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Review Article

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Fetal Cardiac Interventions: A Review of The Current Literature

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Abstract

Congenital heart disease (CHD) is the most common birth defect. Fetal cardiac intervention (FCI) is a novel and evolving field that has enabled us to modify the progression of CHDs and favorably change the postnatal outcomes by altering in utero anatomy and physiology. FCIs are only indicated in specific CHDs; CHDs diagnosed during midgestation that may progress and worsen in utero and cause fetal mortality and neonatal morbidity/mortality may benefit from FCI. These include fetal aortic valvuloplasty in severe aortic stenosis evolving to hypoplastic left heart syndrome (HLHS), fetal pulmonary valvuloplasty in pulmonary atresia with intact ventricular septum, critical pulmonary stenosis, atrial septoplasty and/or atrial stent in established HLHS, and transposition of great vessels with restricted or intact atrial septum. This review focuses on commonly performed interventions, candidate selection criteria, technical details, and outcomes of these procedures, which have been previously reported in the literature. Literature data about FCIs have demonstrated that technical success has improved, FCIs have limited maternal risks, and they do not cause any significant complications. Careful selection of candidates suitable for FCI, a multi-team approach, and performing these interventions in specialized centers and in collaborations will further improve the results.

Keywords: Congenital heart disease, fetal intervention, fetal aortic valvuloplasty, fetal pulmonary valvuloplasty, hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum

Introduction

Congenital heart disease (CHD) is the most common birth defect, with an incidence of approximately 6 per 1000 live births[1]. Advances in fetal imaging have provided a better understanding of the evolution of CHDs in utero. Some CHDs may progress during fetal life and may cause significant morbidity and mortality. Fetal cardiac intervention (FCI) is a novel and evolving field

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that has enabled us to modify the progression of CHDs and favorably change postnatal outcomes by altering in utero anatomy and physiology.

FCIs are only indicated in specific CHDs; CHDs diagnosed during midgestation that may progress and worsen in utero and cause fetal mortality and neonatal morbidity/mortality may benefit from FCI. These include fetal aortic valvuloplasty (FAV) in severe aortic stenosis (AS) evolving to hypoplastic left heart syndrome (HLHS), fetal pulmonary valvuloplasty in pulmonary atresia with intact ventricular septum PA/IVS, critical pulmonary stenosis (CPS), atrial septoplasty and/or atrial stent in HLHS, and transposition of great vessels with restricted or intact atrial septum[2-5]. This review focuses on these commonly performed interventions, selection criteria of the candidates, technical details, and outcomes of these procedures that have been previously reported in the literature. FCs have started in 1975 to treat fetal ventricular tachycardia[6]. In 1987, the first fetal cardiac pacing was performed in a fetus with complete heart block and hydrops fetalis[7]. The first fetal aortic balloon valvuloplasty was performed in 1991, and the infant eventually underwent biventricular (BiV) repair[8].

FAV In Severe AS with Evolving HLHS

FAV is the most commonly performed FCI. Severe AS may initially present as midgestational dilation and dysfunction. Subsequently, slowing and ultimate cessation of left ventricular (LV) growth is observed, leading to HLHS[9]. Despite advances in the surgical management of HLHS, medium-term survival is approximately 70%, and HLHS still causes significant morbidity, including arrhythmias, neurocognitive impairment, hepatic dysfunction, and fontan-specific complications (protein-losing enteropathy, plastic bronchitis etc.) after surgery. In fetuses with severe AS, if FAV is performed at an appropriate period, it may stop or reduce progression to HLHS, and reduction of LV pressure load may prevent the formation of endocardial and myocardial fibrosis. The aim of FCI is to achieve BiV circulation and improve postnatal outcomes[10,11].

Selection of Candidates

The main challenge in performing FAV is to identify fetuses that will progress to HLHS if left untreated. Mäkikallio et al.[12] demonstrated that significant LV dysfunction, narrow aortic jet with a Doppler velocity >2 m/s, retrograde aortic arch flow, left-to-right flow across the patent foramen ovale, monophasic mitral inflow, neo-development of mitral regurgitation, and abnormal pulmonary vein flow are predictive of progression to HLHS at birth. The mitral valve, aortic valve, ascending aortic diameter Z-score, and LV length were not found to be significant parameters of progression to HLHS at birth.

Careful selection of candidates for whom LV recovery may support systemic circulation after FAV is also important. Fetuses with LV hypoplasia (long-axis Z-score <-2), mitral valve hypoplasia (Z-score <-2) or low LV pressure assessed by mitral regurgitation or AS jet velocity (estimated LV pressure <30 mmHg) should not undergo FCI, as these factors are predictors of low probability of LV recovery and strong predictors of single ventricle circulation despite technically successful FAV. McElhinney et al.[13] presented a multivariate scoring system to predict criteria for a BiV outcome. At least four of the following criteria predicted a BiV outcome: (1) LV long-axis Z-score >0, (2) LV short-axis Z-score >0, (3) aortic annulus Z-score >-3.5, (4) mitral valve annulus Z-score >-2, and (5) AS (or mitral regurgitation) with a maximum systolic gradient of ≥20 mmHg[13]. In 2018, Friedman et al.[14] analyzed 123 fetuses that underwent FAV for evolving HLHS at Boston Children's Hospital between 2000 and 2015. They reported that LV pressure >47 mmHg and ascending aortic Z-score >0.57 are predictors of BiV circulation with 92% probabality. Fetuses with a lower LV pressure or mitral valve Z-score <0.1 and mitral valve inflow time Z-score <-2 were unlikely to have BiV circulation with a 9% probability. The remaining fetuses had an intermediate (~40-60%) probability of BiV circulation.

Technical Aspects and Outcomes

The procedure is performed percutaneously with ultrasound guidance under regional (spinal/epidural) or local anesthesia or both between 21 and 32 gestational weeks. The most important aspect of successful procedure is the fetal position, with the fetal chest lying anteriorly. Intramuscular fetal anesthesia and muscle relaxants are used to facilitate fetal pain relief and appropriate fetal positioning. With ultrasound guidance, passing through the maternal abdomen, uterine wall, anterior fetal chest, and LV, 18-G/19-G Hawkins Atkins needle/Chiba needle/M3 coaxial needle and stylet is advanced into the LV apex. A 0.014" coronary guidewire is then maneuvered across the LV outflow tract, and the Maverick/Hiyuru/Relysis coronary artery balloon is positioned at the aortic annulus (Figure 1). The balloon-to-annulus ratio of 1-1.2 (range: 0.7-1.4) provides the best results. The balloon is then inflated, usually twice. After the procedure, technical success was confirmed by Colozr-Doppler findings of a broader jet of anterograde flow across the aortic valve and/or new aortic regurgitation[10]. Complications include pericardial effusion, tamponade, and bradycardia, which require immediate intervention with pericardiocentesis or intracardiac administration of epinephrine or atropine, respectively. Fetal aortic regurgitation is the most common complication that resolves within a few weeks.

In 2014, Freud et al.[11] analyzed the short- and intermediate-term survival of fetuses who underwent FAV in Boston Children's Hospital between 2000-2013. They reported a technical success rate of 77% in 100 FAV procedures, fetal demise rate of 11%, and 43% of these patients underwent BiV repair. Among all live-born patients, those who underwent a technically successful intervention were significantly more likely to have a BiV outcome than those in whom the FAV was unsuccessful (odds ratio, 5.0; 95% confidence interval, 1.3-18.8; p=0.01). The 10-year survival of the cohort was 72%, which is comparable to the 10-year survival reported for patients with HLHS in other contemporary series.

According to the International Fetal Cardiac Intervention Registry (IFCIR) data in 2015, which included FCI results between 2001 and 2014, in which 18 centers participated, a technical success rate of 81% was achieved in additional 86 FAV procedures, and a fetal demise rate of 17%. In this series, there was a suggestion

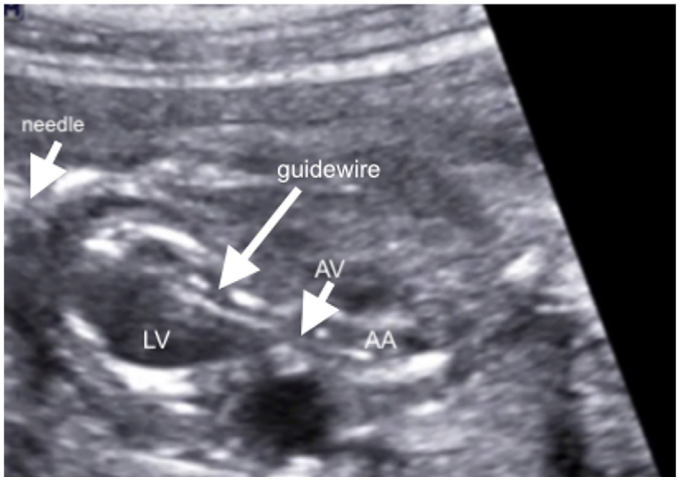

Figure 1. Ultrasound view showing an 18-G needle passing through the maternal abdomen, uterus, fetal anterior chest, and left ventricular apex (24). The coronary guidewire was advanced through the needle, passing through the aortic valve and ascending aorta. LV: Left ventricular, AV: Aortic valve, AA: Ascending aorta

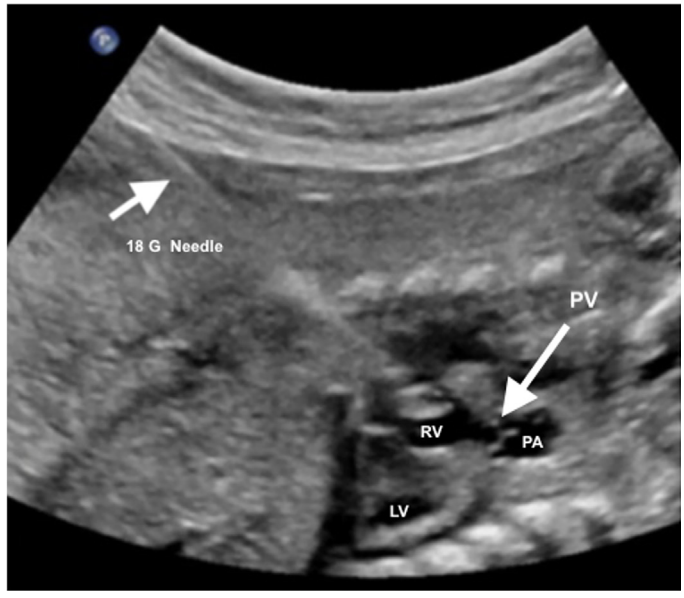

Figure 2. Ultrasound image showing an 18-G needle passing through the maternal abdomen, uterus, fetal anterior chest wall, and right ventricle (24). LV: Left ventricle, PA: Pulmonary artery, PV: Pulmonary valve, RV: Right ventricular, 18-G: 18-Gauge

of improved survival to discharge with BiV circulation; 42.9% in the FAV group versus 19.4% in patients in whom FAV was not performed or were technically unsuccessful, respectively[2].

The largest reported series of FAVs (n=136) were from Boston Children's Hospital. In 2018, Friedman et al.[14] evaluated whether technical success and BiV outcomes after FAV have changed from an earlier (2000-2008) to a more recent (2009-2015) era. In this cohort, the technical success rate was initially 73% and increased to 94%, whereas the fetal demise rate was initially 9.8% and reduced to 6%. BiV circulation was achieved in 41% of live births, with a higher rate of 59%, more recently.

None of the previous studies reported maternal mortality or significant complications related to FCI. Approximately 50% of patients with BiV circulation require aortic valve balloon dilation within the first few years of life, whereas the rest require multiple cardiac catheterizations and surgeries. The postnatal evaluation of BiV post-FAV patients demonstrated that these patients still have LV systolic/diastolic dysfunction and aortic and mitral valve abnormalities. Most patients require interventions after birth, including interventions to the aortic and mitral valve and aortic arch, and endocardial fibroelastosis resection[11]. LV diastolic dysfunction/non-compliance is common, and the development of restrictive LV physiology with left atrial (LA) and pulmonary hypertension remains a concern[11].

In conclusion, the proportion of patients achieving BiV outcomes after FAV has improved because of the improved technical success rate and modification of the selection criteria. Although the initial short-term results and postnatal outcomes are encouraging, medium- and long-term survival data are not yet available.

Pulmonary Valve (PV) Perforation and FPV in PA/IVS or CPS

In fetuses with PA/IVS or CPS, elevated right ventricular (RV) afterload results in RV hypertrophy and reduced compliance, a lack of flow through the right side of the heart, which leads to progressive RV and tricuspid valve (TV) growth arrest, and secondary damage of the RV myocardium. Most fetuses with PA/IVS or CPS with hypoplastic right heart syndrome survive until birth, but they have high morbidity and mortality in postnatal life. In selected fetuses, in utero FPV may lead to a larger RV by reducing afterload and increased filling, thus improving the likelihood of a BiV outcome. The procedure is usually performed between 21 and 32 weeks of gestation in fetuses with membranous PA/IVS or CPS. The exclusion criteria were muscular atresia of the right ventricular outflow tract (RVOT), severe TR with low velocity (<2.5 m/s), severe fetal edema, and presence of large RV sinusoids.

Technical Aspects

Fetal pulmonary valvuloplasty is associated with more technical challenges than FAV. Unlike the LV dilation found in severe AS with evolving HLHS, the RV in these fetuses is small, hypertrophied, and the RV is located under the sternum. The fetal position is again critical for the success of the procedure. The procedure is performed percutaneously with ultrasound guidance under maternal regional (spinal/epidural) or local anesthesia or both. With ultrasound confirmation, an 18 G or 19 G needle is passed through the maternal abdomen, uterus, amniotic cavity, anterior fetal chest wall, and advanced into the RVOT. The RVOT is approached through an intercostal space next to the sternum or by a subcostal approach (Figure 2). The cannula is directed toward the PV and inserted into the RVOT with 10-15-degree angulation. A balloon-annulus ratio of 1.2-1.3 gives the best results. A balloon length of 8-10 mm is usually preferred to prevent RV free wall dilatation[15]. The balloon is placed across the PV and dilated to a balloon-to-valve ratio of at least 80%. Technical success was defined as improved anterograde blood flow through the PV, with subsequent improvement in anterograde flow on color Doppler imaging with or without pulmonary regurgitation. Complications include hemopericardium and bradycardia.

Selection of Candidates and Outcomes

Compared with FAV, there are fewer data on the predictors of disease progression in PA/IVS; therefore, selection criteria are not well established.

TV, Z-score and RV size assessment are currently used. Fetuses with TV Z-score >-2.5 usually have BiV circulation with postnatal interventions, whereas those with TV Z-score <-4 have severe RV hypoplasia that is unlikely to support BiV circulation after FPV. Fetuses with TV Z-score between -2.5 and -4 and qualitatively mild or moderate RV hypoplasia are candidates for FPV.

Gómez et al.[16] reported that tricuspid /mitral annulus ratio (TV/MV) ≤0.83, RV/LV length ratio ≤0.64, pulmonary annulus/aortic annulus ratio ≤0.75, tricuspid inflow duration/cardiac cycle length ≤36.5% can predict a single ventricular outcome with 100% sensitivity and 98% specificity if three of the four criteria are fulfilled[16].

Some centers have reported good results. Tulzer et al.[17] assessed the immediate effects of FPV on fetal RV size and function, in utero RV growth, and postnatal outcomes. Between 2000 and 2017, 35 FPVs were performed on 23 fetuses with PA/IVS (n=15) or CPS (n=8). The median gestational age was 28+4 weeks. There was no fetal demise. Immediately 1-3 days after successful intervention, RV/LV length and TV/MV ratios, RV filling time, and TV-velocity time integral × HR increased significantly, and TR velocity decreased significantly. In fetuses followed longitudinally to delivery (n=5), RV/LV length and TV/MV ratios improved further or remained constant until birth. Fetuses with unsuccessful intervention (n=2) became univentricular; all others (n=21) had either a BiV (n=15), one-and-a-half ventricular (n=3), or still undetermined (n=3) outcome. Five of the nine fetuses with a predicted non-BiV outcome, in which the procedure was successful, became BiV, while two of the nine had an undetermined circulation. The authors concluded that FPV immediately led to a larger RV and thus improved the likelihood of BiV outcomes even in fetuses with a predicted non-BiV circulation.

In another single-center study in 2023, FPVs were performed in 13 fetuses with PA/IVS (n=10) or CPS (n=3)[18]. The median gestational age was 28±4 weeks. All interventions were successful, and no fetal demise were encountered. Pericardial effusion and persistent bradycardia occurred in 15.4% and 38.5% of patients, respectively. The median follow-up period was 11.5 months (6-17). The median postnatal TV Z-score was 1.57 (1.71-0.83). Postnatally, six patients underwent percutaneous pulmonary valvuloplasty and patent ductus arteriosus stenting at the same time (BiV circulation were achieved in four, two had undetermined circulation), three patients were treated with pulmonary balloon valvuloplasty alone, and one patient did not need any intervention.

According to IFCIR data in 2020, in which 14 centers have participated, between 2001 and 2018, among 70 fetuses who were evaluated as PA/IVS and CPS, 58 underwent FPV, and in 12 fetuses, FPV was not attempted[19]. The median gestational age was 26.1 weeks (21.9-31.0) and fetal complications occurred in 55% of the patients (most common pericardial effusion requiring drainage (48%) or bradycardia requiring treatment (36%), including 7 deaths and 2 delayed fetal losses (12%). Among the fetuses who had FPV, 41/58 patients (71%) had technically succesful and 15/58 patients (26%) had unsuccessful intervention, and 2 (58) had unknown data. Measurement of TV increased by 0.32±0.17 mm/week from intervention to birth among those who underwent successful FPV and were higher compared with those who did not have FPV or unsuccessful FPV (0.19±0.15 mm/week). Among 60 liveborn with known outcomes, there was a higher percentage of patients with BiV circulation following successful FPV compared to those who had no FPV or unsuccessful FPV (87% vs. 43%).

In conclusion, FPV may be beneficial for PA/IVS or CPS, although the rates of technically unsuccessful procedures and procedure-related complications, including fetal loss, are significant. Because the FCI criteria for FPV are extremely variable, comparison of patients with intervention and nonintervention are challenging.

Therefore, there is a need for prospective case-controlled studies on fetuses with PA/IVS and CPS using uniform criteria for FPV.

Atrial Septoplasty and/or Atrial Stenting in HLHS with Intact or Restricted Atrial Septum (IAS)

HLHS with intact or restricted IAS causes increased LA and increased pulmonary vascular pressure, which increases morbidity and mortality after stage 1 palliation. These patients have higher mortality risks due to increased LA pressure and low cardiac output than HLHS patients with unrestricted atrial septum. Therefore, atrial septoplasty and/or atrial stenting should be performed in the second trimester to prevent pulmonary vascular changes.

Selection of Candidates

The indications for intervention include restricted/intact IAS (≤1 mm atrial communication), prominent pulmonary vein flow reversal, and pulmonary venous Doppler forward/reverse velocity time integral ratio <3[20].

Technical Aspects and Outcomes

The right or left atrium is punctured perpendicular to the interatrial septum with an 18-G/17-G needle, the stylet, or a 22-G Chiba needle, and atrial septoplasty is performed. Then, a short-length stent (3.5x13 mm) can be inserted. Complications include hemopericardium, stent malposition, and embolization.

According to IFCIR data in 2015, atrial septoplasty was performed in 37 fetuses, and 65% of the patients had successful intervention. However, there was no difference in discharge survival between FCI and non-FCI fetuses[2].

The largest single-center experience described 21 atrial septoplasty interventions, 13/21 interventions resulted in an atrial communication ≥2.5 mm, and the pulmonary vein Doppler profile improved in all such patients. The authors concluded that creation of >3-mm atrial communication was associated with higher postnatal oxygen saturation and better outcomes after stage 1 palliation[21].

Another IFCIR study evaluated 47 fetuses who had FCI; 27 with atrial septoplasty alone (atrial perforation/balloon dilation) and 20 with atrial septal stent placement[22]. The procedural sucess rate was 77%, fetal complications were common, and procedure-related fetal demise occurred in 13%. Cesarean delivery, planned immediate postnatal intervention, restrictive foramen ovale (FO), and neonatal resuscitation were less common in those who underwent procedurally successful FCI than in those with unsuccessful FCI or no FCI. There was a trend toward stents performing better than septoplasties in maintaining a nonrestrictive FO at delivery after procedural success (75% versus 39%). The 1-year survival rate was higher (59%) in FCI fetuses with unrestricted FO at birth compared to in non-FCI fetuses (19%).

