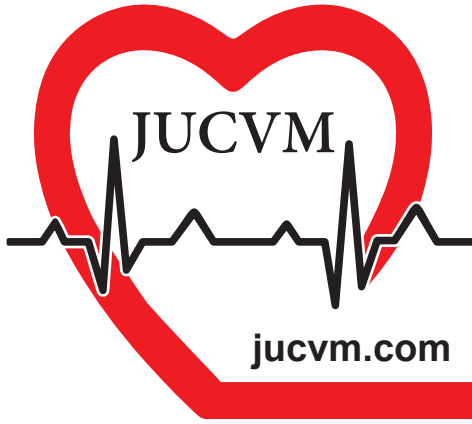




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Cardiologists and Cardiac Surgeons; Arteries and Veins

Teresa Mary Kieser

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Bosentan Reduces Myocardial Ischemia-Reperfusion Injury in Rats

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Şafak Alpat

Editor-in-Chief

Prof. Öztekin Oto, FESC, FACC

*Dokuz Eylül University, Department of Cardiovascular Surgery, İzmir, Türkiye
President, Heart and Health Foundation of Türkiye / İzmir / Türkiye*

 ORCID: orcid.org/0000-0002-8595-6006

Editors

Marko Turina

Dean Emeritus University of Zurich, Switzerland

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The Medical Center of Aurora, Department of Cardiothoracic Surgery, Colorado, USA

 ORCID: 0000-0001-6755-5025

Changsheng Ma

Beijing Anzhen Hospital, Capital Medical University, Clinic of Cardiology, Beijing, China

 ORCID: 0000-0002-5387-5957

Nikolaos Bonaros

Medical University of Innsbruck, Department of Cardiac Surgery, Innsbruck, Austria

 ORCID: 0000-0002-7656-5812

Diana Reser

Hirslanden Heart Clinic of Zurich, Department of Cardiac and Thoracic Vascular Surgery, Zurich, Switzerland

Ali Kutsal

Sami Ulus Children Hospital Department of Cardiovascular Surgery, Ankara, Türkiye

 ORCID: 0000-0003-2742-3209

Harald Kaemmerer

German Heart Centre, Munich, Germany

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Director of Lisbon Cardiovascular Institute, Portugal 
ORCID: 0000-0001-6983-2292

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Hospital Clinico de Barcelona, Department of Cardiovascular Surgery, Barcelona, Spain

 ORCID: 0000-0002-0770-0515

Frank W. Selke

Chief of Cardiothoracic Surgery at Brown Medical School, Rhode Island, USA

Stephan Schueler

Tyne Freeman Hospital, Department for Cardiothoracic Surgery Newcastle, United Kingdom

ORCID: 0000-0002-5702-8851

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 ORCID: 0000-0001-7145-0453

Lazar Davidovic

Belgrade Medical School Cardiovascular Surgery, Belgrade, Serbia

Şafak Alpat

Birmingham Children's Hospital Pediatric Cardiovascular Surgery, Birmingham, UK

 ORCID: 0000-0002-8690-4494

Atike Tekeli Kunt

University of Health Sciences Türkiye, Ankara Numune Training and Research Hospital, Department of Cardiovascular Surgery, Ankara, Türkiye

 ORCID: 0000-0001-9764-7393

Piotr Kasprzak

University Hospital Regensburg, Director of Vascular Surgery, Regensburg, Germany

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 ORCID: 0000-0003-1913-1150

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**Erdem Silistreli**

Dokuz Eylül University, Department of Cardiovascular Surgery, İzmir, Türkiye

 ORCID: 0000-0001-6938-2332

Bektaş Battaloğlu

İzmir Özel Sağlık Hospital, Department of Cardiovascular Surgery, İzmir, Türkiye

 ORCID: 0000-0003-1221-8122

Onur Saydam

Karaman State Hospital Cardiovascular Surgery / Karaman / Türkiye

 ORCID: 0000-0002-8968-6672

Emre Doğan

Trabzon Ahi Evren Cardiovascular Surgery Hospital, Trabzon, Türkiye

 ORCID: 0000-0002-5394-1010

Taylan Adademir

Kartal Koşuyolu Resarch Hospital, İstanbul, Türkiye

ORCID: 0000-0003-1643-3751

Orçun Gürbüz

Meddem Hospital, Clinic of Cardiovascular and Endovascular Surgery, Bursa, Türkiye

 ORCID: 0000-0001-8553-7939

İlhan Mavioğlu

İrmet Hospital, Clinic of Cardiovascular Surgery, Tekirdağ, Türkiye

 ORCID: 0000-0002-8466-9873

İbrahim Erdinç

University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital, Clinic of Cardiovascular Surgery, İzmir, Türkiye

 ORCID: 0000-0003-1659-2859

Mustafa Tok

Uludağ University Faculty of Medicine, Department of Cardiovascular Surgery, Bursa, Türkiye

 ORCID: 0000-0003-2985-1709

Onur Selçuk Göksel

İstanbul University İstanbul Faculty of Medicine, Department of Cardiovascular Surgery, İstanbul, Türkiye

 ORCID: 0000-0001-8103-3709

Özcan Gür

Tekirdağ Namık Kemal University Faculty of Medicine, Department of Cardiovascular Surgery, Tekirdağ, Türkiye

 ORCID: 0000-0001-9398-3402

Selami Gürkan

Tekirdağ Namık Kemal University Faculty of Medicine, Department of Cardiovascular Surgery, Tekirdağ, Türkiye

 ORCID: 0000-0001-5391-9270

Ufuk Tütün

Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Cardiovascular Surgery, Zonguldak, Türkiye

 ORCID: 0000-0002-9661-7632

Utkan Sevük

University of Health Sciences Türkiye, Diyarbakır Gazi Yaşargil Training and Research Hospital, Department of Cardiovascular Surgery, Diyarbakır, Türkiye

 ORCID: orcid.org/0000-0001-7429-5997

Kanat Özişik

Ankara Bilkent City Hospital, Clinic of Cardiovascular Surgery, Ankara, Türkiye

 ORCID: orcid.org/0000-0003-2943-0541

Serdar Günaydın

Ankara Bilkent City Hospital, Clinic of Cardiovascular Surgery, Ankara, Türkiye

 ORCID: orcid.org/0000-0002-9717-9793

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Bariş Akça

*İnönü University School of Medicine, Department of
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*University of Health Sciences Türkiye, Bakırköy Sadi
Konuk Training and Research Hospital, Department of
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Ertan Demirdağ

*Bozok University Training and Research Hospital,
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Yüksel Dereli

*Necmettin Erbakan University Meram Medical Faculty
Hospital, Department of Cardiovascular Surgery, Konya,
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Vehbi Doğan

*Sami Ulus Training and Research Hospital, Clinic of
Pediatric Cardiology, Ankara, Türkiye*

Hüseyin Ede

*Bozok University Training and Research Hospital,
Department of Cardiology, Yozgat, Türkiye*

İlker Ertuğrul

*Sami Ulus Training and Research Hospital, Clinic of
Pediatric Cardiology, Ankara, Türkiye*

Niyazi Görmüş

*Necmettin Erbakan University Meram Medical Faculty
Hospital, Department of Cardiovascular Surgery, Konya,
Türkiye*

Adem Güler

*Gülhane Military Medical Academy, Department of
Cardiovascular Surgery, Ankara, Türkiye*

Mustafa Gülgün

*Gülhane Military Medical Academy, Division of Pediatric
Cardiology, Ankara, Türkiye*

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*Tsukuba Medical Center Hospital, Department of
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*Derince Training and Research Hospital, Clinic of
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*Düzce University Faculty of Medicine, Department of
Cardiology, Düzce, Türkiye*

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*Marmara University Training and Research Hospital,
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Mustafa Seren

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Administration Office

Şair Eşref Bulvarı, 1402 Sk. No: 2/2 Özbaş Apt.
Alsancak / İzmir / Türkiye

Phone: + 90 232 464 19 63 / **Fax:** +90 232 464 24 70

e-mail: info@oztekinoto.com | info@tksv.com

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What to Do When Both Ventricular Outflow Tracts are Obstructed? | 152

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Cardiologists and Cardiac Surgeons; Arteries and Veins

© Teresa Mary Kieser

University of Calgary, Cumming Faculty of Medicine, Department of Cardiac Sciences, Libin Cardiovascular Institute, Alberta, Canada

Keywords: Cardiovascular medicine, cardiovascular surgery, coronary artery disease

Studies of bilateral internal mammary artery (BIMA) over the last 75 years numbering 1,336 (Figure 1) have shown benefit of BIMA for patients with: advanced age (≥ 70 years) Muneretto et al.⁽¹⁾ Medalion et al.⁽²⁾ Hirotani et al.⁽³⁾; urgent/emergent surgery Bonacchi et al.⁽⁴⁾, Hirotani et al.⁽⁵⁾; dialysis Kinoshita et al.⁽⁶⁾; reduced ejection fraction (EF) ($<30\%$, $30-50\%$) Galbut et al.⁽⁷⁾; women Kurlansky et al.⁽⁸⁾. After a first negative results study for BIMA in diabetics, Kouhoukos et al.⁽⁹⁾ many further studies showed benefits Matsa et al.⁽¹⁰⁾, Hirotani et al.⁽¹¹⁾ Lev-Ran et al.⁽¹²⁾, Lev-Ran et al.⁽¹³⁾, Stevens et al.⁽¹⁴⁾ Katsavrias et al.⁽¹⁵⁾, Toumpoulis et al.⁽¹⁶⁾, Puskas⁽¹⁷⁾, Dorman et al.⁽¹⁸⁾, Kieser et al.⁽¹⁹⁾ and routine use. Pevni et al.⁽²⁰⁾ of “routine use” of skeletonized internal mammary arteries (IMAs) was prescient for 2008. 42.3% of patients were >70 years. 34.2% were diabetic. Regrettably for patients, surgeons sometimes incise along both legs trying to find a suitable vein instead of using another artery. God must muse why

humans go to the farthest reaches of the body the ankle, while “he put IMAs right next to the heart”. A pamphlet advertising Sigvaris Compression Stockings states that, 55% of women who have experienced two or more full term pregnancies develop varicose veins. How many women have only one child? (average children/woman globally is 2.3) Maybe this is the reason why women do not fare as well? Veins have one redeeming potential: as per Kim’s paper⁽²¹⁾, when attached to IMAs, due to vasodilator substances from IMAs and lack of aortic force, they have a similar ten-year graft patency: Composite left IMA (LIMA)-arterial (88%) vs. LIMA-saphenous vein (SV) (95.9%). Note the trend of SV in demonstrating superiority. Whereas there is a finite amount of arterial conduit, venous conduit is usually more copious in comparison. Has God (and Kim) provided us a way to use both?



