Hybrid myocardial revascularization—the cardiologist’s view

Jan Horák a,*, Stanislav Šimek a, Tomáš Kovárník a, Michal Semrád b, Jaroslav Lindner b, Aleš Linhart a

a 2nd Department of Medicine, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic
b 2nd Department of Surgery, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic

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Abstract
This article summarizes current knowledge on the mutual position of surgical and interventional treatment of patients with multivessel coronary artery disease. It focuses on the possibilities of their combined use—so called hybrid myocardial revascularization. The use of minimally invasive surgery combined with current technologies of coronary interventions offers new opportunities, taking advantages of both procedures and eliminating some of their disadvantages. This previously rarely used technique could improve the clinical outcomes and treatment comfort in selected groups of patients.

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1. Introduction

Despite the fact that coronary artery disease is one of the most studied diseases in history of medicine and that very effective methods of treatment were developed, the treatment strategy of multivessel coronary artery disease is still controversial. Treatment options and their combinations with continuing development of new techniques of surgical revascularization and percutaneous coronary interventions are in constant progress and the position of each method in the therapeutic range keeps changing. Traditionally, clinicians see coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) as two parallel and mutually exclusive options that can be offered to patients with multivessel coronary artery disease. Both strategies have obvious advantages but also disadvantages. Coronary intervention, using stents, offers virtual painlessness, minimal procedural risk at short-term hospitalization with early mobilization and rapid return to normal life, but with some risk of restenosis and higher risk of having another intervention in the future. Surgical treatment offers uncompromising possibilities of revascularization of all affected arteries with the guarantee of unparalleled long-term patency of arterial grafts at a price of higher perioperative morbidity and mortality, longer hospitalization and slower return to routine activities. However, the development gradually offers a choice of mutual complementary use of both methods. The trend in surgical area is to reduce the demands of the procedure by introducing minimally invasive surgical techniques and on the interventional side to increase the long-term effectiveness of interventional procedures by using drug-eluting stents (DES), which offer outcomes close to surgical revascularization by venous grafts. The use of the best of these separated worlds as a combination of minimally invasive surgery and percutaneous coronary intervention (hybrid techniques) offers new treatment strategies that can be equally or even more effective than the existing ones; and safe for the patient at the same time.

2. Coronary artery bypass grafting versus PCI – analysis of previous trials

The debate over the optimal treatment for patients with multivessel coronary artery disease rages for many years and continues until now. Its importance is enhanced by the fact that the age and severity of comorbidities of the patients with coronary artery disease is increasing and it correlates with the increasing number of patients requiring revascularization for multivessel coronary lesions [1]. Historically, coronary artery bypass grafting was considered a first-line treatment in patients with multivessel coronary artery disease and/or with lesion on left main coronary artery [2], however, advances in PCI in last years have made this option an attractive alternative of surgical treatment, especially after the introduction of drug-eluting stents (DES). Meta-analysis of 4 randomized trials that compared treatment by using standard bare metal stents (BMS) with CABG in patients with multivessel coronary artery disease in five years of follow-up showed similar mortality rate and composite adverse events (death, myocardial infarction and stroke) in both groups (16.7% for PCI vs. 16.9% for CABG) and significantly higher frequency of need for another revascularization in the interventionally treated group (29% vs. 7.9%) [3]. A much larger meta-analysis, which included also trials with simple balloon angioplasty (number of enrolled patients was nearly 10,000) came to similar conclusion – both groups did not differ in mortality, patients with CABG had more frequent perioperative stroke and patients after PCI needed further revascularization (absolute difference in risk after 5 years 33%) [4]. Analysis of individual data from 10 randomized trials (including both trials with simple angioplasty and stent implantation, with a total of 7812 patients) also led to the same results, median of follow-up was 5.9 years, where the difference in total mortality was only 1% (15% CABG vs. 16% PCI) [5].

Development of drug eluting stents led to significant decrease in number of restenoses and subsequent need of revascularization after coronary intervention [6]. It implies that when PCI is chosen as a treatment, drug-eluting stents should be used. In case their use is not possible, some cardiologists use it as an argument for surgical revascularization. There is currently no randomized trial which compares specifically conventional stents with drug-eluting stents in patients with multivessel coronary disease. Comparable data exist from trials ARTS I [2] and ARTS II, which compared conventional bare metal stents and drug-eluting stents, respectively, with surgical treatment in patients with 2-3 affected coronary arteries. There was no difference in mortality between the group of patients treated with conventional and drug-eluting stents after 5 years and as expected, there was a significant decrease in revascularization need in patients with drug-eluting stents (20% vs. 9%) [7]. Observational data from a large New York registry of 17,400 patients with multivessel coronary artery disease show similar survival after CABG and PCI at 18 months, whether there was a double- or triple- vessel disease [8]. The only randomized data comparing drug-eluting stents to CABG in multivessel coronary artery disease come from the SYNTAX trial [9], where 1800 patients with three- vessel disease and/or left main coronary artery lesion were included. Combined incidence of adverse events (death, myocardial infarction, stroke and revascularization) after two years favoured CABG to PCI (14.4% vs. 23.8%, p < 0.001) but the difference was largely due to decreased number of subsequent revascularizations (7.5% vs. 17.4%, p < 0.001). However, the myocardial infarction rate was lower in patients after surgical procedure (2.8% vs. 6.1%, p < 0.009) as well as number of deaths due to cardiac events (2.3% vs. 4.5%, p = 0.05). On the other hand, the frequency of stroke was significantly higher in the group with CABG. The gap between these two groups grew larger with increasing complexity of coronary artery lesions, evaluated by a new scoring system – SYNTAX score. Patients in the lower percentile of Syntax score had similar outcomes in both groups; the superiority of surgical treatment to interventional treatment was evident with increasing value of the score. This trend persisted even after 3 years [10].

