Myocardial infarction with and without reperfusion in sheep: early cardiac and neurohumoral changes

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ABSTRACT

There are few stable and reproducible large-animal models of chronic heart failure produced by ischaemic damage to the myocardium. Here we characterize a novel method of inducing myocardial damage in closed-chest sheep by catheter delivery of thrombogenic coils, and compare this with a newly described open-artery model of cardiac injury in sheep. Sham controls were compared with animals subjected to (a) 90 min of coronary artery occlusion/reperfusion by PTCA (percutaneous transluminal coronary angioplasty) balloon, and (b) permanent coronary artery occlusion induced by catheter delivery of thrombogenic coils (seven sheep/group). Both balloon occlusion/reperfusion and permanent coil occlusion resulted in well-defined anteroapical infarcts, as documented by ECG changes, significant rises in creatine kinase (both groups $P < 0.001$) and troponin-T (both groups $P < 0.05$), and post-mortem examination. Washout of enzymes was much more rapid in the reperfused group ($P < 0.01$). Infarction resulted in significant reductions in left ventricular (LV) ejection fraction (both groups $P < 0.01$) and regional wall abnormalities. Ejection fraction 7 days post-coil ($21.3 \pm 4.2\%$) was significantly lower ($P < 0.01$) than that 7 days post-balloon ($38.8 \pm 4.5\%$). Coil-induced infarction was associated with acutely reduced arterial pressure ($P < 0.05$), and increases in heart rate ($P < 0.05$), atrial pressures ($P < 0.05$), plasma brain natriuretic peptide levels ($P < 0.05$) and adrenaline levels ($P < 0.05$). Rises seen in plasma endothelin levels in sham controls were blunted in the coil group ($P < 0.001$). Haemodynamic changes were less marked in the balloon group. In conclusion, restriction of coronary artery occlusion to 90 min results in infarction, but less LV dysfunction with reduced early remodelling, compared with permanent occlusion. Acute changes in biochemical markers, haemodynamics, neurohormones and LV function confirm that these are excellent models of open- and closed-artery myocardial infarction leading to asymptomatic LV dysfunction.

INTRODUCTION

The prevalence of heart failure is increasing in Western countries, with hospital admission rates continuing to rise during the past two decades [1]. Despite recent advances in therapy, prognosis remains poor, with up to 50% mortality at 3 years. Coronary artery disease and hypertension are the most common causes of heart failure [1]. The complete study of coronary ischaemic syndromes entails observations on acute myocardial
infarction, asymptomatic left ventricular (LV) dysfunction, progressive heart failure and arrhythmias. There is evidence to suggest that available pharmacological therapy can favourably alter the natural history of asymptomatic LV dysfunction which commonly precedes heart failure.

Improved understanding of the pathophysiology of this early phase of LV impairment requires an experimental model that reflects the underlying pathology, as well as the haemodynamic and neurohumoral profile, of the human disease. Models should preferably be chronic, with a reproducible degree of LV dysfunction. Although there may not be an ideal animal model [2], a wide variety of models have been used to study the pathophysiology of heart failure and the efficacy of new pharmacological interventions. These models can be placed in four main categories: (a) pressure overload, (b) volume overload, (c) myocardial ischaemia/infarction and (d) cardiomyopathy (including rapid pacing models). Coronary artery ligation in rats has been used for several decades as a model of myocardial infarction leading to heart failure [3]. However, survival is poor and there is a wide spectrum of responses. Furthermore, haemodynamic measurements and blood sampling are limited by the rat’s small size.