Address for Correspondence: Teresa Mary Kieser, University of Calgary, Cumming Faculty of Medicine, Department of Cardiac Sciences, Libin Cardiovascular Institute, Alberta, Canada

e-mail: ktmprieu@ucalgary.ca **ORCID:** orcid.org/0000-0003-0399-2917

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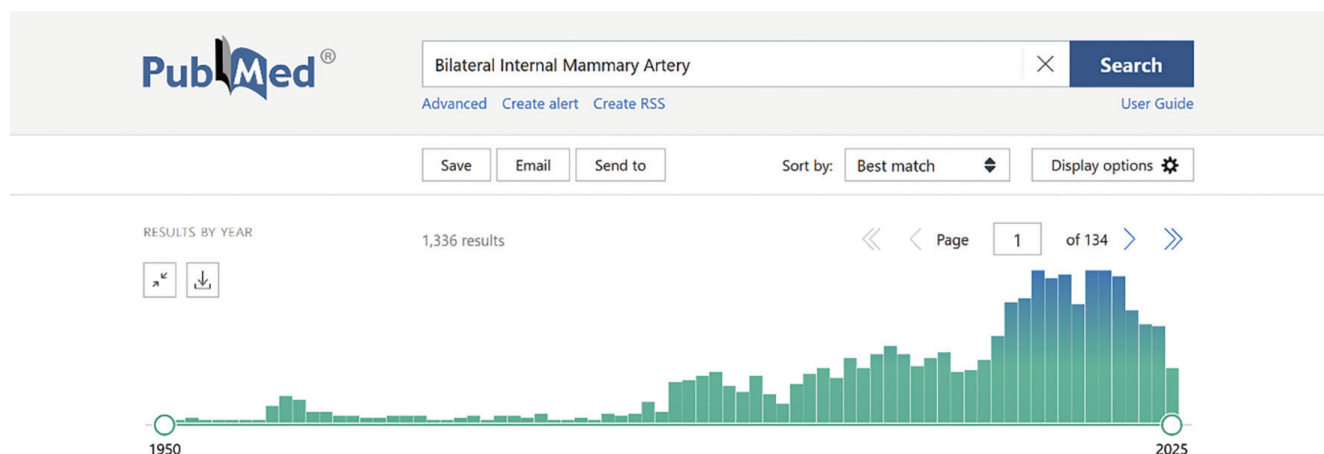


Figure 1. PubMed results published BIMA papers by year 1950-2025
In the last 75 years, there have been 1,336 articles published on bilateral internal mammary arteries

In June 2004, Professor Taggart embarked on the arterial revascularization trial (ART)⁽²²⁾ randomizing between single and BIMAs with a 10-year follow-up. Why was there no difference between single internal mammary artery (SIMA) and BIMA? It was meant to be a trial of one IMA vs. 2 IMAs, but 40% of patients received treatments other than intended ones due to crossover rates: The single internal thoracic artery to BIMA (4%); the BIMA to SIMA (14%); the SIMA with radial artery graft (22%). Gaudino et al.⁽²³⁾ “radial artery superiority over SV” paper was published a year after ART start-up. There was essentially no difference in the “intention-to-treat.” Both groups had the same number of arterial conduits. A substantial difference was seen in the “as-treated” group: Significant improvement in both endpoints (all-cause mortality, and especially composite of mortality, myocardial infarction, and stroke). Experienced surgeons (>50 BIMA cases) had much better results at 5 years regarding both endpoints; the curves start to diverge at 2 to 4 years, even with the “intention to treat” group.

Gaudino et al.⁽²⁴⁾ editorial, after completing the enrollment of 4,375 patients in randomized outcome of multiple arterial grafts (ROMA) (one vs. multiple arterial grafts) on 14 April 2023, lists the key differences between ROMA and ART (respectively). These include primary outcome (major adverse cardiac events vs. all-cause

mortality), intervention (multiple arterial grafting vs. SIMA), population (≤ 70 years vs. all ages), power (event-driven vs. underpowered), and delivery of intervention (experience cut-off: 250 cases vs. 50, continuous vs. no crossover monitoring).

Professor Taggart is responsible for laying the groundwork for ROMA with ART by unmasking how few surgeons actually performed BIMA in everyday practice, and even if they did, they did not feel comfortable enrolling such patients in an randomized controlled trial. Without ART before ROMA, key differences may not have come to light. This author was asked multiple times to join ROMA. The author’s arterial grafting experience includes 30% BIMA in the first 15 years of practice, and 78% BIMA for the last 21 years. One criterion would not allow her to do this: The age of 70 years or younger. In all conscience, the author could not say to a 57-year-old patient: “I do not know whether one or two arteries would make a difference to you.” She did know... This was especially after she defended her PhD in BIMA grafting in 2015 at Erasmus University, Rotterdam⁽²⁵⁾. Having spent 27 years using BIMA in most patients and publishing results from many angles, researchers found there was no equipoise. ROMA has hopefully resolved the debate regarding the benefit of “one vs. more” arterial grafting.

What do the Guidelines say? The 2018 European Guidelines for an additional arterial graft, are Class IIa Level B Evidence⁽²⁶⁾. If one considers the age of 70 years⁽²⁷⁾ as the age below which BIMA grafting can be performed, if the average age of patients in most series is 65-66 years, possibly 66-70% of coronary patients are under the age of 70. Even if one treated 50% of patients under 70 years with BIMA, this would be 34%; if one treated 80% of patients under age 70, this would be 56% - much more than 5% in US and 12% in Europe. However, the 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography & Interventions Joint Committee on Clinical Practice Guidelines⁽²⁸⁾ disturbingly assigned coronary surgery and randomized outcome of percutaneous coronary intervention (PCI) the same Class IIb. Also, the phrasing in the Guidelines table in Section 7.1 e23, (Figure 2) is indecisive: "coronary artery bypass grafting (CABG) may be reasonable" and (... the usefulness of PCI to improve survival is uncertain). Certainly, if given a choice, most patients would prefer PCI over surgery, as both are Class IIb with uncertain outcomes.

In many studies, the use of BIMA has not been a point of comparison between treatment arms. For example, it would have been useful if ISCHEMIA⁽²⁹⁾ had studied the use of 2 arterial grafts in the invasive strategy group. If using a cohort where one internal mammary artery (IMA) is used and the rest are with SV, it may be true that there is no difference when compared with PCI. SV graft patency is at best 50% at 10 years: Fitzgibbon et al.⁽³⁰⁾, from 1978

to 1996, showed 50%⁽³⁾, and approximately 25 years later, Tatoulis et al.⁽³¹⁾ in 2011 reported no significant difference, showing 50.7%. Various treatments are being compared for diverse patient issues. They are not comparable, just as travel by air and travel by road are not the same. Competition between the two best treatments for coronary artery disease is not in our and, especially, patients' best interest. The roles of PCI and CABG should be considered not as a race, but as a relay. We frequently hand off to each other and are each grateful for this. The value of multi-disciplinary rounds individualizes care for both surgical and PCI patients.

Further thoughts: There are three levels of awareness of cardiac surgical expertise: Surgeons who are acutely aware of their immediate results, cardiologists who treat these patients, and the patients themselves. Cardiologists have known the benefits of total arterial grafting for years, e.g., Raphael Mohr, Tel-Aviv, once stated to the author, "our cardiologists will not refer cases to surgeons who do not perform BIMA." Cardiologists see the untreatable vein graft disease, the disabling chronic angina, and the hesitancy to reoperate on patients with patent single LIMA-left anterior descending grafts. Occluded vein grafts may not kill the patient, but they can destroy quality of life. Cardiologists understand the impact of arterial grafts lasting decades; they follow our patients for this period, whereas we surgeons rarely do. And ultimately the patients...who, when they see you for the first time (and this has happened to this author on more than one occasion), ask "Do you do arterial grafting?" Patients are

Multivessel CAD		
2b	B-R	5. In patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD), and anatomy suitable for CABG, CABG may be reasonable to improve survival (10,13-15).
2b	B-R	6. In patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD), and anatomy suitable for PCI, the usefulness of PCI to improve survival is uncertain (14-24).

Figure 2. Section from 2021 ACC/AHA/SCAI 2021 Guidelines Table in Section 7.1 e23 showing same recommendation of "2b" for both CABG and PCI

CAD: Coronary artery disease, SIHD: Stable ischemic heart disease, LAD: Left anterior descending, CABG: Coronary artery bypass grafting, PCI: Percutaneous coronary intervention, ACC: American College of Cardiology, AHA: American Heart Association, SCAI: Society for Cardiovascular Angiography and Interventions

browsing the internet, and now there is also ChatGPT available for information retrieval.