Historically, surgical myocardial revascularization was considered more effective for patients with diabetes [11] in terms of long-term mortality and this eventuality was also
suggested by the analysis of individual data in patients with diabetes from 10 trials performed by Hlatky et al. [5]. So far, the only randomized trial comparing specifically CABG to PCI with stent implantation in patients with diabetes and multivessel coronary artery lesions, including patients with conventional, as well as drug-eluting stents, was terminated prematurely for slow recruitment. There was no difference in 1 year mortality or composite adverse events (death, MI, stroke), however, patients in interventional group had again increased number of subsequent revascularizations (9.9 vs 2%, \( p < 0.001 \)) and the difference was significant even in patients with drug-eluting stents (7.3% vs. 2%, \( p = 0.013 \)) [12]. Recently, the group of diabetic patients in SYNTAX trial treated by interventional therapy using drug-eluting stents also showed higher incidence of subsequent revascularizations compared to CABG (20.3 vs. 6.4%, \( p < 0.001 \)) with similar mortality (that was higher in comparison to patients without diabetes in both revascularization strategies). The difference in mortality was obvious in subgroup with very complex artery lesions – high SYNTAX score value (13.5% vs. 4.1%, \( p = 0.04 \)) [13]. The final decision about relative merits of both approaches in diabetic patients awaits the results of further randomized trials. A group of patients with lesion on left main coronary artery was considered for surgical treatment until now; and it was also reflected in guidelines which classified PCI in patients capable of surgical revascularization to the level of evidence III [14]. However, many of these patients were treated by angioplasty during last years [15]. Recent analysis of available data which showed that PCI may be an alternative for surgical treatment for a significant proportion of patients with left main coronary artery lesion [16] led to reassessment of these guidelines and included PCI to the level of evidence II b for those with suitable anatomy [17]. A large MAIN – COMPARE registry, comparing CABG and PCI outcomes in patients with stem lesion (2240 patients), showed quite consistently similar risk profile of both methods in terms of mortality and reinfarction after 5 years as above, but with higher percentage of subsequent revascularization after PCI, while use of drug-eluting stents significantly decreased number of reinterventions [18]. The same conclusion was reached in a meta-analysis of 3773 patients from different trials treated with both procedures [19]. Patients with left main coronary artery lesion in the SYNTAX study represent the largest cohort of patients previously randomized between both types of treatment (357 PCI, 348 CABG). After 2 years there was no difference in overall adverse events (22.9% and 19.3%), mortality (5.6% vs. 6.2%), even in number of myocardial infarctions (5.5% vs. 4.1%). Patients with percutaneous intervention had decreased rate of strokes (0.9% vs. 3.7%, \( p = 0.01 \)) but gain more revascularizations (17.3 vs. 10.4%, \( p = 0.01 \)). The resulting stratification according to the gravity of coronary artery lesions (SYNTAX score) showed that in patients with lower scores (in first and second tercile, i.e. up to 32), PCI may be even safer and as effective as CABG [20], which would represent about 1/3 of all patients with lesion of left main coronary artery, eventually other coronary arteries.

Generally, it is possible to summarize that PCI and CABG in patients with multivessel coronary artery disease have similar prognosis in terms of mortality and reinterventions when comparable level of revascularization is reached. Coronary artery bypass grafting leads to better long-term relief of symptoms which is reflected in decreased number of subsequent revascularizations but at a price of higher incidence of stroke and perioperative mortality. Coronary artery bypass grafting may be a better alternative in terms of long-term prognosis for patients with diabetes and with complex multivessel coronary artery disease [4–6].

### 3. Left anterior descending artery (LAD) in myocardial revascularization

Prognostic significance of coronary artery bypass grafting is connected to the revascularisation of left main or proximal LAD lesions [21]. The left anterior descending artery is the most important coronary artery as it supplies approximately 60% of the myocardium of the left ventricle [22]. Successful revascularization of this artery is therefore a logical requirement for improving long term prognosis of patients [23,24]. Based on prior evidence, the optimal surgical revascularization method for this artery is a bypass using the left internal mammary artery – LIMA [25–27]. The LIMA graft has excellent long term patency (up to 98% at 1 year, 95% at 10 years and approximately 90% at 15 years or more) [28–33]. In the BARI trial, the superiority of CABG to PCI in patients with diabetes was found only in patients in whom LAD was revascularized with LIMA. Patients with venous LAD grafts had the same prognosis as patients treated with PCI [11]. Grafting LIMA on LAD has therefore become the standard form of surgical revascularization. Direct comparison of the efficacy of revascularization of isolated lesions of LAD between LIMA grafts and coronary angioplasty has been done in a number of smaller trials, most of which used standard bare metal stents. Metanalysis of these trials has shown similar incidence of death and reinfarction with a significantly higher number of follow up revascularizations after PCI [34–36], even in the long term perspective of 10 years [37]. Only two randomized trials have compared mini invasive LIMA–LAD grafts with implantation of drug eluting stents. In both trials, these two methods had similar results regarding occurrence of death, reinfarction, and follow up revascularization in the short term follow up of 6–12 months [38,39]. Long term randomized comparison is missing, but midterm follow up (median of 2 years) of comparable groups of patients, treated with both methods, has shown significantly higher recurrence of angina in patients who have undergone implantation of drug eluting stents [40,41]. Even with the progress that drug eluting stents represent, it would seem that LIMA remains to be the most effective method of LAD revascularization. The high long-term patency of the LIMA graft protects the key LAD region against clinical consequences of atherosclerosis progression on the native vessel [42] (even though grafting has been shown to accelerate the atherosclerotic process of the artery prior to the graft site [43]). On the other hand, coronary intervention using stents only treats a localized lesion in a relatively small part of the artery and has no long term protective effect on other segments of the artery.
4. Minimally invasive surgical revascularization of LAD

The invasive character of standard surgical approach to aortocoronary bypass is related mainly with the need of a sternotomy, extracorporeal blood circulation and manipulation with the heart and aorta during the procedure. The sternotomy is associated with prolonged rehabilitation and possible infectious complications at the sternotomy site [44]. Extracorporeal blood supply causes a strong systemic inflammatory response [45], which, together with coagulation activation and platelet destruction [46], promotes organ dysfunction and post-operative blood loss and therefore increased perioperative morbidity [47]. The manipulation with the heart and ascending aorta together with extracorporeal circulation are associated mainly with a risk of developing perioperative stroke and postoperative cognitive dysfunction [48]. The introduction of operative techniques without extracorporeal circulation (off-pump coronary artery bypass – OPCAB) has led to a significant decrease of perioperative morbidity with equal long term results in mortality and adverse events [49].

