Coronary sinus blood sampling: an insight into local cardiac pathophysiology and treatment?

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ATHEROSCLEROSIS REMAINS THE UNDERLYING CAUSE OF CARDIOVASCULAR DISEASE AND IS A DYNAMIC PROCESS INVOLVING INFLAMMATION, HEMOSTASIS, ENDOTHELIAL DYSFUNCTION, AND ANGIOGENESIS. STUDIES OF CIRCULATING FACTORS FROM PERIPHERAL BLOOD CAN PROVIDE AN INSIGHT INTO THIS PATHOPHYSIOLOGY BUT MAY REMAIN INDICATIVE OF A MORE GENERALIZED, SYSTEMIC PROCESS. MORE LOCALIZED INTERACTION(S) WITHIN THE HEART MAY BE BETTER STUDIED FROM CORONARY BLOOD SAMPLES. INDEED, AN INCREASING NUMBER OF PROSPECTIVE STUDIES SHOW GOOD CORRELATION BETWEEN INDICES OF THESE PROCESSES AND CLINICAL OUTCOMES. AS LOCAL SAMPLING OFFERS A UNIQUE WAY OF ASSESSING THE LOCAL CARDIAC MILIEU, THIS MAY PROVE USEFUL IN THE MONITORING OF BOTH LOCAL/SYSTEMIC DRUG THERAPIES AND INTERVENTIONAL TECHNOLOGIES.

KEYWORDS
Coronary sinus; Circulating factors; Myocardial ischaemia

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and disability in the developed world.1,2 Of those aged less than 65 years, CVD currently accounts for 30% of all deaths3 and substantially contributes to the escalating cost of health care.4 However, the differentiation between coronary and linked vascular death attributable to generalized atherosclerosis (for example, stroke) is less well defined. Population studies have developed scoring systems in an attempt to define risk of future events but these are frequently linked to generalized atherosclerosis than specific coronary event rates. Thus these include generalized population vascular event rate associated with both immutable [age, gender, and family history of premature coronary artery disease (CAD)] and modifiable factors (such as hypertension, diabetes, smoking, and lipid profile).5

Atherosclerosis, the underlying cause of CVD, is a dynamic process involving the pathophysiological processes of inflammation, haemostasis, endothelial dysfunction, and angiogenesis. Studies involving indices reflecting these processes, both from peripheral and the cardiac microcirculation, can provide an insight into this pathophysiology with potential prognostic benefits. One problem with the measurement of blood indices from the peripheral circulation is that measured levels may not reflect intracoronary levels and, instead, can be indicative of a more generalized, systemic process. Other methods to reflect the coronary (or intracardiac) micro-environment are therefore needed.

In order to focus more clearly on the coronary vasculature, selective catheterization of the coronary circulation may be one approach. Coronary sinus (CS) catheterization, for example, is well established as a method to compare proposed myocardial protection strategies in cardiac surgery.6 In routine electrophysiological studies,7 access to the CS allows for diagnostic and therapeutic manoeuvres. Dependent upon their circulating kinetics and responsiveness, assays of these various pathophysiological indices obtained at CS sampling may offer enhanced sensitivity or specificity for coronary events, from assessments of the local intracardiac milieu to a lack of dilution effects. In this review article, we examine the role of measuring plasma indices (biomarkers) of inflammation, haemostasis, endothelial damage/dysfunction, and angiogenesis from the coronary circulation in the pathogenesis, treatment, and prognosis of myocardial ischaemic events.

SEARCH STRATEGY

We performed a search using electronic databases (MEDLINE, EMBASE, CINAHL, and DARE) between 1966 and 2005. Medical subject headings 'sinus', 'circulation', 'venous', 'intracardiac', 'sinus catheterisation' were combined with 'biomarkers', 'inflammation', 'thrombogenesis', 'angiogenesis', 'endothelium' and 'coronary' 'myocardium', 'heart disease', and 'atherosclerosis', 'atheroma', 'plaque' and 'ischaemia'. The search was limited to papers published in the English language and excluded studies involving electrophysiology only with no blood parameters quantified. The reference list of identified studies was scrutinized and relevant citations examined.