Summaries: Technical summary: In order to perform BIMA commonly, one needs to do routinely the things that honour and protect the IMA: Harvest the IMA the best way you know (for the author, it is with the Harmonic Scalpel⁽³²⁾). The anastomosis must be good enough to last decades. Clopidogrel has enabled grafting of challenging arteries. Protect the devascularized sternum by adding multiple preventive layers against infection. Review your work (transit-time flow measurement epicardial ultrasound)⁽³³⁾.

Be patient, meticulous and methodical. Be prepared to not mind being considered as no longer “the fast surgeon.”

Surgeon summary: Successful arterial grafting depends on the “mindset” of the surgeon, with help from mentors, training and cardiological support. Arterial grafting can be used on all patient subgroups with safety and attention to detail. It is not just for some, but for all...

Philosophy summary coronary surgery has come a long way since the days when only one mammary artery was used, when endarterectomy and low EF often necessitated vein grafts. One can connect anything to anything if the connection is technically perfect, with success. Blood flows any and every which way: “Nature abhors a vacuum.” (Aristotle 384-322 BC). Coronary disease is lifelong; use of arterial grafts offers the closest possible approximation to a cure. Interventionalists know that to date, there is no PCI option available that competes with the longevity of BIMA. Drug eluting stents can now last 10 years and more, and are rivaling SV grafts.... Consider performing a few more arterial grafts to maintain your employment status.

Arterial grafting routinely treats all patients with the best conduits available, without bias. No longer is it “Just a CABG.” BIMA is possibly the most critical intervention a surgeon can do for coronary patients. An extra 20 minutes for an extra 20 years⁽³⁴⁾...

One of the youngest patients in the author’s Database of 2022 patients over 21.5 years, age 29 years and 14 weeks pregnant at the time of her surgery, said to the author in an e-mail “Doctors always question the scar on my wrist and are astounded to hear that you used arteries in my heart... it makes only sense.”

Footnotes

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Bosentan Reduces Myocardial Ischemia-Reperfusion Injury in Rats

© Zeynep Yığman¹, © Hüseyin Demirtaş², © Mehmet Burak Gülcan³, © Abdullah Özer²,
© Ali Doğan Dursun⁴, © Ayşegül Küçük⁵, © Mustafa Arslan⁶

¹Gazi University Faculty of Medicine, Department of Histology and Embryology, Ankara, Türkiye

²Gazi University Faculty of Medicine, Department of Cardiovascular Surgery, Ankara, Türkiye

³Erzurum City Hospital, Clinic of Cardiovascular Surgery, Erzurum, Türkiye

⁴Atılım University Faculty of Medicine, Department of Physiology, Ankara, Türkiye

⁵Kütahya Health Sciences University Faculty of Medicine, Department of Physiology, Kütahya, Türkiye

⁶Gazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Türkiye

Abstract

Objectives: This study aimed to investigate the cardioprotective effects of bosentan, an endothelin receptor antagonist, against myocardial ischemia-reperfusion injury (MIRI) in rats.

Materials and Methods: Twenty-four adult Wistar-Albino rats were randomly divided into four groups: control, bosentan only, myocardial ischemia-reperfusion (MIR), and MIR-bosentan (MIR-B). Ischemia was induced by ligation of the left anterior descending coronary artery for 30 minutes, followed by 90 minutes of reperfusion. Bosentan was administered intraperitoneally at 30 mg/kg during ischemia in the MIR-B group. Histopathological evaluation assessed neutrophil infiltration, cardiomyocyte damage, tissue edema, and hemorrhage, while biochemical analyses measured total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), and paraoxonase-1 (PON-1) activity in myocardial tissue.

Results: The MIR group showed significantly increased histopathological injury scores, including neutrophil infiltration, cardiomyocyte damage, edema, and hemorrhage, compared to control and bosentan-only groups ($p<0.001$). Bosentan treatment significantly reduced these injury scores in the MIR-B group compared to the MIR group ($p<0.05$). Biochemically, the MIR group exhibited elevated TOS and OSI levels and reduced TAS and PON-1 activity, indicating oxidative stress.



Address for Correspondence: Zeynep Yığman, Gazi University Faculty of Medicine, Department of Histology and Embryology, Ankara, Türkiye

e-mail: zeynepyigman@gmail.com **ORCID:** orcid.org/0000-0003-1985-9280

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Bosentan administration significantly improved these parameters by lowering TOS and OSI levels, and by increasing TAS and PON-1 activity compared to the MIR group ($p < 0.05$).

Conclusion: In conclusion, bosentan demonstrated significant protective effects against MIRI by attenuating histological damage and oxidative stress in rat myocardium. These findings suggest that endothelin receptor antagonism with bosentan may offer a promising therapeutic approach to reduce myocardial injury following ischemia-reperfusion events such as those occurring during coronary artery bypass grafting. Further studies are needed to explore its clinical potential.

Keywords: Cardiovascular surgery, coronary arteries, heart

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide, with coronary heart disease (CHD) being the major contributor⁽¹⁾. In the 18th century, William Heberden first described angina pectoris in medical history, and later, CHD was identified as a condition caused by reduced blood flow in the coronary arteries⁽²⁾. By the late 19th century, it was established that coronary artery occlusion is fatal, and coronary thrombosis was linked to myocardial infarction (MI)⁽²⁾. CHD refers to a type of CVD resulting from atherosclerosis or atherosclerotic occlusion of the coronary arteries of the heart⁽²⁾. This condition leads to reduced blood flow in the coronary arteries, disrupting the balance between myocardial oxygen demand and supply⁽²⁾. Consequently, clinical symptoms of CHD occur such as a pressure-like sensation in the chest that radiates to the jaw and left arm⁽²⁾. This clinical presentation reflects acute myocardial infarction (AMI) and may progress to heart failure or death⁽³⁾. The two main goals of treatment are to medically relieve angina symptoms and to restore blood flow invasively⁽³⁾. There are two invasive methods to reestablish coronary blood flow: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)⁽³⁾. Although CABG provides collateral circulation in addition to revascularization and thus offers superior protection compared to PCI⁽³⁾, both revascularization techniques are widely available, particularly in Western countries. Rapid revascularization is essential to prevent permanent tissue damage⁽⁴⁾. However, reperfusion itself initiates ischemia-

reperfusion (IR) injury not only in the myocardium but also in distant organs⁽⁴⁾. Ischemia causes an increase in intracellular sodium, hydrogen, and calcium ions, resulting in cellular acidosis⁽⁵⁾. This leads to myocardial hypercontractility, depletion of adenosine triphosphate (ATP), mitochondrial damage, and myocardial stunning⁽⁵⁾. The generation of reactive oxygen species (ROS) begins with the activation of proapoptotic pathways⁽⁶⁾. Restoration of blood flow further contributes to ROS production and complement activation⁽⁶⁾. Therefore, assessing myocardial damage both histologically and biochemically is crucial. Measuring total oxidant status (TOS), total antioxidant status (TAS), and paraoxonase (PON) activity is useful for biochemical evaluation of damage^(7,8). Histological assessment, of tissue edema and hemorrhage is also valuable in evaluating tissue injury^(7,8).

Bosentan is the first endothelin (ET) receptor antagonist that has potential clinical applications⁽⁹⁾. Although bosentan is officially approved only for pulmonary arterial hypertension, the ET system is activated in many cardiovascular conditions such as congestive heart failure (CHF), essential hypertension, acute AMI, and atherosclerosis⁽⁹⁾. ET-1 is the most potent endogenous vasoconstrictor in the human body, being approximately 100 times more powerful than noradrenaline and 10 times more potent than angiotensin II⁽⁹⁾. ET-1 also exhibits pro-fibrotic, pro-inflammatory, and mitogenic activities in vascular tissues and the myocardium⁽⁹⁾. This underlies the potential beneficial effects of bosentan in myocardial ischemia-reperfusion injury (MIRI).

We aim to investigate the protective effects of bosentan against MIRI in rats. MIRI is a common complication following CABG in cardiac surgery. Bosentan may exert beneficial effects against MIRI. Conducting an animal study in this context may help clarify future treatment strategies to reduce MIRI.

Materials and Methods

Animals

This experimental study was conducted at the Gazi University Laboratory Animal Breeding and Experimental Research Center (GÜDAM) in accordance with ARRIVE guidelines. This study was approved by the Gazi University Local Ethics Committee for Animal Experiments (approval no: G.Ü.ET-22.062, date: 22.11.2023). All animals were housed and cared for according to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Establishment of the Experimental Model

Anesthesia was induced by intramuscular injection of ketamine hydrochloride (50 mg/kg; Ketalar® vial, Parke-Davis, USA). The rats were placed in the supine position under a heat lamp. After shaving the surgical areas, a midline vertical cervical incision of approximately 1 cm was made. The trachea was exposed by blunt dissection, and a tracheostomy was performed using a 16G intra-catheter (Medipro Nova Cath®, İstanbul, Türkiye). Subsequently, the rats were connected to a mechanical ventilator (Harvard Apparatus Rodent Model Ventilator, Inspira ASV, Holliston, USA) and ventilated with 100% oxygen at a tidal volume of 10-15 mL/kg and a respiratory rate of 65-80 breaths per minute throughout the procedure. A left thoracotomy was performed through the fourth intercostal space. The pericardial sac was opened, and myocardial ischemia was induced by occlusion of the left anterior descending (LAD) coronary artery using an 8-0 Prolene suture.

In this study, 24 adult Wistar-Albino rats with an average weight of 250 g were used. The animals were randomly divided into four groups (n=6 per group):

Control group (C, n=6): Tracheostomy and thoracotomy were performed, but no myocardial IR was induced. The rats were maintained under anesthesia for 120 minutes and then sacrificed. Myocardial tissue samples were collected for histopathological and biochemical analyses.

Bosentan-only group (B, n=6): Following tracheostomy and thoracotomy, 30 mg/kg bosentan was administered intraperitoneally at the beginning of the procedure. No ischemia was induced. After 120 minutes under anesthesia, the rats were sacrificed, and myocardial tissue was collected.

