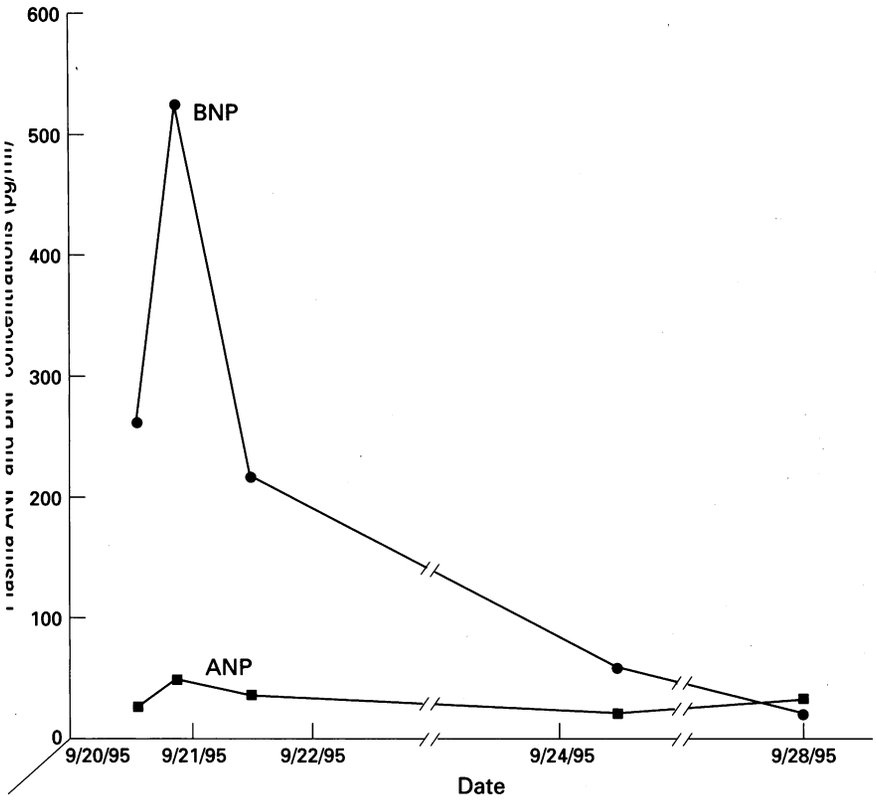

Serial changes in plasma ANP and BNP concentrations.

kinase-MB did not increase. Coronary angiography revealed no organic coronary stenosis, and left ventriculography showed no asynergy of the wall motion without regurgitation. The venograms of the lower extremities revealed varices but not thrombi. The patient was discharged on anticoagulant treatment with warfarin.

The figure shows the changes in the plasma concentrations of ANP and BNP obtained from the peripheral vein measured by immunoradiometric assay.[2] Plasma BNP was raised to 265 pg/ml immediately after admission, and further to 522 pg/ml eight hours after admission. However, after treatment of the pulmonary hypertension, plasma BNP rapidly decreased.

In this case, severe pulmonary hypertension and the subsequent enlargement of the right ventricle were found on admission. The stretch of the right ventricular myocytes would cause the rapid synthesis and secretion of BNP. In accordance with the decrease of pulmonary hypertension and stretch of the right ventricle, plasma BNP concentration also decreased. This suggested that the synthesis and secretion of BNP responded rapidly to the change in right ventricular wall stretch. Although it has been reported that BNP is rapidly produced and secreted by rapid overload in the left ventricles,[6] there has been no report demonstrating the changes in the plasma BNP concentrations in response to right ventricular overload. Besides right ventricular overload, neurohumoral factors secreted following acute pulmonary thromboembolism might stimulate the synthesis and secretion of BNP. In conclusion, this is the first report providing evidence that plasma BNP is rapidly increased in acute pulmonary thromboembolism. Further study is required to examine the pathophysiological roles of BNP in acute pulmonary thromboembolism or pulmonary hypertension.