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Methods to study the local cardiac circulation

Though the venous system of the heart comprises variable anatomical branches, drainage is primarily via the CS into the right atrium (RA) (Figure 1). In addition to electrophysiological mapping and pacing, the CS can be cannulated and used to study changes in flow, temperature, and, more commonly, blood sampling. In this respect, it is important in the first instance to note that alternative venous pathways exist (Figure 2); they are generally not thought to contribute to significant venous drainage and thus, cannulation of the CS can give access to blood sampling and monitoring of heart metabolism. Sampling from the CS is usually achieved by retrograde cannulation of a central venous system (subclavian, internal jugular, brachial, or femoral vein). Further manipulation within the RA generally requires fluoroscopic imaging to allow for selective engagement of the main CS trunk. Specific catheters, some with heparin bonding and distal side-holes, together with transfemoral sheaths have been developed to facilitate cannulation and/or blood withdrawal from the CS without admixture with RA blood. The positioning of the catheter can be verified and recorded with anterograde and retrograde left coronary arterial contrast injection (Figures 3 and 4), although this does not guarantee RA admixture. Other methods used to confirm CS cannulation involved distal pressure assessment at the catheter tip, oxygen saturation, and blood flow analysis. It is therefore assumed that a CS blood sample thus obtained reflects venous cardiac metabolism. In particular, during regional ischaemic injury, sampling of CS blood does appear to define early and accurate measurements of myocardial metabolism, in contrast to concomitant peripheral blood assays which show no change. The accuracy and validity of these assumptions are critically dependent on careful techniques, selective cannulation, and avoidance of admixture. Sadly, this is rarely tested or confirmed in published reports.

In summary, although selective coronary sampling appears simple and safe and clearly appropriate to define regional cardiac biology, the technique leaves scope for significant loss of sensitivity, which can influence biomarker definition.

Myocardial ischaemia and angiographically normal coronary arteries

Patients with cardiac syndrome X are complex but well defined and presumed to have recurrent ischaemia despite angiographically ‘normal’ vessels, although some have evidence of subintimal or non-obstructive atheroma. The pathogenesis of this clinical symptomatic subgroup remains unclear. Microvascular coronary dysfunction has been postulated as a potential mechanism of recurrent ischaemia. A range of surrogate investigations, such as magnetic resonance spectroscopy and positron emission tomography, reveal some supportive evidence of focal abnormalities of coronary perfusion (i.e. nuclear perfusion defects and restrictive regional blood flow patterns, respectively) in these patients.

Buffon et al. used a panel of circulating coronary biomarkers to provide an insight into this phenomenon by analysing the differences between CS and aortic levels of hydroperoxides and conjugated dienes (which are two sensitive markers of ischaemia-reperfusion oxidative stress) in cardiac syndrome X patients. In this study (n = 9), rapid atrial pacing was used to produce electrographic ST changes, with sustained release of these markers in the local circulation compared with a control group consisting of five asymptomatic patients with normal ECG, left ventricular volume, and normal coronary angiogram. Similarly, increased plasma concentrations of the powerful vasoconstrictor, endothelin-1 (ET-1), have been reported in the coronary circulation of such patients in response to atrial pacing, correlating with coronary microvascular dysfunction. Thus, these patients appear to react adversely in terms of their coronary efflux metabolism with signs of
regional ischaemia, presumed to be due to abnormal flow. How this relates to a standard exercise stress test, which is quite distinct from RA pacing-induced stress, is unknown. Importantly, this study did not reveal changes in the peripheral circulatory levels of these metabolic markers.

Several studies have examined the thrombotic balance in the so-called cardiac syndrome X or linked presentations. For example, Oshima et al. found higher plasma fibrinopeptide A levels (reflecting an impaired local coagulation system), with evidence of increased platelet activation in CS sampling in patients with vasospastic coronary disease. In a later study, the same group reported that intracoronary acetyl-choline led to an enhanced CS-arterial gradient of measured soluble P-selectin (a marker of platelet activation) in patients with angiographically normal coronary arteries compared with those with visible atheroma. They suggested that the change in platelet activation seen on coronary sampling was associated with the level of cardiac ischaemia and even possibly, with myocyte necrosis.

Abnormal endothelial-dependent and endothelial-independent relaxations, as well as glucose metabolism in the coronary circulation have also been described in symptomatic patients with exertional chest pain yet angiographically normal coronary anatomy, using local haemodynamic and rheological parameters. In the 1970s, Goldberg et al. compared two groups of patients with negative exercise test (one group had atypical pain and controls with no chest pain) and found a significant increase in cardiac arteriovenous lactate production (a measure of metabolic performance) and in blood flow in the former group with focal coronary artery spasm. Thus, despite near-normal angiography in both cohorts, CS indices provided a sensitive method to assess focal dysfunction in those with arterial vasospasm.

