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# Role of Coronary Collaterals in Off-Pump and On-Pump Coronary Bypass Surgery

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***Background***—Collaterals limit infarct size, preserve viability, and reduce mortality in patients with acute myocardial infarction. In patients with stable coronary disease, collaterals are associated with less angina and ischemia during angioplasty and fewer ischemic events during follow-up. The role of collaterals has not been studied in patients undergoing off-pump or on-pump bypass surgery.

***Methods and Results***—The population consisted of the 281 patients randomized to off-pump or on-pump CABG in the Octopus Study. Collaterals were defined on the baseline angiogram with the Rentrop score and were present in 49% and 51% of the patients in the off-pump and on-pump group, respectively. Perioperative myocardial infarction was defined by a creatine kinase-MB to CK ratio >10% and occurred in 18.2% in the off-pump group and 32.5% in the on-pump group. The unadjusted OR of perioperative myocardial infarction in the presence of collaterals was 0.31 (95% CI 0.17 to 0.84) in the off-pump group and 1.06 (95% CI 0.29 to 3.85) in the on-pump group After adjustment for age, gender, hypertension, hypercholesterolemia, diabetes, multivessel disease, ventricular dysfunction, incomplete revascularization, and ischemic time, the OR was 0.34 (95% CI 0.14 to 0.84) in the off-pump group and 1.28 (95% CI 0.30 to 5.40) in the on-pump group, respectively. Kaplan-Meier estimates of event-free survival at 1 year were 87% in patients with and 69% in those without collaterals after off-pump CABG. These estimates were 66% and 63%, respectively, after on-pump CABG.

***Conclusions***—Collaterals protect against perioperative myocardial infarction during off-pump surgery but not during on-pump surgery and are associated with a better 1-year event-free survival. **(*Circulation*. 2004;110:1738-1742.)**

**Key Words:** bypass ■ collateral circulation ■ surgery ■ myocardial infarction

The presence of collaterals may limit infarct size, preserve viability, and reduce long-term mortality in patients with acute myocardial infarction.[1–4] In patients with stable coronary artery disease, collaterals are associated with less angina and ischemia during angioplasty (PCI)-induced coronary occlusion and with fewer ischemic events during follow-up.[5–7] The protective role of collaterals has not been studied in patients who undergo coronary bypass surgery.

Recently, off-pump bypass surgery (off-pump CABG) has been reintroduced in clinical practice to address the limitations of conventional surgery (on-pump CABG). During the latter, complete ischemic cardiac arrest is induced in combination with the use of cardiopulmonary bypass for construction of the anastomoses. During off-pump CABG, the anastomoses are constructed on the beating heart while the target coronary is occluded for ≈15 minutes.[8] We hypothesized that as a result of the different nature of the 2 operations, collaterals may protect patients against perioperative myocardial damage after off-pump CABG but not after on-pump CABG. For this purpose, we studied the relationship between collaterals and perioperative myocardial infarction (MI) in patients who were enrolled in a randomized comparison between off-pump and on-pump CABG.[9] Subsequent ischemic events during 1-year follow-up were also assessed.

## Methods

### Study Population

The population consisted of the 281 patients enrolled in the Octopus Study, described elsewhere.[9] In brief, patients with stable or unstable angina (Braunwald class I or II, B) with normal or moderately impaired ventricular function were randomly assigned to on-pump or off-pump CABG. Patients were eligible if referred for first-time isolated CABG and if the off-pump procedure was technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the last 6 weeks,