Until recently there were few stable and reproducible large-animal models of heart failure produced by ischaemic damage to myocardium. Coronary artery microembolization leading to chronic heart failure has been reported in dogs [4]. However, due to the extensive coronary collateral circulation, multiple embolizations (between three and nine, 1 week apart) were required to produce a stable model. We have recently described this model in sheep, which have a coronary circulation that is very similar to that of humans [5]. Microembolization produced histological changes similar to the patterns of patchy ischaemic fibrosis sometimes observed in human disease, but with no clearly defined area of infarction. Coronary artery ligation has also been described in sheep [6,7]. While this procedure does produce a stable, reproducible model of heart failure, it does have several drawbacks. The arteries are ligated and hence permanently closed, thus not modelling a large proportion of human disease in which patients have a patent infarct-related artery either as a result of spontaneous thrombolysis or reperfusion through administration of fibrinolytics or balloon angioplasty. Furthermore, the open-chest model of coronary ligation requires the surgical trauma of a thoracotomy. Reek et al. [8] have recently described electrophysiological studies in a balloon occlusion/reperfusion model of myocardial infarction in sheep. However, there remains a prevailing need for the further development of large-animal models of ischaemia-induced cardiac impairment which adequately mimic the wide spectrum of human disease. Accordingly, we here characterize a novel method of inducing myocardial damage in closed-chest sheep by catheter delivery of thrombogenic coils, and compare this with an open-artery model of cardiac injury in sheep. Sham controls are compared with two experimental groups: (a) 90 min coronary artery occlusion/reperfusion by PTCA (percutaneous transluminal coronary angioplasty) balloon, and (b) permanent coronary artery occlusion induced by catheter delivery of thrombogenic coils.

**METHODS**

The Animal Ethics Committee of the Christchurch School of Medicine approved the study protocol, and the investigation conformed with the United States NIH guidelines (NIH Publication No. 85-23, revised 1996). A total of 26 Coopworth ewes (Lincoln University Farm, Christchurch, New Zealand) were housed in an air-conditioned light-controlled room, had free access to water, and received a normal laboratory diet of sheep nuts and chaff, providing a daily intake of 75 mmol of sodium and 150 mmol of potassium.

**Surgical preparation**

Under general anaesthesia (17 mg/kg thiopentone, maintained by a mixture of halothane, nitrous oxide and oxygen), a carotid artery was cannulated with an 8F sheath (Cordis, Miami, FL, U.S.A.) for subsequent measurement of arterial pressure and heart rate, and for cardiac catheterization procedures. A Swan–Ganz catheter (American Edwards, Santa Ana, CA, U.S.A.) was placed into the pulmonary artery via the jugular vein for measurement of cardiac output (thermodilution) and right atrial pressure (RAP), and a polyethylene catheter was placed in the jugular vein for blood sampling. Baseline ventriculography was performed for determination of LV volumes, LV ejection fraction (LVEF) and regional wall motion. A 7F pigtail catheter was passed through the carotid artery sheath into the left ventricle and a 20 ml bolus of contrast medium (Omnipaque; Nycomed, Birmingham, U.K.) was injected under fluoroscopy, with the image captured on video for analysis on an ANCOR workstation (Siemens, Solna, Sweden). Regional wall motion (fractional shortening) was calculated in four quadrants (1–4): posterobasal, diaphragmatic, apical anterolateral and anterobasal respectively.

**Coronary artery catheterization**

The animals were allowed to recover for at least 3 days before baseline haemodynamic and hormonal measurements were carried out with the sheep conscious (time = −60 min), prior to repeat anaesthesia (as above). Within 5 min of induction, 2 ml of heparin was administered intravenously to prevent clotting throughout cardiac catheterization procedures, and blood was
drawn (time = −30 min) prior to cannulation of the left coronary circulation with an 8F left amplatz 1 Softip Guiding Catheter (Schneider, Minneapolis, MN, U.S.A.). A 0.014 inch (0.35 mm) angioplasty wire was advanced down the left anterior descending (LAD) coronary artery as far as practicable towards the apex. Sham (control) animals (n = 7) were anaesthetized for the same duration as the balloon occlusion/reperfusion group and received injections of contrast medium and anti-arrhythmic drugs according to a regime similar to that described below for the experimental animals.

**PTCA balloon occlusion/reperfusion**

Balloon occlusion (n = 9) of the coronary arteries was performed by advancing a PTCA balloon to a position distal to the branching of the first diagonal artery, but proximal to the second diagonal artery. The balloons (3.0–4.0 mm) were sized larger than the coronary artery lumen diameter. Immediately before inflation of the balloon, blood was drawn for hormone measurement (time = 0 min) and 100 mg of lignocaine (Delta West, Bentley, W. Australia) was administered as a slow intravenous bolus. The PTCA balloon was inflated to > 5 × atmospheric pressure and total occlusion was confirmed repeatedly by angiography during 90 min of inflation. A further 50 mg of lignocaine was administered 20 min post-inflation. Atenolol (1–2 mg; Tenormin; Zeneca, Macclesfield, U.K.) was administered at the time of reperfusion. After balloon deflation, arterial patency was confirmed by angiography before removal of the balloon and wire. Sheep recovered from the anaesthetic and were exsanguinated 20–30 min after coronary artery reperfusion. ECG and arterial pressures were monitored throughout the anaesthetic period. The occurrence of ventricular tachycardia, fibrillation or sustained regular ectopic activity was treated with 0.5–1 mg intravenous bolus administrations (maximum total dose 5 mg) of atenolol.

