Best evidence topic - Coronary
Does intermittent cross-clamp fibrillation provide equivalent myocardial protection compared to cardioplegia in patients undergoing bypass graft revascularisation?

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Received 28 April 2009; received in revised form 22 July 2009; accepted 24 July 2009

Summary
A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was: does intermittent cross-clamp fibrillation provide equivalent myocardial protection compared to cardioplegia in patients undergoing bypass graft revascularisation? Altogether, 58 papers were found using the reported search, of which 13 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. We identified 13 studies, of which eight were randomised prospective trials. None of these studies found increased mortality, seven analyzed serum cardiac enzymes and showed that intermittent ischemic arrest provides equal or better protection compared to cardioplegic techniques. Two studies found an increased usage of inotropes and intra aortic balloon pump (IABP) in the intermittent ischemic arrest group. We conclude that intermittent cross-clamp fibrillation is a versatile and cost-effective method of myocardial protection, with the immediate postoperative outcome comparable to cardioplegic arrest in first-time coronary artery bypass graft (CABG). The ischaemic duration associated with intermittent cross-clamp fibrillation is invariably shorter than that associated with cardioplegic arrest, and this may be one explanation for the comparable outcomes. There may also be an element of preconditioning protection during the intermittent cross-clamp fibrillation method, as has been shown experimentally. During elective CABG in patients with no clinical evidence of aortic or cerebro-vascular disease, the incidence of peri-operative microemboli (ME) and postoperative neuropsychological disturbances are shown to be comparable with both techniques of myocardial preservation.

Keywords: Aged; Aorta/surgery; Coronary aneurysm/surgery; Coronary artery bypass methods; Heart arrest; Induced methods hypothermia; Humans

1. Introduction
A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

2. Three-part question
In [patients undergoing on-pump coronary artery bypass surgery] is [intermittent cross-clamp fibrillation] equivalent to [cardioplegic techniques] in terms of [morbidity and mortality]?

3. Clinical scenario
You are at a national conference hearing an eminent speaker reporting his results for coronary artery bypass graft (CABG) using intermittent cross-clamp fibrillation. He continues to say that, although the technique is becoming progressively less popular, it still has the same results compared to cardioplegic arrest. You are not convinced and resolve to check the literature yourself.

4. Search strategy
In addition, the reference lists of all relevant papers were searched.

5. Search outcome
Using the reported search strategy, 58 papers were found and 13 papers were identified and selected as providing the best evidence to answer the question. These are presented in Table 1.

6. Results
Musumeci et al. [2] reported a prospective randomised clinical trial, which enrolled 91 patients undergoing elec-
Outcomes

<table>
<thead>
<tr>
<th>Author, date and country, Study type (level of evidence)</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musumeci et al., (1998), Eur J Cardiothorac Surg, UK, [2] Prospective randomised trial (level 1b)</td>
<td>91 CABG patients prospectively randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=43) vs. SCT (single clamp technique with intermittent antegrade cold (4-8 °C) oxygenated blood cardioplegia; n=48)</td>
<td>Serum CK-MB, troponin T (TnT), troponin I (TnI)</td>
<td>Median peak CK-MB: 26 μg/l IIA vs. 18 μg/l SCT (P&lt;0.02) Median peak TnT: 0.8 μg/l IIA vs. 1.08 μg/l SCT (P&lt;0.03) Median peak TnI: 0.64 μg/l IIA vs. SCT 0.87 μg/l (P=NS)</td>
<td>During elective CABG in patients with no clinical evidence of aortic or cerebro-vascular disease the incidence of peri-operative ME and postoperative neuropsychological disturbances are comparable with both techniques of myocardial preservation. Biochemical analysis suggests that IIA provides more effective myocardial preservation</td>
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<tr>
<td>Pepper et al., (1982), Thorax, UK, [3] Prospective randomised trial (level 1b)</td>
<td>50 CABG patients prospectively randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=25) vs. SCT [cold (4 °C) St Thomas’ Hospital cardioplegia; n=25]</td>
<td>Serum CK-MB, aspartate transaminase (AST)</td>
<td>Mean CK-MB values similar for 24 h after aortic cross-clamp release, at 48 h CK-MB lower (P&lt;0.05) in IIA. Similar AST values between groups</td>
<td>Equal protection of the myocardium was provided in both groups</td>
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<td>Taggart et al., (1994), Br Heart J, UK, [4] Prospective randomised trial (level 1b)</td>
<td>20 CABG patients prospectively randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=10) vs. SCT [cold (4 °C) St Thomas’ Hospital cardioplegia; n=10]</td>
<td>Serial measurement of serum TnT</td>
<td>Peak median serum TnT at 6 h postoperatively [IIA, 1.9 (1.0-3.5) μg/l; SCT, 1.8 (1.0-3.6) μg/l, P=NS]. No difference between groups at any time</td>
<td>This trial shows that intermittent ischaemic arrest provides a similar level of myocardial protection compared to crystalloid cardioplegia</td>
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<td>Dunning et al., (2006), J Cardiothorac Surg, UK, [5] Prospective cohort study (level 2b)</td>
<td>16 CABG patients subjected to cross-clamp fibrillation</td>
<td>Intramyocardial pH probe measured the level of acidosis in the anterior and posterior myocardium in real-time. The pH at the start and end of each period of cross-clamp recorded</td>
<td>Initial pH was 7.133 (range 6.974–7.239). After first cross-clamp period, pH was 6.381 (range 6.034–6.684), recovering to 6.723±0.324 (but highly inconsistent). Patients split into recoverers (6.990±0.561) compared to non-recoverers (6.455±0.067) (P&lt;0.0005). This was repeated after each cross-clamp release. However, no difference in pH at end of bypass (7.062 vs. 7.038)</td>
<td>Cross-clamp fibrillation does not result in reliable repertilution of the myocardium between cross-clamp periods</td>
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Table 1 Best evidence papers
### Table 1 (Continued)

