

Living with Off-Pump Coronary Artery Surgery: Evolution, Development, and Clinical Potential for Coronary Heart Disease Patients

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ABSTRACT

The enormous progress in interventional cardiology during the last 10 years has resulted in a major change in the spectrum of patients referred for coronary bypass surgery. These patients are older and sicker and frequently have had previous percutaneous coronary interventions. Consequently, cardiac surgery is responding by adding new surgical techniques: off-pump open-chest coronary bypass surgery (OPCAB), minithoracotomy bypass surgery, videothoracoscopic (robotic) procedures, etc. Several registries published to date have proved OPCAB to be safe and clinically effective. Randomized studies and meta-analysis research in this field provide scientific support and suggest that myocardial, renal, and neurological functions, amongst others, are better preserved by OPCAB than by classic techniques that use a cardiopulmonary bypass pump (CPB). Moreover, avoidance of CPB yields significantly reduced oxidative stress and systemic inflammatory response. This results in higher safety for ischemic heart disease patients undergoing revascularization, thus offsetting the propensity to lower costs. The present review examines the physiological advantages and clinical outcomes of this simple mode of myocardial revascularisation and evaluates the wider implications arising from its evolution.

INTRODUCTION

Contrary to the published reports [Ascione 1999a; Cooley 2000; Yacoub 2001] "that operation on a beating heart is a relatively new surgical procedure," Murray and Longmire in the 1950s, before cardiopulmonary bypass (CPB) came into widespread use, performed the coronary endarterectomy with a saphenous vein graft [Westaby 1996]. Later, myocardial revascularization by anastomosing the internal mammary artery to the coronary artery was advocated by Demikhov, who undertook a canine study of this technique in 1952; 4 of his dogs survived for more than 2 years with patent grafts

[Demikhov 1962]. In a similar time frame, Sabiston independently achieved similar results by using a saphenous vein graft to bypass the right coronary artery [Westaby 1997], whereas Garrett in 1964 bypassed the left anterior descending artery (LAD) [Westaby 1997]. That same year, Kolesov anastomosed the left internal mammary artery (LIMA) to a marginal branch of the circumflex artery [Spencer 1995]. All of these procedures were done off pump on a beating heart.

After 1968, coronary artery bypass grafting (CABG) with CPB (ONCAB) was widely adopted, and off-pump CABG (OPCAB) was relegated to few centers, mainly for economic reasons. Hence, OPCAB was originally the only possible approach but after the advent of modern CPB techniques was largely viewed as passé.

However, with the introduction of minimally invasive coronary surgery and mechanical methods of target-artery stabilization, interest in OPCAB has been renewed. A major hindrance to OPCAB was the difficulty of performing coronary anastomoses with the needed poise, particularly on the lateral and posterior surfaces of the heart. The challenge was to overcome this problem of the beating heart with a predictable, reliable, and reproducible method of epicardial stabilization. Favaloro in 1970 and Trapp in 1975 described their techniques of beating heart coronary bypass surgery and reported good outcomes [Favaloro 1970; Trapp 1975].

Nevertheless, ONCAB remained the mainstream technique of myocardial revascularization and attracted extensive research. In the 1980s, it was discovered that CPB induced a whole-body inflammatory response capable of causing devastating morbidity and mortality and this discovery raised concerns about the safety of the technique [Kirklin 1983]. Although refinement and modification of the technique of CPB and pharmacotherapy can attenuate its damaging effects, CPB still has the potential to cause physiological injury by direct (embolic) and indirect mechanisms.

In the 1990s, the publication of a large series by Benetti and Buffolo [Benetti 1991; Buffolo 1996] (of a good outcome with OPCAB), with corroborative reports from Pfister and Atkins [Pfister 1992; Atkins 1992] (of the favorable impact on left ventricular function), set the stage for a rejuvenation of this technique. Today 18% to 20% of all coronary bypass operations are performed off pump [Mack 2000]; yet there is wide variability between centers and the whole field is subject

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to large variations based on new technology and new outcome studies. The renaissance of beating heart CABG is rooted in the simple logical concept that deliberate avoidance of CPB would eliminate its physiological insult and yield better outcomes.

