Editorial

Female gender and left ventricular dysfunction in myocardial surgical revascularization: the strange couple

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Congestive heart failure (CHF) a chronic progressive condition, needing lifelong management, associated with poor outcome and shortened survival, is the first cause of hospitalization in the elderly (1-3). Although data from Framingham Heart Study have historically identified arterial hypertension as the primary cause of heart failure (1,2,4), more recent studies suggest that in the developed country, coronary artery disease (CAD) and its complications have become the most common cause of progressive development of severe left ventricular dysfunction with reduced ejection fraction (EF) (1,3,5,6).

Left ventricle function can be reduced suddenly because of acute coronary artery occlusion or slowly due to left and/or right ventricular function deterioration because of decline in muscle contractile proprieties, loss of cardiac myocyte or progressive ventricular remodeling resulting from a complex array of hypertrophy, cell death and myocardial fibrosis.

In recent times, the increased incidence of heart failure in patients with CAD is due as well to increasingly frequent use of thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) with stenting which delay the surgical treatment until CAD progresses to became more severe making surgical revascularization a higher risk operation with an increasing morbidity and mortality rates (5,7).

As reported in large series and registries the incidence of severe left ventricular dysfunction undergoing surgical myocardial revascularization ranged from 3.4% to 15%. This wide swing is due to the wide variations of the definition of left ventricular dysfunction. Some studies choose as suggestive of poor ventricular function an EF of less 30% while other reports use higher values. Both EuroSCORE, and modified Parsonnet score, most used risk stratification systems, define poor left ventricular function as an EF of less than 30% (3).

Despite improvements in medical treatment and surgical technique, the management of patients with CAD associated with low ventricular function is still challenging. Current treatment options for these patients include intensive medical treatment and/or surgical revascularization, at times paired with surgical ventricular reconstruction for ventricular remodeling, surgery for mitral valve regurgitation and last change heart transplantation (8-10).

The goals of treatment in these patients are to improve their clinical outcome, functional capacity and quality of life, reducing hospital re-admission and mortality. The cornerstone of treatment remains guideline-directed medical therapy (GDMT) (11,12). In the last few years various drugs have been used to treat ischemic heart failure and an increasing number of studies have been published to test new drugs in attempt to improve early and late outcome in these patients. Actually first choice for best medical treatment of heart failure remains the association of angiotensin-converting enzyme (ACE) inhibitors or alternatively angiotensin receptor blockers (ARB) with beta blockers and mineralocorticoid receptor antagonist (MRA). In selected symptomatic patients diuretics can reduce the signs and symptoms of congestion (12). Despite medical

therapy showed beneficial effects on shorter-term associated with a significant improvement of Quality of Life, even with new drugs it has not shown to have a significant influence on long-term outcome of patients affected by CAD with low EF (8).

Preferred choice of treatment for these patients remains still surgical revascularization. The coronary artery surgery study (CASS) and afterwards other authors demonstrated that patients with a low EF less than 30% or 35% treated with optimal medical therapy had a lower 5-year survival rate, ranged from 38% to 43%, compared with 63% to 82% 5-year survival of the surgically treated patients (8-10,13). Furthermore, other authors showed that after CABG treatment there was as well a significant improvement in clinical outcome with a significant decrease in anginal symptoms (10,13).

Although, better results in survival and quality of life are obtained with surgical treatment compared with medical therapy, clinical outcomes after surgery of these patients have been shown to be considerably worse than patients with normal EF (3). As reported in literature, patients with very severe left ventricular dysfunction undergoing surgical myocardial revascularization showed higher operative mortality and reduced long-term survival than patients with normal or mildly reduced EF (5,7,8,13). Over the last decades, morbidity and mortality of surgical treatment for patients with low EF has progressively decreased thanks to increasing improvements in myocardial protection, perioperative and postoperative anesthesia management, pharmacologic and mechanical circulatory support. Mortality during the late 1980s was as high as 20%, decreased in the 1990, ranging from 5% to 15%, reached a rate of less than 5% in patients operated on after 2000 (3).

Patients undergoing myocardial revascularization with reduced left ventricular function constitute a distinctive group of patients. Many studies justified the worst results in low-EF patients with the higher incidence of preoperative comorbidities, even if low EF has been shown to be an independent predictor of higher perioperative mortality (8).

The early operative mortality of patients with low-EF (20–30%) has been found to be more than 4 times higher than patients with higher EF ranging from 4.6% to 9% for patients with an EF of little more of 20% and of about 4% in patients with EF of 30% (8,14).

Many studies compared postoperative morbidity and mortality between patients undergone coronary artery revascularization with low EF and those with normal left ventricular function. Unfortunately most of these reports have been limited by inadequate sample size. Topkara and co-works in their interesting report used the data obtained by the New York State cardiac surgery database, a mandatory registry of the state of New York for all adult patients who underwent cardiac surgery (more than 15,000 patients) from 1997 to 1999. They found that increased age, female gender, presence of CHF, hepatic or renal failure, emergent procedure and latest myocardial infarction were significant predictors of in-hospital mortality in patients with low EF. Regrettably, this study was a retrospective study with only the evaluation of the clinical outcome restricted to the early in-hospital postoperative period without any information on late results, survival or quality of life of these patients. In this review the in-hospital mortality was 6.5% for patients with a low-EF of about 20% *vs.* 1.4% for patients with EF >40% with a higher hospital length of stay for low-EF patients (8).