<table>
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<td>Alex et al., (2003), Interact CardioVasc Thorac Surg, UK, [6] Retrospective cohort study (level 3b)</td>
<td>1454 CABG patients over 5-year period divided into 2 groups: A, antegrade − retrograde cold blood St Thomas' cardioplegia (n=671), B, intermittent cross-clamp fibrillation (n=783)</td>
<td>No. of grafts, bypass duration (min)</td>
<td>A: 2.9±0.8, B: 2.7±0.7 (P&lt;0.001) A: 6.4±20.0, B: 56.2±17.4 (P&lt;0.001)</td>
<td>Intermittent cross-clamp fibrillation is a versatile and cost-effective method of myocardial protection, with the immediate postoperative outcome comparable to antegrade − retrograde cold St Thomas blood cardioplegia in elective first-time CABG</td>
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<td>Cohen et al., (1997), Eur J Cardiothorac Surg, UK, [7] Prospective randomised trial (level 1b)</td>
<td>24 consecutive CABG patients (ejection fraction &gt;30%) prospectively randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=13) vs. SCT [cold (4 ‘C) St Thomas’ Hospital cardioplegia; n=11]</td>
<td>Serial measurement (upto 72 h) of: Plasma antioxidant status: Serum TnT</td>
<td>Peak at 1 h, no differences at all time points (P=NS) Similar initial depression and subsequent recovery at all time points (P=NS) No differences between groups at all time points (P=NS)</td>
<td>Equivalent myocardial protection between IIA and SCT in patients undergoing elective CABG in terms of free radical activity and antioxidant status</td>
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<td>Raco et al., (2002), Ann Thorac Surg, UK, [8] Prospective cohort study (level 3b)</td>
<td>800 consecutive CABG patients (May 1996–July 2000) using IIA (intermittent ischaemic arrest with fibrillation) – elective (556), urgent (220) and emergency (224)</td>
<td>Mortality</td>
<td>Elective (0.57%), urgent (3.09%), emergency (5.55%)</td>
<td>Intermittent aortic cross-clamping is a safe technique both in elective and non-elective patients</td>
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<td>Liu et al., (1998), Ann Thorac Surg, UK, [9] Retrospective cohort study (level 3b)</td>
<td>1923 CABG patients (January 1992–May 1997) divided into 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=1345) vs. SCT [cold (4 ‘C) St Thomas’ Hospital blood cardioplegia; n=578]</td>
<td>Mortality</td>
<td>IIA (2.5%), SCT (2.1%), P=0.35</td>
<td>There was no difference in outcome detected between the two techniques</td>
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<td>Alhan et al., (1996), Ann Thorac Surg, Turkey, [10] Retrospective cohort study (level 3b)</td>
<td>399 consecutive low-risk CABG patients divided into 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n=271) vs. SCT [cold (4 ‘C) St Thomas’ Hospital cardioplegia; n=128]</td>
<td>Mortality</td>
<td>IIA (0.4%), SCT (0.0%), P=NS</td>
<td>Both intermittent aortic cross-clamping and cold crystalloid cardioplegia techniques may be used safely in low-risk patients undergoing first-time CABG</td>
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<td><strong>Prospective randomised trial (level 1b)</strong></td>
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<td>Gerola et al., (1993), J Thorac Cardiovasc Surg, Brazil, [11]</td>
<td>60 consecutive CAGB patients were randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n = 30) vs. SCT [Buckberg cardioplegia (and cardioplegic reperfusion enriched with glutamate and aspartate); n = 20]</td>
