Heterogeneous distribution of cardioplegic solution in pigs


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Septal dyskinesia in the left ventricle is detected frequently in many patients after open-heart surgery. The present study was designed to determine whether the antegrade delivery of cardioplegic solution to the regional wall categorized in echocardiography is homogeneous, and whether the distribution to the septal wall differs from that to the lateral wall in the absence of coronary artery disease. To assess these hypotheses quantitatively, radioactive microspheres were mixed into the cardioplegic solution and infused by an antegrade method in eight normal pigs. The cardioplegic distribution to the septal wall was significantly less than to the lateral wall close to the base of the left ventricle (P<0.05). Therefore, antegrade perfusion of cardioplegic solution was non-uniformly distributed to the regional and transmural wall of normal pig hearts. Absence of functional correlation was a limitation of this study. However, these findings suggest that inadequate protection of the ventricular septum by antegrade cardioplegia might be an explanation for the abnormalities of septal wall motion after open-heart surgery.


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Newly developed septal wall motion abnormalities are detected frequently after valve and coronary bypass surgery. The role of pericardiectomy with secondary loss of pericardial restraint, perioperative ischaemia and intrapericardial collections have been suggested as the causes of this abnormality.1 However, non-homogeneous delivery of cardioplegic solution may result in postischaemic myocardial injury. Aldea et al.2 found that flow to discrete myocardial regions was significantly non-homogeneous for both antegrade and retrograde cardioplegia.

We propose two experimental hypotheses that are based on previous work: (i) the antegrade delivery of cardioplegic solution to the regional wall categorized in echocardiography may be heterogeneous in the absence of coronary artery...
disease; and (ii) the distribution of cardioplegic solution to the septal wall may differ from that to the lateral wall.

Methods and results

Eight Yorkshire pigs (weighing 25.3 (1.6) kg; range 20–30 kg) were studied after approval had been obtained from the Animal Care Committee of Ajou University Institute for Medical Sciences. All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (NIH Publication 85–23, revised 1985; National Institutes of Health, USA). After premedication with a mixture of ketamine hydrochloride 10 mg kg\(^{-1}\), midazolam 0.1 mg kg\(^{-1}\) and atropine sulphate 0.05 mg kg\(^{-1}\) i.m., anaesthesia was induced with ketamine 1–2 mg kg\(^{-1}\) i.v. and tracheostomy was performed. Anaesthesia was maintained with a mixture of 100% oxygen and 0.5–1.0% halothane. For muscle relaxation, pancuronium bromide 0.2–0.3 mg kg\(^{-1}\) was administered i.v. The animals were ventilated with a Harvard respirator (Harvard Apparatus, Natick, MA, USA).

Median sternotomy was performed and the pericardium opened. About 3 min after heparinization (10 000 U), a drainage cannula was inserted into the right atrial appendage and connected to 1 litre bags. An aortic root cannula was also inserted for delivery of cardioplegia. The cardioplegic solution (Cardio Sol\(^{19}\); Choongwae, Kyungkee, Seoul, Korea) contained potassium 16 mEq litre\(^{-1}\), and extra potassium was added to yield 20 mEq per 500 ml. The solution was cooled (4°C) in an ice-bath, and about 200 000 microspheres of diameter 15 \(\mu\)m and labelled with chromium 51 (NEN-TRAC\(^{\circledR}\) Microspheres, NEM-032A; New England Nuclear, Du Pont Diagnostic Imaging Division, North Billerica, MA, USA) were injected into the bag containing the cardioplegic solution. The volume of cardioplegic solution was 20 ml kg\(^{-1}\) body weight.

Vascular isolation of the heart was accomplished by sequentially clamping the azygos vein, inferior and superior venae cavae, main pulmonary artery and ascending aorta. Cardioplegic solution was infused into the aorta with a roller pump (COBE\(^{\circledR}\); COBE Laboratories, Lakewood, CO, USA) at a rate sufficient to maintain a perfusion pressure (measured at the aortic root with a transducer) of approximately 90–100 mm Hg until asystole was obtained on the ECG. The volume of fluid in the drainage bag was measured and three samples were obtained to assay the concentration of radioactivity. The heart was excised and placed in formalin solution for 3–5 days to facilitate sectioning. The left ventricle (LV) was divided into five cross-rings from base to apex.\(^3\) The four rings from the basal and mid-wall were divided into six full-thickness sections and the apical ring was divided into four sections. To correlate the regional wall motion abnormalities by echocardiography with the distribution of cardioplegic solution, the LV was divided

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*Fig 1* Cardioplegic flow in the regional wall (A) and septal versus lateral wall distribution (B) of the left ventricle. (A) Subendocardial data are shown as solid circles and subepicardial data as open circles. AS=anteroseptal; PS=posteroseptal; A=anterior; P=posterior; AL=anterolateral; PL=posterolateral; S=septal; L=lateral segment. *\(P<0.05\) compared with median flow of the AS segment; \(^{1}P<0.05\) compared with median flow of the PS segment. (B) Cardioplegic distribution to the septal wall is shown as solid bars and cardioplegic distribution to the lateral wall as open bars. \(^{3}P<0.05\) compared with lateral wall in each cross-section. Data are medians. Section 1 shows basal LV; Section 5 shows apical LV; Sections 2, 3 and 4 show mid-LV.
into 16 segments as recommended by the American Society of Echocardiography. The free wall of the right ventricle (RV) was divided into six basal and six apical segments. Each section of both ventricles was divided into subendocardial and subepicardial halves. Each tissue sample was weighed and placed in counting tubes and analyzed for γ-radioactivity (Cobra II; Packard Instrument, Downers Grove, IL, USA).