Given the rapid intracardiac circulation, neurohormonal effectors, such as short-lived endogenous nitric oxide (NO, an endothelium-dependent vasodilator), can be estimated from CS samples but not from peripheral blood. For example, in one study of 12 patients with left ventricular hypertrophy and normal coronary angiography, rapid RA pacing induced a marked lactate release when intracoronary N(G)-monomethyl-L-arginine (a NO synthesis inhibitor) was infused, but this effect was not seen systemically. Thus, localized regional sampling was able to define the metabolic ischaemic response to regional infusion and revealed the higher NO dependence of the coronary circulation in hypertensive patients.

Reversible myocardial ischaemia with stable coronary plaque

Stable atherosclerotic CAD results in patients with chronic exertional chest pain owing to reversible myocardial ischaemia from an unmet oxygen demand secondary to an obstructive coronary stenosis. The biology of plaque formation is complex and results from an interaction of trigger factors and localized cellular endothelial damage/dysfunction and haemorrhheological and inflammation abnormalities, together with modified lipid infiltration of subintimal tissues. Each of these mechanistic processes can contribute to a variable extent in individual coronary patients and each might be better defined by regional rather than generalized blood sampling.

Endothelial function

An intact vascular endothelium plays an important role in preserving arterial homeostasis by modulating NO production from its precursor, L-arginine, via the enzymatic action of endothelial NO synthase. This pathway regulates regional vascular tone via a wide range of mediators (such as prostacyclin, bradykinin, endothelin, and angiotensin II) that have vasodilatory or vasoconstrictive properties. NO also influences coagulation, platelet aggregation, and smooth muscle cell proliferation and migration. In addition, NO can act to inhibit the degenerative oxidation of low-density lipoprotein cholesterol, which is a key step in plaque infiltration and destabilization.

Regional analyses of endothelial responsiveness specific to the coronary circulation might intuitively provide a more sensitive measure of the role of endothelial dysfunction
and underlying coronary vasomotor regulation in stable patients. Both baseline levels and response to pharmacological vasodilators on epicardial vascular bed can be studied using CS oxygen saturation analyses.

In patients with chronic symptomatic CAD, studies of CS effluent suggest raised intracardiac levels of soluble thrombomodulin in addition to other markers of endothelial damage/dysfunction. In some studies, these biomarker levels were correlated to the presence and angiographic severity of CAD, but this was not the case with peripheral blood sampling of the same markers. The functional response of the endothelium to chronic ischaemic stress can also be assessed using plasma levels of ET-1; for example, after prolonged pacing-induced ischaemia (mean 6 min), local levels of ET-1 were significantly elevated compared with peripheral blood, indicating localized cardiac synthesis and regional metabolic changes.

Angiogenesis
Chronic vascular disease involves well-defined stimuli to a range of vascular growth patterns characterized by new vessel proliferation. In CAD, these responses are intimately linked to the presence of viable but ischaemic myocardium and are controlled and mediated by a distinct range of biomarkers. One key growth factor associated with angiogenesis is vascular endothelial growth factor (VEGF). Circulating peripheral plasma levels are widely documented as elevated in CAD and diabetic atherosclerosis. Endogenous cardiac release of angiogenic growth factors has been described in patients with stable chronic occluded and collateralized coronary arteries—findings not seen in peripheral samples.

In one study, for example, CS sampling from seven patients with left coronary arterial occlusion revealed a four-fold increase in local VEGF levels compared with patients with non-occlusive coronary stenoses. Lambiaise et al. also showed an association of increased CS VEGF levels to coronary collateral flow index (a measure of degree of collateralization in the presence of single-vessel stenosis). Intracardiac sources of earlier precursors (circulating endothelial progenitor cells) were also found to be reduced in the presence of inadequate collaterals, and no such relationships were seen in peripheral blood samples. In acute myocardial injury and ventricular remodelling, the role of circulating VEGF appears less conclusive. This seems hardly surprising, as many other factors relating to the presence of occult collateralization are likely to dominate the ventricular response to infarction.
Thrombogenesis

The association of abnormalities in thrombosis and vascular disease is well established. However, the specific linkage of peripheral blood sample changes in platelet function, coagulation, and fibrinolytic pathways to the stability and responses within the local coronary circulation is much less clear. Although systemic analysis of these systems has been widely investigated in CAD, their role in more regional sampling in patients may reveal more relevant associations.

The difficulty with many haemostatic indices, whether of platelet or thrombotic origin, is that they are widely recognized as being abnormal in peripheral blood in a range of vascular diseases, independent of specific coronary involvement. The list of associations is large and crosses a range of conditions linked to CAD, such as peripheral arterial disease, diabetes mellitus, and myocardial infarction.