IR group (MIR, n=6): After tracheostomy and thoracotomy, myocardial ischemia was induced by LAD occlusion for 30 minutes, followed by 90 minutes of reperfusion. The total experimental duration was 120 minutes. At the end of reperfusion, the rats were sacrificed and myocardial samples were collected.

Bosentan-treated IR group (MIR-B, n=6): Following tracheostomy and thoracotomy, 30 mg/kg bosentan was administered intraperitoneally prior to the induction of ischemia. After drug administration, LAD occlusion was applied for 30 minutes, followed by 90 minutes of reperfusion. At the end of the 120-minute experimental period, the rats were sacrificed under anesthesia, and myocardial tissue samples were harvested for further analysis.

Biochemical Assessment of Myocardial Tissue Samples

Following the completion of the reperfusion period, all animals were sacrificed under anesthesia and heart samples were harvested. To assess the TOS, TAS, and PON-1, half of the heart between the base and a plane at the mid-LAD level, parallel to the atrioventricular (AV) valve plane, was dissected. Parts of hearts were put in liquid nitrogen, then transferred to -80 °C, and stored until the day of assessment. TOS and TAS levels were measured spectrophotometrically with commercially available kits (Relassay, Türkiye)^(10,11), and the oxygenation saturation index (OSI) was calculated according to the following formula: OSI (arbitrary unit) = TOS (μmol

H₂O₂ equivalent/L)/TAS (μ mol Trolox equivalent/L)⁽¹²⁻¹⁴⁾. PON-1 activity was calculated from two consecutive spectrophotometrical measurements with a commercially available kit (Relassay, Türkiye).

Histopathological Assessment of Myocardial Tissue Samples

The part of the heart samples between the apex and mid-LAD level, which is parallel to the AV valve, is fixed in 10% buffered formalin for 48 hours. Fixation is followed by the routine tissue processing procedures to obtain paraffin tissue blocks. To that end, specimens were dehydrated through a graded series of alcohol, then were cleared in xylene. After being infiltrated with liquid paraffin, tissue samples were embedded in paraffin. From each heart, paraffin blocks, four 4 μ m-thick heart sections with 50 μ m intervals, were cut parallel to the base of the heart using a microtome (HistoCore MULTICUT, Leica, Germany). All sections were stained with hematoxylin and eosin (H&E) to evaluate the histopathological changes.

H&E-stained heart specimens were assessed under 200 $\times$ and 400 $\times$ magnifications using a light microscope (Leica DM 4000 B, Germany), and micrographs were taken using the software Leica LAS V4.12. Myocardial injury resulting from IR was assessed in terms of histopathological changes involving neutrophil infiltration, cardiomyocyte injury, interstitial edema, and hemorrhage. Scores ranging between 0 and 3 were assigned to reveal the severity of the individual histopathological changes, of which 0 indicating no change, 1 indicating weak changes, 2 indicating moderate changes, and 3 indicating severe changes. Then, scores of individual histopathological changes, and the total heart muscle injury score, ranging between 0 and 12, were compared between the groups as the sum of the other scores⁽¹⁵⁾.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) 22. The normal distribution of variables was examined visually (histograms and

probability plots) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). The results are presented as mean $\pm$ standard error. Data were evaluated using Kruskal-Wallis variance analysis. Significant variables were assessed using the Bonferroni-corrected Mann-Whitney U test. A Type I error level of 5% was set to indicate statistical significance with $p < 0.05$.

Results

Results of Biochemical Assessment

TAS and TOS levels, as well as OSI values, were found to be significantly different among the groups ($p < 0.001$ for all). TAS levels in the MIR group were significantly lower than in both group C and group B ($p < 0.001$ for both). TAS levels of the myocardial tissues in the MIR+B group were also significantly lower than in group C, and group B ($p = 0.007$ and $p = 0.020$, respectively); however, they were significantly higher compared to those in the MIR group ($p = 0.046$) (Table 1).

TOS levels in the MIR group were found to be significantly higher than those in groups C and B ($p < 0.001$, both). Similarly, TOS levels in the MIR+B group were notably elevated compared to those in group C and group B ($p = 0.023$ and $p = 0.008$, respectively), yet they were still significantly lower compared to those in the MIR group ($p = 0.003$) (Table 1).

Analysis revealed a significant increase in OSI values in the MIR group compared to groups C and B ($p < 0.001$, both). Although OSI values of the MIR+B group were considerably higher than those of group C and group B ($p = 0.005$ and $p = 0.009$, respectively), they were significantly lower than in the MIR group ($p < 0.001$) (Table 1).

PON-1 activity was also significantly different between the groups ($p = 0.003$). PON-1 activity in the MIR group was significantly lower, compared to group C and group B ($p = 0.001$, both), whereas the PON-1 activity in the MIR+B group was significantly greater than that in the MIR group ($p = 0.005$) (Table 1).

Table 1. Oxidative status parameters of cardiac tissue (mean $\pm$ SD)

	Group C (n=6)	Group B (n=6)	Group MIR (n=6)	Group MIR + B (n=6)	P**
TAS (mmol/L)	1.23 $\pm$ 0.15	1.19 $\pm$ 0.14	0.86 $\pm$ 0.10*, &	1.01 $\pm$ 0.09*, &, +	<0.001
TOS (μ mol/L)	8.18 $\pm$ 1.61	7.62 $\pm$ 2.38	14.95 $\pm$ 2.06*, &	11.04 $\pm$ 1.92*, &, +	<0.001
OSI	0.68 $\pm$ 0.20	0.65 $\pm$ 0.19	1.75 $\pm$ 0.32*, &	1.10 $\pm$ 0.27*, &, +	<0.001
PON-1 (U/L)	9.06 $\pm$ 2.57	9.19 $\pm$ 2.43	3.66 $\pm$ 1.69*, &	8.22 $\pm$ 3.10+	0.003

p**: Significance level with Kruskal-Wallis test; p<0.05. *p<0.05: Compared to group C; &p<0.05: Compared to group B; +p<0.05: Compared to group myocardial ischemia-reperfusion injury (MIR). Group C, control group; group B, bosentan group; group MIR, myocardial ischemia reperfusion group; group MIR+B, myocardial ischemia reperfusion and bosentan treatment group. TAS: Total antioxidant statu, TOS: Total oxidant status, OSI: Oxidative stres index, PON-1: Paraoxonase-1, SD: Standard deviation

Results of Histopathological Assessment

Histopathological evaluation of the heart specimens demonstrated a significant difference in neutrophil infiltration, cardiomyocyte injury, interstitial edema, and hemorrhage between the groups, collectively indicated by $p<0.001$ (Table 2). In the observation of H&E-stained heart muscle specimens from groups C and B, a slight interstitial edema and congestion were noted (Figure 1).

Examination of H&E-stained heart muscle samples revealed a much more pronounced neutrophil infiltration in the MIR group compared to groups C and B ($p<0.001$, both). Also, cardiomyocyte injury in the MIR group was greater than that in groups C and B ($p<0.001$, both). Interstitial edema was much more severe in the MIR group compared to groups C and B, with both comparisons showing $p<0.001$. Hemorrhage that was observed in the specimens of the MIR group was much more prominent than that observed in groups B and C ($p<0.001$, both) (Table 2, Figure 2).

The comparison of the scores for the histopathological changes in H&E-stained heart muscle specimens of groups revealed a significantly lower neutrophil infiltration in the MIR+B group compared to the MIR group ($p=0.003$). Additionally, cardiomyocyte injury in the MIR+B group was greater than that in group C and group B ($p=0.003$ and $p<0.001$, respectively); however, it was milder compared to the MIR group ($p=0.044$). Although interstitial edema in the MIR+B group was more severe than interstitial edema in groups C and B ($p=0.001$ and $p<0.001$, respectively), it was found to be significantly reduced compared to

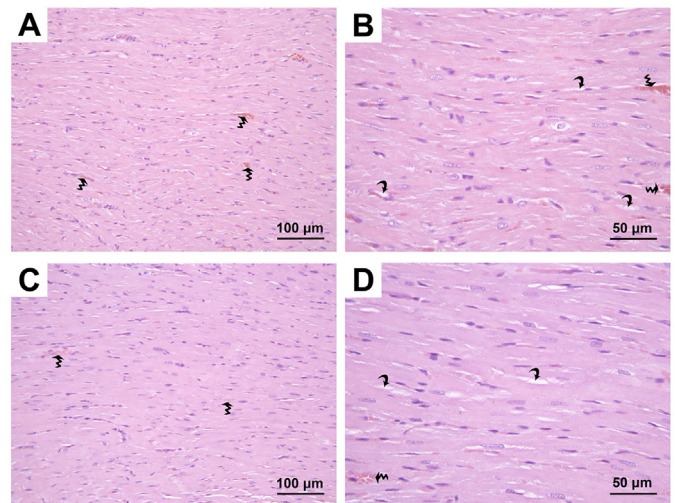


Figure 1. Micrographs of heart specimens from group C (A and B) and group B (C and D). Mild congestion (wavy arrows) and interstitial edema (curved arrows) are observed in sections of groups C and B. Stain: hematoxylin and eosin (H&E). Magnification is 200 $\times$ for images A and C; 400 $\times$ for images B and D.

interstitial edema in the MIR group ($p=0.029$). Also, hemorrhage in the MIR+B group was more apparent than that in group C and group B ($p=0.001$, both); however, it was less notable compared to that of the MIR group ($p=0.004$) (Table 2, Figure 3).

The total heart muscle injury score of the MIR group was found to be significantly higher than that of group C and group B ($p<0.001$, both). While the score of the MIR+B group was also significantly higher than those of group C and B ($p<0.001$, both), it was found to be significantly lower compared to that of the MIR group ($p<0.001$) (Table 2).

