Surgical revascularization of myocardium in population of young women. Is it a group of increased operative risk?

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Abstract

Occurrence of myocardial infarction and advanced atheromatosis of coronary arteries in premenopausal women is unusual. Surgical revascularization of myocardium as an established method of ischaemic heart disease (IHD) management is more often used in this subset of patients. In recent years there have been some studies indicating better outcome of female patients after cardiac surgery, especially in the long term, but it is generally believed that women are more exposed to complications and have poorer prognosis after myocardial revascularization procedures compared with males, especially in the youngest groups. It seems that physiological protectors of the cardiovascular system which are present in a healthy population of young women are not effective in a subset with IHD undergoing coronary artery bypass grafting (CABG). Young women with IHD may represent a high-risk group with a hospital mortality higher than men after CABG surgery.

Key words: premenopausal women, ischaemic heart disease, coronary artery bypass grafting.

Introduction

Ischaemic heart disease (IHD) is more prevalent in men, especially in middle-aged ones, but cardiovascular diseases cause higher mortality in women than in men [1]. Problems of IHD in women are not usually noticed as clearly as in men. Former clinical trials considered a proportionally smaller number of women than men and they were based only on the male population [2].

Prevalence of IHD in premenopausal women is relatively low. Each year in the USA, myocardial infarction (MI) is diagnosed in approximately 123 000 men and in 3 000 women less than 45 years of age [3]. It is probably caused by a protective action of female hormones on the cardiovascular system. Due to the low prevalence of IHD in young women, the rate of coronary artery bypass grafting (CABG) performed in that population is low and it is followed by a small number of publications on this issue.

The issue of whether the female gender should be treated as a group of higher operative mortality after CABG is controversial. The latest studies

have even shown that in-hospital mortality in women after CABG has been decreasing during the last decades [4].

There is no doubt that the age of patients is a factor strongly correlated with the intensity of atheromatous lesions in coronary arteries. However, it should be emphasized that the first episodes of IHD in women are observed with six to ten years delay in comparison with men [5]. According to the Framingham Study [6], in the third decade of life the morbidity rate of IHD for the male gender is 7-fold higher in comparison with the female gender. This difference decreases progressively with age and reaches equality in the seventh decade of life. The clinical stage of IHD in young women is often more advanced than in men at the same age. The occurrence of MI in young women is associated with a higher mortality rate than in their male contemporaries, both when in-hospital [7] and long-term [8] mortality are considered.

Survival analysis of young women after coronary artery bypass grafting

The outcome of CABG in young women is worse than in young men [9, 10]. Women are a group of patients which demands special care and more intensive treatment, both pre- and postoperatively. As far back as in 1985, Gardner *et al*. [11] reported that women, especially before 50 years of age, had a significantly higher in-hospital mortality rate after CABG. Hogue *et al*. [12], analyzing 30-day survival after CABG, found that women younger than fifty had a mortality rate threefold higher, and women between fifty and seventy twofold higher than men at the same age. Also, Herlitz *et al*. [13], who divided their patients after CABG into two groups depending on age with a cut-off value of 65 years, during 5-year follow-up noticed that in the younger group the female gender was associated with twofold higher risk of death in comparison with the male gender, whereas in the older group the risk was equal.

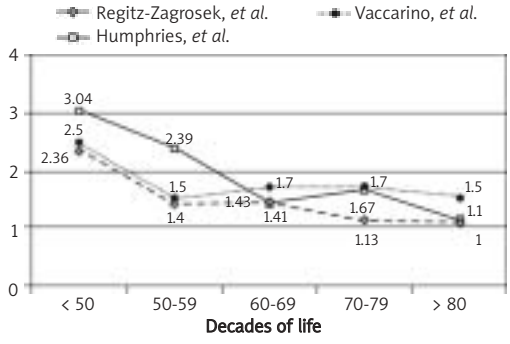

Figure 1. Odds ratio for in-hospital death of women in comparison with men after CABG in consecutive decades of life

In order to assess early postoperative mortality in women Vaccarino *et al*. [9] analyzed 51 000 patients who underwent CABG. Women constituted 29.7% of patients. In the subset of patients under 50 years of age, comprising 5024 subjects, women made up 22.5%. The authors divided the total analyzed population into five age subsets with 10-year intervals. The first group constituted patients below 50 years of age, whereas the fifth group consisted of subjects over 80 years of age. Overall mortality in women was 1.8-fold higher than in men. The highest mortality in female patients in comparison with the male population was observed in "the youngest" group. In this group, the odds ratio (OR) for in-hospital death for women in comparison with men was higher both in univariate analysis (OR = 3) and in multivariate analysis concerning 15 clinical variables (OR = 2.2). In "the oldest" subset of patients, the odds ratio for in-hospital death almost reaches one (OR = 1.1 in univariate analysis and OR = 1.02 in multivariate analysis).

