

# Biochemical markers in the management of pulmonary hypertension

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## Summary

Pulmonary arterial hypertension (PAH) is a severe disease usually diagnosed by echocardiography and further confirmed by right heart catheterisation. Follow-up under treatment consists in assessment of clinical signs, various types of exercise testing and repeated echocardiograms. Several molecules which can be measured in the blood or sometimes in other biological fluids are known to be elevated in PAH. The most extensively studied are members of the family of natriuretic peptides, uric acid, and products generated by nitric oxide activity. Due to the low prevalence of PAH and

their suboptimal specificity, these potential markers are generally of modest positive predictive value which precludes their use as screening tools. However, some of them correlate significantly with prognosis, and thus, in conjunction with classical clinical and paraclinical parameters, they may be a further aid to clinical decision-making for the specialist dealing with PAH patients.

*Key words: pulmonary hypertension; natriuretic peptides; markers*

## Introduction

Pulmonary hypertension is a disease which dramatically limits exercise capacity and seriously reduces life expectancy. The causes of or conditions associated with pulmonary arterial hypertension (PAH) are well documented and were recently reclassified at the 3<sup>rd</sup> World Symposium on PAH (Venice 2003, table 1) [1]. The symptoms and clinical signs of early PAH are notoriously vague and unspecific, and hence PAH is often misdiagnosed for other conditions such as asthma, cardiac ischaemic disease, muscular deconditioning or even depression. Most often the diagnosis is established by transthoracic echocardiography, on the basis of the velocity of the regurgitant tricuspid jet. Commonly used definitions of PH are pulmonary artery systolic pressure (PASP) >35 mm Hg or mean >25 mm Hg at rest, or mean >30 mm Hg at exercise [2]. In some cases, such as emphysema or mild PAH, the tricuspid jet cannot be measured and the diagnosis of PAH may be missed. Echocardiographic findings should be confirmed by right heart catheterisation with invasive haemodynamic measurements and acute vasoreactivity testing [3].

The follow-up of patients with PAH is based on history and clinical evaluation, assessment of exercise capacity according to the NYHA/WHO scale and exercise testing such as the 6 minutes walking test (6MWT) [4]. This latter test has been shown to correlate well with haemodynamic measurements and with survival, and it has thus been a

major endpoint in recent clinical studies. In experienced hands echocardiography can also be a valuable tool for evaluation of the long term response to drug therapy [5].

Until now blood tests have not been used on a regular basis either for screening or follow-up under treatment. Several biological substances are known to be elevated in PAH and have been measured in peripheral blood (table 2). We briefly review the most relevant biomarkers in PAH and analyse their usefulness in the clinical setting.

### Abbreviations:

PAH	Pulmonary arterial hypertension
6MWT	6 minutes walk test
BNP	Brain natriuretic peptide
ANP	Atrial natriuretic peptide
CTnT	Cardiac troponin T
ET-1	Endothelin-1
NO	Nitric oxide
CGMP	Cyclic guanosine monophosphate
ACE	Angiotensin-converting enzyme

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**Table 1**

Clinical Classification of Pulmonary Hypertension (Venice 2003), see reference [1].

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Collagen vascular disease
1.3.2. Congenital systemic-to-pulmonary shunts
1.3.3. Portal hypertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Other
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary haemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxaemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitude
3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Non-thrombotic pulmonary embolism
5. Miscellaneous Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels

**Table 2**

Potential biochemical markers in pulmonary hypertension.

Markers	Main site of synthesis	Selected clinical human studies
Brain natriuretic peptide (BNP)	myocytes	[6, 8]
Pro-brain natriuretic peptide (ProBNP)	myocytes	[9, 11]
Troponin T	myocytes	[14]
Uric acid	ubiquitous	[15, 44]
Endothelin-1	endothelium	[19–22, 47]
Serotonin	platelets (storage)	[29]
Angiotensinogen/angiotensin I–III, ACE	vascular wall	[30, 48]
NO	endothelium	[28]
cGMP	vascular wall: smooth muscle	[24, 49]
D-dimers	from fibrin; ubiquitous (platelets)	[41]

