

# A prospective randomized study to evaluate the renoprotective action of beating heart coronary surgery in low risk patients<sup>☆</sup>

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## Abstract

**Objectives:** Cardiopulmonary bypass (CPB) is widely regarded as an important contributor to renal failure, a well recognized complication following coronary artery surgery (coronary artery bypass grafting (CABG)). Anecdotally off-pump coronary surgery (OPCAB) is considered renoprotective. We examine the extent of renal glomerular and tubular injury in low-risk patients undergoing either OPCAB or on-pump coronary artery bypass (ONCAB). **Methods:** Forty low-risk patients with normal preoperative cardiac and renal functions awaiting elective CABG were prospectively randomized into those undergoing OPCAB ( $n = 20$ ) and ONCAB ( $n = 20$ ). Glomerular and tubular injury were measured respectively by urinary excretion of microalbumin and retinol binding protein (RBP) indexed to creatinine (Cr). Daily measurements were taken from admission to postoperative day 5. Fluid balance, serum Cr and blood urea were also monitored. **Results:** No mortality or renal complication were observed. Both groups had similar demographic makeup, Parsonnet score, functional status and extent of coronary revascularization ( $2.1 \pm 1.0$  vs.  $2.5 \pm 0.7$  grafts;  $P = 0.08$ ). Serum Cr and blood urea remained normal in both groups throughout the study. A significant and similar rise in urinary RBP:Cr occurred in both groups peaking on day 1 ( $3183 \pm 2534$  vs.  $4035 \pm 4079$ ;  $P = 0.43$ ) before reapproximating baseline levels. These trends were also observed with urinary microalbumin:Cr ( $5.05 \pm 2.66$  vs.  $6.77 \pm 5.76$ ;  $P = 0.22$ ). Group B patients had a significantly more negative fluid balance on postoperative day 2 ( $-183 \pm 1118$  vs.  $637 \pm 847$  ml;  $P = 0.03$ ). **Conclusions:** Although renal complication or serum markers of kidney dysfunction were absent, sensitive indicators revealed significant and similar injury to renal tubules and glomeruli following either OPCAB or ONCAB. These results suggest that avoidance of CPB does not offer additional renoprotection to patients at low risk of perioperative renal insult during CABG. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Cardiopulmonary bypass; Pulsatile flow; Renal injury; Off-pump; Myocardial revascularization

## 1. Introduction

Renal dysfunction is a well recognized complication following coronary artery bypass grafting (CABG). Its reported incidence varies considerably with the criteria employed between different studies from about 1% up to almost 40% [1]. Although full-blown acute renal failure necessitating replacement therapy occurs in less than 1% of cases, these patients could face a mortality rate reaching 60% [2]. Survivors may develop chronic renal failure needing regular dialysis with all the attendant morbidities.

There are well-known risk factors associated with

progression to renal failure following CABG, all probably acting in a synergistic manner [3,4]. Old age (>70 years), poor preoperative ventricular function, pre-existing kidney disease and diabetes are commonly recognized to predispose to postoperative renal dysfunction. Among the multifactorial aetiology, renal hypoperfusion and inflammatory damage secondary to cardiopulmonary bypass (CPB) are widely regarded as the most important culprits [2,5]. However, the relative importance of each process has so far not been evaluated. Beating heart coronary revascularization through its complete avoidance of CPB offers an ideal opportunity to study perioperative renal dysfunction and its pathophysiology within a prospective randomized clinical setting.

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## 2. Materials and methods

### 2.1. Study design

Consecutive patients awaiting elective CABG who fulfilled the study criteria (Table 1) were prospectively recruited following informed consent. These were essentially low-risk subjects with normal preoperative cardiac and renal functions. On the preoperative day, they were randomized into those undergoing CABG on the beating heart (Group A: off-pump coronary surgery (OPCAB)) or revascularized conventionally using CPB (Group B: on-pump coronary artery bypass (ONCAB)). The study was approved and monitored by the Southampton & South West Hants Joint Local Research Ethics Committee.

Statistical power calculation was performed at the conception stage utilizing expected differences in outcome based on our previous work in related subjects which employed similar methodology [6]. This suggested that a sample size of 11 in each group will have 90% power to detect a probability of 0.9 that an observation (e.g. urinary markers of differential renal injury) in the OPCAB group is less than a corresponding observation in the ONCAB group using an appropriate test with a 0.05 two-sided significance level. To allow for a generous safety margin, we decided to aim for approximately 20 patients in each study group.

