Current perspectives

Assessment of coronary vasomotor function: old and new tools

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Atherosclerosis has an impact on the vasomotor reaction of coronary segments to iodinated non-ionic contrast agents. Angiographically normal coronary segments show divergent vasomotor reactions to iodixanol or iopromide according to the presence of, and distance from, a coronary atherosclerotic lesion. The mechanism responsible for the above-mentioned vasomotor effect does not seem to involve flow-mediated vasodilation or endothelial nitric oxide synthesis. On the other hand, a cyclooxygenase product may be, at least in part, responsible for the vasodilating effect of non-ionic agents on epicardial coronary arteries. These findings have potential clinical implications that are herein discussed.

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So far coronary angiography has mostly been used to provide data on vascular anatomy and the severity and location of coronary artery disease[1]. With the appreciation of the role of endothelial dysfunction in the pathogenesis of atherosclerosis[2] the attention has been focused on the responsiveness of coronary arteries to vasoactive stimuli, and new uses for coronary angiography have become available. The injection of ergonovine or ergometrine has thus become the gold standard for the induction and reproduction of coronary artery spasm[3]. More recently, the appreciation of the role of endothelium in modulating vascular tone has led to the use of acetylcholine or serotonin to reveal endothelium-dependent responses[4,5]. In normal vessels, a functional endothelium transduces the effects of these substances eliciting an endothelium-dependent response that relaxes underlying smooth muscle cells, thereby inducing vasodilation. Conversely, the presence of frank atherosclerosis, or even the mere presence of a dysfunctional endothelium, such as in the presence of systemic risk factors for coronary artery disease, leads to a loss of the vasodilating properties of vascular endothelium and to impaired vasodilation or net vasoconstriction in response to the direct vasoconstrictive effects of these agents on medial smooth muscle cells. The use of pharmacological endothelium-dependent vasodilators during coronary angiography has not however become routine, for a variety of reasons including the uncertain impact on the patient s prognosis, the lack of consensus on the significance of abnormal vasomotor findings, uncertainties on decision making as a consequence of test outcomes and last but not least difficulties in performing a relatively time-consuming and cumbersome pharmacological test during routine angiography. We have recently documented the variable vasomotor responses of coronary artery segments differently affected by angiographically visible atherosclerosis to the angiographic contrast media routinely used at coronary angiography. From this the possibility arises of using the vasomotor response to contrast media as a possible alternative to pharmacological testing to probe the physiology of epicardial coronary vessels beyond what is presently being done. This commentary will briefly summarize the background for these studies, the main findings, as well as implications and future pathways on this promising line of research.

Vasomotor effects of angiographic contrast media

Contrast media used for angiography induce complex changes in vascular tone of

both conductance and resistance coronary arteries. Following the injection of contrast, most often a vasodilation is seen on the epicardial arteries, but sometimes vasospasm occurs. Vasodilation has been attributed to hyperosmolality (being more evident with high-osmolal, ionic agents than with low-osmolal, non-ionic agents), chemotoxicity, ion content of the medium, or endothelium-dependent flow-mediated changes in vascular tone. Available data are however still inconclusive and the mechanism of contrast-induced vasodilation is still elusive[6-10]. Vasomotor response to contrast media partially depends on the type of medium used. In fact, high-osmolal ionic agents such as diatrizoate may increase epicardial coronary diameter up to 20% for as long as 180 s[6,7], while ioxaglate, a low-osmolal ionic agent, has little or no vasomotor effect on epicardial coronary arteries[11]. Non-ionic agents, regardless of their osmolality or molecular structure (monomeric or dimeric), induce a mild (< 10%) and transient (< 90 s) epicardial coronary vasodilation in subjects with normal coronary arteries[6,11]. Coronary vasoconstriction has been observed after the injection of both ionic and non-ionic contrast agents[12-14]. In experimental studies, the mechanism responsible for the vasoconstriction was found to be mainly a chemotoxic/depolarizing effect on the smooth muscle cells of the isolated vessel[15-17]. Some monomeric, non-ionic contrast media such as iohexol and ioversol have been shown also to induce serotonin-dependent changes in vessel tone through platelet activation and degranulation[18,19].

