ANAESTHETIC MODIFICATION OF REGIONAL MYOCARDIAL FUNCTIONAL ADJUSTMENTS DURING MYOCARDIAL ISCHAEMIA: HALOTHANE VS FENTANYL


SUMMARY
During myocardial ischaemia, functional compensation occurs by non-ischaemic regions of the left ventricle (LV). Anaesthetics may affect compensation by altering contractility, metabolism and perfusion. This was studied in dogs anaesthetized with fentanyl (150 μg kg⁻¹ loading dose and 100 μg kg⁻¹ h⁻¹) or 0.75% and 1.5% halothane and subjected to left anterior descending artery (LAD) occlusion. After 15 min of anterior wall ischaemia, cardiac output, mean arterial pressure and LV maximum dP/dt were diminished in the 1.5% halothane but not in the 0.75% halothane or fentanyl groups. In all groups, stroke volume decreased. LV end-diastolic pressure increased and anterior wall function deteriorated (measured as systolic shortening, peak systolic intramyocardial pressure (IMP), regional wall stroke work (RSW) and slope of preload recruitable stroke work curve (Mw)) with ischaemia. Functional changes in the lateral (non-ischaemic) wall were different between groups. Regional function during occlusion in this area improved with fentanyl (mean (SEM) IMP, RSW and Mw increased by 23 (2) %, 37 (3) % and 69 (7) %, respectively), was relatively well-maintained with 0.75 % halothane and diminished with 1.5% halothane.

KEY WORDS

Recent studies have reported that the development of ischaemia during the perioperative period is common [1, 2]. Myocardial ischaemia and its haemodynamic sequelae are the most serious perioperative anaesthetic complications during cardiac surgery [1, 3, 4]. Many studies have examined the prevention of myocardial ischaemia by measurement of the effects of anaesthetics on myocardial oxygen supply—demand balance [4–7]. However, the potential role of anaesthetics in maintaining global ventricular function when one region of the myocardium becomes ischaemic has received little attention.

In 1935, Tennant and Wiggers reported that an area of the left ventricle (LV) rendered ischaemic by occlusion of a coronary artery failed to contract during systole [8]. Acute myocardial ischaemia has a negative inotropic influence, causing a reduction in external work performed by the ischaemic regions of myocardium, while work performed by non-ischaemic regions increases [9–12]. In addition, the mechanics of the ischaemic myocardium during diastole are known to alter the resting fibre length, resulting in an increase in stiffness [13–15]. Maintenance of global LV function, when one region of LV is rendered ischaemic, depends largely on the severity of ischaemia and the area of ischaemic myocardium involved. However, the compensatory increase in myocardial function in the non-ischaemic portion of the LV is also thought to be an important determinant of global LV function [10, 16–19]. Thus any intervention that suppresses the compensatory adjustments in non-ischaemic regions may compromise LV global function to a greater extent than would be expected on the basis of only the extent and severity of ischaemia.

We postulated that anaesthetics might differentially modify regional myocardial adjustments during ischaemia, particularly in non-ischaemic zones, and thus further influence global LV function. This was tested in dogs anaesthetized with halothane or fentanyl and subjected to brief coronary occlusion.

METHODS
Mongrel dogs weighing 28–34 kg, of both sexes, were anaesthetized with thiopentone 4–5 mg kg⁻¹. The trachea was intubated and the lungs ventilated with 100% oxygen and either halothane or fentanyl was administered to maintain anaesthesia during surgical preparation. Ten dogs were allocated randomly to each group (fentanyl, 0.75 % halothane or 1.5% halothane). Left lateral thoracotomy was performed via the fifth intercostal space. The pericardium was opened and used to cradle the heart, to avoid torsion around the great vessels.

The following instruments were implanted
long axis. Thus the dimension transducers were located equidistant between the base and apex. Intramyocardial ECG leads (flexible copper wire, o.d. 0.025 mm, soldered to a dimension transducer) were used to monitor ECG ST segments from the anterior and lateral regions to ensure that ischaemia was limited to the anterior region. A needle-mounted micromanometer (Millar Instruments, Houston, TX) was inserted into the endocardium in both the anterior and lateral regions in the vicinity of the two pairs of dimension transducers. These were used to measure intramyocardial pressures (IMP) [20]. Correct location of the dimension transducers and the tips of the IMP needles in the myocardium was confirmed by postmortem examination. A tape was placed around the inferior vena cava for brief occlusions to alter preload during the studies.