### 2.2. Anaesthesia and conduct of CPB

A standardized protocol was followed in which fentanyl-based anaesthesia was used in combination with propofol and pancuronium as a muscle relaxant. Each patient had continuous perioperative monitoring of central venous and systemic arterial pressures. Those who subsequently developed poor cardiac output requiring inotropic support were excluded from the study. In ONCAB patients, a standard adult extracorporeal tubing set was used incorporating a 40  $\mu$ m arterial line filter in conjunction with a D903 Avant membrane oxygenator (Sorin Biomedica, Gloucester, UK). The circuit was primed with 1200 ml of Hartmann's solution, 500 ml of gelofusin and 5000 IU of sodium heparin. An S3 roller pump (Stöckert Instrumente GmbH, Munich, Germany) controlled pulsatile flow which was

maintained at or above 2.5 l/min per m<sup>2</sup>. The mean perfusion pressure was titrated to 65 mmHg with a combination of phenylephrine and isoflurane. No vasoactive agent was administered other than for this purpose. Alpha-stat management of acid-base status was used during CPB. Haemodynamic stability with a target mean arterial pressure of 65 mmHg was achieved in OPCAB patients with a combination of preload management (intravenous fluid and autotransfusion with the Trendelenberg posture), external pacing and meticulous thermoregulation (head wrap, forced air warming, warmed transfusion and elevated ambient temperature). Vasoactive agents were not primarily used for blood pressure control.

### 2.3. Surgical procedure

CABG was performed in ONCAB patients with the institution of CPB. The latter was accomplished by draining blood through a single two-stage venous cannula (Medtronic DLP, Medtronic UK Ltd.) inserted into the right atrium/inferior vena cava and making arterial return via a cannula (Medtronic DLP, Medtronic UK Ltd.) placed in the ascending aorta. The procedure was conducted under moderate hypothermia (32 °C) with myocardial protection provided by intermittent antegrade cold blood cardioplegia (4 °C) and topical cooling. The cardioplegic mixture consisted of 20% St. Thomas' Hospital No. 2 solution (Martindale Pharmaceuticals, Essex, UK). Diastolic cardiac arrest was induced with 1000 ml of cardioplegic infusion supplemented at 25 min intervals by further doses of 500 ml. Aortic anastomoses of vein grafts were performed on a reperfused heart following cross-clamp removal.

In the OPCAB group, the heart was exposed through a median sternotomy and pericardiotomy. In addition to multiple traction sutures placed along the cut edges of the pericardium, a heavy-gauge monofilament (2 Prolene™, Ethicon, Edinburgh, UK) stay suture incorporating a sterile stockingnette acting as a cardiac sling was placed in the posterior pericardium of the oblique sinus to facilitate exposure of the heart during coronary anastomoses. Systemic heparin was administered at 1 mg/kg to prolong the activated clotting time to approximately 250 s. A suction-based mechanical stabilizer (Octopus II, Medtronic Ltd., Watford, UK) improved exposure of the target coronary vessel prior to arteriotomy. Distal myocardial perfusion was maintained during distal anastomoses using an intraluminal shunt (Biovascular Inc., Minnesota, USA). Aortic anastomoses of vein grafts were performed using a partial-occlusion clamp in the standard fashion.

### 2.4. Assessment of renal function

Urine and blood samples were collected from each patient at 24 h intervals commencing on surgical admission (baseline) until postoperative day 5. Changes in renal function were assessed by measuring blood urea and serum creatinine (Cr). Differential injury to the renal tubules and

Table 1

Exclusion criteria for subject recruitment<sup>a</sup>

Pre-existing renal disease
Serum creatinine above 135 $\mu$ mol/l
LV ejection fraction less than 40%
Chronic or uncontrolled hypertension
Diabetes mellitus
Age above 80 years
Unstable angina
Regular usage of nephrotoxic agents
Preoperative inotrope dependency

<sup>a</sup> Essentially subjects at low-risk for perioperative renal dysfunction were selected.