The impact of atherosclerosis on coronary vasomotor responses to contrast media

Coronary artery disease alters the vasomotor response to a variety of pharmacological agents. It is conceivable that coronary atherosclerosis might also interfere with the vasomotor reaction of coronary arteries to contrast agents. In a preliminary report, Bentley and Henry[20] observed that low concentrations of diatrizoate, a high-osmolal, ionic agent, induce vasodilation in normal rabbit aortas, but vasoconstriction in atherosclerotic aortas. Similarly, Jost et al.[7] reported that stenosed coronary segments dilate less than angiographically normal coronary segments after injection of diatrizoate in humans. However, the high variability of quantitative coronary angiography measurements of coronary minimal diameter at a stenosis site[21], ranging approximately in order of magnitude of diatrizoate-induced changes, hampers the relevance of these findings. Moreover, in the study of Jost et al.[7], the changes in a patient s segments were averaged for each patient. These averages might have obscured the information offered by a single-segment analysis, since atherosclerosis has a characteristic segmental distribution and may affect the vasomotor reaction of some, but not all the coronary segments in the same patient[22,23].

We have recently performed quantitative coronary angiography in 47 patients without angiographic evidence of coronary artery disease and in 45 patients with clear-cut and discrete coronary artery disease in the left coronary artery[11]. Angiographically smooth coronary segments were analyzed for changes in epicardial coronary lumen diameters in response to three media, the non-ionic dimer iodixanol, the non-ionic monomer iopromide, and the ionic agent ioxaglate. Contrast-induced changes in epicardial coronary artery lumen diameters were evaluated by quantitative coronary angiography by comparing coronary diameters measured during two consecutive contrast injections within a 50 s interval. Baseline coronary diameters were obtained during the first injection, while the differences observed between the first and second injection were considered as induced by contrast. Iodixanol induced vasodilation in segments of subjects without coronary artery disease (+8.8 – 8.6%, $p < 0.001$). In contrast, patients with coronary artery disease exhibited no significant diameter changes in segments 20 mm apart from a stenosis (+4.7 – 9.4%, p = NS), and significant constriction in segments at < 20 mm from a stenosis (-3.8 – 4.6%, $p < 0.05$). Similar results were obtained with iopromide, but no changes were found with ioxaglate. A vasodilatory capacity was preserved in all groups of segments since nitroglycerin resulted in similar dilations regardless of the presence of atherosclerosis or the type of contrast used. Figure 1 shows the distribution of single-segment vasomotor re-

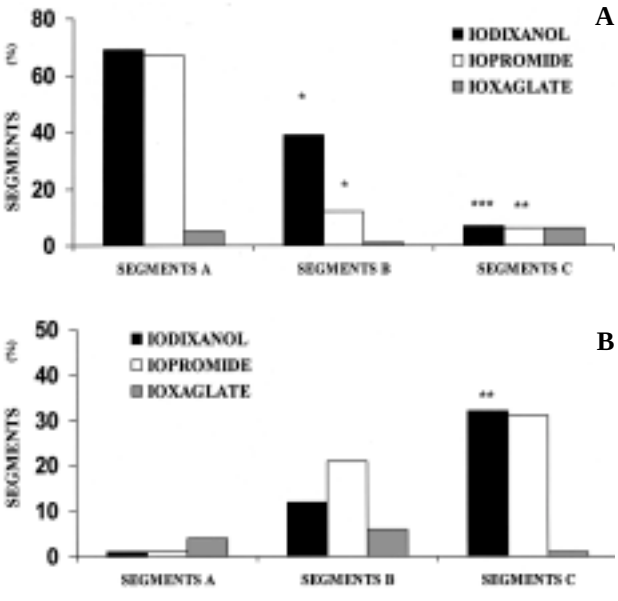

Figure 1. *Bar graphs show the distribution of significant segment dilations* (A) *and constrictions* (B) *induced by iodixanol, iopromide or ioxaglate. Segments* A: *angiographically normal segments in subjects with angiographically normal coronary arteries. Segments* B: *angiographically normal segments located Ž 20 mm far from the closest significant stenosis. Segments C: angiographically normal segments located > 5 mm and < 20 mm from the closest significant stenosis. Segment constriction (or dilation) was considered to be significant when Ž 0.13 mm. * p < 0.05, ** p < 0.01, *** p < 0.001 vs segments A. No significant differences among segments A, B and C were observed in patients injected with ioxaglate.*

actions above the 95% tolerance limits of the variability of the quantitative angiography system. The percentage of segments reacting with a significant dilation after iodixanol or iopromide injection showed a highly significant decreasing trend from segments in normal vessels to segments close to a coronary stenosis, while a trend to an increase was observed for the constrictive reactions.