A recent systematic review and meta-analysis in 2024, which included 31 studies, compared the results of fetal atrial septal intervention (FASI) and expectant management (EM) in fetuses diagnosed with HLHS and intact/restrictive IAS[23]. Among 746 fetuses, 123 fetuses had FASI and 623 fetuses had EM. Among the fetuses who had FASI, 87% had a technically successful intervention. Age at neonatal death was higher in the FASI group than in the EM group (17 days vs. 7.2 days). The postnatal atrial restrictive septum was lower in the FASI group (38%), compared to the EM group (88%). Neonatal outcomes, including live birth, neonatal death, and survival to hospital discharge, were similar between the groups.

Conclusion

In conclusion, more studies concerning short, medium and long-term benefits of fetal atrial septoplasty and/or atrial stenting in fetuses with HLHS and intact/restricted IAS are necessary.

We have recently reported our initial experience of FCI in our country[24]. We performed a total of five FCIs at our university hospital between 26+3 and 28+2 gestational weeks. The procedures were technically successful in two fetuses with CPS and one fetus with critical AS. FPV

was unsuccessful in a fetus with PA/IVS. No fetal death occurred, and there were no procedure-related significant maternal complications. Three interventions were complicated by fetal bradycardia and pericardial effusion necessitating treatment.

International registry data have demonstrated that FCIs have limited maternal risks and can improve technical success. Careful selection of candidates suitable for FCI, a multi-team approach, and performing these interventions in specialized centers and in collaborations will further improve the results.

Footnotes

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Review Article

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Improving Coronary Artery Bypass Grafting in Women: Difficulties and Outcomes

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Abstract

There continues to be a clear distinction between women and men after coronary surgery. Many argue that higher mortality, complication rate, and worse outcomes among women have been attributed to smaller artery size, higher technical complexity, and more comorbidities at the time of presentation. However, evidence of only a physiologic or anatomical reason for poor outcomes is severely lacking. In this paper, we review the sex differences in coronary artery bypass grafting, the influence of race and sex, and the choice of conduit on outcomes in women. Additionally, we elucidate strategies to improve outcomes, such as including female animals in basic science, enforcing the use of guideline-directed treatments, expanding women's representation in clinical trials, increasing the number of women researchers, and developing Centers of Excellence. This review not only highlights the outcomes and challenges of women undergoing coronary surgery but also proposes avenues for potential solutions to this ongoing issue.

Keywords: Cardiovascular surgery, coronary artery bypass grafting, coronary artery disease, gender, heart, multiple arterial grafting

Sex Differences in Coronary Artery Bypass Grafting Outcomes

Heart disease is the number one killer of women, and its incidence is increasing. More women than men died in the United States between 1984 and 2013 due to cardiovascular disease (Figure 1)[1,2]. Although deaths from cardiovascular disease decreased from 1980 to 2010 largely due to reductions in major risk factors and the

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usage of evidence-based medical therapies, the death rate since 2010 has been rising[2-4]. Ford and colleagues noted that the largest contribution to the reduction in death rate was attributed to secondary prevention and that coronary revascularization [with coronary artery bypass grafting (CABG) or percutaneous intervention (PCI)] for stable or unstable coronary artery disease (CAD) accounted for 7% of the decline in death rate[4]. Notably, since 2010, there has been a steady increase in heart disease and mortality, secondary to increasing rates of obesity, diabetes, and hypertension[5]. While CABG use has declined due to increasing utilization of PCI, CABG is the preferred method in multi-vessel disease, left main disease, patients with diabetes who are appropriate CABG candidates, refractory angina, and patients unable to tolerate dual antiplatelet therapy[6,7]. More importantly, there has been a decrease in post-CABG mortality[8]. However, that effect has not been extended to women. Many studies have shown significant sex differences in CABG outcomes[7,9-19]. Women and non-white patients are less likely to receive guideline-directed medical and surgical therapies despite a comparable benefit[7,9-11,20-22]. Women undergoing CABG tend to present with more risk factors and comorbidities, including hypertension, diabetes, and obesity, compared to men. In addition to being on average, ten years older, women present more frequently with a more severe angina class. Despite less extensive coronary disease (and more small vessel disease), women have greater disabling symptoms[13,23]. Notably, women are more likely to have a silent heart attack and to die within one year after their myocardial infarction (MI). These factors lead to higher postoperative morbidity and mortality rates in women. A meta analysis of 903,346 patients in randomized controlled trials (RCTs) found that women experienced an increase in operative mortality, late mortality, major adverse cardiovascular events, MI, stroke, and repeat revascularization after CABG, compared to men. However, there was no difference in operative or late mortality with the use of the off-pump technique or multiple arterial grafts (MAG)[16,21]. It should be noted that these studies do not clarify the definition of operative mortality as including intraoperative and perioperative deaths; however, our interpretation is that operative mortality includes any death, regardless of cause, occurring within 30 days after surgery.

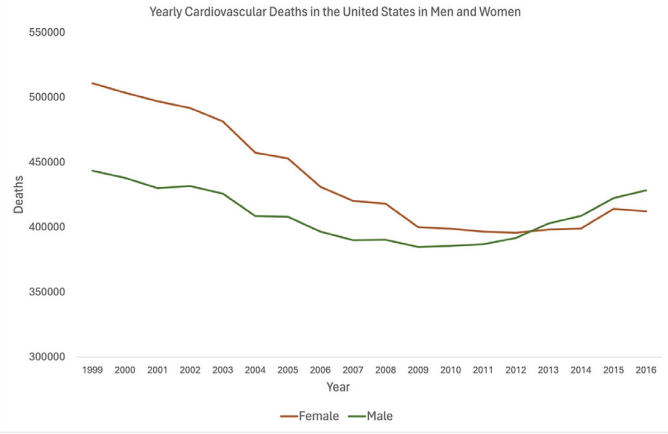

Figure 1. Yearly cardiovascular deaths in the United States in men and women
Mortality from cardiovascular disease in men and women in the United States from 1999 to 2016. The number of deaths were higher in women (orange line) compared to men (green line) from 1999 to 2016. Author made figure with data from Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality: Compressed Mortality File 1999-2016 on CDC WONDER Online Database, released June 2017

While traditional risk factors for heart disease, such as diabetes, smoking, obesity, physical inactivity, hypertension, and dyslipidemia, are well known, unique risk factors in women, such as preterm delivery, hypertensive disorders of pregnancy, gestational diabetes, autoimmune disease, breast cancer treatment, and depression are important, nontraditional risk factors that must be recognized[15] (Figure 2).

Many studies (retrospective, unadjusted) confirm higher operative mortality in women (up to 3 times that of men)[8,19,24-30]. However, studies with risk factor adjustment demonstrate contradictory findings. Several propensity-matched comparisons demonstrate no difference in operative mortality [14,17,19,31-34]. In a study of 1743 patients from the STS database, women required more non-elective interventions, underwent less extensive revascularization,

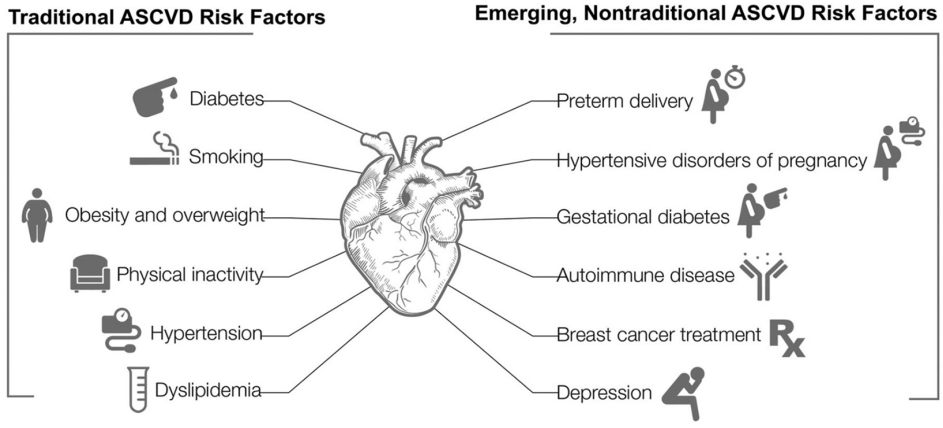

Figure 2. Traditional and emerging non-traditional risk factors for cardiovascular disease in women
An illustration of the increasing traditional risk factors among women, such as diabetes, smoking, obesity, physical inactivity hypertension. Additionally, there are emerging non-traditional ASCVD risk factors such as, preterm delivery, pregnancy complications like hypertensive disorders and gestational diabetes, autoimmune diseases, treatment for breast cancer and depression. Reproduced for Garcia et al.[15]. ASCVD: Atherosclerotic cardiovascular disease

and were less frequently recipients of internal mammary artery grafting, suggesting that female sex itself influenced the extent of coronary artery revascularization and the use of internal thoracic artery grafting[12]. In a nation-wide inpatient sample of 3.6 million propensity-matched patients between 2003 and 2016 undergoing intervention after acute MI, women (33% of the cohort) had higher morbidity, mortality, and longer length of stay, compared to men[18]. This difference persisted over 14 years across PCI and CABG. What is more concerning is that studies have highlighted that women receive fewer arterial grafts than men, potentially affecting long-term outcomes[9].

Influence of Race and Sex on Outcomes

Research suggests that outcomes vary not only by sex but also by race, with disparities in access to care and postoperative outcomes. In a study of over 200,000 women hospitalized for ST-elevation myocardial infarction, non-caucasian women had higher in-hospital mortality and lower odds of PCI compared to other women[35]. Additionally, the study found African-Americans were less likely to receive CABG or mechanical circulatory support[35]. Another study from 1999 to 2014 documented that while overall CABG utilization decreased over the study period, and there was a general decline in post-CABG mortality for all groups, women and black patients consistently exhibited higher mortality rates compared to their male and white counterparts[8]. A study of over a million patients from the Society of Thoracic Surgeons database similarly confirmed that black and female patients had higher odds of mortality and black patients had higher postoperative complications after CABG when compared to other groups[36]. This research underscores the persistent need for tailored interventions to address these disparities and improve outcomes for all patients, especially those in historically marginalized groups.

The Role of Anatomic Differences in Women's CABG Outcomes

Sex differences in CABG outcomes are multifaceted, encompassing anatomic variations, such as smaller coronary arteries in women, which may complicate surgical procedures and affect the choice of conduit, potentially influencing long-term patency rates. The selection of conduit (arterial vs. venous) plays a crucial role, as women may benefit more from arterial grafts, which have shown better long-term outcomes but are underutilized in female patients. Several technical considerations have been proposed for the treatment of women with CAD (Figure 3).

The argument that smaller coronary arteries in women largely underlies the increase in operative mortality is not supported by multiple observations. Firstly, small coronary size is often considered a contraindication to off pump CABG, yet women fare better with off-pump CABG compared to men. In addition, the disparity in operative mortality in women lessens with age, and coronary size does not change with older age[19]. The time to construct a distal anastomosis has been demonstrated to be similar between women and men, suggesting that the technical challenge for smaller arteries does not take more time[12]. Factors contributing to the higher operative mortality in women are thus likely multifactorial and include comorbidities, older age compared to men at the time of CAD diagnosis, and potential bias in treatment.

Does Choice of Conduit Influence Outcomes

It has been evident since 1999 that there has been an underutilization of arterial grafts in women when compared to men[9]. Women have been shown to derive the same benefits from arterial and MAG compared to men[10,20,37]. However, women are less likely to receive left internal mammary artery (LIMA), right internal mammary artery, and radial artery grafts, when compared to men (Figure 4), and the female sex specifically has been associated with non-use of LIMA[10,12,33,38-41]. Compared with male patients, female patients are also less likely to have complete revascularization[9]. Several contemporary studies have confirmed these observations. In the Radial Artery Patency Study, the use of the radial artery to the right coronary or left circumflex artery territory was protective in women, and the patency was better than that of the vein[22]. The use of the radial artery was associated with improved five-year survival in propensity-matched women[37,39,42]. Additionally, a study of 63,402 patients undergoing CABG found that MAG was associated with better outcomes among low-risk, but not high-risk, patients. Specifically, mortality was lower among men undergoing MAG, but not women, at seven years[37].

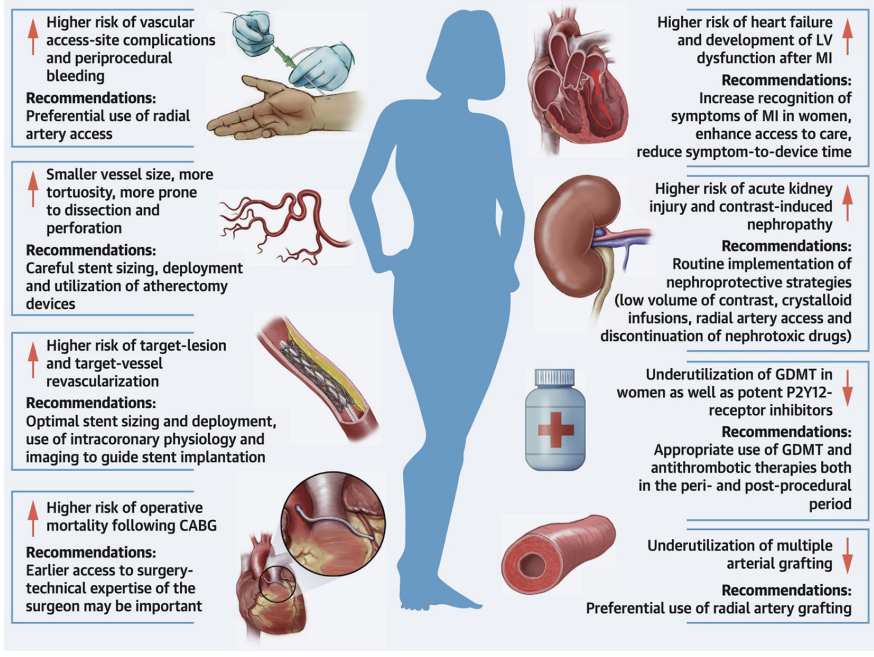

Figure 3. Technical considerations for coronary artery disease treatment in women
Multiple technical considerations have been suggested for the treatment of women with CAD. Reproduced from Gaudino et al.[11] with permission from Elsevier. CABG: Coronary artery bypass graft, CAD: Coronary artery disease, GDMT: Guideline-directed medical therapy, LV: Left ventricular, MI: Myocardial infarction

Strategies to Improve CABG Outcomes in Women

Improving outcomes for women undergoing CABG requires multifaceted strategies that address the unique challenges and disparities they face[41] (Table 1). Delayed diagnosis, treatment conservatism, referral bias, and inaccurate patient and physician perception of risk, all contribute to mortality differences between male and female patients. The lack of angiographically significant CAD, lower utilization of guideline-directed surgical treatment (arterial grafts, of complete revascularization), lower utilization of guideline-directed medical treatment, and lack of involvement of women in clinical trials are also factors that lead to higher mortality in women after CABG[7,37,41]. Efforts to include more women in clinical trials and tailored approaches considering anatomic and physiologic differences are essential for improving outcomes for women in CABG.

Female Animals in Basic Science

The inclusion of female animals in basic science research is a crucial aspect of understanding gender differences in health and disease. While the National Institute of Health (NIH) attempted to increase the enrollment of women in clinical trials in the 1990s, there has only recently been advocacy in the basic sciences[43,44]. The 2015 NIH Initiative on Rigor and Reproducibility dictates that a strong justification must be provided for applications proposing to study only one sex. The predominance of male animals in basic science animal models leads to a gap in knowledge regarding how biological sex influences disease processes and treatment outcomes. There has been a growing emphasis on the importance of including female animals in research to ensure findings are applicable to both sexes.

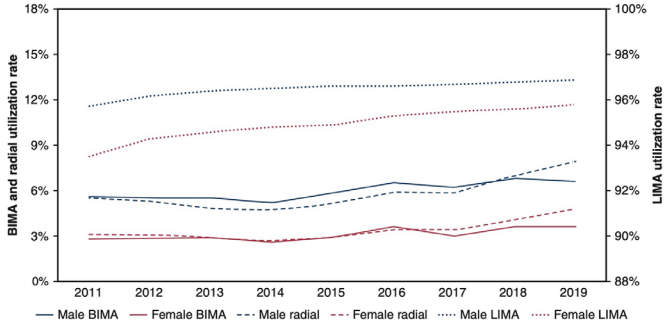

Figure 4. Rates of internal mammary and radial artery utilization Use of arterial grafts in men and women between 2011 and 2019. The illustration shows 1,212,487 patients, women (red lines) and men (blue lines), undergoing CABG from the Society of Thoracic Surgeons (STS) database. The use of bilateral internal mammary artery (BIMA) as solid lines, radial artery graft is depicted as dashed lines, and left internal mammary artery (LIMA) as dotted lines. Women were less likely (significant for all conduits) to receive any arterial graft compared to men. Reproduced from Zwischenberger et al.(41)

Guideline-Directed Medical and Surgical Treatment

Female patients with cardiovascular disease are more likely to receive guideline-recommended care when treated by a female physician[45]. The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization published a class I recommendation for treatment decisions to be based on clinical indication and not on sex, race, or ethnicity[7]. In large part because of the overwhelming evidence, even after controlling for health care access, that once women and non-white patients enter into the health care system, they are less likely to receive reperfusion therapy, an invasive strategy, or revascularization compared with their white male counterparts[7], it is clear there are disparities in treatment. More research is

Table 1. Strategies to reduce mortality in women after coronary artery bypass grafting

Include animals of both sexes in basic science research to understand physiologic differences
Use guideline-directed optimal medical care
Use guideline-directed revascularization strategies including use of arterial conduits
Enroll more women in clinical trials
Surgeon specialization in coronary surgery for women
Establish centers for specialization in the treatment of women with cardiovascular disease

Strategies that can be undertaken to reduce mortality in women after CABG. Reproduced from Zwischenberger et al.(41). CABG: Coronary artery bypass grafting

desperately needed, on eliminating biased non-guideline-directed care from health care systems. Women fare better with off-pump CABG; this technique should be considered. Arterial grafts have shown superior patency rates compared to venous grafts, and tailoring the choice of conduit to account for the anatomic and physiologic differences in women, such as smaller coronary arteries, could enhance outcomes. Specifically, MAG is associated with better outcomes[37]. Women undergoing CABG often present with a higher burden of comorbidities, and a comprehensive approach to better manage these conditions preoperatively can improve postoperative outcomes. Coordinating the focus of multidisciplinary teams could optimize patients' health through medication management, diet and exercise modifications, and closer monitoring.

Enhanced Clinical Trials Representation

Increasing the participation of women in clinical trials is critical. Historically, women have been underrepresented in cardiovascular research, leading to a gap in understanding regarding the most effective treatments for women. By ensuring more balanced gender representation, studies can provide data that is more applicable to the female population, allowing for tailored treatment strategies. Thus, the recruitment and retention of female patients should be a major goal of randomized clinical trials[46]. However, the guidelines for women have been based on research including only men, and there is generally a lack of data on women. The first RCTs on CABG included only men; however, sixteen percent of patients undergoing CABG were female overall[47]. Only 13 STS Database studies from 2011-2019 (1,212,487 patients) were published, and first-time isolated CABG patients were only 25% women (307,145)[41]. In an analysis of 740 clinical trials focusing on cardiovascular disease between 2010 and 2017, 38% of the participants were women[48]. This lack of representation risks development of ineffective therapies or unintended consequences of treatments in women[49].

Promoting Women Researchers in Cardiac Surgery

Encouraging and supporting women researchers in the field can bring new perspectives to addressing the gender disparities in CABG outcomes. The representation of female researchers is significantly lower than that of men in cardiac surgery clinical trials[46]. Women researchers are more likely to investigate issues affecting female patients, potentially leading to innovations in treatment and care strategies tailored to women[50]. In a 2022 study of US clinical trials, of the 266 principal investigators (PIs) that were cardiac surgeons, 6 were women, and women PIs had only 9.5% of all studies funded by industry, and not one woman PI had a clinical trial funded by the NIH[46]. Although resources focus heavily on recruitment strategies and support of junior female researchers, the gender disparity increases significantly at every stage of women's careers, highlighting the need for better strategies for retention throughout a woman's career[51].

