Reflex Vasodilation Induced By Coronary Angiography in Human Subjects

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SUMMARY In order to evaluate the reflex peripheral vascular effects of coronary arteriography, forearm blood flow was measured plethysmographically and forearm vascular resistance calculated before and during coronary angiography with Hypaque-M, 75%, and Renografin-76. The injection of Hypaque into the left coronary artery resulted in a forearm vasodilation which could not be duplicated by an injection of a comparable amount of contrast into the ascending aorta, three centimeters above the coronary ostia. Forearm blood flow rose from 2.95 to 5.41 ml/min/100 ml (83.4%) and forearm vascular resistance fell from 35.8 to 19.9 mm Hg/ml/min/100 ml (44.4%). Renografin injected into the left coronary artery resulted in less forearm vasodilation (21% increase in forearm blood flow and 32% decrease in forearm vascular resistance). When coronary arteriography was repeated following injection of atropine into the brachial artery, no forearm vasodilation occurred. It is suggested that in human subjects myocardial or coronary artery receptors can be activated by the intracoronary injection of iodinated contrast media which results in a forearm vasodilation.

CURRENT INTEREST in ventricular receptors stems from the possibility that they might play a role in the hypotension accompanying acute myocardial infarction. Although the loss of extensive areas of myocardium is a major reason for shock accompanying acute coronary occlusion, it has been suggested that perhaps a depressor reflex secondary to stimulation of ventricular receptors could lead to a failure of the regional circulations to constrict appropriately during systemic hypotension.1-12 Although this hypothesis has been tested in experimental animals and found to be valid, only fragmentary evidence has been presented to suggest that such a mechanism is operative in humans. That this mechanism may be operative in humans is suggested by the frequent finding of low blood pressure readings co-existing with a normal cardiac output in patients with acute myocardial infarction. In addition, only one study has been reported in humans to show that myocardial
receptors do exist and probably play a role in exercise syncope in patients with aortic stenosis. Direct studies in humans that would suggest that acute myocardial infarction can stimulate such receptors are limited to a brief report demonstrating that forearm resistance vessels failed to contract normally in these patients during head-up tilt. It was suggested in those studies that perhaps the regional segmental dyssynergy accompanying acute myocardial infarction might be stimulating ventricular pressure receptors which resulted in a central attenuation of the normal vasocostriction that accompanies assumption of the upright position.

The studies to be reported in this paper intend to add further evidence to show the existence of receptors that produce a vasodilator response. Because of the small but finite risk of coronary angiography, the authors chose not to add to this risk by a prolonged study with multiple interventions. Basically, forearm blood flow was studied during injection of contrast into a coronary artery only if it would result simultaneously in films and plethysmographic tracings of good diagnostic quality. Thus, only two or three injections were performed in the supine or shallow oblique rotations in each subject.

Methods

Studies were carried out in 11 subjects undergoing diagnostic left heart catheterization and coronary arteriography for the evaluation of possible coronary artery disease. Studies were reviewed and approved by the Chancellor's Advisory Committee for Research Involving Human Subjects and informed consent was obtained in all patients. A patient was selected for participation in the study if on clinical evaluation he or she appeared to have atypical chest pain which was thought not to be angina pectoris and if on the initial test injection of angiographic contrast into the left coronary artery no significant coronary artery stenosis was detected on review of the videotape. All injections of contrast into the coronary arteries resulted in cineangiograms of diagnostic quality and no injections were made for the sole purpose of determining the response of the forearm resistance vessels.

Forearm blood flow was measured in the left arm by the venous occlusion technique with a single-strand mercury-in-rubber strain gauge plethysmograph, as previously described. The hand was isolated from the circulation by inflation of a wrist cuff to suprasystolic pressure for at least one minute prior to any determination of forearm blood flow. A venous collection pressure of 30–40 mmHg was used, and the forearm was elevated so that even in a shallow right anterior oblique position (the second projection which was evaluated) the mid left forearm would be no lower than heart level. Arterial pressure was measured directly through a 20-gauge Longdwell teflon needle inserted in the left radial artery and was connected to a Statham P23db pressure transducer. Recordings of forearm blood flow were made at 15 second intervals, and forearm vascular resistance was calculated for two minutes before and following the injection of 8 cc of angiographic contrast over three seconds into the coronary artery.