**Thrombogenic coil occlusion**

Coil-induced coronary artery occlusion (n = 10) was performed by positioning a 5F straight catheter (Cook Company, Queensland, Australia) over the angioplasty wire, with the tip in the same position as the site of balloon occlusion. Under fluoroscopic guidance, impelled by a 0.025 inch (0.64 mm) wire, the thrombogenic coil (Cook Company, Bloomington, IN, U.S.A.) was advanced down the catheter into the artery lumen. Coils (4–5 mm diameter; 3 cm length) were sized larger than the coronary artery lumen diameter. Total occlusion occurred within 2 min and was confirmed by angiography. Sheep recovered from the anaesthetic and were exsanguinated 20–30 min after arterial occlusion. Sheep were monitored as per balloon occlusion/reperfusion sheep, and lignocaine and atenolol (1–3 mg) were administered according to a similar regime.

**Neurohumoral measurements**

Arterial pressure and RAP were measured using Statham pressure transducers (Spectramed Medical Products, Singapore) and an Astromed chart recorder (Astromed Inc., W. Warwick, RI, U.S.A.), and cardiac output was measured by thermodilution. Recordings were made 1 h before (pre-anaesthetic), 2, 4, 6 and 12 h and 1, 2, 3 and 7 days after arterial occlusion. Heart rate and pressure recordings were manually integrated over 5 min periods.

Venous blood was drawn at set times, as shown in the Figures. Blood was taken into chilled EDTA tubes, centrifuged and the plasma stored at −80 °C before assay for plasma atrial natriuretic peptide (ANP) [9], brain natriuretic peptide (BNP) [10], aldosterone [11], plasma renin activity [12], catecholamines [13] and endothelin. Plasma endothelin-1 levels were measured by in-house radioimmunoassay following extraction, based on methods described previously for ANP [14], with the exception of the preincubation step, which was for 3 h at room temperature. Plasma samples (2 ml) were extracted on SepPak C18 cartridges as described previously [15]. The extracts underwent assay using antisera raised to human endothelin-1, with human endothelin-1 as a standard (Peninsula Laboratories, Belmont, CA, U.S.A.). Plasma extracts diluted in parallel to the standard curve, suggesting immunological identity. The detection limit of the assay was 1.1 pmol/litre. Intra- and inter-assay coefficients of variation were 5.9 % and 8.7 % respectively. Recovery of human endothelin-1 spiked into sheep plasma was 69 %. Creatine kinase and troponin-T were measured using commercial ELISA kits (Boehringer, Mannheim, Germany).

Ventriculograms were repeated on day 7, immediately before the sheep were killed. Whole hearts were removed and preserved in 10% buffered formalin before examination of gross pathology.

**Statistics**

Results are expressed as means ± S.E.M. Two-way ANOVA, with time as a repeated measure, was used to determine time and treatment differences between experimental and sham control groups. Significance was assumed at P < 0.05. Where significant differences were identified by ANOVA, a priori Fisher’s protected least-square difference tests were used to identify time points significantly different from those of time-matched sham controls.

**RESULTS**

Premature death (arrhythmias) occurred in two of the balloon group and three of the coil group. Both deaths in the balloon group occurred within 4 min following reperfusion, whereas deaths in the coil group occurred at
Markers of myocardial damage

Acute coronary artery occlusion by balloon or coil consistently induced the ECG changes of myocardial infarction, with marked ST elevation. Sham controls exhibited no changes in ECG. Plasma cardiac enzyme changes are shown in Figure 1. Creatine kinase levels rose above those in time-matched controls after both balloon (P < 0.001) and coil (P < 0.001) procedures. However, creatine kinase peaked at 2 h following reperfusion in the balloon group, whereas in the coil group levels peaked later (6 h), resulting in a difference between the balloon and coil responses (P < 0.001). Similarly, plasma troponin-T levels were raised compared with controls in both balloon (P = 0.012) and coil (P < 0.001) groups.