This is the first human study demonstrating that iodinated non-ionic contrast agents elicit divergent vasomotor reactions in atherosclerotic and normal coronary arteries. Interestingly, the altered vasomotor response was present at the level of angiographically smooth-appearing coronary segments in patients with coronary artery disease, and was related to the distance between the analyzed segment and a stenosis.

Mechanisms for the impaired coronary vasodilation to non-onic contrast agents in atherosclerosis

The mechanism(s) responsible for the divergent vasomotor responses of normal and diseased coronary arteries to non-ionic agents is (are) unknown. Several stimuli and vasoactive agents, such as serotonin or acetylcholine, elicit divergent vasomotor effects on normal and atherosclerotic coronary arteries through a direct vasoconstrictive effect on medial smooth muscle cells and an endothelium-mediated vasodilation[4,22,24-30]. The non-ionic contrast agent iohexol has been demonstrated to induce degranulation of platelets, a potential source of serotonin in the blood stream[18]. However, iodixanol has weak[19] or no effects[31] on platelet function, thus making it unlikely that serotonin or platelet degranulation might be involved in its vasomotor effect. Karstoft et al.[15,17] demonstrated that iodixanol and iotrolan (both non-ionic, dimeric agents), but not ioxaglate (an ionic agent), have a strong direct vasoconstrictive effect on isolated coronary arteries. This direct vasoconstrictive effect of non-ionic agents might be counteracted in normal coronary arteries by an endothelium-dependent dilation. In our study[11], iodixanol and iopromide induced significant hyperemia, as suggested by the increase in coronary venous oxygen saturation, which in turn might have determined epicardial vasodilation through a flow-mediated mechanism. This hypothesis seems unlikely since, in the same study, ioxaglate induced changes in coronary venous oxygen saturation which were even greater than those induced by iodixanol or iopromide, without effects on epicardial coronary diameters. If an endothelium-mediated mechanism has a role in the effect of non-ionic contrast agents on epicardial coronary artery diameters, such a mechanism might involve the synthesis and release of vasodilators such as nitric oxide[32], prostacyclin[33] or the endothelium-derived hyperpolarizing factor[34], as well as vasoconstrictors such as endothelins[35] or endothelium-derived vasoconstricting factors[36]. Our data show that vascular cyclooxygenase inhibition by indomethacin markedly attenuated the epicardial coronary vasodilation induced by iodixanol or iopromide, whereas nitric oxide synthesis inhibition through N^G-monomethyl-L-arginine infusion was ineffective (Fig. 2)[11]. These data indicate that a product of vascular cyclooxygenase activity, such as prostacyclin, or the still elusive endothelium-derived hyperpolarizing factor, may play a role in the epicardial coronary vasodilatory effect of non-ionic contrast media.

Revealing concealed coronary atherosclerosis or endothelial dysfunction: new roles for contrast media?

In patients with angiographically normal epicardial coronary arteries intracoronary acetylcholine and serotonin cause coronary artery dilation, whereas in patients with coronary artery disease they cause non-significant vasomotion or even coronary artery constriction[4,23,37,38]. Similar data are obtained with physiological stimuli such as the cold pressor test[24] or coronary hyperemia[28]. As already stated, the dilation of a coronary artery in response to these stimuli is consistent with normal endothelial function. Conversely, impaired vasodilation may indicate the presence of endothelial dysfunction and/or a more general vasomotor dysfunction involving

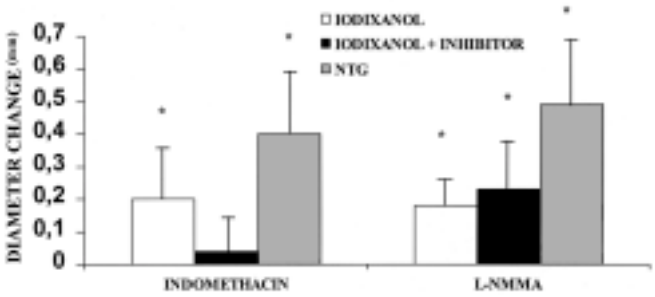

Figure 2. *Effect of intracoronary infusion of N^G-monomethyl-L-arginine (L-NMMA) 50 mmol/min or indomethacin 3 mmol/min on the vasomotor effect of iodixanol on normal epicardial coronary arteries. Data are mean ± SD and represent changes in coronary luminal diameter from basal values. Inhibitor: L-NMMA or indomethacin. NTG: intracoronary nitroglycerin 200 mg. Each group included 4 to 6 subjects with angiographically normal coronary arteries. * p < 0.001 vs basal values.*