Development of Centers of Excellence

Centers of Excellence (COE) have shown improved outcomes and patient satisfaction[52]. The development of COE has the potential to greatly improve outcomes for women. One of many strategies to implement would be to increase patient-physician gender concordance. Female physicians caring for female patients improve patient probability of survival compared to male physicians treating female patients[45,53]. Physician-patient congruence increases patient satisfaction [54]. Additionally, patients with a female physician have been shown to be more likely to receive guideline-directed medical therapy[55]. In a study of the outcomes of surgeries performed by female surgeons, regardless of their surgical specialty, patients had significantly lower rates of 30-day mortality, readmission, or complication within 30 days when their surgery was performed by female surgeons [56].

Establishing specialized centers focused on cardiovascular care for women can ensure that female patients receive the most advanced and tailored treatments

available[57,58]. Like centers of its kind in other specialties, these centers can serve as hubs for research and education, foster innovation in treatment approaches, and raise awareness about cardiovascular care needs of women[52,59]. Multidisciplinary teams that include cardiologists, surgeons, dietitians, rehabilitation specialists, and mental health professionals can provide focused holistic care for women undergoing CABG, but will require a concerted effort from healthcare providers, researchers, and policymakers[60]. This approach ensures that all aspects of a patient's health are addressed, from surgical preparation to recovery and long-term health maintenance. COE allow for increased education of physicians and patients on the nuances of coronary disease and treatment in women.

Educating healthcare professionals about the sex-specific risks and outcomes associated with CABG can improve preoperative planning and postoperative care. Continuous medical education programs should include a review of the anatomic and physiologic differences between men and women, the impact of comorbidities, the nuances of patient management, and recent clinical trial evidence to ensure tailored and effective treatment strategies for women. This will empower women with better knowledge of their condition, treatment options, and the risks and benefits of CABG, which can help in shared decision-making. Optimizing outcomes by these methods involves comprehensive strategies that extend beyond surgical techniques[47] (Table 2).

Recently, the United States government announced a 100 million dollar investment in women's health[61]. The Advanced Research Projects Agency for Health aims to support innovation, investment, research, and patient advocacy to proactively seek solutions in women's healthcare[62]. As the leading cause of death among women continues to be cardiovascular disease, investment in centers devoted to the cardiac care of women should be a priority.

Focusing The Future Research: Improving CABG Outcomes in Women

In conclusion, inequalities between male and female CABG patients have been reported in operative mortality, late mortality, and morbidity. Beyond the potential anatomic disparity, poor outcomes in this population are multifactorial with lower rates of PCI and complete

Table 2. Challenges and solutions for women undergoing coronary artery bypass grafting

Characteristics in women compared with men with CAD	Unique challenges in women with CAD	Potential solutions to improve outcomes in women
Average several years older Multiple risk factors/comorbidities	Delayed CAD diagnosis, treatment conservatism, and referral basis	Preoperative factors Establish effective diagnostic tests in women
More likely to have silent heart attack	Lack of angiographically significant CAD	Improve time to diagnosis Reduce treatment conservatism
More likely to present with sudden death	Diagnostic test inaccuracy	Patient and physician education regarding perception of risk
More likely to die within 1 year after MI	Incorrect patient and physician perception of risk	
More often with urgent or emergent presentation More severe angina class Diabetes more powerful risk factor	Lower intraoperative utilization of guideline directed surgical treatment: arterial grafts, complete revascularization	Intraoperative factors Use of arterial grafts Complete revascularization
Greater disabling symptoms despite less extensive coronary disease (small vessel disease)	Smaller coronaries	Other factors
	Suboptimal involvement in clinical trials	Sex concordance (physician and patient)
Longer time to diagnosis Less likely to undergo ECG, undergo catheterization, receive antiplatelet and statin, and receive revascularization		Centers of specialization for women's health

A summary of the characteristics of CAD in women compared to men, the specific challenges providers face in management of CAD in women, and potential preoperative and intraoperative solutions found to improve CABG outcomes in women. Reproduced from Cho, et al.[47] with permission pending from Wolters Kluwer Health. CABG: Coronary artery bypass graft, CAD: Coronary artery disease, MI: myocardial infarction, ECG: Electrocardiogram

revascularization. Adopting the aforementioned approaches, increasing the number of female surgeons, enhancing heart team discussions at multidisciplinary conferences, and ensuring an adequate offering of PCI or CABG where appropriate, would begin to improve CABG outcomes in women. Healthcare systems and clinicians can significantly enhance the quality of care for women undergoing CABG and thus improve surgical outcomes and patient satisfaction.

Ethics

Footnotes

Authorship Contributions

Literature Search: Briscoe JB, Lawton JS, Writing: Briscoe JB, Lawton JS.

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Quantitative Ultrasonographic Measures of Common Carotid Artery Blood Flow Velocity in Individuals with Prediabetes

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Abstract

Objectives: Prediabetes is often considered an intermediate stage in the development of diabetes. Studies have explored the relationship between prediabetes and various cardiovascular parameters, including quantitative measures of common carotid artery blood flow velocity using ultrasonography. Our research examined prediabetic patients' carotid flow velocity (CFV).

Materials and Methods: The study sample included 120 individuals with prediabetes and 120 controls. In individuals with prediabetes, fasting blood sugar levels ranged from 5.6 to 6.9 millimolar, whereas the levels of glycated hemoglobin ranged from 5.7% to 6.4%. Measurements were performed for the CFVs.

Results: In individuals with prediabetes, there was a significant increase in pulsatility index, and resistive index. Carotid artery blood flow velocity patterns were significantly associated with prediabetes ($p<0.05$ for all).

Conclusion: Prediabetes promoted lower CFV. Prediabetes may cause carotid flow rate decreases owing to endothelial dysfunction.

Keywords: End diastolic velocity, peak systolic velocity, prediabetes, pulsatility index, resistive inde

Introduction

Prediabetes is the transition between type 2 diabetes and normoglycemia. With impaired fasting glucose levels, plasma glucose levels can range from 100 to 125 mg/dL. A 75-g/g oral glucose tolerance test may also diagnose decreased glucose tolerance. Two-hour plasma glucose values between 140 and 199 mg/dL indicate prediabetes. The ADA 2010 guidelines define prediabetes as an HbA1c level of 5.7% -6.4%. Approximately 5% -10% of patients with prediabetes develop type 2 diabetes annually[1,2].

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Brachial artery flow-mediated dilation (FMD) determines the response of arterial diameter to increasing flow. Increased intima-media thickness (IMT) and reduced flow-mediated diameter (FMD) are linked to atherosclerosis. Each Doppler ultrasound stage requires a decision from the examiner. Coronary artery disease (CAD) and death are linked to carotid flow rate[3]. This study examined carotid flow rate parameters in patients undergoing prediabetics.

Materials and Methods

This observational clinical trial was conducted from December 2021 to April 2022. Approval was obtained from the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval no.: 2021/07-30, date: 30.07.2021) and all participants provided written informed consent.

Study Population

The study included 120 patients with prediabetes (72 men, 48 women) and 120 controls (68 men, 52 women). All participants had normal blood pressure (BP) and no coronary disease. The diagnosis of prediabetes follows current standards[4]. In patients with prediabetes, fasting blood sugar was 5.6-6.9 mM and HbA1c 5.7% -6.4%[5]. The exclusion criteria were heart failure, CAD hypertension, and diabetes.

M-mode echocardiograms were conducted in the left lateral decubitus position using Vivid E9 equipment (Bioject Medical Technologies Inc., Portland, OR, USA). ASE guidelines were used to acquire images[6]. Post-physical examination demographics were collected. Smoking status was determined by pack year. The blood glucose, lipid profile, and creatinine levels of all participants were recorded.

Brachial Arterial Reactivity

Ultrasound was used to assess endothelium-dependent dilatation[7]. Alcohol and coffee consumption was restricted for 12 hours before treatment. Imaging was performed in a quiet, dark environment at ambient temperature. All vasoactive medicines were stopped 24 hour before the measurements. The basal diameter was the average of three right brachial artery intima-to-intima measurements after 30 minutes of rest. Imaging and measuring the arterial diameter above the cuff. To induce reactive hyperemia, the longitudinal artery picture was taken 30 seconds before and 2 minutes after deflation after inflating the cuff to 300 mmHg for 5 minutes. The rest of the photos were taken after 5 minutes. After administering 400 g of sublingual glyceryl trinitrate, final arterial images were taken after 3 minutes. A brachial artery EDD indicates endothelial function and predicts cardiovascular (CV) events. Ultrasound was performed following coronary angiography. A brachial artery diameter increase of 10% or more indicated good endothelial function[7].

Laboratory Parameters

All patients underwent antecubital vein punctures to draw blood. Over 30 min, dipotassium-EDTA-treated blood samples were analyzed. Hematological parameters were measured using a Sysmex America Inc. XT-2000i analyzer (Mundelein, IL, USA). Standard laboratory methods assess all biochemical parameters.

Statistical Analysis

All statistical data were calculated using SPSS for Windows (25.0; SPSS Inc., Chicago, IL, USA). The chi-square test was used to evaluate categorical variables across groups. Spearman's rank correlation analysis and Pearson's tests indicated correlations. For statistical significance, $p<0.05$ was used.

Results

The study included 120 patients with prediabetes (mean age: 58.1±0.3 years) and 120 controls (mean age: 57.2±0.4 years). In patients with prediabetes, smoking and hyperlipidemia were considerably greater ($p<0.001$) (Table 1). IMT, pulsatility index (PI), and resistive index (RI) were significantly increased in patients with prediabetes ($p<0.001$, $p=0.013$, and $p=0.024$, respectively) (Table 2). The findings demonstrated a robust positive

correlation between prediabetes and RI, PI, and IMT (r=0.634, p<0.001; r=0.456, p=0.001; r=0.857, p<0.001, respectively) (Table 3).

Discussion

In this study, carotid artery blood flow velocity patterns were associated with prediabetes. The first study to link carotid artery flow velocity to prediabetes. Prediabetes was associated with considerably lower carotid flow velocity, greater upper carotid IMT, and impaired FMD.

Prediabetes and carotid artery blood flow velocity have been studied. Blood flow alterations may indicate vascular dysfunction in patients with prediabetes, which increases the risk of CV disease (CVD). Increased velocity, disrupted flow, or turbulence may cause atherosclerosis, which narrows and hardens the arteries[8,9]. According to some studies, prediabetes may cause carotid artery blood flow alterations that may lead to more serious CV complications. Flow velocity patterns, notably increased velocity or disrupted flow, may indicate early atherosclerotic alterations[10,11].

The basic concept of arterial hemodynamics states that blood flow and BP primarily affect luminal radius and wall thickness[12]. Low NO bioavailability causes arterial endothelial dysfunction (ED), which leads to atherosclerosis, as collagen and elastin thicken walls[3]. Doppler ultrasonography can identify early atherosclerosis in carotid IMT. Suwaidi et al.[13] found that coronary ED increased CVD without obstructive lesions. Our findings revealed that individuals with prediabetes had elevated IMT levels, which was significantly correlated with the presence of prediabetes.

Artery-brachial FMD may help diagnose CAD. Patients with low-FMD may benefit from lifestyle adjustments and other preventive measures. Lower FMD in patients with moderate CAD suggests that FMD can predict early CAD[14]. FMD was linked to increased IMT over a 6-year period. This implies that endothelial function causes atherogenesis[15]. However, Enderle et al.[16] found no correlation between FMD and CAD severity. Lower carotis communis artery (CCA) PSV is associated with greater internal carotid artery (ICA) stenosis[3]. In contrast,

Table 1. Characteristics of the study population

	Controls (n=120)	Prediabetes (n= 120)	p-value
Age, years	57.2±0.4	58.1±0.3	0.612
Gender, male, n, (%)	68	72	0.552
Smoking, n, (%)	22	38	**<0.001**
HL, n, (%)	20	42	**<0.001**
LVEF, (%)	55.4±0.4	55.2±0.6	0.874
BMI, kg/m^2	25.2±0.4	28.6±0.4	**<0.001**
Fasting plasma glucose (mg/dL)	88.2±2.4	114.6±5.7	**<0.001**
HbA1c (%)	4.8±0.3	6.3±0.3	**<0.001**
Cre (mg/dL)	0.72 0.2	0.77±0.1	0.756
TG, mg/dL	174.2±2.8	198.1±2.2	**0.003**
HDL-C, mg/dL	40.6±0.7	33.2±1.4	**0.011**
LDL-C, mg/dL	102.4±3.2	133.3±4.7	**0.022**
TC (mg/dL	142.4±6.0	192.4±5.8	**0.002**
WBC (10^3 × µL)	6.4±1.1	7.6±1.8	0.312
Hgb (g/dL)	13.6±0.3	13.7±0.2	0.734

p-value<0.05. BMI: Body mass index, BP: Blood pressure, Cre: Creatinine, CX: Circumfl ex artery, Glu: Glucose, HGB: Hemoglobin, HbA1c: Glycolized hemoglobin, HDL: High-density lipoprotein, HI: Hyperlipidemia, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, TC: Total cholesterol, TG: Triglyceride, WBC: white blood cell

Table 2. Brachial and carotid artery doppler ultrasound measurements

Brachial doppler measurements	Controls (n=120)	Prediabetes (n=120)	p-value
Brachial vessel diameter (mm)	3.0±0.1	2.9±0.1	0.902
Flow-mediated increase in diameter (mm)	0.32±0.2	0.24±0.3	**<0.001**
Brachial vascular reactivities			
EDD (%)	10.4±0.3	7.6±0.4	**<0.001**
NID (%)	11.2±0.4	9.2±0.4	**0.024**
Hyperaemia (%)	463.2±8.5	427.4±8.6	**0.044**
Carotid doppler measurements			
IMT (mm)	0.74±0.18	1.32±0.14	**<0.001**
PSV (cm/s)	86.2±3.1	77.2±3.1	**0.013**
EDV (cm/s)	31.2±1.5	23.2±2.4	**0.002**
MV (cm/s)	63.6±4.1	55.8±3.8	**0.008**
RI	1.7±0.2	2.4±0.3	**0.024**
PI	0.86±0.1	0.99±0.1	**0.003**

**p-value<0.05. EDD: Endothelium dependent dilation, EDV: End diastolic velocity, IMT: Intima-media thickness, MV: Mean velocity, NID: Nitroglycerin-induced dilation, RI: Resistive index, PI: Pulsatility index, PSV: Peac systolic velocity*

Table 3. Factors associated with prediabetes

Variables	Correlation coefficient (r)	p-value
Age, years	-0.186	0.262
LVEF, (%)	0.004	0.882
Brachial vessel diameter	0.158	0.312
Flow-mediated increase in diameter	-0.648	**<0.001**
EDD (%)	-0.898	**<0.001**
NID (%)	-0.867	**<0.001**
Hyperaemia (%)	-0.752	**<0.001**
IMT (mm)	0.857	**<0.001**
PSV (cm/s)	-0.659	**<0.001**
EDV (cm/s)	-0.758	**<0.001**
MV (cm/s)	-0.713	**<0.001**
RI	0.634	**<0.001**
PI	0.456	**<0.001**

**p-value<0.05, *We conducted a Spearman correlation analysis between the categorical variable prediabetes and other variables. EDD: Endothelium dependent dilation, EDV: End diastolic velocity, IMT: Intima-media thickness, LV-EF: Left ventricular ejection fraction, MV: Mean velocity, NID: Nitroglycerin-induced dilation, RI: Resistive index, PI: Pulsatility index, PSV: Peac systolic velocity*

our study showed that individuals with prediabetes did not have plaque or stenosis in their CCAs. In our study, individuals with prediabetes had normal left ventricular ejection fraction.

Several studies have linked abnormalities in the communis artery (CA) lumen and wall to CV risk factors[17]. CCA measures are less variable and more reliable than ICA and external CA samples[3]. In contrast to carotid atherosclerosis and CVD risk factors, CCA flow velocity and diameter are linked to ischemic stroke[18]. Because fractional shortening and PSV are positively correlated, the carotid flow rate is sensitive to cardiac hemodynamic changes. In addition, middle cerebral artery flow velocity and cardiac index are synergistic in normotensive individuals. The participants in our research had normal BP levels and did not present any cardiac insufficiency symptoms.

Owolabi et al.[19] found a relationship between carotid artery diameter and blood flow velocity in stroke patients. External factors, such as physical activity, temperature, food consumption, light, and noise, can affect carotid flow rates[3]. PI is a semiquantitative indicator that measures arteriolar tone by representing blood flow impedance downstream of sampling[20].

Study Limitations

Limited numbers of patients and controls were included in this study. We did not follow-up long-term.

Left ventricular function, coronary blood flow, carotid blood flow velocity, and arterial stiffness are affected by pulse wave velocity (PWV). Without the PWV estimation, this investigation was limited. Without angiography, subclinical CAD cannot be excluded. However, our patients were asymptomatic and had no echocardiographic evidence of ischemic heart disease. Fifth, we cannot validate the diabetes rate among patients with prediabetes. Finally, extrinsic factors, including physical activity, temperature, food consumption, light, and noise, affect carotid flow rates.

Conclusion

This is the first study to examine carotid blood flow velocity patterns in patients with prediabetes. Reduced carotid flow rate may be caused by ED, increased microvascular resistance in people who are at risk for developing diabetes.

Ethics

Ethics Committee Approval: Approval was obtained from the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval no.: 2021/07-30, date: 30.07.2021).

Informed Consent: All participants provided written informed consent.

Footnotes

Conflict of Interest: The author declare no conflicts of interest concerning the authorship or publication of this article.

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Septal Myectomy without Correction of Moderate and Severe Mitral Regurgitation

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Abstract

Objectives: Septal myectomy (SM) is the gold standard treatment option for patients with hypertrophic obstructive cardiomyopathy (HOCM) whose symptoms do not respond to medical therapy. Extended SM adequately relieves left ventricular outflow tract (LVOT) gradients, abolishes systolic anterior motion (SAM) of the mitral valve and improves mitral regurgitation (MR). However, in patients with moderate and severe MR, controversy remains regarding the necessity of mitral intervention at the time of SM. In this study, we investigated short-term outcomes of SM without correction of moderate and severe MR, as well as risk factors for residual MR ≥2+ after SM.

Materials and Methods: From January 2019 to January 2024, 207 adult patients underwent transaortic SM in our Center. Of these, 119 patients who underwent isolated SM were included in the study: group 1 (n=36) consisted of patients with no or mild MR and group 2 (n=83) consisted of patients with moderate to severe MR. The primary endpoint was the severity of MR after SM. Secondary endpoints included postoperative complications, residual LVOT gradient ≥30 mmHg and residual SAM.

Results: There was no residual MR in the group 1, while 9% of patients in group 2 had moderate MR. Only 3.6% of cases in group 2 required repeated aortic cross-clamping and mitral valve intervention. The mortality rate was 1.2% (1 patient) in group 2, with no deaths in group 1. Complete AV-block requiring permanent pacemaker implantation occurred in 2 patients (5.6%) in group 1 and 6 patients (7.2%) in group 2 (p=0.74). There were 2 patients (5.6%) in group 1 and 4 patients (4.8%) in group 2 with a residual LVOT gradient ≥30 mmHg at discharge (p=0.87). Residual SAM was identified

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in 2 patients (5.6%) in group 1 and 7 patients (8.4%) in group 2 (p=0.58). Multivariate regression analysis identified only residual SAM [odds ratio (OR): 13.994, 95% confidence interval (CI): 2.692-72.744, p=0.02] as a predictor of residual MR ≥2+.

Conclusion: In our study, among patients with moderate and severe MR, only 3.6% required repeated aortic cross-clamping and mitral valve intervention. Before discharge, only 9% of patients had moderate MR. Consequently, in most patients with HOCM and moderate/severe MR not due to organic mitral valve lesion, isolated SM effectively relieves LVOT gradients, SAM of the mitral valve and the associated MR.

Keywords: Cardiovascular medicine, cardiovascular surgery, heart failure

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is the most common hereditary cardiomyopathy characterized by left ventricular hypertrophy[1,2]. The mechanism of left ventricular outflow tract (LVOT) obstruction in patients with HOCM involves both hypertrophic interventricular septum (IVS) and mitral valve (MV) abnormalities. The leaflets of the MV and the submitral apparatus play a significant role in the formation and worsening of LVOT obstruction. Systolic anterior motion (SAM) of the MV, along with its contact with the hypertrophic IVS, results in dynamic LVOT obstruction, impaired coaptation of the MV leaflets, and mitral regurgitation (MR)[3,4].