The segmental length signals were calibrated against known time pulses with specific periods. The sonomicrometer produces a voltage proportional to the excursion between the transducer crystals. This voltage represents the absolute value of the distance between a pair of crystals. This voltage is converted to dimension signals by an interactive computer program. An example of the rise and fall of one of the transducers is shown in Fig. 1 (10 mm Hg).

For the fentanyl studies, fentanyl was administered i.v. at a loading dose of 0.75 µg kg⁻¹ and was then continuously infused at the rate of 0.1 µg kg⁻¹ h⁻¹ during surgery and the study period. Vecuronium 0.1 mg kg⁻¹ was infused during surgery and repeated as necessary during the experiments.

End-tidal carbon dioxide (capnometer with recorder, Puritan Bennett, Wilmington, MA) and pulmonary arterial blood temperature (Swan–Ganz thermistor) were monitored continuously and corrected if necessary to maintain values within normal limits. Arterial blood-gas tensions and serum electrolyte concentrations were measured intermittently. Ringer's lactate solution was infused i.v. to maintain an LV end-diastolic pressure (LVEDP) of 8–10 mm Hg. I.v. infusion was then maintained at a rate of 15 ml kg⁻¹ h⁻¹ during the study.

Fig. 1. Diagram of preparation. 1 = Intra-aortic micromanometer; 2 = left ventricular micromanometer; 3 = silicon rubber catheter in left atrium; 4 = intramyocardial needle-mounted micromanometer (lateral wall); 5 = intramyocardial needle-mounted micromanometer (anterior wall); 6 = ultrasonic dimension transducers (anterior wall); 7 = ultrasonic dimension transducers (lateral wall); 8 = intramyocardial ECG lead; 9 = inferior vena cava occluder; 10 = Swan–Ganz catheter; 11 = coronary occluder.
After at least 30 min of stabilization after completion of surgery, the following control data were obtained: cardiac output (CO) was measured three times and an average obtained. Colour-encoded microspheres (12 μm diameter) were injected into the left atrium via the silicone rubber catheter for each MBF determination [21]. During the injection, a reference blood sample was obtained from the femoral arterial catheter at a rate of 14 ml min⁻¹. At postmortem, the sectors of left ventricle which contained the sites of implantation of the ultrasonic dimension transducers in the anterior wall were divided into endocardial and epicardial halves, each weighing 2 g. The myocardium was digested using sequential enzymatic agents and the microspheres were then counted in a haemocytometer. Twenty millilitre of reference blood was processed and microspheres were counted similarly. rMBF (ml min⁻¹/g tissue) was calculated using the equation:

\[ rMBF = Cm \times Qb/Cb \]

where \( Qb \) is the rate of withdrawal of blood, and \( Cm \) and \(Cb\) are counts of spheres in the tissue and blood samples, respectively. Left ventricular pressure (LVP), aortic pressure (AP), intramyocardial tissue pressures (IMP), maximum LV dP/dt, (dP/dt max) and regional myocardial dimensions were monitored continuously during steady state conditions and as the inferior vena cava was occluded briefly (10-15 cardiac cycles). After these control data were obtained, the left anterior descending artery (LAD) was occluded.

After 15 min of LAD occlusion, data were obtained as during the baseline period. The analogue signals from the pressure transducers were calibrated using a transducer amplifier (Gould Inc., Cleveland, OH) and recorded with calibration signals on both an eight-channel ink jet paper-writer (Gould Inc.) and an eight-channel FM tape recorder (AP Vetter, Inc., Rebersberg, PA). Ultrasonic transducers were connected to a sonomicrometer (Davis Consultants Inc., Durham, NC) that converts the transit time of ultrasound between the transducers into an analogue signal proportional to dimension. This signal was recorded also on FM tape. The signals were digitized and the data analysed with interactive software on a PDP 11/73 computer (Digital Electronics, Maynard, MA).

Data analysis

Fractional segmental systolic shortening (SS) was determined using the equation

\[ SS = (EDL - ESL)/EDL \]

where EDL = end-diastolic length measured at the onset of left ventricular isovolumic contraction and ESL = end-systolic length measured at maximum negative dP/dt. This variable is used frequently as an index of regional contractile function [9, 10].

