Tn-I or NT-proBNP implying that, unlike markers of necrosis and haemodynamic derangement, markers of ischaemia may not be suitable for risk stratification in PH. In addition, in these stable PH patients, myocardial necrosis may occur without preceding ischaemia, as similarly happens in stable dilated cardiomyopathy patients (Sbarouni et al. 2009a). Interestingly, IMA has been investigated in relation to acute pulmonary embolism both in patients as well as in animal models and has been found to be elevated compared with controls (Turedi et al. 2007, 2008, 2009); however, no data on pulmonary artery pressure are reported in these studies. In chronic PH, RV adapts to chronic pressure overload with wall hypertrophy and chamber dilatation whereas in acute pulmonary embolism, RV subendocardial ischaemia due to acute pressure overload of the ventricle is probably intense; this may explain the discrepancy of the findings concerning IMA in the acute and the chronic setting.

IMA, a biomarker of ischaemia, increases following percutaneous coronary intervention (Sinha et al. 2003, Quiles et al. 2003) and coronary artery bypass grafting (Sbarouni et al. 2009b) as well as in relation to acute coronary syndromes (Christenson et al. 2001, Peacock et al. 2006). Regarding IMA, there are limited reports in association to cardioversion (Roy et al. 2004a), radiofrequency ablation (Roy et al. 2004b, Sbarouni et al. 2007) and pacemaker insertion (Sbarouni et al. 2008b); its role in non-invasive evaluation of coronary artery disease is under investigation (Van der Zee et al. 2005, Sbarouni et al. 2006, 2008a, Kurz et al. 2007). In ST segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention IMA correlates with incomplete ST segment resolution and left ventricular ejection fraction and inversely with melatonin levels and is a predictor of short-term mortality (Dominguez-Rodriguez et al. 2008a, b, 2009a, b). Ischaemia, through hypoxia, acidosis, free radical injury and energy-dependent membrane disruption, may reduce the binding capacity of the amino terminus of albumin to bind metals such as cobalt, copper and nickel; numerous investigations, with a well-validated assay, not only demonstrate a correlation between IMA and myocardial ischaemia but also a link to clinical outcome in both acute coronary syndromes and percutaneous coronary interventions (Consuerga-Sanchez et al. 2008, Dusek et al. 2006). IMA seems to be sensitive but not specific as is not only related to cardiac ischaemia, but to muscle (Falkensammer et al. 2007), gastrointestinal (Apple et al. 2002), brain (Abboud et al. 2007), and pulmonary ischaemia (Turedi et al. 2007). We have previously examined whether IMA increases in patients with

Table 1. Baseline clinical characteristics, exercise capacity and echocardiographic and haemodynamic data in 32 patients with advanced, stable pulmonary hypertension.

Age (years)	50 ± 16 (21–71)
Female, *n* (%)	23 (72)
Heart rate (bpm)	81 ± 16 (61–117)
Systolic blood pressure (mmHg)	122 ± 20 (86–150)
Diastolic blood pressure (mmHg)	74 ± 12 (55–102)
NYHA functional class	
I	4
II	15
III	12
IV	1
6-Min walk distance (m)	394 ± 145 (121–688)
Echocardiography	
RV dilatation	
Normal/mild	5
Moderate	21
Severe	6
RV function	
Good	19
Moderate	9
Poor	4
Tricuspid regurgitation	
1-2 +/4+	11
2-3 +/4+	10
3-4 +/4+	11
Pulmonary haemodynamics	
SPAP (mmHg)	85 ± 20 (45–130)
mPAP (mmHg)	56 ± 12 (33–73)
mRAP (mmHg)	11 ± 5 (4–30)
m PCW (mmHg)	15 ± 5.8 (7–31)
mAAP (mmHg)	92 ± 15 (64–117)
CO (l min^{-1})	4.3 ± 1.8 (2–9.1)
CI (l min^{-1} m^{-2})	2.5 ± 1 (1.1–5.2)
Mixed venous O_2 saturation (%)	67 ± 9 (49–86)
Arterial saturation (%)	94 ± 5 (80–99)
PVR (Wood units)	11.2 ± 6.2 (2.6–26.5)
SVR (Wood units)	24 ± 12 (9–59)

Data are presented as mean ± SD (range). NYHA, New York Heart Association; RV, right ventricle; SPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mPCW, mean pulmonary wedge pressure; mAAP, mean aortic arterial pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

clinically stable dilated cardiomyopathy and, as in this study, we found that it does not (Sbarouni et al. 2009a); in contrast other studies have shown that cardiac troponins may be increased and determine prognosis in dilated cardiomyopathy.

BNP is elevated in various forms of PH, correlates with haemodynamics, exercise capacity and NYHA class and is of prognostic significance (Fijalkowska et al. 2006, Nagaya et al. 2000). NT-proBNP is an alternative biomarker that appears to provide the same information, with advantages over BNP on stability of the marker and accuracy of the assay (Fijalkowska et al. 2006, Nagaya et al. 2000). In our study all but six patients had elevated NT-proBNP.

These are all stable patients with chronic PH evaluated in the outpatient department as part of their regular follow-up visit; patients with decompensated heart failure as well as renal failure or liver failure were by protocol excluded from the study. IMA is, however, affected by multiple variables such as exercise and hydration status at the time of sampling that one cannot easily correct for.

In conclusion, in clinically stable patients with advanced PH of variable underlying pathology, IMA levels do not differ compared with age-matched normal subjects.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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