This renewed interest has been attributed to several factors: improvements in surgical and anesthetic techniques, economic advantages related to reduction in length of hospital stay, development of stabilization techniques, and elimination of the risks associated with CPB. Here we review the clinical and the experimental evidence and the mechanism involved and evaluate the wider implications arising from this concept of a new era of OPCAB.

EVIDENCE FROM CLINICAL STUDIES

Whether or not the clinical outcome of OPCAB is superior to ONCAB surgery is still a matter of great debate. In evaluating the relative role and the benefit of a change of strategy in performing CABG, it is useful to note that there are distinct benefits in the amount of increased usage of the radial artery conduit, less myocardial damage, less renal damage, less injury to the brain, reduced incidence of coagulopathy, lower frequency of atrial fibrillation (AF), improvement in left ventricular ejection fraction >5.0% within 1 month, and improvement in the transesophageal echocardiography assessment of ischemic mitral incompetence immediately after revascularization off pump [Puskas 2003; Athanasiou 2004b; Khan 2004]. Interpretation of these studies has led to contemplation about the magnitude of the OPCAB effect, although the only recently published meta-analysis report was based on 37 randomized trials comparing OPCAB with ONCAB [Cheng 2005] and suggested that OPCAB substantially decreases AF, transfusion requirements, inotrope usage, postoperative respiratory infections, ventilation time, length of intensive care unit (ITU) stay, and mean length of hospital stay ($P < .001$).

Based on these observations, recent randomized comparisons of multivessel OPCAB and ONCAB yielded a reduced release of cardiac-specific proteins (troponin T) and a low rate of adverse events [Selvanayagam 2004], reduced postoperative pulmonary compliance, better gas exchange, and earlier extubation when compared with ONCAB [Staton 2005]. Hitherto, attention was warranted in older and diabetic patients [Cumpeeravut 2003; Montes 2004]. Given that the exact pathogenesis of postoperative AF in CABG patients (25%-40%) in particular is still not understood, it is believed that OPCAB also offers an important alternative to CPB; however, its effect on postoperative AF is yet to be conclusively evaluated. The observed relationship between postoperative AF with OPCAB in an elderly population (>70 years) has been reported as having a significant reduction in the incidence of AF [Immer 2003; Athanasiou 2004a; Athanasiou 2004b].

Meta-analyzing the "best available evidence" in the published literature, Stroobant evaluated the effect of ONCAB and OPCAB on postoperative cognitive impairment and cerebrovascular reactivity, with specific attention to the perioperative high-intensity transient signals, and reported a significant decrease in the OPCAB group [Stroobant 2005]. Similarly,

Diegeler et al [1997], in a study of 40 randomized patients, showed that 90% of patients undergoing ONCAB had deficient cognitive scores compared with none in the OPCAB group. In another prospective, nonrandomized trial, fewer cerebral edemas were described in OPCAB than ONCAB surgical patients [Anderson 1999], taking into account the age of the patients selected for each group.

Although the cause of this cerebral injury is unclear, one of the frequently discussed pathophysiologic features in relation to conventional CABG with extracorporeal circulation is focal dysregulation caused by cerebral emboli. Changes in cognitive function with CPB may persist with an incidence of 25% to 30% at 8 weeks after cardiac surgery, with only slightly lower levels at 1 year [Yeatman 2001]. This may be the result of hypoperfusion during CPB, microemboli of gaseous or particulate nature, or the result of inflammatory changes that affect an increase in permeability across the blood-brain barrier with resultant cerebral edema [Varghese 2001]. Recent studies addressing this problem also reported that S100, a marker of neuronal injury, increases after ONCAB but not after OPCAB [Wandschneider 2000]. Motallebzadeh and coworkers reported that S100 in the ONCAB surgery group increased 1.6 times at termination of bypass as compared to OPCAB at completion of anastomoses ($P < .0001$) [Motallebzadeh 2004]. Furthermore, the results of OPCAB have been comparable with ONCAB in terms of mortality, as shown by the studies of Yeatman et al [2001], Varghese et al [2001], Arom et al [2000], Hernandez et al [2001], Hart et al [2000], and Patel et al [2002], thus suggesting that myocardial revascularization can be performed off pump without any increased risk.

