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New guidelines for the diagnosis and management of pulmonary embolism: Key changes

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Abstract

Pulmonary embolism (PE) is an important public health problem. In August 2019, the European Society of Cardiology in collaboration with the European Respiratory Society released new guidelines for the diagnosis and management of PE. We discuss the basic changes between these recent guidelines and the previous guidelines that were published in 2014. Regarding diagnosis, the new guidelines propose the use of an age-adjusted cut-off level of D-dimers instead of a fixed cut-off value. A D-dimer test adapted to clinical possibility should also be considered instead of fixed cut-off level of D-dimer. Detailed recommendations for the diagnosis of PE during pregnancy are also provided. Regarding risk stratification, assessment of PE-related early mortality risk is recommended. Moreover, the importance of right ventricular dysfunction is emphasized in low-risk patients. For further risk stratification of the severity of PE in patients without hemodynamic instability, use of validated scores that combine clinical, imaging and laboratory PE-related prognostic factors might also be considered. Regarding treatment, the possibility of early discharge is mentioned in patients without severe comorbidities, who are not of high risk for sudden death and in whom proper medical management at home and proper medical follow up can be ensured. The new guidelines also suggest that pro-brain natriuretic peptide levels, right ventricular function and the presence of thrombus in the right heart could be useful for guiding the decision of early discharge. Overall, these new guidelines introduce several key changes and knowledge and adherence to them will improve the outcome of patients with PE.

Key words: Pulmonary embolism; Guidelines; Diagnosis; Treatment; D-dimers; Pregnancy

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Core tip: We discuss the basic changes between the recent guidelines published in August 2019 by the European Society of Cardiology in collaboration with the European Respiratory Society regarding the diagnosis and management of pulmonary embolism and the previous guidelines that were published in 2014. The use of age-specific cut-off levels of D-dimers, detailed recommendations for risk stratification and the possibility of outpatient management are some of the key changes. Knowledge and adherence to these new guidelines will improve the outcome of patients with pulmonary embolism.

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INTRODUCTION

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important public health problem. The annual incidence of first-time VTE in the United States is 71-117 cases per 100000^[1]. Moreover, the 28-d case fatality rate after a first episode of VTE is approximately 11%^[2]. However, PE-related mortality rates have declined recently^[3,4]. This decrease could be due to improvements in the diagnosis and managements of PE^[4]. However, the decrease in PE-mortality might also be related to the overdiagnosis of PE, due to introduction and overuse of computed tomographic pulmonary angiography, in which non-clinically important PE is diagnosed and treated^[5].

In August 2019, the European Society of Cardiology (ESC) in collaboration with the European Respiratory Society released the new guidelines for the diagnosis and management of PE^[6]. This editorial will focus on the basic changes between the recent guidelines of the ESC for the diagnosis and management of PE and the previous guidelines that were published in 2014.

CHANGES IN THE DIAGNOSIS OF PULMONARY EMBOLISM

Flow chart for the diagnosis of pulmonary embolism was shown in [Figure 1](#). Based on the new ESC guidelines, instead of a fixed-cut off level of D-dimers (500 ng/mL), an age-adjusted cut-off level of D-dimers should be considered to exclude PE in patients with low or intermediate clinical possibility for PE and in those where PE is unlikely^[7,8]. The age-adjusted cut-off level of D-dimers is calculated by multiplying the age of the patient by 10 (for patients older than 50 years). Thus, in a 60-year-old patient who has a low or intermediate clinical possibility for PE or who is unlikely to have PE, D-dimers levels < 600 ng/mL (*i.e.*, age × 10) instead of D-dimers levels < 500 ng/mL (*i.e.*, the fixed-cut off level) excludes PE. On the other hand, in a 40-year-old patient who has a low or intermediate clinical possibility for PE or who is unlikely to have PE, the fixed-cut off D-dimers level of < 500 ng/mL should be used, since the patient is younger than 50 years.

A D-dimer test adapted to clinical possibility should also be considered instead of fixed cut-off level of D-dimer^[6]. Based on the YEARS study, if D-dimer levels are < 1000 ng/mL and none of the 3 clinical items of Wells score (signs of DVT, hemoptysis or PE being the most likely diagnosis) are present or if D-dimer levels are < 500 ng/mL and one or more clinical items of Wells score are present, then a diagnosis of PE should be excluded^[9].

There is also a change in the class of recommendation for the use of D-dimer levels during pregnancy and the post-partum period. According to the new guidelines, D-dimer measurement and clinical prediction rules should be considered to exclude PE during pregnancy and post-partum period^[6]. Moreover, in case of suspected PE during pregnancy or the first 6 weeks post-partum, a specific diagnostic workup is provided to rule out or confirm the diagnosis of PE^[6]. This updated diagnostic

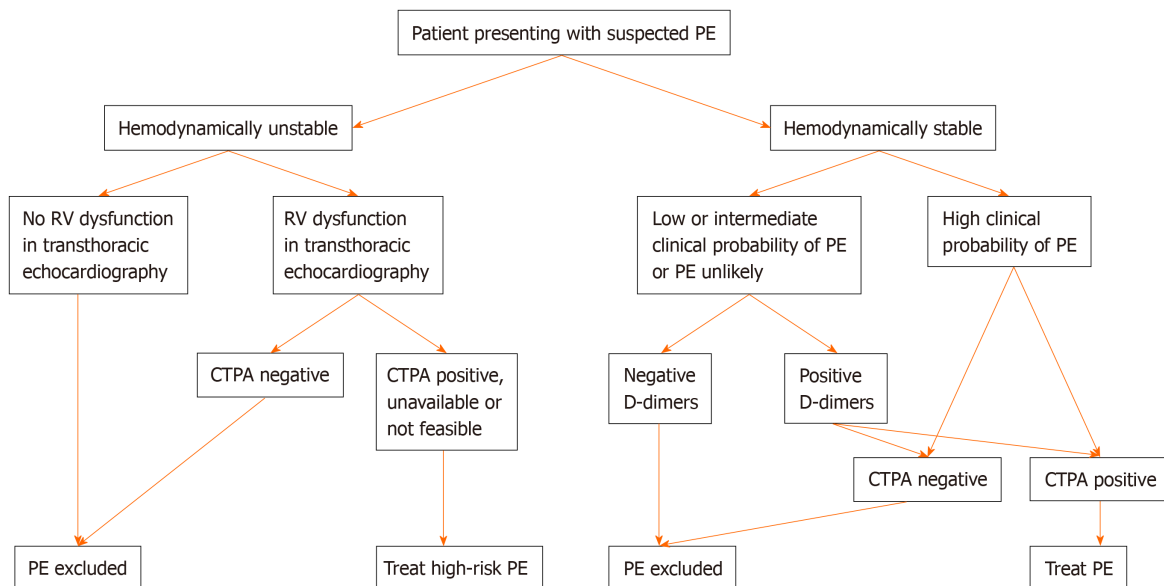


Figure 1 Flow chart for the diagnosis of pulmonary embolism. PE: Pulmonary embolism; RV: Right ventricle; CTPA: Computed tomography pulmonary angiography.

algorithm is based on recently published multicenter trials^[10,11].

Furthermore, the 2019 guidelines summarize not only the advantages and disadvantages of the various diagnostic imaging tests but also describe and compare the exposure to radiation with the different tests.

Another change refers to the use of lower limb compression ultrasonography (CUS). The previous guidelines mentioned that, if CUS reveals proximal DVT in a patient and there is clinical suspicion of PE, a diagnosis of PE is established. However, the new recommendation in the 2019 guidelines, is that, if a positive CUS is used for the confirmation of PE, then risk assessment for PE severity and early mortality should be considered to guide further management^[6].

In the 2019 guidelines, the role of ventilation/perfusion SPECT in the diagnosis of PE is emphasized more compared with the 2014 guidelines. In the new guidelines, it is mentioned that ventilation/perfusion SPECT may be considered for the diagnosis of PE^[6]. However, more studies are needed to define the best SPECT technique.

CHANGES IN RISK ASSESSMENT OF PULMONARY EMBOLISM

In the 2019 guidelines, there is a definition of haemodynamic instability, which indicates acute high-risk PE. Three clinical manifestations of haemodynamic instability are mentioned (cardiac arrest, obstructive shock and persistent hypotension) and for each one, a clear definition is given, so that clinicians can decide if the patient is hemodynamically unstable or not. More specifically, haemodynamic instability is defined as: (1) Cardiac arrest *i.e.*, need for cardiopulmonary resuscitation; (2) Obstructive shock *i.e.*, systolic blood pressure (SBP) < 90 mmHg (or need for vasopressors to achieve SBP ≥ 90 mmHg) despite adequate filling status and end-organ hypoperfusion (altered mental status, cold/clammy skin, oliguria/anuria or increased serum lactate); or (3) Persistent hypotension *i.e.* SBP < 90 mmHg or SBP drop ≥ 40 mmHg, lasting > 15 min and not caused by new-onset arrhythmia, hypovolemia or sepsis.

Although the first risk stratification is based on the clinical manifestations of haemodynamic instability, assessment of PE severity and PE-related, early mortality risk is also recommended for patients with PE but without symptoms and signs of haemodynamic instability^[6]. The prognostic criteria, on which the further risk stratification is based, are separated into 2 categories: (1) Clinical, imaging and laboratory parameters, the most important of which is right ventricular dysfunction; and (2) Comorbidities and other conditions that have an adverse effect on early prognosis.

In the 2019 guidelines, emphasis is given to right ventricular dysfunction, which is associated with increased risk for short-term mortality in hemodynamically stable

patients with PE. Right ventricular dysfunction should be evaluated either with ultrasound or with laboratory prognostic biomarkers [cardiac troponins, brain natriuretic peptide (BNP) or proBNP], even if the Pulmonary Embolism Severity Index (PESI) is low or the simplified PESI (sPESI) is zero^[6,12,13].

For further risk stratification of the severity of PE in patients without hemodynamic instability, use of validated scores (the Bova and the H-FABP scores) that combine clinical, imaging and laboratory PE-related prognostic factors might also be considered^[6,14,15].

CHANGES IN THE TREATMENT OF PULMONARY EMBOLISM

Patients with PE are treated according to their hemodynamic status and their risk profile. More specifically, thrombolysis is recommended in patients with PE who are hemodynamically unstable and at high risk. If thrombolysis is contraindicated or unsuccessful, surgical pulmonary embolectomy or percutaneous catheter-directed therapy might be considered^[6,16,17]. Even though reperfusion therapy might be lifesaving, it is not indicated in all patients with PE because of the increased bleeding risk^[6,16,18].

The new guidelines also mention the possibility of early discharge (*i.e.*, at 24 h) in patients without severe comorbidities, who are not of high risk for sudden death and in whom proper medical management at home and proper medical follow up can be ensured^[6]. This recommendation is based on the results of the multi-center HESTIA trial, which evaluated the out-of-hospital treatment in patients with low-risk PE and showed that they could safely be treated at home. In fact, only 2% of these patients experienced recurrent VTE and none of these episodes occurred during the first 7 d of treatment^[19]. In another study, patients with PE and a low PESI score were treated at home and had a very low PE-related and all-cause mortality^[20]. The new guidelines also suggest that proBNP levels, right ventricular function and the presence of thrombus in the right heart could be useful for guiding the decision of early discharge^[6,21].

Long-term treatment of patients with PE includes anticoagulant therapy for at least 3–6 mo^[6]. Whether the treatment should be extended beyond this period depends on the risk of recurrence^[6]. In patients with PE due to a treatable or transient risk factor, discontinuation of anticoagulation at 3 mo is recommended^[6].

Direct-acting oral anticoagulants are the treatment of choice in patients with PE, except during pregnancy and in patients with severe renal impairment or the antiphospholipid syndrome^[6]. In patients with antiphospholipid syndrome, vitamin K antagonists indefinitely are the treatment of choice^[6]. In pregnant women and in patients with severe renal impairment, low-molecular weight heparin is the recommended treatment^[6]. Patients with cancer should also be treated with low-molecular weight heparin even though Direct-acting oral anticoagulants can also be considered based on the results of recent trials^[22,23].

The use of vena cava filters is suggested only in patients with absolute contraindications to anticoagulant treatment^[6]. However, they do not appear to reduce the risk of PE recurrence or PE-related mortality^[24,25].

Finally, all patients with PE should be followed-up regularly because of the increased incidence of cancer (which might not be detectable at the time of PE), the risk of bleeding complications and the risk for development of chronic thromboembolic pulmonary hypertension^[6].

CONCLUSION

The recent guidelines for the diagnosis and treatment of PE include several key changes which facilitate the management of this common and potentially life-threatening medical emergency (Table 1). Knowledge and adherence to these guidelines will improve the outcome of these patients.

Table 1 Key changes in the 2019 guidelines of the European Society of Cardiology regarding the diagnosis and treatment of pulmonary embolism

Diagnosis	An age-adjusted cut-off level of D-dimers can be used instead of a fixed cut-off value
Risk assessment	Assessment of PE-related early mortality risk is recommended
	The importance of right ventricular dysfunction is emphasized in low-risk patients
Treatment	The possibility of early discharge is mentioned in patients without severe comorbidities, who are not of high risk for sudden death and in whom proper medical management at home and proper medical follow up can be ensured

PE: Pulmonary embolism.

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Management of adults with coarctation of aorta

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Abstract

Coarctation of the aorta (CoA) is a relatively common congenital cardiac defect often causing few symptoms and therefore can be challenging to diagnose. The hallmark finding on physical examination is upper extremity hypertension, and for this reason, CoA should be considered in any young hypertensive patient, justifying measurement of lower extremity blood pressure at least once in these individuals. The presence of a significant pressure gradient between the arms and legs is highly suggestive of the diagnosis. Early diagnosis and treatment are important as long-term data consistently demonstrate that patients with CoA have a reduced life expectancy and increased risk of cardiovascular complications. Surgical repair has traditionally been the mainstay of therapy for correction, although advances in endovascular technology with covered stents or stent grafts permit nonsurgical approaches for the management of older children and adults with native CoA and complications. Persistent hypertension and vascular dysfunction can lead to an increased risk of coronary disease, which, remains the greatest cause of long-term mortality. Thus, blood pressure control and periodic reassessment with transthoracic echocardiography and three-dimensional imaging (computed tomography or cardiac magnetic resonance) for should be performed regularly as cardiovascular complications may occur decades after the intervention.

Key words: Coarctation of aorta; Cardiac surgery; Cardiac catheterization; Balloon angioplasty; Stents

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Core tip: Coarctation of the aorta (CoA) is a common congenital cardiac defect with few symptoms and difficult to diagnose. Early diagnosis and treatment are important as long-term data demonstrate reduced life expectancy and increased risk of cardiovascular complications. Surgical repair has traditionally been the mainstay of therapy for correction, although advances in endovascular technology with covered stents and stent grafts permit nonsurgical approaches for the management of children and adults with native CoA and complications. Persistent hypertension and vascular dysfunction can lead to an increased risk of coronary disease, which remains the greatest cause of long-term mortality.

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INTRODUCTION

Coarctation of the aorta (CoA) is one of the most common congenital cardiac anomalies causing a narrowing of the proximal descending^[1,2] varying within a range of arch abnormalities from a discrete narrowing to a long segment of arch hypoplasia^[3]. It was first described by Thiene^[3] in 1760 and accounts for 4%-6% of all congenital heart defects, with an incidence is of 3-4 cases per 10000 live births^[4,5]. Males are commonly affected than females with a ratio between 1.27:1 and 1.74:1, respectively^[1,6-8].

CLASSIFICATION AND MORPHOLOGY

The narrowing of CoA is classically situated between the left subclavian artery and the ligamentum arteriosum at the aortic isthmus. CoA can also occur in atypical locations, between the transverse aortic arch and the bifurcation of the abdominal aorta^[9]. Traditionally, CoA was classified as pre-ductal, juxta-ductal, and post-ductal based on its relationship with the ductus arteriosus (Figure 1). However, the degree of narrowing of the aorta and the association with arch vessels are regarded as more clinically relevant^[10]. Approximately 40%-80% of patients have associated transverse arch hypoplasia, which varies in severity and must be accurately defined prior to planned intervention^[11-13]. Although the ratio of the narrowed segment's diameter to that of the distal descending aorta was formerly used to define the degree of CoA^[14], arch hypoplasia is currently defined by z-scores of -2 or lower^[15]. Rarely, we can observe tubular hypoplasia representing a combination of small arch diameter and increased length between segments of the arch^[16]. CoA ranges in severity from complete aortic luminal atresia to a mild, precisely defined posterior shelf like lesion, and it needs to be differentiated from an interrupted aortic arch, in which there is a true discontinuity of the aortic walls (Figure 1)^[17].

ASSOCIATIONS

Cardiac

Studies have shown evidence of a common molecular pathogenic mechanism for the co-existence of CoA with other left heart obstructive pathologies such as aortic stenosis and hypoplastic left heart syndrome^[18-20]. Although 75% of patients with CoA have a co-existent bicuspid aortic valve (BAV)^[21,22], in patients with BAV and previous repaired CoA, the probability of requiring surgery for the aortic valve or ascending aorta is lower than in isolated BAV^[23] with a slower progression of ascending aorta dilation on serial echocardiography^[24]. Higher prevalence of CoA in BAV patients justify the need for routine screening and arch imaging for CoA in patients with BAV^[25]. Other associated cardiac anomalies include left heart obstructive lesions like cor triatriatum, parachute mitral valve and discrete subaortic stenosis, referred as Shone syndrome as well as ventricular septal defect, patent ductus arteriosus, double

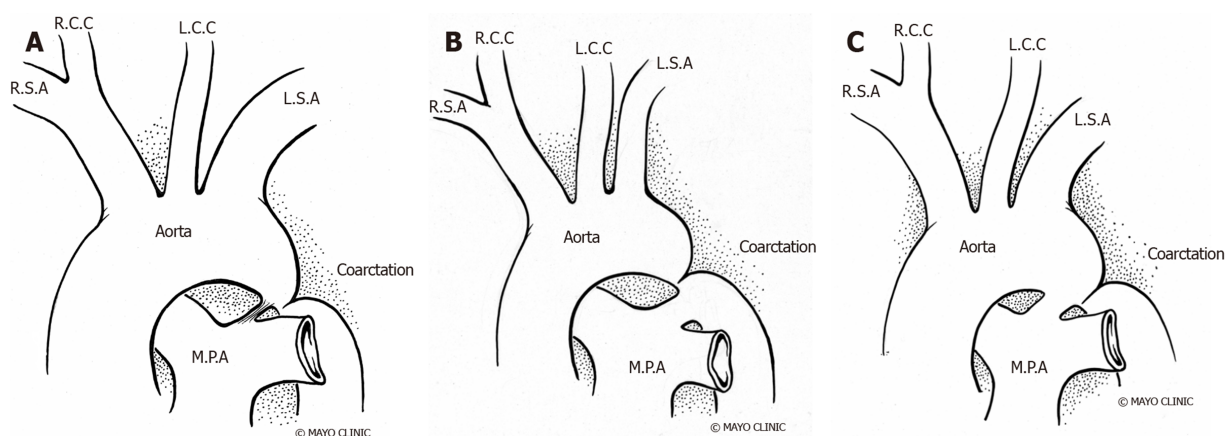


Figure 1 Coarctation of Aorta types. A: Ductal; B: Pre-ductal; C: Post-ductal. R.S.A: Right subclavian artery; R.C.C: Right common carotid; L.C.C: Left common carotid; L.S.A: Left subclavian artery; M.P.A: Main pulmonary artery.

outlet right ventricle, transposition of great arteries, atrio-ventricular canal defects^[22,26-28] and rarely, aberrant arch vessels (Figure 2).

Non-cardiac

Chromosomal abnormalities like Turner's syndrome (23 X0) can be associated with multiple congenital extra-cardiac anomalies (short stature, wide set nipples, webbed neck and infertility), aortic aneurysm, an 18% incidence of coarctation^[29] and increased risk of aortic dissection^[30-32]. CoA is also associated with a number of syndromes like PHACES (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft, and supra-umbilical raphe) syndrome^[33], Williams-Beuren syndrome^[34], Alagille syndrome^[35], and Noonan syndrome^[36]. Cerebral artery aneurysms and various anomalies of the pulmonary and aortic arch vessels have been associated with CoA^[37].

HISTOLOGY AND PATHOGENESIS

Abnormal histology of the arterial wall adjacent and distal to CoA site often observed with medial degeneration noted in pre- and post-stenotic specimens leading to increased incidence of aortic dissection and aneurysm. Hence, CoA is considered a generalized arteriopathy^[38]. The ductal tissue with in-folding of aortic media is observed in the tissue ridge, which is often noted extending from the posterior aortic wall and protruding into aortic lumen, on examination of the lesions of the coarctation^[39].

The underlying pathogenesis is not completely understood. However, the most commonly accepted theories include hemodynamic, ductal hypothesis, and abnormal genetic mutations. Hemodynamic theory states that reduced anterograde intrauterine blood flow to the fetal arch leads to its underdevelopment^[40,41]. Ductal hypothesis postulates the migration of ductal tissue into the wall of the fetal thoracic aorta^[42-45]. The NOTCH1 gene, which plays an important role in cardiovascular development, and several other genes have been implicated in the etiology of CoA^[38]. Increasing evidence of genetic contribution to CoA has been documented^[46,47] with siblings having a 0.5% risk of CoA at birth and a 1% risk of congenital heart disease^[48]. In the development of the aorta, vascular endothelial growth factor (VEGF) plays a crucial role, acting as a chemoattractant and stimulating angioblast migration toward the midline^[2]. Studies have shown that targeted VEGF disruption leads to significant impairment of aortic formation^[49] with increased pre-coarctation collagen and decreased smooth muscle content when compared to the post-coarctation aorta or proximal aorta in young transplant donors^[50]. Mechanical models indicate that blood flow abnormalities, defective endothelial cell migration, and excessive deposition of aortic duct tissue at the aortic isthmus can lead to coarctation^[51]. Coarctation can also be acquired in inflammatory diseases of aorta, such as Takayasu arteritis^[52], and also in severe atherosclerosis^[53]. Environmental factors such as chemical exposures, particularly solvents have been suggested to have a possible role in development of CoA and studies noting the geographical variations in CoA also suggest the same^[54].