The troponin-T response differed significantly between the balloon and coil groups (P = 0.002), with levels peaking earlier in the balloon group (6 h post-reperfusion).

**Ventriculography and macroscopic pathology**

Data derived from ventriculography are summarized in Table 1. End-systolic volume tended to increase in both balloon and coil groups, although these changes were not statistically significant. LVEF was significantly reduced 7 days post-balloon (P = 0.007) and post-coil (P = 0.002), to values of 38.8 ± 4.5% and 21.3 ± 4.2% respectively. LVEF was significantly different between the balloon and coil groups (P = 0.002). Ventriculography revealed significant hypokinesis, with some akinesis and dyskinesis, with pooling and delayed clearance of contrast media in the infarcted anteroapical regions. Hypokinesis was quantified by significant reductions in fractional shortening observed in the third (balloon and coil) and fourth (coil) quadrants.

Post-mortem macroscopic examination of the hearts from balloon and coil sheep (day 7) revealed well-defined
transmural anteroapical infarcts. Infarction induced by coil occlusion was predominantly in the left ventricle and septum, with infarct extending to the right ventricle in one sheep (30% of infarcted area). Infarcts were all of similar size in the group, measuring $27.3 \pm 2.0$ cm$^2$, with marked transmural thinning compared with control hearts ($4.9 \pm 0.6$ mm versus $12.0 \pm 0.8$ mm). Infarcts induced by balloon occlusion/reperfusion were of similar size, measuring $22.9 \pm 5.7$ cm$^2$, again with marked transmural thinning compared with control hearts ($6.1 \pm 0.8$ mm versus $12.0 \pm 0.8$ mm). Three infarcts in the balloon group extended beyond the left ventricle/septal region into the right ventricle (15–20% of infarcted area).

**Haemodynamic response**

Mean arterial pressure tended to be reduced following balloon occlusion, and was significantly reduced acutely following coil occlusion ($P = 0.018$), compared with control animals (Figure 2). However, arterial pressure had returned to sham control levels by day 3. Heart rate (Figure 2) increased acutely (2–6 h) in all three groups. However, heart rate was significantly different between the coil and control groups ($P = 0.028$), remaining elevated throughout the study period in the coil group. RAP (Figure 2) was not significantly different from control in the balloon group, but was raised acutely (2–6 h) in the coil group ($P = 0.043$). Cardiac output was not significantly different between groups (Figure 2).

**Hormone response**

Plasma ANP levels (Figure 3) were raised acutely (0–6 h) in response to manipulations in all three groups. However, the response was greater up to 12 h post-balloon occlusion compared with controls ($P = 0.04$). Plasma ANP was not significantly different between the coil and sham groups. Calculation of the ANP/RAP ratio revealed a significant reduction in the coil group compared with the balloon group ($P = 0.019$). Plasma BNP
levels (Figure 3) were raised in response to manipulations in all three groups, with the response following both balloon (P = 0.001) and coil (P = 0.026) procedures being greater than in control animals. Augmentation of plasma BNP levels was apparent only during the acute response (0–24 h) in the balloon group, while BNP levels remained elevated for the duration of the study in the coil group (P < 0.001).

Compared with control animals, plasma catecholamines (Figure 4) were increased in both infarction models, with significant increases in noradrenaline after balloon occlusion (P = 0.024) and in adrenaline after coil occlusion (P = 0.011). Plasma aldosterone and plasma renin activity were increased by all three manipulations, but there was no statistical difference between the groups (Figure 4).

DISCUSSION

There are few reproducible large-animal models of stable, chronic LV dysfunction induced by ischaemic damage to the myocardium which adequately mimic the wide spectrum of human disease. Both PTCA balloon coronary artery occlusion/reperfusion and thrombogenic coil permanent occlusion resulted in well defined transmural anteroapical infarcts, as documented by ECG changes, significant rises in cardiac enzymes (with a different pattern of temporal changes observed between the two models) and post-mortem examination. Infarction resulted in LV systolic dysfunction, as documented by significant reductions in LVEF and regional wall motion abnormalities. Infarction was associated with an acute decrease in arterial pressure, and with increases in heart rate, atrial pressures, and plasma levels of cardiac natriuretic peptides and catecholamines.