EVIDENCE FROM EXPERIMENTAL STUDIES

Advocates of OPCAB surgery are emphasizing the reduced inflammatory response and attenuated myocardial injury when avoiding CPB, cardioplegic arrest, and the associated adverse effects, including ischemia/reperfusion injury. There is increasing evidence that CPB activates the complement cascade, causes activation of neutrophils, and increases production of cytokines. This promotes neutrophil adhesion to vessel walls and migration into the tissues and makes parenchymatous cells, including myocytes, more susceptible to neutrophil-derived products. Addressing this effect, several studies documented a reduction of myocardial biomarkers in OPCAB patients, which reflects an improved myocardial preservation [Edmunds 1998; Wan 1999; Matata 2000; Alwan 2004; Rastan 2005].

During OPCAB surgery, ischemia and reperfusion occur in the heart as well as in the lungs, activating an inflammatory process. This importance of OPCAB was increasingly established when Lockowandt and Franco-Cereceda from Sweden demonstrated that ONCAB surgery appears to be more harmful to the coronary endothelium, in terms of acetylcholine-induced vasoconstriction, than OPCAB surgery [Lockowandt 2001] because the lungs are continuously perfused in the off-bypass setup.

Moreover, it is suggested that OPCAB attenuates indices of complement activation, such as C3a and C5a, and

decreases reactive oxygen species-induced injuries [Wan 1999; Matata 2000]. Moller and associates [2003], in a prospective randomized study of 30 patients, showed that there was a temporary platelet dysfunction in the first 24 hours after OPCAB. Similarly, Casati et al [2001], in their comparison of the impact of ONCAB and OPCAB on activation of coagulation and fibrinolysis, observed a transient decrease in platelet counts, with plasminogen activation and increased D-dimer formation only after on-pump CABG. All these studies highlight the detrimental effects of CPB on coagulation mechanisms and provide consistent evidence that off-pump surgery reduces release of proinflammatory cytokines, myocardial cellular damage, and lipid peroxidation [Schulze 2000; Wildhirt 2000]. Reasons for these findings remain speculative and include severe wall stress, myocardial trauma induced by direct manipulation, as well as an increased ischemic injury rate.

OPCAB IN HIGH-RISK PATIENTS:

Off-pump surgery is being routinely used for intermediate- and low-risk patients [van Dijk 2001; Nathoe 2003]. However, growing confidence in the techniques of OPCAB and the favorable clinical outcome has provided the impetus for extension of OPCAB to high-risk patients. Although elderly patients with comorbidities have been shown to have increased morbidity and mortality after conventional myocardial revascularization on CPB [Stamou 2000], Chamberlain et al [2002], in a retrospective analysis of 1570 consecutive high-risk CABG-only patients, showed that OPCAB resulted in significantly reduced blood loss, transfusion requirements, and ITU and hospital stays. Similarly, OPCAB offers good early and long-term results in patients with acute myocardial infarction (MI), left ventricular dysfunction, obesity, and chronic renal failure, and patients with peripheral vascular disease have been reported to have a lower risk of postoperative stroke rate ($P = .005$) [Chamberlain 2002; Karthik 2004].

This inference is unchanged after risk adjusting, and the female sex has been shown to be an independent risk factor for mortality in CABG surgery. A report analyzing the early outcomes in women undergoing OPCAB [Petro 2000] determined that myocardial revascularization in women can be performed safely without CPB and that the mortality in off-pump revascularization was lower than in on-pump cohorts despite older age and higher incidence of diabetes in the former group.

Evidence in the literature suggests that an off-pump operation provides some renal protection. Ascione and associates [1999a] demonstrated a protective effect with OPCAB when compared with the on-pump technique. A recent study by Stallwood and colleagues [2004] showed the benefits of OPCAB in renal failure patients, and the patients were 2.6 times more likely to develop the complication when treated with CPB. There is now emerging scarcely reported evidence that OPCAB grafting using in situ arterial grafts can be performed on patients with chronic hemodialysis, but this procedure is subject to suitable anatomy of the target coronary arteries [Osaka 2001; Fukushima 2005].

Similarly, diabetes mellitus along with hypercholesterolemia has gained new importance in the light of the con-

cept of "a metabolic syndrome" that predicts adverse outcomes after percutaneous coronary artery interventions. From a cardiac surgical point of view, it is important to consider OPCAB an established technique that has particular benefits for the specific high-risk subgroup of diabetic patients, benefits such as a significantly reduced incidence of cerebrovascular events and renal dysfunction in the immediate postoperative period and shorter ITU postoperative lengths of stay [Srinivasan 2004].