In this study, as in many other reports, female sex is conventionally considered a risk factor of operative mortality up to twofold greater (4,15) and has been included as a poor prognostic factor in the most used cardiac operative risk score such as the Society of Thoracic Surgeons score EuroScore II, and modified Parsonnet score (2,16). Females comprise less than 30% (ranging from 24% to 31%) of patients undergone surgical myocardial revascularization (4). Blasberg *et al.* in their review reported the results of some series comparing the in-hospital mortality between men and women undergone CABG. They reported a female mortality approximately twice that of men with an overall in-hospital mortality in women ranging from 1.5% to 7.1% compared with that of men ranging from 1% to 4% (4,16). However they found that in high-risk patients this difference disappeared and there was no difference between male and female mortality (2).

Many explanations have been proposed to justify poorer surgical outcomes in females. Women typically are older and are at increased risk for gender-specific co-morbidities associated with perioperative mortality after CABG as well as diabetes, hypercholesterolemia, hypertension, abnormal renal function, reduced preoperative hematocrit and peripheral artery and cerebrovascular disease. Furthermore clinical symptoms related to CAD in women onset at least a decade later than in women (2,4,16). Moreover, CAD in young females less than 55 years of age carries a poor prognosis; compared to matched males, mortality is increased 1.7% after myocardial infarction (MI), 4.3% after

percutaneous intervention, and 3.4% after CABG (4).

Sex hormones plays a complex role in the development of CAD and myocardial infarction (4,17). Estrogen has long been theorized to restrict atherosclerotic development reducing CAD formation and delaying the appearance of symptomatic CAD in females (17). However administration of exogenous estrogen in women after menopause has not proved a protective effects for CAD and may be associated with increased thrombotic complications (18). Beside often women have smaller BSA than males. A BSA of less than 1.6 m^2 is an additional risk factor in CABG, independent of gender, associated with a fivefold increased mortality and reduced graft patency (19). In postmenopausal women, this worse outcome after CABG can be referred to reduced endothelium-derived nitric oxide (eNOS) levels produced by internal mammary artery endothelial cells (20). Frequently a smaller body surface area is predictive for smaller epicardial coronary arteries, leading to technical difficulties after CABG and making women prone to higher risk for poor graft patency (16). In effect, based on autopsy and intravascular ultrasound results, female coronary arteries are 10% to 15% smaller in diameter compared with male ones (4,16,19).

Women more often present with a lower New York Heart Association (NYHA) functional class and acute or unstable coronary disease frequently requiring urgent intervention, because of the delayed development of CAD at an advanced age with significant associated co-morbidities that can influence the severity of symptoms at presentation, the influence of age on the biology of disease is proved by life-table statistics; on average women live longer than men (77 *vs.* 72 years), and present with symptomatic CAD at a more advanced age (4,16,21).

A delay in presentation of the CAD in women is more likely due to these previously reported factors, rather than 'referral bias' which many authors ultimately associate with an increased risk for operative death, Some authors have reported that females are addressed less often for elective myocardial revascularization or are referred later in the course of disease, therefore more likely they show acute or unstable CAD (2,4). The atypical nature of symptoms and lower diagnostic accuracy of noninvasive testing in women make prompt diagnosis and treatment challenging (16).

Early and late results after surgical revascularization in women are associated with parameters specific to gender, namely smaller coronary artery size, fewer bypass grafts, increased preoperative risk factors and underutilization of the internal mammary (4,22).

Females are more likely to have postoperative myocardial infarction, prolonged postoperative need of inotropic and/or vasopressor agents, and increased ventilatory support requirements with an increased risk for deep sternal wound infection and respiratory failure (4,21).

As reported, also mid-term outcome following myocardial revascularization is inferior in women, likely due to the increased preoperative risk factors for systemic disease including renal failure, diabetes, and diffuse atherosclerosis. After adjustment of these risk factors, gender is not necessarily associated with worse 5-year outcome (4,21).

Conflicting results on the influence of gender on the results of myocardial revascularization are reported in the study of Pina and co-workers (2) that investigate the influence of gender on early and long-term results of surgically myocardial revascularization in patients affected by CAD associated with ischemic left ventricular dysfunction, enrolled in the STICH Trial (Surgical Treatment for Ischemic Heart Failure). This trial has been the first randomized study which compared patients with CAD and left ventricular EF ≤35%, treated with surgical myocardial revascularization plus medical treatment (MED) versus patients treated with medical therapy alone. The STICH trial enrolled 1,212 patients, 148 (12%) women and 1,064 (88%) men. In this recent study the trial STICH investigators analyzed long-term (10-year) outcomes of these patients according to sex (2).

Both women and men receiving CABG plus medical therapy had lower event rates, such as mortality or cardiovascular hospitalization, than patients receiving medical therapy alone.

Despite women were older with a higher body mass index and more preoperative risks factors for CAD, when randomized for treatment, female sex is not associated with the effect of CABG on all-cause mortality and operative death so that it can not be considered a risk factor for perioperative mortality in these patients. Furthermore, women had significantly lower rates of long-term all-cause mortality, cardiovascular mortality and hospitalization than men (2).

It is however generally agreed that CABG in patients with left ventricular dysfunction showed good result with acceptable morbidity and mortality compared to medical therapy alone. We hope new evolving procedures, including new techniques for conventional surgery, minimally invasive and percutaneous treatments, spread available therapeutic strategy improving further the results.

Despite these conflicting results reported for CABG in women, we think that improved awareness of heart disease in females, decreasing referral bias and delayed surgical intervention, careful recognition of preoperative systemic disease and future efforts to maximize the use of LIMA graft are necessary to improve their clinical outcome closing the gender gap. Anyway female sex should not influence treatment decisions about surgical myocardial revascularization for CAD with or without left ventricular dysfunction.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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