Peripheral blood analyses of markers of platelet or thrombin activation in patients with CAD undergoing acute exercise stress do not show any changes in measured levels. In contrast, regional analyses of CS blood, from studies in the 1980s, confirm a potential role of regional platelet activation, prostaglandin production, and the effects of aspirin therapy in chronic stable CAD patients.

Similarly, higher levels of thromboxane (associated with platelet activation), but not components of complement activation, were also found in this setting but not in peripheral blood.

CS sampling also facilitates the analysis of regional therapeutic response to platelet inhibition. Montalescot et al. reported that CS blood assays of platelet-activating factor are unchanged during pacing, potentially eliminating its participation in thromboxane release; there was good thromboxane inhibition with low-dose aspirin (50 mg/day) both at rest and during reversible and brief ischaemic episodes.

Furthermore, intracoronary assay of fibrinolysis has been studied in the context of coronary events in smokers compared with those who do not smoke. A lower level of tissue plasminogen activator activity (impaired local fibrinolysis) appears more pronounced in smokers with established coronary atheroma on vascular ultrasound, in keeping with a potential mechanistic link between smoking and CAD event.

Other atherosclerotic risk factors

Cardiovascular risk factors such as hypertension, obesity, and impaired glucose metabolism are linked with CAD and myocardial ischaemia, with complex range of underlying pathophysiological mechanisms. Several metabolic and neurohormonal markers relevant to one or more of these states have been assessed in patients, using CS sampling. Adiponectin is a protein secreted by adipocytes with both anti-inflammatory properties and the potential to suppress atherosclerosis in relevant animal models. Systemic levels of adiponectin are lower in the presence of type 2 diabetes or CAD. Intracardiac adiponectin levels have also been shown to be reduced in diabetic patients (samples from the aortic and CS sites), with some evidence of transcatheter metabolism of adiponectin.

With respect to regional circulatory control of coronary perfusion, CS cannulation may provide information on the direct role of factors of the renin-angiotensin-aldosterone system (RAAS) in vasomotor regulation. Fairly predictably, local measurement of angiotensin II, together with intracardiac epinephrine levels, was associated with vasoconstriction during inducible ischaemia in patients with chronic CAD. Assessment of coronary blood flow responses confirms a role for angiotensin-converting enzyme inhibition therapy in mediating coronary vasodilatation, independent of the presence or absence of CAD. Finally, measurement of CS blood may help in the definition of regional cardiac autonomic tone and sympathetic nervous responses, which appear to correlate with sudden death or worsening cardiac function in patients with pre-existing left ventricular failure.

Myocardial ischaemia and unstable coronary plaque

The factors which trigger coronary plaque destabilization and promote plaque rupture are of critical importance. Again with population studies, peripheral blood sampling has defined a range of indices reflecting pathophysiological processes, but the relative importance of each to individualized coronary events is less clear. As with stable disease, indices of activity within autonomic/neural, thrombotic, or inflammatory tone are likely to be more sensitive if derived from the relevant regional circulation, particularly if sampled during defined ‘disease instability’ (e.g. acute coronary syndromes) without the overt myocardial damage/loss seen with acute infarction.

Plaque rupture is believed to be preceded by cap thinning and/or exposure of a core of lipid-laden activated macrophages which are highly thrombogenic to circulating platelets. The degree of plaque disruption (erosion, fissure, or ulceration) and the extent of overlying mural thrombus are key factors in the thrombogenic signal generated from a local arterial site. In addition, activation of macrophages, T-lymphocytes, and smooth muscle cells leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors. The end-result may be myocardial ischaemia and infarction, depending on the duration of the thrombosis and the location of the associated endothelial dysfunction and vasoconstriction.

Investigations using regional CS blood sampling have played an important role in providing a quantitative assessment of the various systems involved in the pathogenesis of acute coronary syndromes and help in identifying/optimizing new potential therapy areas. The key studies involving endogenous platelet activation and thrombogenesis under acute ischaemic conditions that have been conducted using CS samples are summarized in Table 1. It is well recognized that exposure of tissue factor, cell-surface protein expressed by cells within a vulnerable plaque, can lead to activation of the coagulation/fibrinolytic pathways. In an investigation of patients with ACS, levels of tissue factor pathway inhibitor (TFPI) can be objectively measured on the basis of difference noted between aortic and CS levels, thus reflecting the intracoronary environment, and can be used in addressing future treatment. This consumption of TFPI within the coronary circulation contributes directly to and regulates intracoronary thrombus activation.
Effects of interventions