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**TABLE 1. Baseline and Perioperative Characteristics of Patients Undergoing Off-Pump or On-Pump Bypass Surgery**

| Variables | All Patients (n=281) | Collaterals Present (n=129) | Collaterals Absent (n=152) | P |
|---|---|---|---|---|
| Demographics | | | | |
| Mean age, y | 61.3 | 60.5 | 61.9 | 0.17 |
| Male gender, % | 68 | 69 | 68 | 0.83 |
| Cardiovascular risk factors, % | | | | |
| History of smoking | 73 | 72 | 74 | 0.77 |
| Hypertension | 42 | 39 | 45 | 0.30 |
| Hypercholesterolemia | 68 | 74 | 64 | 0.07 |
| Diabetes | 13 | 10 | 15 | 0.21 |
| Obesity (body mass index >30 kg/m$^2$) | 15 | 14 | 15 | 0.78 |
| Antecedents of cardiovascular disease, % | 57 | 54 | 59 | 0.47 |
| Stable angina, % | 75 | 78 | 72 | 0.34 |
| Serum creatinine, mg/dL | 1.02 | 1.01 | 1.04 | 0.99 |
| Angiographic characteristics, % | | | | |
| Multivessel coronary disease | 74 | 77 | 71 | 0.28 |
| Moderately impaired left ventricle | 22 | 26 | 18 | 0.08 |
| Perioperative characteristics, % | | | | |
| Off-pump surgery | 51 | 49 | 52 | 0.51 |
| On-pump surgery | 49 | 51 | 48 | 0.51 |
| Incomplete revascularization | 16 | 16 | 14 | 0.41 |
| Myocardial infarction | 26 | 18 | 32 | 0.05 |

Antecedents of cardiovascular disease are the sum of previous stroke, MI, peripheral vascular disease, and coronary revascularization. See text for other definitions.

or poor left ventricular function. The goal of surgery was to obtain complete arterial revascularization. On-pump CABG was performed with cardiopulmonary bypass in combination with cold crystalloid cardioplegia for myocardial protection. Off-pump CABG was performed with the use of the Octopus cardiac stabilizer.[9]

## Coronary Collaterals

Collaterals were defined by visual assessment of the baseline angiogram with the Rentrop criteria (0, no filling of collaterals; 1, filling of collaterals without any filling of the epicardial artery; 2, partial filling of the epicardial artery; and 3, complete filling of the epicardial artery).[10] Collaterals were considered present in case of filling of the epicardial artery (Rentrop >1). The angiograms were graded in random order by 2 cardiologists who were blinded as to treatment assignment and clinical data. The reproducibility of the Rentrop score has been described as high ($\kappa$=0.85, 95% CI 0.77 to 0.93).[11]

## Perioperative MI and Cardiac Outcome at 1 Year

Perioperative MI was defined by a creatine kinase isoenzyme (CK-MB) to total creatine kinase (CK) ratio >10% occurring within 48 hours after CABG.[12,13] In accordance with the Octopus Study protocol, CK-MB and CK enzyme activity was determined before and 2, 4, 8, 12, and 20 hours after CABG, and additionally when necessary. CK-MB:CK ratio was calculated by dividing CK-MB by the total CK activity at each time point.

Cardiac outcome at 1 year was defined by the composite of all-cause death, nonfatal stroke, nonfatal MI (perioperative or follow-up), and repeat revascularization (PCI or CABG). Death was considered cardiac unless otherwise documented; stroke was defined as focal brain injury that persisted for >24 hours, combined with an increase in handicap of at least 1 grade on the Rankin scale. After 48 hours after CABG, a non–Q-wave MI was defined by a CK-MB to total CK ratio >10% and a Q-wave MI as the appearance of new pathological Q waves.[9,12,13] All events were evaluated and adjudicated by an independent Clinical Event Committee.

## Data Analysis

The association between collaterals and perioperative MI was determined by calculating the crude OR for patients who underwent off-pump and on-pump CABG, separately. Multivariate regression analysis was used to correct the unadjusted ORs for variables that were considered confounders of the association examined. Distinction was made between patients with and without collaterals to identify potential determinants of collateral presence. The contribution of putative indicators was analyzed by univariate logistic regression analysis. A $\chi^2$ or Student $t$ test was used to discern statistically significant differences. All reported probability values were 2-sided. A probability value <0.05 was considered statistically significant.

The relation between collaterals and 1-year outcome was studied by calculating event-free survival, since the time of randomization, by the Kaplan-Meier method. Kaplan-Meier curves were constructed for both groups with distinction within each group between patients with and without collaterals. Probability values were calculated by the log-rank test. All data were analyzed with SPSS version 10.0.

