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CRP AND VASCULAR RISK INFORMATION SHEET

INTRODUCTION

Virtually all people develop the first lesions of vascular disease before the age of ten. This lesion may evolve into typical plaques which may progress through various stages, from the relatively simple structure of the fatty streak, to the stable or sometimes unstable plaques of advanced atherosclerosis. The evolution of these lesions revolves around a complex interplay between the vascular endothelium, vascular smooth muscle, and the immune system. It is know well understood that atherosclerosis represents a chronic inflammatory lesion, with overall great similarity to other chronic inflammatory processes e.g. Rheumatoid Arthritis (RA). The principal response of the immune system is migration of macrophages and T cells to the vascular intimal space, after recruitment by the activated endothelium. The local production of cytokines directs plaque evolution and induces migration of vascular smooth muscle cells, in an attempt to contain and stabilise the vascular injury, through evolution into a stable fibrotic plaque. Alternatively, an unstable atherosclerotic plaque, prone to rupture and catastrophic occlusion, may result. As in other inflammatory lesions, the macrophage is thought to have a key role in both the development and the destabilisation of the plaque.

The ability to predict patients at risk of progression to an acute vascular event allows measures such as life style modification, commencement of aspirin and HMG Co-A inhibitor treatment to be instituted. In the recent past there has been an addition of several molecular markers to the well established risk factors of smoking, family history, hypertension, diabetes and high levels of LDL cholesterol. These include the inflammatory markers C-reactive protein (CRP), serum amyloid A and interleukin-6. Of these inflammatory markers high sensitivity CRP measurement has been shown to be the most significant predictor of cardiovascular events. The presence of inflammatory markers such as CRP, before a clinical event, is likely to indicate ongoing inflammation associated with plaque evolution. This continuing inflammation, associated with vascular events, must indicate a greater likelihood of a plaque becoming unstable.

CHANGES TO THE ESTIMATION OF SERUM LEVELS OF CRP

Until recently, the major reason for measuring serum CRP levels was to help determine the activity of chronic inflammatory processes such as RA, in which CRP levels become markedly elevated. Determination of the normal range for serum CRP has been done using normal population based studies. However, atherosclerosis is virtually a universal finding within this population and thus the normal range for CRP also, to some extent, reflects the level of inflammation, due to atherosclerosis, that is present in normal individuals.

To reliably measure serum CRP levels in the normal range requires some changes to the assay. Till recently, the CRP assays were largely geared to measure elevated levels and were relatively insensitive, especially at the lower end of the normal range. These assays have now been improved so that it is possible to gain a much more precise measurement CRP, even to the lower end of the normal range. This has made it possible to use serum CRP measurement to help determine the relative risk for the development of an acute obstructive vascular event such as myocardial infarction or thrombotic strokes.

Sydpath has recently changed to this new more sensitive CRP assay and it is now possible to use our estimations for vascular risk prediction. In this context it is important to note that measurement of CRP is only useful or interpretable in patients without active inflammatory diseases (e.g. RA), acute infections or pulmonary embolism. Although patients with inflammatory diseases are at increased risk of developing vascular disease, the usefulness of CRP measurement to predict cardiac risk is not clear.

USING SERUM CRP LEVELS FOR CARDIOVASCULAR RISK ASSESSMENT IN THE WELL PATIENT

Probably the best validated and quantitated relationship of CRP level to vascular risk is in otherwise well subjects. In large prospective studies the risk of developing a vascular event such as myocardial infarction or stroke has been quantified, and is presented in the table below. It may be used, with other risk factors, in the patient assessment and management of vascular disease [4].

	Serum CRP levels within the normal range (mg/L)				
	<0.6	0.6-1.0	1.0-2.0	2.0-3.0	>3.0
Relative risk for development of vascular occlusion	1	1.2	1.4	1.7	2.1

RESEARCH STUDIES ON THE RELATIONSHIP OF CARDIOVASCULAR RISK TO CRP LEVELS

Whilst in these areas, data is not sufficiently robust and standardised for routine clinical use, there is a growing body of evidence that CRP estimation may also be helpful for cardiovascular risk assessment in other more acute situations. The results of some of these studies are summarised below:

CRP may be useful in the context of acute chest pain. It has been estimated that 15 % of patients presenting with chest pain who go on to develop myocardial infarction have a negative troponin. In this scenario an elevated CRP may indicate patients who require more urgent intervention. In stable angina, patients CRP levels >3mg/L are twice as likely to

develop serious cardiac events than similar patients with lower levels (<1.5 mg/L, male; <3.8 mg/L, female) [1,2].

In patients with unstable angina a CRP >3mg/L predicted an increased likelihood of having an infarction within three months. These levels are also associated with an increased risk of dying from heart disease, and the higher the level, the greater the risk. In patients with established angina it is ideal to have a CRP level less than 1.5 mg/L [3,4].

In patients who are having a myocardial infarction, CRP levels rise to a peak within two to four days. The higher the peak, the greater the risk of early complications such as recurrent heart attacks, and cardiac death. Generally peak levels greater than 25 mg/L indicate a higher risk of additional complications of myocardial infarction, such as re-infarction [1,3].

In patients who have undergone successful angioplasty stenting procedures, CRP levels higher than 5 mg/L can help predict poor long-term results, such as restenosis or additional cardiac symptoms. There is also a small amount of evidence that persistently raised CRP levels 96 hrs after a stenting procedure predicts in-stent stenosis at 6 months [5].

The predictive value of CRP may be extended to the pre-operative assessment of patients going to have major, non-cardiac, vascular surgery. Higher CRP levels in this situation are associated with a higher incidence of future myocardial infarction, independent of traditional markers of disease. A raised CRP (>4 mg/L) in this situation maybe useful for identifying those patients who would benefit from additional anti-inflammatory treatment [6].

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