

Effect of intracoronary glyceryl trinitrate on perfusion distribution in the collateralised human myocardium

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SUMMARY The effect on myocardial perfusion distribution of intracoronary glyceryl trinitrate in a dose (60 µg) insufficient to cause alterations in systemic blood pressure or heart rate was studied in eight patients with angiographically demonstrated collaterals from the left coronary system to the distal right coronary artery. Double isotope imaging using technetium-99m and iodine-131 labelled albumin macroaggregates allowed each patient to serve as his own control. The reproducibility of the imaging and data handling techniques was shown in 12 control patients. Glyceryl trinitrate caused a significant diminution in the collateral-mediated fractional perfusion while increasing that of the native coronary bed.

While there is general agreement about its peripheral actions, the direct effects of glyceryl trinitrate on collateral vessel mediated myocardial perfusion remain controversial.¹⁻³ Experimental,^{1 2 4} and intraoperative⁵ pressure and flow measurements, though providing useful data about the functional behaviour of the collateral bed, do not allow direct conclusions regarding myocardial perfusion. In this study myocardial imaging after intracoronary injections of technetium-99m and iodine-131 labelled human albumin macroaggregates was used to determine the effect of intracoronary glyceryl trinitrate on myocardial perfusion distribution in eight patients with angiographically demonstrable left-to-right collaterals. The double isotope technique allowed each patient to serve as his own control.

Subjects and methods

PATIENT POPULATION

The study group consisted of eight patients (seven men, one woman) with a history of myocardial infarction six or more months previously, who were submitted to selective coronary arteriography because of angina. Left ventriculography and selective coronary arteriography were performed using

Renografin-76. Selective arteriography was performed using Judkins coronary catheters introduced percutaneously into the femoral artery by the Seldinger technique. Each patient's entry into the study was decided at the time of arteriography and was based on opacification of the distal right coronary artery via angiographically visible collateral vessels during selective injections of the left coronary system. All patients had either total (100%) or subtotal (99%) occlusion of the right coronary artery. Seven of the eight patients also had significant (50%) obstruction of the left anterior descending coronary artery and three of these had circumflex lesions as well.

STUDY PROCEDURE

The procedure was designed to allow each patient to serve as his own control. After completion of left ventriculography and selective coronary arteriography, 10 minutes were allowed to elapse before injection of the macroaggregates. Previous studies have shown⁶ that contrast medium-induced hyperaemia subsides well within this time. Human albumin macroaggregates (mean particle diameter 10 to 40 µ) labelled with either 500 µC technetium-99m (^{99m}Tc) or 100 µC iodine-131 (¹³¹I) suspended in 2 ml normal saline were used in each study. The order in which the two isotopes were administered was randomly chosen. The macroaggregate suspension was well agitated before injection. After each injection the coronary catheter was flushed with 2 ml heparinised saline. Seconds

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after injection of the first isotope into the left coronary artery, glyceryl trinitrate 60 μg was injected after which the catheter was withdrawn from the coronary ostium. The aortic pressure and heart rate were continuously monitored throughout the procedure. Thirty seconds after the glyceryl trinitrate injection, the catheter was repositioned in the left coronary ostium and the macroaggregate suspension bearing the second isotope was injected. Approximately 10 minutes after completion of the above procedures, simultaneous dual isotope myocardial imaging in the anterior, 45° right and left anterior oblique (RAO and LAO), and left lateral views was performed using an Ohio Nuclear dual probe rectilinear scanner with 20 per cent energy windows around peaks at 140 and 370 kV. Digital counts over a 64 \times 64 matrix from each image were stored on magnetic tape.

Twelve other patients underwent an identical study procedure but received 2 ml normal saline instead of glyceryl trinitrate. They served as controls for the validation of the dual isotope technique and the subsequent quantitative image analysis.

ANALYSIS OF RESULTS

Colour isocount displays were reconstructed on an oscilloscope by retrieving the digitised data stored during scintiscanning. Orthogonal matrices composed of 7 \times 4 and 6 \times 4 square cells were superimposed on right and left anterior oblique images, respectively. The matrices were centred around the cardiac contour and were positioned identically over the two isotope images. The fraction of digital counts within each matrix element relative to the total counts over the whole matrix was calculated and expressed as a percentage.