<td>Ischaemic duration (min): IIA 36.1 ± 12 SCT 46.9 ± 18, P = 0.007</td>
<td>CK-MB</td>
<td>Myocardial biopsies</td>
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<td>Anderson et al., (1994), Ann Thorac Surg, UK, [12]</td>
<td>40 consecutive CAGB patients were randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n = 20) vs. SCT [cold (4 °C) St Thomas’ Hospital blood cardioplegia; n = 20]</td>
<td>Ischaemic duration (min): IIA 27 ± 6 SCT 38 ± 10</td>
<td>CK-MB</td>
<td>Median peak: IIA, 1.6 ng/ml: SCT, 2.2 ng/ml (P = NS). Area under activity curve was no different</td>
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<td>Casthely et al., (1997), J Thorac Cardiovasc Surg, USA, [13]</td>
<td>60 CAGB patients were divided into 3 groups (dependent on operating room): I, anterograde cardioplegia (n = 20); II, anterograde and retrograde cardioplegia (n = 20); III, intermittent ischaemia arrest with fibrillation (n = 20)</td>
<td>Ischaemic duration (min): I, 52 ± 4; II, 50 ± 3; III, 40 ± 1 (P &lt; 0.05)</td>
<td>E/A ratio reduced in all groups at 5 min, but only recovered to near normal at 60 min in group III</td>
<td>The degree of LV diastolic impairment (during CPB) was less when ventricular fibrillation and intermittent aortic cross-clamping were used, and greater when anterograde and retrograde cardioplegia were used</td>
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<td><strong>Prospective cohort study (level 2b)</strong></td>
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<td>Ischaemic duration (min): I, 52 ± 4; II, 50 ± 3; III, 40 ± 1 (P &lt; 0.05)</td>
<td>Left ventricular diastolic function, measured with pulsed-wave Doppler transesophageal echocardiography (peak flow velocities during early filling and atrial contraction (E/A ratio) and by systolic diastolic superior pulmonary venous flow ratio) measured before CPB and at 5 min and 60 min post-CPB</td>
<td>Haemodynamic measurements</td>
<td>Cardiac index was significantly higher in group III (P &lt; 0.05)</td>
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<td>Sunderdiek et al., (2000), Eur J Cardiothorac Surg, Germany, (14)</td>
<td>103 CABG patients were randomised to 2 groups: IIA (intermittent ischaemic arrest with fibrillation; n = 52) vs. SCT (cold [4 °C] crystalloid Bretschneider-HTK cardioplegic solution; n = 51)</td>
<td>Mortality</td>
<td>IIA, 4 (7.7%); SCT, 2 (4%); P = NS</td>
<td>Both cardioprotective methods seem to offer sufficient myocardial protection in normal CABG procedures. Cardioplegic arrest seems to offer more beneficial effects in procedures with prolonged ischaemia</td>
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<tr>
<td>Prospective randomised trial (level 1b)</td>
<td>Cooling to 27–30 °C for IIA and 30 °C for SCT</td>
<td>Ischaemic duration (min): IIA 37 ± 10; SCT 48 ± 10 (P &lt; 0.02)</td>
<td>CK-MB</td>
<td>Peak: IIA, 18.7 ± 12.4 U/l; SCT, 13.7 ± 11.1 U/l; P = NS</td>
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<td>TnI</td>
<td>Peak: IIA, 60.5 ± 36.4 ng/ml; SCT, 41.2 ± 18.7 ng/ml; P = NS</td>
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<td>IIA patients with ischaemic duration &gt; 40 min had higher enzyme levels than SCT patients</td>
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IABP, intra aortic balloon pump; CPB, cardiopulmonary bypass; MI, myocardial infarction; LV, left ventricle; ECG, electrocardiogram.