Different modalities such as balloon angioplasty, stent use, and atherectomy during percutaneous intervention can lead to differing patterns of platelets activation, coagulation, and fibrinolysis.66 For instance, plasma levels of tissue factor, thrombin–antithrombin III complex, plasminogen activator inhibitor, and tissue plasminogen activator are elevated up to 24 h after all coronary procedures, whereas only mechanical atherectomy seems to induce significant elevations in the coronary circulation and coronary sinus.74 By further analysing CS gradient of angiotensin II and its messenger RNA, there is an enhanced production in its local cardiac production of angiotensin II, which is associated with the upregulation of intracoronary cytokines, such as tumour necrotic factor, IL-6, and interferon-gamma.75 This is in contrast to the lack of a significant change in the activity of peripheral levels of RAAS measured in the same cohort.

Plaque burden and coronary sinus sampling

Imaging techniques, such as vascular ultrasonography, electronbeam-computed tomography, and magnetic resonance imaging, have made differing contributions to the estimation of plaque burden and characterization.69 The relationship of CS measures to each of these imaging methods will vary, dependent on their ability to define the extent of disease burden and/or its relative biological stability. CS catheterization complements these with the added benefit of quantifying the degree of local activation at vulnerable atherosclerotic plaques in the coronary beds.

In unstable angina, activation of neutrophils and platelets was accurately assessed in the coronary circulation and compared with stable CAD.70 Furthermore, white cell expression of the CD11b/CD18 adhesion receptor in the CS,71 as indices of granulocyte and monocyte activation, further reflects enhanced inflammation in unstable atherosclerotic plaques. In acute myocardial infarction, differing platelet reactivity and aggregability with subsequent effect of prostacyclin inhibitors therapy within the coronary artery are well documented.72

Renin–angiotensin–aldosterone system

Angiotensin II is an important mediator of interleukin (IL)-6 expression by vascular smooth muscle cells and vascular cell adhesion molecule-1 and MCP-1 expression by endothelial cells in vitro.73 In keeping with the many clinical trials of renin–angiotensin blockade in preventing cardiovascular events, a possible direct effect on the myocardium has been postulated given that CS assays show a local cardiac production of angiotensin.74 By further analysing CS gradient of angiotensin II and its messenger RNA, there is an enhanced production in acute coronary syndrome, which is associated with the upregulation of intracoronary cytokines, such as tumour necrotic factor (TNF-α), IL-6, and interferon-gamma.75 This is in contrast to the lack of a significant change in the activity of peripheral levels of RAAS measured in the same cohort.

C-reactive protein and inflammation

Produced in the liver, C-reactive protein when defined using high-sensitivity analysis is now recognized to have a potentially direct pro-inflammatory role in acute coronary syndromes.76 The mechanistic links are numerous, but C-reactive protein is intimately linked to IL-1b, IL-6, and TNF-α, as well as the expression of intercellular and vascular

Table 1 Examples of key studies analysing platelets activation and thrombosis markers during coronary sampling

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Hypothesis investigated</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craft et al.120</td>
<td>19 PCI</td>
<td>Platelet activation using PMP in coronary circulation</td>
<td>Heparin use led to a ↓ PMP and contrast led to an ↑ PMP; effect seen in the regional</td>
</tr>
<tr>
<td></td>
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<td>arterial samples only</td>
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<tr>
<td>Rauch et al.121</td>
<td>30 PCI</td>
<td>Interaction of leucocyte and platelets using adhesion molecule CD 15</td>
<td>CS level of CD15 following PCI correlates with ISR</td>
</tr>
<tr>
<td>Johansen et al.122</td>
<td>26 PCI</td>
<td>PDGF and BTG</td>
<td>↑ levels of both PDGF and ↑ BTG seen in aortic root and CS following PCI; only arterial</td>
</tr>
<tr>
<td>Watkins et al.123</td>
<td>21 PCI</td>
<td>Thrombin activity using Fibrinopeptide A (Fib A)</td>
<td>↑ Fib A levels seen following heparin cessation in PCI and in AMI (effect seen earlier</td>
</tr>
<tr>
<td>Fornitz et al.124</td>
<td>19 PCI</td>
<td>Platelet activation using beta thromboglobulin</td>
<td>Regional BTG levels did not vary following PCI irrespective of heparin therapy</td>
</tr>
<tr>
<td>Mizuno et al.125</td>
<td>43 PCI</td>
<td>Impaired local fibrinolysis</td>
<td>Impaired cascade with ↑ PAI-1/↑ tPA seen centrally</td>
</tr>
<tr>
<td>Mizuno et al.126</td>
<td>35 PCI</td>
<td>Coagulation pathway using TF, TAT complex, and pro-PF</td>
<td>Combination of above after PCI correlates with ISR</td>
</tr>
<tr>
<td>Patel et al.127</td>
<td>23 UA, 16 CSA</td>
<td>Platelet and neutrophil interaction using CD62P</td>
<td>↑ in platelet expression (CD62P) in an unstable plaque</td>
</tr>
</tbody>
</table>

