Factors that modify the flow response to intracoronary injections

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ABSTRACT Coronary sinus flow (CSF) was measured in seven patients with normal coronary arteries (group A) during intracoronary injections of 6 ml arterial blood, 6 ml blood from the coronary sinus, 3 and 6 ml isotonic saline, 3 and 6 ml hypertonic glucose, and 6 ml of a contrast agent (sodium metrizoate). In 10 patients with coronary artery disease (group B), CSF was measured after administration of 6 ml isotonic saline, 6 ml sodium metrizoate, and 6 ml of another contrast medium (iohexol). In group A, arterial blood did not affect CSF, while coronary sinus blood induced a 33% increase. After 6 ml isotonic saline, there was a 35% increase in flow and after hypertonic glucose an increase of 70%. Metrizoate induced a rise in flow of 109%. In group B, the increase in CSF after intracoronary injection of saline, metrizoate, and iohexol was 30%, 83%, and 67%, respectively. Blood from the coronary sinus, in contrast to arterial blood, induced a marked rise in peak flow, suggesting a role for reactive hyperemia secondary to myocardial hypoxia in this response. A similar mechanism might have been operative after injection of isotonic saline, as well as after the hyperosmolar contrast agents. However, additional mechanisms mediated by the high osmotic pressure of these substances, such as induction of the Bezold-Jarisch reflex, which will induce coronary vasodilation, may have played a role. Finally, when hyperosmolar agents are used, the possibility of some direct vasodilating properties of the agents cannot be excluded.


Material and methods

Patients. Seventeen patients who had been admitted to the hospital for coronary angiographic examination due to anginal-like chest pain were investigated. Seven patients (group A) had angiographically normal coronary arteries. Two were women and five men, and their median age was 57 years (range 39 to 62). Group B consisted of 10 patients, all of whom proved to have significant coronary artery disease with narrowing of at least one vessel of more than 70%. There were two female and eight male patients in this group and their median age 57 years (range 48 to 62). No cardiac medication was given for 12 hr before the study. Informed consent was obtained from each patient and the Hospital Ethics Committee approved the study.

Catheterization. A Judkins catheter was used to engage the ostium of the left coronary artery of each patient. A thermodilution pacing catheter (Wilton-Webster Lab.) was positioned in the coronary sinus. The position of the catheter was confirmed by injection of radiopaque dye and was adjusted during flow measurement until there was a stable baseline flow curve. With a bolus injection of 10 ml of isotonic saline in the right atrium during temperature recording in the coronary sinus, the presence of reflux as a source of measurement error could be detected and was eliminated when necessary by changing the position of the catheter.

Measurements. The CSF was determined with the continuous-infusion thermodilution method. Isotonic saline solution at room temperature was infused into the coronary sinus at a rate of 44 ml/min by infusion pump. Blood oxygen saturation was determined by a photometric method and the erythrocyte volume fraction (EVF) was estimated after 10 min centrifugation of
FIGURE 1. Changes in CSF after intracoronary injections in group A. Values are mean ± SEM *p < .007 compared with control value, which is the p value necessary for statistical significance after adjustment for the multiplicity of testing (see text).

the blood sample. The electrocardiogram was continuously recorded with a bipolar chest lead with one electrode in the V₅ position and the other in the right subclavicular region.

Procedure. Coronary sinus temperature and the electrocardiogram were recorded continuously before, during, and after the intracoronary injections. All substances were administered by injection by the same person throughout the study, and the injection rate was 2 ml/sec. In group A, the following injections were given: 6 ml arterial blood (drawn from the coronary artery catheter), 6 ml coronary venous blood (obtained via the coronary sinus catheter), 3 and 6 ml isotonic saline, 3 and 6 ml hypertonic glucose (30% solution, which corresponds to 1400 mOsm/kg), and 6 ml sodium metrizoate (Isoopaque Coronar 370, Nyegaard & Co A/S), which is an ionic contrast medium with calcium added and with an osmolality of 2100 mOsm/kg.

There was an interval of at least 5 min between the injections. Two injections of each substance were given and the mean difference in the increase in flow between duplicate measurements was 8 ± 3% and did not exceed 15% for any of the agents. In the first three patients, repeat injections were also given of solutions (saline and contrast medium) at body temperature. Since the flow response was within the limits of the variation in the duplicate measurements mentioned above, only solutions at room temperature were used in the remaining patients.

In group B, all injections were given during atrial pacing to a rate 20% above resting heart rate. Three different substances were injected: 6 ml isotonic saline, 6 ml sodium metrizoate, and 6 ml iohexol (Omnipaque 350, Nyegaard & Co). The latter is a new nonionic and low osmolar (700 mOsm/kg) contrast agent. At least 5 min were allowed between the injections. Two injections of each substance were given. The coronary flow was measured during the first injection, and blood samples for analysis of oxygen saturation and EVF were collected at 0, 30, 120, and 300 sec after the second injection. Atrial pacing was performed throughout the procedure in group B patients.

Calculations. CSF was calculated with the formula \( Fb = \frac{Fi \times k \times (Tb - Ti)}{(Tb - Tm)} - 1 \), where \( Fb = \) blood flow in the coronary sinus (ml/min); \( Fi = \) infusion rate of saline (ml/min); \( Tb, Ti, Tm = \) temperature of blood, injectate, and mixture of blood and injectate, respectively; \( k = \) a constant derived from the density and specific heat of saline solution and blood.