Peak systolic IMP was measured also. IMP is the pressure generated in a specific region of myocardium and represents the average stress within the regional myocardium. It is determined primarily by local contractile function, but also passively by transmission of left ventricular intracavitary pressure. Peak systolic IMP has been utilized as an index of regional myocardial systolic function [12, 22-24].

A third index of regional function is regional stroke work (RSW). The integrated area within the LVP-regional segmental dimension loop during an individual cardiac cycle represents regional stroke work and is also used widely in studies of regional myocardial function [25]. However, the calculation of RSW based on LVP-segmental dimension loop (LVP-RSW) assumes that wall stress is distributed uniformly throughout the LV wall, and is determined solely by LVP. Recently, direct measurements of intramyocardial tissue pressure (IMP) using needle-mounted microtransducers have demonstrated clearly that IMP is not uniform across the wall (transmurally) or around the LV circumference (regionally) [12, 21-24]. IMP in ischaemic injured myocardial regions is markedly less than LVP in normal regions of myocardium. Thus using LVP for the calculation of RSW may be misleading in studies in which ischaemically injured regions of myocardium are examined. Our calculation of RSW was based therefore on the IMP-segmental dimension loop (IMP-RSW).

Our final index of regional function was the slope of the preload recruitable stroke work relationship (Mw) and end-diastolic segmental length at zero load (L0). SS or dP/dt as indices of contractile status are influenced by ventricular loading conditions [26]. The Frank-Starling relationship (stroke work-LV end-diastolic pressure curve) often used in \textit{in vivo} studies is difficult to use in measuring ventricular function, mainly because of its non-linearity [27]. Substituting end-diastolic pressure for end-diastolic pressure to assess global LV function) or substituting end-diastolic segmental length for end-diastolic pressure (to assess regional LV function), the function curve is linear and independent of changes in LV loading conditions. The slope of this relationship (Mw) has been used as an index of global and regional myocardial contractile function [27]. The extrapolated x-intercept (L0) represents end-diastolic segmental length at zero loading. During ischaemia, lengthening of L0 (or "creep") is the hallmark of diastolic dysfunction and results in increased stiffness of the myocardial wall [13, 14, 27].

To generate the relationship over a range of loading conditions, the IVC was occluded briefly to vary preload. Only the first 10 beats during IVC occlusion were used to construct these relationships, to avoid any reflex activation of the sympathetic nervous system.

All results are expressed as mean (SEM). Statistical differences were tested using analysis of variance (ANOVA). Scheffé’s test was used in assessing the statistical significance of pairwise comparisons to adjust for the number of comparisons made. Significance was assumed at \( P < 0.05 \).

RESULTS

Changes in haemodynamic state and global LV function induced by anterior wall ischaemia are summarized in table I. Because 0.75% halothane...
### TABLE I. Left ventricular global function (mean (SEM)) in dogs anaesthetized with 1.5 % halothane or fentanyl, before and during 15 min of anterior wall ischaemia: cardiac output (CO), mean arterial pressure (MAP), maximum dP/dt (dP/dt max mm Hg s⁻¹), left ventricular end-diastolic pressure (LVEDP) and heart rate (HR). Each group included 10 dogs. P < 0.05: * compared with fentanyl group; † compared with baseline control values

<table>
<thead>
<tr>
<th></th>
<th>CO (litre min⁻¹)</th>
<th>MAP (mm Hg)</th>
<th>dP/dt max (mm Hg s⁻¹)</th>
<th>LVEDP (mm Hg)</th>
<th>HR (beat min⁻¹)</th>
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<tr>
<td>Baseline</td>
<td></td>
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<tr>
<td>Fentanyl</td>
<td>4.5 (0.3)</td>
<td>111 (8)</td>
<td>1655 (228)</td>
<td>7.8 (0.9)</td>
<td>89 (4)</td>
</tr>
<tr>
<td>Halothane</td>
<td>4.3 (0.2)</td>
<td>111 (7)</td>
<td>1937 (203)</td>
<td>9.0 (0.6)</td>
<td>103 (4)*</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>3.9 (0.2)</td>
<td>72 (3)†</td>
<td>1175 (138)*</td>
<td>13.5 (2.0)†</td>
<td>12.8 (1.3)†</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>Halothane</td>
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### TABLE II. Regional myocardial function and blood flow (mean (SEM)) in the anterior wall of dogs anaesthetized with 1.5 % halothane or fentanyl, before and during 15 min occlusion of the left anterior descending artery: systolic shortening (SS), intramyocardial tissue pressure (IMP), regional wall stroke work (RSW), slope of preload recruitable stroke work curve (Mw), end-diastolic segmental fibre length at no loading condition (L_o) and regional myocardial blood flow (rMBF). Each group included 10 dogs. P < 0.05: * compared with fentanyl group; † compared with baseline control values

