MYOCARDIAL DISTRIBUTION OF CARDIOPLEgia ADMINISTERED BY ANTEGRADE AND RETROGRADE ROUTES TO ISCHEMIC MYOCARDIUM

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OBJECTIVE: To study the distribution of a cardioplegic solution delivered by antegrade and retrograde routes to ischemic myocardium. Retrograde administration has been suggested to improve protection of the ischemic myocardium. However, there are insufficient data on perfusion of ischemic and necrotic zones by the retrograde route.

DESIGN: A laboratory study in dogs.

METHOD: In 12 dogs, 500 mL of hyperkalemic crystalloid cardioplegia containing 0.5 mCi of thallium-201 was injected antegradely or retrogradely through the coronary sinus after 3 hours of occlusion and 2 hours of reperfusion of the left anterior descending coronary artery. Myocardial distribution of the cardioplegic solution was measured by computer planimetry in the normally perfused zone, in the ischemic area and in the necrotic zone.

RESULTS: The mean (and standard deviation) area at risk of ischemia (% of the left ventricle) delimited by Evans blue perfusion was smaller in dogs receiving a retrograde injection than in those receiving an antegrade injection (34% [3%] v. 42% [4%], p = 0.15). The infarct size (% of the area at risk indicated by triphenyltetrazolium dye) averaged 25% (11%) and 20% (7%) respectively (p = 0.36). The ratio of thallium-201 activity in ischemic to normal myocardium averaged 76% (13%) in the retrograde and 89% (12%) in the antegrade groups (p = 0.75). The ratio of thallium activity of infarct to normal myocardium averaged 56% (8%) in the retrograde group and 93% (19%) in the antegrade group (p = 0.18). Large areas of hypoactivity in the left ventricular myocardium were noted on scintigraphic imaging in all dogs that received retrograde perfusion.

CONCLUSIONS: The retrograde injection of cardioplegia through the coronary sinus does not improve the distribution of cardioplegic solution in the acutely ischemic myocardial area nor in the zone of acute infarction in the dog. Because some cells may remain viable in the border zone and into the necrotic area, retrograde cardioplegia may result in suboptimal protection and incomplete prevention of further damage to the myocardium.
Retrograde administration of cardioplegic solution through the coronary sinus has been proposed as an essential component of warm blood cardioplegia. It is widely used in clinical practice with the hope that oxygen is being delivered continuously and uniformly throughout the myocardium. However, animal experiments have shown that the right ventricle and the interventricular septum are less than adequately perfused by the retrograde route. In addition, the distribution of cardioplegic solution administered antegrade or retrogradely has not yet been well defined in acutely ischemic myocardium. The objective of the present study was to evaluate the myocardial distribution of cardioplegic solution in normal, ischemic and necrotic myocardium after antegrade and retrograde administration. We hypothesized that the distribution of cardioplegia in ischemic and necrotic myocardium will be homogeneous with the retrograde route and heterogeneous with the antegrade route; therefore, the retrograde route should result in a better preservation of ischemic myocardium.

MATERIAL AND METHODS

Myocardial distribution of cardioplegic solution during antegrade injection into the ascending aorta and retrograde injection through the coronary sinus was studied in 12 dogs, ranging in weight from 25 to 30 kg. The animals were anesthetized with sodium pentobarbital (30 mg/kg), and ventilated mechanically (Harvard Apparatus, South Natick, Mass.). A median sternotomy was performed. After systemic injection of 1000 units of heparin and perfusion of 100 mg of lidocaine, the left anterior descending (LAD) coronary artery was occluded distal to the first diagonal branch for 3 hours, followed by 2 hours of reperfusion. A catheter was placed in the ascending aorta for the administration of the cardioplegic solution in the 6 dogs of the antegrade group. Transatrial cannulation of the coronary sinus with a coronary sinus catheter (self-inflating 14 French balloon catheter; Research Medical Inc., Midvale, Utah) for retrograde infusion of cardioplegia was performed on the 6 dogs of the retrograde group. Thallium-201 (Tl), 0.5 mCi, was added to 500 mL of hyperkalemic crystalloid cardioplegia containing 130 mmol of sodium, 135 mmol of chloride, 3 mmol of calcium, 28 mmol of lactate, 20 g of mannitol, 0.17 g of sodium bicarbonate and 34 mmol of potassium chloride per litre. The crystalloid solution was administered at room temperature (21°C) in both groups.