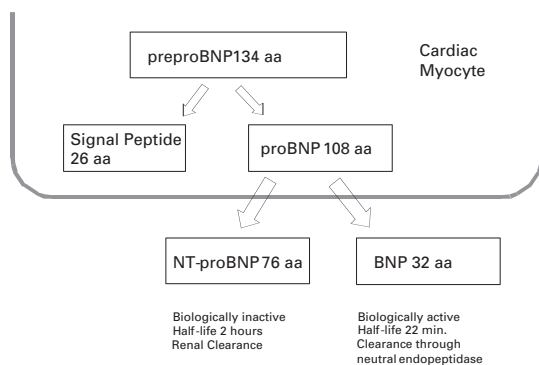
## Natriuretic peptides

Atrial natriuretic (ANP) and brain natriuretic peptide (BNP) represent the major hormones of the natriuretic peptide system. These peptide hormones are synthesised and excreted mainly by the cardiac myocytes from both the right and left ventricles. BNP is first synthesised as a precursor,

preproBNP, which is enzymatically cleaved to form proBNP. ProBNP is further processed into mature BNP and an N-terminal fragment, NT-proBNP, which is biologically inactive (figure 1). Mature BNP has a short half-life of about 22 min in plasma, whereas NT-proBNP has a half-life of

**Figure 1**

Intra- and extracellular processing of brain natriuretic peptide.



2 hours. This latter peptide is cleared through the kidneys and hence its blood level rises in a significant way in the event of altered renal function, which is not the case of BNP.

BNP has been shown to be elevated in various form of PAH including idiopathic PAH [6], PAH associated with interstitial lung disease [7], with congenital systemic-to-pulmonary shunts [8], with chronic obstructive pulmonary disease [9], and in chronic thromboembolic pulmonary hypertension [10]. Thus, whereas BNP levels are not discriminative for the aetiology of PAH, they correlate with other classical endpoints such as the NYHA functional class, the 6MWT and haemodynamic parameters [6].

Since NT-proBNP shares the same intracellular precursor with BNP, it comes as no surprise that similar findings have been published with this peptide. In particular, NT-proBNP is elevated in PAH associated with systemic sclerosis [11], and in idiopathic PAH [9]. In this latter study, various terminal chronic pulmonary diseases, even with mild to moderate PAH, were not associated with elevated NT-proBNP.

ANP is also elevated in idiopathic and other forms of PAH. Wiedemann and colleagues observed a tenfold increase in 18 patients, including 11 with idiopathic PAH. However, ANP does not appear to be elevated in moderate PAH associated with various conditions [12].

A large body of evidence shows that in normal individuals natriuretic peptides are secreted from the atrium, whereas in the case of left or right ventricular hypertrophy or failure, both ventricles could be the major sources of synthesis. It is therefore obvious that in any case where cardiopathy affecting the left heart coexists with PAH, the diagnostic or prognostic value of natriuretic peptide levels are meaningless. Other conditions such as acute respiratory distress syndrome are also known to raise natriuretic peptide levels [13].

## Troponin

Cardiac troponin T (cTnT) is a specific marker of cardiomyocyte injury which is detectable when either the left or the right ventricle is injured. Torbicki and colleagues have recently evaluated the prognostic value of this biochemical parameter in 56 patients with severe PAH [14]. Significant levels of cTnT were detected in 8 patients. Despite similar cardiac haemodynamics, these patients had significantly worse survival than the remaining 48. Indeed, cTnT was found by multivariate analysis to be an independent risk factor for mortality in a 24-month period, together

with the 6MWT and pulmonary vascular resistance. It is therefore likely that cTnT is a marker of excessive stress to the right ventricle, and the authors suggest that cTnT may be of use in making therapeutic decisions such as starting intravenous epoprostenol or putting the patient on the waiting list for lung transplantation. Experience to date with cTnT relies on the experience of a single centre, and therefore the data, to be fully validated, require confirmation by publications from other investigators.