Limited lateral thoracotomy in the 4–5th intercostal space is an alternative surgical access that allows LAD revascularization with LIMA (but other arteries as well) without the need of a sternotomy. The retraction of ribs allows manual preparation of LIMA and performance of anastomosis under direct visual control. This technique is called minimally invasive direct coronary bypass – MIDCAB. Its expansion has been accelerated with the development of methods that stabilize the heart during OPCAB, and those that facilitate grafting of anastomosis on the beating heart. Data from many trials show that MIDCAB has a fully comparable long term patency of LIMA graft with the classical approach with a sternotomy, with low perioperative morbidity, mortality and very good mid- and long term results, comparable with OPCAB access [50,51]. It can be performed safely even after prior sternotomy [52] and in multivessel disease [53]. It allows revascularization of LAD in patients with high risk of sternotomy or other postoperative complications, as long as the patient is able to tolerate ventilation with one lung. The disadvantage can be a worse control of postoperative pain due to extensive retraction of the ribs [54].

In an effort to avoid the necessary wide retraction of ribs during the procedure, an alternative method with the mobilization of LIMA thoracoscopically, allowing to limit the width of the thoracotomy, was developed. This technique does not require a wide retraction of ribs, which is a must for the LIMA preparation. This technique has been called endoscopic atraumatic coronary bypass – EndoACAB. Perioperative and long term results in the largest population of patients operated this way (607) were excellent, with the graft patency at five years being 98.5% and 95% of the patients without cardiovascular event at five years [55]. This method requires insufflation of left hemithorax with possible negative effects on hemodynamic state and oxygenation of the patient. Its usage is therefore limited in patients with pulmonary obstruction or hypertension and in patients with severe left ventricular dysfunction or active ischemia. It also cannot be used in patients with prior thoracic operations and in patients with pleural adhesions [56]. The necessity of managing advanced endoscopic techniques and a related long learning curve is probably the reason that has prevented the widespread use of this technique.

The development of robotics in recent years has allowed endoscopic collection of LIMA with the aid of robotic systems. The end-anastomosis on LAD can be performed manually using a limited thoracotomy without rib retraction. The technique is called robotically enhanced minimally invasive direct coronary bypass – RECAB. Trials published to date show a high primary success rate with the patency of the graft being 95–100%. There is low perioperative morbidity and a high rate of patient satisfaction [57–60]. Finally, robotic techniques allow the entire operation to be performed endoscopically – without a sternotomy. This technique is called totally endoscopic coronary bypass – TECAB. Initially, the procedure was performed on a non- beating heart with extracorporeal circulation [61,62]. This fact greatly decreased the attractiveness of this procedure. Performance of this procedure on a beating heart is technically challenging and only a small number of centers have been able to perform it to date. The only larger multicentre trial with this technique included 111 patients. No significant differences have been found in the efficacy when comparing this procedure to on- and off- pump surgery. The need of conversion to classical bypass with a sternotomy or to lateral thoracotomy was not insignificant (28%). The success of revascularization defined as a finding of a patent bypass during angiography or the absence of ischemia on an electrocardiogram during exercise testing was 97%. No attempt to compare this method with other mini invasive techniques or classical bypass has been made [63]. In smaller trials, the patency of LIMA has been shown to be between 92 and 96% [64,65]. In expert hands, even a multivessel revascularization with arterial grafts in combination with PCI is possible [66]. This method, however, still awaits its place in the wide range of revascularisation procedures [67].

5. Surgical revascularization outside the LAD territory – comparison with PCI

Even with an increasing use of arterial grafts for complete revascularization, the majority of surgical procedures still include the use of one or more venous grafts [68]. When compared to the revascularization with LIMA, the long- term patency of venous grafts is substantially worse. After one year, the incidence of bypass closure is given in the range of 12–30% [69,70]. In a large trial with more than 3000 patients, 26% of all venous grafts were occluded in 12 months and at least one bypass was occluded or non-functional in 42% of patients [71]. This trial represents data similar to real life. In the five year follow-up further degradation of venous grafts occurs, and only 60% of the grafts remain patent. After 10 years, only about half of the grafts are patent [72]. The use of other arterial grafts has contradictory results. In some trials, long term patency of radial artery grafts was similar to the patency of venous grafts [73,74]. Other trials have shown superioriity of radial artery grafts [75]. A recent metaanalysis
of randomized trials did not show a significant benefit of radial artery grafts compared to venous grafts [76]. On the other side, long term patency of right mammary artery grafts lies somewhere in the middle of venous grafts and LIMA [9,72]. This is probably the reason for the improvement of long term prognosis of patients in whom both mammary arteries are used when compared with classical revascularization with LIMA and venous grafts [77-79]. However, revascularization using RIMA is not widely used for concerns with higher incidence of infectious complications at the sternotomy site [80,81], even though the use of skeletonization probably reduces this risk [82]. Considering the above, revascularization of arteries other than LAD with drug eluting stents is an acceptable alternative to venous or other types of arterial grafts, even with the anticipated clinically significant restenosis of approximately 10% [6].