Currently, septal myectomy (SM) has been the treatment of choice for patients with HOCM and LVOT obstruction[1,2]. However, there remains controversy regarding whether MV procedures should be performed simultaneously. Some authors believe that isolated resection of the IVS is sufficient to eliminate MR[4-6], whereas others advocate for intervention on the MV and submitral structures[7-13].

The purpose of this study was to analyze the clinical and echocardiogram outcomes of SM without correction of moderate and severe MR; and to identify risk factors for residual MR ≥2+ after SM.

Materials and Methods

Patient Selection

From January 2019 to January 2024, 207 patients underwent SM at our center. The exclusion criteria were: 1) age below 18 years old; 2) need for coronary artery bypass grafting and 3) organic aortic and MV disease requiring surgery. Thus, 119 patients who underwent isolated intervention were included in the study. These patients were divided into two groups: group 1 (n=36), consisting of patients with no or mild MR; and group 2 (n=83), consisting of patients with moderate or severe MR (Figure 1).

HOCM was diagnosed based on transthoracic echocardiogram and magnetic resonance imaging (MRI) results, in accordance with the clinical guidelines[1,2]. The indications for surgery included septal thickness >15 mm and LVOT pressure gradient ≥50 mmHg at rest or after exercise (valsalva maneuver / exercise test). The severity of MR was measured by color Doppler ultrasonography and classified as mild (0-1+), moderate (2+), moderate/severe (3+), or severe (4+).

In accordance with the clinical guidelines, all patients received β-blockers without vasodilating effect and/or calcium channel blockers before surgery[1,2].

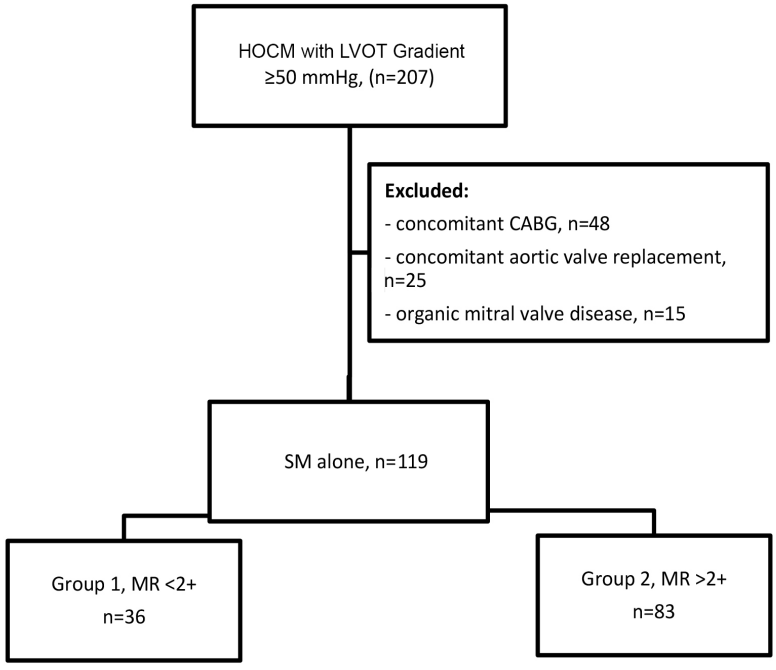

Figure 1. Study Design
HOCM: Hypertrophic obstructive cardiomyopathy, SM: Septal myectomy, CABG: Coronary artery bypass grafting, MR: Mitral regurgitation, LVOT: Left ventricular outflow tract

Patient Characteristics

The clinical and demographic characteristics of the patients along with preoperative echocardiogram findings are presented in Table 1. The age of patients was higher in group 2 than in group 1 (56.5±12.7 years vs. 50.4±13.4 years, p=0.02). Most patients in both groups had New York Heart Association functional class II-III heart failure. Patients with MR 2+ had a higher LVOT gradient (73 [57;99] mmHg vs. 54 [50;68] mmHg, p<0.001), whereas no significant differences were found in septal thickness (23.6±5.1 mm vs. 23.9±4.9 mm, p=0.79). In group 2, 51 patients (61%) had MR 2+, and 32 patients (39%) had MR 3+. Group 2 also had a higher operative risk according to EuroSCORE II (p=0.04). The conducted study complies with the standards of the Declaration of Helsinki, is approved by the Independent Ethical Committee of the Federal State Budgetary Institution Federal Center For Cardiovascular Surgery Ministry of Health of the Russian Federation (Khabarovsk) (approval no: 39, date: 11.11.2023).

Endpoints

The primary endpoint was the severity of MR after SM. The secondary endpoints included the need for repeated aortic cross-clamping to correct MR postoperative complications, residual LVOT gradient, residual systolic SAM, and IVS thickness.

Operative Treatment

All surgeries were performed by two experienced surgeons via a transaortic approach. Separate bicaval venous cannulation was performed in patients with moderate to severe MR. The heart was arrested using antegrade crystalloid (Custodiol solution (Dr. Franz Kohler Chemie GmbH, Germany) or warm blood cardioplegia. A standard SM, as described by Morrow[14], was performed. If diffuse IVS thickening was present, the excision was extended as distally as possible up to the base of the papillary muscles (Figure 2). The aorta was then closed in a double-layer fashion. After bypass, the anatomy and function of LVOT, LVOT gradient,

and MR grade were evaluated using transesophageal echocardiography. In cases of residual high gradient or severe MR, cardiopulmonary bypass (CPB) was resumed for correction.

Statistical Analysis

Statistical calculations were performed using the SPSS software, version 21 (SPSS, Chicago, IL, USA). Categorical variables were presented as numbers and percentages and

Table 1. Baseline characteristics

Parameter	Group 1 (MR <2+) n=36	Group 2 (MR <2+) n=83	p-value
Age (years), M±SD	50.4±13.4	56.5±12.7	0.02
Female gender, n (%)	16 (44.4)	45 (54.2)	0.33
BMI, kg/m², Me [IQR]	29.0 [24.8;34.7]	29.4 [26.6;33.1]	0.88
Family history of HOCM, n (%)	3 (8.3)	3 (3.6)	0.28
Syncope, n (%)	11 (30.6)	22 (26.5)	0.75
Angina, n (%)	16 (44.4)	59 (71.1)	**0.01**
NYHA functional class, n (%): I II III IV	 5 (13.9) 21 (58.3) 9 (25) 1 (2.8)	 4 (4.8) 44 (53.0) 32 (39.0) 3 (3.6)	0.24
Atrial fibrillation, n (%)	5 (13.8)	16 (19.2)	0.48
Ventricular arrhythmias, n (%)	4 (11.1)	12 (14.4)	0.62
ICD insertion, n (%)	2 (5.6)	1 (1.2)	0.17
Diabetes mellitus, n (%)	4 (11.1)	6 (7.2)	0.48
Hypertension, n (%)	27 (75)	68 (82.0)	0.34
COPD, n (%)	5 (13.8)	9 (10.8)	0.64
LVEF, %, Me [IQR]	64 [62;72]	69 [64;73]	**0.02**
LVEDV, mL, Me [IQR]	81 [72;107]	81 [70;101]	0.74
LVESV, mL, Me [IQR]	29 [21;38]	24 [20;33]	0.12
SPAP, mmHg, Me [IQR]	24 [18;29]	30 [21;35]	**0.04**
IVS thickness, mm, M±SD	23.9±4.9	23.6±5.1	0.79
LVOT gradient, mmHg, Me [IQR]	54 [50;68]	73 [57;99]	**<0.01**
SAM, n (%)	35 (97.2)	83 (100)	0.13
MR grade, n (%): 1+ 2+ 3+ 4+	 35 (100) 0 0 0	 0 51 (61.4) 32 (38.6) 0	<0.01
EuroSCORE II, Me [IQR]	0.8 [0.56;0.80]	1.1 [0.75;1.5]	**0.04**

M±SD: Mean ± standard deviation, BMI: Body mass index, Me [IQR]: Median interquartile range, HOCM: Hypertrophic obstructive cardiomyopathy, NYHA: New York Heart Association, ICD: Implantable cardioverter defibrillato, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end-systolic volume, SPAP: Systolic pulmonary artery pressur, IVS: Interventricular septum, LVOT: Left ventricular outflow tract, SAM: Systolic anterior motion, MR: Mitral regurgitation

compared using a χ^2 test or Fisher's exact test. The normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as the mean ± standard deviation and compared using t-test. Continuous variables with non-normal distribution were presented as median [25th percentile-75th percentile] and compared using the non-paired Mann-Whitney U test. The statistical hypotheses were tested at a significance level of p=0.05, indicating that a difference was considered statistically significant if p<0.05. Univariate and multivariate logistic regression analysis was performed to identify risk factors

Table 2. Operative and postoperative data

Parameter	Group 1 (MR <2+) (n=36)	Group 2 (MR <2+) (n=83)	p-value
CBP time, min, Me [IQR]	49 [43.6;57.3]	58 [45;69]	**0.03**
Cross-clamp time, min, Me [IQR]	31.5 [25.3;39.8]	34 [26;47.3]	0.18
Hospital mortality, n (%)	0	1 (1.2)	0.51
VSD, n (%)	0	0	1
Repeated aortic cross-clamping, n (%)	1 (2.8)	4 (4.8)	0.61
Mitral valve repair, n (%)	1 (2.8)	2 (2.4)	0.91
Mitral valve replacement, n (%)	0	1 (1.2)	0.51
Stroke, n (%)	0	1 (1.2)	0.51
Bleeding, n (%)	2 (5.6)	1 (1.2)	0.17
Atrial fibrillation, n (%)	7 (19.4)	14 (16.8)	0.12
Renal impairment, n (%)	1 (2.8)	0	0.13
PPM implantation for heart block, n (%)	2 (5.6)	6 (7.2)	0.74
Duration of stay in the ICU, days, Me [IQR]	2 [2;2]	2 [2;3]	0.5
Duration of postoperative stay in hospital, days, M±SD	11.3±2.9	10.8±2.6	0.29

CBP: Cardiopulmonary bypass, VSD: Ventricular septal defect, PPM: Permanent pacemaker, ICU: Intensive care unit, Me [IQR]: Median interquartile range, M±SD: Mean ± standard deviation

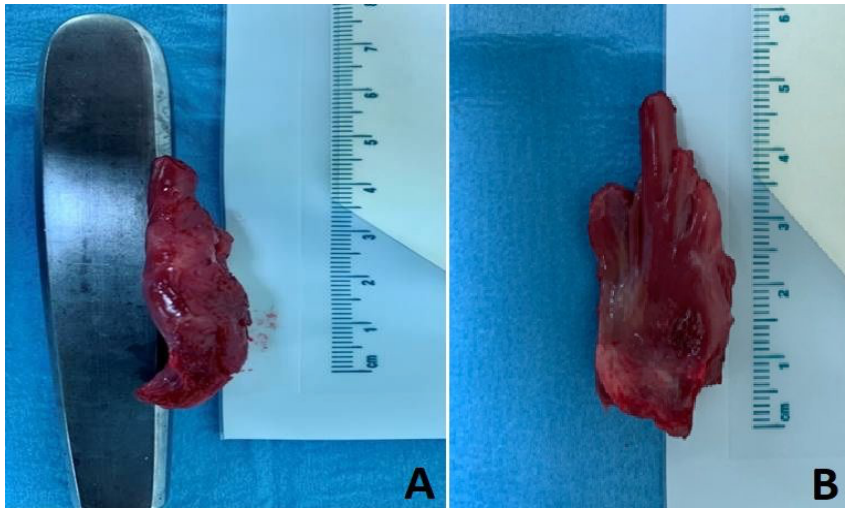

Figure 2. A) Segment of the interventricular septum excised as distally as possible (up to 5 cm)

for residual MR ≥2+ after surgery. Data from the analysis are presented as ORs and 95% confidence intervals (OR; 95% CI).

Results

Surgical and Postoperative Periods

The mean CPB time was longer in the group with MR >2+ (58 [45;71] minutes or min. vs. 50 [44;57] minutes or min., p=0.01), with no difference in the cross-clamp time between the groups (32 [25;40] minutes or min. vs. 36 [26;48] minutes or min., p=0.09). One patient in group 1 (2.8%) and three patients in group 2 (3.6%) required repeated aortic cross-clamping to correct severe MR. In three cases, successful correction of MR was achieved by MV repair according to Calafiore; one patient from group 2 underwent MV replacement with a mechanical valve after an unsuccessful attempt at MV repair according to Calafiore. One patient in group 2 required repeat aortic cross-clamping and ascending aorta and hemiarch replacement due to aortic rupture. There were no cases of acute interventricular septal defect or repeated aortic cross-clamping to perform additional IVS resection due to a high residual LVOT gradient. One patient (1.3%) died in

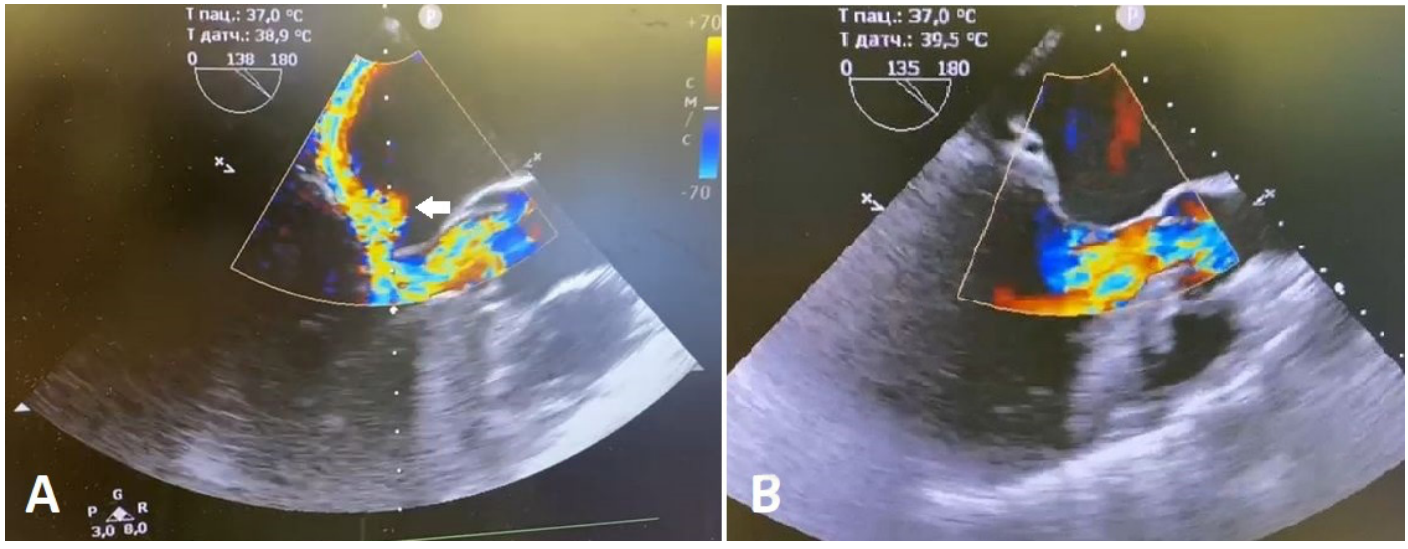

Figure 2. B) Mitral regurgitation before (A, white arrow) and after (B) septal myectomy

Table 3. Hemodynamic parameters before discharge

Variables	Group 1 (MR <2+) n=36	Group 2 (MR <2+) n=79	p-value
IVS thickness, Me [IQR]	12 [10;13]	13 [11;14]	0.36
LVOT gradient, Me [IQR]	11 [9;17]	11 [7;18]	0.93
Residual SAM, n (%)	2 (5.6)	7 (8.4)	0.58
Residual LVOT gradient >30 mmHg, n (%)	2 (5.6)	4 (4.8)	0.87
MR grade, n (%): 1+ 2+ 3+ 4+	 36 (100) 0 0 0	 75 (91) 7 (9) 0 0	0.07

IVS: Interventricular septum, LVOT: Left ventricular outflow tract, SAM: Systolic anterior motion, MR: Mitral regurgitation, Me [IQR]: Median interquartile range, CI: Confidence interval, M±SD: Mean ± standard deviation

Table 4. Risk factors for residual mitral regurgitation ≥2+ after isolated septal myectomy

Risk factors for residual MR ≥2	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p-value
IVS thickness after SM	0.981 (0.885-1.089)	0.722	1.065 (0.893-1.269)	0.483
LVOT gradient after SM	1.106 (0.957-1.279)	0.183	1.003 (0.975-1.032)	0.821
Residual SAM	16.640 (3.387-81.747)	**0.001**	13.994 (2.692-72.744)	**0.02**

MR: Mitral regurgitation, IVS: Interventricular septum, SM: Septal myectomy, SAM: Systolic anterior motion, LVOT: Left ventricular outflow tract, OR: Odds ratio, CI: Confidence interval

group 2 due to mesenteric thrombosis; there were no deaths in group 1. two patients (5.6%) in group 1 and six patients (7.2%) in group 2 required permanent pacemaker implantation due to complete atrioventricular block (p=0.74). The groups did not differ significantly in terms of the frequency of other postoperative complications or duration of intensive care unit or hospital stay (Table 2).

Postoperative Hemodynamics

According to transthoracic echocardiography and MRI (Table 3), the majority of patients in group 2 (91%, n=75) and all patients in group 1 had MR grades 0-1 at discharge (Figure 2). Residual MR grade 2+ was identified in 7 patients (9%) in group 2. There was a significant decrease in IVS thickness in both groups, with no significant differences between the groups (group 1: 12 [10;13] mm, group 2: 13 [11;14] mm, p=0.36). The LVOT gradient was 11 [9;17] mmHg in group 1 and 11 [7;18] mmHg in group 2 (p=0.93) (Figure 3). Two patients (5.6%) in group 1 and four patients (4.8%) in group 2 had residual LVOT gradient ≥30 mmHg (p=0.87). Residual SAM was identified in 2 patients (5.6%) in group 1 and 7 patients (8.4%) in group 2 (p=0.58). Univariate regression analysis identified residual SAM (OR: 16.640, 95% CI: 3.387-81.747, p=0.001) as a predictor of MR ≥2+ after SM (Table 4). Multivariate regression analysis identified only residual SAM (OR: 13.994, 95% CI: 2.692-72.744, p=0.02) as a predictor of residual MR ≥2+.

Discussion

In this study, we evaluated the clinical and hemodynamic results of isolated SM in patients with moderate and severe MR and compared them with patients with no or mild MR.

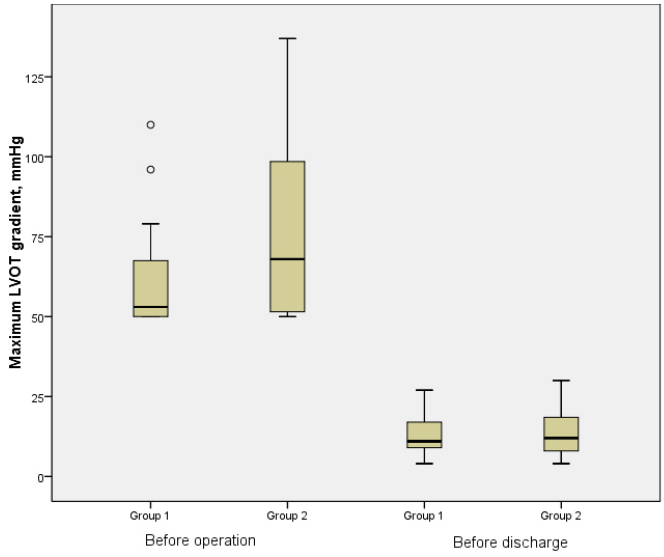

Figure 3. Maximum LVOT gradient before and after septal myectomy
LVOT: Left ventricular outflow tract

We used MR grade after surgery as the primary endpoint. The main finding of the study was that most patients with severe MR after isolated SM experienced a reduction in the severity of MR, with MR grade 2 persisting in only 9% of cases. The frequency of repeated aortic occlusion for unplanned MV intervention due to persistent or increasing severe MR was 3.4%; and MV replacement was performed in only one case (0.8%).

The need for MR correction among patients with HOCM remains a topic of debate.