In six subjects, a mixture of meglumine diatrizoate 50% and sodium diatrizoate 25% (Hypaque-M, 75%) was injected into the left coronary artery. In three subjects, left coronary artery injection was repeated following an interval of five minutes. In these six subjects, a similar injection of angiographic contrast was performed in the ascending aorta 3 cm above the coronary ostia, and its effect on forearm vascular dynamics was assessed.

In five additional subjects, the angiographic contrast was meglumine diatrizoate 66% and sodium diatrizoate 10% (Renografin-76). In these subjects, arterial pressure was measured through a left brachial arterial Longdwell needle. The determination of forearm vascular resistance during coronary arteriography was performed before and following the injection of atropine 0.5 mg into the left brachial artery.

Statistical analysis was performed utilizing the Student's paired t-test.

Results

Immediately following the injection of Hypaque into the left coronary artery, a fall in blood pressure routinely occurred within the first 5–10 seconds. Forearm blood flow determined 15 to 30 seconds after the injection of contrast agent was characteristically higher than that in the control state and calculated forearm vascular resistance at that time was significantly lower (figs. 1 and 2). Forearm blood flow went from 2.95 ± 0.31 (standard error of the mean) to 5.41 ± 0.67 ml/min/100 ml (P < 0.01), and forearm vascular resistance significantly fell from 35.8 ± 4.1 to 19.9 ± 4.8 mm Hg/ml/min/100 ml. In these same subjects, the injection of a comparable amount of angiographic contrast into the ascending aorta resulted in no significant change in either forearm blood flow or forearm vascular resistance (figure 3). In three subjects in whom a second left coronary artery injection was performed, comparable changes in forearm blood flow and forearm vascular resistance occurred. An example of this is shown in figure 1. In those subjects, forearm blood flow increased 62% and 70% and forearm vascular resistance decreased 40% and 42% respectively during consecutive injections of contrast into the left coronary artery.

In those six subjects who were studied utilizing Renografin-76 rather than Hypaque-M, 75%, the increase in forearm blood flow, though significant, was only 21% (3.06 ± .75 to 3.69 ml/min/100 ml, P < .01), and the fall in forearm vascular resistance was 32% (39.7 ± 5.4 to 28.8 ± 3.1, P < .01). Following the intrabrachial administration of atropine, coronary angiography failed to produce an increase in forearm blood flow (3.60 ± .61 to 3.86 ± .29 ml/min/100 ml, P > .05) or a reduction in forearm vascular resistance (26.9 ± 3.2 to 25.5 ± 2.8, P > .05). Mean arterial pressure fell during coronary angiography from 92.5 to 85.6 mm Hg prior to atropine and from 92.3 to 91.2 mm Hg post intra-arterial atropine.

Discussion

In the initial six subjects who were studied with Hypaque-M, 75%, the injection of contrast into the left coronary artery resulted in a significant forearm vasodilation (figs. 1 and 2). That this was a reflex effect and not a direct effect of the contrast refluxing from the sinuses of Valsava and reaching the brachial artery was confirmed by the finding
that the injection of a comparable amount of contrast into the ascending aorta resulted in no significant change in forearm vascular resistance (fig. 3). Currently, Renografin-76 is being used in our laboratory for coronary angiography. Although the injection of this contrast into the left coronary artery resulted in a significant forearm vasodilation, the magnitude was less than that produced by Hypaque. This is consistent with the findings of Carson and Lazzara that 50% Hypaque produced a greater bradycardia than 60% Renografin.

Following intra-arterial atropine a forearm vasodilation was not seen during injection of contrast into the coronary arteries. Although this would suggest a sympathetic cholinergic efferent mechanism this cannot be concluded with certainty since forearm vascular resistance was lower after atropine. Thus it is possible that a further vasodilation might have been demonstrated and the abolition of the vasodilation might have been a nonspecific effect of the atropine. However, a forearm vascular resistance of 26.9 mm Hg/ml/min/100 ml is still in the high-normal range.