The latest review of information from randomized controlled trials demonstrate that performing coronary surgery on the beating heart without CPB reduces morbidity in elective overweight patients who have a body mass index of ≥ 25 kg/m². Unadjusted analyses in this group showed significant benefits of off-pump surgery in terms of hospital deaths, arrhythmias, inotropic use, use of intra-aortic balloon pump, blood loss, transfusion requirement, postoperative hemoglobin, chest infections, neurological complications, and ITU and hospital stay (all $P < .05$) [Ascione 2002].

In a like manner, in the results of prior studies of the relationship between a critical left main coronary artery stenosis (LMCS) and OPCAB have led LMCS to be considered a contraindication for OPCAB. There is concern about hemodynamic changes during the displacement of the heart, even though the procedure is becoming more common and the results are encouraging even in high-risk and elderly patients [Saba 2004; Virani 2005].

These studies support the concept of differences between the regional ischemia caused by OPCAB and the global ischemia caused by CPB with aortic cross clamping. These differences might be the explanation behind the myocardial protective effect of the OPCAB technique as evident in the low incidence of MI. Undoubtedly, these findings made OPCAB a safe alternative technique for surgical treatment of patients with recent acute MI and also denied some theoretical contraindications about the use of OPCAB in patients with critical LMCS [Vlassov 2001; Yeatman 2001; Di Giammarco 2004].

It has been suggested that the distortion of the mitral valve during positioning of the heart for OPCAB could result in either functional mitral stenosis or increased mitral regurgitation with subsequent raised left atrial pressures. This distortion may be a significant contributor to the hemodynamic disturbance seen during the procedure [Al-Ruzzeh 2004]. Whether these findings are unique or comparable with compression devices remains to be shown; however, recent developments, such as the apical suction device, might play a beneficial role in reducing the distortion of the mitral valve.

OPCAB AND 1-YEAR CORONARY BYPASS GRAFT PATENCY

Nonrandomized studies have consistently shown excellent patency rates for OPCAB surgery, but the majority of these studies involved patients who were receiving 1 or 2 grafts, with a lower proportion of patients receiving circumflex-artery grafts, indicating a specifically selected population [Puskas 2001; Nathoe 2003]. The PRAGUE-4 [Widimsky 2004] ran-

domized trial reported on 1-year follow-ups of coronary angiography in OPCAB and ONCAB patients. The authors reported that arterial graft patency after 1 year was 52% in OPCAB patients in contrast to 46% in ONCAB patients; grafts anastomosed distally to collateralized chronic total occlusions of native coronary arteries remained patent in 100% on the LAD ($P < .0001$). On the other hand, Khan and coworkers [2004] in a randomized study discussed 3-month postoperative follow-up angiographic findings. The authors discussed that overall patency rate for grafts performed on pump was significantly higher than the patency rate for those performed off pump. Significantly, more radial-artery grafts were used in the OPCAB group and might explain the discrepancy with results from previously published studies [Puskas 2001; Nathoe 2003; Widimsky 2004]. Taken as a whole, the patency of arterial coronary bypass grafts done on the beating heart is excellent and equal to grafts done on pump.

OUTCOME OF ENDERARTERECTOMY IN OPCAB

Comparing the early and midterm results of off-pump coronary endarterectomy (OPCE) with those of conventional coronary endarterectomy (CCE) performed with CPB, it has been reported that OPCE can be performed safely with morbidity and mortality rates comparable to those of CCE [Naseri 2003]. Similarly, a retrospectively reviewed experience with OPCE in patients with severely reduced left ventricular function and diffuse atheromatous coronary artery disease that evaluated the early and midterm results revealed an endarterectomized coronary artery patency rate of 89% at 28.4 months [Eryilmaz 2003]. This finding suggests that endarterectomy without CPB can be performed in patients with severe left ventricular dysfunction who are expected to benefit from the complete revascularization [Kunt 2005].