The Mayo Clinic, which has the greatest experience in the surgical treatment of HOCM (over 3000 patients), believes that isolated SM adequately eliminates left

ventricular (LV) obstruction and SAM-induced MV regurgitation under two conditions. First, the MR was likely due to SAM without MV pathology and anomalies. Second, sufficient extended SM, including excision of the IVS toward the apex beyond the mitral-septal contact, should be performed. When these conditions are met, concomitant MV surgery is rarely required. The frequency of unplanned correction of MR due to insufficient depth and length of IVS excision was 2.8%. After isolated SM, the proportion of patients with MR >3+ decreased from 54.3% to 1.7%[4-6].

Afanasyev et al.[15] reported that 69% of patients with HOCM had moderate to severe MR before surgery, including those with independent MV pathology. MV annuloplasty due to MV pathology was performed in 8.6% of cases, and MV replacement was performed in 14.1% of cases. Residual MR >2+ was observed in 73 patients (12.8%), with the surgeon's individual experience (OR: 3.4, 95% CI: 1.5-7.7, p=0.003) and insufficient resection of the IVS (OR: 2.3, 95% CI: 1.4-3.8, p=0.002) identified as predictors by logistic regression analysis.

Proponents of a more aggressive approach to MR advocate for additional interventions on the MV, including MV replacement, edge-to-edge repair, anterior mitral leaflet plication, and secondary chordal resection. However, modern guidelines suggest that routine MV replacement should not be considered for patients with HOCM to eliminate LVOT obstruction, SAM, and MR because it is associated with increased early and long-term mortality risk[2]. Some authors have reported acceptable results of edge-to-edge SAM repair[10]. Nonetheless, the Alfieri stitch does not completely eliminate LVOT obstruction in cases of incomplete SM, may result in higher MV gradients, and could lead to mitral stenosis or MR in the long term. Anterior mitral leaflet plication, which was first proposed by Cooley[11] and McIntosh et al.[12] , is actively used in Cleveland (25% of all septal myectomies). This technique involves longitudinal plication of the anterior MV leaflet with several separate mattress stitches using 4-0 Prolene sutures and may be beneficial for patients with HOCM and an elongated anterior MV leaflet.

Anomalies of the submittal structures can significantly contribute to the mechanism of LVOT obstruction, SAM, and MR, particularly in patients with lesser IVS thickness (<18 mm)[10,16]. These structures should be carefully evaluated for potential intervention, which may include: mobilization and excision of the accessory papillary muscle, excision of fibrous and muscular attachments between the mitral apparatus and the head of the papillary muscle, LV free wall, and IVS, and resection of the secondary chordae of the MV anterior leaflet. In our study, septal thickness did not influence the persistence of MR after surgery. Bogachev-Prokophiev et al.[9], drawing on the experience of Ferrazzi et al.[8], studied the effects of intervention performed on the submitral apparatus on postoperative gradient, residual MR, and SAM. All patients had moderate to severe MR at baseline. In the submitral intervention group compared with the isolated SM group, there was no residual MR (0% vs. 15%, p=0.013), SAM persisted less frequently (5% vs. 28%, p=0.007), and a lower LVOT gradient was observed (8 mmHg vs. 13 mmHg, p=0.019). Additionally, the need for repeated aortic cross-clamping was more common in the isolated SM group (17.5% vs. 2.5%, p=0.031). The authors concluded that, in most cases, extended SM is sufficient to achieve good results in patients with HOCM. However, when anomalies of the submittal structures are present, intervention may be the preferred approach.

The analysis of the secondary endpoints of this study (mortality, atrioventricular block, acute IVS defect, residual SAM, LVOT gradient >30 mmHg) demonstrated that our results were comparable to those obtained at centers with the greatest experience in surgical treatment of patients with HOCM. Mortality following SM was reported to be 0%-0.9% in the literature and 0.8% in our study population. The frequency of permanent pacemaker implantation was 0.9%-15% in the literature and 6.7% in our study; the frequency of acute IVS defect was 0%-5% in the literature and 0% in our study[3,15,17]. The most

experienced centers report residual SAM in 7-35% of cases and residual LVOT gradient >30 mmHg in 0%-11% of cases; in our study, residual SAM and residual LVOT gradient were reported in 7.6% and 5% of cases, respectively[5,10,15]. The surgeon's experience, depth, and length of IVS excision are commonly reported to be independent predictors of these adverse hemodynamic events[5,15].

Study Limitations

This study is retrospective and based on our database, reflecting the experience of a single center. Both groups were represented by a small sample of patients. Long-term outcome studies and randomized trials are needed to select the optimal treatment for these patients.

Conclusion

In our study, among patients with moderate and severe MR, only 3.6% required repeated aortic cross-clamping and MV intervention. Before discharge, only 9% of the patients had moderate MR. Consequently, in most patients with HOCM and moderate/severe MR not due to organic MV lesions, isolated SM effectively relieves LVOT gradients, SAM of the MV, and associated MV regurgitation.

Ethics

Ethics Committee Approval: The conducted study complies with the standards of the Declaration of Helsinki, is approved by the Independent Ethical Committee of the Federal State Budgetary Institution Federal Center For Cardiovascular Surgery Ministry of Health of The Russian Federatio (Khabarovsk) (approval no: 39, date: 11.11.2023).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Kobzev EE, Rosseykin EV, Desai V, Concept: Kobzev EE, Rosseykin EV, Desai V, Design: Kobzev EE, Rosseykin EV, Desai V, Data Collection and/or Processing: Kobzev EE, Analysis and/or Interpretation: Kobzev EE, Literature Search: Kobzev EE, Writing: Kobzev EE, Rosseykin EV, Desai V.

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The Dynamic Relationship Among Atrial Pacing, Premature Atrial Beats, Mode Switching, and Atrial High-Rate Episodes in Patients with Sick Sinus Syndrome

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Abstract

Objectives: This study aimed to explore the association between atrial pacing percentage, frequency of premature atrial beats, and mode-switch episodes and the occurrence of atrial high-rate episodes (AHREs) in patients with sick sinus syndrome (SSS) who underwent dual-chamber pacemaker (DDDR) implantation.

Materials and Methods: This prospective, single-center, observational study included 60 patients with SSS and Medtronic DDDR pacemakers. Patients with pre-existing atrial fibrillation, ischemic stroke, heart failure, chronic renal failure, or insufficient follow-up data were excluded. Key parameters, such as atrial pacing percentage, premature atrial beats, mode-switch episodes, and AHREs, were evaluated at 1, 3, and 6 months and at 1 and 2 years after implantation.

Results: The mean age of the participants was 65.5 years, with 53.3% of them being male. During the first 3 months, atrial pacing percentage showed an inverse correlation with AHREs (83.7±19.8% at 1 month and 85.2±19.9% at 3 months; p=0.026 and p=0.046, respectively). mode-switch episodes and premature atrial beats were significantly associated with AHREs within the first 6 months (mode-switch episodes: 11.2±4.3 at 1 month, 11.4±3.2 at 3 months, and 6.7±3.1 at 6

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months; p=0.015, p=0.033, p=0.041; premature atrial beats: 6.8±2.3% at 1 month, 7.1±2.1% at 3 months, and 7.2±1.9% at 6 months; p=0.015, p=0.022, p=0.031). AHRE prevalence increased progressively from 9.7±2.3% at 1 month to 18.1±4.1% at 3 months and 23.3±5.9% at 6 months. However, these associations diminished after 6 months, persisting less significantly at 1 and 2 years. Receiver operating characteristic curve analysis determined a 94.5% atrial pacing percentage cut-off at 1 month, with a sensitivity of 68% and specificity of 82% [area under the curve (AUC): 0.806, p<0.001], and a 94% cut-off at 3 months, with sensitivity and specificity of 68% and 90%, respectively (AUC: 0.801, p<0.001). For mode-switch episodes, a 1.5 cut-off value at both 1 and 3 months yielded sensitivities of 73% and 74% and specificities of 99% and 98%, respectively (AUC: 0.890 and 0.895, p<0.001).

Conclusion: This study highlights a time-dependent relationship between pacing parameters and AHREs in patients with SSS. The early post-implantation periods showed significant correlations, which diminished over time. These findings underscore the importance of regular monitoring for optimal management of SSS patients with DDDR pacemakers.

Keywords: Atrial high-rate episodes, sick sinus syndrome, atrial pacing, atrial premature beat, mode switch episodes

Introduction

Atrial high-rate episodes (AHREs) are asymptomatic atrial tachyarrhythmias identified through cardiac implantable electronic devices (CIEDs). These episodes were observed in individuals without a documented history of atrial fibrillation (AF) or AF on standard electrocardiograms. Although AHREs are associated with an increased risk of thromboembolism, this risk is generally lower than that observed in clinical AF. Notably, a higher AHRE burden is correlated with an elevated thromboembolic risk, which may progress over time and potentially precede the development of clinical AF[1,2].

Sinoatrial node dysfunction, commonly referred to as sick sinus syndrome (SSS), can result in various cardiac anomalies. These irregularities may cause symptoms such as palpitations, fatigue, dizziness, syncope, and reduced tissue perfusion. SSS primarily affects individuals aged 65 years and older with a history of cardiac conditions, with an estimated prevalence of 1-2% in this demographic, impacting both genders equally[3].

SSS is characterized by a disruption in sinoatrial node activity, leading to electrocardiographic manifestations, such as sinus bradycardia, sinus arrest, and sinoatrial block. These abnormalities are often accompanied by episodes of supraventricular tachyarrhythmias, forming a condition known as "tachy-brady syndrome". In cases with significant clinical impact, pacemaker implantation is typically required. SSS is one of the leading indications for pacemaker implantation, accounting for 30%-50% of such procedures in the United States[4].

Permanent pacemakers are recommended for patients with sinus node dysfunction accompanied by symptomatic bradycardia or chronotropic incompetence. Dual-chamber pacemakers (DDDRs) are often preferred in these cases because of their ability to address the increased likelihood of atrioventricular (AV) block[5].

The relationship between atrial pacing algorithms and the prevention of AHREs remains an ongoing research. SSSs and AF frequently coexist and influence each other in a complex manner. This study aimed to explore the association between atrial pacing percentages, early atrial beat frequencies, mode-switching episodes, and the occurrence of AHREs over a long-term follow-up period in patients diagnosed with SSS who have received DDDRs and have no prior diagnosis of AF.

Materials and Methods

This prospective, single-center observational study included a cohort of 60 patients who met the inclusion criteria. Participants were selected from individuals diagnosed with SSS who underwent DDDR pacemaker

implantation. All pacemakers used in the study were Medtronic devices, with the AHRE detection feature activated in each device.

To maintain a uniform study population, only patients with a confirmed diagnosis of SSS and DDDR pacemaker implantation using Medtronic devices were included. Individuals with a prior diagnosis of AF and those with a history of ischemic stroke, heart failure, or chronic renal failure were excluded. Patients with incomplete follow-up data were also excluded from the analysis.

The atrial leads in these pacemakers are capable of detecting atrial electrical activity and identifying pre-specified events, including AHREs. AHREs were defined as episodes lasting at least 5 minutes with an atrial rate exceeding 175 beats per minute (bpm) (Figure 1). AF was categorized into three types: paroxysmal AF (self-terminating within 7 days), persistent AF (lasting more than 7 days but less than 1 year), and permanent AF (persisting for over 1 year). All detected AHREs were independently reviewed by two clinicians, and classification decisions were made through mutual agreement. The devices continuously monitored atrial rhythm and automatically recorded relevant data, including arrhythmia events.

Mode switching was defined as the pacemaker's transition from tracking mode to non-tracking mode during episodes of atrial tachyarrhythmia, with a return to tracking mode following the termination of the arrhythmia. Atrial premature beats (APBs) were defined as extra beats originating from atrial regions other than the sinus node preceding a normal heartbeat.

Demographic and clinical data, including age, sex, and comorbid conditions, were documented for all participants. A structured follow-up protocol was designed to assess AHRE trends over time, with evaluations conducted at 1, 3, and 6 months, as well as at 1 and 2 years after implantation. The parameters assessed during each follow-up were AHRE percentage, atrial pacing percentage, number of APBs, mode-switch episodes, and AF status.

The primary endpoint of this study was to investigate the relationship between atrial pacing percentage, APB frequency, and mode-switch episodes and the occurrence of AHREs in patients with SSS implanted with DDDR pacemakers.

The ethical principles outlined in the Declaration of Helsinki were strictly adhered to throughout the study. Approval for this research was given by the ethics committee under the Protocol on the Conduct of Research Conducted Between Osmaniye Provincial Health Directorate and the Owner of the Scientific Research (approval no.: E-77378720-605.01-224398439, date:

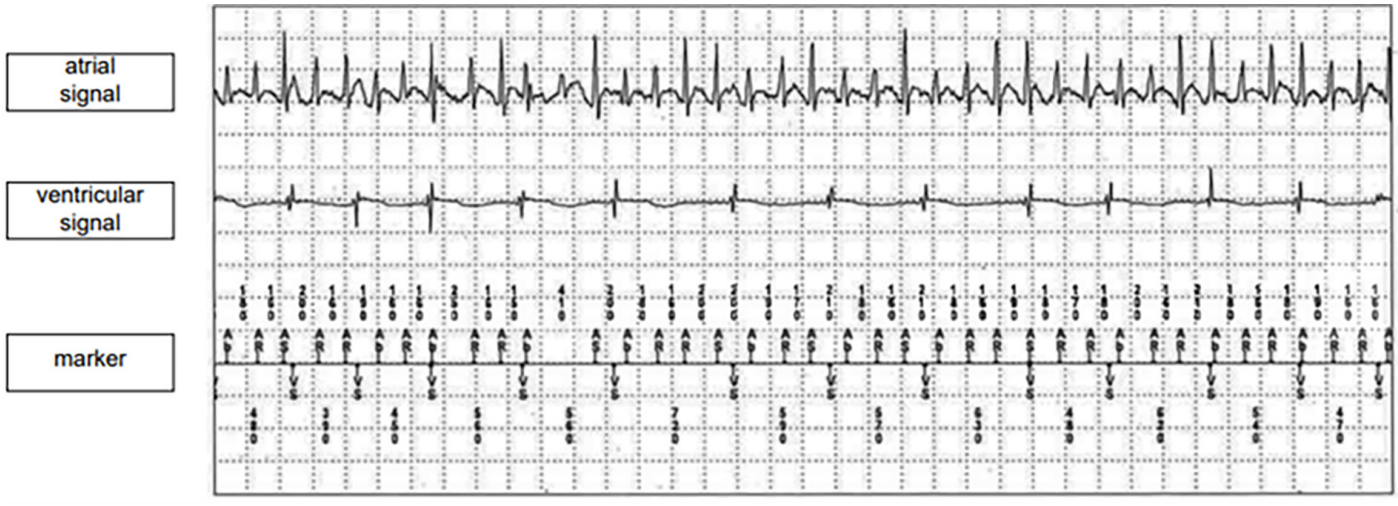


Figure 1. AHRE example recorded from patient
AHRE: Atrial high-rate episode

13.09.2023). All participants provided written informed consent before study enrollment.

Statistical Analysis

Descriptive statistics were used to summarize patients' demographic and clinical characteristics, with results presented as means, standard deviations, frequencies, and percentages. Categorical variables, such as AHRE presence and mode changes, were analyzed using chi-square or Fisher's exact test. For continuous variables, including atrial and ventricular pacing percentages, independent t-tests were used for data with normal distributions.

To examine the influence of device events on AHRE development, a multivariate Cox regression analysis was conducted. Additionally, receiver operating characteristic (ROC) curve analysis was performed to determine the impact of atrial pacing frequency and mode-switch episodes on AHRE occurrence. Statistical significance was set at a p-value of <0.05. All statistical analyses were performed using IBM SPSS version 25 (Chicago, IL, USA).

Results

The study enrolled a total of 60 patients, with a mean age of 65.5 years (±7.3). Male participants comprised 53.3% of the group (32 individuals). Hypertension was reported in 48.3% of the participants, and coronary artery disease was noted in 30.0%. Regarding antiarrhythmic therapy, 61.7% (37 patients) were prescribed beta-blockers, 23.3% (14 patients) were treated with calcium channel blockers, 5.0% (3 patients) used propafenone, 3.3% (2 patients) were on sotalol, and 11.7% (7 patients) received amiodarone (Table 1).

At the end of the 2-year follow-up, 38 patients were diagnosed with atrial AF. Of these, 27 were initiated on direct oral anticoagulants and 3 were prescribed warfarin. Three patients with a CHA_2DS_2-VASc score of 1 were started on acetylsalicylic acid, and no antiplatelet or anticoagulant therapy was initiated for five patients with a CHA_2DS_2-VASc score of 0. During the monitoring period, ischemic stroke occurred in five patients, and one patient receiving warfarin experienced a hemorrhagic stroke.

Device data from all participants who underwent pacemaker implantation for sick SSS were thoroughly analyzed. Each participant had a Medtronic pacemaker with a DDDR. The average lower rate limit of the pacemakers was 61.2 bpm (±3.6). At the end of the follow-up period, 63.3% (38 patients) developed AF.

The atrial pacing percentage, APBs, mode-switch episodes, and AHREs were evaluated at specified intervals-1, 3, and 6 months, as well as 1 and 2 years after implantation-and are summarized in Table 2.

Cox regression analysis identified a significant inverse association between atrial pacing percentage and AHRE occurrence during the 1st and 3rd months (p=0.026 and p=0.046, respectively). However, this relationship was not observed at 6 months, 1 year, or 2 years. Additionally, a significant association was found between mode-switch episodes, APBs, and AHREs during the initial 1st, 3rd, and 6th months (p=0.015, p=0.033, and p=0.041 for mode-switch episodes; p=0.014, p=0.022, and p=0.031 for APBs). These associations diminished by the 1st and 2nd years of follow-up (Table 3).

ROC curve analysis was performed for the 1st and 3rd months to evaluate the predictive impact atrial pacing

Table 1. Patient characteristics and antiarrhythmic drugs

Patient characteristics	(n=60)
Age (years) (mean±SD)	65.5 ± 7.3
Sex (male) (%)	32 (53.3)
Active smoker (%)	29 (48.3)
DM (%)	13 (21.7)
HT (%)	28 (46.7)
CAD (%)	18 (30.0)
Valvular disease*(%)	13 (21.7)
Hyperlipidemia (%)	19 (31.7)
Antiarrhythmic drugs	
Beta-blocker	37 (61.7)
Calcium channel blocker	14 (23.3)
Propafenone	3 (5.0)
Sotalol	2 (3.3)
Amiodarone	7 (11.7)

*CAD: Coronary artery disease, DM: Diabetes mellitus, HT: Hypertension, SD: Standard deviation. *moderate to severe valve regurgitation or valve stenosis*

percentage and mode-switch episodes on AHREs. In the 1st month, an atrial pacing percentage cut-off value of 94.5% yielded a sensitivity of 68% and a specificity of 82% [area under the curve (AUC): 0.806, p<0.001]. This cut-off remained consistent in the 3rd month at 94%, with a sensitivity of 68% and a specificity of 90% (AUC: 0.801, p<0.001). Regarding mode-switch episodes, the 1st month cut-off value was 1.5, achieving 73% sensitivity and 99% specificity (AUC: 0.890, p<0.001). The same cutoff was maintained in the 3rd month, with 74% sensitivity and 98% specificity (AUC: 0.895, p<0.001) (Figure 2).

Discussion

In this study, we explored the complex relationship between atrial pacing, mode-switch episodes, premature atrial contractions, and the occurrence of AHREs in patients with SSS who received DDDR. During the first 3 months following pacemaker implantation, an inverse association was observed between atrial pacing percentage and AHREs. However, this link diminished over longer follow-up periods. Similarly, mode-switch episodes and the frequency of premature atrial beats were significantly correlated with AHREs during the initial six months, but these associations were no longer evident beyond that timeframe. These findings emphasize the importance of the early post-implantation period in AHRE development in this patient group.

AF is a well-documented comorbidity in individuals with SSS[6]. However, the causal relationship between AF and SSS remains debated-whether AF is a precursor to SSS or SSS predisposes patients to AF. AF induces structural and functional changes in the sinus node at cellular and molecular levels, which may contribute to SSS. Mechanisms such as sinus node dysfunction, AF, and electrical remodeling are thought to play a role in initiating AF, supporting previous research in this area[7,8]. Additionally, evidence suggests that AHREs detected by CIEDs serve as predictors for future AF episodes, although the specific prevalence and predictors of AHREs in SSS patients with pacemakers remain less defined[9,10].