# Results

A total of 281 patients were randomized to off-pump CABG (n=142) and on-pump CABG (n=139). Seven patients whose surgeries were converted before the operation (2 from off-pump to on-pump, 5 from on-pump to off-pump) were analyzed according to the received treatment. Eight patients

**TABLE 2. Cardiovascular Events up to 1 Year After Off-Pump and On-Pump Bypass Surgery**

| | Off-Pump Surgery (n=132) | | | On-Pump Surgery (n=117) | | |
|---|---|---|---|---|---|---|
| Event | In-Hospital | Follow-Up | 1 Year | In-Hospital | Follow-Up | 1 Year |
| All events: <48 hours* | | | | | | |
| MI, perioperative | 24 (18.2) | ... | 24 (18.2) | 38 (32.5) | ... | 38 (32.5) |
| All events: 48 hours to 1 year* | | | | | | |
| Death, all-cause | 0 (0.0) | 2 (1.5) | 2 (1.5) | 1 (0.9) | 1 (0.9) | 2 (1.7) |
| Stroke | 1 (0.8) | 0 (0.0) | 1 (0.8) | 1 (0.9) | 0 (0.0) | 1 (0.9) |
| MI, other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (1.7) | 2 (1.7) |
| Coronary reintervention | 1 (0.8) | 5 (3.8) | 6 (4.5) | 0 (0.0) | 4 (3.4) | 4 (3.4) |
| All events, cumulative | 2 (1.5) | 7 (5.3) | 9 (6.8) | 2 (3.3) | 7 (6.0) | 9 (7.7) |
| First event: operation to 1 year† | | | | | | |
| Any first event | 24 (18.2) | 2 (1.5) | 26 (19.7) | 38 (32.5) | 4 (3.4) | 42 (35.9) |
| Free from any first event | ... | ... | 106 (80.3) | ... | ... | 75 (64.1) |

Values are number of events (%).
*All events were counted in case more than 1 event occurred in the same patient.
†Only the first event was counted when more than 1 event occurred.

in the off-pump group were excluded from analysis (1 conversion to PCI before the operation and 7 to on-pump CABG during the operation). Another 24 patients were excluded because of missing CK-MB:CK values. Therefore, 249 patients (132 off-pump and 117 on-pump) were included in the analysis.

Baseline characteristics of the total population are summarized in Table 1. Most patients were male, with a mean age of 61 years and preserved ventricular function. Multivessel disease was present in 74% of the patients (50% with double-vessel disease and 24% with triple-vessel disease). Collaterals were present in 49% of patients in the off-pump group and 51% of patients in the on-pump group. The mean number of grafts per patient was 2.4 in the off-pump group and 2.6 in the on-pump group. Complete arterial revascularization was achieved in 86% of patients in the off-pump group and 80% of those in the on-pump group. Perioperative MI occurred in 18.2% of the patients in the off-pump group (CK-MB, median value of the area under the curve 164 units/L) and in 32.5% of the on-pump group (CK-MB, median value of the area under the curve 277 units/L; Table 2).

Protection of collaterals against perioperative MI was only found in patients who underwent off-pump CABG and not in those who underwent on-pump CABG (Table 3). The unadjusted ORs of perioperative MI in the presence of collaterals were 0.31 (95% CI 0.17 to 0.84) in the off-pump group and 1.06 (95% CI 0.29 to 3.85) in the on-pump group (Table 3). After adjustment for baseline and perioperative variables that