Table 2  
Demographic and perioperative variables<sup>a</sup>

	OPCAB	ONCAB
Age (years)	64.8 ± 6.9	62.1 ± 9.3
Gender ratio (M:F)	15:5	17:3
NYHA function class	1.8 ± 0.8	1.8 ± 0.8
CCS angina grade	2.2 ± 0.7	2.1 ± 0.9
Parsonnet score	4.2 ± 3.7	4.6 ± 5.6
Coronary grafts	2.1 ± 1.0	2.5 ± 0.7
LIMA usage (%)	19 (95)	18 (90)

<sup>a</sup> No significant difference was observed. NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; LIMA, left internal mammary artery.

glomeruli were detected respectively by urinary excretion of retinol binding protein (RBP) and microalbumin (MA). These sensitive markers were indexed to Cr excretion in the urine to adjust for variations in the glomerular filtration rate. The scientific rationale for monitoring urinary RBP:Cr as a parameter for early renal tubular injury had previously been discussed [6]. Assessment of glomerular injury by measuring urinary MA:Cr has also been validated to be both accurate and sensitive in cardiac surgical patients [7]. In essence, both RBP and MA offer very early detection of differential renal injury at a stage long before conventional parameters such as blood urea and serum Cr become abnormal. Aliquots of urine (20 ml) were collected in sterile tubes and stored frozen (−40 °C) until analysis. Urinary RBP was analyzed using a very sensitive latex-enhanced immunoassay technique with nephelometric detection which has been custom-developed in our own laboratory [8]. Urinary MA was measured using a turbidimetric assay.

Daily fluid balance, demographic variables and perioperative characteristics were also collected.

### 2.5. Statistical analysis

Data are presented as the mean ± standard deviation. Differences in categorical variables between groups were compared using Fisher's exact test. The Mann–Whitney *U*-test was applied to non-parametric data including New York Heart Association (NYHA) functional class, Canadian Cardiovascular Society (CCS) grading for severity of angina, Parsonnet score and extent of coronary grafting. The remaining data were analyzed with unpaired two-tailed

*t*-test and repeated measures analysis of variance with Bonferroni correction. Numerical values of urinary markers of differential renal injury were naturally transformed to approximate normal distribution before data analysis and detransformation. A statistically significant difference was considered when  $P < 0.05$ .

## 3. Results

### 3.1. Group characteristics

Forty-five patients satisfied inclusion criteria and were randomized into two equal groups with no cross-over. Five patients were subsequently excluded from the study because of intra- and postoperative inotrope dependency: two in the OPCAB group and three in the ONCAB group. Noradrenaline was the sole agent used in four cases to counteract excessive vasodilation whereas dopamine was used for a few hours following discontinuation of CPB in two subjects. A persistent low cardiac output state was not encountered in the study population. There was no significant difference between the groups in terms of age, gender, NYHA functional class, CCS angina grade, Parsonnet score, left internal mammary artery usage and number of coronary artery bypass grafts performed (Table 2). No mortality or major postoperative morbidity, specifically renal impairment, was encountered.

### 3.2. Renal function and differential injury

No significant difference in serum Cr or blood urea was detected between the groups during the study period with both parameters staying within the normal range throughout (Table 3).

Starting from comparable baseline values, a dramatic and significant rise in urinary RBP:Cr ( $P < 0.001$ ) occurred to similar extents in both groups peaking on day 1 ( $3183 \pm 2534$  vs.  $4035 \pm 4078$ ;  $P = 0.43$ ) before returning to baseline levels by the end of the study period (Fig. 1). These trends were also observed with changes in urinary MA:Cr, again of similar magnitude in both groups ( $5.05 \pm 2.66$  vs.  $6.77 \pm 5.76$ ;  $P = 0.22$ ) (Fig. 2).

Table 3  
Serum markers of renal function<sup>a</sup>

	Preop.	Day 1	Day 2	Day 3	Day 4	Day 5
Serum Cr (μmol/l)						
OPCAB	94.6 ± 18.0	91.4 ± 15.8	98.7 ± 19.0	91.8 ± 16.8	91.7 ± 16.9	91.9 ± 17.9
ONCAB	93.2 ± 12.2	95.1 ± 18.2	99.1 ± 17.3	93.8 ± 15.9	97.3 ± 16.4	92.8 ± 17.7
Blood urea (mmol/l)						
OPCAB	5.5 ± 1.0	5.5 ± 1.1	5.3 ± 1.2	5.1 ± 1.2	5.2 ± 1.3	5.2 ± 1.3
ONCAB	5.5 ± 0.7	5.6 ± 1.1	5.8 ± 1.0	5.5 ± 1.2	5.5 ± 0.9	5.2 ± 0.8

<sup>a</sup> No significant difference was detected. Cr, creatinine.