Table 2. Myocardial ischemia-reperfusion injury scores (mean $\pm$ SE)

	Group C (n=6)	Group B (n=6)	Group MIR (n=6)	Group MIR+B (n=6)	P**
Neutrophil infiltration	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	2.00 $\pm$ 0.44', &	0.67 $\pm$ 0.33+	<0.001
Cardiomyocyte injury	0.50 $\pm$ 0.22	0.33 $\pm$ 0.21	2.67 $\pm$ 0.33', &	1.83 $\pm$ 0.31', &, +	<0.001
Interstitial edema	0.67 $\pm$ 0.21	0.33 $\pm$ 0.21	2.83 $\pm$ 0.17', &	2.00 $\pm$ 0.37', &, +	<0.001
Hemorrhage	0.50 $\pm$ 0.22	0.50 $\pm$ 0.22	2.67 $\pm$ 0.21', &	1.67 $\pm$ 0.21', &, +	<0.001
Total heart muscle injury score	1.67 $\pm$ 0.61	1.16 $\pm$ 0.48	10.17 $\pm$ 0.98', &	6.17 $\pm$ 0.31', &, +	<0.001

p**: Significance level with Kruskal-Wallis test; p<0.05. 'p<0.05: Compared to group C; & p<0.05: Compared to group B; +p<0.05: Compared to group myocardial ischemia-reperfusion injury (MIR). Group C, control group; group B, bosentan group; group MIR, myocardial ischemia reperfusion group; group MIR+B, myocardial ischemia reperfusion and bosentan treatment group, SE: Standard error

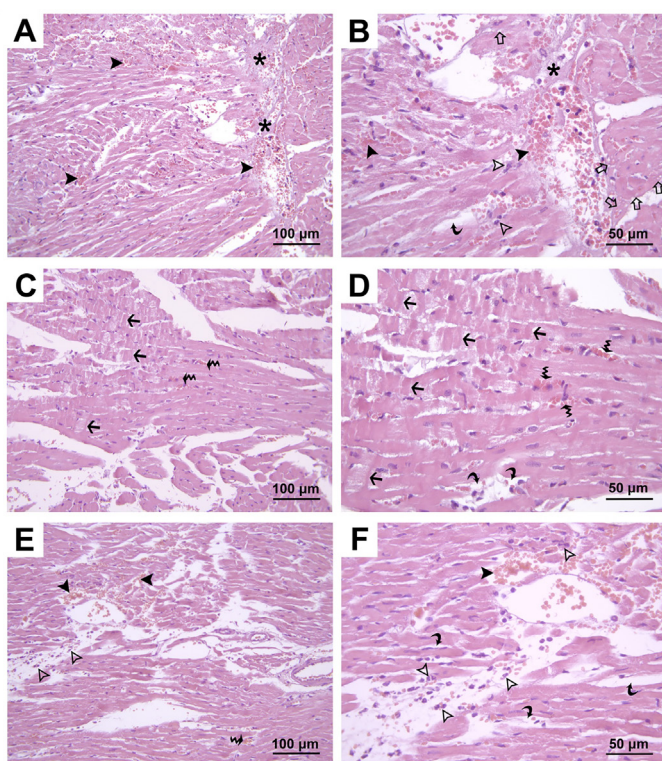


Figure 2. Micrographs of heart specimens from group MIR. Besides congestion (wavy arrows in images C, D and E), more pronounced interstitial edema (curved arrows in images B, D and F) than the other groups is noted. Varying degrees of cardiomyocyte injury are present in the myocardium so that the regions with no myocardial cellular integrity (asterisks in images A and B), myocardial cells with contraction bands (black arrows in images C and D), and myocardial cells exhibiting vacuoles (hollow arrows in image B) are visible. Hemorrhage (black arrowheads in images A, B, E, and F) and neutrophil infiltration (hollow arrowheads in images B, E, and F) are also notable. Stain: hematoxylin and eosin (H&E). Magnification is 200 $\times$ for images A, C and E; 400 $\times$ for images B, D and F. MIR: Myocardial ischemia-reperfusion injury

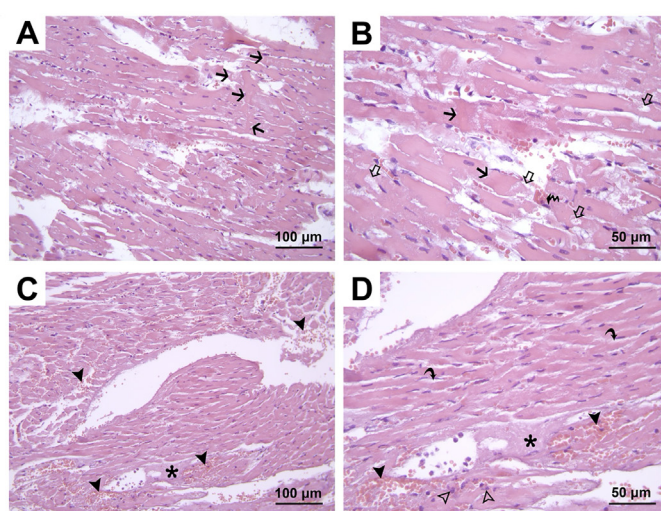


Figure 3. Micrographs of heart specimens from group MIR+B. Congestion (wavy arrow in image B), interstitial edema (curved arrows in image D), neutrophil infiltration (hollow arrowheads in image D), and hemorrhage (black arrowheads in images C and D) appear milder than the myocardial ischemia-reperfusion injury (MIR) group. Myocardial cells with contraction bands (black arrows in images A, B) and myocardial cells exhibiting cytoplasmic fragmentation, or vacuoles (hollow arrows in image B) are less widespread. Regions with no myocardial cellular integrity (asterisks in images C and D) are not as extensive as those seen in the MIR group. Stain: hematoxylin and eosin (H&E). Magnification is 200 $\times$ for images A and C; 400 $\times$ for images B and D

Discussion

During ischemia, lowered oxygen levels trigger ATP depletion, which activates anaerobic glycolysis, leading to increased hydrogen and lactate levels and resulting in acidosis⁽¹⁶⁾. Decreased ATP levels inhibit the sodium-potassium-ATPase enzyme, causing sodium and chloride accumulation and subsequent cell swelling⁽¹⁶⁾. Although

calcium levels increase, the calcium sensitivity of myofibrillar proteins decreases, impairing contraction⁽¹⁶⁾. Myocyte necrosis exacerbates the inflammatory response⁽¹⁶⁾. Ischemic myocytes and activated leukocytes initiate ROS generation, causing peroxidative damage to membrane phospholipids⁽¹⁶⁾. This process results in increased membrane leakage⁽¹⁶⁾. Consequently, oncosis and apoptosis begin⁽¹⁶⁾. Upon reperfusion, mitochondrial oxidative phosphorylation recovers quickly, but contraction returns gradually due to myocardial stunning⁽¹⁷⁾. During reperfusion, acidosis resolves rapidly through hydrogen efflux and sodium influx, followed by activation of the sodium-calcium exchanger; calcium accumulation then triggers cell death⁽¹⁷⁾. Subsequently, mitochondrial permeability transition pores open, triggering ROS generation and the release of proinflammatory factors such as tumor necrosis factor alpha, toll-like receptors, nuclear factor kappa B, and danger-associated molecular patterns⁽¹⁷⁾. These chemoattractant cytokines then recruit neutrophils into the reperfused area⁽¹⁷⁾. We aim to interrupt this vicious cycle, which leads to increased inflammation, elevated ROS production, and further cell damage.

The ET family consists of 21-amino-acid peptides and includes three types: ET-1, ET-2, and ET-3⁽⁹⁾. These ETs exert their effects by binding to ET_A and ET_B receptors⁽⁹⁾. ET_A receptors are located on smooth muscle cells and mediate the vasoconstriction effects of ET-1⁽⁹⁾. ET_B receptors are primarily found on endothelial cells, where they bind ET-1 and ET-3 and are responsible for vasodilation through the release of nitric oxide (NO) and prostacyclin^(9,18,19). The vasoconstriction effects of ET-1 occur in the pulmonary, coronary, renal, and systemic vascular beds⁽⁹⁾. Additionally, ET-1 acts as an agonist of the sympathetic nervous system and the renin-angiotensin-aldosterone system⁽⁹⁾. ET-1 also activates neutrophils, mast cells, and monocytes, which in turn stimulate a wide range of cytokines, explaining its role in inflammation⁽¹⁸⁾. Beyond its mitogenic, profibrotic, and proinflammatory activities in the myocardium and vascular beds, ET-1, negatively affects the heart through the hypertrophic effects mediated by noradrenaline and angiotensin II, as

well as the profibrotic effects of aldosterone⁽⁹⁾. Moreover, ET-1 levels are elevated in CHF and AMI^(7,20,21). ET-1 blood levels also correlate with one-year mortality after AMI^(9,19). Bosentan is a specific antagonist of ET-1 that blocks both ET_A and ET_B receptors⁽⁹⁾. However, bosentan is 100 times more selective for ET_A receptors, which accounts for its clear vasodilatory effects⁽⁹⁾. These properties of bosentan led us to consider its potential cardioprotective effects. Our study's histological and biochemical analyses demonstrated that bosentan significantly attenuates MIRI, thereby supporting its proposed cardioprotective role.