6. Hybrid myocardial revascularization in patients with multivessel coronary artery disease

Hybrid revascularization is defined as planned combination of surgical revascularization of LAD with percutaneous coronary intervention on other coronary arteries. The aim is to achieve complete or functionally adequate myocardial revascularization. The rationality for hybrid revascularization procedures is based on three premises, as written in the above analysis.

a. The LIMA–LAD graft is probably the best revascularization method for this artery considering the long term patency and the resulting influence on the prognosis of the patient.
b. Percutaneous coronary intervention with stent implantation on other arteries has comparable results with surgical revascularization with venous or other arterial grafts. It alone does not lead to impaired prognosis when compared with surgical treatment.
c. Minimally invasive surgical techniques allow for LIMA grafting to LAD with a limited operational trauma and with exclusion of extracorporeal circulation.

Combined minimally invasive surgery and PCI on LAD is the reasonable outcome of the development in both fields because it offers the best of each of the so far separated disciplines and the smallest possible burden for the patient. The basic requirement to this procedure is, naturally, the technical feasibility of PCI on coronary arteries other than LAD, with the possibility of achieving a functionally satisfactory revascularization.

6.1. Indications for hybrid myocardial revascularization

HMR might be considered in patients with multiple coronary artery disease including the proximal LAD who are indicated for surgery, and standard surgery is for some reason considered risky [83,84]. This concerns the higher risk of sternotomy as well as the risks arising from the overall patient’s condition. Previous sternotomy (reoperation), history of sternal infection, previous mediastinitis, tumors affecting the sternum (i.e. myeloma), previous thorax radiation treatment, corticosteroid therapy, severe obesity with diabetes or important mobility impairment restricting the subsequent rehabilitation (crutches, wheelchair) are all conditions increasing the complications rates for sternotomy.

The overall risk factors include advanced age, marked frailty, multiple comorbidities, important cerebrovascular impairment with the history of cerebral stroke or paraplegia, serious carotid arteries disease and pulmonary illness- if it enables single-lung ventilation. Specific cardiac risk factors comprise poor left ventricular function, recent myocardial infarction and difficulty to perform surgery on coronary arteries other than LAD, for example proximal stenosis eligible for PCI and quality of distal arteries unsuitable for a reliable bypass Anastomosis or absence of suitable conduits, respectively (i.e. unavailability of venous grafts). This concerns equally the patients who had the emergent PCI performed on coronary arteries other than LAD due to acute coronary syndrome and have LAD stenosis that is not optimally suitable for further intervention, for example chronic occlusion or complex lesions. Further risk factors include vast calcifications of the aorta or mitral annulus that increase the risk of perioperative cerebral stroke while being manipulated. The preference of a patient demanding the less invasive procedure even after being informed about the bypass surgery as a standard procedure in the particular case, should be also taken into consideration [60].

6.2. Contraindications for hybrid myocardial revascularization

Elective hybrid revascularization is contraindicated in hemodynamically unstable patients including acute myocardial infarction and cardiogenic shock, in patients with severe decompensated ischemic cardiomyopathy and in patients with serious lung disease that enables ventilation of one lung or with severe right ventricular dysfunction. Conditions impeding the reliable performance of LIMA to LAD anastomosis are history of pericarditis, previous left thoracotomy or left pleural area surgery, extensive pleural adhesions in left pleural space, use of, or damage to LAD in previous cardiac surgery, unsatisfactory quality of LAD and important stenosis or occlusion of left subclavian artery when not treated beforehand. It is obvious that it is not suitable to consider combined therapy in case that PCI on coronary arteries other than LAD is not technically feasible or highly risky. Renal dysfunction with the risk of contrast induced nephropathy and intolerance of prolonged Clopidogrel treatment may also play an important role in the decision-making process.

The decision whether to perform the revascularization in classical surgical way, hybrid revascularization or PCI only, is always multifactorial, strictly individualized and it should be carried out in close cooperation between surgeons and cardiologists [85].

6.3. Strategy for hybrid myocardial revascularization

Regarding the timing of the particular procedure, three basic strategies are possible: 1. PCI first, followed by bypass surgery, 2. bypass surgery followed by PCI or 3. both performed simultaneously throughout one integrated procedure. In case
of separate procedures, they may be executed hours to weeks apart. Each of these techniques has advantages and disadvantages which must be taken into consideration when planning the treatment tactics. PCI before the surgery allows the complete surgical revascularization in case of unsuccessful intervention. This is a primary method in acute coronary syndromes except to those caused by LAD. In some cases it allows improvement of collateral flow for LAD and thus decreases the risk of vast ischemia during subsequent surgery to this artery. In contrast, delayed mammary bypass performance does not allow for checking its patency immediately after surgery. However, the main disadvantage is the conflict of using the dual antiplatelet therapy including Clopidogrel after the PCI and the need of satisfactory hystasis after surgery. It follows that the risk of postoperative bleeding and blood losses is increased [86–88]. Nevertheless, most of the evidence regarding increased postoperative bleeding after clopidogrel, stems from the trials using classical surgical techniques without use of minimally invasive surgery. Moderate-sized trials with periprocedural clopidogrel treatment comparing the hybrid access to classical surgery showed low bleeding complications rate and blood losses in hybrid group [89–91]. In a group of 17 patients taking Clopidogrel before surgery, there was only 1 important bleeding event [82]. Direct comparison of bleeding complications between groups with PCI before versus after surgery is not available.

Another potential problem may be the termination of heparin effect after surgery that could lead to possible stent thrombosis. However, there are no records of acute stent thrombosis immediately after surgery in current patients’ files. One of the effective and at the same time milder anticoagulation possibilities during PCI as well as surgery is use of Bivalirudin instead of Heparin. There were 3 bleeding events requiring surgical revision in a group of 58 such patients [60].