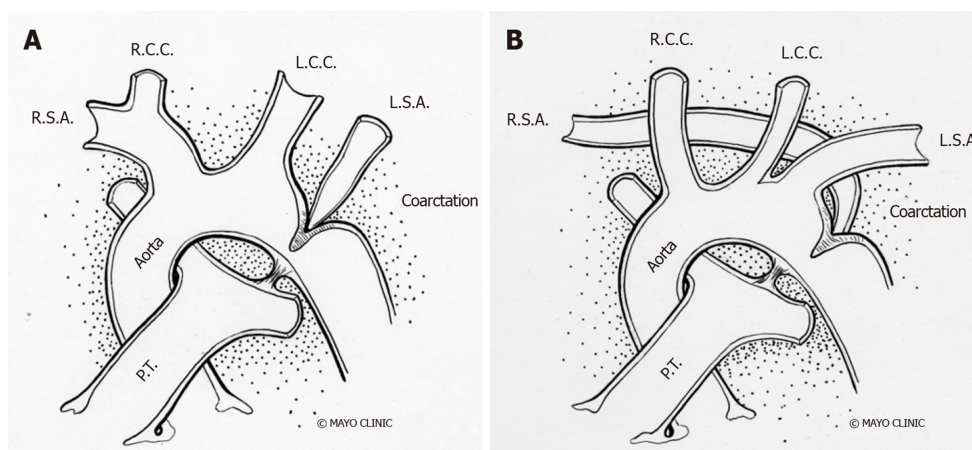


Figure 2 Anatomical variations of subclavian artery in coarctation of aorta. A: Right subclavian artery arising from the site of coarctation; B: Left subclavian artery arising from the site of coarctation. R.S.A: Right subclavian artery; R.C.C: Right common carotid; L.C.C: Left common carotid; L.S.A: Left subclavian artery; P.T: Pulmonary trunk.

PATHOPHYSIOLOGY

Narrowing of the aorta causes an increase in left ventricular afterload and reduced lower body perfusion, resulting in activation of the renin-angiotensin-aldosterone system and subsequent upper body hypertension. Compensatory mechanisms ensue, including left ventricular hypertrophy, pre- and post- stenotic vessel dilation and development of collateral flow in the intercostal, internal mammary and scapular vessels (Figure 3 and Figure 4). Flow disturbances in the aorta caused by the coarctation can increase the risk of endocarditis, especially when associated with congenital heart disease, such as bicuspid aortic valve^[55]. The clinical presentation may vary from a critically ill neonate with heart failure to an asymptomatic hypertensive adult based on the balance between the extent of aortic narrowing and the above compensatory mechanisms^[56]. Moreover, there may be an increased risk of aortic aneurysm or dissection and cerebral berry aneurysm development depending on the possible existence of underlying intrinsic aortopathy and hypertension^[38].

NATURAL HISTORY

Natural history is mainly obtained from hospital post-mortem records and from case series prior to the availability of surgical correction first performed in 1948^[57]. The prognosis of CoA depends on the hemodynamic severity and is generally poor without intervention. Historical data shows that patients who survived beyond infancy died at a mean age of 34 years with a 75% mortality rate by age 43 years from congestive heart failure, aortic dissection or rupture, endocarditis, endarteritis, intracranial bleed and myocardial infarction^[39]. Studies suggest a less than 5% chance of developing hypertension by early adulthood in patients repaired in infancy versus 25%-33% in those operated after the age of one year^[58-61].

CLINICAL PRESENTATION

A substantial number of asymptomatic subjects with aortic coarctation are not detected until adult life, underestimating the incidence at birth^[5]. The age of presentation and manifestations depend on the severity of narrowing, relationship with arch vessels, and collateral vessel formation. Therefore, the clinical presentation of coarctation differs significantly in pediatric patients and adults. In the fetus and neonate coarctation may be suspected because of right ventricular enlargement associated with decreased left ventricular flow and greater flow through the ductus arteriosus. Infants may remain asymptomatic when there is associated patent ductus arteriosus. However, after ductal closure, severe CoA results in heart failure and/or shock from acute left ventricular pressure overload. Clinical presentation in children and adolescents is typically through lower extremity fatigue and exertional dyspnea. Presentation in adults is relatively rare, 10.3% of patients with CoA being diagnosed after the age of 40 years^[62]. In virtually all cases, CoA presents with upper extremity

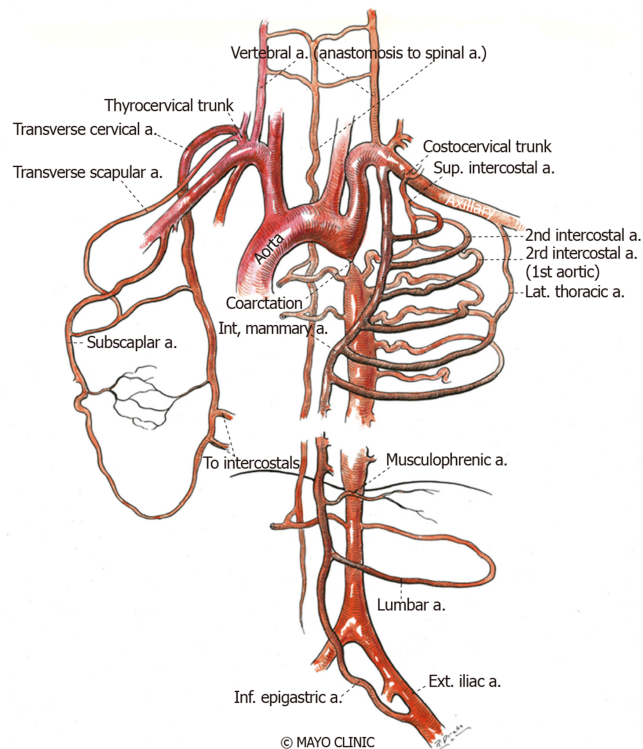


Figure 3 Collateral vessels development due to luminal narrowing, allowing blood flow from high to low pressure areas. Figure shows the collaterals in intercostal, internal mammary, scapular and lumbar vessels.

hypertension and lower blood pressure in the lower extremities with delayed femoral pulses. Pulse and blood pressure reading patterns will vary with the origin of the subclavian arteries relative to CoA site. The classic bilateral upper extremity hypertension occurs when the left subclavian artery is proximal to the coarctation. Occasionally, left subclavian originates distal to the coarctation, resulting in unequal arm blood pressure readings with diminished left brachial pulse and pressure. Rarely, when both the right and left subclavian originate distal to the coarctation as in anomalous origin of the subclavian artery from the descending aorta, pulses and pressures in all four extremities are equally decreased. Despite the blood pressure variability in the extremities, regional blood flow is usually maintained by autoregulatory mechanisms causing vasoconstriction in hypertensive areas and vasodilation in hypotensive areas^[63]. Several theories support the etiology of hypertension: Imbalance within the autonomic nervous system^[64], impaired vascular function^[65], and hyperactivation of the renin-angiotensin system^[66,67], which are the most widely accepted. According to the renin-angiotensin system theory, lower body hypoperfusion results in activation of the renin-angiotensin-aldosterone system and consequent upper body hypertension. Symptoms and complications secondary to hypertension include headaches, epistaxis, exercise intolerance, angina, shortness of breath due to left ventricular dysfunction, heart failure and ruptured cerebral artery aneurysms^[37,68]. Other potential mechanisms for hypertension in CoA include endothelial dysfunction, reduced arterial compliance, and blunted baroreceptor function^[69].

Patients can also present with colder and fatigued lower extremities, claudication, and abdominal angina. Occasionally, an initial presentation of CoA may include dissection and/or aneurysm/pseudoaneurysm of the aorta and branch vessels, including the spinal and intercostal arteries^[70,71]. Complications such as premature coronary atherosclerosis, cerebrovascular events, left ventricular systolic dysfunction, and endocarditis can occur. Timely recognition of CoA and risk factor modification and treatment improves survival but life expectancy remains lower compared to normal individuals. Analysis of 80 adolescents who underwent surgical repair of CoA in childhood did not find intracranial aneurysms, implying the possibility of aneurysms developing with age and preferentially in the presence of hypertension^[72]. Late hypertension may be associated with residual or recurrent obstruction^[2]. Hence, ambulatory blood pressure monitoring use can help in early diagnosis of late hypertension^[73]. Blood pressure is usually 10%-20% higher in the lower extremities due to wave amplification. An upper to lower extremity pressure gradient of 10

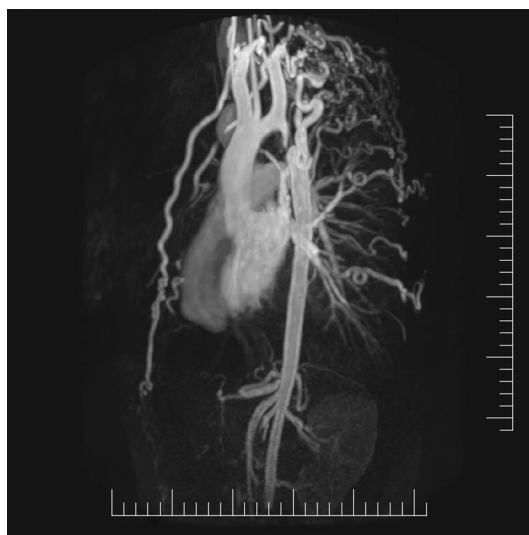


Figure 4 Magnetic resonance imaging demonstrating extensive collaterals in patient with unrepaired coarctation of aorta.

mmHg should raise suspicion of coarctation, and a gradient of 35 mmHg or greater is considered highly specific for CoA^[74]. Occasionally, claudication can be noted due to the ischemia of the lower limb. Cardiac auscultation may demonstrate a harsh systolic murmur in the left sternal border with radiation to the inter-scapular region in the back. In the suprasternal notch, an associated thrill may also be palpable, and occasionally, a left ventricular lift can be observed if there is left ventricular pressure or volume overload. The development of arterial collaterals is suggested by continuous murmur, especially in patients with long-standing unrepaired coarctation and may diminish the pressure gradient.

DIAGNOSIS

Initial workup includes blood pressure measurements in all four extremities. Clinical diagnosis is usually based upon the characteristic findings on physical examination such as delayed or diminished femoral pulses, systolic hypertension in the upper extremities, and low or undetectable blood pressure in lower extremities. Confirmation is usually done by imaging techniques; echocardiography being the most widely used initially but three-dimensional techniques like contrast enhanced computed tomography (CT) or cardiovascular magnetic resonance imaging (MRI) are the most cost-effective.

Electrocardiogram

Patients with CoA may have a normal Electrocardiogram (EKG) or show the evidence of left ventricular hypertrophy and dilatation from long-standing left ventricular pressure overload. Ischemic changes may also be found infrequently^[38].

Chest radiography

Chest radiograph may show a normal cardiac contour or can be mildly enlarged. A characteristic finding of "Figure of 3" beneath the aortic notch suggests the narrowing of the descending aorta at the level of coarctation and dilatation pre and post coarctation (Figure 5). Bilateral inferior rib notching may also be seen in the third to eighth ribs suggesting the presence of dilated intercostal collateral arteries^[68].

Echocardiography

Transthoracic echocardiography (TTE) is the imaging modality most often used in the assessment of cardiac disease but has limitations in evaluating extra cardiac structures and collateral circulation. TTE can help confirm suspected CoA, assessing pressure gradient severity and providing diagnosis of other associated cardiac and valvular abnormalities, most commonly, left-sided obstructive lesions (subvalvular and supravalvular aortic stenosis parachute mitral valve and cor-triatriatum) but especially ruling out the presence of a bicuspid aortic valve.

The presence of any associated aortopathy can be evaluated by following the serial measurements of aortic root and ascending dimensions. Long axis (candy cane) view

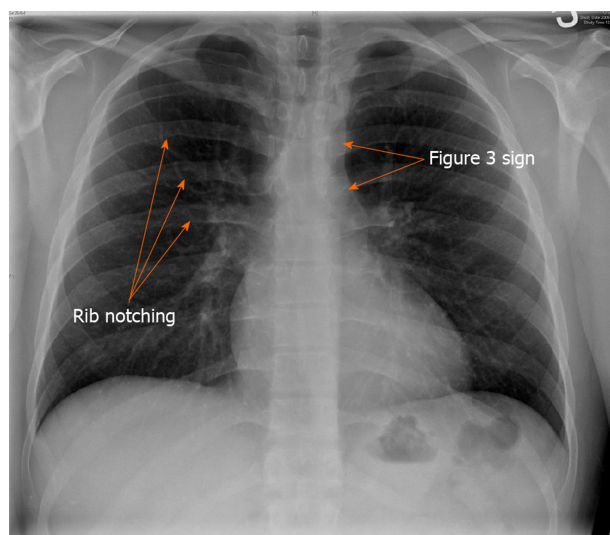


Figure 5 Chest X-Ray demonstrating rib notching and **Figure 3** sign.

demonstrates a focal area of narrowing of the proximal descending thoracic aorta distal to the origin of subclavian artery and color flow Doppler demonstrates associated flow turbulence (**Figure 6**). The severity of CoA can be estimated using continuous-wave Doppler, by calculating the pressure gradient across the narrowed area, although appropriate correction for velocity proximal to the site of coarctation is important to avoid overestimation of the true gradient^[1]. The mean systolic gradient often provides an excellent estimate of coarctation gradient. The severity of CoA can also be estimated by calculating the ratio of the maximal velocity across the coarctation in the suprasternal view to the peak velocity in the abdominal aorta in the subcostal view^[75]. If transverse arch hypoplasia is present, the proximal velocity increases as well; therefore, the systolic pressure gradient should be calculated with the Bernoulli equation^[76]. Diastolic flow persistence with velocities over 1 m/s is a characteristic finding in CoA (**Figure 7**). Sometimes, in the presence of collateral blood flow, pressure gradients across the coarctation, may be less severe than expected^[77]. Severe obstruction, eccentric gradient, or long, tortuous vessels may also affect the Doppler gradient by potentially under or overestimating the degree of severity and echo derived gradient.

Subcostal views are used to assess the distal thoracic and upper abdominal aorta. In healthy individuals without obstruction, pulse wave Doppler in the abdominal aorta shows a rapid systolic upstroke, short deceleration time, followed by a brief early diastolic flow reversal and little anterograde flow throughout diastole. The presence of coarctation causes a delay (> 50 ms from the EKG R wave) and reduction in systolic upstroke velocity (< 55 cm/s) with anterograde diastolic flow persistence and loss of early diastolic flow reversal^[2,78] (**Figure 7**). Prolonged diastolic flow and reduced peak systolic velocity are sensitive indicators of aortic obstruction. Transesophageal echocardiography (**Figure 8**) can provide accurate imaging of the descending aorta, but has limited acoustic windows in the arch because trachea-bronchial shadowing and is not widely used in the diagnosis of CoA.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) demonstrates superior visualization of the thoracic aorta when compared to echocardiography and can clearly define the location and severity of CoA, collaterals, branching patterns, and CoA pressure gradients^[75,79,80]. Gadolinium-enhanced magnetic resonance angiography, provides excellent flow-independent resolution of vascular structures and is helpful in providing anatomic information in adults prior to surgical or catheter-based intervention, and is also recommended for follow-up imaging^[81]. CMR is generally preferred over cardiovascular CT for serial imaging because it lacks ionizing radiation^[82]. However, CMR is more susceptible to metallic artifacts than CT, leading to difficulties in the assessment of vessel lumen patency, identifying re-coarctation, aneurysm, or fracture stented patients^[68].

Phase-contrast flow imaging is useful to quantify the flow volumes and velocity^[83] and to determine the degree of collateral flow. Collateral flow joining the descending aorta is identified by the increase in flow by 30% or more from proximal to distal aorta^[84]. Four-dimensional flow MRI is an emergent tool in evaluating the

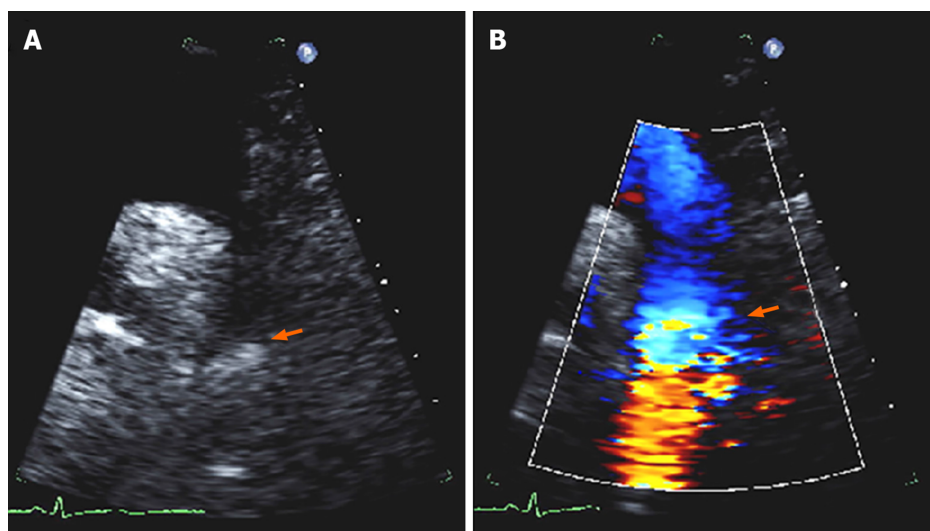


Figure 6 Echocardiographic findings in coarctation of aorta. A: Two-dimensional suprasternal view on transthoracic echocardiogram demonstrating narrowing in the aortic lumen at the isthmus (arrow); B: Color Doppler imaging demonstrating turbulent flow at the site of the coarctation (arrow).

hemodynamic significance of collateral blood flow^[85]. CMR should be routinely applied in adult patients who previously had surgical or interventional treatment of coarctation in childhood.

Computed tomographic angiography

Computed tomographic angiography (CTA) also provides invaluable information in the diagnosis and management of patients with CoA. CTA has better spatial resolution, shorter acquisition times, causes less claustrophobia than CMR and allows for the presence of metallic implants as well as previous stent implantation without a signal noise artifact^[68]. Similar to CMR, it can be performed to visualize the CoA segment, any aneurysms distal to CoA, hypoplasia of aortic arch, re-coarctation post repair, to follow serial aortic dimensions, and to demonstrate associated vascular anomalies (Figure 9 and Figure 10). However, it requires ionizing radiation and contrast, and cannot provide hemodynamic information such as peak pressure gradient and the degree of collateral circulation^[38]. However, dose saving algorithms reduce the radiation exposure.

Cardiac catheterization and angiography

Cardiac catheterization and angiography (CA) is the gold standard in assessing the pressure gradients across the CoA and provides high-resolution images of the aorta^[38]. Coarctation is classically defined as a catheterization-measured peak systolic gradient > 20 mmHg. Hemodynamic assessment should include coarctation gradient assessment, right and left heart catheterization including assessment of left ventricular end diastolic pressure. Aortic angiography is obtained to determine the site, severity of obstruction and associated vascular abnormalities^[86].

TREATMENT

Indications for intervention (surgical or transcatheter intervention) in coarctation of aorta are: (1) Peak to peak coarctation gradient ≥ 20 mmHg: This gradient can be measured as a difference between systolic blood pressures from the upper and lower extremities, from catheterization data in which peak pressure distal to the coarctation is subtracted from peak pressure proximal to the coarctation, or with echocardiography. However, the resting gradient may be lower in significant left ventricular systolic dysfunction due to the low forward stroke volume^[81]; (2) Radiographic evidence of significant collateral flow; (3) Coarctation-attributed systemic hypertension; (4) Coarctation-attributed heart failure; and (5) Exercise limitations from limited lower extremity blood flow (*i.e.*, claudication).

Surgical management

Various surgical techniques have been utilized for CoA repair.

Resection with end-to-end anastomosis: Crafoord^[87] and Gross^[88] described the first

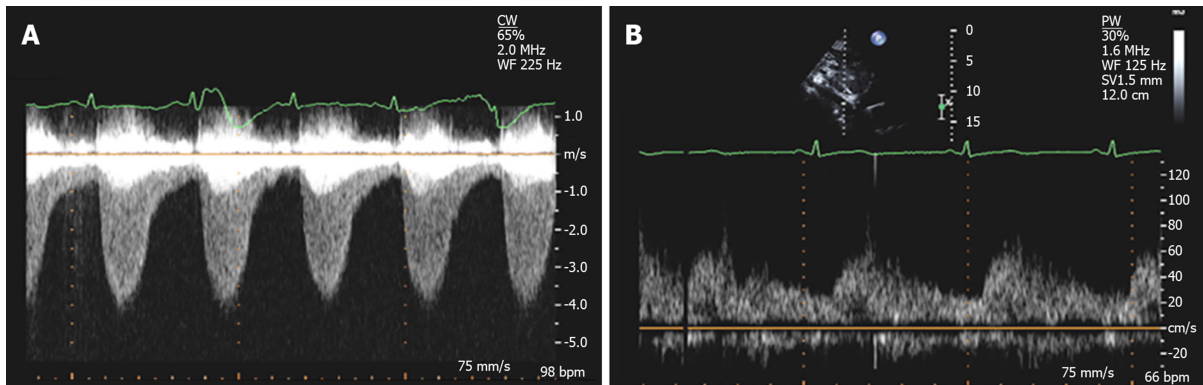


Figure 7 Doppler echocardiographic findings in coarctation of aorta. A: Continuous wave Doppler across the coarctation segment in suprasternal view demonstrating significant increase in flow velocity with a peak velocity of 4 m/s, comparable to a peak gradient of 64 mmHg based on simplified Bernoulli's equation; B: Abnormal Doppler pattern in abdominal aorta in a patient with severe coarctation demonstrating blunted velocity with delayed systolic upstroke and continuous diastolic run-off.

successful surgical intervention *via* a left lateral thoracotomy in 1945. The intervention involves resection of the coarcted segment followed by direct suture anastomosis of the transected ends (Figure 11). The incidence of re-coarctation was comparatively high following the initial repair, with the incidence rates of 41% to 51%^[89-92] and highest in neonates.

Prosthetic patch aortoplasty: Vosschulte first described the usage of a prosthetic patch to augment the aorta (Figure 12)^[93]. Dacron grafts showed to have a lower rate of re-coarctation^[94], but had a high incidence of aortic aneurysm formation (20%-40%) and are no longer performed^[95] despite patch material evolution from Dacron to polytetrafluoroethylene (PTFE), which, reduced aneurysm formation to 7%, but increased the rate of re-coarctation to 25%^[96].

Subclavian flap aortoplasty: Waldhausen *et al*^[97] first described the technique in 1966. A flap is generated from the subclavian artery, which is ligated close to the left vertebral artery origin by an incision extending down onto aortic isthmus and across the coarcted segment. Re-coarctation rates are close to 3% in older children, but up to 23% in neonates^[98-100]. Sacrificing the subclavian artery might cause claudication in the left arm in the long term, although it usually does not result in left arm ischemia^[99].