Triads of matrix elements deemed to overlie myocardial regions perfused largely by one of the three major coronary arterial systems were chosen as depicted in the Figure. In the right anterior

oblique view, regions perfused by the left anterior descending and right coronary artery were chosen in a manner that excluded intermediate areas in which the source of perfusion may have been overlapping. Matrix elements close to the lateral borders were probably outside the cardiac silhouette as evidenced by the low fractional counts (< 1.0%) within them. Since part of the region assigned to the right coronary artery distribution in this view may have been overlying the circumflex distribution, left anterior oblique views were also analysed. In this projection the left anterior descending and circumflex distributions assumed an anteroposterior separation which permitted their individual analysis.

Since imaging through the energy windows corresponding to the two isotopes was performed simultaneously, a strict one-to-one correspondence was ensured between matrix elements of the two images obtained. Accordingly, paired Student's *t* tests were performed to assess the statistical significance of changes of fractional counts within the above-described triads of matrix elements.

Identical data handling and statistical analysis were applied to the images from patients in the control group.

Results

Intracoronary injections of glyceryl trinitrate in the doses used in this study caused no alterations in aortic blood pressure (systolic, diastolic, or mean) or heart rate. There were no complications in any of the eight patients during, or as a result of the study procedure.

The results of the statistical analysis described in the previous section are summarised in the Table. In the overall group of eight patients, each triad of matrix elements yielded 24 pairs of fractional distribution. Statistical analysis of these data (Table) showed that after intracoronary glyceryl trinitrate

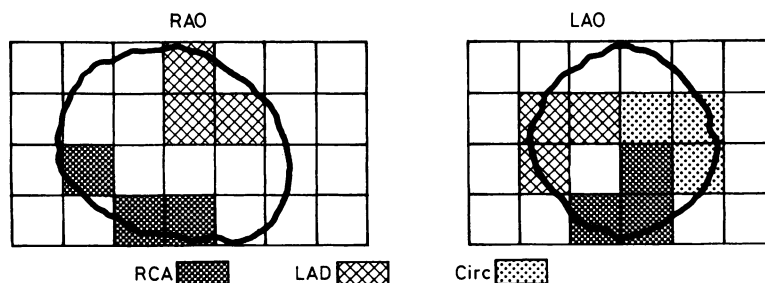


Fig. Analysis of myocardial perfusion images. Orthogonal matrices were superimposed on 45° right anterior oblique (RAO) and left anterior oblique (LAO) images. Triads of matrix elements were assigned, as illustrated, to represent regional perfusion in the distribution of the right (RCA), left anterior descending (LAD), and circumflex (Circ) coronary arteries.

Glyceryl trinitrate and collateral perfusion

Table Summary of statistical data* analysis†

View	Coronary distribution	No.	Control (%)	After glyceryl trinitrate	Significance of difference
Right anterior oblique	Left anterior descending	24	6.87 ± 0.38	7.90 ± 0.46	p < 0.01
	Right coronary artery	24	3.49 ± 0.22	2.95 ± 0.21	p < 0.001
Left anterior oblique	Left anterior descending	24	5.86 ± 0.53	6.71 ± 0.67	p < 0.01
	Circumflex	24	7.19 ± 0.57	6.90 ± 0.65	p > 0.05
	Right coronary artery	24	7.33 ± 0.62	6.61 ± 0.59	p < 0.05

* Fractional perfusion expressed as mean per cent of total counts ± SE. † Paired Student's t test.

there was a significant fall in the proportion of the total left coronary perfusion distributed by collateral vessels to the right coronary artery region ($p < 0.001$ from right anterior oblique views, $p < 0.05$ from left anterior oblique views). At the same time the proportion of perfusion in the left anterior descending distribution increased significantly after glyceryl trinitrate ($p < 0.01$ from right anterior oblique views, $p < 0.01$ from left anterior oblique views). There was no significant change in the proportional perfusion of the circumflex distribution ($p > 0.05$) as analysed from left anterior oblique views. Thus, the circumflex distribution could not have contributed to the very significant differences within regions assigned to the right coronary artery distribution in the right anterior oblique views.

Analysis of imaging data obtained from the 12 control patients showed no statistical difference ($p > 0.05$) in the fractional perfusion of any of the coronary arterial distributions as assessed by the two isotopes injected before and after saline. These findings validated the reproducibility of the method and analysis of data used in this study with respect to the two isotopes.