In another study concerning this problem, Regitz-Zagrosek *et al*. [10], after analyzing 17 500 European patients, obtained similar findings. Analyzing gender as a predictor, the authors showed that the highest relative risk of postoperative death for women exists in the subset of patients aged less than fifty. Similarly as in the study by Vaccarino *et al*. based on an American population, Regitz-Zagrosek *et al*. [10], assessing European material, found that the relative risk of death for women in comparison with men decreases together with age and in older patients is nearly the same. Regitz-Zagrosek *et al*. [10] also determined in their population a cut-off value of age at the level of 70.5 years. In patients older than 70.5 years gender seemed no longer to be an independent predictor of mortality.

In one of the latest studies, Humpries *et al*. [14], on the basis of extensive material of 25 000 patients who underwent CABG between 1991 and 2004 in the province of British Columbia in Canada, reported significantly better postoperative prognosis in women. However, 30-day mortality was higher in women than in men in each age subset. What is the most interesting, the authors observed the biggest difference in mortality in patients younger than fifty.

The detailed results of the three above-mentioned studies are presented in Figure 1. Convergent conclusions were also drawn by Zwoliński *et al*. [15], who assessed operative mortality after CABG in a Polish population of patients aged 45 or younger. The mortality rate in women was 3.27-fold higher than in men, which is concordant with other observations made on the basis of American and European populations (Table I).

In the studies quoted above, the relative risk of death for young women in comparison with young men was the highest in the material of Zwoliński *et al*. [15]. This bias can probably be explained by the fact that these authors analyzed patients 5 years younger than the others. Following this way of thinking, one can suppose that a trend towards decrease of relative mortality in women in comparison with men starts in the youngest age groups.

The clinical profile of young patients referred for coronary artery bypass grafting

In the materials of Vaccarino *et al*. [9] and Regitz-Zagrosek *et al*. [10], female patients referred for CABG in comparison with male patients had a bigger burden of preoperative risk factors. Women below 50 years of age more frequently had a history of stroke, heart failure, diabetes, arterial hypertension and renal insufficiency. Compared with men, more women were in functional class III or IV according to the Canadian Cardiovascular Society. They were also more often operated on non-electively. Diabetes was a factor which significantly differentiated young women from men. In Vaccarino *et al*. [9] study hyperglycaemia was observed 2.3-fold more frequently among women than among men aged under 50, whereas there was no difference in this parameter in octogenarians. Prevalence of stroke and diabetes and severity of angina in the oldest group were also comparable.

Postoperative morbidity rate also indicates that women in premenopausal and menopausal age, in comparison with men below 50 years, have worse prognosis after CABG. In this age group, Vaccarino *et al*. [9] observed statistically more postoperative complications in women than in men. Women had a significantly higher rate of acute renal failure, neurological events and MI in early postoperative periods. It should be emphasized that the female gender, in comparison with the male one, showed unfavourable outcome after CABG when below 50 years of age. In the youngest group of patients, postoperative worsening of renal function was 2.2-fold more frequent in women than in men. However, starting from the seventh decade of life, this complication was observed more often in men. In the female group, neurological and MI events also decreased with age. Hogue *et al*. [12] analyzed neurological outcome after CABG (stroke, transient ischaemic attack and coma) and found that it was significantly more frequent in women than in men (3.8 vs. 2.4% respectively). In patients below 50 years, the risk of neurological complications was 1.6-fold higher in women than in men, whereas in patients older than 70 years this relative risk was "only" 1.3. What is more, in the early postoperative period (4-8 weeks) women have a higher rate of depression, worse physical efficacy and higher rate of readmission to hospital [16]. The probability of readmission to hospital after CABG is about 70% higher in women older than 65 years and more than 2-fold higher in younger women, in comparison with respective age groups of men [16].

Probable mechanisms and hypotheses

The issue of higher mortality rate in women in comparison with men, in the subset of young patients with IHD treated surgically, has been analyzed for no longer than several years. Until recently, few researchers dealt with this problem. However, it seems possible to put forward some hypotheses and indicate some probable mechanisms underling an adverse prognosis in young female patients undergoing CABG.