**TABLE 3. Unadjusted and Adjusted Risk of Perioperative MI in Relation to Presence of Collaterals**

| | Off-Pump Surgery (n=132) | | On-Pump Surgery (n=117) | |
|---|---|---|---|---|
| Variables | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Presence of collaterals, unadjusted | 0.31 (0.17–0.84) | 0.01 | 1.06 (0.29–3.85) | 0.93 |
| Presence of collaterals, adjusted for: | | | | |
| Age | 0.43 (0.21–0.89) | 0.02 | 1.07 (0.29–3.91) | 0.92 |
| Male gender | 0.34 (0.17–0.75) | 0.01 | 1.13 (0.31–4.17) | 0.85 |
| History of hypertension | 0.40 (0.20–0.85) | 0.01 | 1.01 (0.29–3.84) | 0.93 |
| History of hypercholesterolemia | 0.40 (0.20–0.81) | 0.01 | 1.28 (0.35–4.75) | 0.71 |
| Diabetes | 0.40 (0.19–0.80) | 0.01 | 1.16 (0.32–4.24) | 0.83 |
| Multivessel coronary disease | 0.38 (0.18–0.77) | 0.01 | 1.06 (0.29–3.87) | 0.93 |
| Moderately impaired left ventricle | 0.40 (0.20–0.81) | 0.01 | 1.02 (0.28–3.78) | 0.97 |
| Intraoperative ischemic time* | 0.43 (0.20–0.93) | 0.03 | 1.18 (0.32–4.32) | 0.80 |
| Incomplete revascularization | 0.46 (0.23–0.94) | 0.03 | 1.19 (0.33–4.31) | 0.79 |
| All variables mentioned above | 0.34 (0.14–0.84) | 0.02 | 1.28 (0.30–5.40) | 0.74 |

*Ischemic time in the off-pump group was defined by the coronary occlusion time, which is the sum of the time of occlusion of all coronary arteries that were grafted and, thus, temporally occluded for construction of the anastomoses. Ischemic time in the on-pump group was the time of the use of cardiopulmonary bypass.

were considered confounders of the examined association, the ORs were 0.34 (95% CI 0.14 to 0.84) and 1.28 (95% CI 0.30 to 5.40), respectively (Table 3).

The Kaplan-Meier estimates of the occurrence of any first event in patients with and without collaterals are depicted in the Figure. The presence of collaterals was associated with a significantly lower rate of any first event in the off-pump group (13% versus 31%, $P=0.01$) but not in the on-pump group (34% versus 37%, $P=0.79$).

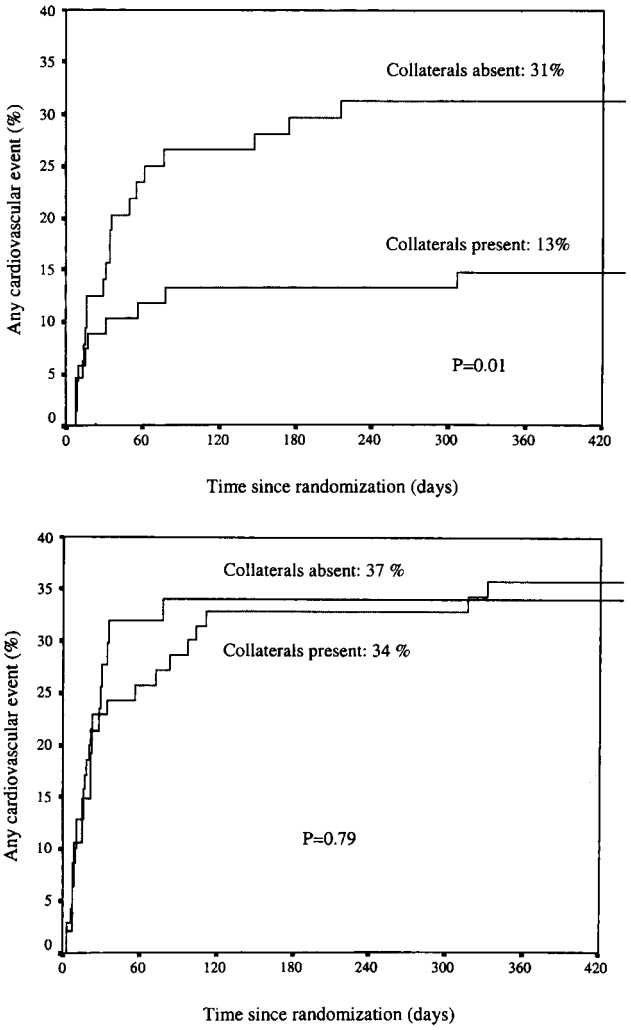
## Discussion

The main finding of this study is that collaterals offer protection in terms of fewer perioperative MIs in patients who undergo off-pump CABG but not in those who undergo on-pump CABG. This finding must be viewed and interpreted in the context of the population, methods of assessment, and analysis.