Retrograde coronary sinus cardioplegic solution was injected at low perfusion pressure (20 to 40 mm Hg) after ligation of the ayzygos vein and the superior and inferior vena cava, and aortic cross-clamping. The ascending aorta and the left and right ventricles were vented. Effluent solutions from vented catheters were collected and analysed. In the antegrade group, effluent solutions from vented left and right atria and from left and right ventricles were collected and analysed. The antegrade injection was performed at high perfusion pressure (50 to 100 mm Hg) in the ascending aorta. Tl activity in the myocardium, and in effluents from the left ventricle, the right ventricle and the aorta was calculated and expressed as a percentage of the total dose of injected radioactive tracer.
The data are presented as means (and standard errors). Differences between groups were studied by Student’s *t*-test, and analysis of variance for repeated measures was used when appropriate. A correlation coefficient was calculated to study the relationship between two variables. The level of statistical significance was established at 95%. All animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals.6

**RESULTS**

**Quantitative assessment of ischemic and necrotic myocardium**

After ligation of the LAD coronary artery, the area of myocardium at risk of ischemia averaged 34% (3%) of the total left ventricular area in retrogradely perfused dogs and 42% (4%) in antegrade perfused dogs. In retrogradely perfused hearts, a non-significant difference (*p* = 0.15). The necrotic zone averaged 25% (11%) of the area at risk of ischemia in the retrograde perfusion group and 20% (7%) in the antegrade perfusion group, again a non-significant difference (*p* = 0.36).

Evaluation of the capillary flow showed that 79% (5%) and 80% (6%) of total ²⁰¹TI activity was recovered in the myocardium of retrogradely and antegrade perfused hearts respectively (*p* = 0.93). The remaining radiotracer was recovered in the aorta, and in the right and left ventricular and right atrial effluents.

The release of troponin T during the experiment was similar in both groups (retrograde 3.1 [1.3] μg/L, antegrade 5.2 [2.3] μg/L, *p* = 0.5). A strong correlation was found between maximal level of troponin T and infarct size (*r* = 0.91, *p* = 0.00001). A significant negative correlation was also found between the maximal level of troponin T and the normal and residual areas of the left ventricle after coronary ligation and reperfusion (*r* = −0.87, *p* = 0.0002).

**Myocardial distribution of cardioplegic solution**

The ratio of ²⁰¹TI activity of the area at risk of ischemia to normal myocardium in retrogradely and antegrade perfused hearts averaged 76% (13%) and 89% (12%) respectively, a nonsignificant difference (*p* = 0.75). The ratio of radioactivity of necrotic to normal myocardium averaged 56% (8%) and 93% (19%) respectively, a nonsignificant decrease in retrograde perfusion of necrotic myocardial areas (*p* = 0.18).

The ratio of ²⁰¹TI activity of subendocardial to epicardial area in ischemic zones averaged 139% (19%) in retrogradely perfused hearts compared with 133% (28%) in the antegrade group, a nonsignificant difference (*p* = 0.86). The ratio of subendocardial to epicardial radioactivity in the necrotic area averaged 121% (25%) in retrogradely perfused hearts and 83% (10%) in antegrade perfused hearts, a non-significant decrease in antegrade perfused hearts (*p* = 0.16).

**Analysis of scintigraphic images**

Analysis of scintigraphic images of retrogradely perfused hearts showed large areas of hypoactivity in the left ventricular free wall corresponding to the area of myocardial necrosis delineated by the TTC method. On the other hand, the distribution of ²⁰¹TI activity was more homogeneous in the left ventricle of antegrade injected hearts, where no significant zone of hypoactivity was shown (Fig. 1).

**DISCUSSION**

Several studies have shown that retrograde administration of cardioplegic...
FIG. 1. Example of scintigraphic images (left) and schematic representation (right) of a left ventricle after antegrade (bottom) and retrograde (top) perfusion. The myocardium at risk of ischemia represents 41% of the total left ventricular area in antegrade (bottom) and 42% in retrograde (top) perfused hearts. The necrotic zones represent 48% of the ischemic area in antegrade (bottom) and 63% in retrograde (top) perfused hearts. Large areas of hypoperactivity are shown in the infarcted myocardium of retrogradely perfused hearts (top left) and small areas of thallium-201 hypoperactivity are shown in the left ventricle of antegrade perfused hearts (bottom left).
solution through the coronary sinus provides excellent clinical results in protecting myocardial function during valve and coronary artery bypass surgery. The retrograde approach has been recommended in patients with complete coronary occlusion, particularly when the LAD coronary artery is occluded, and in patients with myocardial hypertrophy.