The largest group, where PCI is performed before surgery, is represented by patients with acute coronary syndrome caused by arteries other than LAD, which has to be treated urgently. Also in case of important complex lesions outside LAD, where risk of unsuccessful intervention is higher (type C lesions, chronic occlusions), it is probably better to keep the possibility of complete surgical revascularization as a backup plan. This method must be considered when complications arising from possible occlusion of other artery during LAD revascularization are imminent – for instance impending occlusion of a large vessel in the presence of critical stenosis by possible blood pressure drop [92].

In relation to the concerns about bleeding complications mentioned above, bypass to LAD before PCI is preferred at most workplaces. It offers the advantage of intervention in protected setting of revascularized LAD, which is particularly important when severe disease of left main coronary artery is present. It can be then safely intervened with the aim of immediate correction of a possible patency problem. On the contrary, presence of surgical team allows aggressive coronary intervention, as in case of its failure immediate surgical resolution is possible. The advantage of an intervention in safe conditions of total anesthesia with complete patient monitoring is also not negligible. Yet, simultaneous procedure with the necessity of subsequent dual antiplatelet therapy opens again the question of possible bleeding complications. Regarding the fact that clopidogrel is administered after the surgery, this risk is likely lower [89,97]. One of the disadvantages is also the necessity of an adequate equipment of the operation theater with high-quality angiographic system - so called hybrid rooms are currently by far not a standard for cardiac surgery suites. Simultaneous hybrid revascularization requires impeccable cooperation and coordination of two different teams - surgical and the cardiologic one. This often accounts for a logistical problem, disregarding the mental barriers that may as well impede the implementation of such methods [98]. The development of hybrid procedures in areas differing from ischemic heart disease therapy indicates that the appropriate personnel and instrumental conditions for simultaneous surgical and interventional procedures will be increasingly accessible [99].

6.4. Outcomes of hybrid myocardial revascularization

In spite of the theoretical attractiveness of hybrid revascularization concept, the quantity of workplaces dedicated to this issue remains quite small and published data are scarce. First data about hybrid revascularization performed on 6 patients were published by Angelini et al. in 1996 [100]. The majority of studies that followed were monocentric observational studies comprising limited number of patients. In addition, they are considerably heterogenous with respect to selection criteria, hybrid procedure strategy, surgical technique, mode of intervention, outcomes assessment and follow-up length [60,65,82,83,88–90,92,95,101–114]. The most important studies, evaluating the postsurgical outcomes, mammary graft patency and medium-term follow-up, are summarized in Table 1. From presented data it is possible to say that HMR is safe. Perioperative mortality ranged between 0 to 2%, average mortality of all studies is 0, 3%. Medium-term graft patency to LAD is high—92 to 100% and fully comparable to the data from standard methods [50,51]. Target arteries revascularization (including LAD) is 10% on average, with bare-metal stents or simple balloon-angioplasty used in most studies. Medium term survival without adverse events is 90% on average. These results could be compared, for instance, to the surgical branch of SYNTAX study, where patients with multiple coronary artery disease were revascularized mostly...
Table 1 – Summary of hybrid revascularization trials outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>N</th>
<th>Type of procedure</th>
<th>PCI</th>
<th>Hybrid revascularization strategy</th>
<th>Follow-up</th>
<th>30 days mortality (%)</th>
<th>LIMA patency (%)</th>
<th>TVR (%)</th>
<th>Adverse event-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zenati[103]</td>
<td>1999</td>
<td>31</td>
<td>MIDCAB</td>
<td>BMS-66%</td>
<td>PCI followed by MIDCAB 7%; same day-52%; MIDCAB followed by PCI-41%</td>
<td>11 M</td>
<td>0</td>
<td>100</td>
<td>9.6</td>
<td>90</td>
</tr>
<tr>
<td>Lloyd[102]</td>
<td>1999</td>
<td>18</td>
<td>MIDCAB</td>
<td>PTCA-34%</td>
<td>MIDCAB, PCI thereafter-77%; simultaneous-23%</td>
<td>6 M</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>89</td>
</tr>
<tr>
<td>Wittwer[104]</td>
<td>2000</td>
<td>35</td>
<td>MIDCAB</td>
<td>BMS-52%</td>
<td>MIDCAB followed by PCI</td>
<td>11.5 D</td>
<td>0</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Presbitero[106]</td>
<td></td>
<td></td>
<td>MIDCAB</td>
<td>PTCA-70%</td>
<td>MIDCAB followed by PCI</td>
<td>18 M</td>
<td>2</td>
<td>92</td>
<td>14</td>
<td>83</td>
</tr>
<tr>
<td>deCanniere[88]</td>
<td>2001</td>
<td>20</td>
<td>MIDCAB</td>
<td>BMS-30%</td>
<td>MIDCAB followed by PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lloyd[102]</td>
<td>2001</td>
<td>18</td>
<td>MIDCAB</td>
<td>PTCA-70%</td>
<td>PCI, MIDCAB thereafter 45%; MIDCAB, PCI thereafter 55%</td>
<td>24 M</td>
<td>0</td>
<td>100</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Wittwer[104]</td>
<td>2002</td>
<td>35</td>
<td>MIDCAB</td>
<td>BMS-58%</td>
<td>MIDCAB followed by PCI</td>
<td>24 M</td>
<td>0</td>
<td>97</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>Presbitero[106]</td>
<td></td>
<td></td>
<td>MIDCAB</td>
<td>PTCA-58%</td>
<td>MIDCAB followed by PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stahl[106]</td>
<td>2002</td>
<td>54</td>
<td>RECAB</td>
<td>BMS-48%</td>
<td>RECAB, PCI thereafter - 65%; PCI RECAB thereafter - 35%</td>
<td>11.7 M</td>
<td>0</td>
<td>100</td>
<td>NA</td>
<td>87</td>
</tr>
<tr>
<td>Ciwowski[107]</td>
<td>2002</td>
<td>50</td>
<td>Endo ACAB</td>
<td>PTCA - 22%</td>
<td>EndoACAB followed by PCI</td>
<td>6-24 M</td>
<td>0</td>
<td>100</td>
<td>13</td>
<td>88</td>
</tr>
<tr>
<td>Davidavicius[111]</td>
<td>2005</td>
<td>20</td>
<td>RECAB</td>
<td>BMS-95%</td>
<td>PCI, RECAB thereafter-70%; PCI followed by PCI</td>
<td>19 M</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Katz[65]</td>
<td>2006</td>
<td>27</td>
<td>TECAB</td>
<td>BMS-37%</td>
<td>PCI followed by TECAB-41%; TECAB followed by PCI</td>
<td>9 M</td>
<td>0</td>
<td>100</td>
<td>29.6</td>
<td>70</td>
</tr>
<tr>
<td>Us[82]</td>
<td>2006</td>
<td>17</td>
<td>MIDCAB</td>
<td>BMS</td>
<td>Simultaneous</td>
<td>21 M</td>
<td>0</td>
<td>100</td>
<td>18</td>
<td>87</td>
</tr>
<tr>
<td>Gilard[109]</td>
<td>2007</td>
<td>70</td>
<td>Conv. CABG</td>
<td>BMS</td>
<td>CABG followed by PCI</td>
<td>33 M</td>
<td>1.4</td>
<td>100</td>
<td>2.3</td>
<td>97</td>
</tr>
<tr>
<td>Kon[90]</td>
<td>2008</td>
<td>15</td>
<td>MIDCAB</td>
<td>DES</td>
<td>Simultaneous</td>
<td>12 M</td>
<td>0</td>
<td>100</td>
<td>6.7</td>
<td>93</td>
</tr>
<tr>
<td>Kiai[60]</td>
<td>2008</td>
<td>58</td>
<td>RECAB</td>
<td>DES</td>
<td>Simultaneous</td>
<td>20 M</td>
<td>0</td>
<td>100</td>
<td>10.3</td>
<td>NA</td>
</tr>
<tr>
<td>Holzhey[83]</td>
<td>2008</td>
<td>117</td>
<td>MIDCAB, TECAB</td>
<td>BMS, DES</td>
<td>MIDCAB, PCI thereafter - 48%; PCI, MIDCAB thereafter-48%; simultaneous-4%</td>
<td>12 M/5 Y</td>
<td>1.9</td>
<td>NA</td>
<td>NA</td>
<td>92.5 75.5</td>
</tr>
<tr>
<td>Gao[114]</td>
<td>2009</td>
<td>10</td>
<td>RECAB, TECAB</td>
<td>BMS-67%</td>
<td>RECAB followed by PCI</td>
<td>5 M</td>
<td>0</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vassilaidas[92]</td>
<td>2009</td>
<td>95</td>
<td>Endo ACAB</td>
<td>DES</td>
<td>PCI followed by EndoACAB-6.6%; EndoACAB followed by PCI</td>
<td>12 M</td>
<td>0</td>
<td>98</td>
<td>5.8</td>
<td>90</td>
</tr>
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</table>