Extended end-to-end anastomosis: Amato *et al*^[101] first described the technique in 1977 and is currently frequently applied. The aortic arch is clamped proximally, including the subclavian artery and distally below the coarcted segment (Figure 13). An end-to-end anastomosis of the aortic arch, which has been opened on its inferior aspect and the descending aorta, is performed after the division of ductus arteriosus. This technique showed lower re-coarctation rates of 4%-13% and low perioperative mortality^[102].

Interposition graft: The resection and graft interposition were first described by Gross in 1951^[88,103,104] and is the preferred approach in adults. A tube graft of either aortic homograft or Dacron is sewn into the aorta, after the cross-clamping of the aorta and resection of the coarcted segment. It is useful in patients with long-segment CoA; however, it requires longer cross-clamp time and does not grow with the patient thus being unsuitable for pediatric patients^[2]. A surgical follow-up study described a high prevalence of dilatation of interposition grafts to 150% of the original diameter, with most dilatation occurring in the first year after the procedure^[105]. Dilatation was most pronounced in knotted (Gel-seal and Gel-soft; Vascutek Ltd., Inchinnan, Renfrewshire, Scotland) grafts compared with woven (Gel-weave; Vascutek Ltd., Renfrewshire, United Kingdom) grafts^[105]. Hence, routine serial arch imaging is recommended for patients after surgical repair. Another study reported no perioperative mortality or re-coarctation events during a mean follow-up of 10 years \pm 7.6 years^[106].

Extra-anatomical correction: This procedure is possible when concomitant cardiac procedures such as coronary artery bypass grafting or aortic valve replacement need to be addressed^[107]. It is performed in adults through median sternotomy with cardiopulmonary bypass support and provides additional blood flow to the distal aorta leaving the stenosed aorta in situ^[108]. A prosthetic conduit is anastomosed

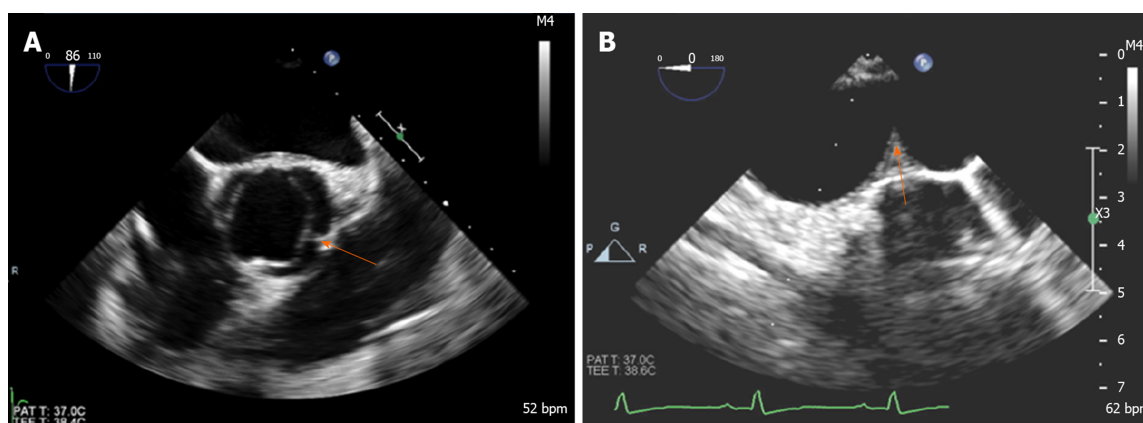


Figure 8 Transesophageal echocardiogram in a patient with coarctation demonstrating. A: Bicuspid aortic valve with raphe between left and right coronary cusps (arrow); B: Coarctation in distal aortic arch (arrow).

proximally to the ascending aorta or distally to the subclavian artery^[109], bypassing the coarcted segment. A study of 80 patients who underwent ascending-to-descending aortic bypass (Figure 14) followed for 7 years \pm 6 years showed improvement in blood pressure, no early deaths and no paraplegia or stroke. Late deaths occurred in 6%, while 4% required re-intervention (for peri-prosthetic regurgitation and mitral valve replacement)^[110]. Some have noted anastomotic stenoses and pseudoaneurysm formation.

When considering surgery, the prognostic benefit and age-related risks for procedural complications need to be discussed. A study assessing re-coarctation 20 years \pm 7 years after surgical repair in infancy showed moderate-to-severe re-coarctation in 34% of patients highlighting that re-coarctation is common in follow-up patients after surgical repair of CoA^[111]. However, surgery might still be the preferred option in the setting of significant arch hypoplasia or long coarctation segments^[112].

Catheter based therapies/ endovascular management

Transcatheter procedures play an important and evolving role in the repair of native CoA and the treatment of re-coarctation or aneurysm formation after the initial repair.

Balloon angioplasty: Transcatheter balloon angioplasty was first described by Singer *et al*^[113] in 1982, and became widely used over the following two decades. A balloon catheter is advanced up to the obstructed segment and inflated to induce intimal tear and limited medial tear in the arterial wall. There remains a potential risk for later aneurysm formation with this approach, especially when treating a native CoA^[38]. Short-term results were satisfactory in infants and children, but long-term outcomes less favorable, with re-coarctation rates of up to 80%^[114-117].

A follow-up study of 99 patients who underwent balloon angioplasty for re-coarctation showed that re-intervention was required in 28 patients^[118]. Comparison of balloon angioplasty with surgery in 80 patients aged 12 years \pm 10 years, showed increased aortic complications during follow-up, with 26% requiring re-intervention for re-coarctation and 21% for aneurysm formation^[119]. Hence, this approach may be reasonable to stabilize critically ill infants as a bridge to surgery and an alternative for mild coarctation in adolescents. A recent meta-analysis showed that balloon dilation is less likely to achieve treatment success as measured by the proportion of patients achieving a blood pressure gradient \leq 20 mmHg when compared to stenting. Odds ratio for re-coarctation in patients undergoing balloon dilation versus stenting was 7.01 and 3.340 for aortic wall injuries^[120].

Stent implantation: Stent implantation has become the mainstay of interventional treatment for CoA, with a reduction in clinically significant residual gradient and aortic wall abnormalities when compared with balloon angioplasty alone^[121]. It improves luminal diameter, results in minimal residual peak pressure gradient and sustained hemodynamic benefit. Additionally, it prevents vascular recoil resulting in re-coarctation and can tack intimal flaps to the aortic wall allowing the wall to heal, reducing the risks of dissection and aneurysm^[38]. Balloon-expandable intravascular stents have emerged as the preferred treatment option for patients with native CoA and re-coarctation (Figure 15)^[122].

Stent placement is considered a reasonable treatment option in patients weighing more than 30 kg, as children weighing less than 30 kg may need repeated

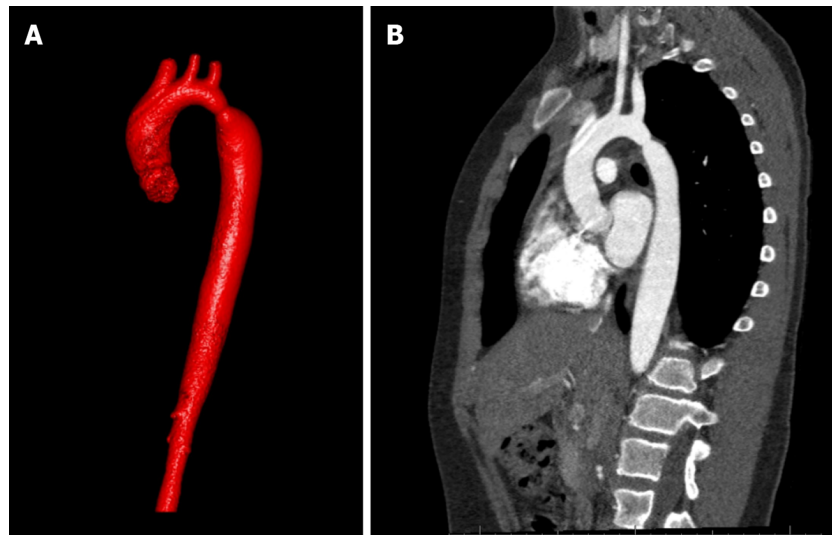


Figure 9 Contrast-enhanced computed tomography demonstrating coarctation of aorta. A: 3D reconstruction image; B: Sagittal cross-sectional view.

interventions for stent expansion in the face of growth with the potential injury risk to the femoral arteries during vascular access for stent delivery^[123,124]. Studies support the safety and efficacy of stent placement for both native and recurrent coarctation^[125-127]. Stent placement was successful in 99% in the Coarctation of the Aorta Stent Trial (COAST) I trial in which 105 children and adults underwent stent implantation for the treatment of native CoA and re-coarctation^[127]. Nine patients required re-intervention for aneurysms during the first two years, and 10 patients required re-intervention after two years. Another study of 578 CoA patients who underwent stent placement showed a 98% implantation success rate, which was defined as a reduction in the pressure gradient to < 20 mmHg or a ratio of post-stent coarctation to descending aorta of > 0.8^[125,128].

Stents can be classified based on the design as closed-cell, open-cell, and hybrid design, or as bare metal or covered. Cheatham-platinum (CP) stent, Palmaz series, Genesis XD and Intra Stent are some of the stents commonly used. Rarely, formula or Vallejo stents are used in small children as a bridge to anticipated surgery. In closed-cell design, all internal inflection points of the structural components are connected, whereas they are not in open-cell design. Open-cells have an advantage of longitudinal flexibility of the cells due to the absence of connections^[38]. Stents can be made of different metals such as stainless steel, platinum-iridium alloy, and chromium-cobalt alloy. Covered stents usually have a polytetrafluoroethylene sleeve that can exclude aneurysms from the circulation and may prevent endoleaks within the sleeved section of the stent. Deployment of a second covered stent may be of utility in the acute management of aortic rupture at the time of stenting^[129]. Premounted covered stents are potentially very valuable for rapid deployment in the event of significant aortic wall injury. Some studies have suggested routine use of covered stents in face of more severe degree of coarctation and in older patients.

Previous studies suggested that bare metal stents might have a higher risk of aneurysm development^[95,130,131] but a more recent study compared did not observe this difference^[132]. Serial re-dilation of purposely under-deployed, covered stents is a strategy considered in growing children and when there is a concern of aortic rupture by deployment to the size of the normal aorta^[133,134]. **Table 1** summarizes the major studies that used covered stents in the treatment of CoA.

Complications

Re-coarctation: Factors predisposing to re-coarctation include: (1) Patient age < 30 days^[135]; (2) Isthmic hypoplasia^[136]; and (3) Coarctation segment diameter of 3.5 mm or less and 6 mm or less prior to angioplasty and post-intervention respectively^[135]. Persistent post-procedural hypertension, post-procedure peak pressure gradient of ≥ 20 mmHg, or collaterals usually warrant re-intervention^[137-139].

Aneurysm: Aneurysm development is dependent on abnormal aortic tissue at the site of CoA. The pathological aorta consists of a medial layer with fragmented elastic fibers, fewer smooth muscles, and a higher amount of ground substance, unlike a pseudoaneurysm which, forms between the tunica media and tunica adventitia^[140].



Figure 10 Computed tomography 3D reconstruction images of aortic arch. A: Pre-intervention; B: Post-intervention.

Aneurysm can arise proximal or distal to the coarctation and occasionally from the origin of branch vessels such as the left subclavian artery (Figure 16). Incomplete removal of the pathological tissue during surgical repair^[141,142] or balloon angioplasty also favors the development of an aneurysm. The distal aortic arch aneurysm formation is highest after subclavian flap and lowest with end-to-end anastomosis^[143]. Balloon angioplasty is reported to have a higher incidence of aneurysm formation compared to surgery by Shaddy *et al*^[144], while other studies reported a lower incidence at catheterization after balloon angioplasty^[145,146]. Stents were shown to have a lower likelihood of aneurysm formation (as low as in 5% of patients) due to reducing trauma to the vessel wall through the dispersion of force^[147-149].

Late systemic hypertension: Hypertension is frequently found and a great concern post CoA repair. Age at repair is perhaps the most important predictor^[59,150,151]. O'Sullivan *et al*^[187] showed a prevalence of hypertension of 30% in patients repaired at a mean age of 0.2 years, at a mean follow-up of 12 years after repair. An abnormal structure and function of the pre-coarctation arterial conduits is the pathological mechanism thought to be involved. Arterial wall compliance is diminished, and rigidity is increased due to more collagen and less smooth muscle mass^[50,152-155]. Other factors contributing to hypertension in post-coarctectomy patients are reduced baroreceptor sensitivity and residual aortic arch gradients^[156-158]. Hence, patients with persistent hypertension after the repair may need long-term anti-hypertensive treatment.

Need for re-intervention

Surgical treatment for re-intervention: Surgical repair is mandatory when there is a persistent endoleak or prosthetic infection after stent graft placement. The mortality rate in surgical repair for re-intervention is higher than the native CoA repair and ranging from 1%-3%, to 5%-10% in patients with significant comorbidities, although guidelines recommend an endovascular approach initially for re-coarctation^[159].

Perioperative complications are often aggravated by dense adhesions including revision for bleeding (2%), pulmonary-associated complications such as pneumothorax and pleural effusion (8%), and trauma of the thoracic duct or the esophagus (0%-4%)^[160,161]. Other complications are lower body ischemia and spinal cord trauma with subsequent paralysis.

Endovascular treatment for re-intervention: Guidelines recommend an interventional approach as the initial treatment strategy for re-coarctation^[138,139,162,163]. Balloon angioplasty is the preferred treatment option for recurrent coarctation after previous surgical repair, although it has a high rate of re-coarctation after native CoA repair^[159]. The scar tissue has a lower tendency for vascular remodeling and aortic wall injury occurring in only 1%-2% of cases^[118,164]. Studies have shown good outcomes with balloon angioplasty of re-coarctation^[164-171], with a high procedural success rate and lower complication rate when compared to surgical repair^[145,172]. The procedural success rate ranges between 80%-100%^[118,125,126,173], and a simple re-dilation often leads

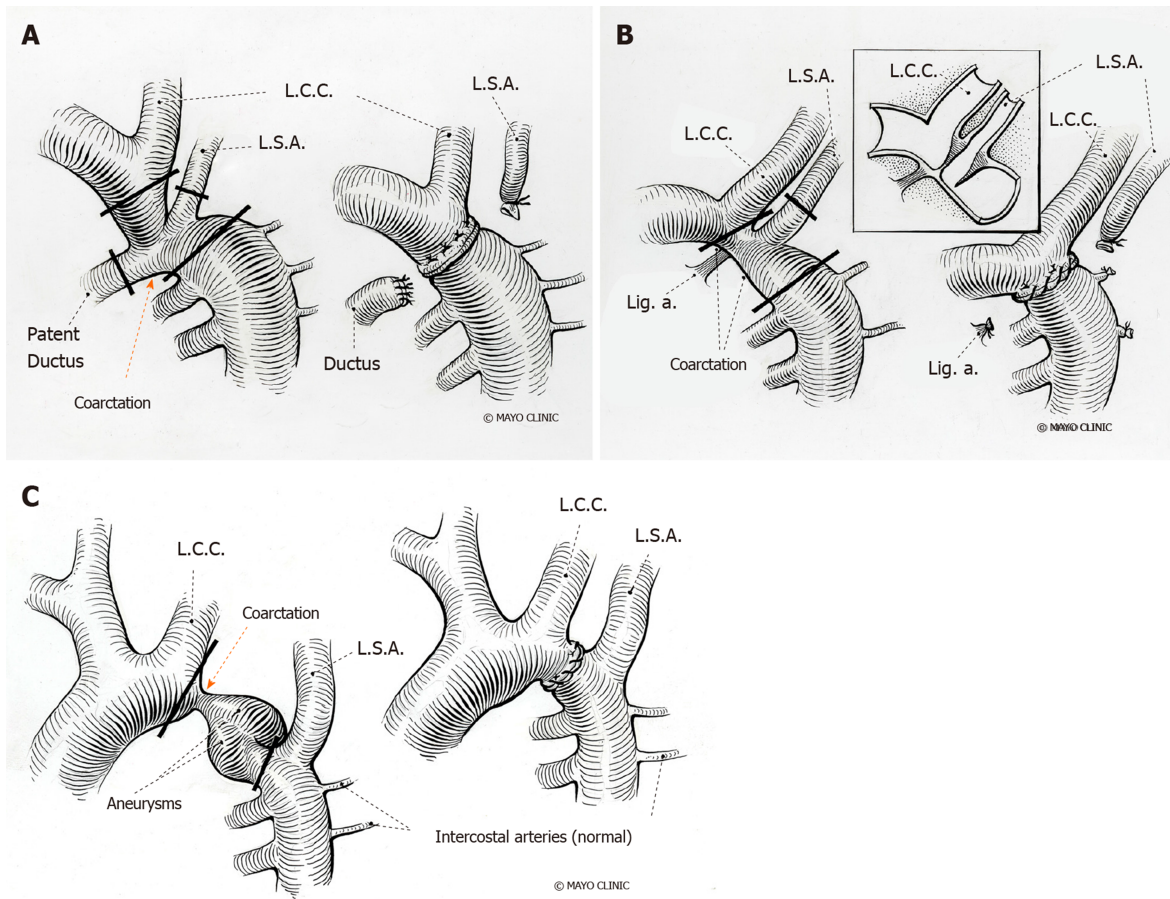


Figure 11 Surgical repair of coarctation of aorta. A: End to end anastomosis- Resection of the coarctation segment followed by direct suture anastomosis of the transected ends with associated patent ductus arteriosus; B: End-end anastomosis of coarctation without associated patent ductus arteriosus; C: End-end anastomosis of coarctation with associated aneurysm. L.C.C: Left common carotid; L.S.A: Left subclavian artery; Lig. a: Ligamentum arteriosum.

to satisfying results when re-coarctation occurs^[174].

First described in 1991, stent graft placement is an alternative approach to balloon angioplasty^[175] and has been used in treating re-coarctation. The procedural success rates range between 94%-97%^[149,176]. **Figure 17** demonstrates exclusion of aneurysm of proximal descending thoracic aorta by deploying a covered stent across the aneurysm.

OUTCOMES AND FOLLOW-UP

A number of studies have described the outcomes of interventions in CoA patients. The Congenital Cardiovascular Interventional Study Consortium trial and other studies^[125,177-180] showed a successful outcome following stent implantation in children and adults, with a 98% success rate of reducing peak pressure gradient to less than 20 mmHg. The COAST^[127] trial, which assessed the safety and efficacy of CP stents in children and adults with native or re-coarctation showed no deaths, serious adverse events or need for surgical intervention during the two-year follow-up. Complication rates were low, including aneurysms (5.7%) and stent fracture (11%). Many other studies support a low rate of complications and mortality^[177,181]. The COAST II trial studied 158 patients with native and re-coarctation, showing a success rate of 92% with covered CP stent^[127]. However, there was no significant difference between bare metal and covered stents in a randomized trial of 120 patients^[132]. A study by Forbes *et al*^[182] showed a lower rate of acute complications after stent implantation compared to balloon angioplasty or surgery, similarly to another study by Carr *et al*^[183].

Patients with CoA have a reduced life expectancy and increased risk of morbidity after intervention, despite good long-term survival rates. Follow-up protocols after intervention vary by institution but most commonly, routine visits at 3, 6, and 12 mo in the first year are followed by annual visits, obtaining blood pressure in all limbs

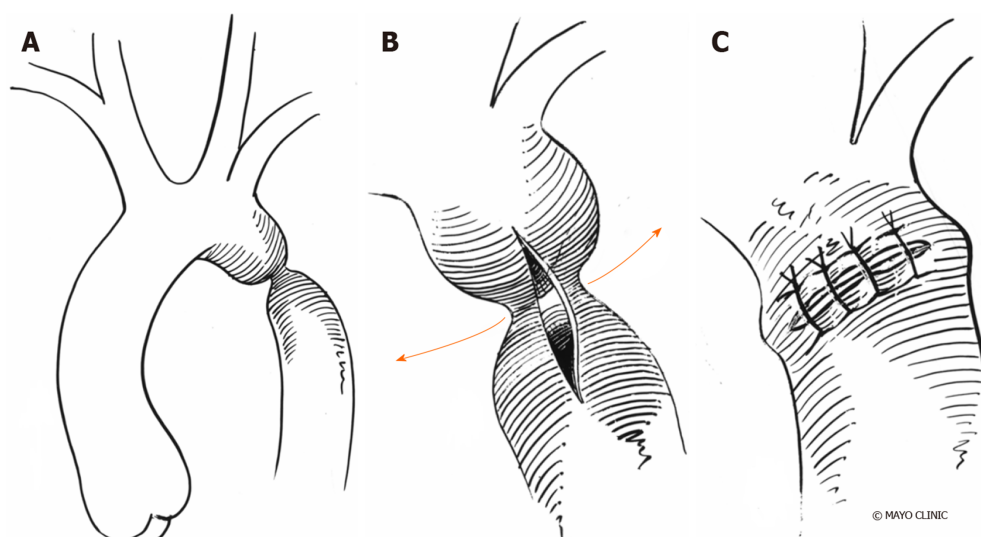


Figure 12 Prosthetic patch aortoplasty. A: Coarctation before intervention; B: Aorta is incised longitudinally through the coarctation to increase vessel diameter; C: A prosthetic patch used for augmentation of aorta.

and EKG at each visit with consideration for echocardiograms for concerns about restenosis or ventricular function. CTA or CMR can be done at 6-12 mo after the intervention to detect late complications such as aneurysm and repeated at five years or less depending on the findings. Perhaps the most important and prevalent long-term complication is chronic hypertension, occurring in 35%-68% of patients^[58,184-185]. Furthermore, exercise-induced hypertension occurs in over one-third of normotensive patients at rest^[186]. Follow-up should include ambulatory 24 h blood pressure measurement and exercise testing, as exercise-induced hypertension can predict future systemic hypertension^[58]. Usually, normotensive patients at rest and with exercise lead normal lives without restriction, excluding extensive static sports. Patients with chronic hypertension, residual obstruction, or other complications should avoid strenuous sports and heavy exercises^[162].

PREGNANCY AND COARCTATION OF AORTA

Patients with CoA should be evaluated before pregnancy for appropriate counseling and undergo arch imaging to assess aneurysm formation that might result in complications related to the increased cardiac output during pregnancy. Possible re-coarctation should be managed before conception to avoid uncontrolled upper body hypertension and possible reduced placental perfusion. Case studies have reported aortic rupture and dissection occurring with pregnancy after CoA repair but remain rare. However, there is a greater risk of developing hypertension during pregnancy^[187]. A study reported acceptable outcomes of pregnancy in patients after CoA repair with no significant cardiovascular complications during pregnancy and delivery^[188]. Another study showed that serious complications were uncommon in women with a hemodynamically significant gradient (≥ 20 mmHg) after repair^[189]. However, women with unrepaired and repaired CoA are at increased risk of arterial hypertension, re-coarctation, aortic dissection or rupture, and rupture of a cerebral aneurysm during pregnancy and delivery.