<table>
<thead>
<tr>
<th></th>
<th>SS (%)</th>
<th>IMP (mm Hg)</th>
<th>RSW (µJ cm⁻² × 10⁶)</th>
<th>Mw (µJ cm⁻² × 10⁶)</th>
<th>L_o (mm)</th>
<th>rMBF (ml g⁻¹ min⁻¹)</th>
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<tr>
<td>Baseline</td>
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<tr>
<td>Fentanyl</td>
<td>15.0 (2.6)</td>
<td>121.0 (9.4)</td>
<td>1.76 (0.21)</td>
<td>1.66 (0.19)</td>
<td>102 (11)</td>
<td>11.0 (3.0)</td>
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<tr>
<td>Halothane</td>
<td>11.0 (1.3)*</td>
<td>96.0 (8.0)</td>
<td>1.46 (0.19)†</td>
<td>1.31 (0.22)</td>
<td>125 (14)</td>
<td>9.7 (1.0)</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>-2.2 (1.2)†</td>
<td>55.0 (8.0)†</td>
<td>0.47 (0.12)†</td>
<td>0.26 (0.07)†</td>
<td>87 (16)</td>
<td>9.7 (1.2)</td>
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<tr>
<td>Change from baseline (%)</td>
<td>-113 (7)</td>
<td>-32 (5)</td>
<td>-73 (10)</td>
<td>-64 (11)</td>
<td>+17 (6)</td>
<td>-95 (1)</td>
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### TABLE III. Regional myocardial function and blood flow (mean (SEM)) in the lateral, non-ischaemic wall of dogs anaesthetized with 1.5 % halothane or fentanyl, before and during 15 min ischaemia of the anterior wall: systolic shortening (SS), intramyocardial tissue pressure (IMP), regional wall stroke work (RSW), slope of preload recruitable stroke work curve (Mw) and end-diastolic segmental fibre length at no loading condition (L_o). Each group included 10 dogs. P < 0.05: * compared with fentanyl group; † compared with baseline control values

<table>
<thead>
<tr>
<th></th>
<th>SS (%)</th>
<th>IMP (mm Hg)</th>
<th>RSW (µJ cm⁻² × 10⁶)</th>
<th>Mw (µJ cm⁻² × 10⁶)</th>
<th>L_o (mm)</th>
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<tr>
<td>Baseline</td>
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<tr>
<td>Fentanyl</td>
<td>11.0 (3.0)</td>
<td>102 (11)</td>
<td>1.10 (0.18)</td>
<td>0.68 (0.19)</td>
<td>9.7 (1.0)</td>
</tr>
<tr>
<td>Halothane</td>
<td>8.3 (1.0)</td>
<td>89 (8)</td>
<td>1.00 (0.20)</td>
<td>0.88 (0.21)</td>
<td>9.3 (1.0)</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>12.1 (2.5)</td>
<td>125 (14)†</td>
<td>1.51 (0.25)†</td>
<td>0.82 (0.18)*</td>
<td>9.7 (1.0)</td>
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### ANAESTHESIA AND myocardial FUNCTION DURING ISCHAEMIA
produced similar, although sometimes smaller, effects compared with 1.5% halothane, data from this group are not included. LVEDP was increased comparably in all groups. CO, MAP and dP/dt\text{max} decreased significantly during ischaemia in the 1.5% halothane group only. Stroke volume decreased similarly in all groups (−22%, −15% and −25%, for fentanyl, 0.75% halothane and 1.5% halothane, respectively).