with arterial grafts and where the overall mortality after 12 months was 3.5%, necessity for subsequent revascularization 5.9% and adverse events—free survival 87.6% [9]. Nonetheless, this kind of comparison of heterogeneous patient cohorts can be misleading. Only 3 out of all studies compared minimally invasive hybrid revascularization outcomes to classical surgical revascularization in comparable patient's cohorts, the remaining studies were observational. De Canniere retrospectively compared 2 groups of patients with 2-vessel disease (20 patients in each), who underwent hybrid revascularization (MIDCAB with subsequent balloon angioplasty or standard stent implantation) or classical on-pump bypass. Postoperative complications rate was significantly lower in hybrid group (15% vs. 65%) with lower need of blood transfusions (0% vs. 20%). Intensive care unit stay, global hospitalization average length and return to work time were shorter. Three patients from hybrid group had recurrence of angina after 6 months with subsequent PCI for restenosis or new lesion, none of the classically operated patients required intervention, all patients were asymptomatic after 2 years [88]. Kon compared 15 patients with hybrid revascularization (MIDCAB+simultaneous DES implantation) with a group of 30 similar patients treated with OPCAB. Hybrid group patients had fewer postoperative complications (0% vs. 23%, \( P = 0.05 \)), mainly due to lower occurrence of perioperative infarction.