CONCLUSION

Coarctation of the aorta is a relatively common congenital cardiac defect that often has few symptoms and therefore can be difficult to diagnose. The hallmark physical exam finding is upper extremity hypertension, and for this reason the diagnosis of coarctation of the aorta should be considered in any patient with systemic hypertension with assessment of a lower extremity blood pressure. The presence of a significant arm to leg gradient is highly suggestive of the diagnosis. Early diagnosis and treatment are important as long-term data consistently demonstrate that patients with CoA continue to have a reduced life expectancy and increased risk of cardiovascular complications. Surgical repair has traditionally been the mainstay of

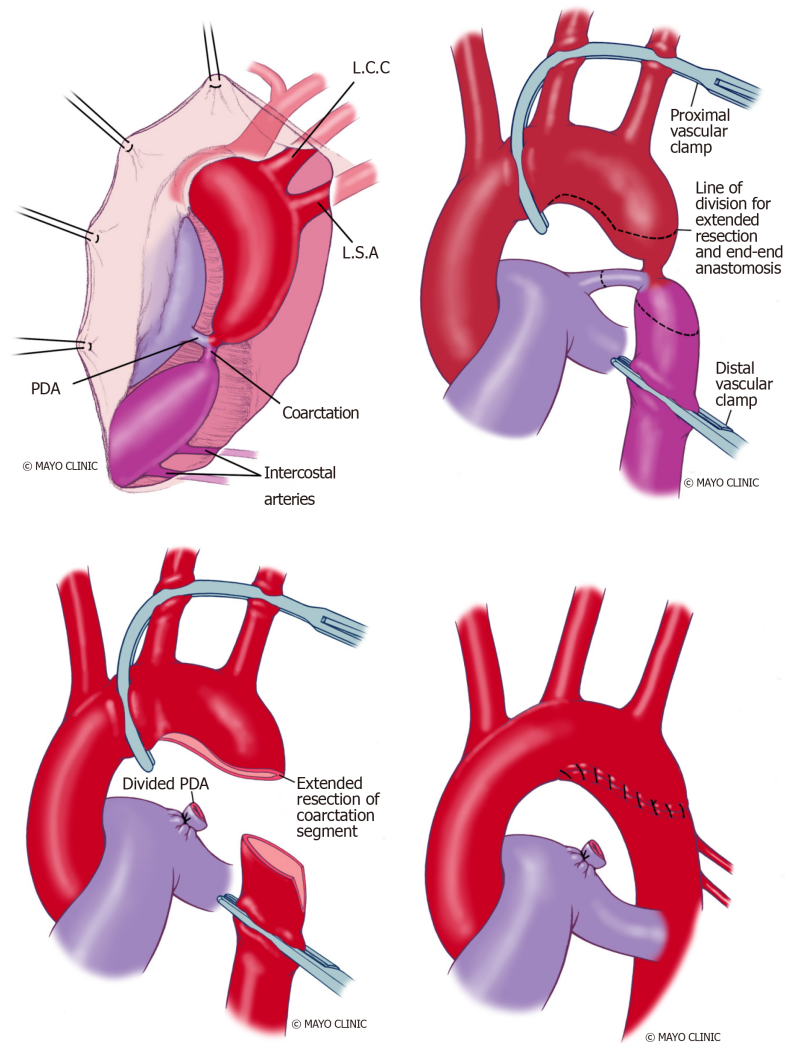
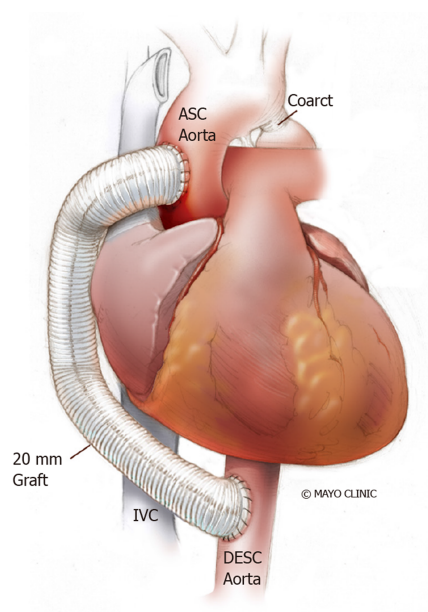


Figure 13 Extended resection and end-end anastomosis. PDA: Patent ductus Arteriosus; L.C.C: Left common carotid artery; L.S.A: Left subclavian artery.

therapy for correction but advances in endovascular technology with covered stents and stent grafts now permit nonsurgical approaches for the management of children and adults with native CoA and complications. Persistent hypertension and vascular dysfunction can lead to an increased risk of coronary disease, which remains the greatest cause of long-term mortality. Thus, blood pressure control and periodic reassessment with TTE and CMR for evaluation of the heart and aorta should be performed regularly as cardiovascular complications may occur decades after the intervention.

Table 1 Covered stents in the treatment of coarctation of aorta

Ref.	Patients (n)	Age of patients (yr)	Native coarctation (n)	Aneurysm (n)	Presenting gradient (mmHg)	Post stenting gradient (mmHg)	Aortic complications	Re-coarctation/ Serial re-dilatation
Tzifa <i>et al</i> ^[190]	30	28 ± 18	14	8	36 ± 20	4 ± 4	Dissection, spontaneously resolved (n = 1)	4 (serial dilatation)
Butera <i>et al</i> ^[191]	33	6-66	20	2	20-75, median 39	0-12, median 0	-	1
Bruckheimer <i>et al</i> ^[133]	22	8-39	22	0	29 ± 9	7 ± 7	Aortic tear treated with second covered stent (n = 1)	9 (serial dilatation)
Kenny <i>et al</i> ^[192]	37	9-65	13	7	10-60, median 26	0-20, median 4	Aortic rupture, surgery required (n = 1)	-
Tanous <i>et al</i> ^[129]	22	39 ± 14	14	6	29 ± 17	3 ± 5	Aortic tear treated with second covered stent (n = 1)	3

**Figure 14** Ascending-to-descending aortic bypass. ASC: Ascending; IVC: Inferior venacava; DESC: Descending.

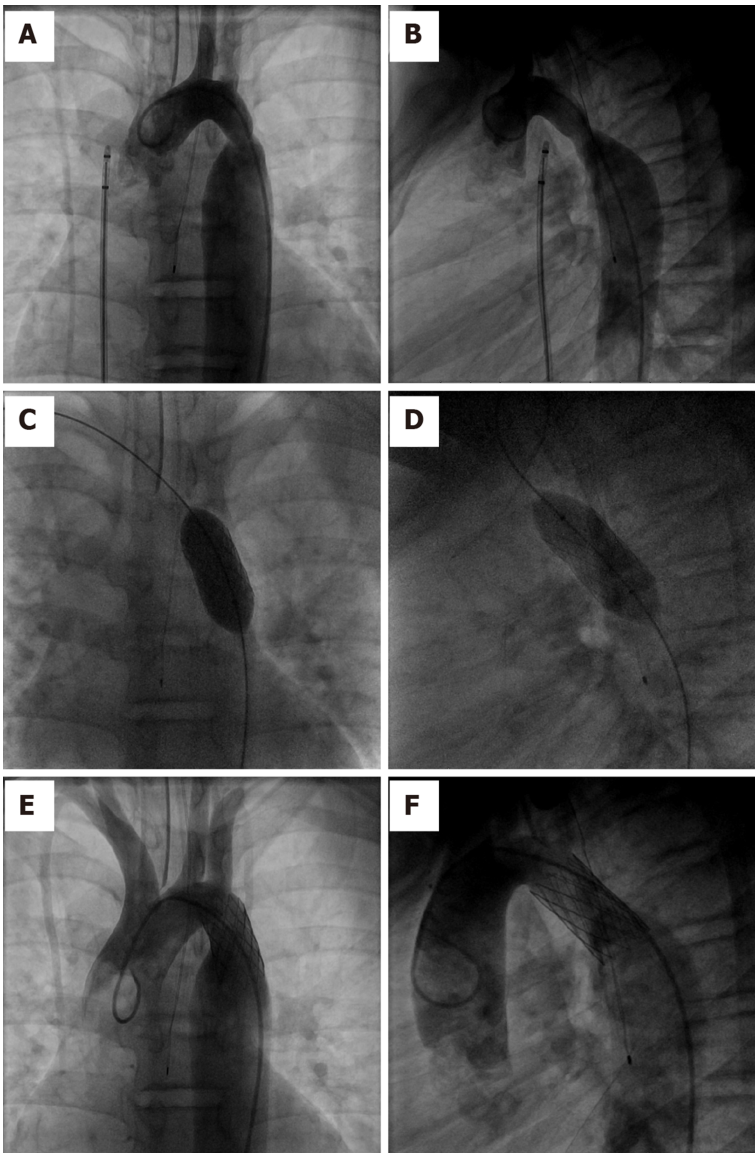


Figure 15 Transcatheter repair of Coarctation of Aorta. A, B: Angiogram of aortic arch demonstrating coarctation of aorta in antero-posterior and lateral views; C, D: Deployment of covered stent in antero-posterior and lateral views; E, F: Post-intervention aortic arch angiogram demonstrating resolution of coarctation in antero-posterior and lateral views.

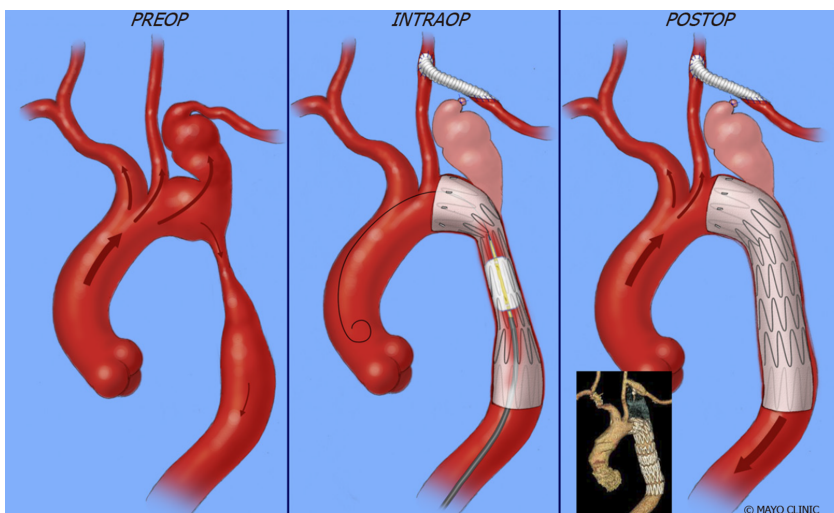


Figure 16 Aneurysm at the origin of left subclavian corrected by deploying a covered stent across the origin of subclavian artery and concomitant surgical anastomosis of left subclavian to left common carotid artery.

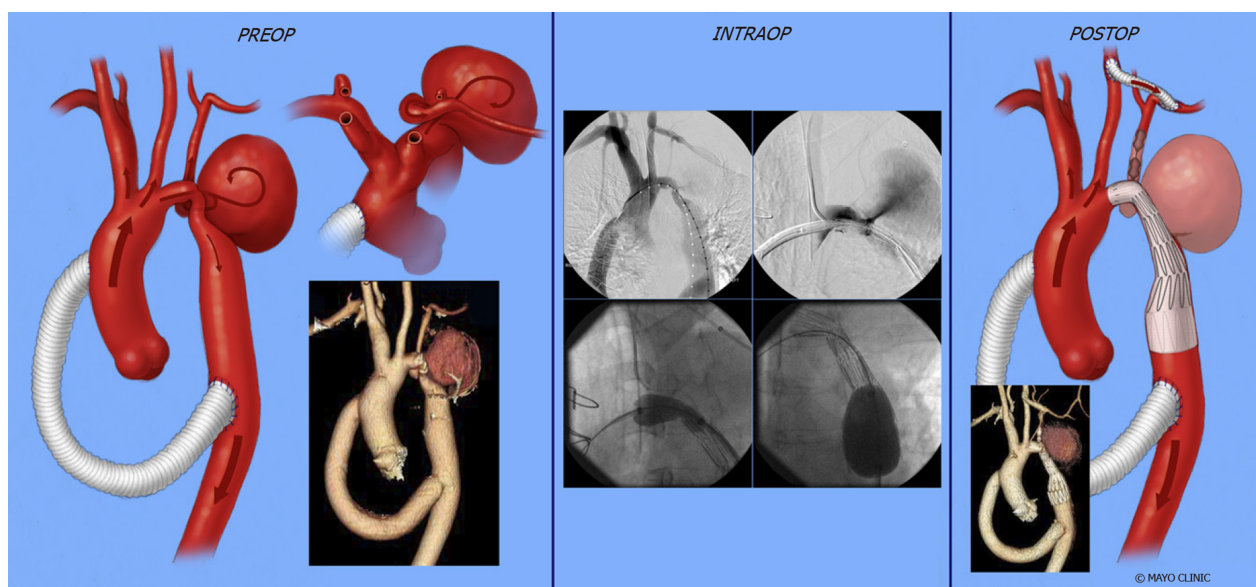


Figure 17 Exclusion of aneurysm of proximal descending thoracic aorta by deploying a covered stent across the aneurysm and concomitant surgical anastomosis of left subclavian to left common carotid artery.

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Basic Study

Nicotine-induced adrenal beta-arrestin1 upregulation mediates tobacco-related hyperaldosteronism leading to cardiac dysfunction

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Abstract**BACKGROUND**

Tobacco-related products, containing the highly addictive nicotine together with numerous other harmful toxicants and carcinogens, have been clearly associated with coronary artery disease, heart failure, stroke, and other heart diseases. Among the mechanisms by which nicotine contributes to heart disease is elevation of the renin-angiotensin-aldosterone system (RAAS) activity. Nicotine, and its major metabolite in humans cotinine, have been reported to induce RAAS activation, resulting in aldosterone elevation in smokers. Aldosterone has various direct and indirect adverse cardiac effects. It is produced by the adrenal cortex in response to angiotensin II (AngII) activating AngII type 1 receptors. RAAS activity increases in chronic smokers, causing raised aldosterone levels (nicotine exposure causes the same in rats). AngII receptors exert their cellular effects *via* either G proteins or the two β arrestins (β arrestin1 and-2).

AIM

Since adrenal β arrestin1 is essential for adrenal aldosterone production and nicotine/cotinine elevate circulating aldosterone levels in humans, we hypothesized that nicotine activates adrenal β arrestin1, which contributes to RAAS activation and heart disease development.

METHODS

We studied human adrenocortical zona glomerulosa H295R cells and found that nicotine and cotinine upregulate β arrestin1 mRNA and protein levels, thereby enhancing AngII-dependent aldosterone synthesis and secretion.

RESULTS

United States).

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In contrast, siRNA-mediated β arrestin1 knockdown reversed the effects of nicotine on AngII-induced aldosterone production in H295R cells. Importantly, nicotine promotes hyperaldosteronism *via* adrenal β arrestin1, thereby precipitating cardiac dysfunction, also *in vivo*, since nicotine-exposed experimental rats with adrenal-specific β arrestin1 knockdown display lower circulating aldosterone levels and better cardiac function than nicotine-exposed control animals with normal adrenal β arrestin1 expression.

CONCLUSION

Adrenal β arrestin1 upregulation is one of the mechanisms by which tobacco compounds, like nicotine, promote cardio-toxic hyperaldosteronism *in vitro* and *in vivo*. Thus, adrenal β arrestin1 represents a novel therapeutic target for tobacco-related heart disease prevention or mitigation.

Key words: Adrenocortical zona glomerulosa cell; Aldosterone; β arrestin; Nicotine; Signal transduction; Tobacco-related heart disease

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Core tip: Adrenal β arrestin1 is a novel molecular target for mitigation of the aldosterone-dependent cardiotoxic effects of tobacco. Angiotensin II induces aldosterone production in adrenocortical zona glomerulosa (AZG) cells by binding to its adrenal angiotensin II type 1 receptor, which then activates β arrestin1. Nicotine and cotinine are known to activate the renin-angiotensin-aldosterone-system (RAAS), promoting hyperaldosteronism. We report herein that these main tobacco compounds chronically upregulate adrenal β arrestin1, promoting excessive aldosterone synthesis and secretion from human AZG cells *in vitro* and from adrenal glands *in vivo*. Thus, adrenal β arrestin1 critically mediates tobacco-induced RAAS activation, which contributes to heart disease development/progression.

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INTRODUCTION

Aldosterone exerts various deleterious effects on the failing heart, while elevated in chronic heart failure (HF)^[1-4]. Accordingly, aldosterone levels serve as biomarker of HF severity^[5] and mineralocorticoid receptor antagonists have several beneficial effects in HF^[6,7]. Aldosterone is produced upon renin-angiotensin-aldosterone-system (RAAS) activation^[8]. Together with Angiotensin II (AngII), it exerts a variety of cardiovascular effects in order to maintain renal perfusion and correct electrolyte/blood volume imbalances^[1]. In the presence of heart disease however, aldosterone is markedly elevated, hindering cardiac function^[1-4].

The main compound in tobacco, nicotine, and its major metabolite in humans, cotinine^[9], have been reported to initially inhibit adrenal aldosterone production, causing compensatory RAAS activation upon chronic use in humans (*i.e.*, in chronic smokers)^[10-14]. This chronic RAAS activation leads to chronic elevation of aldosterone levels in smokers^[10-14]. Given the harmful effects of both AngII and aldosterone in the heart and blood vessels, RAAS activation contributes to HF development in chronic tobacco smokers.

Aldosterone is produced by adrenocortical zona glomerulosa (AZG) cells in response to AngII acting through its type 1 receptors (AT₁Rs)^[8,15,16]. AT₁Rs are G protein-coupled receptors^[8] that can also signal through G protein-independent pathways^[17-19]. The two universal receptor adaptor proteins β arrestin-1 and -2 (also known as arrestin-2 and -3, respectively) play a central role in mediating this G protein-independent signaling^[17,18]. AngII stimulates aldosterone production *via* G_{q/11}-mediated activation of the extracellular signal-regulated kinase (ERK)1/2^[20]. ERKs

upregulate Steroidogenic Acute Regulatory (StAR) protein, which increases mitochondrial uptake of cholesterol to initiate steroid biosynthesis^[15,21,22]. β arrestin1 is a crucial mediator of AT₁R signaling to aldosterone production and secretion from human AZG cells^[22-29]. The molecular signaling mechanism underlying this crucial role of β arrestin1 in adrenal aldosterone production also involves activation of ERK1/2, which upregulate StAR and, ultimately, aldosterone synthesis and release^[22,28].

Since nicotine and cotinine activate RAAS and promote AngII actions at its various tissue targets, including aldosterone production in the adrenal cortex, we hypothesized that these tobacco compounds may chronically increase AngII-dependent aldosterone production in AZG cells, possibly *via* adrenal β arrestin1 upregulation. Indeed, we found that this is the case both in AZG cells *in vitro* and *in vivo*.

MATERIALS AND METHODS

Materials

All chemicals (nicotine, cotinine, AngII, DMSO) were from Sigma-Aldrich (St. Louis, MO, United States; $\geq 98\%$ purity, as assessed by High Performance Liquid Chromatography).

H295R cell culture and transfections

H295R cells were purchased from American Type Culture Collection (Manassas, VA, United States; RRID: CVCL_0458) and cultured, as previously described^[22,26]. For siRNA-mediated knockdown, cells were transfected *via* the Lipofectamine method (Invitrogen, Carlsbad, CA, United States) with a custom-ordered rat β arrestin1 (*Arrb1*)-specific siRNA or control scrambled siRNA constructs (custom-made by Sirion Biotech, Cambridge, MA, United States). 48 h after transfection, cells were placed in serum-free medium and treated with the indicated agents for the indicated times.

Aldosterone measurements

In vitro aldosterone secretion in the culture medium of H295R cells and aldosterone levels in rat blood serum were measured by EIA (Aldosterone EIA kit, Cat. #: 11-AD2HU-E01; ALPCO Diagnostics, Salem, NH, United States), as described^[22-26].

Real-time polymerase chain reaction

Total RNA isolation with TRIzol reagent (Life Technologies, Grand Island, NY, United States), reverse transcription and real-time polymerase chain reaction (RT-PCR) were carried out as previously described^[30-32]. The following primer pairs were used: 5'GGCCCCGAGACTTCGTAA3' and 5'TGGCAGCCACCCCTTGA3' for rat StAR; 5'CCACATCGGGAAGTCCAGA-3' and 5'-CAGGCCGCTGACGAGCAA-3' for rat β arrestin1; 5'-TCAAGAACGAAAGTCGGAGG-3' and 5'-GGA CAT CTA AGGCATCAC-3' for 18S rRNA. Real time PCR was performed using SYBR® Green Supermix (Bio-Rad Laboratories, Hercules, CA, United States). Normalization was done with the housekeeping gene 18S rRNA levels. No bands were seen in the absence of reverse transcriptase.

Western blotting

H295R cell and rat adrenal protein extracts were prepared as described previously^[22,23], in a 20 mmol/L Tris pH 7.4 buffer containing 1% Nonidet P-40, 20% glycerol, 10 mmol/L PMSF, 1 mmol/L Na₃VO₄, 10 mmol/L NaF, 2.5 μ g/mL aprotinin, and 2.5 μ g/mL leupeptin. Protein concentration was determined *via* the BCA method and equal amounts of protein per sample were loaded. The following antibodies were used for immunoblotting: sc-28869 (Santa Cruz Biotechnology, Santa Cruz, CA, United States) for β arrestin1; sc-25806 (Santa Cruz Biotechnology) for StAR; and sc-47724 (Santa Cruz Biotechnology) for GAPDH. Immunoblots were revealed by enhanced chemiluminescence (ECL, Life Technologies, Grand Island, NY, United States) and visualized in the FluorChem E Digital Darkroom (Protein Simple, San Jose, CA, United States), as described previously^[23-26]. Densitometry was performed with the AlphaView software (Protein Simple) in the linear range of signal detection (on non-saturated bands).