Table II summarizes changes in regional function of the anterior ischaemic wall. Systolic function in the anterior wall decreased markedly and L\text{e} increased significantly in all groups. There were significant differences in the baseline values of the groups; RSW and Mw in the fentanyl group were significantly greater than in the 1.5% halothane group, but similar to those in the 0.75% halothane group. These differences were maintained during ischaemia. Therefore, there was no difference between groups in these regional variables induced by anterior wall ischaemia, with the exception of SS, which demonstrated a proportionately greater decrease in the fentanyl group and 0.75% halothane group only.

As shown in Table III and figure 2, there were marked differences in the response of the lateral non-ischaemic wall to anterior wall ischaemia. There were significant increases in IMP, RSW and Mw only in the fentanyl group. Although such marked compensatory increases in regional function did not occur in both halothane groups, there were slight differences in non-ischaemic wall function, indicated by increases (not significant) in IMP (7%) and Mw (8%) in 0.75% halothane group, while they decreased further in the 1.5% halothane group. The changes in rMBF in the anterior wall were not significantly different. Occlusion of the LAD decreased endocardial blood flow by more than 95% in all groups. Changes in regional diastolic mechanical properties were similar in the groups: L\text{e} increased in the ischaemic region, but no changes occurred in the non-ischaemic region.

Fig. 2. Changes (percent of baseline values, SEM) in regional myocardial function of the lateral wall during 15 min of anterior wall ischaemia under 0.75% (□), 1.5% (◇) halothane and fentanyl (●) anaesthesia in dogs. Each group consisted of 10 dogs. SS = Systolic shortening; IMP = intramyocardial pressure; RSW = regional stroke work; Mw = slope of preload recruitable stroke work curve. * P < 0.05 compared with either halothane group.

Despite remarkable advances in anaesthesia and monitoring techniques, perioperative myocardial ischaemia and infarction in patients with coronary artery disease remain serious complications of anaesthesia [1,3]. Haemodynamic monitoring techniques currently in clinical use are limited mostly to measurements of global ventricular function, such as heart rate, systemic and pulmonary pressures, cardiac output and ventricular filling pressure. Alterations in left ventricular (LV) global function that occur during myocardial ischaemia are detected frequently with such systems [1,4,28]. However, the changes are varied, ranging from insignificant to catastrophic haemodynamic collapse [1,2,29]. In general, it is assumed that the severity and extent of myocardial ischaemia are largely responsible for the varying degree of functional deterioration [16-19,30]. A less well-recognized, but equally important element is the role of compensatory mechanisms available to remaining non-ischaemic regions of the LV in maintaining global LV function [8-12]. In 1935, Tennant and Wiggers observed such compensatory adjustments in non-ischaemic regions of the LV when one area of the LV is rendered ischaemic [8]. Subsequently, other investigators have reported similar observations: ischaemic regions of the LV cease contracting or actually bulge during systole, while non-ischaemic regions become hypercontractile [9,12].

Particularly when the ischaemic region bulges during systole and loses synchrony with the contraction of non-ischaemic regions, LV systolic pump function becomes largely ineffective, requiring additional external work by non-ischaemic regions in order to maintain systolic global function [31]. In addition, ischaemic regions of myocardium are less compliant, which further undermines systolic function [13-15]. Therefore, it is clear that regional function in non-ischaemic regions of the LV plays an important role in maintaining global function during regional myocardial ischaemia. Although the exact mechanism that causes compensatory adjustments in non-ischaemic regions is not yet clear, it is expected that, if the compensatory ability of non-ischaemic regions is suppressed, depression of overall global function may be exaggerated during regional myocardial ischaemia [10,16].

In this study, we tested the hypothesis that anaesthetics modify regional functional adjustments between ischaemic and non-ischaemic regions and their summated effects on LV global function during a brief period of coronary artery occlusion.