Although sympathetic cholinergic fibers have been described in a wide variety of mammals, their existence in humans is still controversial. Whereas vasodilation during mental stress has been suggested to be a cholinergically-mediated phenomenon, an active cholinergic vasodilation during fainting was not demonstrated by other workers. Others have presented a preliminary report that is consistent with our findings. In those studies, systemic administration of atropine appeared to partially block the reflex fall in blood pressure to coronary arteriography, presumably by blocking a systemic cholinergic vasodilation. In those studies, the forearm blood flow response was different from ours. The authors noted a decrease in forearm blood flow during coronary arteriography rather than the increase in flow which we observed. Since they did not report their changes in terms of forearm vascular resistance, it is difficult to compare their limb vascular responses with ours. Why we observed a limb vasodilation and they did not is not readily apparent. There may have been differences in the technique of data acquisition or handling. We made our flow determinations very early during the course of arteriography and specifically evaluated the maximum vasodilator response.

Although it is possible that anxiety was the mechanism by which we produced the vasodilation in our subjects, comparable injections of contrast into the aorta mitigate against this. During those injections, the patient was comparably prepared and a similar sequence of verbal cues was presented to the catheterization staff as though a coronary injection were to take place. The only difference was that aortic root injection was performed and the cine cameras were not activated. It is still possible that the noise of the cameras may have played a role by producing anxiety.

It is impossible to precisely define the afferent limb of this reflex and the receptor or combination of receptors stimulated by coronary angiography. At least two types of ventricular receptors and coronary artery receptors have been described. Ventricular epicardial receptors fire only sporadically and are not coordinated with the phases of ventricular contraction; the afferent limb appears to be subserved by nonmedulated vagal fibers which have a low threshold for stimulation. Some observers have suggested that this leads to a peripheral withdrawal of vascular alpha
adrenergic tone, whereas others have implied that these receptors might activate vasodilator cholinergic fibers. These receptors can be stimulated chemically and are probably responsible for the Bezold-Jarisch reflex, whereas others have implied that all but a minimal sinus node depressant effect of the contrast agent. In our studies, no attempt was made to evaluate the bradycardia response since atropine was only infused locally into the forearm. Alternatively, coronary angiography might have stimulated these receptors secondary to the acute transient left ventricular dilation that occurs secondary to the negative inotropic effects of the radiographic contrast.

In contrast to the epicardial receptors, ventricular pressure receptors, mediated by a medullated fiber vagal afferent limb, fire during the isovolumic portion of ventricular systole and also result in a peripheral vasodilation. Some workers feel that it is this group of receptors that are mechanically stimulated with stretch of the coronary arteries by increased intracoronary pressure, while others ascribe the reflex so evoked to be secondary to specific separate coronary mechanoreceptors. The vasodilation secondary to stimulating the coronary arteries in this manner appears to be blocked by atropine. Vasodilation induced by stimulating both types of receptors may have a cholinergic component; either type may be operative in the reflex response to coronary arteriography.

There is also a second type of coronary artery mechanoreceptor. This reflex is mediated via a sympathetic afferent limb and responds to an increased coronary artery pressure by an increase in sympathetic vasoconstrictor tone. If this reflex were significantly stimulated in our studies, it might have been responsible for attenuating the vasodilation we observed. It is unlikely that it plays a major role in the coronary angiography reflex, since, if it did, atropine should have converted the dilator response to one of vasoconstriction. This was not observed. The most important observation in these studies is that in human subjects, central cardiac receptors can be activated by coronary arteriography and this results in a peripheral vasodilation.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Mr. Robert Klecker and Mr. William Lee and the secretarial assistance of Ms. Judy Holzer, Mrs. Nancy Carston, and Ms. Tima Leu.

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Reflex vasodilation induced by coronary angiography in human subjects.
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Circulation. 1976;53:490-493
doi: 10.1161/01.CIR.53.3.490

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/53/3/490

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