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Applying the Gender Lens to Risk Factors and Outcome after Adult Cardiac Surgery

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Keywords
Gender · Cardiac surgery · Outcome · Risk factors

Summary
Background: Applying the gender lens to risk factors and outcome after adult cardiac surgery is of major clinical interest, as the inclusion of sex and gender in research design and analysis may guarantee more comprehensive cardiovascular science and may consecutively result in a more effective surgical treatment as well as cost savings in cardiac surgery. **Methods:** We have reviewed classical cardiovascular risk factors (diabetes, arterial hypertension, hyperlipidemia, smoking) according to a gender-based approach. Furthermore, we have examined comorbidities such as depression, renal insufficiency, and hormonal influences in regard to gender. Gender-sensitive economic aspects have been evaluated, surgical outcome has been analyzed, and cardiovascular research has been considered from a gender perspective. **Results:** The influence of typical risk factors and outcome after cardiac surgery has been evaluated from a gender perspective, and the gender-specific distribution of these risk factors is reported on. The named comorbidities are listed. Economic aspects demonstrated a gender gap. Outcome after coronary and valvular surgeries as well as after heart transplantation are displayed in this regard. Results after postoperative use of intra-aortic balloon pump are shown. Gender-related aspects of clinical and biomedical cardiosurgical research are reported. **Conclusions:** Female gender has become an independent risk factor of survival after the majority of cardiosurgical procedures. Severely impaired left ventricular ejection fraction independently predicts survival in men, whereas age does in females.

Schlüsselwörter
Geschlecht · Herzchirurgie · Outcome · Risikofaktoren

Zusammenfassung
Hintergrund: Ziel unserer Untersuchungen war es, das Geschlecht in den Fokus des klinischen Interesses nach erfolgter herzchirurgischer Operation zu setzen, da die Berücksichtigung des Geschlechts in Forschungsdesign und -analyse eine umfassendere kardiovaskuläre Wissenschaft garantieren und folglich zu einer effektiveren chirurgischen Therapie sowie zu Kosteneinsparungen im Fach Herzchirurgie führen kann. **Methode:** Die klassischen Risikofaktoren (Diabetes mellitus, arterielle Hypertonie, Hyperlipidämie, Nikotinabusus) wurden unter Geschlechteraspekten überprüft. Komorbiditäten wie Depression, Niereninsuffizienz und hormonale Einflüsse wurden genauer betrachtet. Ökonomische Aspekte wurden untersucht und das Outcome nach koronarer und valvulärer Operation sowie nach Herztransplantation wurde ausgewertet. Die Anwendung der intraaortalen Ballonpumpe wurde geschlechtsbezogen analysiert. Geschlechtsbasierte Unterschiede in der klinischen und biomedizinischen Forschung wurden evaluiert. **Ergebnisse:** Die Resultate nach Auswertung der kardiovaskulären Risikofaktoren für Männer und Frauen werden geschildert. Die genannten Komorbiditäten spielen für Männer und Frauen eine unterschiedlich große Rolle in Hinblick auf die Herzoperation. Aus gesundheitsökonomischer Sicht besteht ein großer Unterschied zwischen Männern und Frauen. Das Outcome nach koronarer und valvulärer Operation sowie nach Herztransplantation wurde für Männer und Frauen separat ausgewertet. Die Ergebnisse bei Anwendung der intraaortalen Ballonpumpe werden aufgezeigt. Geschlechtsbasierte Unterschiede in der klinischen und biomedizinischen Forschung werden geschildert. **Schlussfolgerungen:** Das weibliche Geschlecht wurde als unabhängiger Risikofaktor für das Überleben nach verschiedenen herzchirurgischen Operationen identifiziert. Bei Frauen spielt vor allem das Alter und bei Männern die stark eingeschränkte linksventrikuläre Pumpfunktion für das Überleben eine entscheidende Rolle.

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Introduction

In many diseases, including the cardiovascular field, male and female patients present with different symptoms. Often, gender-sensitive diagnostics are not applied. Consecutively, therapeutic options may be inadequate. A better knowledge of gender differences in medicine could personalize treatment and increase the quality of healthcare [1, 2].