These ovine models of myocardial infarction and LV dysfunction have a number of significant advantages over other experimental large-animal models currently used in the study of heart failure. Firstly, the underlying pathology is comparable with that commonly found in the human situation. The widely used rapid LV pacing models [16], while demonstrating all of the peripheral haemodynamic, renal and neurohumoral stigmata of human congestive heart failure, have the heart rate fixed, and resulting ventricular remodelling is less typical. Moreover, the cardiac lesion bears little resemblance to the human disease, allowing no assessment of regional changes in the myocardium. Secondly, because sheep have a coronary circulation similar to that of many humans, without well developed collaterals [6], LAD coronary artery occlusion results in predictable and reproducible anteroapical infarcts. Both the balloon and coil models demonstrate that occlusion of the LAD coronary artery, with or without reperfusion, produces pathological, haemodynamic and hormonal features that characterize clinical LV dysfunction secondary to myocardial infarction.

Myocardial infarcts, particularly large transmural infarcts, cause complex alterations in ventricular architecture, resulting in disproportionate dilation and thinning of infarcted myocardium, and dilation and hypertrophy of non-infarcted myocardium [17], collectively known as remodelling. Remodelling is thought to be the major mechanism underlying the progression from asymptomatic ventricular dysfunction to overt heart failure [18]. The results of the present study show that these models have a similar underlying pathology to that found in much human infarction, with the early stages of dilation and transmural thinning in the infarcted regions apparent after 7 days. There was also early evidence of both functional and structural remodelling of the left ventricle. In addition to post-mortem findings, ventriculography revealed a reduction in LVEF (more marked in the coil
group) and marked hypokinesis, with decreases in fractional shortening in the third and fourth quadrants (more apparent in the coil group). Thus, despite the fact that the position of occlusion was similar in the two models, reperfusion after 90 min (balloon group) resulted in less severe LV dysfunction compared with the permanently occluded model (coils), as documented by significant differences in LVEF measured at day 7. This is consistent with human infarction, whereby early reperfusion, by means of either thrombolysis or PTCA, is beneficial to both short- and long-term outcome [19,20].

Reperfusion protects the myocardium and salvages viable tissue, and also reduces mechanical remodelling of the ventricle. Thus further improvement of short- and long-term prognosis can be achieved if reperfusion occurs more rapidly and if a persistent TIMI (‘thrombosis in myocardial infarction’) grade 3 flow of the infarct-related artery can be achieved [21]. The balloon and coil groups described in the present study clearly model patent infarct-related artery/complete reperfusion (equivalent to TIMI grade 3) and total occlusion (equivalent to TIMI grade 0) respectively. As closed-chest models, they offer significant advantages over previously described coronary ligation models [6,7], which are complicated by the surgical trauma associated with thoracotomy.

Acute changes apparent immediately following reperfusion in the balloon group included very rapid or transient rises in heart rate, plasma catecholamines and natriuretic peptides. Changes were observed very rapidly (within 1–2 min) on deflating the balloon, with dramatic increases in heart rate and greatly increased incidence of ectopy, tachycardia and fibrillation, resulting in death in two animals. All balloon sheep required additional anti-arrhythmic treatment (1–2 mg of atenolol) at the time of reperfusion. Thus this model provides an opportunity to study the pathophysiology of reperfusion injury. Fatality rates were 22% in the balloon group (all immediate upon reperfusion) and 30% in the coil group (first 12 h). As all deaths were arrhythmic in nature, it is possible that survival may be improved by administration of either higher doses of or additional/alternative anti-arrhythmic drugs.

A distinct difference between the two models described in the present study was noted in the cardiac enzyme profiles. Both creatine kinase and troponin-T showed different temporal changes between the two models, with washout of enzymes being much more rapid in the reperfused group. This parallels data in humans, whereby time to enzyme peaks is significantly less in patients obtaining complete reperfusion compared with lower grades of perfusion [22]. Peak enzyme levels measured in the coil group were lower than those measured in the reperfused group, which probably reflects abrupt ‘washout’ from the reperfused myocardium. We were unable to accurately compare ‘area under the curve’ in the present study due to the frequency and/or timing of sampling, with samples for creatine kinase not collected between 6 and 24 h and for troponin-T not collected beyond day 3 in the coil group. Thus more frequent sampling with calculation of area under the curve may have given less disparate results.