Myocardial ischemia, inflammatory reaction and coagulation activation indicators were lower in hybrid group. These patients required significantly fewer transfusions, had substantially shorter intubation length, ICU stay and overall hospitalization length. These differences were reflected in lower hospitalization costs. The return to work time (\( p = 0.002 \)) and time to postoperative wound pain disappearance (\( p = 0.004 \)) was significantly shorter in hybrid group. After one year, adverse events were recorded in 7% of patients from hybrid group (1 re-intervention for angina pectoris) and 23% in OPCAB group. CT angiography performed after 1 year proved 85% bypass graft patency, while in hybrid group only one stent failed (7%). The overall patient satisfaction with the procedure was significantly higher in the hybrid group [90]. Vassiliades et al. retrospectively compared group of 91 hybridly treated patients (EndoACAB+subsequent DES implantation 93%, 7% in reverse order) with cohort of 4175 patients with OPCAB, who were operated at the same institution at the same time interval. Thirty days mortality in both groups was 0% and 1.8%, myocardial infarction incidence 1.1% and 0.5%, target vessels revascularization 0% and 0.3% and overall cardiovascular adverse events 1.1% a 3%—there was no significant difference in early postoperative indicators. Twelve month mortality rate for hybrid group was 1.1% and myocardial infarction occurred in 3.3%. Five patients in total (5.8%) required reintervention due to restenosis (4 patients) or mammary graft restenosis (1 patient). Overall adverse events rate was 10% and did not significantly differ from OPCAB group [92]. Study shows that hybrid revascularization is at least equally safe as standard OPCAB and in case of DES use; the rate of subsequent revascularizations is low. Nevertheless, these outcomes must be interpreted with caution—it was a non-randomized study and hybrid group patients were certainly selected, contrary to the OPCAB group. Moreover, the number of patients in hybrid group is too small for valid statistical comparison [115]. It is worth to mention as well the data from Zhao et al., who performed routine angiography during standard surgery (i.e. with sternotomy and on-pump in part of patients) in 366 patients. In 112 of them, PCI with stent implantation was performed—either electively (in 67 patients, i.e. 60%, mostly with the aim of lowering the operation risk or revascularization of arteries that would be problematic for bypass anastomosis) or unplanned - due to graft patency problem during perioperative angiography or unfeasible anastomosis to target vessel (45 patients, i.e. 40%). Patients with hybrid revascularization were compared to those with bypass only (254 patients). The mortality rates in both groups were similar (2.6% vs. 4.15%). The blood losses and reoperation rates due to bleeding were even (3%), although 19% of patients in hybrid group took clopidogrel before and 31% after the surgery. One patient in hybrid group died due to acute stent thrombosis after use of Heparin antagonist Protamine (0.9%). Patients in hybrid group had higher levels of cardiac-specific enzymes as a marker of perioperative damage to myocardium [116]. Although the work gives more evidence to the usefulness of perioperative angiography than to the value of hybrid revascularization, it shows that concerns regarding the postoperative bleeding, caused by dual antiplatelet therapy, need not to be great.

All remaining studies dealing with hybrid revascularization are just observational. The largest one comprises a total of 117 patients. MIDCAB was performed in 110 of them and TECAB in 10 patients. PCI before the surgery was carried out in 48%, in 48% afterwards and in 4% simultaneously. Classic to drug eluting stent ratio was not mentioned. The predicted operative mortality was 4.3% (by EuroScore). Two patients died (1.9%), only one of them due to cardiac event. One patient was reoperated due to acute stent thrombosis (0.9%) and 6 patients were surgically revised due to bleeding (5.7%). Postoperative ventilation length was very short – 3 and 5d h on average, as well as the ICU stay length (7 and 9h). One year survival was 92.5%, 5-year survival 84.8%, 1-year and 5-year survival with no cardiac adverse events 85.5% and 75.5% respectively. Twenty three patients underwent angiography due to angina pectoris recurrence (4.3%). Authors conclude that hybrid method is safe and the long-term outcomes are good [83].

The largest study of hybrid revascularization with robotic-assisted LIMA harvest (RECA) was published by Kiaii et al. [60]. Percutaneous intervention was performed in hybrid theater immediately after bypass anastomosis in 58 patients out of 60 indicated (97%), conversion to sternotomy with full surgical revascularization was performed in 2 patients due to arrhythmias during bypass stitching. In both procedures, Bivalirudin was used for anticoagulation. Clopidogrel was administered after the PCI completion. Most of the 65 stents used were drug eluting ones (82%). Angiography immediately after surgery proved LIMA patency in 93% of grafts. Postoperative revision for bleeding was necessary in 3 patients (5%), none of the patients died. ICU stay length was shorter than 12 h in 95% of patients. The average follow-up time was 20 months, none of the patients had angina. LIMA patency rate was 91% at coronary angiography in total of 54 patients. In 2 patients there was unsatisfactory bypass patency and
intervention was performed – once on bypass anastomosis and once on native artery, despite the fact both patients were asymptomatic. There was restenosis in 9 stents (15%, 7 cases), stent occlusion in 2 patients. Reintervention was performed in 2 patients only (3.4%). Similar outcomes were achieved by RECAB in trial on 54 patients by Stahl et al., in which 35% of patients underwent PCI before and the rest after the surgery. Perioperative mortality was insignificant, 69% of patients were extubated in operating theater and the average ICU stay length was 24 h. Blood transfusion was required in 29.6% of cases. Coronary re-angiography was performed in 18.5% patients during follow-up (average 11 months). The mammary graft was patent in all cases; two patients had in-stent restenosis and one patient had stent occlusion (5.2% out of total number of implanted stents). Reintervention was performed in one patient. Overall event-free survival was 87% and 97% of patients had no angina pectoris [106]. Davidavicius et al. published an interesting concept of rationalization for hybrid revascularizations [111]. In 20 patients, who were potentially eligible for hybrid revascularization (RECAB), functional evaluation of stenosis on arteries excluding LAD was performed using the fractional flow reserve – FFR. In 14 patients it was performed before robotic-assisted procedure, in 6 of them thereafter. PCI was performed only in case of hemodynamically significant stenosis (FFR value lower than 0.80) – in 14 patients, all of whom had a standard stent implanted (95%). The intervention was postponed in 6 patients who did not have a hemodynamically significant stenosis. The robotic-assisted bypass to LAD was complication-free, all arterial grafts were patent at postoperative angiography. At medium-term check-up after 19 months on average, none of the patients had cardiovascular adverse event and their stress test was negative. Only one patient underwent coronary re-angiography due to chest pain with angiographically and functionally non-significant in-stent restenosis (FFR higher than 0.80). FFR measurement enables restriction of PCI use only to lesions causing ischemia and thus lowering the risk of the procedure itself as well as the risk of significant restenosis. Postponing the intervention for lesions that are not hemodynamically significant is equally safe or possibly safer than the intervention [117,118].