There is a certain amount of innovative gender-sensitive approaches to be found in cardiac surgery although only a small percentage of researchers is paying heed to sex and gender. Clinical findings, however, demand the necessity, as demonstrated by the mortality rate of women after myocardial infarction (MI). Independent of improved therapeutic options, mortality rates in women remain almost twice as high compared to men in the Western world [3].

Previous research has demonstrated that male and female bodies show innate physiological and hormonal differences which result in different responses to drugs and treatment, influencing health status and outcome after surgery [1, 4].

Regitz-Zagrosek described the New York Heart Association (NYHA) classification as the strongest predictor of the development of heart failure and its mortality in men whereas in women it is age. Definite explanations for this finding are yet unknown [4–6].

It is also known that, independent of the underlying pathology, the incidence of heart failure increases dramatically within the female population aged 55 years and older. This also appears to account for the stronger correlation between age and mortality observed in women with cardiovascular disease [4–6].

Women bear a greater risk for postoperative morbidity and mortality in cardiac surgery. After adjusting for cofactors such as higher age, smaller body surface, and less blood volume, female gender remains as an independent risk factor. Despite a growing scientific effort in gender medicine, the underlying mechanisms still remain elusive.

Cardiovascular Risk Factors

The classical risk factors play a major role during the development and progression of cardiovascular disease among men and women. Their impact, however, may be different among male and female patients. In women, this specifically accounts for type 2 diabetes, arterial hypertension, renal insufficiency, obesity, and depression, while obesity and smoking in combination with hyperlipidemia are strong risk factors for men.

In this regard, women experience gendered exposure to several risk factors such as pregnancies/reproductive history and related complications, which may play a major role and could lead to a specific onset of symptoms [3].

In order to give a clinical example: The lifetime risk of developing coronary artery disease (CAD) in women with autoimmune diseases, rheumatoid diseases, and preeclampsia is 50% (for each entity). Following American Heart Association (AHA) guidelines, these women receive preventive medication of aspirin and statin. Coronary angiography in these women must not necessarily show pathological results [6]. If they undergo functional tests, these may show myocardial microangiopathy. Treatment follows the appropriate manner as suggested in specific guidelines by the European Society of Cardiology (ESC) and the AHA [3, 7, 8].

Polycystic ovary syndrome and preeclampsia may carry an increased risk for the development of arterial hypertension, diabetes, as well as MI or stroke later in life [9, 10].

Diabetes

Men and women differ in regard to the prevalence of prediabetes, cardiovascular complications, and preventive measures.

Women more frequently demonstrate an early disturbed glucose tolerance, whereas men are prone to showing pathologic fasting glucose levels. The use of more oral glucose tolerance tests may lead to a higher incidence of diagnosed prediabetes among women. In comparison to non-diabetic female patients, diabetic women show a doubled risk for developing cardiovascular complications. More frequently, diabetic women develop heart failure. Their risk to suffer from and die of MI is increased 4-fold. Among men, this risk is twice as high [11, 12].

Arterial Hypertension

Prevalence of arterial hypertension is increasing with age. At a younger age (<35 years) more men are affected. Around the age of 50 years hypertension is rapidly increasing among women, consecutively leading to a higher incidence of arterial hypertension among women aged 75 years and above. High blood pressure (>120/80 mm Hg) is leading to a 4-fold increased risk of coronary heart disease among women [13]. Arterial hypertension is an independent risk factor for the development of left ventricular myocardial hypertrophy. The risk of dying from it is higher among women than in men [14, 15]. A concentric hypertrophy and diastolic heart failure with normal ejection fraction (HFnEF) has been observed more often among women. Men tend to develop a left ventricular dilatation with systolic heart failure (HFrEF = heart failure with reduced ejection fraction).

Hyperlipidemia

Lipid metabolism is changing at and after menopause [16]. Total and low-density lipoprotein cholesterol increase by approximately 10%, while serum high-density lipoprotein levels seem to be less influenced. Triglyceride concentration is rising. Key enzymes of lipid and glucose metabolisms are estrogen-dependent, i.e., changes in lipid or glucose levels may be related to the hormonal status after menopause.

Hyperlipidemia has the same impact among men and women as cardiovascular risk factors.