Due to infrequent incidence of IHD in premenopausal women, there is a common belief that dangerous aggravations of IHD are very rare in this population. That is why general practitioners are usually unwilling to refer young women to cardiologists [17]. In consequence, young female patients presenting with symptoms of myocardial ischaemia are sent to cardiac centres later and in worse clinical state than their male contemporaries. In addition, while assessing a coronary angiography in this subset of patients, it is easy to underestimate the severity of stenosis as non-critical. Atheromatous plaques of young women are less calcified than those of men or older women. This may be one of the reasons for the significant oversight of lesions on X-ray imaging. A decision of coronary angioplasty is made less frequently in women than in men [18].

The higher number of risk factors in young women in comparison with men referred for CABG may be a reason for their higher perioperative mortality rate.

The role of diabetes, which is diagnosed more frequently in young women than in young men referred for CABG, should be especially emphasized.

Table I. Comparison of mortality rate after CABG in subsets of women and men

	Number of operated women under 50 years old (*< 45)	Odds ratio for in-hospital death of women compared with men
Zwoliński *et al*. [15]	65*	3.27
Vaccarino *et al*. [9]	1130	3.04
Humphries *et al*. [14]	251	2.51
Hogue *et al*. [11]	13 323	2.46
Regitz-Zagrosek *et al*. [10]	196	2.36

In premenopausal women with diabetes, both relaxation of the blood vessel wall and its reaction to adrenergic stimulation are diminished [19]. In premenopausal women, whose blood vessels are theoretically supposed to be protected by circulating oestrogens, diabetes causes a lesion of endothelial function of similar degree as in diabetic men [20]. Among young women with IHD, in comparison with healthy women, hyperinsulinaemia develops more often [21]. Due to its adverse effect on lipid profile and endothelial cell proliferation, this state may promote the progress of atherosclerosis [21].

Another risk factor is addiction to nicotine. Smoking in combination with use of oral contraceptives significantly enhances the development of IHD and aggravates its course in the subset of young women [22]. Smoking accelerates the menopause [23]. The addiction to nicotine probably does not affect atheromatous plaque rupture, but it significantly promotes the development of the plaque's erosion [24].

It has been believed that higher postoperative mortality correlates with the degree of atheromatosis in the coronary arteries. However, Vaccarino *et al*. [9] and Regitz-Zagrosek *et al*. [10] observed that in the subset of women younger than 50 years, angiograms showed fewer atheromatous lesions than in young men. The conclusion is that the reasons for poorer prognosis in young women are more complex and may be associated with other mechanisms.

The higher relative mortality rate of women after CABG may also result from technical problems which can occur during the operation. Smaller diameter and more tortuous course of the coronaries may in consequence cause some technical problems for the surgeon during graft anastomosis, which may affect postoperative outcomes. Early postoperative mortality increases with diminishing of the coronary artery diameter, and this phenomenon is more clearly seen in women than in men [25]. Nishida *et al*. [26] found an advantage of using arterial grafts in comparison to venous grafts in patients with coronaries of small diameter. Some authors report that the use of arterial grafts is less common in women than in men, and this fact, according to Nishida *et al*. [26] observations, may contribute to worse prognosis in female gender subsets. In long-term follow-up, a lower rate of patent venous grafts was observed in women [27]. It should be emphasized that according to Sheifer *et al*. [28], women have smaller coronary vessels than men, regardless of body surface area.

A possible explanatory answer to the question of why women have a higher relative risk of death after CABG in the youngest decades probably lies in the mechanisms associated with sex hormones. The protective effect of oestrogens on the cardiovascular system is well known [29]. However, there is a subset of women who present with angina as soon as in premenopausal age. This may result from a loss of estrogens' protective influence on the vascular wall. Two mechanisms may be involved in this process: a decrease or total lack of blood oestrogens, or dysfunction of the oestrogen receptors (ER). The Nurses' Health Study [23] found a correlation between early menopausal age and high risk of IHD development. Bilateral ovariectomy in pre-menopausal women also results in a rapid fall of oestrogen level and in consequence in an increase of IHD prevalence [30].