Several experimental studies have indicated a concern regarding myocardial distribution and capillary flow when the retrograde route is used for cardioplegic administration. In a recent experiment, we showed that 70% to 80% of the total 201TI activity injected retrogradely in the coronary sinus was recovered in the myocardium, indicating that a high transcapillary flow resulted from retrograde infusion. However, small areas of the right ventricular and septal walls were found to be nonhomogeneously perfused by retrograde cardioplegic infusion when the myocardium was supplied by fully open coronary arteries.

Misare and colleagues reported that the systolic function of ischemic myocardium remains well preserved after retrograde, continuous, warm blood cardioplegia, suggesting that in ischemic areas, retrograde myocardial perfusion was adequate after a short period of coronary occlusion and myocardial reperfusion. In our experiments, similar ischemic and necrotic areas of the left ventricle were obtained in both antegrade and retrograde groups after ligation of the LAD coronary artery and myocardial reperfusion. The ratio of 201TI activity of ischemic to normal myocardium was similar in antegrade and retrogradely perfused hearts, whereas the ratio of radioactivity of necrotic to normal myocardium was higher with antegrade than retrograde perfusion, although the difference was not statistically significant.

Scintigraphic images of retrogradely perfused hearts showed large areas of hypoenhancement in the left ventricle compared with hearts perfused antegrade (Fig. 1). This suggests that the radioactive tracer did not access the necrotic area when injected by the retrograde route as opposed to the antegrade route. This suggestion is in agreement with the lower ratio of 201TI activity of necrotic to normal myocardium in retrogradely than in antegrade perfused hearts, although the difference was not significant. After intravenous injection, early myocardial uptake of 201TI is proportional to regional blood flow and myocardial extraction. In animal models, hypoxia or myocardial stunning does not affect myocardial uptake of 201TI. However, integrity of the cellular membrane is necessary for 201TI to concentrate in the cell. Necrotic myocardium does not take up 201TI when injected after reperfusion preceded by 3 hours of coronary occlusion. However, early post-reperfusion thallium uptake may overestimate myocardial viability, possibly because of increased blood flow.

In our study, even though infarct size was similar in both groups, 201TI activity in the necrotic zone was almost equal to that of the normal area in the antegrade model (93%), in contrast to the retrograde model (56%). Possible explanations are that viable myocardial cells remained in the infarct area and were still able to concentrate 201TI, myocardial perfusion was increased due to hyperemic blood flow and, finally, some of the 201TI may have been present in the extracellular compartment since hearts were harvested minutes after cardioplegic arrest. Whatever the mechanism involved, a higher 201TI uptake in the antegrade model is suggestive of increased blood flow or increased myocardial viability, or both, compared with the retrograde group. Whereas both the antegrade and the retrograde routes provide hyperperfusion of subendocardial muscle irrigated with an open coronary artery, there is underperfusion with the antegrade route when the artery is occluded. In our study, ischemic areas located in the subendocardium were hyperperfused in both groups, and necrotic areas in the subendocardium were hyperperfused by retrograde injection and slightly underperfused by antegrade injection. Thus, retrograde and antegrade injection routes had a similar distribution pattern in the ischemic myocardial wall. The low ratio of 201TI activity in necrotic areas perfused by the retrograde route suggests a significant maldistribution of the solution, whereas the subendocardium remained hyperperfused when compared with the subepicardial zone.

Microvascular damage, particularly to the system of small post-capillary venules, could explain the no-reflow phenomenon shown with retrograde infusion of the cardioplegic solution in necrotic areas. Although there are conflicting results in regard to the effect of retrograde warm blood cardioplegia in the setting of acute global ischemia in animals, reperfusion of necrotic zones and of the viable component of the border zone through the retrograde route could have been suboptimal. Despite the limitations of an animal model, our data suggest that both the antegrade and the retrograde route do not perfuse the ischemic or necrotic zones normally.

**Conclusion**

Retrograde administration of cardioplegic solution through the coronary sinus did not result in improved perfusion of acute ischemic myocardium in the dog when compared with antegrade perfusion.
REFERENCES


CJS, Vol. 40, No. 2, April 1997 113

RETROGRADE CARDIOPLEGIC PERFUSION IN ISCHEMIC MYOCARDIUM