QUALITY OF LIFE FOLLOWING OPCAB

With the considerable reduction of mortality associated with CABG surgery in recent years, subtler outcome indicators such as quality of life (QOL) become more important. It has been shown that physical role function and emotional role function were significantly better in OPCAB than in ONCAB patients ($P < .01$). Midterm QOL after myocardial revascularization is fairly well preserved compared with an age- and sex-matched standard population and is superior after OPCAB compared with ONCAB [Immer 2003]. Current data underline that patients undergoing OPCABG show a tremendous improvement of health-related QOL status as early as 3 months postoperatively with regard to pain reduction and can resume everyday activities [Bonaros 2005]. In a recently quoted randomized single-surgeon trial among unselected patients with angiographic follow-up, OPCAB achieved not only similar graft patency in the hospital and at 1 year but also significantly improved health-related QOL at 30 days and 1 year with lower cost incurred [Puskas 2004]. Whether this is due only to avoidance of CPB remains to be elucidated.

ECONOMIC OUTCOME OF OPCAB

Emphasis on cost containment in coronary artery bypass surgery is becoming increasingly important. The revival of interest in OPCAB may influence the economic outcome. The present era of healthcare places major emphasis on reducing costs and resources while maintaining quality of care and patient satisfaction. As ONCAB is a common and expensive procedure, there are now a number of alternative therapies claiming lower costs, such as minimally invasive direct coronary artery bypass grafting, and OPCAB surgery through a midline sternotomy [Gray 2003]. However, we should not lose sight of the fact that the first and foremost concern remains the comprehensive management of the patient, which might be jeopardized if cost is used as the only determinant of procedure.

OPCAB surgery is reported to provide better myocardial protection, lower perioperative morbidity, conserve blood constituents, and avoid neurological deficits caused through under-perfusion during CPB and embolic events from the CPB pump and cross clamping of the aorta [Puskas 2003; Athanasiou 2004b; Khan 2004]. Buffolo and coworkers showed in a retrospective study that OPCAB is a safe and cost-effective procedure, with a mortality rate of 2.5% and perioperative MI rate of 4.8% [Buffolo 1996], suggesting that OPCAB offers significant overall savings when compared with conventional on-pump coronary surgery. Furthermore, these cost reductions are distributed from the operative theater to postoperative management [Ascione 1999b].

CONSCIOUS OPCAB—A STEP FURTHER

Over the past few years, conscious cardiac and thoracic surgeries have been reported infrequently. There are reports, including our own (*BBC News Online: World South Asia December 3, 2000; Patient Conscious During Heart Op*), about an alternative anesthetic technique for performing the conscious off-pump coronary artery bypass (COPCAB) operations under thoracic epidural anesthesia as the sole anesthetics without general anesthesia. The techniques avoid ischemic events during intubation of the trachea, cardiac depression due to general anesthesia and premedication drugs, injury during tracheal intubation, and ventilator-related problems. Other benefits such as cost reduction and reduced ITU and hospital stay are also reasons for advocating this technique [Chakravarthy 2003; Karagoz 2003]. Chakravarthy and colleagues lately performed 151 COPCAB surgeries using epidural anesthesia and reported the 18-month follow-up. They concluded that COPCAB can be performed in a select group of patients by incorporating a few changes in the surgical technique [Chakravarthy 2005].

TRAINING IN OFF-PUMP CORONARY REVASCLARIZATION

The less invasive surgical approach for coronary revascularization off-pump CPB has evolved rapidly over the years. Initially, off-pump CPB coronary revascularization was performed primarily by senior surgeons who were instrumental

Best Available Evidence on Safety and Efficacy of OPCAB

Feature	Available Evidence	Grade
Systemic inflammatory response	OPCAB reduces systemic inflammatory response.	Level 1c
Neurocognitive dysfunction	OPCAB results in less potential for generation of cerebral emboli and appears to produce a lower incidence of cognitive dysfunction in short and intermediate term follow-up periods.	Level 1a
Pulmonary dysfunction	OPCAB reduces ventilation time but no significant difference noted in static or dynamic elastance, work of breathing and PaO ₂ /FiO ₂ with ONCAB.	Level 1c
Myocardial dysfunction	OPCAB causes less myocardial cell damage, as proven by the release of less troponin T or CPK isoenzyme. OPCAB patients require less inotropic support and have a low output syndrome and lower MI rates.	Level 1a
Renal dysfunction	OPCAB causes less postoperative renal and mesenteric dysfunction.	Level 1c
Blood loss/ transfusion	OPCAB results in less blood loss and reduced requirement for transfusion.	Level 1a
Graft patency	OPCAB graft patency rates are equal to or greater.	Level 1d
Atrial fibrillation	OPCAB is associated with reduced incidence of AF.	Level 1a
Safety for high-risk patients	OPCAB is safer and carries a significantly lower mortality rate for high-risk populations.	Level 1b
Economics	OPCAB is significantly less costly.	Level 1b