## Uric acid

Uric acid may be elevated in the blood of patients with chronic hypoxic conditions such as heart failure or COPD. The elevation is thought to be the consequence impaired oxidative metabolism of the tissue, with increased degradation of adenine nucleotides such as ATP. Uric acid is known to be a risk factor for long term mortality

in heart failure. Uric acid has been found to be elevated in the serum of patients with idiopathic pulmonary hypertension, and correlates with pulmonary vascular resistance [15]. In the light of a study with a 31-month follow-up period in 90 patients, uric acid also appears to be an independent risk factor for mortality [15].

## Endothelin-1

Endothelin-1 (ET-1) is a 21 aminoacid peptide with potent vasoconstricting and remodelling properties. Increased gene expression of this molecule has been observed in the arterial wall of patients with idiopathic PAH [16] and synthetic antagonists of ET receptors have proved to be beneficial in various forms of PAH [17, 18]. Several reports have shown elevated plasma levels for ET-1, or its precursor Big ET-1, in PAH [19–21] and in PAH associated with COPD [22]. However, ET-1 measurement is complicated by technical difficulties: 1. the half-life of the molecule is extremely

short (merely a couple of minutes), 2. a significant part of the plasmatic ET-1 pool is cleared through the pulmonary vascular bed by neutral endopeptidase, and therefore sampling from the pulmonary bed may differ significantly from venous peripheral blood, 3. ET-1 levels appear to be quite sensitive to physiological or pathological factors such as upright versus supine position, venous blood stasis, systemic hypertension etc. For these reasons plasma ET-1 is far from being a real-life ideal marker outside the setting of carefully conducted clinical studies.

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## Products of NO metabolism

Nitric oxide (NO) plays a critical role in the regulation of pulmonary vascular resistance [23]. The endothelial isoform of NO synthase (ecNOS) generates free NO in the nanomolar range which acts in a paracrine way on the smooth muscle cells to generate cyclic guanosine monophosphate (cGMP) and eventually smooth muscle relaxation. Theoretically a low plasma NO could be a marker of endothelial dysfunction and possibly of PAH, but NO itself is too labile to be measured in its gaseous form in the blood. Plasma cGMP has been used as a surrogate marker of ecNOS activity through activation of guanylate cyclase, especially in hypertension affecting the neonate [24]. It is important to bear in mind, however, that both NO and natriuretic peptides are able to generate cGMP, and therefore plasma cGMP levels usually correlate with BNP or ANP levels and are elevated

in PAH [25]. cGMP can also be measured in the urine and is elevated in PAH compared with controls or patients with acute asthma [26]. It is interesting to note that urinary cGMP correlates with haemodynamics in PAH patients, especially with cardiac index. In accordance with pathophysiological knowledge, plasma nitrite levels were found to be low in patients with chronic hypoxic lung diseases [27]. Currently, plasma nitrite is not considered as a marker of pulmonary hypertension. Although NO can also be measured in exhaled air [28], endogenous production of NO by the airway mucosa usually far exceeds the fraction diffusing from the lung vessels, thus precluding its measurement as a marker of pulmonary circulation homeostasis. As is the case of the natriuretic peptides, products of NO metabolism are elevated in either chronic or acute congestive heart failure.

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## Serotonin

Serotonin is a vasoactive substance that is synthesised in enterochromaffin intestinal cells, actively stored in platelets and cleared through the vascular endothelium. In clinical conditions an increase in plasma serotonin could be the result of either platelet activation (as in thrombosis) or defective endothelial clearance. Mean plasma serotonin concentration was elevated in 16 patients with severe idiopathic PAH compared with controls and correlated with pulmonary vascular resistance [29]. It is interesting to note that

epoprostenol treatment, a known antiaggregating agent conventionally used for stage IV PAH, did not modify plasma serotonin levels in PAH patients despite haemodynamic improvement. While the exact origin of elevated plasma serotonin remains unclear, this study demonstrates that platelet activation is not involved and that defective endothelial clearance is the more likely culprit. Serotonin concentration cannot be used to monitor treatment efficacy in patients with PAH [29].