Statistical methods. In group A, the effects on CSF of seven substances were investigated, and a double-sided test was performed for each substance. To adjust for testing multiplicity, Bonferroni’s method was used. According to this technique, the alpha error of an individual test is reduced to 0.05/7, which approximates 0.007. This value corresponds to the probability of one or more of the seven individual hypotheses being erroneously rejected. Thus, only a p value below .007 was considered to indicate statistical significance. In group B, multiple comparisons of results with each substance at different time intervals after intracoronary injections were performed (Wilcoxon matched-pairs signed-ranks test). In accordance with the discussion above, Bonferroni’s method was used, and thus only p values less than .0167 (0.05/3) were considered to indicate statistical significance. In addition, the reactions to the individual substances were tested against each other at the different time intervals, and the p value was similarly corrected.

Results

Group A. All patients were in sinus rhythm before and during the intracoronary injections and the mean heart rate was not significantly changed after any of the injections. Figure 1 illustrates the reaction of CSF to injection of the various substances. This parameter was not affected by the injection of arterial blood. Blood from the coronary sinus, on the other hand, did produce a 33 ± 12% increase after intracoronary injection. After 3 and 6 ml isotonic saline, the CSF rose

FIGURE 2. CSF recordings in one patient in group A.

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22 ± 9% and 35 ± 11%, respectively. Hypertonic glucose induced increments in flow that were two to three times greater than those induced with isotonic saline. The most pronounced increase in CSF was seen after sodium metrizoate (109 ± 38%). Figure 2 shows typical responses of flow to various intracoronary substances in one patient.

**Group B.** Figure 3 illustrates the effects on CSF of intracoronary saline, iohexol, and sodium metrizoate. The peak increase was most pronounced after metrizoate (83%). The corresponding values for iohexol and saline were 67% and 30%, respectively. The same pattern was noted regarding the oxygen saturation of CSF and EVF, i.e., metrizoate produced the most marked increase in oxygen saturation and the greatest fall in EVF (figures 4 and 5).

**Discussion**

Injection of all but one of the various substances tested into the left coronary artery elicited a transient
increase in CSF. The exception was arterial blood, which did not induce any significant alteration in flow. This implies that the injection per se was not a stimulus for a change in coronary blood flow.

In group A patients, the increase in CSF varied markedly depending on the substance injected. There was a 20% to 30% rise in flow after injection of isotonic saline or coronary venous blood. Injection of hypertonic glucose solution resulted in 60% increase and after metrizoate the flow more than doubled. It was also noted that the coronary flow response was more marked when a larger volume of the same substance was injected.

The time sequence of the increase in blood flow after injection of isotonic saline, iohexol, and metrizoate was demonstrated in more detail in the group B patients. The maximal flow occurred at about 10 sec after the injection and in these patients as well as in those in group A, the most marked increase was seen after metrizoate. At the time of increase in coronary flow there was also a significant increase in oxygen saturation of the coronary sinus blood. Again, the most pronounced response was noted after metrizoate injection. The increase in oxygen saturation was short-lasting and returned to the baseline level at 20 sec after saline and iohexol, while the reaction to metrizoate lasted somewhat longer.

The observed changes in coronary hemodynamics after intracoronary injections in this study resemble the reactive hyperemia seen after a brief coronary artery occlusion, when an increase in coronary sinus oxygen saturation is regularly seen and there is an overpayment of flow as well as of oxygen debt.6

A similar flow response can be elicited by hypoxia.7,8 The mechanism of hypoxic vasodilation is not known in detail. Local release of adenosine, increased extracellular potassium concentration, or local prostaglandin synthesis are proposed but not proved mechanisms for vasodilation.9,10 The most likely cause is a direct action of lowered Po2 on the coronary vasculature causing vasodilation. Experimentally, coronary flow has been demonstrated to vary inversely with the arterial oxygen content.11 Since the intracoronary injection of all substances except arterial blood produced a short period of myocardial hypoxia in the present study, this mechanism may be an important factor in the reactive hyperemia observed in our patients.

There was a progressively increasing hyperemic response to the same amount of saline, hypertonic glucose, and metrizoate. This suggests gradually increasing hypoxic stress on the coronary circulation, which might be explained by different degrees of hyperosmolality. The change in EVF, which was most marked after metrizoate, suggests a varying degree of hemodilution for the different substances. If the hyperosmolar solution causes diffusion of water from extravascular

![FIGURE 5](image-url)

**FIGURE 5.** Changes in EVF in group B. Values are mean ± SEM. Symbols of significance are as in figure 3.
to intravascular space, the volume of fluid with low oxygen content passing the vascular bed will increase. This will cause a more marked hypoxic stimulus of reactive hyperemia. However, exact interpretation of these changes cannot be made since dehydration of erythrocytes in a hyperosmolar solution also could contribute to changes in EVF.

Additional mechanisms might partly explain the changes in coronary flow. For example, it has been demonstrated that the intracoronary injection of contrast material induces bradycardia and peripheral vasodilatation (the so-called Bezold-Jarisch reflex). The explanation for this reaction is probably that mechanoreceptors in the coronary arteries are activated by injection of hyperosmolar agents. Thus, coronary vasodilation due to this mechanism might contribute to the increase in flow after injection of hypertonic glucose solution, iohexol, and metrizoate. On the other hand, the increase in coronary flow caused by injection of isotonic saline and coronary venous blood is not explained by this type of reflex.

Direct vascular actions of the injected substances, i.e., pharmacologic vasodilatation, could also have a hyperemic effect. However, it seems improbable that isotonic saline could have such an effect.

In conclusion, several factors seem to influence the degree of reactive hyperemia after an intracoronary injection. The hypoxic stimulus of the injection, direct and/or indirect effects of hyperosmolarity, and pharmacologic properties of the substances injected seem to be some of the most important determinants of the response.

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