tive CABG. Hearts were protected by intermittent global ischaemic arrest with fibrillation or single aortic clamp and multiple cold blood cardioplegia infusions. Measurements of peak serum levels of troponin I (TnI), troponin T (TnT) and creatine kinase (CK-MB) showed higher levels in the single clamp technique, but no difference in function measured by echocardiography immediately postoperatively or at six months. In addition, the intra-operative levels of cerebral microemboli (ME) were comparable, as was the incidence of neuropsychological disturbances, assessed by the Luria Nebraska Neuropsychological Battery (LNNB) tests for motor, visual, reading, memory and intellectual processes at one day postoperatively and one week and six months postoperatively.

Pepper et al. [3] performed a prospective randomised trial, which enrolled 50 patients to either cold crystalloid cardioplegia or intermittent global ischaemic arrest with fibrillation. Mean serum levels of CK-MB and aspartate transaminase (AST) were similar throughout 24 h postoperatively. Cytochemical analysis of left ventricular full-thickness biopsies (taken before and after cardiopulmonary bypass) showed no differences between groups. Clinical outcome and requirement for inotropic support was also similar, indicating similar levels of myocardial protection.

Taggart et al. [4] enrolled 20 patients in a prospective randomized trial comparing multiple brief (10–15 min) periods of ischaemic arrest with fibrillation to cold crystalloid cardioplegia. Serial measurements of TnT showed similar levels throughout 72 h postoperatively in the two groups. In this study, the duration of ischaemia was similar (30 min and 32 min for cardioplegia and intermittent cross-clamp fibrillation (ICCF), respectively). Thus, protection was similar with both techniques.

Dunning et al. [5] performed a prospective cohort study, in 16 patients undergoing CABG using intermittent cross-clamp fibrillation. Intramyocardial pH (in real time) was measured throughout each cross-clamp fibrillation period. They found that, during the reperfusion period when the cross-clamp was open, pH recovery was rapid in some patients but in others it failed to recover completely. After cardiopulmonary bypass (CPB), however, the pH was close to the initial pH in both groups and was not different between the groups. It was concluded that cross-clamp fibrillation does not result in reliable myocardium perfusion between periods of cross-clamping.

Alex et al. [6] reported an experience between two surgeons in consecutive first-time CABG over a 5-year period in a retrospective non-randomised trial of 1454 patients. They examined the immediate postoperative outcome of two groups of patients: 671 underwent CABG using antegrade-retrograde cold St Thomas’ blood cardioplegia (with partial occlusion for proximal anastomoses) and 783 had intermittent cross-clamp fibrillation. Postoperative inotropes, myocardial infarction (MI), arrhythmias, neurological and renal complications, multi-organ failure, sternal rewiring, ventilation, length of stay and mortality were comparable between the two groups; however, the intermittent ischaemic arrest group had a significantly longer intensive therapy unit (ITU) stay. It was concluded that ICCF was a versatile and cost effective method of myocardial protection with comparable immediate (hospital stay) postoperative outcome to blood cardioplegia.

Cohen et al. [7] examined a small cohort of 24 consecutive CABG patients within a prospective randomized trial. Patients were randomised to intermittent cross-clamp fibrillation for distal anastomoses (with proximal anastomoses constructed using side-biting clamp during reperfusion), or antegrade cold crystalloid cardioplegia for all distal anastomoses. Measurements of lipid peroxidation, antioxidant status and TnT demonstrated no differences between the two groups, indicating similar protective properties for these techniques.

Raco et al. [8] examined 800 patients conducted by a single surgeon who underwent first-time CABG using intermittent cross-clamp fibrillation in a prospective cohort study. Patients were subsequently divided into elective (520), urgent (226) and emergency (54). Subgroup analysis indicated that this technique was safe for all patients with lower morbidity and mortality characteristics in relation to Parsonnet score.

Liu et al. [9] reviewed 1923 non-emergency patients who underwent first-time elective or urgent CABG from January 1992 to May 1997, by four consultant surgeons. Antegrade cold blood cardioplegia for distal anastomoses was used in
578 patients. Intermittent aortic cross-clamp fibrillation for distal anastomosis construction with reperfusion and defibrillation for proximal anastomosis construction was used in 1345 patients. There were no differences between the groups in terms of mortality (2.52% in ICCF and 2.07% in blood cardioplegia) or for morbidity parameters (although there was a significant difference in incidence of balloon pump usage of 2.4% compared to 1.0% for ICCF or blood cardioplegia, respectively). It was concluded that either technique of myocardial protection is acceptable; it was suggested, however, that ICCF should only be used if each distal anastomosis is done within a 15-min period.