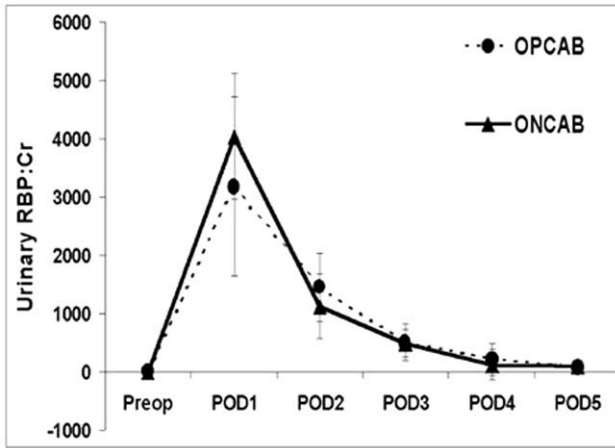


Fig. 1. A significant and dramatic rise was observed in both groups peaking on postoperative day 1 before re-approximating baseline values by day 5 ( $P < 0.001$ ). No inter-group difference was found. RBP, retinal binding protein; Cr, creatinine; OPCAB, beating heart coronary surgery; ONCAB, coronary surgery with cardiopulmonary bypass; POD, postoperative day.

### 3.3. Fluid balance

An overall trend towards an increasingly negative daily fluid balance with time was observed in both groups (day 1 vs. day 5;  $P < 0.001$ ). ONCAB patients lost significantly more fluid on postoperative day 2 ( $-183 \pm 1118$  vs.  $637 \pm 847$  ml;  $P = 0.03$ ) (Fig. 3). Otherwise data remained comparable between the two cohorts at other time points.

## 4. Discussion

Given the low-risk nature of our study cohort, the absence of clinically overt renal dysfunction was perhaps not surprising. This was reflected in the stability of the serum markers (blood urea, serum Cr) and a lack of postoperative

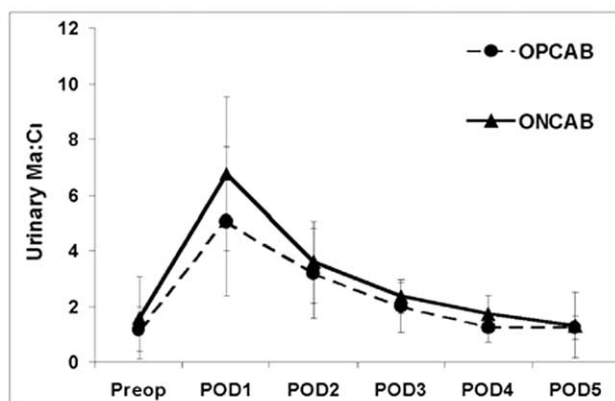


Fig. 2. A significant and dramatic rise was observed in both groups peaking on postoperative day 1 before re-approximating baseline values by day 5 ( $P < 0.001$ ). No inter-group difference was found. MA, microalbumin; Cr, creatinine; OPCAB, beating heart coronary surgery; ONCAB, coronary surgery with cardiopulmonary bypass; POD, postoperative day.

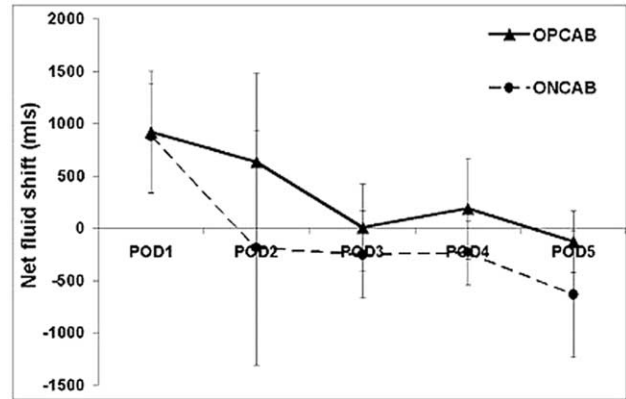


Fig. 3. A significant temporal trend towards more negative fluid balance was seen in both groups ( $P < 0.001$ ). ONCAB patients lost significantly more fluid on postoperative day 2 ( $P < 0.05$ ). No significant difference was otherwise detectable. OPCAB, beating heart coronary surgery; ONCAB, coronary surgery with cardiopulmonary bypass; POD, postoperative day.