The flow rate of cardioplegic solution in each sample ($Q_m$) was calculated using the equation $Q_m = (C_m/C_t) \times Q_t$, where $C_m$ is the radioactivity of the myocardial sample, $C_t$ is the total radioactivity in all of the heart tissue and $Q_t$ is the total cardioplegic flow rate (total volume of cardioplegic solution/time required for infusion). Flow rate may underestimate total flow if a significant fraction of microspheres are shunted across the circulation. Therefore, cardioplegic flow was corrected by dividing cardioplegic flow by the extraction fraction. To obtain the extraction fraction, shunt fraction was calculated by dividing the concentration of radioactivity (counts min$^{-1}$ ml$^{-1}$) in the RV effluent by the concentration of radioactivity (counts min$^{-1}$ ml$^{-1}$) in the cardioplegic solution.

Statistical analysis was performed by repeated measures analysis of variance and the Wilcoxon signed ranks test. A probability of $P<0.05$ was considered significant.

We studied eight animals. The median LV and RV flow was 1.30 (range 0.73–1.85) and 1.16 (0.14–1.78) ml min$^{-1}$ g$^{-1}$ and the relative distribution of cardioplegia between RV and LV was 0.97 (0.18–1.03).

Distribution of cardioplegic solution to discrete myocardial regions of the LV is shown in Fig. 1A. The distribution of cardioplegic solution around each LV cross-section was uneven. Heterogeneous distribution was prominent in basal cross-section (section 1). The median cardioplegic flow of total basal RV and total apical RV was 1.22 (0.20–1.40) and 1.09 (0.08–2.22) ml min$^{-1}$ g$^{-1}$, and there was no significant difference between them. Cardioplegic distribution in the free wall of the RV was relatively uniform (no statistical difference between each of the six samples within basal and apical RV of both groups).

Median septal versus lateral wall distribution in the LV was 1.55 (0.86 to 1.76) versus 2.45 (1.29 to 3.99) ml min$^{-1}$ g$^{-1}$ (not statistically significant). However, in LV cross-sections the cardioplegic distribution to the lateral wall was significantly greater than that of the septal wall in sections 1 and 2 (Fig. 1B).

Distribution of cardioplegia within both ventricles was significantly greater in the subendocardium than in the subepicardium. Median subendocardial to subepicardial ratio (endo/epi) ratio of the LV was 1.97 (1.66–2.55) in the septal wall, 1.52 (1.11–2.23) in the anterior wall, 2.10 (0.99–3.35) in the lateral wall and 1.53 (0.96–2.04) in the posterior wall, and the endo/epi ratio of the septal wall was significantly higher than that of the posterior wall. There was no significant difference between basal (1.58) and apical (1.31) endo/epi ratios of the RV.

### Comment

We confirmed that there was a significantly higher distribution to the lateral wall compared with the septal wall closer to the basal LV in normal pig hearts. Although the reason is not clear, we postulate that there might be some collateral circulation to the distal septal wall through small endocardial anastomoses between the right and left coronary arteries.

Many experiments dealing with cardioplegia have supported the idea that non-homogeneous delivery of cardioplegic solution might result in postischaemic myocardial injury. Aldea et al. reported that, even in hearts with normal coronary anatomy, some regions of the myocardium may have limited delivery of cardioplegic solution and thus inadequate protection. However, Stirling et al. reported that antegrade cardioplegic distribution around each LV cross-section was relatively uniform compared with retrograde cardioplegic distribution in the canine model.

Distribution to the RV has been shown to be two-thirds of that to the LV, and LV subepicardial distribution was approximately one-half of subendocardial flow in canine hearts. Our results revealed that median RV distribution was about 97% of that to the LV. The fact that a greater RV/LV ratio is reported here can be explained as a species difference. For example, the left circumflex coronary artery and left anterior descending artery each supply about 40% of the myocardium, whereas the right coronary artery supplies about 15% in the dog. In pigs, the right coronary and left anterior descending arteries are about equal and the left circumflex plays a relatively minor role, as in man. We also obtained results for the endo/epi ratio similar to those reported previously. More abundant subendocardial perfusion may be related to the greater capillary density and decreased capillary resistance compared with the epicardial surface. Interestingly, the distribution to the posterior, especially subendocardial wall was less than that to the anterior septal wall in mid-papillary and mid-lower cross-sections (sections 3 and 4) (Fig. 1A). This finding corresponds to a significantly lower endo/epi ratio of the posterior wall compared with the septal wall. Therefore, these results suggest that posterior LV walls could be more vulnerable to inadequate myocardial protection.

There are two limitations of our investigation. First, extrapolation to the human should be considered cautiously, because there are species differences in coronary anatomy. The animal model most commonly used for coronary circulation studies has been the dog. Dogs seem to have a collateral system that is extensive and highly recruitable: they usually have three or four relatively large subepicardial collateral vessel anastomoses. There seems to be little doubt that the pig coronary vascular system is closer to that of man. Secondly, the limitations of this study include the lack of demonstration of a functional outcome of cardioplegic distribution. Assessment of regional myocardial performance in regions that did and did not receive adequate...
cardioplegia would help to support the assumption that cardioplegic delivery is essential for providing myocardial protection. However, we could not investigate the relationship between cardioplegic distribution and functional recovery because intraoperative echocardiography was not available in our laboratory.

In conclusion, antegrade perfusion of cardioplegic solution was non-uniformly distributed to the regional and transmural walls of normal pig hearts. Although further functional studies are needed, inadequate protection of the ventricular septum by antegrade cardioplegia might be one of the explanations for postoperative septal wall motion abnormalities after open-heart surgery.

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References