†, increased level; ↓, decreased level; PCI, percutaneous coronary intervention; PMP, platelet microparticle; ISR, in-stent restenosis; PDGF, platelet-derived growth factor; BTG, beta-thromboglobulin; AMI, acute myocardial infarction; CS, coronary sinus; CSA, chronic stable angina; UA, unstable angina; Fib A, fibrinopeptide A; PAI-1, plasminogen activator inhibitor; tPA, tissue plasminogen activator; TF, tissue factor; TAT complex, thrombin–anti-thrombin complex; PF, prothrombin fragment.
in situ as a result of myocardial necrosis and, hence, are systemic acute phase reactant. No increase or ‘consumption’ suggested the origin (and role) of C-reactive protein as a systemic event in acute coronary syndromes. A recent study of 41 sites with intracoronary sampling. A recent study of 41 patients with acute myocardial infarction also confirmed similar findings from the site of plaque rupture and segments of the coronary arteries.84 Of course, these findings are dependent upon the venous system, and activity was lowered in CS blood draining from aortic blood and segmental branches of the coronary arteries.84

Assays of C-reactive protein from the CS have been used to compare the level within the coronary tree and systemically in differing clinical conditions. Techniques to harvest blood using distal protection coronary devices have further helped to elucidate the role of C-reactive protein during the mechanical treatment of acute coronary plaque disease. Indeed, CS levels of C-reactive protein have been found to be significantly higher in patients with chronic CAD and in patients with unstable angina,85 but interestingly, not in those with an acute myocardial infarction. This is despite elevated markers such as IL-1b, IL-8, and TNF-α found following coronary culprit lesion in the setting of acute myocardial infarction.81

The precise reason as to why CS levels of C-reactive protein are not elevated in occlusive coronary disease is unclear. One possible explanation of this paradox is that many cytokines, such as TNF-α and IL-6, are produced in situ as a result of myocardial necrosis and, hence, are an ‘after effect’ of the acute infarction process. In unstable angina, a low-grade chronic inflammatory process exists, as suggested by high-C-reactive protein levels that precede cardiac troponin release and the ensuing activation of cytokines. Further in-depth understanding of the role of various inflammatory cytokines has been gained by combining CS site with intracoronary sampling. A recent study of 41 patients with acute myocardial infarction also confirmed similar findings from the site of plaque rupture and suggested the origin (and role) of C-reactive protein as a systemic acute phase reactant. No increase or ‘consumption’ of C-reactive protein was seen before and after lesion in these patients, whereas changes in IL-6 and TNF-α levels correlated well with the extent of myocyte necrosis, as measured by the level of troponin rise.

CS catheterization has also been utilized to evaluate the extent of the inflammatory response within the coronary circulation during unstable symptoms. For example, Buffon et al.81 found that the local response in acute coronary syndromes was not restricted to the unstable plaque but was present throughout the coronary vasculature. Levels of neutrophil myeloperoxidase activity (with enzymatic depletion mirroring enhanced inflammatory processes) were assayed from aortic blood and segmental branches of the coronary venous system, and activity was lowered in CS blood draining the site of coronary culprit lesion as well as non-affected areas.84 Of course, these findings are dependent upon the response moment and circulatory half life of the biomarkers concerned, as well as being confounded by re-circulation.

Endothelial (dys)function

Endothelial dysfunction is integral to the development of atherosclerosis and correlates with serum C-reactive protein in peripheral blood. Novel molecules could potentially offer avenues to improve our recognition of any early change within the coronary anatomy at a stage before angiographically visible plaque.

For example, using immunologically defined circulating endothelial cells (CECs) shed from affected vascular beds may be a novel technique for the assessment of the extent or degree of endothelial injury. We have recently shown that CEC levels in the peripheral blood 48 h following acute coronary syndromes predict major adverse clinical events at 1 and 12 months. The marked difference in CEC count may be associated with a greater degree of vascular injury, and CEC release could potentiate pro-thrombotic mediators and platelet aggregation.