Obesity

Depending on the extent of obesity, the cardiovascular risk is increased. Female patients with a body mass index > 40 kg/m^2 demonstrate a 4-fold increased cardiovascular risk in comparison to non-obese women. In 10–13% of overweight women a polycystic ovary syndrome is existent, but not diagnosed [17].

Body fat distribution depends on sex and gender: men show a central fat distribution and women a so-called gluteal-femoral pattern. A measure to evaluate fat distribution is the waist-to-hip ratio, with >0.9 being pathologic among women and >1.0 among men. The visceral fat storage is accompanied by an elevated risk for cardiovascular complications and diabetes [18]. Estrogen seems to act directly on fatty tissue.

Smoking

Still more men than women are smoking; however, the prevalence of smoking women is increasing, specifically at a younger age. Smoking is a very strong cardiovascular risk factor among men, especially in combination with hyperlipidemia [19].

Depression

Worldwide epidemiologic studies have demonstrated that women suffer twice as often from depression [20]. Serotonin levels or cyclic changes are being discussed as underlying causes.

Women with cardiovascular disease are frequently affected, e.g., women with heart failure suffer 3–5 times more often from depression compared to the general population. In women, the prevalence of depression after MI and coronary artery bypass grafting (CABG) is increased by 20 and 43%, respectively, in comparison to men after MI and CABG [21].

Depression among men is underdiagnosed. Symptoms such as aggression may differ from women.

Hormones

The importance of hormonal changes among men and women has been addressed in the medical literature in regard to drug-related side effects or missing drug response among women. Although endogenous estrogen is showing positive effects on vascular structure and function, it is known that hormonal replacement therapy after menopause does not lead to a preventive or protective effect on the cardiovascular system [6, 22].

It is known that women suffer from cardiovascular disease 8–10 years later than men. The main reasons for this are estrogen protection and genetic factors [22].

Estrogens inhibit the growth of vascular smooth muscle cells (VSMC) and improve endothelial cell growth. In research and clinical studies a reduced development of atherosclerosis in the vascular wall under estrogen influence has been demonstrated [22, 23]. Estrogens aim at vasodilatation via fast nitric oxide release and prostanoids. Most effects are mediated by the nuclear estrogen receptors (ER) alpha and beta. They are located in vascular endothelial cells, VSMC, as well as cardiac fibroblasts and myocytes. ER alpha and beta have been shown to be more expressed in myocardial hypertrophy and heart failure, while ER beta occurs more frequently in female than in male hearts [6]. In animal experiments, estrogens demonstrated a stronger positive effect in females regarding the reparative fibrous formation after MI as well as a decreased inflammatory response to MI. The survival rate was better among males than in females [24].

An additional effect of estrogens constitutes the inhibition of the activated renin-angiotensin-aldosterone system (RAAS) under pathologic circumstances. Activated RAAS may lead to myocardial hypertrophy, reduced systolic myocardial function, atherosclerosis, and finally cardiovascular disease.

Little is known about the other sexual hormones and their effect on the vascular system. Testosterone shows an effect opposite to estrogen.

Gender-specific behavior may also affect the hormonal status. One example is nursing as it increases the circulating levels of prolactin, a hormone with multiple biological activities [25].

Renal Insufficiency before Cardiac Surgery

Renal insufficiency generally seems to have a stronger impact on women than on men. The investigation by Deutsch et al. [26] evaluated the gender influence in dialysis-dependent patients undergoing cardiac surgery. The authors retrospectively reviewed the data of 204 dialysis-dependent patients (68.6% male, age 66.6 ± 9.9 years) with end-stage renal disease undergoing cardiac surgery and compared them to propensity-score-pair-matched controls, also consisting of 204 patients. The 30-day mortality was 13.2% (14/106) for CABG, 19.3% (6/31) for aortic valve replacement, and 23.8% (16/67) for combined procedures. Postoperative bleeding was significantly higher in men (1,007 ± 946 ml) than in women (687 ± 598 ml, p = 0.014).