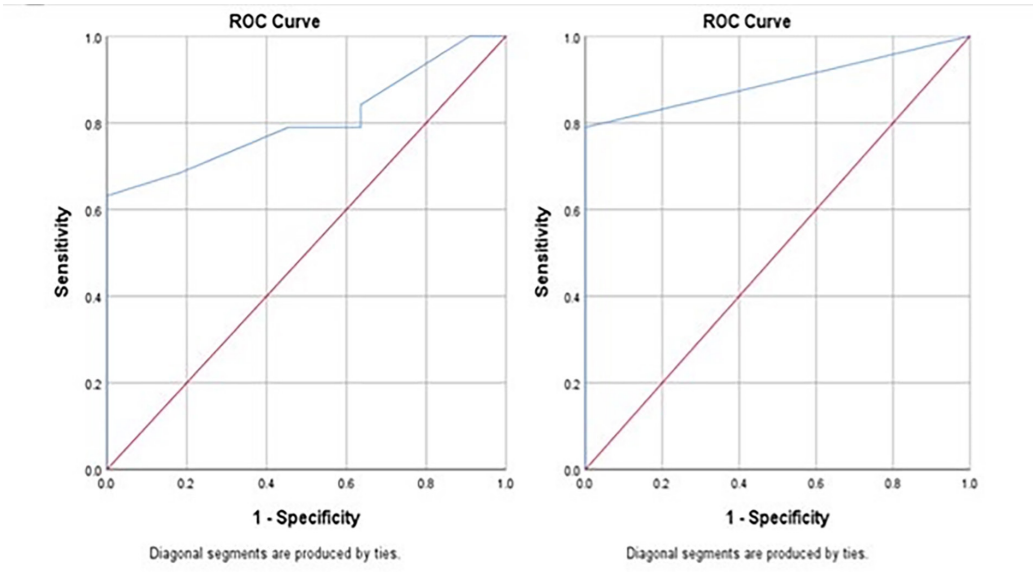
Table 2. Data obtained in follow-up from the pacemakers

Mean pacemaker lower rate limit (bpm) (mean±SD)	**61.2±3.6**
Atrial pacing percentage (mean ± SD)	
First month	83.7±19.8
Third month	85.2±19.9
Sixth month	84.7±23.1
First-year	86.5±22.3
Second year	87.4±20.7
Atrial premature beat percentage (mean±SD)	
First month	6.8±2.3
Third month	7.1±2.1
Sixth month	7.2±1.9
First-year	6.9±2.3
Second year	7.0±2.1
Mode switch episode (mean±SD)	
First month	11.2±4.3
Third month	11.4±3.2
Sixth month	6.7±3.1
First-year	2.4±1.9
Second year	2.1±1.1
Atrial high-rate episode (mean±SD)	
First month	9.7±2.3
Third month	18.1±4.1
Sixth month	23.3±5.9
First-year	29.2±6.3
Second year	35.8±8.1
Patients diagnosed with atrial fibrillation n (%)	38 (63.3)

SD: Standard deviation, bpm: Beats per minute

Table 3. Effects of device events on the development of Atrial High-Rate Episodes

Multivariable cox regression analysis			
Device events	**Hazard ratio**	**95% Confidence interval**	**p-value**
Atrial pacing percentage			
First month	0.984	0.971-0.998	**0.026**
Third month	0.986	0.973-0.999	**0.046**
Sixth month	0.989	0.978-1.000	0.059
First year	0.990	0.978-1.001	0.085
Second year	0.989	0.976-1.002	0.095
Atrial premature beat percentage			
First month	1.040	1.013-1.078	**0.014**
Third month	1.038	1.006-1.072	**0.022**
Sixth month	1.035	1.007-1.064	**0.031**
First year	1.040	0.974-1.110	0.241
Second year	1.037	0.909-1.183	0.590
Mode switch episode			
First month	1.020	1.004-1.036	**0.015**
Third month	1.015	1.001-1.030	**0.033**
Sixth month	1.012	1.001-1.024	**0.041**
First year	1.031	0.983-1.082	0.210
Second year	1.012	0.980-1.046	0.461



Risk Factor	AUC (95% CI)	Cutoff	P Value	Sensitivity	Specificity
Atrial pacing percentage					
First month	0.806	94.5	<0.001	0.68	0.82
Third month	0.801	94.0	<0.001	0.68	0.90
Mode switch episode					
First month	0.890	1.5	<0.001	0.73	0.99
third month	0.895	1.5	<0.001	0.74	0.98

AUC: Area Under the Curve, CI: Confidence Interval

Figure 2. Representation of the effect of atrial pacing frequency and mode-switching episodes in terms of the development of AHRE by ROC analysis
AHRE: Atrial high-rate episode, AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristic

The sinus node is involved in the pathogenesis of both SSS and AF. Mechanistic theories, such as the "wavelength of re-entry" and "focal source hypothesis," underscore the role of electrical remodeling and sustained re-entry in arrhythmogenesis[11,12]. In SSS, slowed atrial conduction often leads to compensatory pauses and activation of ectopic atrial foci, which may trigger AHREs. Multifocal atrial rhythms, which are often observed before AHRE onset, further illustrate the interplay between sinus node dysfunction and atrial arrhythmias[13].

Our analysis revealed that atrial pacing was inversely associated with AHRE development during the initial 3 months of follow-up, although this protective effect waned over time. Additionally, mode-switch episodes and premature atrial contractions were strongly associated with AHREs during the first six months but showed no significant correlation was observed in subsequent follow-up periods. These temporal patterns highlight the dynamic nature of these relationships and suggest the need for targeted monitoring and management in the early post-implantation period.

DDDR pacemakers are instrumental in optimizing cardiac function by preserving AV synchrony and preventing bradycardia-induced tachyarrhythmias. Studies have suggested that higher pacing rates in such devices may allow for greater beta-blocker dosing, potentially

reducing the incidence of AHREs[14-16]. However, the potential impact of elevated pacing percentages and ventricular pacing on long-term AHRE risk requires further investigation. Current guidelines advocate the use of DDDR that maintain AV synchrony as the preferred approach for managing SSS[17-19].

Mode-switching algorithms designed to detect and respond to atrial tachyarrhythmias play a pivotal role in preventing inappropriate atrial pacing and tracking during arrhythmic events. The frequency of mode-switch episodes is a reliable marker of AHRE burden given the sensitivity and specificity of modern pacemaker algorithms. Despite their effectiveness, occasional atrial sensing disruptions due to AHREs may occur, but these are typically resolved through tracking algorithms[20].

Premature atrial contractions, which were once considered benign, are now recognized as significant risk factors for AF. The observed association between AHREs and early atrial contractions in our study underscores their role as precursors to arrhythmias like AF. These findings emphasize the importance of early detection and intervention for managing atrial arrhythmias and preventing progression to more severe conditions[21,22].

Study Limitations

This study has several limitations that should be considered. First, the sample size was relatively small, which may limit the generalizability of our findings to a broader population. Second, this was a single-center study, and potential variations in clinical practices or patient populations at other institutions were not considered. Third, although the follow-up period was sufficient to observe the early and mid-term dynamics of AHREs, longer follow-up may be required to understand the full trajectory of AHRE development and its clinical implications. Additionally, the study did not account for potential confounding factors such as variations in comorbid conditions, medication adherence, or changes in pacemaker settings over time. Future studies with larger multicenter cohorts and longer follow-up periods are necessary to validate and expand upon these findings.

Conclusion

Our study highlights the dynamic interplay between atrial pacing percentage, mode switch episode, and premature atrial beats in relation to the development of AHREs in patients undergoing SSS post-DDDR implantation. The initial 3 months after implantation demonstrated a significant inverse relationship between atrial pacing percentage and AHREs, alongside notable associations between mode switch episode and APBs with AHREs during the first six months. However, these relationships weakened over time, suggesting that early monitoring and intervention are crucial in mitigating the risk of AHREs in this patient population. Our findings underscore the importance of ongoing research to further elucidate the mechanisms and long-term implications of AHREs in patients with SSS.

Ethics

Ethics Committee Approval: The ethical principles outlined in the Declaration of Helsinki were strictly adhered to throughout the study. Approval for this research was given by the ethics committee under the Protocol on the Conduct of Research Conducted Between Osmaniye Provincial Health Directorate and the Owner of the Scientific Research (approval no.: E-77378720-605.01-224398439, date:13.09.2023).

Informed Consent: The need for patient consent for enrollment and publication was waived because of the retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Yaylak B, Süleymanoğlu C, Concept: Polat F, Süleymanoğlu C, Design: Yaylak B, Süleymanoğlu C, Data Collection and/or Processing: Polat F, Süleymanoğlu C, Analysis and/

or Interpretation: Yaylak B, Polat F, Literature Search: Yaylak B, Polat F, Writing: Polat F.

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Potential Protective Effects of Boldine in Rat with an Experimental Myocardial Ischemia-Reperfusion Model

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Abstract

Objectives: Myocardial ischemia-reperfusion injury (MIRI) remains a major challenge in cardiovascular medicine due to its complex pathophysiology involving oxidative stress, inflammation, and cellular dysfunction. Boldine, a potent natural alkaloid with antioxidant and anti-inflammatory properties, has demonstrated protective effects in various pathological conditions. However, its potential cardioprotective effects in MIRI remain largely unexplored. This study aims to evaluate the protective effects of Boldine in a rat model of MIRI by assessing oxidative stress markers, histopathological changes, and inflammatory responses.

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Abstract

Materials and Methods: Male Albino Wistar rats were randomly assigned to four groups: Control, Boldine, myocardial ischemia-reperfusion (MIR), and myocardial ischemia-reperfusion + Boldine (MIR+B). Myocardial ischemia was induced by ligating the left anterior descending coronary artery for 30 minutes, followed by 120 minutes of reperfusion. Boldine (50 mg/kg) was administered intraperitoneally at the onset of reperfusion. Cardiac tissue samples were collected for histopathological evaluation and biochemical analysis, including total antioxidant status (TAS), total oxidant status (TOS), and Oxidative Stress index (OSI).

Results: Histopathological analysis revealed significant myocardial disorganization and inflammation in the MIR group compared to controls ($p=0.05$). Boldine treatment significantly reduced inflammation and myocardial disorganization in the MIR+B group ($p<0.05$), suggesting a protective effect. Biochemical analysis showed a marked decrease in TAS levels and an increase in TOS and OSI in the MIR group ($p<0.001$). However, Boldine administration significantly restored TAS levels and reduced TOS and OSI in the MIR+B group ($p< 0.001$), indicating attenuation of oxidative stress.

Conclusion: Boldine exhibits significant cardioprotective effects in a rat model of MIRI by reducing oxidative stress, mitigating myocardial disorganization, and alleviating inflammation. These findings suggest that Boldine may serve as a therapeutic agent in ischemic heart disease. Further research is warranted to elucidate its precise mechanisms of action and potential clinical applications.

Keywords: Myocard, ischemia-reperfusion, boldine, TAS, TOS, OSI, interstitial fibrosis, inflammation, myocardial disorganization

Introduction

Ischemic heart disease (IHD) remains one of the leading causes of morbidity and mortality world-wide, with cardiovascular diseases accounting for nearly half of all deaths annually in developed countries[1]. The most common form of IHD, coronary artery disease, is characterized by the progressive narrowing of coronary arteries due to atherosclerotic plaque formation, and, in some cases, vasospasm[2]. This reduction in myocardial blood supply often manifests clinically as angina, myocardial infarction, or chronic heart failure, placing a substantial burden on healthcare systems globally[3]. The pathophysiological hallmark of IHD is an imbalance between myocardial oxygen supply and demand, which leads to ischemic injury and subsequent complications[4]. As therapeutic interventions continue to advance, current research is increasingly focused on strategies to mitigate ischemic damage and promote myocardial recovery[5-7].

Myocardial ischemic injury results from a significant disruption in coronary blood flow, leading to a spectrum of clinical manifestations. Decades of research have provided insights into the complex responses of myocardial tissue to ischemia, uncovering a cascade of metabolic and structural changes that can progress to irreversible damage[2-4]. Ischemia is marked by oxygen deprivation due to insufficient blood supply, which causes cellular energy depletion and the accumulation of toxic metabolic byproducts[2,8,9]. Although the restoration of blood flow is essential for clearing metabolites and initiating tissue repair, reperfusion paradoxically exacerbates tissue damage through mechanisms such as oxidative stress, calcium overload, and inflammatory responses[2,10,11]. This dual-edged nature of ischemia-reperfusion (IR) injury highlights the intricate complexity of myocardial pathology.

Myocardial ischemia-reperfusion injury (MIRI) involves a cascade of metabolic, structural, and histopathological changes that begin during ischemia and are exacerbated upon reperfusion. During ischemia, the deprivation of oxygen and nutrients leads to a decline in

oxidative phosphorylation, resulting in a marked reduction in the synthesis of high-energy phosphates such as adenosine triphosphate (ATP) and phosphocreatine. This energy deficit impairs the Na^+/K^+-ATPase pump, leading to intracellular accumulation of sodium and calcium ions[12]. Elevated calcium levels activate proteases and phospholipases, compromising the integrity of cellular membranes and contractile proteins[2,12]. Anaerobic glycolysis becomes the primary energy source, producing lactate and hydrogen ions, which cause intracellular acidosis and disrupt ion transport systems. This acidosis promotes the production of pro-inflammatory cytokines and diminishes antioxidant enzyme activity, rendering cells highly vulnerable to oxidative stress upon reperfusion[2,4]. Histologically, ischemic cardiomyocytes exhibit early changes such as mitochondrial and sarcoplasmic reticulum swelling, cytoplasmic vacuolization, and chromatin clumping in the nucleus[2,12]. Prolonged ischemia leads to irreversible damage, including contraction band necrosis due to hypercontracted myofibrils and calcium phosphate deposition in mitochondria. These changes are accompanied by membrane defects and leakage of intracellular contents. Upon reperfusion, the rapid influx of oxygen exacerbates these injuries by generating excessive reactive oxygen species (ROS). ROS destabilize mitochondrial membranes, further activating proteases and phospholipases, and amplifying cellular damage[3,12]. Reperfusion also elicits significant inflammatory responses, marked by neutrophil infiltration. These inflammatory cells release proteolytic enzymes and ROS, compounding the damage. Histopathological findings include interstitial edema, hemorrhage, and microvascular obstruction commonly referred to as the "no-reflow" phenomenon. In infarcted zones, necrotic myocytes display cellular and organelle swelling, while apoptotic cells exhibit nuclear fragmentation and membrane blebbing. These injuries often extend beyond the infarcted region, contributing to adverse ventricular remodeling and long-term myocardial dysfunction[2-4]. This intricate interplay of metabolic and structural damage, coupled with the inflammatory response, underscores the dual challenge posed by IR injury and highlights the critical need for targeted therapeutic strategies to mitigate its effects.

Boldine, an alkaloid derived from the Chilean boldo tree (Peumus boldus), has gained recognition as a potent natural antioxidant with remarkable pharmacological properties[13,14]. Its antioxidant efficacy is primarily attributed to its ability to neutralize ROS, prevent lipid peroxidation (LPO), and enhance cellular antioxidant defenses[14,15]. Studies have demonstrated that Boldine effectively inhibits free radical-induced erythrocyte hemolysis and protects against LPO in human liver microsomes[13,16]. In diabetic animal models, Boldine has been shown to normalize elevated activities of manganese superoxide dismutase (SOD) and glutathione (GSH) peroxidase in pancreatic mitochondria, underscoring its role in mitigating oxidative stress-induced damage[14,17]. Furthermore, Boldine exhibits protective effects on the vascular system by reducing oxidative stress and improving endothelial function. Specifically, Boldine attenuates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated superoxide production, a mechanism implicated in endothelial dysfunction in conditions such as hypertension and diabetes. By decreasing superoxide levels, Boldine preserves nitric oxide (NO) bioavailability, a critical factor for maintaining vascular health[17]. Additionally, studies in animal models have reported that Boldine treatment reduces malondialdehyde levels, a marker of LPO, and enhances mitochondrial integrity in organs such as the liver and pancreas[18-21]. Boldine's neuroprotective properties have also been demonstrated under ischemic conditions. Konrath et al.[22] observed that Boldine significantly reduced lipoperoxidation and enhanced cellular viability in hippocampal slices subjected to oxygen and glucose deprivation, mimicking stroke-induced oxidative stress. Its dual antioxidant and anti-inflammatory properties extend to suppressing inflammatory cytokines, such as interleukin-6 (IL-6), and mitigating oxidative damage in inflammatory conditions.

Although Boldine has been extensively studied for its antioxidant and cytoprotective effects across various organ systems, research specifically addressing its impact on myocardial tissue remains limited. Cardiomyocytes are particularly vulnerable to oxidative damage, especially during IR injury, as the imbalance between ROS production and antioxidant defenses results in cellular dysfunction and necrosis. While Boldine's efficacy has been well-documented in neuroprotective and hepatoprotective models, its potential to safeguard myocardial tissue from IR injury has yet to be fully explored.

This study aims to evaluate the protective effects of Boldine in a rat model of experimental MIRI. By investigating its antioxidant properties and underlying mechanisms of action, we seek to determine whether Boldine can mitigate oxidative damage, preserve myocardial function, and reduce overall tissue injury during IR. This research aims to provide new insights into Boldine's therapeutic potential in cardiovascular medicine and explore its applicability as a cardioprotective agent in IHD.

Materials and Methods

Animals

This study was conducted using male Albino Wistar rats, aged 12 weeks and weighing between 270 and 320 grams. The animals were sourced and raised within a specialized experimental research facility in Ankara, Türkiye (approval no: E-66332047-604.01-1128916, date: 27.12.2024) and were performed in a dedicated laboratory for animal research. The rats were housed individually in a controlled environment, with the temperature maintained at 20-21 °C and humidity levels kept within a range of 45-55%. A 12-hour light/dark cycle was strictly observed, and the animals had unlimited access to standard laboratory chow and purified water.

Chemicals

Boldine was obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). For treatment, a fresh solution was prepared by dissolving the powdered compound in distilled water, which was then administered via intra-abdominal injection at a dose of 50 mg/kg. The dosage used in this study was based on previously established reference data[23].

Experimental Protocol

The animals were randomly divided into four groups, each consisting of six rats: Control group (C), Boldine group (B), myocardial ischemia-reperfusion (MIR) group, and myocardial ischemia-reperfusion + Boldine group.

Anesthesia was induced using intraperitoneal injections of 50 mg/kg ketamine and 10 mg/kg xylazine, with the same dose of ketamine administered to all rats to standardize its effect on cardiac output[10]. The rats' trachea was cannulated for artificial ventilation, and the rats' chest was shaved before securing the rats in a supine position on the operating table. A left thoracotomy was performed approximately 2 mm left of the sternum, between the fourth and fifth intercostal spaces. After opening the pericardium, the left anterior descending (LAD) coronary artery was visualized, and an 8/0 silk suture was carefully placed around it using a 10-mm micropoint reverse-cutting needle. Ischemia was induced by tightening the suture with a plastic snare for 30 minutes. Reperfusion was initiated by releasing the tension and allowing unrestricted blood flow for 120 minutes. Boldine (50 mg/kg)[23] was administered intraperitoneally 30 minutes after LAD occlusion. This timing was chosen based on previous studies suggesting optimal absorption and bioavailability during ischemic stress, thereby enhancing its cardioprotective effects during subsequent reperfusion[6].

Throughout the procedure, anesthesia depth was monitored every 10 minutes by assessing reflex responses (intermittent tail pinch and corneal reflex). If a positive response was observed, additional doses of 20 mg/kg ketamine and 5 mg/kg xylazine were administered intraperitoneally[10]. At the end of the reperfusion period, all rats were deeply anesthetized with 50 mg/kg ketamine and 10 mg/kg xylazine; Then they were sacrificed via

aortic blood collection (5-10 mL)[6-10]. After the cessation of both heartbeat and respiration, death was confirmed by the absence of the corneal reflex and spontaneous breathing for an additional 2 minutes. Following 120 minutes of reperfusion, myocardial tissue samples were carefully excised for biochemical and histopathological analysis. The tissues were collected intact to prevent trauma and were immediately processed. Samples intended for histopathological examination were fixed in 10% formalin, while those for biochemical analysis were frozen in liquid nitrogen and stored at -80 °C.