Discussion

The use of intracoronary injections of radioactive labelled human albumin macroaggregates, first reported by Ashburn *et al.*,⁷ has been shown to be both a valid and safe technique of assessing myocardial perfusion distribution.^{8,9} A double isotope technique using indium-113m and ^{99m}Tc-macroaggregated albumin was first used by Ritchie *et al.*⁶ to compare the regional myocardial perfusion distributions before and after stress-induced ischaemia.

Intracoronary glyceryl trinitrate in the dosage

used in this study (60 µg) produced no significant alterations in systemic blood pressure or heart rate. Thus, the technique allowed observations to be made about the action of glyceryl trinitrate on the coronary circulation independently of its peripheral actions. The group of control patients showed that the technique of dual isotope imaging as well as the data analysis yielded statistically reproducible estimates of segmental myocardial perfusion using the two isotopes. We felt it important to validate this point since selective injections into the branches of the left main coronary artery could conceivably occur either by virtue of physical entry of the catheter tip into one of the branches in patients with a short left main segment or streaming of the injectate under pressure without adequate mixing. The application of the procedure to the control patients did not rule out this possibility but did demonstrate that if the catheter is removed from the coronary ostium and then reinserted by the same operator using the same technique, the catheter position is reproducible between injections and, therefore, similar injections result in reproducible macroaggregate distributions. The use of each patient as his own control made it possible to analyse the data in a paired fashion minimising interindividual differences in coronary perfusion distribution and focusing attention on the changes induced by glyceryl trinitrate.

It is important to point out that this technique does not allow estimation of absolute myocardial perfusion and that our findings concern only the proportional distribution of the total flow. Experimental studies previously reported on the direct effects of glyceryl trinitrate on collateral perfusion have been contradictory.¹⁻³ The contradictions, however, were among studies performed by very different techniques and, therefore, not really comparable. Peripheral coronary pressure from regions distal to ligation of the left anterior descending artery in dogs has been shown to increase significantly after administration of glyceryl trinitrate.^{1,2,4} Studies in humans at the time of coronary artery bypass surgery showed a similar increase in peripheral coronary pressure and, more importantly, the calculated resistance of the collateral bed was found to decrease significantly in response to glyceryl trinitrate.⁵ It is important to point out that the resistance of the native coronary bed was not simultaneously measured and may decrease even more. This would result in a shift of fractional distribution in a manner favouring the native coronary bed and away from the collateral bed. It is possible that despite the relatively small decrease in fractional distribution to the collateralised area shown in our study (usually 10%) the

absolute perfusion of these regions in terms of ml/min per 100 g myocardium may in fact have increased but to a lesser degree than a simultaneous increase to the region supplied by the left anterior descending artery. Ganz and Marcus³ have found that the efficacy of glyceryl trinitrate in the relief of angina induced by pacing in patients in whom the blood pressure was not allowed to respond to glyceryl trinitrate was severely limited. These authors concluded that the effect of glyceryl trinitrate on the coronary circulation was a relatively minor component of its beneficial effect in ischaemia. Cohen *et al.*¹⁰ reported that the administration of a coronary vasodilator (isoprenaline) after acute coronary occlusion in dogs resulted in a shift in myocardial perfusion away from regions supplied by collateral vessels. As in other dog experiments, however, the behaviour of the collateral circulation may be very different from that in the human since collateral vessels are known to be readily available in the acute setting in dogs while in humans collaterals are believed to develop slowly over long periods of time in response to chronic ischaemia. Collaterals which develop in this manner may have different vasoreactivity from those which are present in the dog in the absence of chronic ischaemia.

The observed effect of glyceryl trinitrate on myocardial perfusion distribution in the collateralised human heart implies a lesser responsiveness of the collateral circulatory bed to the dilatatory effect of glyceryl trinitrate compared with the native coronary circulation. This could be the result of either an intrinsic difference in the sensitivity of the resistive elements in the two circulations or ischaemia-mediated dilatation in the former which might pre-empt a portion of the maximal inducible dilatatory response.¹¹ Our observations support previous findings that the effect of glyceryl trinitrate on the coronary circulation is a relatively minor component of its beneficial effects in ischaemia.^{2,3} If absolute coronary flow does not increase, the direct effect of glyceryl trinitrate on myocardial perfusion distribution may be detrimental but could still be overridden by its beneficial systemic actions. Further studies will be required to elucidate the reasons for these differences in glyceryl trinitrate responsiveness. Such studies might improve our understanding about the physiological behaviour of the collateral circulation and permit interventions aimed at maximising its beneficial function in ischaemic heart disease.

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