The authors identified significant differences in terms of 30-day mortality, i.e. 17.6 versus 4.6% (p = 0.0001) for overall mortality, 13.2 versus 3.4% (p = 0.014) for CABG, 19.3 versus 0% (p = 0.051) for aortic valve replacement, and 23.8 versus 9.1% (p = 0.02) for combined procedures. Multivariate analysis identified preoperative MI, prolonged extracorporeal circulation time, operation time, and surgical reexploration as independent predictors of 30-day mortality. There was a higher occurrence of bleeding complications in men that remained significant even after correction for body surface area [26].

Economic Considerations Related to Cardiovascular Risk Factors

Gender differences might influence the treatment costs as well as reimbursement of healthcare facilities. Gulbins et al.

[27] described the possible economic implications of gender-related differences in cardiovascular surgery. They demonstrated that women cause higher healthcare costs during their lifetime, whereas a large part of this difference is rather caused by reproductive history than by disease. After consideration of costs related to pregnancy/birth, however, a difference with higher costs for women is remaining, although the origin of this disparity is not clear. In cardiovascular medicine, especially the risk factor metabolic syndrome including diabetes had a higher prevalence in women and was shown to have a greater impact on cardiovascular disease compared to men. This concerned both costs and outcome. In contrast to this, women experienced poorer preventive treatment of all classic cardiovascular risk factors including metabolic syndrome, especially concerning lipid levels. This influenced the costs of hospital treatment as well as the prognosis, e.g. following CABG. Gulbins et al. postulated that the greater influence of several risk factors on cardiovascular disease in women should lead to improved preventive strategies specifically in female patients. Further research is necessary to provide more evidence for gender-related differences due to the impact of several risk factors on treatment costs. As a result, this could also influence reimbursement strategies, taking these gender-disparities into account [27].

If and to which extent these findings do correlate to 'surgical' outcome is mainly unknown. In the following, we report on the major fields of adult cardiac surgery.

Coronary Surgery

Since 2002, MI and stroke, but not cancer, have been the leading causes of death in women [3].

Incomplete revascularization negatively affects survival after CABG. Since gender and classification technique might impact outcome and reporting, the effect on revascularization patterns and mortality rates has been reported on by Oertelt-Prigione et al. [28].

The authors investigated a total of 1,545 patients (23% female). A degree of revascularization was established by a mathematical difference between affected vessels upon diagnosis and number of utilized grafts. As expected, men displayed more triple vessel disease and, therefore, were treated by complete revascularization more frequently than women (85 vs. 77%, $p < 0.001$). This does not come as a surprise for cardiac surgeons, being known reasons for coronary size, higher NYHA class, and older age among women. However, by means of the calculation techniques and statistical models interestingly analogous percentages of incompletely revascularized patients were obtained, although there was only a 50% overlap between the two groups. Mathematically, more women, older patients, and patients with NYHA class III/IV appeared incompletely revascularized. Incomplete revascularization was a significant risk factor for mortality among men and women (hazard ratio (HR) 2.62; 95% confidence interval (CI) 1.76–3.89; $p < 0.001$) [28].

In another study, Lehmkuhl et al. [29] undertook a study on early mortality after CABG. Independent of the surgical technique, it was higher in women than in men (6.9 vs. 2.4%; HR 2.91; 95% CI 1.70–4.96; $p < 0.001$). Women were older than men (+4.7 years, $p < 0.001$), had a lower self-assessed preoperative physical activity, and demonstrated higher rates of postoperative low cardiac output syndromes (6.6 vs. 3.3%, $p = 0.01$), respiratory insufficiency (9.4 vs. 5.3%, $p = 0.006$), and resuscitation (5.2 vs. 1.8%, $p = 0.001$). The combination of the identified factors explained 71% of the gender difference in early mortality; age and physical condition alone accounted for 61%. Adjusting for these variables, the HR for female gender was 1.36 (95% CI 0.77–2.41; $p = 0.29$) [29].