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## Other endothelial markers

The expression of various endothelial markers has been investigated in the context of PAH. Angiotensin-converting enzyme (ACE) genotype DD appears to be more often expressed in severe

idiopathic PAH [30, 31]. Locally, expression of immunoreactive ACE has been observed in plexiform lesions, a hallmark of almost all forms of PAH [32]. Increased serum ACE activity has been measured

in patients with collagen vascular disease-associated PAH compared with unaffected patients. However, there is a large overlap between the two groups, suggesting that a clinically useful threshold would be difficult to establish.

Abnormalities in von Willebrand factor

[33-35], plasmin- $\alpha$ 2 inhibitor complex [36], thrombomodulin [37], lipoprotein(a) [38], and angiopoietin [39] have all been described in animal models or human PAH. However, more clinical studies are needed to evaluate their practical usefulness as surrogate markers in patients with PAH.

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## Fibrinogen metabolism products

It is now well recognised that *in situ* microvascular thrombosis does occur in all forms of PAH and accelerate the progression of the disease [40]. On the basis of these observations Shitrit and colleagues investigated the significance of the well known D-dimer assay in 14 patients with idiopathic PAH [41]. D-dimer assay correlated with

exercise capacity assessed both by the NYHA scale or the 6MWT, and correlated inversely with one year survival ( $p = 0.004$ ). The median value was 1085  $\mu\text{g/L}$  with a range from 20-6200  $\mu\text{g/L}$ . These preliminary data obviously need confirmation in a larger group of patients and adequate control groups.

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## Potential clinical applications

An ideal marker should be sensitive, reproducible and easy to perform. It is not sufficient for a biological parameter to be elevated in affected patients and to correlate more or less closely with

other clinical variables. In the case of PAH, a potential application of biochemical markers may be for screening or for clinical follow-up of treated patients.

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## Screening

PAH is too rare a disease (incidence  $4/10^6$  inhabitants per year for idiopathic PAH) for screening to be applied to the general population [42]. However, screening could be relevant in risk groups such as familial PAH, systemic sclerosis, cardiac shunt or liver disease. Allanore and colleagues have published the results of screening in 40 consecutive patients with limited or diffuse disease [11]. Systemic sclerosis is a disease which may be complicated by PAH in 10-30% of cases. Using systolic PA pressure measured by echocardiography, the authors identified 10 patients with PAH. The negative predictive value of a commercially available kit for NT-proBNP determination was quite high at 96%, meaning that when an NT-proBNP value is below the 97<sup>th</sup> centile the probability of PAH is very low. However, the positive predictive value was only at 69.2%, that is, the significance of high NT-proBNP is questionable in the context of PAH. In patients where the preva-

lence of PAH is lower, e.g. in rheumatoid arthritis or in HIV patients, the predictive positive value would fall still further. It must also be emphasised that in this study of scleroderma, patients with heart failure were carefully excluded by nuclear ventriculography. The cost-effectiveness of screening is obviously unfavourable compared with echocardiography, which provides both diagnoses in the same examination. It is worth recalling that echocardiography has been shown to have 90% sensitivity and a 75% specificity in the context of PAH associated with systemic sclerosis [43]. To arrive at a definitive assessment of a biochemical marker as a screening tool for PAH it would be necessary to conduct a study comparing conventional echocardiography and the putative marker, using right heart catheterisation as the gold standard. To the best of our knowledge no such study has been yet published.

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## Clinical follow-up

Right heart catheterisation cannot be performed repeatedly and in many cases pulmonary systolic pressure measured by echocardiography does not change despite obvious improvement or deterioration of a patient's condition. Other meth-

ods of clinical evaluation such as the 6MWT are conventionally used for patient follow-up. Biochemical markers such as BNP and proBNP [11, 44], uric acid [45], D-dimers [41] and troponin T [14] have shown promising results in that they



appear to correlate with survival, often independently of haemodynamics. It will be of interest to evaluate how these markers compare with new developments in echocardiography and magnetic resonance imaging [5, 46]. Although these positive data need to be confirmed in larger studies, a plausible case can be made that in the future such markers, used in conjunction with conventional clinical evaluation, could be of assistance in therapeutic decision-making such as medication change or lung transplantation. It is however premature to recommend their routine use in daily practice. At present these markers are of interest to pulmonary hypertension specialists in possibly providing

deeper insights into the pathophysiology of the disease.

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