Experimental animals and adrenal-specific siRNA delivery

All animal procedures and experiments were performed in accordance with the guidelines of the IACUC committee of Nova Southeastern University. Adrenal-specific *in vivo* siRNA delivery in -300 g adult (3-month-old) male Sprague-Dawley

rats was done, essentially as described^[23,30,33], *via* direct injection of 1 µg total siRNA [dissolved in sterile phosphate-buffered saline], in each of the two adrenal glands of each animal with a 31-gauge needle. Daily i.p. injections of 1 mg/kg nicotine (or saline), starting on the day of the adrenal-specific siRNA delivery, followed for 7 d in a row. Groups of five animals per treatment were generally used for analysis.

Echocardiography

Two-dimensional guided M-mode and Doppler echocardiography using a 14-MHz transducer (Vevo 1100 Echograph, FUJIFILM Visualsonics, Inc., Toronto, ON, Canada) were performed in rats, as described previously^[23,25,30]. Three independent echocardiographic measurements were taken in both modes. Echocardiography was performed immediately prior to the adrenal siRNA *in vivo* deliveries and then again at the end of the nicotine (or saline) treatments. The operator was blind regarding the type of treatment (*Arrb1* or scrambled siRNA and drug or saline) each animal that was echo'd had received.

Statistical analyses

Data are generally expressed as mean ± SEM. Unpaired 2-tailed Student's *t* test and one- or two-way ANOVA with Bonferroni or Dunnett's test was performed for statistical comparisons using the SPSS 23 software (SPSS, Inc., Chicago, IL, United States). For all tests, a *P* < 0.05 was generally considered to be significant. All sample sizes were calculated for a one-way ANOVA with equal sample sizes in each group and based on previous publications and preliminary data. For the animal experiments, estimation of sample size was done using nQuery Advisor 7.0 software (Informer Technologies, Inc.).

RESULTS

Tobacco compounds upregulate β arrestin1 in AZG cells

To determine whether β arrestin1 is involved in tobacco-dependent adrenal aldosterone production, we took advantage of the human AZG cell line H295R, which endogenously expresses the AT₁R (but not the AT₂R) and β arrestin1^[15,22]. This cell line produces and secretes aldosterone in response to AngII stimulation^[15]. Treatment of H295R cells with standard concentrations (10 µM) of either nicotine or cotinine (10 µmol/L is very close to the cotinine concentration attained in chronic smokers^[9]) for 24 h led to significant upregulation of both mRNA (Figure 1A) and protein (Figure 1B and C) levels of β arrestin1.

β arrestin1 mediates tobacco-induced enhancement of AngII-dependent aldosterone production in AZG cells

Given that β arrestin1 is critically involved in AngII-dependent aldosterone production in AZG cells^[34,35], we next examined the impact of its tobacco-induced upregulation on aldosterone turnover in H295R cells. As expected, both nicotine and cotinine markedly enhanced AngII-induced aldosterone secretion (Figure 2A) from H295R cells, as well as StAR mRNA (Figure 2B) and protein (Figure 2C and D) levels in these cells.

Since StAR upregulation signals aldosterone biosynthesis, these results suggest that tobacco compounds significantly enhance aldosterone synthesis and secretion in AZG cells. To prove that this augmentation of aldosterone production by nicotine/cotinine is mediated by the tobacco-upregulated β arrestin1, we knocked it down *via* siRNA in H295R cells (Figure 3A) and treated them again with nicotine and cotinine to examine the effect on aldosterone synthesis and secretion. Indeed, β arrestin1 knockdown almost completely abrogated the nicotine- and cotinine-induced enhancement of AngII-dependent aldosterone secretion (Figure 3B), StAR mRNA levels (Figure 3C), and StAR protein levels (Figure 3D and E) in H295R cells.

Adrenal β arrestin1 siRNA-mediated knockdown ameliorates tobacco-induced hyperaldosteronism and cardiac dysfunction in vivo

To demonstrate the physiological significance of our *in vitro* findings in H295R cells, we also treated adult male (otherwise healthy) rats with daily i.p. injections of nicotine for 7 d and, at the end of the 7-d-long treatment period, we measured their circulating aldosterone levels and cardiac function [ejection fraction (EF %)]. Of note, the daily dose of nicotine administered (1 mg/kg per day) is known to lead to blood circulating levels of nicotine comparable to those of chronic human smokers^[9]. As shown in Figure 4A, nicotine exposure led to a significant hyperaldosteronism in these animals after one week of treatment. This led to cardiac dysfunction beginning

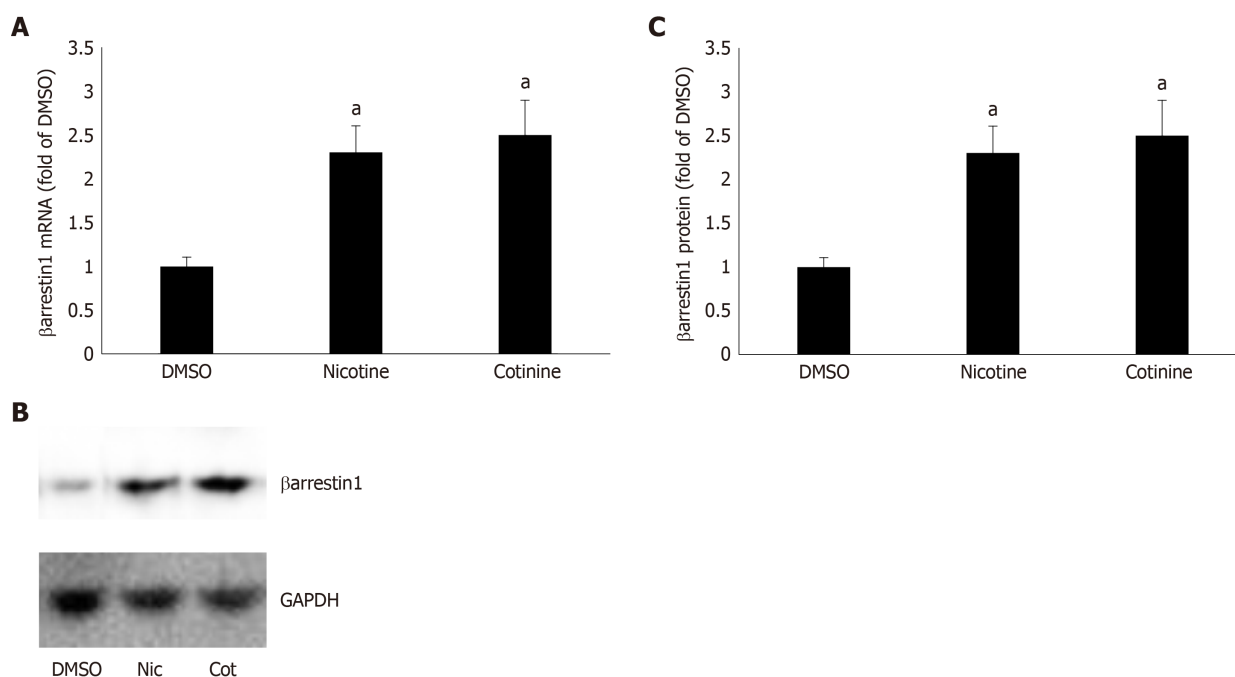


Figure 1 Effect of tobacco compounds on β arrestin1 levels in AZG cells. A: β arrestin1 mRNA levels in H295R cells treated for 24 h with 10 μ mol/L nicotine or 10 μ mol/L cotinine or vehicle. B-C: Protein levels in H295R cells treated for 24 h with 10 μ mol/L nicotine or 10 μ mol/L cotinine or vehicle. Representative western blots are shown in (B), along with glyceraldehyde 3-phosphate dehydrogenase as loading control, and the densitometric quantitation of three independent cell extracts per condition run in duplicate (and normalized with glyceraldehyde 3-phosphate dehydrogenase levels) is shown in (C). ^a $P < 0.05$ vs vehicle, $n = 3$ independent experiments/treatment in duplicate. DMSO: Vehicle; Cot: Cotinine; Nic: Nicotine; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

to set in, since the nicotine-exposed animals displayed slightly but, nevertheless, significantly less EF compared to control saline-injected animals (Figure 4B). Notably, all animals used in the study had comparable EF at the beginning of the 7-d-long treatments (*i.e.*, prior to group randomization) ($69\% \pm 4.2\%$).

Importantly, in rats having β arrestin1 knocked-down *via* siRNA specifically in their adrenals (Figure 4C), nicotine exposure at the same concentration and for the same time-period (7 d) led to substantially less hyperaldosteronism (Figure 4D) and better cardiac function (higher EF) (Figure 4E) than in control animals receiving scrambled siRNA in their adrenals at the end of the 7-day-long treatments. Of note, adrenal β arrestin1 knockdown significantly lowered circulating aldosterone levels even in saline-treated animals (Figure 4D), which is consistent with β arrestin1's essential role in adrenal aldosterone production *in vivo*^[24]. However, this did not translate into better cardiac function of saline-treated animals (Figure 4E), probably because these animals were overall healthy and their cardiac function was optimal to begin with (there was a non-statistically significant trend toward higher EF though also in the saline-treated, *Arrb1*-siRNA rats, see Figure 4E). In any case, taken together, the *in vivo* results of Figure 4 strongly suggest that adrenal β arrestin1 mediates tobacco-related hyperaldosteronism and cardiac dysfunction *in vivo*, as well.

DISCUSSION

In the present study, we have identified adrenal β arrestin1 as a novel molecular target for mitigating the aldosterone-dependent cardiotoxic effects of tobacco. AngII induces aldosterone production in AZG cells by binding to its adrenal AT₁R, which then activates β arrestin1^[22]. Nicotine and cotinine are known to activate RAAS^[13], promoting hyperaldosteronism. We report herein that these tobacco compounds chronically upregulate adrenal β arrestin1, promoting excessive aldosterone synthesis and secretion from human AZG cells *in vitro* and from adrenal glands *in vivo*. Thus, adrenal β arrestin1 appears to be a crucial component of tobacco-induced RAAS activation, which contributes to heart disease development/progression.

AngII-dependent aldosterone secretion and aldosterone biosynthesis, as measured by the expression levels of StAR, the rate-limiting enzyme in aldosterone biosynthesis, were found significantly higher in H295R cells treated with either nicotine or cotinine compared to control, vehicle-treated cells. Importantly, we uncovered that this was due to significant upregulation of β arrestin1, at both the mRNA and protein levels, in

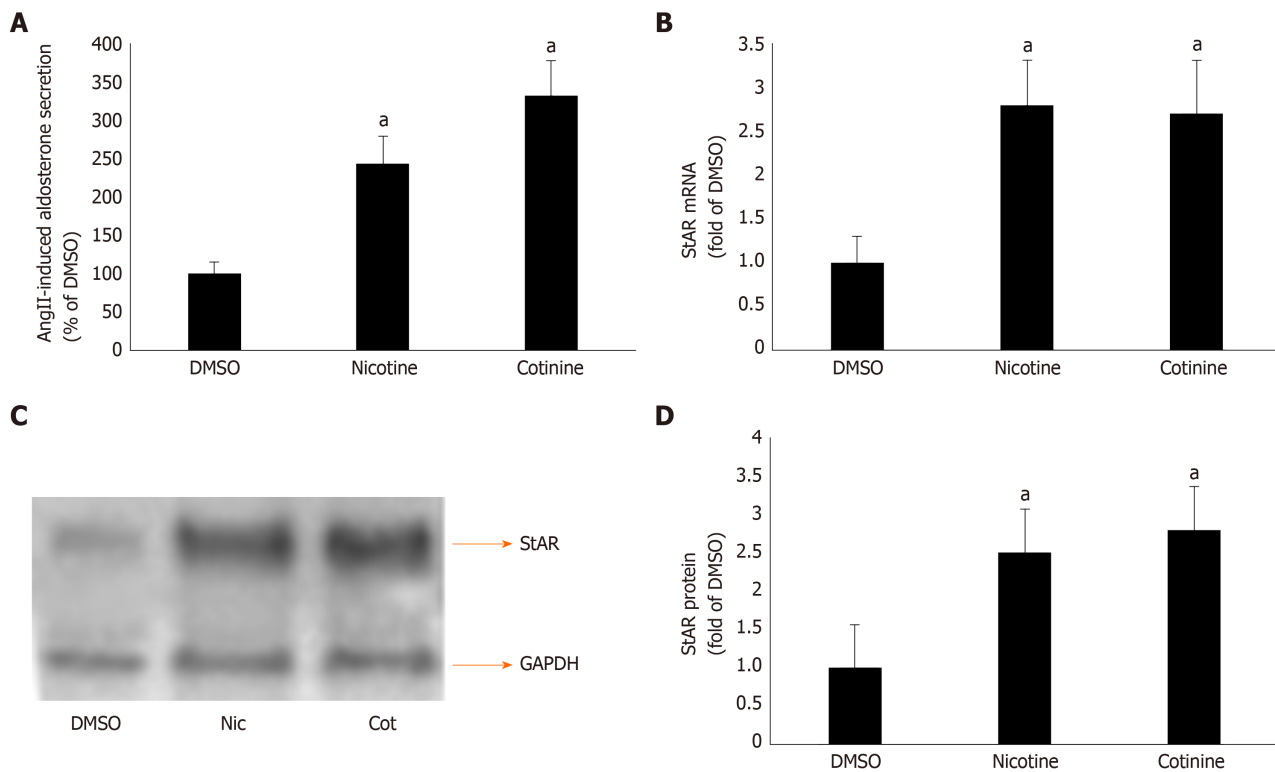


Figure 2 Effect of tobacco compounds on AngII-dependent aldosterone synthesis and secretion in adrenocortical zona glomerulosa cells. A: Aldosterone secretion into the culture medium from H295R cells in response to a 6-hour-long 100 mmol/L AngII challenge, as measured 24 h post-treatment with 10 μ mol/L nicotine or 10 μ mol/L cotinine or vehicle (DMSO). Data are expressed as % of the AngII response in DMSO-treated cells. ^a $P < 0.05$, vs DMSO; $n = 5$ independent measurements per treatment performed in duplicate; B: StAR mRNA levels in H295R cells treated for 24 h with 10 μ mol/L nicotine (Nic) or 10 μ mol/L cotinine (Cot) or vehicle (DMSO). C-D: Protein levels in H295R cells treated for 24 h with 10 μ mol/L nicotine (Nic) or 10 μ mol/L cotinine or DMSO. Representative western blots are shown in (C), along with glyceraldehyde 3-phosphate dehydrogenase as loading control, and the densitometric quantitation of three independent cell extracts per condition run in duplicate (and normalized to glyceraldehyde 3-phosphate dehydrogenase) is shown in (D). ^a $P < 0.05$, vs DMSO; $n = 3$ independent experiments/treatment in duplicate. DMSO: Vehicle; Cot: Cotinine; Nic: Nicotine; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

these cells, since β arrestin1 siRNA-mediated knockdown reversed the tobacco compound-induced increases in AngII-dependent aldosterone secretion and in StAR expression (*i.e.* aldosterone biosynthesis).

Of note, chronic nicotine exposure increased adrenal β arrestin1-mediated aldosterone synthesis and secretion, causing hyperaldosteronism, also *in vivo*. This led to development of cardiac dysfunction (ejection fraction drop/functional decline) in animals *in vivo*. As a proof of concept, adrenal-specific β arrestin1 siRNA-mediated knockdown *in vivo* normalized the elevated circulating aldosterone levels and significantly attenuated the cardiac functional decline induced by the chronic nicotine exposure *in vivo*. These findings strongly suggest that adrenal β arrestin1 inhibition (or genetic knockdown/ablation) might be of value in prevention or amelioration of tobacco-related heart disease progression and risk elevation.

The mineralocorticoid receptor (MR) is known to underlie HF pathology and it was recently documented to promote cardiac dysfunction and cardiomyopathy in transgenic mice, even in the absence of a cardiac insult^[36]. Thus, aldosterone, the endogenous natural MR agonist, needs to be suppressed for heart disease therapy. Given various reports that this hormone oftentimes acts in an MR-independent manner^[37], which circumvents the actions of MR antagonist (MRA) drugs, cutting aldosterone production at its source, *i.e.* the adrenal cortex, *via* β arrestin1 inhibition poses as an even more efficient approach to combat aldosterone's (and tobacco's) cardiotoxic actions than simply using MRA's.

Adrenal β arrestin1 blockade has been shown to effectively suppress adrenal aldosterone production^[28]. This is obviously feasible *via* gene therapy to knock down or knock out the protein specifically from the adrenal glands. Pharmacologic blockade of the adrenal AT₁R with candesartan or valsartan, which are very potent β arrestin1 inhibitors, is another possible approach^[25,26]. Of course, whether any ARB, like candesartan or valsartan, can effectively suppress the nicotine (tobacco)-induced elevation in aldosterone production from AZG cells is an open question right now and one that needs to be addressed in future studies. Alternatively, the β arrestin1-mediated signaling to aldosterone synthesis could be targeted with barbadin, a

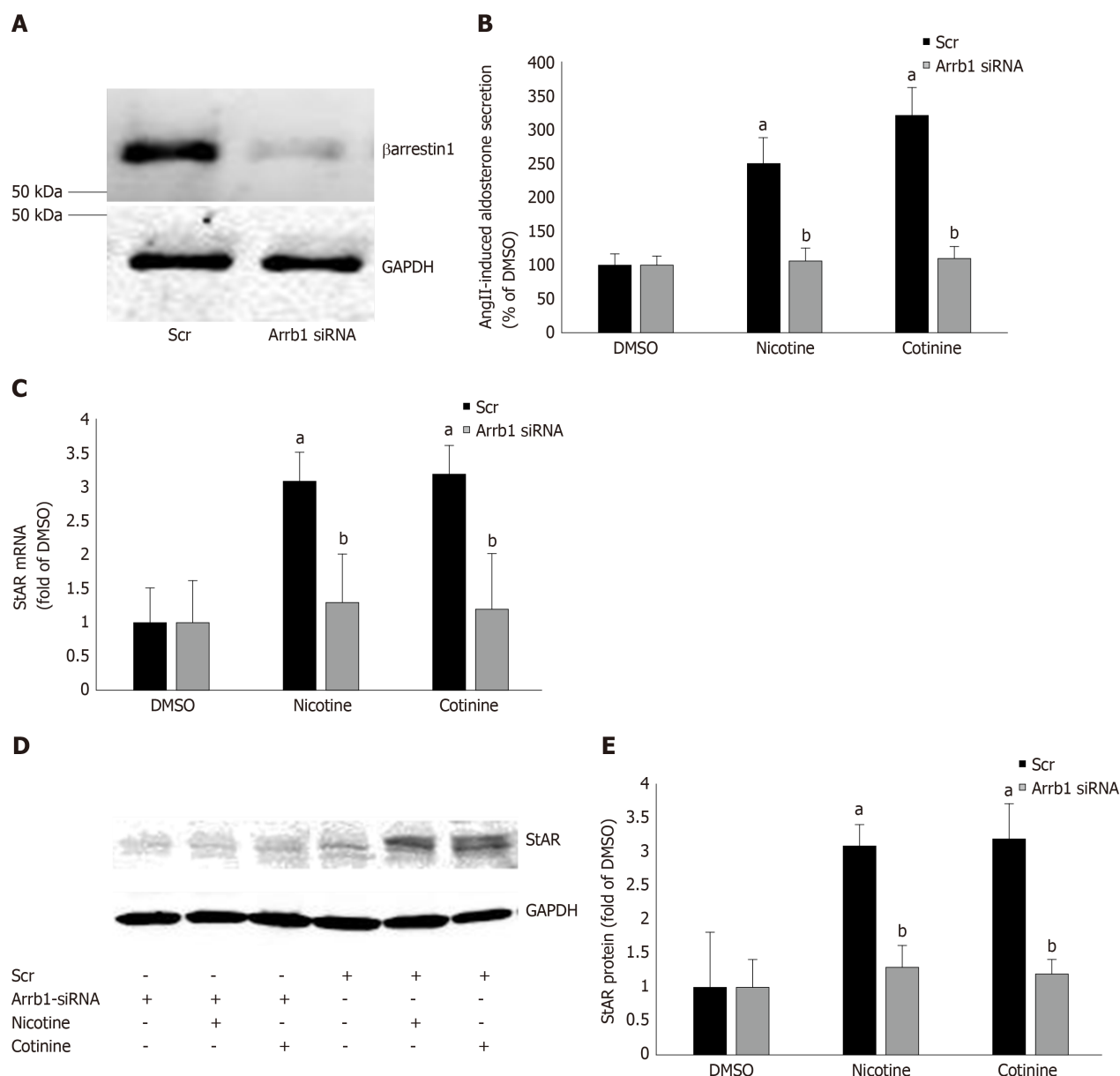


Figure 3 Effect of β arrestin1 knockdown on tobacco-induced aldosterone production in adrenocortical zona glomerulosa cells *in vitro*. A: Immunoblotting for β arrestin1 in H295R cell extracts 48 h post-transfection with β arrestin1-specific (*Arrb1*) siRNA or scrambled (Scr) siRNA to test the efficiency of the β arrestin1 siRNA-mediated knockdown. A representative blot of three independent cell extracts run in duplicate is shown, along with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as loading control, confirming an > 80% β arrestin1 protein knockdown; B: Aldosterone secretion into the culture medium from H295R cells in response to a 6-hour-long 100 nmol/L AngII challenge, as measured 24 h post-treatment with 10 μ mol/L nicotine or 10 μ mol/L cotinine or vehicle (DMSO) in H295R cells having *Arrb1* siRNA or not (scrambled siRNA-transfected, Scr). Drug treatments were carried out 48 h after siRNA transfection (*i.e.*, AngII was added at 72 h post-transfection). Data are expressed as % of the AngII response in DMSO-treated cells. ^a $P < 0.05$, vs DMSO (*Arrb1* siRNA or Scr); ^b $P < 0.05$, vs Scr; $n = 5$ independent measurements per treatment performed in duplicate; C: StAR mRNA levels in these cells; D-E: Protein levels in these cells. For StAR immunoblotting, representative blots are shown in (D), along with GAPDH as loading control, and the densitometric quantitation of three independent cell extracts per treatment condition run in duplicate (and normalized to GAPDH) is shown in (E). ^a $P < 0.05$, vs DMSO (vehicle); ^b $P < 0.05$, vs Scr; $n = 3$ independent experiments/treatment in duplicate. DMSO: Vehicle; Scr: Scrambled; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; *Arrb1*: Arrestin1-sepcific.

compound that was recently identified as an inhibitor of β arrestin-dependent internalization and signaling^[38].