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Assessment of endothelial function using plasma markers

SIR,—As the endothelium is undoubtedly the target organ for the disease process in coronary artery disease, assessment of its function is a valuable tool. Mullen and colleagues[1] recently underlined this statement in their editorial on the non-invasive assessment of endothelial function. Although this was an excellent review of recent literature, we were surprised at the lack of any discussion of established plasma markers of endothelial damage or dysfunction as a non-invasive assessment of endothelial function. While they believed that "research on the benefit of an early intervention has been limited by the lack of a clinical marker of atherogenesis which could be used to identify groups of individuals with early disease and to measure the effects of intervention", we have recently discussed three such possible markers in this journal and elsewhere.[2,3]

One marker, von Willebrand factor, warrants attention as it is widely believed that raised plasma concentrations reflect endothelial cell dysfunction, and are found in patients with all the major risk factors for this disease.[2,4–8] Such high concentrations are reversible with treatment of the particular risk factor[5,6] and raised concentrations are predictive of future adverse disease in patients with existing atherosclerosis or its risk factors, or indeed in members of the community without clear disease.[7,8] It follows that strategies aimed at reducing levels of von Willebrand factor (for example, by stopping smoking and reducing cholesterol) ought to translate in to an improved outcome.

Less is known about another plasma endothelial marker, soluble thrombomodulin (CD141), which is normally found in its intact state on the surface of the endothelium where it has anticoagulant properties. Increased concentrations are also likely to reflect a damaged endothelium, and are found in ischaemic heart disease and peripheral vascular disease.[9,10] Although the relations between the risk factors for atherosclerosis and soluble thrombomodulin are only partially understood,[11] raised concentrations, like those of von Willebrand factor, are predictive of adverse outcome in subjects surviving a myocardial infarction.[12]

Increased concentrations of adhesion molecule E-selectin (CD62E) appear at the surface of the endothelium in response to inflammatory stimulation, and raised concentrations of a soluble form appear in tissue culture supernatants and in the plasma under similar conditions.[13] However, early indications that increased soluble E-selectin in vivo may mark endothelial cell dysfunction have not been realised and concentrations are influenced by only some risk factors. In addition, we have found that concentrations are only weakly raised in ischaemic heart disease,[10] are not raised in peripheral vascular disease,[14] and do not predict adverse outcome following myocardial infarction or in patients with hypercholesterolaemia.[8,12] However, the recent report by Belch *et al*[15] found not only increased concentrations of E-selectin in patients with peripheral vascular disease, but also that raised concentrations predicted patients at risk of restenosis following angioplasty.

The gold standard plasma marker for endothelial cell function would ideally be a specific product of this cell. Regrettably, some of the measurable markers (at least in theory) also derive from other cells such as platelets. Despite this caveat, von Willebrand factor currently appears to be the most promising as a plasma marker of endothelial function, especially as much is known about the behaviour of this molecule in physiology and pathology. This marker also has well established relations to cardio-

vascular disease, risk factors, interventions, and prognosis, fulfilling criteria for a suitable non-invasive assessment of endothelial function. Furthermore, several groups have targeted this molecule as a means of intervening in the thrombotic process.[16] The next five years will tell if this approach is successful.

The non-invasive approach outlined by Mullen and colleagues has provided invaluable opportunities to dissect the pharmacology of the endothelium. However, by its very nature such an approach is unlikely to provide epidemiological data or even data to compare groups with large numbers of subjects. We submit that plasma markers such as von Willebrand factor and soluble thrombomodulin are likely candidates for providing data of this nature.

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This letter was shown to the authors, who reply as follows:

We read with interest the letter from Drs Blann and Lip regarding the advantages and limitations of plasma markers of endothelial cell function. We share their interest in this area of research and its potential clinical application. We feel, however, that evaluation of nitric oxide mediated arterial physiology in large conduit arteries using the non-invasive techniques described[1] may provide insight into the pathophysiology of vascular disease, be an early marker of endothelial injury, and a means of evaluating interventions early in the natural history of atherogenesis.

The value of these measures in predicting disease development and outcome is not known and is central to current research efforts. Our published data, however, indicate that this technique can be used to study endothelial function in large groups of subjects from early in childhood, to provide epidemiological data, compare groups of subjects with risk factors, and demonstrate beneficial response to interventions.[2–5]

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CORRECTION

Pregnancy and congenital heart disease
C M Oakley Heart 1997;78:12–14.

The first sentence of the section **Atrial septal defects** should have read:

"The only frailty of patients with unrepaired atrial septal defects is intolerance of blood loss that can force left to right shunting, to the sudden detriment of left ventricular and coronary flow."

And not as published. The error is regretted.