*OPCAB indicates off-pump coronary artery bypass.; MI, myocardial infarction.

in popularizing the beating heart operation as a safe alternative to traditional CABG. As such, resident experience was initially limited because of evolving techniques and acceptance of beating heart coronary revascularization, by both cardiac surgeons and cardiologists, as an equal alternative to conventional CABG, which depended on the demonstration of superior patient outcome. In parallel with these developments, a systematic effort has been made to teach cardiothoracic residents to be proficient in techniques used to completely revascularize the heart by off-pump CPB. As the population ages, the proportion of elderly patients requiring coronary revascularization has increased. A report from New York [Karamanoukian 2000] summarizes the experience of training residents in cardiothoracic operations with complete revascularization of the heart by off-pump CPB. The report concluded that it is technically feasible to teach residents-in-training to perform these operations under ideal conditions, using current generation stabilizers and blowers, and with modification of the LIMA stitch into a single-suture technique. The residents in our program have repeatedly commented that this experience, although structured serendipitously, is excellent in that it allows the trainee to appreciate the nuances of both operations (unpublished report). It should be remembered that our study examines the experience of residents in a single tertiary center, and that the clinical significance of this observation cannot be derived outside of prospective studies examining patients undergoing either of the 2 procedures in a randomized manner. Such technical refinements have justified the teaching of these procedures to the cardiothoracic resident without compromising patient care.

The evidence suggests that in situations in which suitable senior expertise exists, OPCAB surgery can be introduced into surgical practice and safely taught to trainees without detriment to patients. This introduction is achieved by a progressive increase in the complexity of the case mix and careful early supervision. The introduction of OPCAB has coincided with the increasing use of control charts as quality control tools. Performance monitoring provides reassurance that

patients are not being put at risk during the introduction of OPCAB; control chart methods can be used prospectively for real-time performance monitoring by consultant surgeons and residents alike [Caputo 2004; Glance 2005]. These techniques may ultimately be used to determine proficiency and accreditation. Increasing use of parallel training techniques, the development of structured training programs that encompass OPCAB, and other new technologies in cardiac surgery, coupled with objective performance monitoring, are warranted to meet the needs of a changing patient population.

CONCLUSION

Surgical myocardial revascularization without CPB is not new, with the first consecutive series of patients appearing in the early 1980s. There has been increased interest in this alternative approach, especially in patients with comorbidities, and OPCAB surgery is being increasingly reported to show better outcomes compared with conventional CABG. There is evidence from large retrospective and a few small prospective randomized trials that OPCAB surgery reduces postoperative morbidity and organ dysfunction compared with conventional myocardial revascularization using CPB and cardioplegic arrest (Table). It can be accomplished in the large majority of patients presenting for surgical treatment.

With proper training and with the aid of specific supporting technology, surgeons can safely access, expose, and immobilize vessels on all cardiac surfaces without significant hemodynamic disturbance. With strict attention to proper grafting strategies and myocardial protection, OPCAB can be performed using any conduit with excellent early graft patency rates. Morbidity and mortality rates appear to be at least as good as those achieved with conventional CABG on CPB. Extensive data presented will allow off-pump surgery to become the routine standard in all elective primary CABG operations with full revascularization.

A very recent report on a consecutive series of 3866 OPCAB patients from Buffolo and coworkers [2006] suggested that

hospital mortality was reduced to 1.9% with low incidence of cerebrovascular accident (5 cases in the entire series). The applicability of the off-pump technique increased to 49% in the last 5 years from 18% of cases in the beginning of their experience. Therefore, OPCAB surgery is an alternative method of myocardial revascularization that should be considered for every patient. This is because the simple concept of avoiding CPB, a direct and indirect source of physiological injury with potentially devastating clinical implications, can have a favorable impact on clinical outcome.

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