There are studies similar to ours in the literature. For instance, Gong et al.⁽²²⁾ found that bosentan has positive effects on neuronal ischemia and reperfusion. Similarly, Demirtaş et al.⁽²³⁾ demonstrated beneficial effects of bosentan on IR injury in the rat hind limb. Although their study focused on the hind limb⁽²³⁾ and ours concerns MIRI both studies reflect the role of ETs in ischemia-reperfusion injury. In this regard, Skovsted et al.⁽²⁴⁾ investigated the effect of ET-1 on MIRI in an experimental rat model. They found that the MEK-ERK-1 pathway plays an important role in MIRI through the transcription of ET-1⁽²⁴⁾. Ai et al.⁽²⁵⁾ reported different results on this topic, in their experimental rat model, they found that a combination of ET-1 and NO may reduce MIRI. In contrast to their findings, Tamareille et al.⁽²⁶⁾ showed that ET-1 release may be an early mediator of MIRI. They claimed that ET-1 release triggers calcium overload, which activates apoptosis, and therefore, blocking ET-1 could reduce MIRI⁽²⁶⁾. Their hypothesis aligns with our biochemical and histological findings. In our study, bosentan was administered prior to ischemia to block the early surge of ET-1 activity. Since ET-1 release during the onset of reperfusion has been shown to aggravate myocardial injury through vasoconstriction, calcium overload, oxidative stress, and inflammation^(24,26), the optimal clinical timing of bosentan administration in acute MI or CABG might be immediately before reperfusion (e.g., before coronary revascularization or aortic cross-clamp removal). Further studies are warranted to clarify this therapeutic window.

Additionally, several important studies have reported that bosentan has positive effects against MIRI, which supports our results. Wang et al.⁽²⁷⁾ demonstrated in an experimental study conducted on pigs that bosentan significantly reduces MIRI. They claimed that bosentan exerts cardioprotective effects and improves blood flow, especially in the reperfused area⁽²⁷⁾. We used a rat model in this study due to its cost-effectiveness and wide acceptance in preclinical IR research. Despite lower overall costs, our findings were consistent with those reported in more complex or higher-cost experimental models. In a different study, Wang et al.⁽²⁸⁾ focused on bosentan's cardioprotective effects, this time in rats, and reported similar findings. Bosentan showed cardioprotective effects on isolated rat hearts through ET inhibition. Consistent with our findings, Li et al.⁽²⁹⁾ reported that bosentan has positive effects on MIRI, protecting both the myocardium and endothelium. Gupta et al.⁽³⁰⁾ revealed that bosentan reduces oxidative stress and has beneficial effects against MIRI. Their study confirms the critical role of ET-1 during AMI and demonstrates that blocking its effects with bosentan confers cardioprotection⁽³⁰⁾. These findings are consistent with and supportive of the results of our study.

On the other hand, our study focused solely on the effects of bosentan, therefore, dose-dependent studies on this topic are needed. Additionally, potential side effects of bosentan, such as hepatotoxicity, should be considered⁽³¹⁾.

In conclusion, this study demonstrates that bosentan, an ET receptor antagonist, exerts significant protective effects against MIRI in rats. Histopathological analysis revealed that bosentan administration during IR notably reduced neutrophil infiltration, cardiomyocyte damage, tissue edema, and hemorrhage compared to untreated IR groups. Biochemically, bosentan treatment improved the oxidative balance by decreasing TOS and OSI while increasing TAS, indicating a reduction in oxidative damage. These findings support the role of ET-1 in exacerbating IR injury through vasoconstriction, inflammation, and oxidative stress, and highlight bosentan's potential as a cardioprotective agent

by antagonizing these effects. Given the clinical relevance of IR in CABG and other cardiac interventions, bosentan may represent a promising therapeutic strategy to mitigate myocardial damage and improve outcomes. Further studies are warranted to explore its clinical applicability and long-term benefits in human subjects.

Study Limitations

This study provides valuable insights into the cardioprotective effects of bosentan in a rat model of MIRI. However, several limitations must be acknowledged. First, the sample size was relatively small, with six animals per group, which may limit the statistical power and generalizability of the results. Although statistically significant differences were observed, a larger sample size would provide more robust and reproducible outcomes.

Second, the study was conducted exclusively on healthy, young adult male Wistar-Albino rats. The exclusion of female subjects and animals with comorbid conditions (e.g., diabetes, hypertension, or hyperlipidemia) may not fully reflect the complex pathophysiology of IR injury observed in human patients, particularly those undergoing CABG. Future studies should incorporate models with relevant comorbidities to enhance translational value.

Third, bosentan was administered as a single intraperitoneal dose, and no dose-response relationship was explored. The absence of multiple dosing regimens and pharmacokinetic analyses limits the ability to determine the optimal therapeutic window and systemic effects of bosentan. Moreover, the study did not evaluate potential adverse effects such as hepatotoxicity, which has been reported in clinical settings⁽³¹⁾. In clinical practice, bosentan use has been associated with liver enzyme elevations, peripheral edema, anemia, headache, and hypotension. Preventive strategies include careful patient selection, baseline and periodic monitoring of liver function tests, avoidance of concomitant hepatotoxic medications, and timely dose adjustment or discontinuation in case of significant aminotransferase elevation. Although these adverse effects were not observed in our short-term

experimental protocol due to single-dose administration and limited observation time, they represent an important consideration for any future translational or clinical applications.

Another limitation is that we did not directly measure myocardial or plasma ET-1 levels. Instead, we focused on oxidative stress parameters (TAS, TOS, OSI, and PON-1) and histopathological injury scores to evaluate the extent of myocardial damage and the protective effect of bosentan. The omission of ET-1 measurement was primarily due to technical and financial limitations, as specific assays for ET-1 were not available during the study period. Nevertheless, direct measurement of ET-1 would provide valuable mechanistic insight, and future studies incorporating ET-1 quantification are warranted to better elucidate the molecular pathways underlying bosentan's cardioprotective effects.

Fourth, the observation period after reperfusion was limited to 90 minutes. Myocardial damage due to reperfusion injury may evolve over a longer period, and the short-term follow-up may not capture delayed histological or biochemical changes. Long-term assessments, including survival, cardiac function, and fibrotic remodeling, would provide a more comprehensive evaluation of bosentan's cardioprotective effects.

Lastly, although biochemical and histopathological endpoints were thoroughly assessed, molecular mechanisms underlying bosentan's protective effects such as its influence on ET-1 receptor signaling, inflammatory cytokine expression, or mitochondrial pathways were not investigated. Future investigations incorporating molecular analyses may clarify the specific cellular pathways through which bosentan exerts its effects during IR injury.

Despite these limitations, the findings of this study lay a foundation for further research and support the potential utility of e ET receptor antagonism as a cardioprotective strategy.

Conclusion

In this experimental study, bosentan a dual ET receptor antagonist demonstrated significant cardioprotective effects against MIRI in rats. The administration of bosentan during the ischemic phase led to a marked attenuation in histopathological scores of tissue injury, including neutrophil infiltration, cardiomyocyte necrosis, interstitial edema, and hemorrhage. In parallel, bosentan significantly modulated oxidative stress by lowering TOS and OSI, while increasing TAS and PON-1 activity.

These findings suggest that antagonism of ET-1 receptors can effectively disrupt the pathophysiological cascade triggered by ischemia and reperfusion, characterized by vasoconstriction, inflammation, and oxidative damage. Given the central role of ET-1 in cardiovascular pathology, bosentan may represent a promising pharmacological intervention to limit myocardial injury in settings such as CABG or acute MI.

The translational relevance of these findings may pave the way for novel cardioprotective strategies in the perioperative management of myocardial revascularization procedures.

While our results provide compelling preclinical evidence supporting the efficacy of bosentan in ameliorating MIRI, further research including dose-response studies, long-term functional assessments, and clinical trials is necessary to validate its therapeutic potential and safety profile in human subjects.

Ethics

Ethics Committee Approval: This study was approved by the Gazi University Local Ethics Committee for Animal Experiments (approval no: G.Ü.ET-22.062, date: 22.11.2023). All experimental procedures were conducted at a certified animal research laboratory, Gazi University Center for Experimental Research and Practice (GÜDAM), in Ankara, Türkiye, in compliance with national and institutional ethical guidelines.

Informed Consent: All animals were housed and cared for according to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Demirtaş H, Özer A, Yiğman Z, Concept: Yiğman Z, Demirtaş H, Gülcan MB, Özer A, Dursun AD, Küçük A, Arslan M, Design: Yiğman Z, Demirtaş H, Gülcan MB, Özer A, Dursun AD, Küçük A, Arslan M, Data Collection and/or Processing: Yiğman Z, Demirtaş H, Gülcan MB, Özer A, Dursun AD, Küçük A, Arslan M, Analysis and/or Interpretation: Yiğman Z, Demirtaş H, Gülcan MB, Özer A, Dursun AD, Küçük A, Arslan M, Literature Search: Demirtaş H, Arslan M, Writing: Demirtaş H, Arslan M, Gülcan MB, Yiğman Z.

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Intracardiac Access for Hemodialysis in Small Children: Final Options, Guidance, and Tips

Ömer Faruk Gülaştı, Gökmen Akkaya

University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Cardiovascular Surgery, İzmir, Türkiye

Abstract

Hemodialysis access in small children with genetic syndromes and end-stage renal failure possesses various challenges. Traditional options may quickly support an upper sternal approach over thoracotomy to enhance exposure and facilitate effective catheter placement. Overall, eight attempts were made in two cases involving both techniques. Either thoracotomy or sternotomy has inherited advantages and disadvantages. However, the sternal approach allows wider exposure, more precise catheter placement, and easier future surgeries.

Keywords: Atrium, cardiac, cardiovascular surgery, veins

Introduction

Maintaining durable and functional vascular access for children with end-stage renal disease is a challenging goal. When peritoneal dialysis is not feasible, particularly in pediatric patients, permanent tunneled venous catheters (PTVCs) are often preferred due to the complexities associated with creating and maintaining arteriovenous fistulas. However, prolonged use of PTVCs frequently leads to complications such as fibrosis, infection,

thrombosis, and catheter-related fibrin sheath formation around the central vein, with small children being particularly susceptible to these issues⁽¹⁻³⁾.