The LV dysfunction observed in the coil group was associated with acute haemodynamic changes, including increases in RAP and heart rate, reduced arterial pressure and a trend for cardiac output to fall. In keeping with the milder degree of LV dysfunction observed in the balloon group, haemodynamic changes were qualitatively similar to those in coil animals, but not significantly different from those in sham controls. However, it is important to note that, while significant haemodynamic changes were observed in this study, they were in the main short-lived (1–2 days), with values returning to or towards sham control values, presumably reflecting a state of compensated LV dysfunction.

Depending on its severity, myocardial infarction may result in activation of several different neurohormonal systems, including cardiac natriuretic peptides, catecholamines and the renin/angiotensin/aldosterone system [23]. In recent years the cardiac natriuretic peptides, ANP and BNP, have been shown to be strong diagnostic and prognostic markers [24,25]. BNP may also prove useful as a screening test for detection of patients with mild or asymptomatic LV dysfunction [26]. In the present study, plasma BNP was significantly increased in both models, and ANP was increased in the balloon group. These changes occurred acutely, within 6–12 h post-infarction. In the case of the coil group, in contrast with the transient haemodynamic disturbance, BNP remained elevated for the duration of the study (7 days). That plasma BNP remained elevated in the coil group, but not the balloon group, probably reflects the relative severity of LV dysfunction. In human infarction, late or no reperfusion is associated with significantly higher plasma BNP levels between 7 and 30 days post-infusion, compared with those measured in patients with successful early reperfusion [27]. Furthermore, these authors suggested that BNP may be a useful marker for the prediction of progressive ventricular remodelling within the first 30 days after acute myocardial infarction.

As noted above, compared with sham controls, plasma ANP levels were significantly increased in the balloon occlusion/reperfusion group, but not in the coil group. The lack of responsiveness of ANP in the coil group is surprising, especially given the acute rises in RAP (approx. 4 mmHg at 4–6 h). Indeed, there is a dissociation of the ANP/RAP relationship, with calculation of the ANP/RAP ratio revealing a significant reduction in the coil group compared with the balloon group (P = 0.019). Presumably tachycardia plays a role in the ANP response to reperfusion in the balloon group. The balloon group received more β-blockers than the coil group (additional 1–2 mg), with administration at the...
time of reperfusion, possibly affecting natriuretic peptides, although the difference in dose was only modest. It is also possible that reperfusion yields other products, such as free radicals, which may disturb or exaggerate ANP release at any given RAP.

In contrast with the natriuretic peptides, the renin/angiotensin/aldosterone system was not activated in the present studies. This is consistent with findings in patients who have experienced small to moderate infarcts, in whom the renin/angiotensin/aldosterone system is activated only moderately and transiently, if at all [28]. Indeed, the rise in levels of natriuretic peptides may act to suppress any activation of the renin/angiotensin/aldosterone system and contribute to compensation of early LV dysfunction. Administration of the β-blocker, atenolol, may also have limited any tendency for renin to rise, since blockade of β1 receptors on juxtaglomerular cells is well known to inhibit renin release. Plasma catecholamines were activated in these models, consistent with clinical studies that report sympathetic activation during acute myocardial infarction leading to LV dysfunction. These data suggest that endothelin release may have adverse consequences in acute myocardial infarction, including a reduction of myocardial blood flow and increased contractility in non-ischaemic myocardium. In contrast, the present study showed no evidence of activation of plasma endothelin in response to infarction, either with or without reperfusion. In fact, in the coil group, plasma endothelin levels were significantly reduced compared with sham controls, and levels also tended to be reduced in the balloon group. Experimental factors such as anaesthesia, anti-arrhythmic drugs or mechanical stimulation of the vascular endothelium due to the cardiac catheterization procedures probably contributed to the activation of endothelin levels in the present study. Suppression of plasma endothelin levels may have been mediated by the elevated levels of cardiac natriuretic peptides, which have been demonstrated to inhibit endothelin secretion in vitro [33].

In conclusion, both PTCA balloon occlusion for 90 min followed by reperfusion and thrombogenic coil permanent occlusion of LAD coronary arteries in sheep result in well defined transmural anterolateral infarcts. Restriction of coronary arterial occlusion to 90 min resulted in less LV dysfunction with reduced early remodelling compared with permanent occlusion at the same site in the infarct-related artery. Changes in biochemical markers, haemodynamics, neurohormones and LV function confirm that these are excellent closed-chest, large-animal models of open and closed artery acute myocardial infarction leading to LV dysfunction.

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