The experience with totally endoscopic robotic-assisted coronary revascularization (TECAB) associated with PCI is limited. Katz et al. published a set of 27 patients where 41% had PCI before and 44% after robotic surgery, DES were used in 63% of cases. Only 1 patient had symptoms of myocardial infarction in perioperative period, no other important event occured. All patients underwent coronary angiography 3 months later, 1 patient had graft stenosis in the anastomosis (3.7%), which was treated by angioplasty. Seven patients in total had PCI for in-stent restenosis during further follow-up period (4 patients) or new lesion on previously intervened artery (3 patients), therefore the total number of subsequent revascularizations was unusually high (29%). Five of these lesions were detected by coronary angiography as early as 3 months after revascularization [65].

Results of these observational and comparative studies show that minimally invasive hybrid revascularization procedures in patients with multivessel coronary artery disease carry minimal perioperative mortality risk, low morbidity and do not increase the risk of postoperative bleeding. The medium-term cardiovascular adverse events rate including the necessity of further revascularization is acceptable. The advantage they offer in comparison to classical surgical revascularization is indeed faster rehabilitation and patient's return to normal life. Nevertheless, available studies do not allow any definite conclusions neither about the overall effectivity on hard clinical endpoints (mortality, myocardial infarction) when compared to standard surgery methods, nor about the long-term effects. Patient cohorts were highly selected and they represent just a small proportion of surgical interventions even at sites dealing intensely with minimally invasive and hybrid procedures. The share of hybrid procedures on total number of revascularization interventions in the work of Vassiliades et al. was only 2.1% [92]. HRM share on all minimally invasive revascularization procedures at a different institution was 6.4% [83]. Selection pointed towards the patients who had relatively benign coronary lesions designated for PCI. This reflected the fact that in majority of hybrid procedures the percutaneous intervention was performed on only one additional coronary artery. The question is whether the outcomes would be the same if patient selection was less rigorous, i.e. if the selection comprised also patients with multiple lesions outside LAD territory, as we observe in real-life patients indicated for classical surgery. Would it be possible to improve the outcomes of the interventional branch of SYNTAX trial, where coronary disease was complex and required on average implantation of 4, 6 stents [9]? Similarly, could the outcomes of patients, considered to be treatable only by surgery who were included into the surgical register of this trial, be improve this way? Could the outcomes of specific subgroups improve – for example in patients with left main coronary artery disease? On the other hand, for many cardiologists today the only limitation to adequate interventional revascularization is chronic LAD occlusion which is impossible to cross. In many patients indicated for hybrid revascularization, LAD or left main coronary artery were patent, therefore the intervention with modern instruments was not entirely unfeasible. Up to date, there is no comparison of hybrid revascularization to percutaneous intervention available in such patients.

The only way to assess the real clinical value of hybrid revascularization in comparison to classical surgery (or percutaneous interventional treatment) is to provide an adequately large randomized trial which would monitor the classical hard endpoints such as perioperative and postoperative mortality indicators and overall patient quality of life through short-term and long-term follow-up. These trial should include low-risk patients so that the hybrid procedures could be introduced into the common clinical practice. An equally based trial should be performed, comparing the hybrid revascularization to PCI to answer the question whether it is clinically beneficial to expand the hybrid procedure indications to patients with less severe LAD disease. Logistic and organizational obstacles to such trials are immense, though, starting with surgical technique selection (MIDCAB, EndoACAB, RECAB, TECAB?), continuing with the right procedure-timing (prior to, after-, simultaneously, when and in whom?), ending up with high financial requirements, considering the necessity of randomizing thousands of
patients in many centers. The greatest obstacle to larger spreading of hybrid revascularization methods and organization of necessary trials is probably the need of a narrow cooperation between so far separated specialties represented by cardiac surgeons and cardiologists, who would have to discuss the particular patient together and assess the optimal revascularization scenario for the particular coronary anatomy, clinical situation and socioeconomic status, such as it was carried out in SYNTAX trial mentioned above [119]. Meanwhile, the use of hybrid revascularization procedures will probably be limited to highly selected patients who for any reason cannot (or do not wish to) undergo one of the established revascularization methods.

Conclusion

Modern medicine offers many options of treatment to patients with ischemic heart disease and multiple coronary lesions. The treatment possibilities include conventional aortocoronary bypass using the extracorporeal circulation, OPCAB on the beating heart, multiple PCI with standard or drug eluting stents or hybrid revascularization procedures comprising minimally invasive surgical techniques combined with percutaneous intervention.

The population ageing and growing number of polymorbid patients requiring revascularization determines increasing need of individualized approach and necessity of tailoring the treatment to each of them, aiming to reach the optimal ratio of clinical efficacy and safety of the particular procedure. Hybrid revascularization using minimally invasive surgical techniques combined with PCI offer to a part of patients an advantage of optimal revascularization of the most important artery of the heart, together with adequate myocardial revascularization in a relatively delicate way. Indeed, to patients with high operative risk of standard surgery, it offers an alternative which should be considered carefully. The results of published hybrid revascularization trials show low perioperative mortality, morbidity and quick rehabilitation as well as very acceptable medium-term outcomes. Nevertheless, present studies are mostly retrospective and observational, carried out on quite small number of patients and therefore do not allow a clear short or medium-term comparison of hybrid to standard techniques. Long-term outcomes are not available at all. Larger HRM penetration into clinical practice is limited by technical demands of certain techniques requiring specialized equipment as well as by inertia of established decision-making schemes, lack of cooperation and sometimes even competition between specialists of two so far separated domains.

Questions concerning the clinical merit of particular methods and use of hybrid revascularization techniques in treatment of patients with multiple coronary artery lesions can be answered only by randomized and adequately large prospective clinical studies. Meanwhile, the decision for hybrid revascularization in a particular patient will be based more on experience and possibilities of specific site than on evidence-based medicine. Now it is time to answer the challenge of providing such evidence.

References