In accordance with our own data, we reported on 30-day and 1-year mortality rates of 3,441 patients (733 women and 2,708 men) undergoing CABG performed either conventionally or with off-pump coronary artery bypass (OPCAB) [30]. The objective was to investigate the gender-related mortality in both groups. 252 women and 854 men were operated using OPCAB and 481 women and 1,854 men using extracorporeal circulation (ECC). Medical data was retrospectively reviewed and analyzed by means of Kaplan-Meier estimates and Cox proportional hazards models. To test for gender differences, linear and logistic regression models were used. As demonstrated by the authors, the 30-day mortality when using ECC was 5.2% in women versus 2.5% among men ($p = 0.001$). The 1-year mortality under ECC amounted to 8.7% in women versus 4.8% in men ($p = 0.0008$). For OPCAB, 30-day and 1-year mortality in women were 1.7%. The mortality in men amounted to 2.1% after 30 days and to 3.7% after 1 year. Regarding the gender-specific mortality, the 30-day mortality in women was 1.7% when using OPCAB and 5.2% when using ECC ($p = 0.002$), while the 1-year mortality in women was 1.7% using OPCAB versus 8.7% using ECC ($p = 0.0004$). In men, the 30-day and 1-year mortality for OPCAB were 2.1 and 3.7%, respectively; when using ECC, early and late mortality amounted to 2.5 and 4.8%, respectively [30].

As demonstrated in all of the studies mentioned, female gender is a strong independent predictor and risk factor of increased early and midterm postoperative mortality rates after CABG, and specifically when ECC is used.

Valvular Heart Disease

Many patients undergo a replacement of the aortic valve. Roedler et al. [31] evaluated gender-related differences in patients undergoing mechanical aortic valve replacement (MAVR) over a follow-up period of 10 years. The Austrian group investigated >600 patients (median age 60 years) undergoing MAVR with the CarboMedics valve. Of these, 215 patients were female (34%). Registered in-hospital mortality for males was 7.3 versus 11.0% in females ($p = 0.005$). For female gender, independent predictors of survival calculated by Cox regression analysis constituted additional CABG (HR 2.15; 95% CI 1.08–4.28), redo surgery (HR 3.64; 95% CI 1.78–

7.46), as well as age (HR 1.48; 95% CI 1.06–2.06). Left ventricular ejection fraction (LVEF) < 30% (HR 2.47; 95% CI 1.23–4.93) and age (HR 1.75; 95% CI 1.25–2.43) were independent predictors of survival among men [31].

The knowledge of gender-specific differences concerning mitral valve (MV) pathology and postoperative outcome is highly limited. Seeburger et al. [32] investigated the results of 3,761 patients consisting of 2,124 males (56.5%, 58.8 ± 12.5 years) and 1,637 females (43.5%, 64.5 ± 13 years). All patients underwent minimally invasive MV surgery. Demographic data as well as pre-, intra-, and postoperative characteristics have been collected, including details on MV pathology and surgical technique. Data was analyzed in consideration of gender-specific differences. Interestingly, mitral regurgitation (MR) was equally observed in women (91.3%) and men (92.4%). Among men, additional MV stenosis has been diagnosed in only 2.7%, but in 13.9% amongst women ($p < 0.001$). Calcification of the posterior MV leaflet was registered in 20.1% of the women compared to 6.5% in men. A posterior leaflet prolapse was present in men with 63.1 versus 35.7% in women ($p < 0.001$). Distinct MV repair differences were retrospectively detected between the sexes: posterior mitral leaflet (PML) resection was carried out in 17.9% of the men versus 10.1% in women, while PML chordae replacement was performed in 39.3% of the men compared to 20.4% in women. Prosthetic MV replacement was necessary in 26.8% of the women compared to only 10.7% in men. Concomitant tricuspid valve (TV) surgery was mostly performed in women (14.4 vs. 8.2%). After 1, 5, and 10 years, male patients showed a significantly better postoperative long-term survival than females with 96, 89, and 72% compared to 92, 82, and 58% ($p < 0.0001$), respectively. The underlying reasons may be multifactorial: older age, concomitant TV disease, and higher rate of MV replacement may explain the inferior long-term result in women to some extent, especially since female gender has previously been described as a risk factor on its own regarding the survival rates of patients undergoing MV surgery. Rankin et al. [33] investigated MV patients from the STS database (409,904 MV procedures), identifying female gender as a negative predictor to significantly influence patient outcome after MV surgery (odds ratio (OR) 1.4).