Thanks to advancements in interventional techniques, unconventional vascular access options have been developed and adopted over the years^(4,5). Despite these innovations, some exceptional cases still lack viable venous access for the Seldinger technique⁽⁶⁾. In such situations, emergent surgical exploration remains a critical, life-saving approach.



Address for Correspondence: Gökmen Akkaya, University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Clinic of Pediatric Cardiovascular Surgery, İzmir, Türkiye

e-mail: akkayagokmen@gmail.com **ORCID:** orcid.org/0000-0002-0509-1971

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Transpleural or mediastinal approaches may be employed for direct cardiac catheterization. While these procedures are within the expertise of surgeons, they extend beyond simple cut-down methods and require meticulous attention.

In this article, we share our experience with eight instances of direct right atrial PTVC insertion, performed through sternotomy and thoracotomy, in two pediatric patients.

Case Presentation 1

A four-year-old female patient, weighing 16 kg, diagnosed with Emery-Dreifuss muscular dystrophy and congenital arthrogryposis multiplex, had been undergoing renal replacement therapy for over a year due to hemolytic-uremic syndrome. She was referred to our department after exhausting traditional vascular access options for PTVC placement. The patient's history included consanguineous marriage, with a heterozygous SYNE1 gene mutation (ENST00000367255.5 c.1257C>G, p.Tyr419Ter) detected. Neuromuscular development was impaired, leaving her immobile and on dual therapy for recurrent seizures. Multiple central catheter placements, port catheter placements, and hemodialysis catheter placements were attempted, but even successfully placed devices were non-durable, necessitating frequent replacements due to stenosis, thrombosis, or sepsis.

Upon initial consultation in pediatric cardiac surgery, both iliac veins showed slight re-canalization after non-surgical catheter removals, despite anticoagulant therapy. Several punctures through the jugular and subclavian veins failed because the guidewire could not advance. These challenging conditions led to the consideration of direct atrial catheter implantation. To avoid the complications associated with sternotomy, a right thoracotomy was preferred. The procedure was uneventful; the atrium was accessed via the fourth intercostal space, and the pericardium was incised. A purse-string suture with pledgets was placed on the atrial wall, and the PTVC was inserted in a manner similar to the method used in the cardiopulmonary bypass procedure (Figure 1A, 1B).

Four months post-surgery, the patient was referred due to inefficient hemodialysis. A redo surgery was performed, using a limited J-sternotomy for better exposure. The previous catheter was removed, and a new catheter was positioned to mimic the natural course of the superior vena cava, avoiding sharp angles and leaflet interference to ensure optimal suction and flow (Figure 2).

Despite these interventions, two additional surgeries were required due to sepsis and thrombosis. These subsequent replacements were successfully conducted through redo sternotomies, after which the patient achieved stable hemodialysis without further complications.

Case Presentation 2

A 4-year-old boy, weighing 14 kg, diagnosed with Denys-Drash syndrome and homozygous MTHFR C677T mutation, had been on dialysis since infancy. Over the past two years, peritoneal dialysis was discontinued due to recurrent peritonitis, sepsis, and therapy was switched to a PTVC. The patient also presented with multiple congenital anomalies, including impaired neurological development, hydrocephalus, recurrent thrombosis, cryptorchidism, and parathyrotoxicosis. All conventional vascular access sites had been exhausted, and Doppler ultrasound failed to identify any patent jugular or subclavian veins. Attempts to use femoral sites were also unsuccessful. The last inserted catheter was located in the persistent left caval vein, which was inadequate for providing sufficient hemodialysis.

Given the challenging anatomy and the previously used sternotomy approach, the surgical team opted for a thoracotomy. The initial surgical steps mirrored those of the previous case. However, to prevent catheter kinking and migration toward the tricuspid valve, a vertical, straight-line tunnel was created. This technique, while effective, introduced additional challenges: lung inspiration, could cause tension on the catheter line, necessitating a safety margin for the portion of the catheter within the atrium. Unfortunately, a miscalculation led to the distal orifice of the PTVC being positioned in the inferior vena cava, requiring an early revision for adjustment (Figure 3).

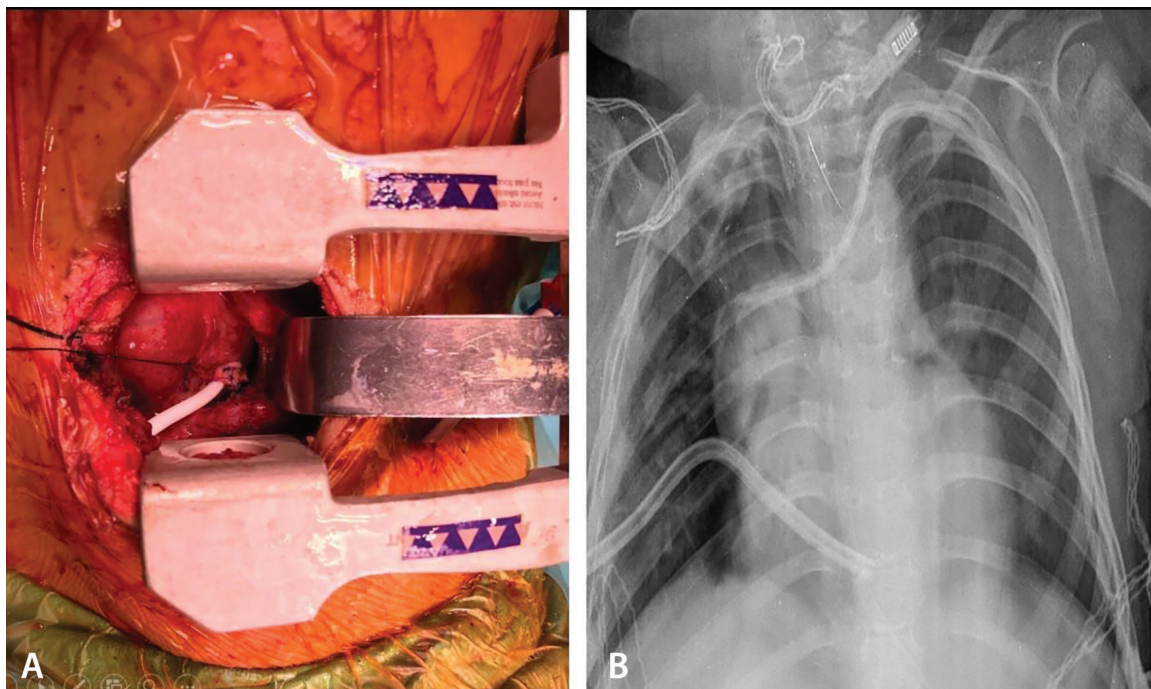


Figure 1. (A) Surgical view of the catheter directly inserted directly through right atrium, (B) X-ray view of the catheter, with the tip positioned near the tricuspid valve

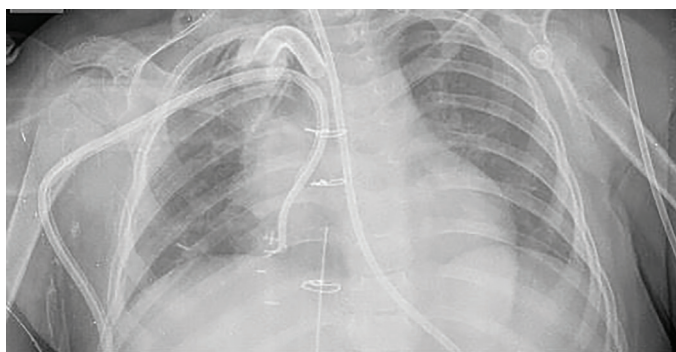


Figure 2. Right atrial catheter via thoracotomy with better course without any sharp angle

Nine months later, the patient accidentally dislodged the catheter. Fortunately, bleeding resolved spontaneously without leading to tamponade. The patient was subsequently operated on electively, and a new catheter was inserted into the right atrium via sternotomy. Due to reduced adhesion formation, the new catheter tunnel was created on the left side, following the upper portion of the clavicle, and entering the mediastinum through the suprasternal notch (Figure 4 A, B). The catheter functioned optimally thereafter.

Discussion

End-stage renal failure (ESRF) necessitates effective vascular access when transplantation or peritoneal dialysis is no longer a viable option. Although arteriovenous fistulas offer adequate blood flow with large puncture sites and reduced infection rates, their reliability in pediatric patients, especially in small toddlers, remains limited^(2,3). While most studies focus on adolescents, data on younger children, particularly those under four years of age, are scarce⁽⁷⁾. As a result, PTVs are more commonly employed in pediatric populations.

The need for dialysis in children with congenital genetic syndromes and various disorders compounds the challenge, as these conditions often lead to early and rapid exhaustion of vascular access sites⁽⁸⁾. Given these complications, the process of selecting and managing vascular access requires a multidisciplinary approach. In many countries, pediatric nephrologists, pediatric surgeons, pediatric cardiovascular surgeons, interventional radiologists, and pediatric radiologists are

involved in managing these cases. Despite this, pediatric surgeons and interventional radiologists typically assume the primary responsibility for catheter placement globally, with the majority of published reports stemming from their expertise. Unfortunately, in Türkiye, as in many other regions, individual hospitals may develop their own protocols, which can lead to complications, particularly from a medico-legal perspective.