Histopathological Analysis

For histological analysis, cardiac tissue samples were fixed in 10% neutral-buffered formalin for 48 hours and subsequently processed for paraffin embedding. The fixed tissues were dehydrated using a graded alcohol series (70%, 80%, 96%, 96%, 100%, 100%), cleared in xylene, and embedded in paraffin blocks. Five-micrometer-thick sections, parallel to the apex-to-base plane, were obtained from paraffin blocks using a microtome (Leica RM2245, Germany), and stained with hematoxylin (05-06004/L, BioOptica, Italy) and eosin (05-11007/L, BioOptica, Italy). Histopathological assessments focused on inflammation, myocardial disorganization, and interstitial fibrosis, which are key indicators of MIRI. Hematoxylin and eosin-stained sections were examined under 200× and 400× magnifications using a light microscope (Leica DM 4000B, Germany) equipped with a computer, and images were analyzed using Leica LAS V4.9 software (Germany). Inflammation was evaluated based on the presence of inflammatory cell infiltration (neutrophils and mononuclear cells) in the interstitial space. Myocardial disorganization was assessed by examining cardiomyocyte alignment, loss of striation, and nuclear changes, including pyknosis and karyolysis. Interstitial fibrosis was analyzed by assessing collagen deposition within the myocardial interstitium. Each parameter was scored using a semi-quantitative grading system, as previously described in the literature. A blinded histologist independently assessed and scored each tissue sample. Mean scores for inflammation, myocardial disorganization, and interstitial fibrosis were calculated for each group and statistically compared using ANOVA followed by post-hoc Tukey tests[5,6,10].

Biochemical Analysis

At the end of the study, serum and cardiac tissue samples were frozen in liquid nitrogen and stored at -80 °C until analysis. Total oxidative status (TOS), total antioxidant status (TAS), and Oxidative Stress index (OSI) were measured to evaluate oxidative stress and antioxidant capacity. Cardiac tissue samples were homogenized in phosphate-buffered saline (PBS, pH 7.4) using a mechanical homogenizer at 4 °C. The homogenates were centrifuged at 10,000 × g for 10 minutes at 4 °C, and the supernatant was collected for biochemical analysis. TAS reflects the total antioxidant capacity of the tissue, which counteracts oxidative stress. TOS quantifies the total oxidant load, representing the degree of oxidative damage. OSI, calculated as the ratio of TOS to TAS, provides a comprehensive measure of redox balance and oxidative stress intensity. TAS levels were assessed using a commercial TAS assay kit (RelAssay Diagnostic®, Türkiye), following the manufacturer's instructions. Briefly, 500 µL of reagent 1 (measurement buffer) was mixed with 30 µL of the tissue homogenate, and the initial absorbance (A1) was recorded at 660 nm using a spectrophotometer (NanoDrop® ND-1000, Thermo Scientific, USA). Subsequently, 75 µL of reagent 2, which contains 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid, was added to the reaction mixture. The sample tubes were sealed with paraffin and incubated in a 37 °C water bath (ST 30, NUVE, Türkiye) for 5 minutes. Following incubation, the second absorbance (A2) was measured at 660 nm. For standard calibration, a 1 mmol/L Trolox equivalent (Trolox Eq) solution was used. All measurements (A1 and A2) were performed in triplicate, and the mean values were recorded. The change in absorbance ($^{\Delta}$Abs) was determined as A2-A1, and TAS levels were expressed as mmol Trolox Eq/L. TOS was determined using a commercial TOS assay kit (RelAssay

Diagnostic®, Türkiye) according to the manufacturer's protocol. 500 µL of reagent 1 (measurement buffer) was mixed with 75 µL of the cardiac tissue homogenate, and the initial absorbance (A1) was measured at 530 nm using a NanoDrop® ND-1000 spectrophotometer (Thermo Scientific, USA). Next, 25 µL of reagent 2 (pro-chromogenic solution) was added to the reaction mixture. The tubes were sealed with paraffin and incubated in a 37 °C water bath (ST 30, NUVE, Türkiye) for 5 minutes. After incubation, the A2 was recorded at 530 nm. For standard calibration, a 10 µmol/L hydrogen peroxide (H_2O_2) equivalent solution was used. The change in absorbance ($^{\Delta}$Abs) was calculated as A2-A1, and TOS levels were expressed as mmol H_2O_2 Eq/L. The OSI was calculated as: OSI = (TOS (µmol H_2O_2 Eq/L) / TAS (µmol Trolox Eq/L) x 100

OSI values provided a quantitative measure of oxidative stress levels in cardiac tissue samples[5,24,25].

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the data was assessed visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). For parametric data, results were presented as mean ± standard error. For histopathological assessments and biochemical analysis, differences among groups were analyzed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons in normally distributed data. A type I error level of 5% ($p<0.05$) was considered statistically significant.

Results

Histopathological Findings

Histopathological evaluations revealed significant differences in inflammation and myocardial disorganization across experimental groups. Inflammation was significantly higher in the MIR group compared to the C and B-only groups (p=0.005 for both comparisons). However, the MIR+B group exhibited a significant reduction in inflammation compared to the IR group (p=0.048), as shown in Table 1 and Figures 1-4.

Similarly, myocardial disorganization was significantly more pronounced in the MIR group, compared to the C and B groups (p=0.003 for both). Notably, the MIR+B group demonstrated a significant reduction in myocardial disorganization compared to the MIR group (p=0.037), suggesting a protective effect of Boldine against structural disorganization (Table 1, Figures 1-4).

In contrast, interstitial fibrosis did not differ significantly among the groups (p=0.073), although the IR+B group exhibited a trend toward reduced fibrosis compared to the IR group (Table 1, Figures 1-4).

Biochemical Findings

Biochemical assessments of cardiac tissue revealed significant intergroup differences in oxidative stress parameters, including TAS, TOS, and OSI. TAS levels were significantly lower in the MIR group compared to the C and B groups ($p<0.001$ and p=0.012, respectively). However, TAS levels were significantly elevated in the MIR+B group compared to the MIR group (p=0.028),

Table 1. Histopathological scores of myocardial tissues (Mean ± SE)

	Control (C)	Boldine (B)	Myocardial ischemia-reperfusion (MIR)	Myocardial ischemia-reperfusion + Boldine (MIR+B)	p-value
Inflammation	0.17±0.17	0.17±0.17	1.17±0.31*;&	0.50±0.22+	0.015
Myocardial disorganization	0.33±0.21	0.33±0.21	1.33±0.33*;&	0.67±0.21+	0.010
Interstitial fibrosis	0.33±0.21	0.33±0.21	1.17±0.31	0.50±0.22	0.073

*p: Statistical significance level was determined using the ANOVA test, with p<0.05 considered significant. *p<0.05: indicates a significant difference compared to the Control group (C). & p<0.05: indicates a significant difference compared to the Boldine group (B). + p<0.05: indicates a significant difference compared to the myocardial ischemia-reperfusion group (MIR), SE: Standard error*

indicating an enhancement of antioxidant capacity with Boldine treatment (Table 2).

TOS levels were markedly higher in the MIR and MIR+B groups compared to the C and B groups ($p<0.001$ for both comparisons). Importantly, the MIR+B group demonstrated significantly reduced TOS levels compared to the MIR group ($p<0.001$), highlighting Boldine's potential to mitigate oxidative burden (Table 2).

OSI, which represents the balance between oxidants and antioxidants, was significantly elevated in the MIR and MIR+B groups relative to the C and B groups ($p<0.001$ for all comparisons). However, the MIR+B group exhibited significantly lower OSI values compared

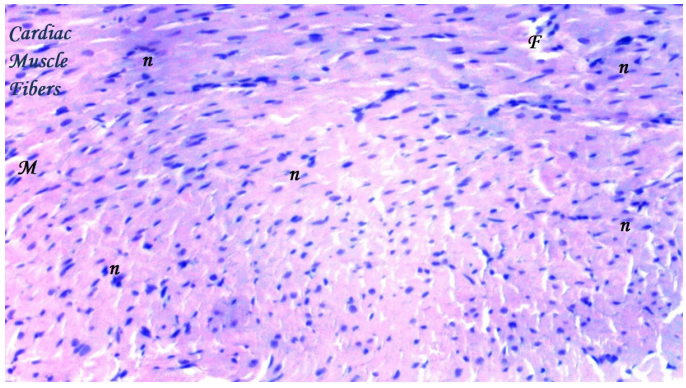

Figure 1. Group Control
M: Myocard, F: Fibrosis, n: Nucleus, H&Ex100

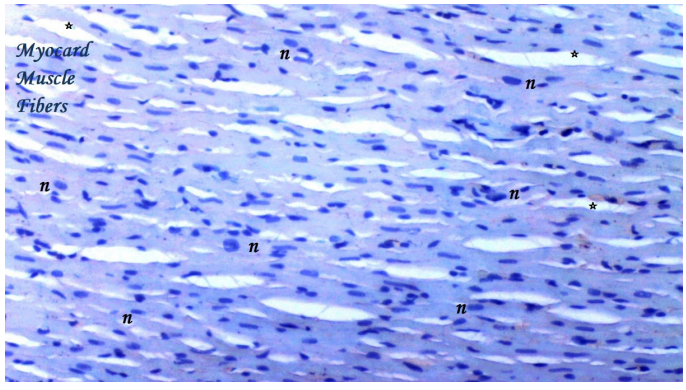

Figure 2. Group Boldine
n: Nucleus, H&Ex100

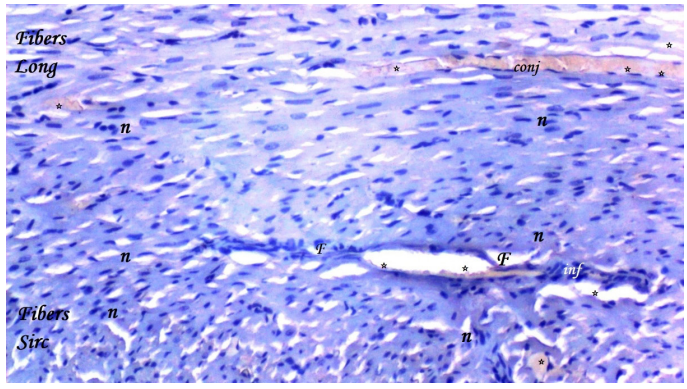

Figure 3. Group Ischemia-reperfusion
F: Fibrosis, n: Nucleus, conj: Congestion, inf: Inflammation, H&Ex100

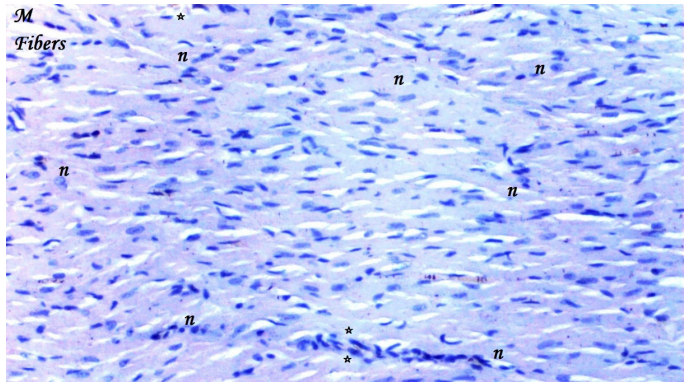

Figure 4. Group Ischemia-reperfusion + Boldine
M: Myocard, n: Nucleus, H&Ex100

Table 2. Oxidative stress parameters in myocardial tissue (Mean ± SE)

	Control (C)	Boldine (B)	Myocardial ischemia-reperfusion (MIR)	Myocardial ischemia-reperfusion + Boldine (MIR+B)	p-value
TAS (mmol/L)	2.47±0.22	2.13±0.15	1.57±0.09*;&	2.05±0.05+	0.003
TOS (µmol/L)	7.78±0.60	10.26±1.20	52.34±3.00*;&	32.25±1.33*;&;+	<0.001
OSI	0.33±0.04	0.51±0.08	3.40±0.27*;&	1.58±0.06*;&;+	<0.001

*p: The statistical significance level was calculated using the ANOVA test, where $p<0.05$ is considered significant. *$p<0.05$: indicates a significant difference compared to the Control group (C). & $p<0.05$: indicates a significant difference compared to the Boldine group (B). + $p<0.05$: Indicates a significant difference compared to the myocardial ischemia-reperfusion group (MIR), TAS: Total antioxidant status, TOS:* Total oxidant status, *OSI: Oxidative Stress index, SE: Standard error*

to the MIR group ($p<0.001$), reflecting the restoration of redox balance with Boldine administration (Table 2).

Discussion

MIRI occurs when blood flow is restored to previously ischemic myocardial tissue, paradoxically resulting in additional cardiac damage. This injury is mediated by several interrelated mechanisms, including oxidative stress, inflammation, calcium overload, mitochondrial dysfunction, and the activation of cell death pathways[12,26]. During the ischemic phase, the deprivation of oxygen and nutrients forces myocardial cells to rely on anaerobic glycolysis, leading to the accumulation of hydrogen ions and lactate, which disrupts cellular homeostasis[4]. Upon reperfusion, the rapid reintroduction of oxygen triggers a burst of ROS production, primarily from mitochondria and NADPH oxidase, resulting in oxidative stress[4,12]. This oxidative damage affects lipids, proteins, and DNA, further aggravating tissue injury and contributing to cardiomyocyte necrosis and apoptosis[3]. In addition, inflammation plays a pivotal role in the pathogenesis of MIRI, with the nuclear factor-kappa B (NF-κB) pathway serving as a central regulator of the inflammatory response[12,26]. NF-κB activation occurs during reperfusion in response to signals such as cytokines, Toll-like receptors, and hypoxia-inducible factors, leading to the release of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukins, which exacerbate myocardial damage. Collectively, these processes contribute to the complex pathophysiology of MIRI, which represents a significant contributor to myocardial infarction-related injury.

This study evaluated the potential protective effects of Boldine on myocardial tissue in a rat model of experimentally induced IR injury. To the best of our knowledge, this is the first comprehensive study investigating Boldine's role in mitigating oxidative stress and preserving myocardial structure and function during IR injury. The findings of this research highlight Boldine's ability to enhance antioxidant capacity, reduce oxidative burden, and attenuate inflammation and myocardial disorganization. These results provide a foundation for future advanced studies to explore Boldine's mechanisms of action, including its impact on molecular and signaling pathways involved in MIRI.

Boldine exerts its antioxidant and anti-inflammatory effects through various mechanisms, making it a promising therapeutic agent. As a natural alkaloid derived from the Peumus boldus tree, Boldine exhibits potent free radical scavenging properties, protecting cells from oxidative stress by neutralizing ROS and inhibiting LPO[14]. Although most studies have focused on systems other than the myocardium, their findings provide valuable insights relevant to our research. For instance, a study by Subramaniam et al.[27] demonstrated Boldine's ability to reduce oxidative stress and modulate tumor-related biomarkers in diethylnitrosamine-induced hepatocarcinogenesis in rats. The study observed improvements in oxidative stress markers, including SOD, catalase, and reduced GSH. Similarly, Calbiague et al.[28] investigated Boldine's antioxidant effects in protecting retinal cells against high glucose-induced oxidative damage in diabetic retinopathy. They found that Boldine decreased oxidant levels and increased antioxidant enzyme activity by modulating oxidative-nitrosative stress markers and mitochondrial function. Shuker et al.[18] also studied the antioxidative effects of Boldine in steroid-induced liver toxicity by assessing parameters such as LPO, GSH, GSH reductase, GSHPx, and SOD. Their findings highlighted Boldine's role in reducing oxidative damage by improving antioxidant enzyme activity. Moreover, Konrath et al.[22] evaluated Boldine's antioxidant and cytoprotective effects in hippocampal slices under ischemic stress. They measured ROS levels, lactate dehydrogenase release, and lipoperoxidation, concluding that Boldine effectively reduced oxidative damage at low doses, although potential pro-oxidant effects were observed at higher concentrations. Beyond animal models, Srivastava et al.[29] provided a detailed chemical and spectroscopic analysis of Boldine, emphasizing its antioxidant potential and the

structural properties contributing to its pharmacological effects. Using Raman and IR spectroscopy alongside computational modeling, the study demonstrated that Boldine's molecular structure enhances its radical-scavenging properties. In our study, TAS levels in the Boldine-treated MIR group were significantly higher than both the control and MIR-only groups. Although the exact mechanism underlying Boldine's antioxidant effects remains unclear. It can be inferred that Boldine enhances antioxidant enzyme activity in myocardial tissue. The observed reduction in TOS levels with Boldine treatment further supports its ROS-scavenging capability.

Boldine's role extends to reducing vascular oxidative stress, improving endothelial function, and preventing vascular damage associated with hypertension and diabetes[17]. Lau et al.[17] highlighted Boldine's therapeutic relevance in endothelial dysfunction by modulating NO bioavailability, decreasing ROS levels, and improving vascular relaxation. Shuker et al.[18] also examined NO levels as a parameter, reporting a significant increase in NO levels in the methylprednisolone (MPL)-treated group, which was linked to oxidative and nitrosative stress. This rise in NO was attributed to the activation of the NF-κB/inducible nitric oxide synthase (iNOS) pathway, a key mechanism in ROS/RNS-mediated oxidative damage. Co-administration of Boldine with MPL significantly reduced NO levels, suggesting that Boldine inhibits iNOS activation and mitigates nitrosative stress, thereby protecting tissues from NO-mediated injury. In the context of MIRI, excessive NO production contributes to tissue damage via peroxynitrite formation and endothelial dysfunction. Biochemical markers in our study indicate an overall reduction in oxidative stress, evidenced by improved TAS and reduced TOS and OSI. These findings suggest that Boldine likely mitigates oxidative and nitrosative stress in myocardial tissues by modulating the NF-κB/iNOS pathway and reducing NO levels. However, further studies focusing on specific molecules and signaling pathways are required to fully elucidate Boldine's antioxidative mechanisms.

In addition to its antioxidant properties, Boldine demonstrates significant anti-inflammatory effects across various tissues. For instance, Shuker et al.[18] reported that Boldine exhibited hepatoprotective effects in steroid-induced liver toxicity by attenuating inflammation and apoptosis. The study observed a reduction in IL-6 and TNF-α levels, along with histopathological evidence of decreased apoptosis and inflammation. Similarly, Pandurangan et al.[30] investigated Boldine's anti-inflammatory effects in dextran sulfate sodium-induced colitis. They found that Boldine reduced the expression of inflammatory cytokines, including TNF-α and IL-6, by inhibiting the NF-κB and IL-6/STAT3 signaling pathways. Histopathological analysis of colonic tissue further confirmed Boldine's anti-inflammatory effects, showing reduced inflammation and crypt damage. Another study on xylene-induced ear edema and carrageenan-induced paw edema in rodents highlighted Boldine's effectiveness in mitigating inflammation through the JAK2/STAT3 and NF-κB pathways[31]. This was supported by histological improvements in edema and reductions in TNF-α and IL-6 levels. Furthermore, Catalán et al.[32] explored Boldine's ability to prevent inflammation in cardiac fibroblasts. They demonstrated that Boldine inhibits the SGK1-NFκB signaling pathway, reducing the expression of pro-inflammatory cytokines such as IL-1 beta and TNF-α, as well as adhesion molecules like ıntercellular adhesion molecule 1 and vascular cell adhesion molecule 1, which are critical mediators of leukocyte recruitment to inflamed tissues. In our study, histopathological assessments were performed to evaluate inflammation, myocardial disorganization, and interstitial fibrosis. Scoring revealed a significant reduction in inflammation and myocardial disorganization in the MIR group treated with Boldine compared to the untreated MIR group. These findings align with existing literature, reinforcing Boldine's anti-inflammatory effects. However, no significant differences in interstitial fibrosis were observed across the groups. This lack of effect may be attributed to the limited time frame and the single-dose protocol employed in our study. While our histological findings regarding inflammation

and myocardial disorganization are consistent with previous studies, future investigations should include a broader range of doses and parameters to provide a more comprehensive understanding of Boldine's therapeutic potential.

Study Limitations

This study is subject to several limitations that should be acknowledged to contextualize the findings appropriately. First, the experimental design employed a single-dose regimen of Boldine, which may not adequately reflect the potential dose-response relationship. Future research should involve dose-escalation studies to identify the optimal therapeutic window and evaluate possible dose-dependent toxicities. Second, the relatively short duration of the experimental protocol restricts the ability to assess long-term outcomes, such as chronic myocardial remodeling, fibrosis progression, or recovery of cardiac function. Longitudinal studies with extended observation periods are necessary to determine whether the acute benefits of Boldine translate into sustained cardioprotection. Third, while the biochemical and histopathological assessments demonstrated significant reductions in oxidative stress and inflammation, the precise molecular mechanisms underlying Boldine's effects remain insufficiently characterized. Advanced molecular investigations, including transcriptomic, proteomic, and metabolomic analyses, are warranted to elucidate the signaling pathways and cellular processes modulated by Boldine during IR injury. Finally, the use of a preclinical rat model limits the direct applicability of these findings to human MIRI. Although the rat model provides valuable insights into pathophysiological mechanisms, species-specific differences in metabolism, pharmacokinetics, and cardiovascular physiology may affect the translational relevance of Boldine. Thus, additional studies involving larger animal models and, eventually, human clinical trials are essential to validate Boldine's therapeutic potential in clinical settings.