Whether this marker is able to define a discrete coronary endothelial response or a more generalized response of the arterial (and/or venous) circulation is as yet unclear. During angiography or angioplasty, CECs may also provide information as to the extent of intramyocytic release, though no such data are available. Studies of regional response(s) in peripheral and CS blood would be valuable to explore this further.

Myocardial ischaemia and the development of pre-conditioning

Intermittent periods of reversible ischaemia allow the development of metabolic resistance to subsequent ischaemic stress and have the potential to reduce myocardial loss at subsequent vessel occlusion. In animal models, a technique of intermittent pharmacological retrograde perfusion of the CS during surgical ischaemia can allow reduction of tissue hypoxia, impaired wall motion score, and histological necrotic area.88 In stable coronary patients undergoing percutaneous coronary intervention (PCI), the lactate extraction ratio determined by simultaneous blood sampling from the aorta and the CS reveals that repeated balloon inflation can—in the short term, at least—enhance ischaemic preconditioning without collateral recruitment. Various strategies aiming at minimizing myocardial injury peri-CABG has been evaluated using similar surrogates defined in indices measured in the CS blood.89

Coronary retroperfusion, a technique involving CS cannulation, subsequent balloon occlusion, and retrograde venous injection, has also been used in an attempt to enhance ischaemic preconditioning and reduce complications particularly in those undergoing PCI. Berland et al. successfully cathereterized the CS (average time < 3 min), with subsequent placement of an auto-inflatable balloon catheter in the great cardiac vein. The protocol involved synchronized retrograde perfusion using this catheter at the time of intracoronary balloon inflation during the PCI procedure. Of the 12 patients studied, fewer episodes of chest pain were reported during the 101 (± 36) s of balloon occlusion, and quantitatively, electrographic ST was reduced (10.4 ± 7.8 mm compared with 18.8 ± 10.6 mm in controls; P < 0.01).

Further studies are therefore needed to fully evaluate the clinical impact and potential optimal use of procedural variables such as duration and frequency of balloon inflation or stent type and deployment in ischaemic preconditioning during PCI.
Coronary sinus sampling during coronary interventional procedures and outcomes

PCI including stent placement remains the commonest method of revascularization for CHD, in both the USA and the UK. By reducing the incidence of acute vessel closure, recoil, and maintaining luminal patency, stent deployment is now the preferred method when compared with plain balloon angioplasty. However, the rate of angiographic in-stent restenosis remains high, at up to 40% with bare metal stent and 25% with drug-eluting stent (DES) in complex PCI. Furthermore, complications such as subacute thrombosis can develop in both bare metal and DES-treated patients.

CS sampling has been used infrequently to address potential markers of in-stent stenoses which may be distinct from endogenous atheroma. In a study of plasma levels of inflammatory cytokines, as well as cytokine-generation capacities of monocytes, before PCI and after 3–6 months follow-up period in 34 consecutive patients, inflammatory indices were significantly decreased in patients without restenosis compared with those with restenosis. CS levels of IL-6 are increased after PCI, and higher levels in response to PCI have been associated with late restenosis. In Indo-Asians undergoing PCI, platelet function or activity of vessel or stent restenosis or thrombosis, there are complications of PCI. Indeed, plasma levels of PAI-1 activity and fibrin D-dimer were evaluated in two groups of patients who underwent either elective balloon PTCA alone or with stent implantation. Following PTCA, PAI-1 activity was higher in patients with subsequent clinical recurrence with restenosis (P < 0.005 in both groups) than in those without, whereas no differences were found in fibrin D-dimer levels.

The role of neutrophil adhesion molecules (using CD11a, b, c and CD18 epitopes) in patients undergoing PCI has also been studied in the process of restenosis. The percent change in the expression of CD18 at 48 h after PTCA (from baseline) and that of CD11b were significantly correlated (r = 0.73, P = 0.0008) in patients with restenosis. Similarly, activation of neutrophil adhesion molecule Mac-1 at 48 h after PTCA may have value as a predictor of subsequent restenosis.

CS levels of thrombin activity can be used to assess the localized effectiveness of a given dose of heparin during PCI. In one study, plasma levels of fibrinopeptide A (marker of thrombin activity) were elevated from the coronary circulation with proximal occlusion of the vein. This radiographic effect persisted for at least 30 min. Delivery of autologous bone marrow can be done effectively in an animal model via the CS and transient occlusion, resulting in improved angiogenesis in areas with myocardial injury.