During the baseline period, MAP and dP/dt\text{max} were significantly reduced in the 1.5% halothane group only. CO was slightly reduced and heart rate was greater in both halothane groups, although these differences were not statistically significant. As a result, the calculated stroke volume was significantly less in the halothane groups (37 (SEM 4) ml and 40 (2) ml compared with 51 (5) ml in the 0.75% and 1.5% halothane and fentanyl groups, respectively). These findings are in general agreement with previous reports that halothane depresses LV func-
tion more than fentanyl in the normal heart [32–34]. After induction of anterior wall ischaemia by LAD occlusion, CO, MAP and $dP/dt_{max}$ were further depressed significantly in the 1.5% halothane group, but relatively unchanged in the 0.75% halothane and fentanyl groups. However, stroke volume was decreased and LVEDP increased to the same extent in all groups. The changes induced by LAD occlusion in anterior wall function measured by Mw, RSW and IMP were comparable in all groups. In contrast, the lateral (non-ischaemic) wall function during anterior wall ischaemia changed in different directions: IMP, RSW and Mw increased markedly in the fentanyl group only, increased slightly (ns) in 0.75% halothane group and decreased in the 1.5% halothane group. SS, another variable used to estimate regional wall function, followed the same trends as the other variables, but was not significantly different between groups. IMP and RSW, which incorporate afterload changes, and Mw, which is independent of loading conditions, clearly showed the differences in compensatory increases in systolic regional myocardial function in the non-ischaemic regions. The validity of RSW and Mw as measures of regional function of ischaemic myocardium has been questioned [35]. However, in the present study other variables such as SS and IMP changed in the same direction. A final point is that the changes in $L_o$, which represent myocardial fibre length at zero loading condition, were not different in either the ischaemic or non-ischaemic regions of all groups. $L_o$ increased in the anterior ischaemic wall, with no significant changes in non-ischaemic lateral wall. These findings are comparable to those of previous reports: ischaemic myocardium becomes less compliant, but diastolic mechanics are not modified by the anaesthetic agents.

The differential changes in LV global function observed in this study during regional myocardial ischaemia with the different anaesthetics were the result of differences in severity and extent (size of involved LV wall mass) of anterior wall ischaemia, differences in the compensatory responses of non-ischaemic regions of LV or differences in activation of other systemic mechanisms such as reflex sympathetic activity. Because we did not measure this directly, it is not known if the area of myocardium affected by occlusion of the LAD was identical in all groups (although ligation was at the same anatomical site, proximal to the major diagonal branches). The decrease in rMBF in the anterior wall was comparable in all groups, and the elevation of ST segments in the intramyocardial ECG of the anterior wall was comparable also, suggesting that severity of ischaemia was equivalent in the groups. However, comparable decrease in SV, together with equivalent increases in LVEDP during LAD occlusion in the presence of significant increase in compensatory function in non-ischaemic regions of LV in fentanyl group, suggest the possibility that a greater area of anterior wall of LV became ischaemic in the fentanyl group, presumably because of greater baseline myocardial oxygen consumption [6]. Another possibility is that a larger area of the anterior wall of the LV became ischaemic in the halothane groups after LAD occlusion, as the perfusion pressure was smaller, accounting for the greater decrease in global ventricular function in those groups [32, 36]. However, previous studies have suggested that halothane might decrease the ischaemia area [37] and enhance functional recovery after ischaemia [38], making this last possibility less likely. In any case, the directly measured regional myocardial function (systolic IMP, RSW and Mw) of non-ischaemic regions of LV increased significantly in the fentanyl group, increased slightly (ns) in the 0.75% halothane group and decreased in the 1.5% halothane group, regardless of the size of ischaemic myocardium. Thus our results indicate clearly that compensatory mechanisms by non-ischaemic regions of LV during acute regional myocardial ischaemia were modified by the type or depth of anaesthesia.

Although the exact mechanisms responsible for the compensatory increase in myocardial function of non-ischaemic regions are not clear, it is known that cardiac sympathetic activity is increased during acute myocardial ischaemia or infarction [39], suggesting that reflex activation of the sympathetic nervous system is one of the mechanisms. If this is the case, the different effects of anaesthetics or anaesthetic depth on the sympathetic nervous system may have been responsible for the observed modifications of compensatory function in non-ischaemic regions of LV in our study. The slight increase in heart rate in the fentanyl group, although not statistically significant, is compatible with this view and partially responsible also for the better maintained CO in that group.

In conclusion, compensatory adjustments of regional myocardial function in non-ischaemic regions of the LV play an important role in determining LV global function during regional myocardial ischaemia. In the present study, these compensatory adjustments were better preserved under fentanyl or 0.75% halothane anaesthesia than under 1.5% halothane anaesthesia.

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8. Tennant R, Wiggers CJ. The effect of coronary occlusion on