The expression of the ER in smooth muscle cells of the coronary arteries is higher in atheromatosis-free vessels. The correlation between ER expression and the absence of atheromatous plaques has the highest statistical significance in premenopausal women. In one of the studies [31], smooth muscle cells of the arteries of healthy women showed expression of ER in more than 83% of cases. This means that there must be another beneficial effect of oestrogens, acting directly on the vascular wall. A high expression of ER near atheromatous plaques saturated with lipids and infiltrated by macrophages was observed in the intima of arteries of young and obese women [32]. However, such increased expression of ER was not found near plaques rich in collagen. Thus, at the level of ER expression, the impact of a lesion's character alone may be of higher significance than the degree of vessel stenosis. In such advanced lesions, ER activation by oestrogens may be associated with overproduction of proteolytic enzymes such as metalloproteinases produced by macrophages. In consequence, it may lead to the plaque's erosion, initialization of the clotting cascade and total occlusion of the vessel. The overexpression of ER which is observed in the coronaries of young and obese women may be a compensative mechanism preventing the development of atheromatosis. There are some interesting studies which suggest that oestrogens protect the atheromatous plaque from rupture only, but not from erosion [24]. In premenopausal women, plaque erosion is observed more frequently than in men of the same age [24].

A lack of oestrogens' protective effects on the cardiovascular system in premenopausal women may result from polymorphism of the *ER* gene. One *ER* gene is the *ESR1* gene, in which the allelic sequence c.454-397CC in intron 1 is burdened with 3-fold higher risk of myocardial infarction than the sequence c.454-397TT/CT [33]. A premature manifestation of IHD in patients with a positive family history of cardiovascular diseases suggests a genetic background to the development of atherosclerosis in coronary arteries. Ischemic

heart disease dependent to a higher degree on genotype than environmental conditions is more likely to occur in younger patients and often has a more dramatic clinical manifestation and worse prognosis.

In the developed countries, another risk factor of IHD is obesity, which is very common among younger women. These patients often present with some abnormalities associated with the effects of oestrogens, such as infertility and dysmenorrhoea [32]. In such cases, dysfunction of ER both in adipocytes and in endothelial cells may be associated with abnormal transcription pathways which do not signal proper vascular protection.

In women with normal endocrinal ovary function, other hormonal dysfunctions affecting development of IHD may be present. In a study comparing a subset of women with a history of MI and angiographic evidence of coronary artery atheromatosis to a subset of women free of IHD, a lower level of dehydroepiandrosterone (DHEA) was found in the first subset [21]. Dehydroepiandrosterone is a hormone believed to have some anti-atheromatous properties.

Anovulatory cycles and hyperandrogenism are features of polycystic ovarian syndrome (PCOS). Polycystic ovarian syndrome is estimated to be present in 6-10% of women in procreative age [34]. It is a major problem of not properly diagnosed women, simultaneously burdened with other risk factors of IHD such as dyslipidaemia, visceral obesity, arterial hypertension or glucose intolerance. Fifteen percent of women with PCOS are estimated to develop diabetes before menopause [35]. The risk of IHD in this population of women is 4 to 11-fold higher than in healthy women [36]. Thus, it is possible that among candidates for CABG below 50 years of age, loaded with other predictors of poor prognosis, are also women with PCOS.

A risk factor which may contribute to the development of IHD to an extent depending on menopausal status is lipoprotein α [Lp (α)]. Among women with a level of Lp (α) higher than 30 mg/dl, the risk of hospitalization due to acute coronary syndrome is 5-fold higher in premenopausal women and 2.4-fold higher in postmenopausal women, in comparison with women in whom the level of Lp (α) is lower than 6 mg/dl [37].

Myocardial infarction in young patients frequently correlates with a large area of ischaemia. This phenomenon is probably caused by less developed collateral circulation in younger patients in comparison with older ones.

Conclusions

A higher mortality rate in the early postoperative period among women has been reported in clinical trials since the 1970s. Despite recent data demonstrating an improved surgical outcome in women, common and classical literature findings still show a poorer prognosis in this subset of patients after CABG surgery. The youngest decades are negatively affected by gender. This is surprising because the fact that premenopausal women are protected against atherogenesis by the high levels of oestrogens is commonly known. Generally, premenopausal women are very rare candidates for CABG. On the other hand, the hormones which usually protect them against the development of IHD in these infrequent cases seem not to affect the operation's outcome beneficially. It is suggested that this is because there must be a kind of defect at the level of the ovary or the ER. The lower diameter of the coronaries as well as the higher number of risk factors characterizing young women may also contribute to enhancement of the adverse prognosis in this subset of patients. Diabetes seems to play a role in this phenomenon because it is more prevalent in young women than in young men.

The results of the trials cited in the present review were based on both American and European populations; however, it would require conducting subsequent trials on another population to draw some clinical implications. The need to elaborate guidelines requires that multicentre randomized clinical trials be performed. Studies allowing a comparison of the long-term survival of young women and young men after CABG will be of special importance.

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