Alhan et al. [10] conducted a retrospective analysis of 399 consecutive low-risk patients undergoing first-time CABG using either ICCF or cold crystalloid cardioplegia for myocardial protection. There were no differences in mortality or morbidity between these groups. Subsequently, a prospective randomised trial in 40 consecutive low-risk patients was conducted, measuring haemodynamics, enzyme release and ultrastructural changes in left ventricle (LV) biopsies. These measurements also showed no differences between the groups, and it was concluded that either myocardial protection technique was safe in low-risk patients.

Gerola et al. [11] conducted a prospective randomised controlled trial in 60 elective CABG patients to compare the efficiency of ICCF and the Buckberg method of cardioplegic protection (involving cold blood cardioplegia for induction and maintenance of arrest, with warm cardioplegia enriched with glutamate and asparate for the initial 5 min of reperfusion). Haemodynamics and enzyme release (CK-MB) showed no differences between these groups, and it was concluded that the two methods had similar myocardial protection efficiency.

Anderson et al. [12] randomised 40 patients undergoing elective CABG to intermittent cross-clamp fibrillation or cold blood cardioplegia. Enzyme markers of myocardial injury (CK-MB and TnT) were measured for 48 h postoperatively. Analysis of peak values together with area under the curve of total enzyme release showed no differences between the two groups. It was concluded that either method of myocardial protection was effective in elective patients.

Cathely et al. [13] examined the effects of three myocardial protection techniques on diastolic function in 60 patients scheduled for elective CABG. They were divided into three equal groups of either antegrade cold blood cardioplegia, antegrade and retrograde cold blood cardioplegia or intermittent cross-clamp fibrillation. All patients had normal diastolic function preoperatively, assessed by pulsed-wave Doppler transesophageal echocardiography, and ejection fraction was also determined. At 5 min after discontinuation of cardiopulmonary bypass, diastolic function was impaired in all groups but had only returned to normal control values at 60 min post-CPB in the ICCF group. No differences in haemodynamics were detected between groups. It was concluded that ICCF causes less impairment of function (manifest as reduced myocardial stunning) than the cardioplegia techniques.

Sunderdiek et al. [14] conducted a prospective randomised trial in 103 consecutive CABG patients using either cold crystalloid cardioplegia (Bretschneider-HTK solution) or ICCF. Measurements up to 10 days postoperatively of inotropic support, biochemical enzyme release (CK-MB and TNI) and electrocardiogram (ECG) changes demonstrated no significant differences between the groups. Analysis of patients with ischaemic durations in excess of 40 min suggested that ICCF may be less effective under these circumstances.

7. Clinical bottom line

We conclude that intermittent cross-clamp fibrillation is a versatile and cost-effective method of myocardial protection, with the immediate postoperative outcome comparable to cardioplegic arrest in first-time CABG. The ischaemic duration associated with intermittent cross-clamp fibrillation is invariably shorter than that associated with cardioplegic arrest, and this may be one explanation for the comparable outcomes. There may also be an element of preconditioning protection during the intermittent cross-clamp fibrillation method, as has been shown experimentally [15]. During elective CABG in patients with no clinical evidence of aortic or cerebro-vascular disease, the incidence of peri-operative ME and postoperative neuro-psychological disturbances are shown to be comparable with both techniques of myocardial preservation.

References


eComment: Myocardial protection in high risk coronary surgery

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doi: 10.1510/icvts.2009.209437A

I congratulate the authors for their efforts [1]. Both intermittent cross-clamp fibrillation (ICCF) and cold blood cardioplegia are commonly used in coronary artery bypass surgery. I agree with the authors that ICCF is a versatile technique that can be used in patients with no aortic disease when the repeated application and removal of the aortic cross-clamp could lead to more emboli to the brain.

We have published a retrospective study on 615 patients with significant left main disease to compare the postoperative clinical outcome of these two techniques [2]. We found no difference between the two techniques in mortality, the use of IABP, the use of inotropes, ventilation duration and the hospital stay. I believe that the real difference between myocardial protection techniques should be evident when tested against high risk patients.

References