Finally, nicotine (and tobacco in general) has been known for decades to cause sympathetic activation and to increase circulating catecholamines, *e.g.*, by stimulating catecholamine secretion from the adrenal medulla *via* direct agonism of nicotinic cholinergic receptors expressed on chromaffin cell membranes^[30,39,40]. We report here that it can also promote production and secretion of another major adrenal hormone with important effects on the myocardium and the vasculature, *i.e.*, aldosterone from the adrenal cortex. Nicotine achieves this thanks to direct upregulation of β arrestin1 in AZG cells, an AT₁R-adaptor protein that is an essential transducer linking the AngII hormone signal with aldosterone production in these cells^[28]. Therefore, β arrestin1 might be a crucial molecular master-switch controlling tobacco-dependent stimulation

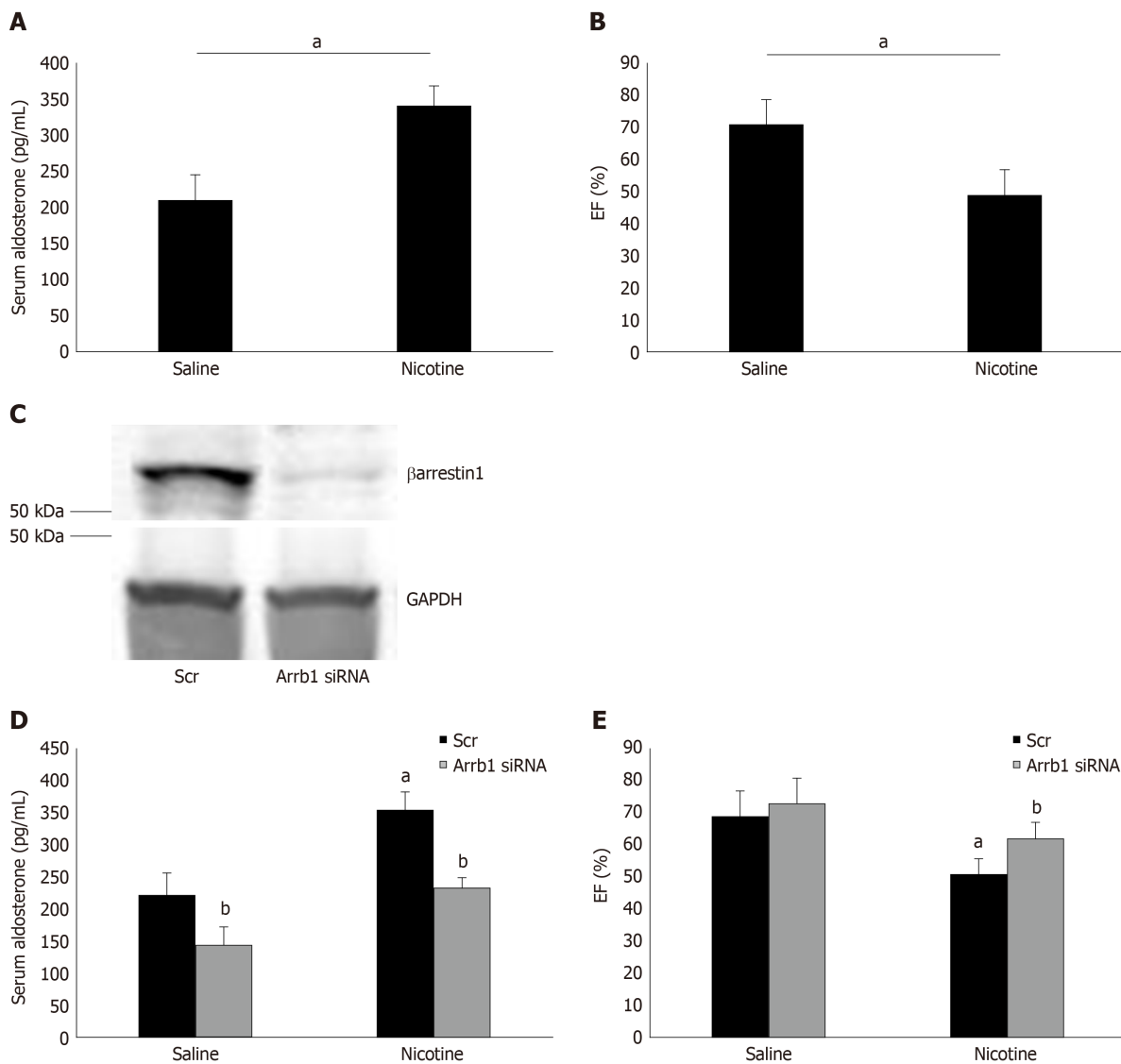


Figure 4 Effect of adrenal β arrestin1 knockdown on nicotine-dependent hyperaldosteronism and cardiac dysfunction *in vivo*. A: Circulating aldosterone levels in rats injected i.p. with 1 mg/kg per day nicotine or saline (control) for 7 consecutive d. ^a $P < 0.05$; $n = 5$ rats/group; B: Ejection fraction [EF (%)] of these animals at the end of the saline or nicotine treatments. ^a $P < 0.05$; $n = 5$ rats/group; C: Immunoblotting for β arrestin1 in adrenal protein extracts isolated from rats at 7 d post-injection with β arrestin1-specific siRNA or scrambled (Scr) siRNA directly into their adrenal glands. A representative blot of three independent rat adrenal protein extracts is shown, along with glyceraldehyde 3-phosphate dehydrogenase as loading control, confirming an $> 90\%$ β arrestin1 protein knockdown in the adrenal glands *in vivo*; D: Circulating aldosterone levels of rats having adrenal β arrestin1 knocked-down (β arrestin1-specific siRNA) or not (scrambled siRNA-injected, Scr) and treated with 1 mg/kg per day i.p. nicotine or saline (control) for 7 consecutive d, at the end of these treatments. E: EF (%) of rats having adrenal β arrestin1 knocked-down (β arrestin1-specific siRNA) or not (scrambled siRNA-injected, Scr) and treated with 1 mg/kg per day i.p. nicotine or saline (control) for 7 consecutive d, at the end of these treatments. ^a $P < 0.05$ vs Saline; ^b $P < 0.05$ vs Scr; $n = 5$ rats/group. Scr: Scrambled; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; *Arrb1*: Arrestin1-sepcific; EF (%): Ejection fraction.

of hormone production in the adrenal gland, which has enormous repercussions for cardiovascular homeostasis, in general, and for the function of the myocardium.

The present study has two major limitations: (1) The small animal group sizes—more data are needed in more animals and with other nicotine doses and routes of administration to fully confirm the present results; and (2) The study has to be repeated in larger animals (*e.g.*, pigs or rabbits) that more closely resemble human physiology and disease conditions. In addition, all of the animals used in the present study were male; experiments need to be repeated in female rats, as well. Finally, AngII is only one of several stimuli for adrenal nicotine-induced aldosterone production. Perhaps different results will be obtained, if the aldosterone response to a different hormone is studied.

In conclusion, nicotine, and its major metabolite in humans cotinine, induce hyperaldosteronism *via* adrenal β arrestin1 upregulation, which mediates enhanced AngII-dependent aldosterone production from the adrenal cortex *in vitro* and *in vivo*. Thus, adrenal β arrestin1 upregulation is an essential biological mechanism underlying the tobacco-induced increase in RAAS activity observed in chronic

smokers and in chronically tobacco-exposed animals. This results in raised aldosterone levels and thus, in increased cardiac dysfunction and cardiovascular risk. Therefore, adrenal β arrestin1 inhibition, either pharmacologically or genetically (*via* siRNA-mediated knockdown or even CRISPR/Cas9-mediated gene excision), poses as an attractive therapeutic or even preventive strategy for mitigating the devastatingly toxic effects of tobacco on the heart, by reducing the neurohormonal (aldosterone) burden of the myocardium.

ARTICLE HIGHLIGHTS

Research background

Nicotine, the main addictive compound in tobacco, is associated with major cardiovascular adverse events, such as heart failure and hypertension. One of the molecular mechanisms underlying nicotine-induced cardiotoxicity is elevation of renin-angiotensin-aldosterone system (RAAS) activity. Nicotine, and its major metabolite in humans cotinine, have been reported to induce RAAS activation, resulting in hyperaldosteronism. Aldosterone has myriad adverse cardiac effects and is produced by the adrenal cortex in response to angiotensin II (AngII) acting through its type 1 receptors (AT₁Rs). AT₁Rs induce aldosterone production *via* both G_{q/11} proteins and β arrestin1 (Arrestin-2).

Research motivation

It was hypothesized that nicotine activates adrenal β arrestin1, thereby contributing to RAAS activation and heart disease development.

Research objectives

We tested our hypothesis by investigating the effects of nicotine on aldosterone production *in vitro* and on aldosterone levels and cardiac function of experimental animals *in vivo*.

Research methods

We used the human adrenocortical zona glomerulosa (AZG) cell line H295R, in which we performed real-time polymerase chain reaction (PCR) and western blotting to measure β arrestin1 mRNA and protein levels, respectively, as well as ELISA to measure aldosterone secretion. We also manipulated β arrestin1 expression *via* siRNA-mediated knockdown in H295R cells. For the *in vivo* studies, we used adult male Sprague-Dawley rats, which we exposed to chronic nicotine administration after adrenal-specific, β arrestin1 siRNA-mediated knockdown or control scrambled siRNA delivery *in vivo*.

Research results

Nicotine and cotinine upregulate β arrestin1 mRNA and protein levels in AZG cells, which augments aldosterone synthesis and secretion. In contrast, siRNA-mediated β arrestin1 knockdown mitigates the effects of nicotine on AngII-induced aldosterone production. *In vivo*, nicotine-exposed experimental rats with adrenal-specific β arrestin1 knockdown display lower circulating aldosterone levels and better cardiac function than nicotine-exposed control animals with normal adrenal β arrestin1 expression.

Research conclusions

Adrenal β arrestin1 upregulation is one of the mechanisms by which tobacco, *i.e.* nicotine, promotes cardio-toxic hyperaldosteronism that accelerates cardiac functional decline, both *in vitro* and *in vivo*.

Research perspectives

Adrenal β arrestin1 pharmacological blockade or genetic deletion (or knockdown) represents a novel therapeutic strategy to ameliorate tobacco-related heart disease morbidity and mortality.

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Observational Study

Access to smart devices and utilization of online health resources among older cardiac rehabilitation participants

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Abstract

BACKGROUND

Newer models of cardiac rehabilitation (CR) delivery are promising but depend upon patient participation and ability to use technological media including Internet and smart devices.

AIM

To explore the availability of smart devices, current utilization and proficiency of use among older CR program attendees.

METHODS

Study participants were enrolled from four CR programs in Omaha, Nebraska United States and completed a questionnaire of 28 items.

RESULTS

Of 376 participants approached, 169 responded (45%). Mean age was 71.1 (SD \pm 10) years. Demographics were 73.5% males, 89.7% Caucasians, 52% with college degree and 56.9%, with income of 40K\$ or more. Smart device ownership was 84.5%; desktop computer was the most preferred device. Average Internet use was 1.9 h/d (SD \pm 1.7); 54.3% of participants indicating for general usage but only 18.4% pursued health-related purposes. Utilization of other health information modalities was low, 29.8% used mobile health applications and 12.5% used wearable devices. Of all participants, 72% reported no barriers to using Internet. Education and income were associated positively with measures of utilization and with less perceived barriers.

CONCLUSION

have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Among an older group of subjects attending CR, most have access to smart devices and do not perceive significant barriers to Internet use. Nonetheless, there was low utilization of health-related resources suggesting a need for targeted education in this patient population.

Key words: Cardiac rehabilitation; Smart devices; Internet; Perceived barriers

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Core tip: The success of newer models of cardiac rehabilitation (CR) that deliver home based CR with remote monitoring depends on patients' ability to use smart devices. However, unlike the Millennials, elderly patients may have limited proficiency in using these devices. In this study, we surveyed attendees of 4 CR programs in Omaha, United States to assess access, proficiency and barriers to the use of smart devices. Based on our data, we identified that most elderly patients have access to smart devices and reported no perceived barriers to use. Despite this, use of smart devices for health care related applications was minimal.

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INTRODUCTION

Cardiac rehabilitation (CR) is an important component in the management of patients with heart disease^[1]. However, despite abundant evidence demonstrating its benefits and strong recommendations from multiple international and national associations, it remains underutilized^[2,3]. Newer models of CR delivery such as home-based CR, which can be implemented and monitored using Internet, have emerged as potential solutions to address some of the barriers to widespread adoption of CR. Furthermore, there is increasing evidence that such models can be equally effective and can be used to complement or extend traditional CR^[4]. Highlighting this gap and opportunity, the American Heart Association (AHA) issued a presidential advisory for improving access and utilization of CR. In this advisory, AHA emphasized the importance of adopting newer models and chronic disease management interventions that can be delivered and monitored *via* telephone, Internet or other means of communication^[2].

Nonetheless, implementation and success of such models outside the research setting can be limited by participant access to Internet and "smart" "devices", as well as proficiency and ease of utilization^[5,6]. Approximately 90% of the general population uses Internet, with 60% of these reporting use for digital health information (DHI). In contrast, among seniors, approximately 60% report using Internet and less than half of these use Internet to access DHI^[7-9]. These observations highlight the barriers to access and underscore the need to understand the reasons for such barriers so as to enable effective delivery of smart models for CR in older adults. The purpose of this study was to explore the availability of Internet/smart devices, current utilization patterns, and proficiency in using them for health-related issues in an older cohort of attendees within an urban outpatient CR program.

MATERIALS AND METHODS

Study participants were enrolled from four American Association of Cardiovascular and Pulmonary Rehabilitation-certified, hospital-based CR programs within a single healthcare system in Omaha, NE, United States. Subjects were recruited over a period of six months in 2018 to participate in a survey consisting of 28 items. Indications for CR were: Stable angina, myocardial infarction, heart failure, percutaneous coronary intervention and cardiac surgery. Internet utilization was measured as usage time per day in hours. On-site subject recruitment and survey administration were conducted by a single investigator. Participation was voluntary and there were no financial or

other incentives offered for participation. The survey was only available in English. Subject education status was categorized as “College” (completion of a four-year college degree or greater) and “No College” for participants with some college education, a high school degree, or less. Data were described using averages and percentages. Potential relationships between various items were assessed using Chi square tests for categorical data and Pearson’s coefficient for continuous data. A significance level of 0.05 was used, and all data analyses and graphics were developed using the STATA14 statistical package (College Station, TX, United States).

RESULTS

A total of 169 (45%) of the eligible 376 CR participants consented and completed the survey. Patients wishing to forgo participation reported lack of interest as the primary reason. Demographic characteristics of participants are displayed in [Table 1](#). Study participants were 74% male, 90% Caucasian, and 52% had college degrees or above. Among the participants, 15% did not own any smart device and 85% owned a smart device (any of smartphone, tablet or personal computer). Of those who owned a smart device, 34% owned ≥ 3 devices. Smartphone ownership was 47%, and this is consistent with previously published data in this age group^[7]. Approximately two-thirds of survey participants (63.8%) were daily users with an average Internet time of 1.9 hours (SD \pm 1.7). Although 54% of participants used Internet for general purposes such as emails, paying bills, shopping and social media, only 18% used Internet for health-related purposes. Of those who used online health resources, 33% reported accessing online reviews of doctors, 42% used patient portals offered by their electronic health record, and 22% reported that they cross checked or verified information provided by their providers. However, 50% reported either difficulty or they had never tried searching for information related to their medical condition.

The utilization of other DHI was low; 22.2% watched health-related videos online, 29.8% used mobile health applications, 12.5% used wearable devices, and 2.8% used smart fitness tools. As for barriers to utilization, 71% of participants reported perceiving no barriers to using Internet, 5.9% did not have Internet, 4.2% could not afford Internet, and 16.9% either found Internet difficult to operate or preferred not to use it. Mean use time was higher in participants who were < 65 years (2.5 h/d) compared to those who were ≥ 65 years of age (1.8 h/d) though this was not statistically significant (NS, $P = 0.12$). Age had a weak negative correlation with use time (Pearson's $r = -0.16$, $P = 0.08$). Perceived barriers to Internet use were not different between the 2 groups (< 65 years: 24% *vs* ≥ 65 years: 28%, $P = 0.63$). Participants who had a college education or above had a higher mean use-time of 2.3 h/d *vs* 1.6 h/d in the “No College” group ($P = 0.02$) ([Figure 1](#)). Of all participants without a college education, 39% perceived barriers to Internet use versus only 20% of participants with a college degree who perceived a barrier to Internet use ($P = 0.028$). Finally, a significantly greater proportion of participants (39%) with an income of $< \$40$ K, perceived barriers to Internet use compared to 17% of those with an income $\geq \$40$ K ($P = 0.007$).

DISCUSSION

The major findings of our study are: (1) The majority of CR attendees had Internet access and device ownership was high (85% in general, and 47% for smart phone); (2) Despite three quarters of CR attendees reporting no perceived barriers, only 18% used the Internet for DHI; and (3) Consistent with the general population, younger age, college education, and higher income predicted greater use of the Internet and less perceived barriers^[9]. In a randomized trial of 80 patients (mean age of 63 years), Widmer *et al*^[10] demonstrated that digital health interventions significantly improved weight loss and reduced cardiovascular-related emergency department visits following acute coronary syndrome. Additionally, the positive impact of “home-based or self-delivery” CR models using a variety of smart technologies has also been demonstrated in patients with chronic heart failure (HF)^[11,12]. However, patient education is absolutely essential to the success of such programs. While utilization of Internet and smart devices is common in younger individuals, adoption of technology is less pronounced among older individuals^[13]. However, recent trends are encouraging and demonstrate that an increasing number of older individuals are adopting these tools. Our survey indicates that the Internet and device-use in this patient population is consistent with the general population as reported by the Pew Research Center and US Census Bureau^[7,8].

Table 1 Patient characteristics, n (%)

Patient characteristics	n = 169
Age	
mean (SD)	71.1 (10.3)
< 65 yr	37 (21.9)
≥ 65 yr	132 (78.1)
Gender	
Males	124 (73.5)
Females	45 (26.5)
Race	
Caucasian	152 (89.7)
African American	9 (5.4)
Hispanic	3 (1.8)
Others	5 (3.1)
House-hold income ¹	
< 20 K	11 (6.33)
20-39 K	28 (16.46)
40-89 K	53 (31.65)
≥ 90 K	43 (25.32)
Not reported	34 (20.25)
Education	
High school or less	37 (21.82)
Some college	44 (26.06)
College degree	49 (29.09)
Postgraduate degree	29 (16.97)
Doctoral degree	10 (6.06)

Data are percentages of the total.

¹Household income in thousands of US dollars.

Given the findings in our survey, device ownership and access to Internet are unlikely to be limiting factors in delivering home-based CR using smart technology. However, despite device availability and perception of ease of use, the actual utilization of devices and internet for health-related applications was low with less than one third of study participants using these various devices for accessing DHI. Multiple factors likely contribute to this discrepancy between degree of use of smart tools for general purpose applications *vs* health-related applications. Some of these factors could be attitudinal, *i.e.*, older patients trust their health care providers much more than younger patients and may prefer to maintain this trust by not seeking online resources and tools^[14]. Generational beliefs pertaining to religion, social norms, and preference for personal interactions could also contribute to the reluctance of older adults to use smart devices for DHI^[15,16]. Furthermore, older people are more likely to have negative views about the societal impact of Internet and smart devices. Finally, people older than 50 years have been shown to have a greater concern over internet privacy and this may add to their reluctance to use smart devices for DHI^[17].

Aside from the aforementioned attitudinal factors, a number of physical and cognitive impairments that are frequently seen in this demographic group are known to contribute to the lower use of smart devices among older adults. These may include visual or hearing impairments, small joint arthritis, tremor, and impaired fine motor skills or coordination, all of which impair ability to use keyboard, mouse or touch screen functions etc^[15,16,18]. In addition, memory issues and cognitive dysfunction can hinder ability to retrieve passwords, impair learning ability (necessary for learning new skills), and ability to recall information, thereby resulting in disinterest and disengagement with technology and smart tools^[15,16,18]. It is also worth mentioning that a number of devices and apps are designed with the younger user in mind and there is an increasing appreciation of the need to redesign these interfaces to improve technology engagement among senior citizens^[19]. Not surprisingly, interfaces that provide healthcare-related information are often more complex and not as user friendly as commercial platforms that cater to entertainment or shopping, *etc.* This results in technology anxiety and lower self-efficacy in the interactions of older adults

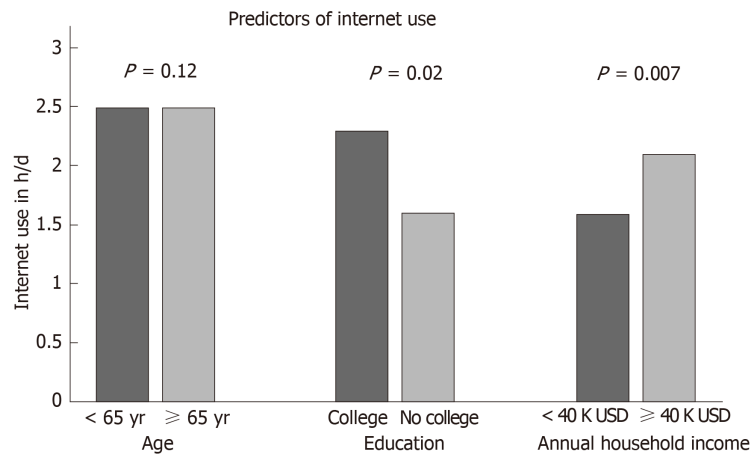


Figure 1 Bar graph of Internet use time in h/d by age, education and annual house-hold income.

with health-related smart apps. All of the above age-related factors interact in a complex fashion and result in decreased technology adoption for health-related applications among older individuals. Interestingly, although younger persons reported greater Internet time (2.5 h) *vs* older persons (1.8 h) per day, this difference was not statistically significant although this could be a result of the small sample size of our study.

A major strength of our study is its novelty and an assessment of the ownership of smart devices, usage patterns and barriers has not been previously identified in the CR population. Our study has some limitations that include small sample size and lack of sample diversity. Our subjects were mostly urban Caucasian males thus limiting the generalizability of our findings. Only 45% of eligible patients responded to our survey and there is a possibility of responder bias. Our survey was not pilot-tested for validity and should be considered exploratory. Finally, variables such as usage time were self-reported rather than measured and could be impacted by recall bias.

In conclusion, our study demonstrates that most older patients attending CR in an urban metropolitan area have access to Internet/smart devices and do not perceive significant barriers to use. Despite this, most participants did not utilize these devices for health-related applications. Further studies involving larger diverse groups of patients, sampled to account for geographic, racial and gender differences, are needed to add to the existing evidence on the impact of smart technology-based CR although two such studies are currently ongoing^[20,21]. In addition to building more evidence to support potential clinical benefits, further research to enhance our understanding of the barriers, our ability to design supportive educational programming and develop protocols that can enable effective and efficient delivery of home-based smart CR are urgently needed.