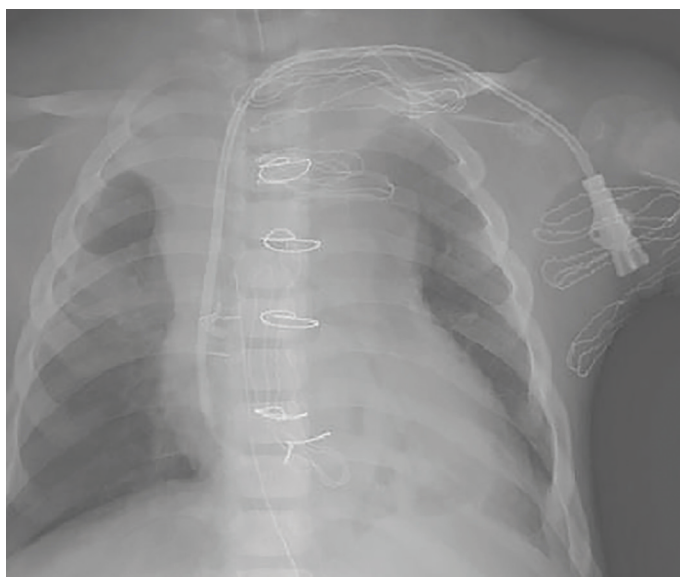


Figure 3. Revised catheter course following adjustment

We strongly advocate for the establishment of specialized, experienced catheter teams and for practitioners to exhaust all interventional options before resorting to surgery. Once all interventional methods have been exhausted, surgical intervention becomes necessary. Although non-traditional approaches such as trans-lumbar, trans-hepatic, and trans-renal catheter placements are available, only some of these approaches are feasible in young children^(9,10). Most of the existing literature on intra-cardiac PTVCs primarily reports on adult patients. Philipponnet et al.⁽¹¹⁾ reviewed 51 cases of intra-atrial catheter placement, with the youngest patient being 30 years old. This cohort was largely derived from Oguz et al.⁽¹²⁾, which compiles and analyzes scattered reports on intra-cardiac catheterization. Notably, mortality and complication rates were significantly higher compared to those associated with interventional catheter placements or even cardiac surgery. Seven patients died within 15 days of surgery, and another six died later, a consequence likely attributed to their pre-existing poor health. Interestingly, some patients required multiple surgeries, despite reasonable follow-up periods. Only one patient from Chavanon et al.⁽¹³⁾ underwent surgery three times.

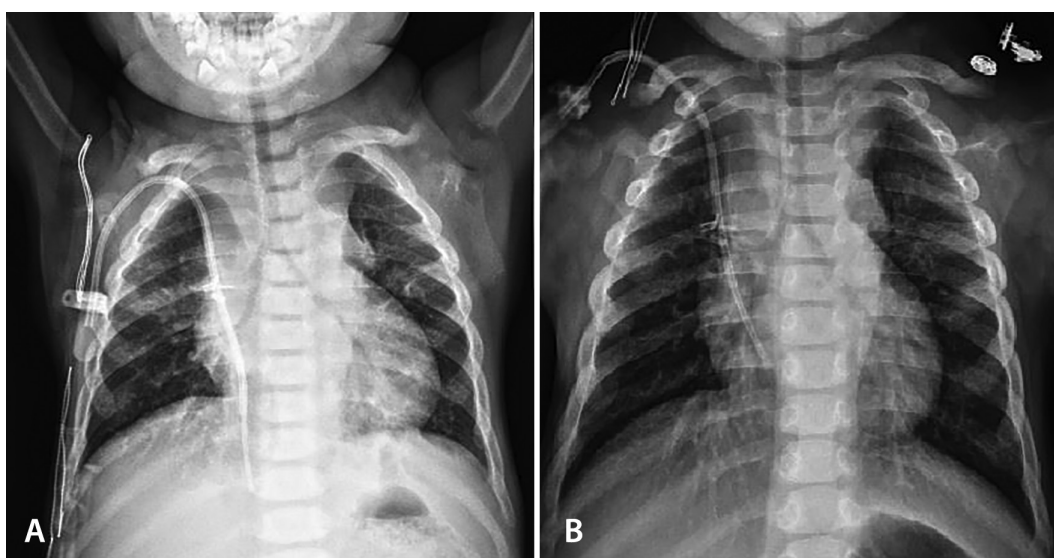


Figure 4. (A) Proper catheter alignment with no sharp angle, ensuring optimal flow. (B) The length of the catheter adjusted so as to end in the right atrium

In isolated cases of intra-cardiac catheter placement, a trans-thoracic approach is typically used⁽¹²⁻¹⁹⁾, while a sternal approach is generally reserved for concomitant surgeries. In our practice, we performed four consecutive surgeries with different techniques, in both of our patients, over the past two years. Initially, we preferred thoracotomy to minimize the risks associated with sternotomy. However, this technique presents several disadvantages: pleural adhesions are more difficult to manage than those encountered during sternotomy, and the likelihood of lung injury and prolonged chest drainage is higher. Over recent decades, advancements in surgical tools and expertise have led pediatric cardiac surgeons to favor sternotomy, especially for procedures such as modified Blalock-Taussig shunts, pulmonary artery banding, and patent ductus arteriosus closure⁽²⁰⁻²²⁾. This increased confidence in sternotomy procedures has encouraged surgeons to reconsider sternotomy procedures for repetitive surgeries.

In addition to managing adhesions, careful attention must be paid to the safety margin required to prevent tension on the catheter during inspiration, as well as the catheter's entry angle. Improper calculations can lead to catheter migration into the caval vein or tricuspid valve, both of which impair dialysis function. Direct cardiac implantation of PTVCS generally reduces vessel-induced complications. We recommend using a catheter one size larger than usual for the child's body weight to ensure long-lasting results.

As a result, we have increasingly opted for upper sternotomy rather than thoracotomy in these cases. This approach offers better exposure, allows for more precise catheter placement, and facilitates future surgeries. Additionally, the length and trajectory of the catheter tunnel are crucial for maintaining effective hemodialysis. The closer the catheter path mirrors the natural venous flow, the better the dialysis outcomes.

We secure the catheter with sutures and pledgets at the insertion site and use silk stitches to attach the

pericardium to the catheter. If possible, the catheter can be passed through the thymus to stabilize it, and in the event of accidental removal, the thymus may help in minimizing bleeding by constricting the surrounding area. However, a combination of genetic disorders, ESRF, and sepsis can impair wound healing, making it easier for even a child to dislodge the catheter with minimal effort. For this reason, the catheter must be securely fixed at the atrial entrance, pericardium, jugulum, and skin incision sites.

In summary, small children with genetic syndromes and ESRF are at increased risk for complications such as sepsis and thrombosis, which can rapidly deplete all available vascular access options. Once these interventional methods are exhausted, salvage surgery is necessary. We recommend an upper sternal approach over thoracotomy, as it provides better exposure, more precise catheter placement, and easier future surgeries. Surgeons must be mindful that these patients are often candidates for further, repetitive surgeries, and each step in the process should be carried out with this consideration in mind.

Ethics

Informed Consent: The signed informed consent forms were obtained from each parents of the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Gülaştı ÖF, Concept: Gülaştı ÖF, Design: Akkaya G, Data Collection and/or Processing: Gülaştı ÖF, Analysis and/or Interpretation: Akkaya G, Literature Search: Akkaya G, Writing: Akkaya G.

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What to Do When Both Ventricular Outflow Tracts are Obstructed?

© Şafak Alpat

Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery, Division of Paediatric Cardiac Surgery, Ankara, Türkiye

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Dear Editor,

I have read with great interest, the manuscript by Said⁽¹⁾ in which he thoroughly reviewed the current surgical techniques in the management of pediatric hypertrophic obstructive cardiomyopathy (HOCM). Despite the fact that there are well-established different techniques for the management of left ventricle obstruction in HOCM, it remains controversial when right ventricle (RV) is also affected by the disease. Fortunately, RV involvement in HOCM is quite uncommon and primarily associated with genetic disorders such as Noonan syndrome and other RASopathies. The author effectively demonstrated his own technique for patients with HOCM and right ventricular outflow tract (RVOT) obstruction, which includes infundibular incision, limited RV myectomy, and patch augmentation of the incision. He also noted that because of the septal connection of the tricuspid valve on the right side, conduction tissue and tricuspid valve apparatus are both at risk for iatrogenic injury, which may complicate the procedure. I have a few comments and remarks.

First, it was observed that 28-44% of patients with HOCM display varying degrees of RV pathology⁽²⁾. The proposed mechanisms include the disease process primarily affecting RV cardiomyocytes, resulting in RV hypertrophy, RV dysfunction secondary to postcapillary pulmonary hypertension, and RV failure related to altered ventricular inter-dependence^(2,3). Regardless of the underlying etiology, patients with RV involvement exhibit a dismal prognosis, characterized by an elevated risk of ventricular tachycardia and sudden cardiac death. Consequently, tailored therapy approaches are necessary based on the underlying pathophysiological mechanisms. Given that RV hypertrophy is predominantly present in all the aforementioned situations, could the author explain how the author distinguished which patients may benefit from limited RV myectomy?

Second, the author noted that he preferred patch augmentation of the RV incision after the myectomy. I am concerned about using the patch to enlarge the RVOT in patients with HOCM, as it would compromise the RV function and further abolish ventricular inter-



Address for Correspondence: Şafak Alpat, Hacettepe University Faculty of Medicine, Department of Cardiovascular Surgery, Division of Paediatric Cardiac Surgery, Ankara, Türkiye

e-mail: safakalpat@hacettepe.edu.tr **ORCID:** orcid.org/0000-0002-8690-4494

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dependence⁽⁴⁾. Others proposed that the adequate resection of hypertrophied tissue resulted in elimination of obstruction, an increase in the RV cavity size, and improvement in RV function without patch augmentation⁽⁵⁾.

Second, the author indicated a preference for patch augmentation of the RV incision following the myectomy. I am apprehensive about employing the patch to augment the RVOT in individuals with HOCM, as it might jeopardize RV function and further disrupt ventricular interdependence. Some suggested that sufficient excision of hypertrophied tissue leads to the removal of obstruction, an enlargement of the RV cavity, and enhancement of RV performance without the need for patch augmentation. Do you have any complications that are associated with this?

Third, I would like to know when he offers transplantation for a pediatric patient with severe biventricular obstructions in the form of HOCM.

Footnotes

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