The baseline characteristics and events during the follow-up period, in particular, disclose that this analysis concerns a low-risk population. Despite this, a protective effect from collaterals was observed in the off-pump group. In the present population, this effect was restricted to a reduction in perioperative MI. Perioperative MI was the most frequent and virtually the only clinical event in the entire population. There were very few events during follow-up, mainly related to repeat revascularization. We cannot exclude that collaterals may also have a protective effect on other outcomes, such as cardiac death and repeat revascularization. The sample size and number of events were too small to explore this further. It is likely that the reduction in perioperative MI will also influence the long-term outcome as documented after on-pump surgery and PCI.[14–17] Also, we could not explore whether collateral grade influenced outcome.

To study the relation between collaterals and perioperative MI, we chose to first calculate the unadjusted OR of perioperative MI in the presence of collaterals followed by calculation of the adjusted OR. The latter was done after adjustment of variables assumed to have an effect on the outcome of interest and thus to confound the analysis. Comparison of the unadjusted and adjusted ORs discloses that collaterals indeed play an important protective role in the occurrence of perioperative MI. The difference between these ORs, however, indicates that other factors are involved. Still, when all variables were included in the analysis, collaterals proved protective against perioperative MI (OR 0.34, 95% CI 0.14 to 0.84), which indicates the robustness of the finding.

In addition to the methods of analysis, the use of angiography for the definition of collaterals and the threshold value (Rentrop score $>1$) to discern their presence or absence may have influenced our observations. Quantitative assessment, which is considered superior to morphological assessment, was not used.[18] We thus may have underestimated the protective effects of collaterals. Recent studies, however, report a good correlation between angiographic and functional methods of assessment in patients with stable angina referred for coronary angioplasty.[19,20]




Kaplan-Meier estimates of proportion experiencing any event (composite of all-cause death, nonfatal stroke, nonfatal MI, and coronary reintervention) at 1 year after bypass surgery in patients with or without collaterals. Probability values were calculated with log-rank test. Top, Off-pump bypass surgery ($P=0.01$); bottom, on-pump bypass surgery ($P=0.79$).

The finding of the present study is in accordance with our hypothesis and is understandable from a pathophysiological point of view.[21] The 2 groups stem from a randomized study, and collaterals were uniformly distributed over the 2 groups (49% versus 51%). It thus appears that induction of complete cardiac arrest during on-pump CABG attenuates and even prohibits the potential protective role of collaterals, if present. During off-pump CABG, the target coronary is only temporally occluded to allow construction of the anastomoses on the beating heart. The findings of the present study may help guide patient management and risk stratification. Patients undergoing off-pump CABG but without collaterals may benefit from a number of measures such as ischemic myocardial preconditioning by short periods of repeated coronary occlusions, the use of intracoronary or aortocoronary shunting of blood, or a reduction of the coronary occlusion time by novel anastomosis techniques.[22–26] After preconditioning, less CK-MB release during PCI and less troponin release

during off-pump CABG have been reported.[22,23] The safety of such novel surgical techniques has not been elucidated yet. Tissue formation due to endothelial damage at the site of the application may occur. Also, patients who undergo on-pump CABG may benefit from a number of measures, such as retrograde blood cardioplegia, cardioplegia administered down to the graft after placement, or grafting of the noncollateralized regions first to reduce the perioperative infarct rates.

We conclude that in a well-defined low-risk population, collaterals protect against perioperative MI during off-pump coronary bypass surgery and are associated with a better 1-year outcome. This is not found in patients who undergo on-pump surgery.

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