ARTICLE HIGHLIGHTS

Research background

Newer models of cardiac rehabilitation (CR) delivery are promising and there is increasing evidence that such models can be equally effective and can be used to complement or extend traditional hospital-based CR. Highlighting this opportunity, the American Heart Association issued a presidential advisory emphasizing the importance of adopting these newer models for improving access and utilization of CR. However, effective use of these smart models depends upon patients' ability to use technological media including Internet and smart devices. There is a dearth of knowledge on the availability of internet, ownership of smart devices, usage patterns and barriers to use specifically among CR attendees. CR attendees tend to be older than the general population or patients attending routine chronic disease management clinics. The purpose of this study was to explore the availability of such technology, current utilization and proficiency of use among older CR program attendees. This knowledge can help us understand the feasibility of such smart home-based CR programs in routine clinical practice outside of research trials.

Research motivation

CR is an important component in the management of patients with heart disease. Despite abundant evidence demonstrating its benefits and strong recommendations from multiple international and national associations, it remains underutilized. Potential reasons for this

underuse are the need for patients to travel significant distances multiple times in a week, lack of transport, and inflexible schedules. Proposed solutions include newer models of CR delivery such as home-based CR using smart device-based instruction and monitoring. To be able to implement and deliver these home-based CR regimens, we would need to know whether CR attendees who are generally elderly have access to such tools and whether they can use them proficiently. Hence this study was designed to address some of these gaps in knowledge.

Research objectives

The objectives of this study were to assess access to smart devices, predictors of their use and perceived barriers to the use of smart devices among CR attendees.

Research methods

This was an observational study assessing access to internet, smart device ownership and usage among attendees of 4 American Association of Cardiovascular and Pulmonary Rehabilitation-certified, hospital-based CR programs in Omaha, Nebraska, United States. This was a voluntary survey using a pilot survey tool consisting of 28 items. Subjects were recruited over a period of six months in 2018. On-site subject recruitment and survey administration were conducted by a single investigator. The survey was only available in English. Data are described using averages and percentages. Potential relationships between various items were assessed using Chi square tests for categorical data and Pearson's coefficient for continuous data. A significance level of 0.05 was used, and all data analyses and graphics were developed using the STATA14 statistical package (College Station, TX, United States). There has been no such study focusing on CR attendees in United States with most data currently available coming from general population surveys done by the Pew research center.

Research results

We approached 376 attendees of our program, of which 169 responded (45%). Patients as expected were relatively older with a mean age of 71 years, 90% were Caucasians and $\approx 75\%$ were males. Approximately half of the respondents had college education and had a household income of ≥ 40000 USD. Smart device ownership was 84.5% with desktop computer being the most common and preferred device for connecting to the internet. Approximately half of them owned a smart phone and $1/3^{\text{rd}}$ owned multiple devices (phones, tablets *etc.*). On average, Internet use was 1.9 h/d. Only about 18% used their smart devices and computers for health-related purposes. Utilization of other health information modalities was low, 29.8% used mobile health applications and 12.5% used wearable devices. Of all participants, 72% reported no barriers to using Internet. Education and income were associated positively with measures of utilization and with less perceived barriers while age had a negative correlation. In this survey, we did not address the medical comorbidities that may impact patients' ability to use smart devices for health-related applications and patients' attitudes towards such use.

Research conclusions

Our study demonstrates that most older patients attending CR in an urban metropolitan area have access to Internet/smart devices and do not perceive significant barriers to use. Unlike data from prior decades where elderly patients did not have access to smart devices, our study proves that access is no longer an issue. Despite this, the majority of participants did not utilize these devices for health-related applications. We hypothesize that attitudinal factors such as concern about internet privacy, physical and cognitive impairments that make it difficult to interface with smart devices such as small joint arthritis or memory impairment and lack of education on how to use the devices may be contributing to the low rates of use of smart devices for health related applications. Patient income, educational attainment and age correlated with use of smart devices in our study confirming the findings of prior studies across different age groups. Our findings have significant implications for the efforts to transition CR away from hospitals and closer to home and to create hybrid models of CR. These models not only increase access for patients, increase participation and engagement but may also prove economical and more sustainable for prolonged periods of time. More importantly, the ability to deliver CR in this fashion may be the only way to ensure safety of our patients in this current time of the corona virus 19 pandemic.

Research perspectives

Our study demonstrates that access to smart devices is no longer a limiting factor to the implementation of smart models of home-based CR. Limited use of smart devices for healthcare applications in our elderly patients was likely a result of attitudinal factors, cognitive impairments and lack of proper education. Further research is necessary to confirm our findings in larger diverse groups of patients, sampled to account for geographic, racial and gender differences using validated survey tools. Future avenues for research include investigation into the impact of smart device and apps' design as well as the impact of targeted education to improve technologic proficiency among older adults on the adoption of these technologies. The ultimate success of these smart models of CR will depend on their ability to improve clinical outcomes and their comparative efficacy and cost effectiveness vis-à-vis traditional hospital/center-based CR.

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Observational Study

Preoperative nuclear stress testing in the very old patient population

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Abstract

BACKGROUND

Elderly patients awaiting moderate to high-risk surgery may undergo nuclear stress testing (NST) in order to evaluate their cardiovascular risk. The prognostic utility of such testing in the very elderly (≥ 85 years) has yet to be fully evaluated. Octogenarians and nonagenarians frequently have a number of concurrent conditions including a high rate of coronary disease, and therefore the prognostic value of NST for their preoperative risk assessment has been questioned. Our evaluation assesses the ability of nuclear stress testing to predict peri-operative cardiac outcomes in this patient population.

AIM

To investigate the ability of NST to predict peri-operative cardiac outcomes in elderly patients awaiting moderate to high-risk surgery.

METHODS

Patients ≥ 85 years undergoing pre-operative NST were retrospectively evaluated. Patients undergoing low-risk surgery were excluded. Major adverse cardiac events (MACE) were considered any adverse event that occurred prior to discharge and included acute heart failure, arrhythmia, acute myocardial infarction, unstable angina, or death. Associations between patient risk factors, MACE, and the obtained results of the pre-operative stress testing, ejection fraction ($< 40\%$ or $\geq 40\%$), summed stress score (≤ 8 , ≥ 9), and the summed difference score (≤ 0 , > 0) were analyzed.

RESULTS

A total of 69 patients (mean age 88 ± 2.6 years, 31 males) underwent nuclear stress testing prior to surgery. There were 41 (60%) patients found to have an abnormal NST. Sixteen (23%) patients were noted to experience post-operative MACE. No significant associations between risk factors and MACE were noted. Patients with an abnormal NST and/or a summed stress score ≥ 9 were

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significantly ($P < 0.01$) more likely to develop peri-operative MACE.

CONCLUSION

Indicated preoperative NST is useful to assess pre-operative risk in elderly patients ≥ 85 years undergoing moderate to high-risk surgery.

Key words: Pharmacologic nuclear stress testing; Prognosis; Elderly; Preoperative assessment; Outcomes

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Core tip: It is common practice for elderly patients awaiting moderate to high-risk surgery to undergo nuclear stress testing in order to evaluate their cardiovascular risk. However, the prognostic utility of such testing in the very elderly (≥ 85 years) has yet to be evaluated. Octogenarians and nonagenarians frequently have a number of concurrent conditions in addition to a high rate of coronary disease and therefore the prognostic value of nuclear stress testing for their preoperative risk assessment has been questioned. We sought to assess the ability of nuclear stress testing to predict peri-operative cardiac outcomes in these patients. We found that there were no significant associations between risk factors and major adverse cardiac events. Patients with an abnormal nuclear perfusion result and/or a summed stress score ≥ 9 were significantly ($P < 0.01$) more likely to develop peri-operative major adverse cardiac events. Indicated nuclear stress testing, therefore, is useful to assess pre-operative risk in elderly patients ≥ 85 years undergoing moderate to high-risk surgery.

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INTRODUCTION

The overall prognostic utility of both treadmill and pharmacologic stress testing is well established^[1-4]. However, the utility of stress testing in those ≥ 85 years old is not well established. Octogenarians and nonagenarians typically have an elevated rate of coronary artery disease. Furthermore, to our knowledge no prior study has specifically examined the utility of nuclear stress testing (NST) with respect to surgical outcomes in the ≥ 85 years old age group. Thus, the prognostic value of nuclear stress testing for preoperative risk assessment has been questioned in this patient population.

In the present study, we sought to determine whether results of indicated pre-operative nuclear stress tests (NST's) have prognostic value in predicting peri-operative and post-operative cardiac events (one or more, none) in elderly patients undergoing moderate to high-risk surgery.

MATERIALS AND METHODS

Patient selection

We performed a retrospective descriptive study of 69 patients ≥ 85 years of age who underwent pre-operative nuclear stress testing (Figure 1). Patients undergoing low-risk surgery as defined by the American College of Cardiology/ American Heart Association guidelines^[5] were excluded. Other exclusion criteria were patients aged less than 85, and patients undergoing resting nuclear perfusion studies (*i.e.*, viability studies).

Stress testing

Either pharmacologic ($n = 67$) or exercise treadmill stress testing ($n = 2$) was employed. An intravenous line was inserted prior to the start of the test. Exercise testing patients underwent symptom-limited treadmill exercise testing using a standard Bruce protocol. Heart rate, blood pressure, and 12-lead electrocardiograms

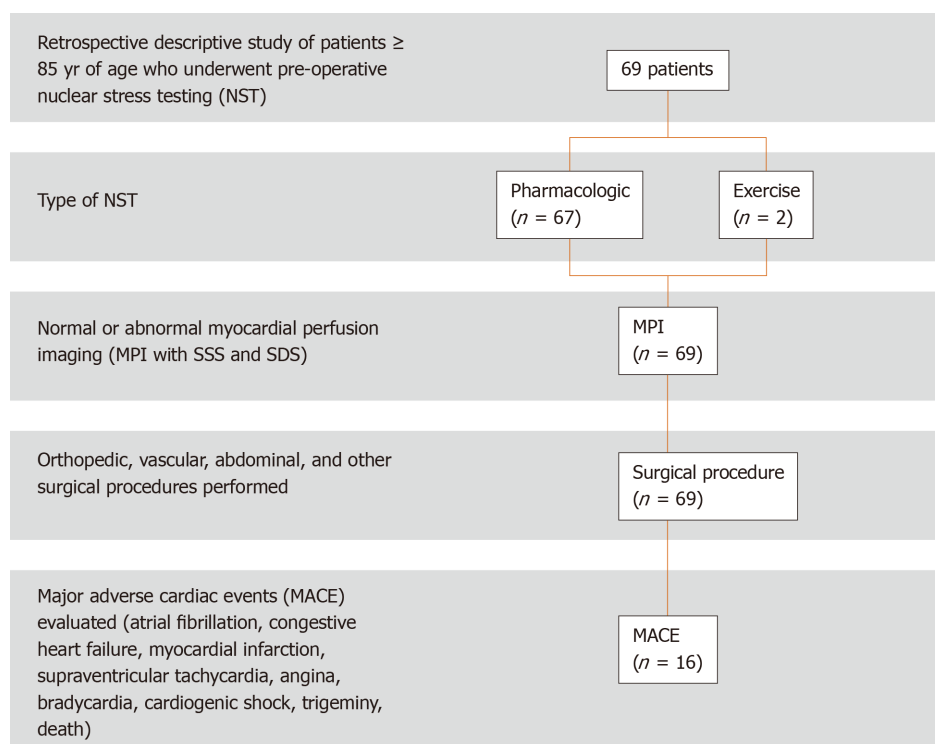


Figure 1 Study population flow chart. SSS: Summed stress score; SDS: Summed difference score.

were recorded before (supine and upright positions) and during each minute of exercise and recovery. Patients exercised until the point of fatigue unless marked electrocardiographic abnormalities, hemodynamic instability, chronotropic incompetence, ventricular tachycardia or fibrillation, or disabling chest pain symptoms occurred. Exercise was discontinued if exertional hypotension, malignant ventricular arrhythmias, marked ST depression, or limiting chest pain occurred. An abnormal electrocardiogram was defined as ≥ 1 mm ST depression.

In the pharmacologic testing patients, adenosine or dobutamine pharmacologic stress was performed. Adenosine was infused intravenously, at a dose of 140 mcg/kg per min over 6 min, with an administration of the radiopharmaceutical at the midpoint of the infusion. If patients exhibited persistent side effects from the adenosine, 75-125 mg of aminophylline were administered intravenously as needed. Dobutamine was infused using standard incremental dosing from 5-40 mcg/kg per min during which patients remained under continuous clinical, and electrocardiographic monitoring. Test endpoints included completion of the final stage of the protocol, severe ischemia (severe angina, > 2 mm ST depression), hypertension (systolic blood pressure > 220 mmHg), hypotension (drop in systolic blood pressure > 20 mmHg), arrhythmias, or side effects intolerable to the patient. Atropine (1 mg IV) was administered in patients who failed to attain 85% of age-predicted maximal heart rate at peak dose.

Myocardial perfusion imaging

Single photon emission computed tomography (SPECT) was performed at one institution (Long Island Jewish Medical Center) using one or two-day single-isotope protocols, employing either ^{99m}Tc -sestamibi or ^{99m}Tc -tetrofosmin. At our other site (North Shore University Hospital), a dual isotope (^{201}Tl and ^{99m}Tc -sestamibi) one-day protocol was employed. The myocardial single-photon emission computed tomography perfusion image acquisition was acquired at rest and after peak stress using a dual head Optima NX gamma camera at one site and a dual-head Millennium gamma camera (General Electric, TM Milwaukee, WI, United States) at our other respective site. The images were processed using standard commercial software (PegasysTM, Milwaukee, WI, United States). All SPECT acquisitions were acquired at rest and after peak pharmacologic stress using a circular orbit (180°), in a 64×64 matrix. Image processing was performed in a standard manner. All image sets (horizontal and vertical long-axis and short-axis planes) were normalized to the maximal myocardial activity in that set and displayed in the standard American College of Cardiology orientation. An experienced observer blinded to clinical outcome data reviewed all scans. Stress images were compared with rest images. A

20-segment scoring system that uses 3 short-axis slices [distal (apical), mid, and basal] of the left ventricle, with the apex represented by 2 segments visualized on a midvertical long-axis image was used. Each segment was scored as follows: 0 = normal, 1 = slight reduction of uptake, 2 = moderate reduction of uptake, 3 = severe reduction of uptake, and 4 = absence of radioactive uptake.

Adverse cardiac Events

A major adverse cardiac event (MACE) was considered for any adverse event that occurred prior to post-operative discharge. MACE included arrhythmia, myocardial infarction, unstable angina, heart failure, or death. The associations between patient risk factors, MACE, and the results of the pre-operative NST [normal (nl), abnormal (abnl)], the ejection fraction (EF < 40% or ≥ 40%), summed stress score (SSS ≤ 8, ≥ 9), and the summed difference score (SDS ≤ 0, > 0) were examined.

Statistical analysis

The use of logistic regression to examine the multivariate effects of nuclear stress test results and presence of cardiac risk factors prior to admission on intraoperative cardiac events (one or multiple) was undertaken. A Cox proportional hazards regression analysis was used to examine the multivariate effects of nuclear stress test results, presence of cardiac risk factors prior to admission and intraoperative cardiac events on time until first post-operative cardiac event.

In the analysis of in-hospital adverse events, it is generally felt preferable to use survival methods; we therefore examined length of stay since patients staying longer are more likely to have events regardless of other risk factors. However, because this was a retrospective chart review, it was not possible to obtain the dates of all events with certainty. Therefore, rather than deleting patients from the analysis, the analysis was carried out without regard to time. In order to examine the association between length of stay and stress test result, we estimated length of stay (LOS) using the product limit method, and compared LOS stratified by stress test results using the log rank test only for those patients not having an event in hospital. Presumably, any difference in LOS would then be due to the test result and not the occurrence of an adverse event. Similar analyses were carried out for ejection fraction, summed stress score, and summed difference score.

RESULTS

Clinical characteristics and stress test results

From the group of 69 patients (mean age 88 ± 2.6 years, 31 males) who underwent NST prior to surgery, **Table 1** highlights the study population demographics. A majority of the patients had hypertension (82.6%) and 33.3% had hyperlipidemia. Abnormal NST was found in 60% (41/69) of the patients. A majority of the patients (37.7%) underwent orthopedic procedures followed by vascular surgeries (21.7%) and abdominal surgeries (21.7%).

Adverse cardiac events and in-hospital outcomes/mortality

Sixteen (23%) patients suffered post-operative MACE. Adverse events are detailed in **Table 2**. No significant associations were noted between risk factors and MACE (**Table 3**). Patients with an abnormal NST and/or an SSS ≥ 9 were significantly more likely ($P < 0.02$) to develop peri-operative MACE (**Table 4**). Patients with an abnormal stress test were 6.3 times more likely ($P < 0.03$) than those with a normal test to have a MACE prior to discharge (95% confidence interval: 1.3-30.5). Those with an EF < 40% or SDS > 0 (denoting ischemia) did not each show a statistical significance to developing peri-operative MACE, although in those with an EF < 40%, there was a trend toward significance with a P value of 0.065. **Figure 2** shows the example of a patient who suffered post-operative heart failure after hip fracture repair. The images reveal an area of infarct in the proximal inferolateral wall with ischemia in the mid to distal inferolateral wall. A SSS of 22, and a SDS of 7 were noted in this patient.

DISCUSSION

Our investigation adds significant information to the body of evidence that shows prognostic utility of both treadmill and pharmacologic stress testing, but it adds this information in the population of octogenarians and nonagenarians who were under-represented in many of the landmark prognostic evaluations of NST. Furthermore, no prior study has specifically examined the utility of NST with respect to surgical

Table 1 Patient demographics

Characteristic	Number of patients (%)
Gender	
Male	31 (44.9)
Female	38 (55.1)
Mean age	88 yr
Risk factors	
Hypertension	57 (82.6)
Diabetes mellitus	13 (18.8)
Hyperlipidemia	23 (33.3)
Obesity	1 (1.4)
Smoking	7 (10.1)
Medications	
ASA	13 (18.8)
Plavix	4 (5.8)
Beta blocker	34 (49.3)
Statin	20 (29.0)
ACE-I/ARB	27 (39.1)
Digoxin	8 (11.6)
Nitrates	9 (13.0)
CC blocker	17 (24.6)
Diuretics	23 (33.3)
Procedures	
Orthopedic	26 (37.7)
Vascular	15 (21.7)
Abdominal	15 (21.7)
Other	13 (18.8)

ASA: Aspirin; ACE-I/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CC blocker: Calcium channel blocker.

outcomes in the ≥ 85 year old age group. This information is useful as it is not uncommon for these patients to undergo surgical operations, particularly orthopedic procedures. We found that clinical underlying risk factors did not predict outcomes. This is an important finding as many of these patients are sent to surgery without prior further stratification aside from risk factor assessment and modification. Also, although the SSS was a significant predictor of MACE, the SDS and the EF were not. This may be due to the small sample size as there is a trend in the *P* values towards significance. Prior studies^[1,2] support the fact that the SSS is the major predictor of adverse events as opposed to the SDS. The NST, specifically an abnormal nuclear perfusion result and/or a SSS ≥ 9 (severely abnormal study), identified those patients significantly ($P < 0.01$) more likely to develop peri-operative MACE.

Few prior investigations have examined the question of the prognostic utility of NST in the very elderly (≥ 85) age group^[6-15]. Although these studies demonstrate the utility of NST in the elderly for predicting cardiac events, they do not focus on the specific situation of pre-operative risk assessment; our study does. Another discrepancy in these studies is the age cutoff for an “elderly” patient. Some authors ascribe an “elderly” patient to the ≥ 55 years range^[13], while others use the cutoff of ≥ 65 years^[6,11,12], ≥ 70 years^[14,15], ≥ 75 years^[9], or even ≥ 80 years^[7,8,10]. Our study specifically assessed prognostic outcome after moderate-to high-risk surgery in patients ≥ 85 years, thus targeting a special population of very elderly individuals.

In the evaluation by Steingart *et al*^[6], the clinical, electrocardiographic (ECG) stress test, NST, and follow-up data for 626 patients aged ≥ 65 years (mean age 70 ± 4.4) with interpretable electrocardiograms undergoing symptom-limited exercise NST between 1992 and 1996 were evaluated with follow-up occurring after 4.4 ± 1.3 years. They found that the following factors predicted death or myocardial infarction: Male sex, increasing age, an abnormal rest ECG result, lower exercise tolerance and lower peak exercise heart rates, exercise ST-segment depression, left ventricular dilatation, and the number of ischemic regions. After multivariable analysis, only increasing patient

Table 2 Major adverse cardiac events

Adverse event	Number of subjects (%)
Atrial fibrillation	3 (0.04%)
Congestive heart failure	6 (0.09%)
Myocardial infarction	1 (0.01%)
Supraventricular tachycardia	1 (0.01%)
Angina	2 (0.03%)
Bradycardia	1 (0.01%)
Cardiogenic shock	1 (0.01%)
Trigeminy	1 (0.01%)
Death	3 (0.04%)
Total	16 (0.23%)

age, male sex, limitation of exercise tolerance, and the number of ischemic segments by NST were predictive of death or myocardial infarction. They concluded that in elderly patients undergoing exercise NST, age, sex, exercise tolerance, and ischemia on NST provide significant prognostic information in this patient population. Nuclear imaging provided incremental prognostic information that was significant in comparison to clinical information and results of exercise testing^[6].

Goraya *et al*^[11] assessed treadmill exercise testing in an elderly population (≥ 65 years of age) to evaluate the incremental value of the testing to clinical data. A comparison was undertaken with a median follow-up of 6 years with results of treadmill testing in younger patients (< 65 years). Elderly patients, as compared with younger patients, had more comorbidities, achieved a lower workload (6.0 *vs* 10.7 metabolic equivalents; $P < 0.001$), and had a greater likelihood of an abnormal exercise ECG (28% *vs* 9%; $P < 0.001$). Overall survival (63% *vs* 92%; $P < 0.001$) and cardiac event-free survival (66% *vs* 95%; $P < 0.001$) were worse among the elderly persons. The amount of workload achieved was the only treadmill exercise testing variable associated with all-cause mortality ($P < 0.001$) in both age groups. Workload was also the only additional treadmill exercise testing variable that was predictive of cardiac events ($P < 0.05$). Notably, each one metabolic equivalent rise in exercise capacity was associated with a 14% and 18% reduction in cardiac events among younger and elderly persons, respectively. They conclude that in elderly persons, treadmill exercise testing provided incremental prognostic information that was significant and incremental in comparison to clinical information. ECG results of stress testing (*e.g.*, the presence of ST-segment depression) was likely not a significant contributor to prognosis, because in the elderly there is a higher occurrence of resting (baseline) ST-segment changes and higher use of medications that may cause falsely positive ECG changes. Exercise workload on the treadmill was the only variable that was strongly associated with outcome, and its prognostic effect was equal in both the young and elderly age groups^[11].