renal intervention. However, the important biochemical injury as evident by changes in the sensitive urine indicators (RBP:Cr, MA:Cr) revealed extensive subclinical damage to both renal tubules and glomeruli. The greatest impact was seen on postoperative day 1 followed by a rapid return to normality within 4 days. These findings concurred with our previous work in this area and clearly suggest that maximal injury must have occurred intraoperatively [6,9]. More interestingly, based on our understanding of the pathophysiology of renal injury during CABG, one might have expected some degree of benefit to emerge in the OPCAB patients. With the study groups being well matched both in their demographic makeup and perioperative variables, our findings may initially appear to be counterintuitive. The risk of a type II error is inherently an important consideration when negative results are reported. However, this is unlikely to confound the interpretation of our findings given the data produced by initial statistical power calculations and our eventual sample size.

The aetiology of renal failure following open heart surgery is complex with multiple factors acting perhaps synergistically. Central to these are renal hypoperfusion and systemic inflammation associated with CPB. Inadequate perfusion to the nephrons may result from circulatory failure, renal vasoconstriction or a combination of the two. It is well documented that CPB could trigger both processes thus leading to progressive renal impairment in susceptible individuals [2]. Systemic inflammation secondary to the use of extracorporeal circuit is also universally believed to play a crucial part in the mechanism of postoperative renal injury [5]. Avoidance of CPB would eliminate the latter component although an inflammatory response of some extent could still be triggered by surgical trauma. It would therefore follow that the extent to which inflammatory damage may be responsible for perioperative renal insult could only be attenuated but not completely abolished in the beating heart approach.

Compared to the state of controlled shock during CPB, transient but significant periods of circulatory failure and global hypoperfusion may have occurred during OPCAB. It has been established that cardiac output and thus organ perfusion can be temporarily compromised with specific manoeuvres employed to optimize exposure of target vessels on a beating heart [10]. The ‘apex-to-ceiling’ position adopted for grafting the obtuse marginal and distal circumflex territory in particular can cause a significant but reversible dip in cardiac performance. Therapeutic steps such as increasing preload with warm intravenous fluid or autotransfusion (Trendelenberg posture) and external pacing can be taken to prevent major cardiovascular downturns and maintain haemodynamic stability. The cumulative effects of these brief and otherwise insignificant episodes of hypoperfusion may result in ischaemic renal injury comparable in magnitude to that produced by CPB. Demonstration of this phenomenon would require a continuous cardiac output monitoring device with real-time measurement capability which is not currently possible with thermodilution pulmonary artery catheters.

Pulsatility of flow during CPB has long been advocated for renoprotection. The loss of pulsatile flow is believed to enhance renal vasoconstriction, reduce effective renal plasma flow and predispose to ischaemic injury [11]. Adoption of pulsatile CPB in the control group was designed to reflect the contemporary practice within our cardiac surgical unit. It is, however, conceivable that this factor may have had a profound influence on the study findings in that pulsatile flow provided a degree of renoprotection which the OPCAB approach was unable to better. Of immediate relevance to this observation is the results of a previous study investigating renal function in such patients but over a shorter period (up to 48 h postoperatively): a significant benefit was demonstrated in the beating heart group in reducing both glomerular and tubular injury [12]. Apart from a number of methodological differences, an important distinguishing feature is the use of non-pulsatile flow in their study design which could wholly or partly account for the varying outcome [13].

The temporal trends in daily fluid balance in both groups may reflect a steady resolution of the trauma response following surgery. Stress hormones cause salt and water retention leading to a net fluid gain. Diuresis accompanied by an increasing net fluid loss signified a diminishing catabolic state. A significantly more negative fluid balance observed in the ONCAB patients during the early postoperative period may be related to extra fluid loading with pump-prime and hence an exaggerated baseline volume status.