Conclusion

This study demonstrates the potential cardioprotective effects of Boldine in a rat model of MIRI. The findings indicate that Boldine significantly attenuates oxidative stress, reduces inflammation, and mitigates myocardial disorganization, highlighting its role as an effective antioxidant and anti-inflammatory agent. The observed improvements in oxidative stress markers, such as enhanced TAS and reduced TOS and OSI levels, as well as histopathological improvements, underscore Boldine's capacity to protect myocardial tissue during IR events. While these results provide a foundation for understanding Boldine's therapeutic potential in cardiovascular diseases, further investigations are required to elucidate its molecular mechanisms of action, dose-response relationships, and long-term effects. Translational studies and clinical trials are essential to determine its safety, efficacy, and applicability in human IHD.

Ethics

Ethics Committee Approval: The animals were sourced and raised within a specialized experimental research facility in Ankara, Türkiye (approval no: E-66332047-604.01-1128916, date: 27.12.2024) and were performed in a dedicated laboratory for animal research.

Informed Consent: This study was conducted using male Albino Wistar rats, aged 12 weeks and weighing between 270 and 320 grams.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Demirtaş H, Özer A, Yıldırım AK, Concept: Demirtaş H, Yıldırım AK, Özer A, Dursun AD, Sezen ŞC, Yığman Z, Küçük A, Arslan M, Design: Demirtaş H, Yıldırım AK, Özer A, Dursun AD, Sezen ŞC, Yığman Z, Küçük A, Arslan M, Data Collection and/or Processing: Demirtaş H, Yıldırım AK, Özer A, Dursun AD, Sezen ŞC, Yığman Z, Küçük A, Arslan M, Analysis and/or Interpretation: Demirtaş H, Yıldırım

AK, Özer A, Dursun AD, Sezen ŞC, Yığman Z, Küçük A, Arslan M, Literature Search: Demirtaş H, Arslan M, Writing: Demirtaş H, Arslan M. Yıldırım AK.

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Late Diaphragmatic Paralysis After Atrial Fibrillation Cryoablation

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Abstract

Atrial fibrillation (AF), a common cardiac arrhythmia, is often managed with catheter ablation, specifically cryoablation, to electrically isolate pulmonary veins by tissue freezing. Despite its effectiveness, a significant complication is phrenic nerve injury, which can result in diaphragmatic paralysis. This case report presents a 70-year-old female with a history of coronary artery bypass surgery, hypertension, and diabetes, who underwent AF cryoablation. Post-operatively, she was asymptomatic and discharged in sinus rhythm. However, several weeks later, she developed dyspnea and was diagnosed with right diaphragmatic paralysis due to phrenic nerve injury. Initial management included respiratory therapy, leading to significant symptom improvement and partial recovery of diaphragmatic movement within two months. The discussion highlights the prevalence, causes, and management of early and late phrenic nerve injuries, emphasizing the need for early diagnosis and appropriate treatment to ensure patient recovery.

Keywords: Atrial fibrillation cryoablation, late diaphragmatic paralysis, phrenic nerve palsy

Introduction

Atrial fibrillation (AF), a prevalent cardiac arrhythmia, is frequently managed with catheter ablation. Cryoablation is a common method for electrically isolating the pulmonary veins through tissue freezing. However, a significant complication of this procedure is injury to the phrenic nerve, potentially resulting in diaphragmatic paralysis.

Case Presentation

A 70-year-old female was referred to the cardiology outpatient clinic complaining of palpitations. AF cryoablation was planned for the patient, who has a known history of coronary artery bypass surgery, hypertension, and diabetes. In our center, ablation procedures were conducted with deep sedation utilizing intermittent doses of midazolam and fentanyl for all

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patients. Throughout the procedure, oxygen saturation and electrocardiography (ECG) findings were monitored non-invasively. The right femoral vein and left femoral vein/artery were accessed by using the Seldinger technique. A 6 French steerable decapolar catheter was inserted into the coronary sinus. A single transseptal puncture was performed using fluoroscopic guidance and a modified Brockenbrough technique (BRK-1 transseptal needle; St. Jude Medical, St. Paul, MN, USA), with the insertion of an 8.5 French transseptal sheath (Fast-Cath transseptal guiding introducer, St. Jude Medical, St. Paul MN, USA) into the left atrium (LA). Immediately following transseptal puncture, unfractionated heparin was administered to maintain an activated clotting time of at least 300 s. The transseptal sheath was then exchanged over a guidewire (0.032 in., 180 cm Super Stiff, St. Jude Medical, St. Paul, MN, USA) for a 12 French steerable sheath (Flexcath Advance; Medtronic, Minneapolis, MN, USA). A 15-or 20-mm circular mapping catheter (Achieve, Medtronic, Minneapolis, MN, USA) was used to guide the cryoballoon within the LA and attempt real-time recordings from the targeted pulmonary vein. The balloon was inflated within the LA and directed toward the pulmonary vein ostia. Balloon occlusion was assessed by injecting contrast agent through the central lumen of the catheter. Each freezing cycle lasted 180-240 seconds, with an additional freeze applied if the pulmonary vein isolation was not obtained beyond 60 s. 20 mm, 4th generation Achieve catheter was used. Right phrenic nerve stimulation is always performed during freezing of right pulmonary veins and right hemidiaphragm contraction is assessed manually until balloon deflation. High-output pacing was performed using the ablation catheter during ablation near the pulmonary veins on the right side and output pacing was performed through the ablation catheter. Same procedure was performed in aforementioned case and right diaphragmatic movement was intact both after right upper and lower pulmonary vein balloon deflation. Post-operative course was uneventful and patient was discharged in sinus rhythm following day without any relevant complications. After the procedure, chest radiography was normal and 12 lead ECG showed sinus rhythm (Figure 1).

However, 4 weeks after the procedure, the patient presented with dyspnea with effort capacity. A physical examination revealed decreased breath sounds on the right hemithorax. An elevated right hemidiaphragm was noted plain chest radiography (Figure 2). The patient was initially managed conservatively with respiratory therapy. At the two-month follow-up, the patient's symptoms had significantly improved, and repeat imaging showed partial recovery of the diaphragmatic movement (Figure 3).

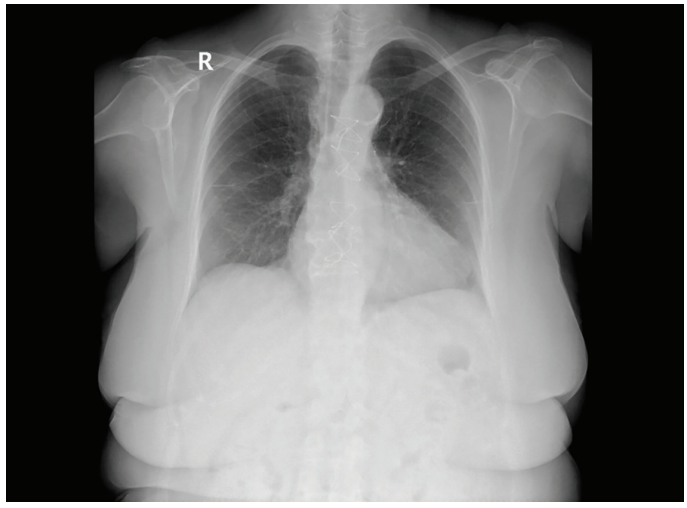

Figure 1. Chest radiography after the procedure

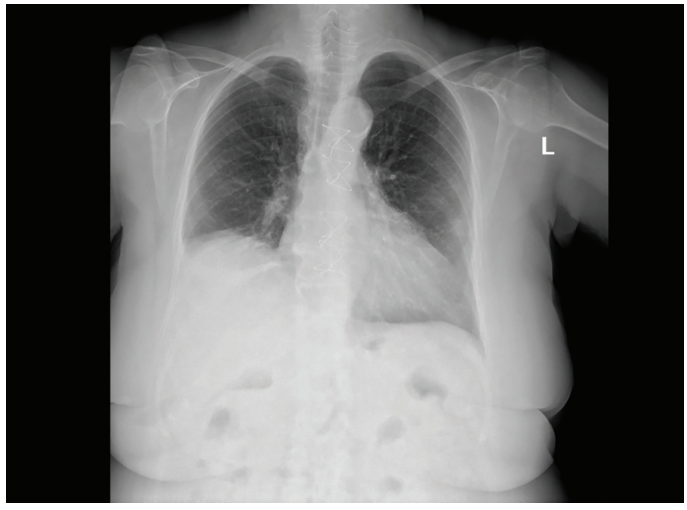

Figure 2. Right diaphragmatic elevation observed four weeks post-procedure

Discussion

In this case, late phrenic nerve paralysis (PNP) was observed. The development of shortness of breath, not evident during the procedure but evident during follow-up assessments, may indicate the development of late phrenic nerve injury. Phrenic nerve injury during cryoablation typically occurs because of the close anatomical proximity of the right phrenic nerve and right pulmonary veins[1] and the prevalence has been reported to be between 3-7% after cryoablation of AF[2,3]. However, early and late PNP are two distinct complications that can occur after cryoablation of pulmonary veins, each with its own characteristics and management considerations[4]. The primary cause of early paralysis is the direct injury to the phrenic nerve during ablation. Late paralysis is often caused by inflammatory or edematous changes that develop post-procedure, leading to compression or irritation of the phrenic nerve[5,6]. In the current case, the mechanisms of delayed inflammatory response, progressive edema and cryoablation lesion expansion related to late-onset PNP were considered. Further investigation into these potential mechanisms is necessary to better understand and prevent late-onset PNP in future patients.

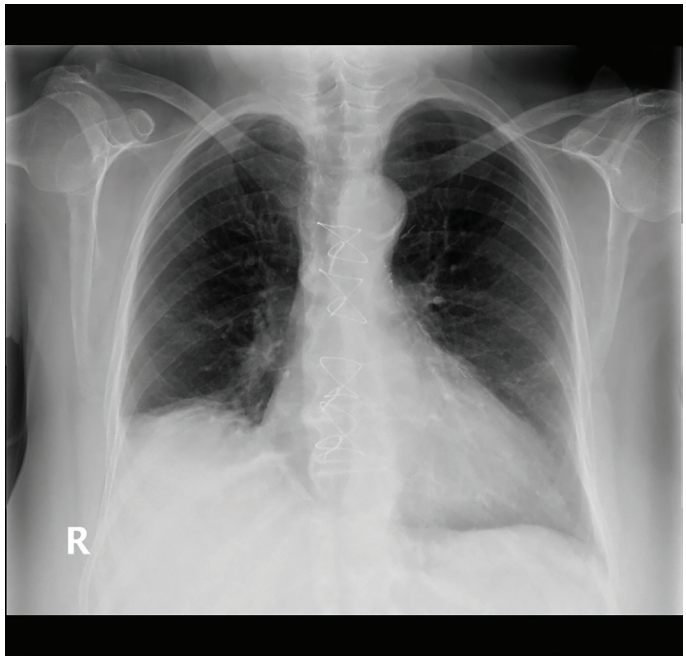

Figure 3. Partial recovery of the right hemidiaphragm

Conclusion

Phrenic nerve injury leading to right hemi diaphragmatic paralysis is a potential late complication of AF cryoablation. One should always consider late diaphragmatic paralysis due to right phrenic nerve injury in differential diagnosis of dyspnea after cryoballoon isolation of pulmonary veins due to AF. Early diagnosis and appropriate management are crucial for patient recovery.

Ethics

Informed Consent: Informed consent was obtained from the patient before the procedure.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Çakmak Karaaslan Ö, Güray Ü., Concept: Çakmak Karaaslan Ö, Güray Ü., Design: Çakmak Karaaslan Ö, Güray Ü., Data Collection and/or Processing: Çakmak Karaaslan Ö, Güray Ü., Analysis and/or Interpretation: Çakmak Karaaslan Ö, Güray Ü., Literature Search: Çakmak Karaaslan Ö, Güray Ü., Writing: Çakmak Karaaslan Ö, Güray Ü.

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Case Report

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Mitral Anterior Leaflet Perforation Due to Jet Flow in Aortic Valve Insufficiency

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Abstract

Mitral valve disease is one of the most common pathologies of heart valve diseases. Mitral regurgitation may develop due to pathologies in the valve apparatus (primary regurgitation) or due to pathologies related to the atrium and/or ventricle (secondary regurgitation). Treatment options include medical, transcatheter, and surgical approaches, depending on the course of the disease. In this study, we present a patient with perforation in the mitral anterior leaflet secondary to aortic valve regurgitation. Mid-aortic regurgitation (jet flow directed toward the mitral anterior) was observed on echocardiography. It was interesting that the perforation in the mitral anterior leaflet developed secondary to aortic valve regurgitation. Aortic valve replacement and mitral valve repair were performed. The successful surgery and images of the case are wanted to be shared.

Keywords: Mitral regurgitation; aortic regurgitation; mitral repair

Introduction

Mitral insufficiency is the most common heart valve disease in the United States and the second most common heart valve disease requiring surgical intervention in Europe[1]. Its prevalence increases to approximately 9% in the population over 75 years of age[2]. Mitral regurgitation is classified as primary or secondary, depending on the etiology. In primary mitral insufficiency, valve defects prevent cooptation. In secondary failure, although the valve is normal, there are problems in parts of the heart other than the valve (atrium and/or ventricle). Treatment options may include medical, transcatheter, and surgical approaches, depending on the course of the disease [3].

Etiological distribution of patients requiring surgery; primary myxomatous, 61%; rheumatic, 22%; endocarditis, 5%; non-ischemic cardiomyopathies, 3%; and ischemia-induced, 1.3%[4].

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In this study, we present a patient who developed perforation in the mitral anterior valve due to aortic valve regurgitation. Eccentric mid-aortic insufficiency (jet flow toward the mitral anterior) was observed on echocardiography. It was interesting that the perforation in the mitral anterior leaflet developed secondary to aortic valve insufficiency. Aortic valve replacement and mitral valve repair were performed. We wanted to share images of successful surgery and cases.

Case Presentation

The patient was 67 years old and male. He had complaints of exertional dyspnea and orthopnea that had been present for 2 months. He had a history of chronic obstructive pulmonary disease, hypertension, and smoking. No history of coronary or vascular intervention. As a result of echocardiography, the ejection fraction was 60%, sinus valsalva was 3.8 cm, ascending aorta is 3.7 cm, aortic regurgitation is moderate and eccentric (jet flow is mitral anterior leaflet oriented), severe mitral regurgitation, left atrial dilatation (left atrium 4.9 cm), mitral Cleft and color transition were observed in the anterior leaflet, and pulmonary artery pressure was found to be 43 mmHg. In the preoperative examinations, blood samples, chest X-ray, and coronary angiography were evaluated as normal. Electrocardiogram was in sinus rhythm. The surgery decision was made by the Cardiology and Cardiovascular Surgery Council. Informed consent was obtained from the patient. Median sternotomy was performed under general anesthesia. The valve was accessed via right atriotomy and atrial septostomy with cardiopulmonary bypass. A large perforated area was observed in the mitral anterior leaflet (Figure 1). This area was first repaired with 5/0 polypropylene suture, and mitral annuloplasty was performed with a 32-mm 3D ring (Figure 2). The aortic valve was then reached via aortotomy. The valve was tricuspid. The aortic valve was too degenerative for repair. Therefore, the aortic valve was replaced with a mechanical valve number 27. There was no bacterial growth in the aortic valve tissue taken. We completed the surgery using the standard procedure. The patient was extubated at 6 hours after surgery. We did not observe any pathology on control echocardiography and we discharged him on the 5th day after surgery.

Discussion

Mitral regurgitation can develop due to pathology in the valve apparatus, as well as pathologies related to the atrium (atrial fibrillation, atrial dilatation, etc.) and/or ventricle (cardiomyopathy, ischemia, etc.). The causes of valve pathology include rheumatic valve disease, degeneration, endocarditic and myxoma[1].

Aortic valve regurgitation jet stream; It can be quite heterogeneous, as it can develop depending on the valve structure, valve asymmetry, aortic root dilatation, and acquired abnormalities (endocarditic or degenerative)[5]. Mitral regurgitation due to aortic valve regurgitation jets has been reported in the literature[6]. In some cases of

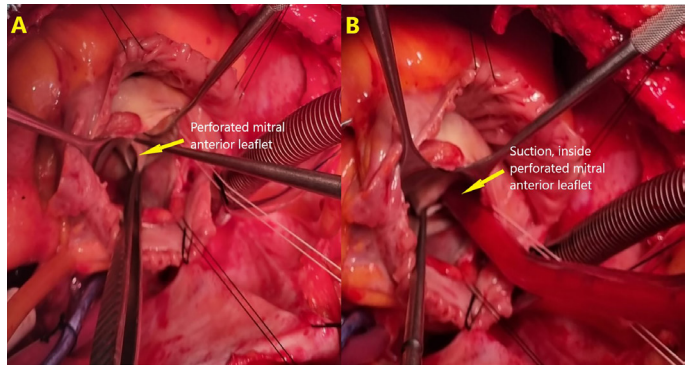

Figure 1. (A,B) Images of the perforated mitral anterior leaflet

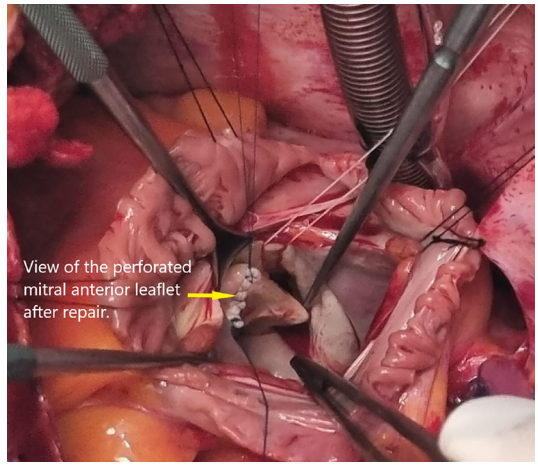

Figure 2. Post-repair view of the perforated mitral anterior leaflet

the bicuspid aortic valve, the regurgitation jet is directed toward the anterior mitral leaflet, thereby affecting valve patency[7].

The patient had no previous history of coronary or vascular intervention. It was determined that he did not have febrile illness similar to infective endocarditic. Infection parameters were normal in the analysis performed. In echocardiography; The aortic valves were tricuspid. We found that moderate aortic jet flow was directed toward the anterior mitral valve leaflet. Aortic valve insufficiency is a characteristic of degenerative valve disease. As a result, we concluded that severe mitral regurgitation is a newly developing condition caused by aortic jet flow.

In non-ischemic mitral valve regurgitation, mitral valve repair is preferred over valve replacement. Lower cost and valve-related complications, including bleeding and thrombosis events, have been reported[8]. Similarly, significantly fewer complications and better quality of life have been reported in patients undergoing aortic valve repair compared with mechanical valve replacement[9]. In the present case, we repaired the valve primarily because there was only mitral valve anterior leaflet perforation, and the other valve apparatus was normal. Since the insufficiency of the aortic valve was degenerative, it could not be repaired, and mechanical valve replacement. Although 67 years old, he was vigorous. For this reason, we used a mechanical valve with better durability instead of a bioprosthetic valve.

Conclusion

As a result, it should be kept in mind that mitral valve perforation may occur in patients with newly developing mitral insufficiency who are followed up with aortic regurgitation.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Işık M, Cavlak MB, Yıldırım S, Dereli Y, Concept: Işık M, Yıldırım S, Dereli Y, Design: Işık M, Data Collection and/or Processing: Işık M, Cavlak MB, Analysis and/or Interpretation: Işık M, Literature Search: Işık M, Yıldırım S, Dereli Y, Writing: Işık M, Yıldırım S, Dereli Y.

Conflict of Interest: The author declare no conflicts of interest concerning the authorship or publication of this article.

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