Akram and colleagues [34] demonstrated an incidence of 62% for annular MV stenosis in women in an echocardiographic survey with a total of more than 7,000 patients. Calcification of the mitral annulus has been predominantly described in women without CAD and vice versa in men with CAD. Thus, it can be assumed that exclusive mitral annulus calcification is related to a high incidence of coronary atherosclerosis irrespective of a patient's gender; however, it is more common in men [34]. The somewhat inverted prevalence of mitral annulus calcification in women might be explained by different calcium metabolism and bone resorption among postmenopausal women, although definite proof is lacking [35, 36]. As described in this study, women were 6 years older at the time of operation, presenting a significantly higher operative risk. Therefore, this finding itself may explain higher mortality rates among women. In addition, the higher rate of leaflet calcification most likely led to a higher rate of prosthetic MV replacement, which correlates favorably with the inferior long-term survival in women. This emphasizes the importance of time at diagnosis and surgical treatment of women with MV disease.

Another valvular disease affecting men and women differently is tricuspid regurgitation and consecutively TV surgery. The proportion of women in TV surgery is 60% and above, especially in redo surgery. There seems to be a different epidemiology for male or female patients regarding the incidence of TV regurgitation. Pfannmueller et al. [37] undertook a retrospective analysis of 92 patients (37 men, 55 women) undergoing isolated TV surgery due to symptomatic severe tricuspid regurgitation and/or active endocarditis. Mean age was 60.5 ± 15.8 years, mean log European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 12.1 ± 11.3%, and 51.4% of the operations were redos (men: 27%, women: 65%; $p < 0.001$), while 36% were due to active endocarditis (men: 62%, women: 18%; $p < 0.001$). Follow-up was 95% complete with a mean duration of 34.2 ± 33.0 months. The authors revealed an overall 30-day mortality of 5.4% (men: 5.4%, women: 5.5%). 5-year survival was 70.2 ± 11.4 versus 76.3 ± 6.8% ($p = 0.3$), and 5-year freedom from TV-related reoperation was 95.8 ± 4.1 versus 84.6 ± 8.5% for men and women ($p = 0.4$), respectively. There was no significant gender-dependent difference regarding the overall postoperative outcome. In a binary logistic regression analysis with the dependent variable gender, for the categories age, log EuroSCORE, endocarditis, previous cardiac surgery, and preoperative cardiac rhythm an OR of 0.17 for men regarding the factor endocarditis (95% CI 0.05–0.57; $p = 0.004$) as well as, for women, an OR of 3.2 regarding the factor previous cardiac surgery (95% CI 1.0–10.1; $p = 0.04$) and an OR of 5.9 regarding the factor presence of a permanent pacemaker (95% CI 1.4–24.7; $p = 0.02$) was shown [37].

Heart Transplantation

The survival rates after heart transplantation (HTx) in men and women show controversial results in the medical literature. Symptoms and severity of disease before the transplantation are gender-dependent [38–40]. Gender differences of donor and recipient may also have a major impact on survival after HTx. Of the 67,855 HTx carried out worldwide between January 1980 and June 2009 and registered at the International Society for Heart & Lung Transplantation (ISHLT), 13,863 (20.4%) were in women. According to the ISHLT registry, the rate of HTx in women amounted to 19.9% between 1992 and 2001 and increased to 22.9% between 2002 and 2009 [38–40].

Several mechanisms by which donor/recipient sex mismatch might affect outcomes in transplantation have been identified, including hormonal and chromosomal differences as well as antigen development. Modifications of these factors

seem almost impossible in clinical practice, with size discrepancy remaining as a modifiable factor to reduce the differences among male and female hearts [40]. Furthermore, there are some epidemiological reasons which may explain the numerical differences between male and female patients awaiting HTx. On the one hand, the vast majority of male HTx recipients may be caused by the earlier age at which heart failure develops in men. The increase of ischemic end-stage chronic heart failure may be related to the higher percentage of men awaiting HTx. On the other hand, the underrepresentation of women may include referral or selection bias and less access as well as less acceptance of HTx among women [38–40]. Although the surgical procedure did not differ between sexes, we suspected gender-specific differences regarding the outcome. Therefore, we studied the outcome of HTx recipients from the ISHLT registry to investigate possible sex-based differences in short- and long-term outcomes from a gender-specific perspective.