We chose to exclude subjects who for various reasons became inotrope dependent following surgery. Using almost identical methods, dopamine had clearly been shown to exacerbate renal tubular injury in cardiac surgical patients even in the absence of any perioperative haemodynamic compromise [9,13]. It would therefore become impossible to attribute changes in the renal indices to differences in

surgical techniques in the presence of dopamine or related inotropes. As the actual numbers of cases excluded for this criterion were similar in each group, this factor is unlikely to have any significant influence on the interpretation of our findings.

The success of any therapeutic procedure is likely to be greatest when it is optimally targeted. In this respect, the selection of candidates deemed at low risk of developing perioperative renal dysfunction in this study may seem illogical. However, as the majority of patients undergoing beating heart CABG would fall into this category probably as a result of the ‘learning curve’ effect, our findings would consequently be more widely applicable [14]. It is important to recognize that although OPCAB appears to offer no added protection to low-risk individuals against perioperative renal dysfunction, this may not be the case in high-risk subjects and would form the basis of a separate investigation.

### Acknowledgements

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## Appendix A. Conference discussion

**Mr A. Ritchie** (Cambridge, UK): Can I turn the question around on its head for you. Why should an off-pump patient who has no disturbances in his hemodynamics have any problem with his renal function or change at all?

**Mr Tang:** Good question. I think most surgeons who have done off-pump surgery would realize that in fact hemodynamic control during surgery is not as smooth as he or she wishes to think. I think the ability of the anesthetist to control the hemodynamic profile while you are doing beating heart surgery is central to stability of the circulation during the operation. Now, there are studies which have looked at cardiac output during the various maneuvers while you do off-pump surgery, one of them is from the Bristol group, and when they use real time beat-to-beat cardiac output monitoring, they actually demonstrated that with certain maneuvers, like the apex to ceiling position, you get a significant reduction in cardiac output. Now, that's even with, we anticipate, a preload management like Trendelenburg and warm fluid infusion, et cetera.

Although when you actually look at the anesthetic chart and you see transient periods of mild hypotension which would otherwise be fairly insignificant, the summary effects of this will probably be equivalent to the kind of damage you see with cardiopulmonary bypass.

**Mr Ritchie:** I think the real answer to that is the actual fact that these groups of patients off-pump get a significant volume load from the anesthetist during the procedure. That's what happens. And although

they are supposed to have no change in their kidney function, they get a problem with volume overload in their immediate perioperative patients. I see this routinely with pulmonary edema, and we give them a shot of furosemide at the end of the case to try and deal with that. But that has probably more than anything to do with the hemodynamic thing, the cause of that.

**Mr Tang:** I think the other aspect also is the inflammatory injury you can get.

**Mr Ritchie:** You do get a much bigger inflammatory injury with using cardiopulmonary bypass.

**Mr Tang:** You do.

**Mr Ritchie:** But the OPCAB patients are not free of volume load.

**Mr Tang:** Yes, you are spot on, absolutely.

**Mr S. Stoica** (Cambridge, UK): The conclusions are very powerful, but can you comment about the sample size calculation and the power of the study? I know that you have used a physiological end point, and the worry is that a Type II error can be there.

**Mr Tang:** Obviously with any study that uses a negative finding, the concern is a Type II error. This particular point has been addressed in the design of the study. My interest in this area of research started in the first study when we looked at the role of dopamine in coronary patients, and the slide I showed earlier on came from that paper. In a second study we looked at the same kind of parameters but in high risk cardiac patients. And it is based on our previous findings that the power calculations we performed prior to conducting the study demonstrated that the chance of us showing a 50% difference was 95%, given only 12 patients in each group. So I think on that basis, which is all the objective evidence we can get, the chance of a Type II error is minimal.

**Dr P. Macchiarini** (Hannover, Germany): I have a last question from the design structure of the study. Do you think that the indications for the two types of surgery might have, the difference in this indication might have influenced the end results?

**Mr Tang:** If I interpret your question correctly, what you are saying is whether the two groups of patients were comparable. The answer is yes. They were randomized the day before surgery. The surgeon, who is a single operating surgeon, who did all the cases, and that surgeon has already climbed the learning curve before we started the study, and he would have been happy to perform either on or off-pump in any of those cases.

**Dr Macchiarini:** The indications, if they were the same, clinical indications. I presume that you don't operate on the same patient off or on pump?

**Mr Tang:** Well, in our institution, the one surgeon who performs both on and off-pump surgery was involved in the randomization.