altered smooth muscle cell relaxation[24,25,39,40]. Angiographically concealed atherosclerosis, which is not evident to angiography due to the occurrence of vascular remodeling, external plaque growth and/or diffuse longitudinal arteriosclerotic involvement of the arterial wall (e.g. in the case of chronic heart transplant rejection), is still presently undetectable without the use of intravascular imaging techniques. The observation that altered coronary vasomotor response to acetylcholine may be observed also in subjects without evidence of coronary artery disease at coronary angiography raised the possibility that acetylcholine could be used to detect non-angiographically evident atherosclerosis[5,41,42]. However, Reddy et al.[43] and Mano et al.[44] failed to demonstrate the presence of coronary disease by high resolution intravascular ultrasounds in patients with coronary risk factors, no angiographically evident coronary artery disease, and altered vasomotor response to acetylcholine. Thus, the acetylcholine test seems more capable of evaluating vasomotor impairment in the presence of coronary risk factors than detecting the presence of angiographically concealed coronary atherosclerosis. Besides acetylcholine, other substances such as serotonin, bradykinin, substance P and histamine, or physiological stimuli such as the cold pressor test, may be used to test endothelial function and vascular reactivity[4,23,24,37,38,45,46]. Although most of these tests are used to assess vascular endothelium-dependent vasomotion, it must be emphasized that different tests involve the activation of different receptors and different metabolic pathways, thus often leading to quantitatively and/or qualitatively different vasomotor responses[45,47]. Similarly, different tests may lead to different conclusions with regard to the ability of drug treatments in reversing vascular dysfunction. This is the case of therapy with ACE-inhibitors in hypertensive patients, which selectively reverses altered vasomotor response to bradykinin and to the cold pressor test while not restoring the physiological vasomotor response to acetylcholine[45].

The assessment of coronary vasomotor effects of non-ionic contrast media is a promising new tool in the search for a practical test for coronary endothelial dysfunction which might prove to be valuable in the assessment of concealed coronary atherosclerosis. Compared to other stimuli, the test is conceivably more practical than the intracoronary administration of exogenous substances. In addition, the non-ionic contrast test likely provides a different metabolic standpoint in the evaluation of coronary vasomotion, since vasomotor responses to non-ionic contrast media appear to involve a product of the cyclooxygenase pathway rather than endothelial nitric oxide bioavailability (Fig. 2), as in the case of acetylcholine, serotonin or the cold pressor test. Finally, preserved contrast-induced coronary vasomotion was observed in patients with normal coronary angiograms, although all these patients had a history of chest pain and the majority of them had at least one risk factor, i.e. hypercholesterolemia, hypertension, cigarette smoking, diabetes or family history of coronary artery disease[11]. In patients with similar clinical characteristics, both Reddy et al.[43] and Tousoulis et al.[41] observed localized coronary vasomotor dysfunction with the acetylcholine test. Therefore, the non-ionic contrast test might be less prone to detect a coronary vasomotor dysfunction in the absence of concealed coronary atherosclerosis compared to tests evaluating the nitric oxide pathway.

Future pathways to evaluate clinical implications of altered coronary vasomotor responses to contrast media

These findings have potential implications. From a clinical standpoint, the vasoconstrictive response to non-ionic contrast media in atherosclerotic segments might worsen myocardial ischemia or even contribute to the development of arterial thrombosis, also possibly favored by the lesser antiplatelet and anticoagulant properties of non-ionic versus ionic media[48]. From a diagnostic standpoint, these findings question the comparability of quantitative angiographic data obtained when different invasive cardiology laboratories do not standardize the use of contrast medium, unless rigorous attention is paid to only obtaining angiograms destined to quantitative angiography shortly after the use of nitrates or with adequate time intervals between consecutive angiograms.

Further studies utilizing intravascular ultrasound imaging techniques as a gold standard are necessary in order to evaluate the ability of the non-ionic contrast test to reveal concealed atherosclerosis and to distinguish it from vascular vasomotor dysfunction secondary to the presence of cardiovascular risk factors. Longitudinal studies are also needed to assess the prognostic significance of an altered coronary vasomotor response to non-ionic agents. Finally, a comparative analysis of the information provided by contrast-induced vasomotion (cyclooxygenase-dependent) and that induced by the more classic nitric oxide-dependent stimuli (acetylcholine, serotonin, hyperemia, etc.) appears worthy of being done.

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