In contrast to other studies, the data for gender differences (donor gender and recipient gender) were calculated with respect to actuarial and conditional survival (without 30-day mortality).

Kaczmarek et al. [41] reported the highest 1-year survival in male recipients of male donor hearts (mR/mD: 83.74%). Male recipients of female donor organs (mR/fD: 78.95%) showed the lowest 1-year outcome. The best 5-year survival rates were shown by male recipients with male donor organs (70.75%, $p < 0.0001$). These differences disappeared in survival conditional to 1 year, indicating that gender predominantly influences short-term outcome.

The combination male recipient/female donor carries a higher risk for early mortality, whereas female recipient/male donor reveals favorable short-term results. Gender-matched HTx would be ideal but is not suitable in practice because of organ shortage [41].

Use of Intra-Aortic Balloon Pump after Cardiac Surgery

The use of intra-aortic balloon counterpulsation (IABP) in cardiosurgical patients has been reported by Beiras-Fernandez et al. [42] in 57 consecutive female patients (mean age 73 ± 9 years) requiring an IABP (January 2007 to January 2010). Data were retrospectively analyzed and compared to 182 male patients receiving IABP support within the same period. The collected data included patient demographics, preoperative state, operative details, postoperative pharmacological treatment, IABP-associated complications, and in-hospital mortality. Preoperative mortality risk was calculated by logistic EuroSCORE. The authors demonstrated no differences regarding type of operation and preoperative renal or hepatic failure, although the prevalence of peripheral artery occlusive disease was higher in men. Furthermore, female patients receiving an IABP were significantly older (73 ± 9 vs. 67 ± 10 years), had a higher ejection fraction (45 ± 24 vs. 36 ± 14%), and a higher EuroSCORE (25 ± 20 vs. 19 ± 17%) ($p < 0.05$). Postoperative catecholamine support was significantly higher in female patients. Women had a prolonged intensive care unit (ICU) stay (10.64 ± 9.7 vs. 7.6 ± 7.6 days), a higher incidence of renal replacement therapy, and a higher mortality (19 (19.4%) vs. 35 (33.9%); $p < 0.05$) after the use of IABP. Women show a worse outcome after postoperative IABP use, including length of stay at the ICU, postoperative renal failure, and in-hospital mortality, despite a higher ejection fraction when compared to men [42].

Cardiosurgical Research

There is a need to perform more gender-related clinical and biomedical research in particular by conducting experiments not only in one sex (today mostly males in animal studies), but by repeating them also in the other sex and by comparing the results. This is of great importance since results from male animals cannot necessarily be applied to females and vice versa [43]. The exclusion of female animals typically occurs as a means to control hormonal variation. However, exactly these hormonal variations are the key differences which deserve to be much better studied. Therefore, it would be desirable if researchers incorporated hormonal variations into the study designs in order to understand their important influence.

Kellermann et al. [43] studied the role of sex hormones and gender impact on functional cerebral outcome and brain morphology in rats 14 days after a 45-min deep hypothermic circulatory arrest (DHCA). Therefore, 80 animals (40 males, 40 females) were assigned to neutering or sham-neutering 4 weeks prior to surgery and were divided into a DHCA and a control group (naïve rats) (n = 40). Neurologic outcome was assessed pre- and postoperatively, and cognitive performance was tested with the modified hole-board test over 14 postoperative days. Neuronal damage was assessed using hematoxylin and eosin staining. Cerebral inflammation and apoptosis were determined immunohistochemically [44].

The cognitive performance and behavior 14 days after 45 min of DHCA was comparable between males and females. Postoperative motor skills were better in females, accompanied by less neuronal damage as well as more neuronal nuclear factor kappaB (NFκB) and activated caspase-3. Poly (ADP-ribose) polymerase and tumor necrosis factor (TNF)-α were elevated in both male groups. Of note is the secondary finding of a high mortality rate in the female groups (16 out of 38) during the early postoperative phase, especially in the female normal group (13 out of 23). This finding necessitates continuous investigations to analyze the impact of gender and hormones on other organs beyond the brain [44].

Disclosure Statement

The authors have nothing to declare.

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