Thus, the feasibility of percutaneous selective coronary venous cannulation and injection provides the potential as a novel approach for local myocardial drug delivery. This aspect can be extended to include intracardiac monitoring and possibly, tailoring of treatment. For example, in Fabry’s disease (an X-linked inborn metabolic disorder caused by deficient activity of α-galactosidase A), assays of enzymatic delivery and customization of intravascular levels have been successfully performed using samples from the CS. One case report also used the coronary venous system to ‘retrogradely’ perfuse ischaemic myocardium. In this patient—who had diffuse CAD, not amenable to conventional revascularization—a percutaneous fistula was created between the left anterior descending artery and the interventricular branch of the coronary circulation with proximal occlusion of the vein. This fistula was still patent at 12 months, with subjective improvement in symptoms.

The impact of systemic drugs on the coronary circulation and, in particular, on PCI has been evaluated using CS sampling. In a small number (n = 9) of patients undergoing PCI, nifedipine CR has been shown to reduce the intracardiac C-reactive protein level and vasospasm periprocedurally.

Limitations of coronary sinus catheterization

A large body of literature is broadly supportive of CS sampling as a better means of defining both acute and chronic cardiac responses to ischaemia and atheroma (Figure 5). The invasive nature of CS cannulation carries a small risk from the additional venous access site, transient supraventricular arrhythmias, and failure to achieve a stable catheter position with adequate exclusion of atrial blood. Furthermore, activation of platelet and thrombin production remains a potential drawback for CS cannulation and manipulation, although this effect is attenuated using heparin-bonded catheters. Though well recognized in right-heart catheterization cases from the 1980s, CS thrombosis is poorly documented with contemporary techniques and catheters. A recent review of over 10 000 CS cannulations for the induction of retrograde cardioplegia

Responses to vascular growth therapies in CAD

Manipulating the growth factors regulating angiogenesis has been widely studied as potential treatment to enhance coronary perfusion, particularly in patients not suitable for conventional revascularization. Given the potential therapeutic application of vascular growth factors in coronary heart disease, animal models have been mostly used to demonstrate the efficacy of percutaneous intramyocardial delivery using CS. In one animal model, for example, venous injection of radiographic contrast following balloon occlusion of the CS led to infiltration of targeted myocardial regions. This radiographic effect persisted for at least 30 min. Delivery of autologous bone marrow can be done effectively in an animal model via the CS and transient occlusion, resulting in improved angiogenesis in areas with myocardial injury.
during cardiac surgery shows an incidence of < 0.1% of complications.\textsuperscript{117} In PCI, concomitant use of contrast media can influence coagulation and platelet but limited data exist concerning the effect of newer low-osmolarity contrast media on coronary blood profiles.\textsuperscript{118} These issues, together with limited technological support and intrusive longitudinal studies, understandably limit the enrolment of patients into CS studies.

Emerging evidence seems to suggest that plasma levels from coronary artery ostium can be used. This may prove quite attractive in quantifying the ‘local’ environment, as it can be included in the left-heart catheterization procedure without the need for additional right-sided instrumentation. Thus, when evaluating the expression of P-selectin by platelets in response to adenosine diphosphate,\textsuperscript{119} no difference was seen in blood samples from the culprit coronary arterial ostial blood and the CS. However, these findings need to be reproduced consistently with different assays. What is needed is rigorous evaluation and comparative studies using multiple sites including CS.

**Conclusions**

Even under stable clinical conditions, atherosclerosis remains a dynamic process. Coronary circulatory measures via the CS can be used to provide an insight into the intricate pathophysiological processes underlying myocardial ischaemia. This invasive approach has helped in our understanding of these factors at intracardiac level and hence, potentially guides therapy during unstable plaque disease. Indeed, the use of CS blood sampling can provide investigators a method to assess the local changes in the myocardium, including ‘downstream’ changes following local therapeutic interventions, such as stem cell and drug administration. Furthermore, the potential ability to study the change along the different coronary circulation at different branches of CS is a possibility. Access via the venous circulation of the heart has also been used for the administration of drugs locally. Nonetheless, the invasive nature of this technique has limited its use in small study populations, and serial measurements over time are impractical.

In conclusion, CS sampling offers a unique way of assessing the cardiac milieu and may prove useful in the monitoring of both local and systemic drugs and technologies. In future, larger studies will be needed to correlate CS sampling of various biomarkers with clinical outcomes.

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