A report by Zafrir *et al*^[8] examined 162 consecutive patients (mean age 83 ± 3 years) who underwent NST with a duration of follow-up of 45 ± 12 months. Nineteen percent of patients (31) had major cardiac events recorded; including 26 cardiac deaths and 5 MI events, in 6 of the 61 women (10%) and 25 of the 101 men (25%) ($P < 0.03$). The univariate predictors of cardiac death or MI, aside from known coronary artery disease (CAD), included NST variables such as left ventricular dilatation, increased lung uptake, abnormal scan, and the presence and extent of myocardial ischemia. The only predictors for major cardiac events, however, were: left ventricular (LV) dilatation (OR = 6.9, 95%CI: 2.7-17.4, $P < 0.0001$) and ischemia by scan (OR = 2.75, 95%CI: 1.09-6.96, $P < 0.03$). Survival curves demonstrated significant differences in survival between patients with or without LV dilatation and patients with or without ischemia. They conclude that in octogenarian patients with CAD or with suspicion of CAD, LV dilatation and myocardial ischemia are useful predictors of cardiac death and MI^[8].

A report by De Winter *et al*^[9] further used not only perfusion imaging in the prognostic assessment of elderly patients, but adds left ventricular function analysis as a further criterion in the evaluation. The clinical and gated SPECT predictors of cardiac and all-cause death in 294 patients aged ≥ 75 years with known or suspected CAD who were referred for tetrofosmin cardiac gated SPECT imaging were examined. During a median follow-up of 25.9 months, a total of 47 patients (16%) died. In their multivariate Cox proportional hazards regression analysis, the summed

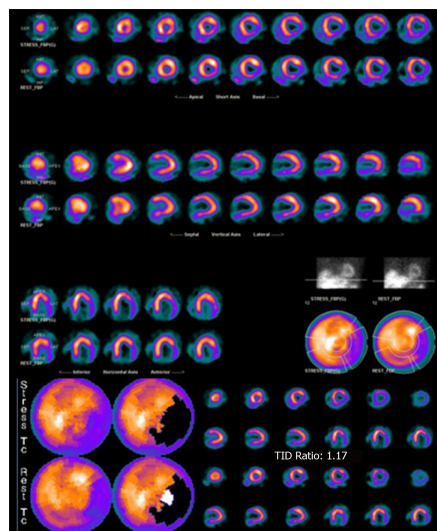


Figure 2 This image shows the nuclear stress testing result of one of our patients: An 88 year old man who presented with a fracture of his left hip. He was risk stratified by undergoing adenosine pharmacologic nuclear testing. The images reveal an area of infarct in the proximal inferolateral wall with reversibility (ischemia) in the mid to distal inferolateral wall.

rest score, transient ischemic dilatation index, and resting left ventricular ejection fraction were independent predictors of all-cause death. The summed rest score and resting end-systolic volume were independent predictors of cardiac death. They conclude that NST left ventricular functional data assessed during myocardial gated SPECT provides independent and incremental information above clinical and perfusion SPECT data for the prediction of cardiac and all-cause death in patients aged ≥ 75 years^[9].

Study limitations

The relatively small sample size of the study group limits our study findings. The small number of post-operative MACE is also a limitation, but may just be a credit to our advancing health-care techniques in the peri-operative period. Additional study of larger numbers of individuals would allow more specific analyses of NST's. For example, prognosis may be stratified by different categories of summed stress scores. Another limiting factor is that our analysis only included those patients who underwent surgery. It is not unreasonable to surmise that many patients who had abnormal NST might have had their surgeries cancelled due to their assumed high risk. This may introduce referral bias into the analysis, with potential for decreasing the correlation between abnormal studies and unfavorable surgical outcomes. It is also assumed that certain surgical techniques may have been modified as a result of the findings on NST.

In the analysis of in-hospital events, it is generally preferable to use survival methods, so that length of stay is considered, since patients staying longer are more likely to have events regardless of other risk factors. Since this was a retrospective chart review, and it was not possible to obtain the dates of all events with certainty, rather than deleting patients from the analysis, we carried out the analysis without regard to time. However, if there were an association between risk factor and length of stay, then this analysis would be biased, since patients with a longer stay would be more likely to have experienced an event simply because they were in the hospital longer. On the other hand, patients experiencing an event may have longer stays as a result of the event. Therefore, in order to examine the association between length of stay and stress test result, we estimated length of stay (LOS) using the product limit method, and compared LOS stratified by stress test results using the log rank test only for those patients not having an event in hospital. Presumably, this way any difference in LOS would then be due to the test result and not the occurrence of an adverse event. Similar analyses were carried out for ejection fraction, summed stress score, and summed difference score. These analyses showed no associations between any of the test results and LOS for subjects not having an in hospital event.

In conclusion, the use of nuclear stress testing is a useful tool to assess pre-operative risk and post-operative outcome stratification in elderly patients ≥ 85 years undergoing moderate to high-risk surgery in whom the test is indicated based on latest preoperative risk stratification guidelines. In a time when recommendations

Table 3 Major adverse cardiac events and risk factors

Major adverse cardiac event		Yes, n (%)	No, n (%)	P value
Hypertension	Yes	13 (23)	44 (77)	NS
	No	2 (17)	10 (83)	
Diabetes	Yes	3 (23)	10 (77)	NS
	No	12 (21)	44 (79)	
Hypercholesterolemia	Yes	2 (9)	21 (91)	NS
	No	13 (28)	33 (72)	
Smoking	Yes	2 (29)	5 (79)	NS
	No	13 (21)	49 (79)	
Obesity	Yes	1 (100)	0 (0)	NS
	No	14 (21)	54 (79)	

NS: Non-significant.

now tend to less commonly recommend pre-operative testing, because the prediction of the development of post-operative complications using NST is possible, the use of NST in the appropriate patients should yield important and applicable information for it to benefit the patient and affect management. As our study demonstrates, an abnormal NST, and more specifically a significantly abnormal study with SSS ≥ 9 , was noted to be highly predictive for the development of MACE in the immediate operative period in elderly patients ≥ 85 years undergoing moderate to high-risk surgery.

Table 4 Major adverse cardiac events and nuclear stress test variables

		Yes, n (%)	No, n (%)	P value
Nuclear stress test result	Abnormal	13(32)	28 (68)	< 0.02
	Normal	2 (7)	26 (93)	
Ejection fraction	< 40%	6 (46)	7 (54)	0.065
	≥ 40%	9 (17)	45 (83)	
Summed stress score	≥ 9	11 (37)	19 (63)	< 0.02
	≤ 8	4 (11)	34 (89)	
Summed difference score	> 0	10 (26)	28 (74)	0.387
	≤ 0	5 (17)	24 (83)	

ARTICLE HIGHLIGHTS

Research background

It is common for elderly patients awaiting moderate to high-risk surgery to undergo nuclear stress testing in order to evaluate their cardiovascular risk. However, the prognostic utility of such testing in the very elderly (≥ 85 years) has yet to be evaluated.

Research motivation

The very elderly (octogenarians and nonagenarians) frequently have a number of concurrent conditions in addition to a high rate of coronary disease and therefore the prognostic value of nuclear stress testing for their preoperative risk assessment has been questioned.

Research objectives

We sought to assess the ability of nuclear stress testing to predict peri-operative cardiac outcomes in these patients.

Research methods

We undertook a retrospective descriptive study of 69 patients ≥ 85 years of age who underwent pre-operative nuclear stress testing. Patients undergoing low-risk surgery as defined by guidelines were excluded. Other exclusion criteria were patients aged less than 85, and patients undergoing resting nuclear perfusion studies (*i.e.*, viability studies).

Research results

We found that there were no significant associations between risk factors and major adverse cardiac events (MACE). Patients with an abnormal nuclear perfusion result and/or a summed stress score ≥ 9 were significantly ($P < 0.01$) more likely to develop peri-operative major adverse cardiac events.

Research conclusions

Indicated nuclear stress testing is useful to assess pre-operative risk in elderly patients ≥ 85 years undergoing moderate to high-risk surgery.

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Incidental discovery of right ventricular lipoma in a young female associated with ventricular hyperexcitability: An imaging multimodality approach

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Abstract

BACKGROUND

Cardiac lipomas are rare benign tumors commonly found in the right atrium or left ventricle. Patients are usually asymptomatic, and clinical presentation depends on location and adjacent structures impairment. Right ventricle lipomas are scarce in the literature. Moreover, the previous published cases were reported in over 18-year-old patients.

CASE SUMMARY

We report a giant right ventricle lipoma discovered incidentally in a 17-year-old female while performing preoperative work-up. The diagnosis was confirmed by histopathological examination, and a conservative approach was performed.

CONCLUSION

Multimodal cardiac imaging and histopathological examination are required for a definitive diagnosis. The therapeutic approach depends on clinical presentation.

Key words: Cardiac lipoma; Polymorphic premature ventricular contractions; Giant cardiac tumor; Cardiac magnetic resonance imaging; Case report

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Core tip: We describe an extremely rare case of cardiac lipoma raising from the right ventricle in a young patient aged less than 18-years-old. It was discovered incidentally

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while performing preoperative workup. Variable cardiac imaging modalities such as transthoracic echocardiogram, cardiac computed tomography-scan, positron emission tomography-scan and cardiac magnetic resonance were used. Then, the diagnosis was confirmed by histopathological examination.

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INTRODUCTION

A lipoma is a benign fat tissue tumor that can grow in most body parts. However, cardiac lipomas occur exclusively in adults^[1,2]. These tumors are commonly asymptomatic and discovered incidentally while performing cardiac investigations for other disease or diagnosed on autopsies. Large size or huge lipoma may cause symptoms *via* mass effect on the adjacent structures such as coronary arteries provoking angina and left ventricle causing heart failure. Cardiac lipomas arising from the myocardium are more likely to induce arrhythmia by infiltrating the electrical circuit. Indeed, clinical presentation depends on location and size of cardiac lipomas. We present a right ventricular lipoma that was found incidentally during a preoperative work-up in a young patient with excessive premature ventricular contractions detected afterwards.

CASE PRESENTATION

Chief complaints

We report a case of giant cardiac lipoma in a 17-year-old female previously healthy while performing preoperative work-up for tonsillectomy.

Clinical history and physical exam

A 17-year-old female with a known case of Prader-Willi syndrome since childhood was hospitalized for a preoperative tonsillectomy evaluation. She was referred for surgery due to several episodes of infective tonsillitis (> 6) in the last year. Physical exam was unremarkable for cardiopulmonary findings. The patient was asymptomatic with normal hemodynamic parameters. Laboratory studies revealed normal white blood cell count and C-reactive protein and electrolyte panel with normal renal and liver function. Electrocardiogram showed regular sinus rhythm with T waves inversion in all territories. Subsequently, Holter electrocardiogram found repetitive polymorphic ventricular contraction. Afterwards, an electrocardiogram stress test was performed with suboptimal results due to many premature ventricular contractions originating from the apex and inferior wall.

Imaging investigations and diagnosis

As a result, we proceeded with transthoracic echocardiogram, which revealed a giant mass located apically in the right ventricle and extended to the epicardium measuring transversally 8.4 cm on its maximal diameter (Figure 1). Computed tomography scan showed a well-circumscribed and homogeneously hypodense mass obscuring the apical right ventricle (Figure 2). Searching for the etiology, cardiac magnetic resonance imaging (MRI), the diagnostic modality of choice, showed a right ventricular septate mass with fat signal transmission and homogenous contours that had normal gadolinium enhancement protruding to the apical epicardium without extracardiac structures involved. The patient had normal biventricular function (Figures 3-7). In order to differentiate primary from secondary cardiac tumors and to search for secondary localizations, we performed a positron emission tomography scan that showed a nonfunctional mass (Figure 8).

Afterwards, percutaneous myocardial biopsy was done, and histopathological examination showed adipose tissue without malignant features confirming cardiac lipoma (Figure 9).

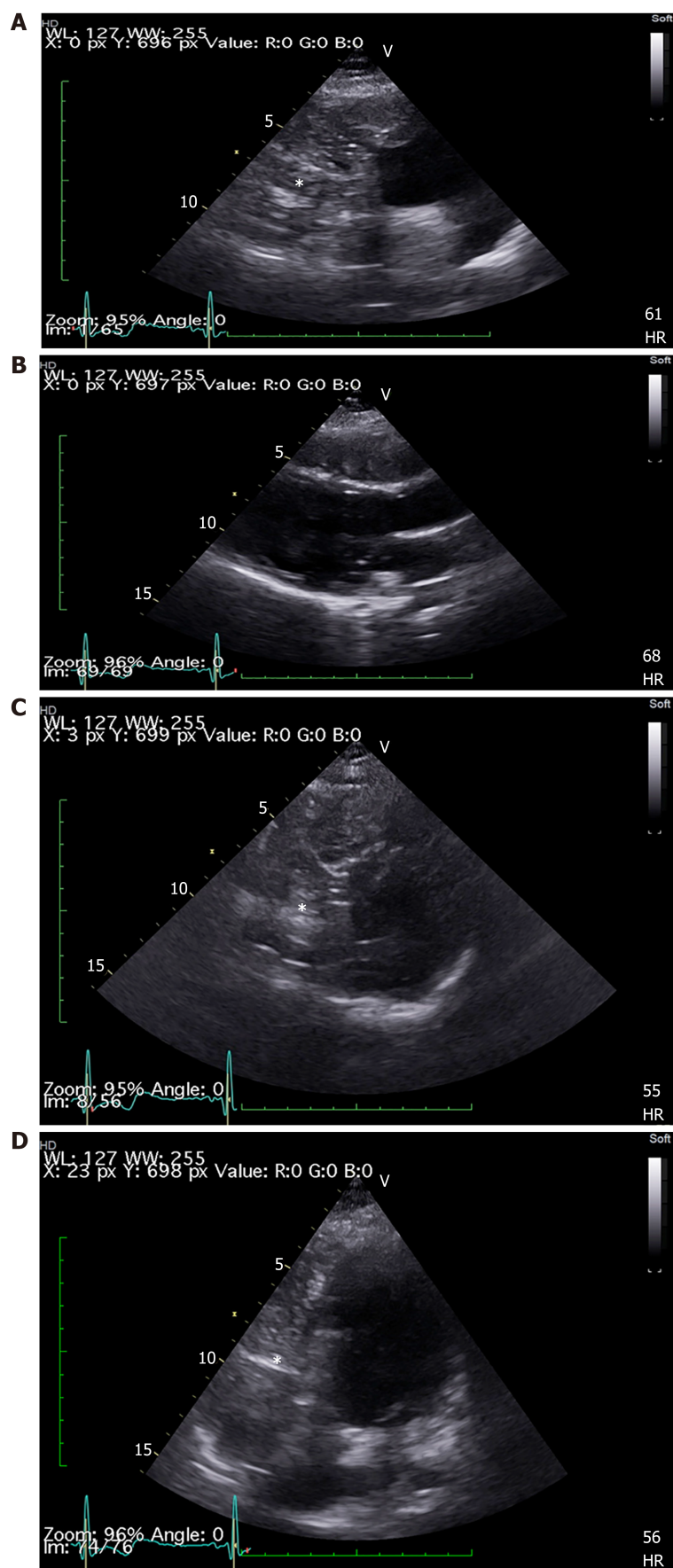


Figure 1 Transthoracic echocardiogram. A, C: Right ventricular mass (star) in short axis view; B: No mass in long axis view; D: Four-chamber view.

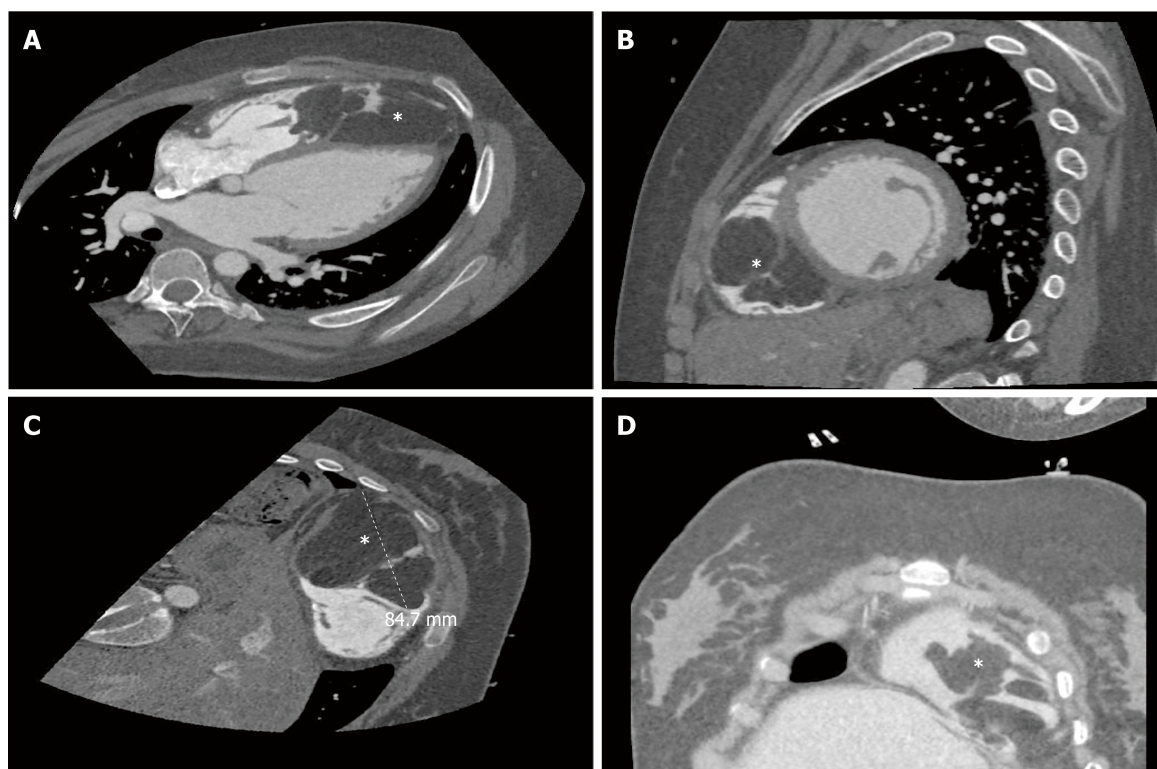


Figure 2 Computed tomography scan. A, B: A mass (star) occupying the right ventricle in axial plane (A), sagittal plane (B); C, D: Atypical plane maximal diameter 84 mm (star).

FINAL DIAGNOSIS

Right ventricular lipoma.

TREATMENT

After a multidisciplinary decision, surgical excision was avoided as the patient was asymptomatic with no hemodynamic instability or ventricular function impairment. The patient started sotalol to reduce the risk of ventricular arrhythmia in the presence of documented excessive premature ventricular contractions in view of reported ventricular arrhythmias in cardiac lipomas patients.

OUTCOME AND FOLLOW-UP

Patient was discharged with regular follow-up.

DISCUSSION

Cardiac lipomas are rare^[3,4] and found mostly in asymptomatic patients^[5,6]. A review of articles related to cardiac lipomas shows that interatrial septum is the most common position for lipomas and lipomatous hypertrophy^[7]. They have a predilection for the right atrium and left ventricle but can originate in any part of the heart. However, right ventricle involvement is rare^[8,9]. They also have a predilection for the pericardium, but it may originate from all three layers of cardiac tissue^[10]. Symptoms depend mostly on anatomical location and mass effect to adjacent structures causing hemodynamic compromise or conduction abnormalities, which can ultimately lead to heart failure^[11].

Various imaging modalities can accurately determine localization, size and shape and most importantly differentiate lipomas from liposarcomas.

Transthoracic echocardiogram is usually the first exam to be done due to high accessibility with a high safety profile. Intracavitary cardiac lipomas are usually hyperechogenic while pericardial lipomas are hypoechogenic^[12]. It is not known if this

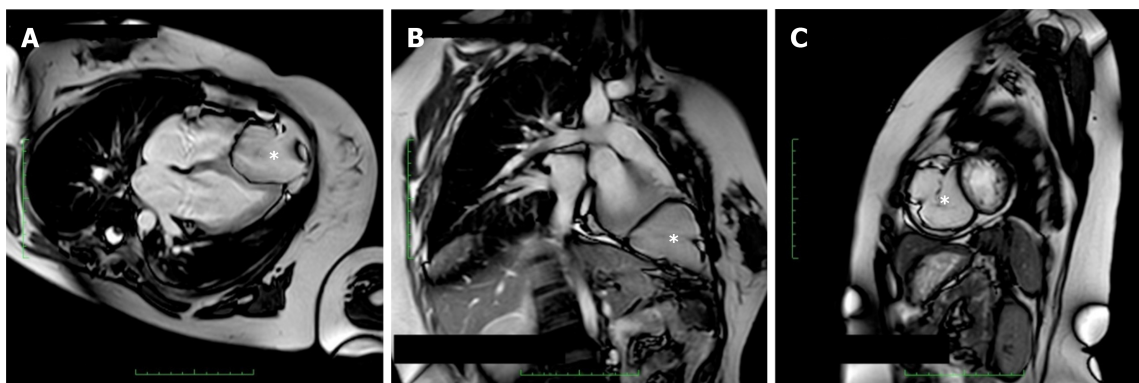


Figure 3 Cine-cardiac magnetic resonance imaging. An encapsulated mass (star) occupying the apical right ventricle. A: Horizontal long axis; B: Vertical long axis; C: Short axis.

variability in echogenicity is related to the position of the lipoma. In our case it is isoechogenic. Heterogenic and large size lipomas are suspicious for liposarcomas.

On computed tomography scans, lipomas typically appear as well-circumscribed and homogeneously hypodense masses, which was seen in our patient. Calcifications raise the suspicion for liposarcomas^[13], but differentiation with certainty between them is only assured by histopathology.

MRI is very utile in delineating contours and distinguishing characteristics with specificity reaching as high as 100%. In addition, MRI is helpful in discriminating any atypical features and in better visualizing adjacent structure invasion. Malignant features include the presence of septa > 2 mm, intralesional nodules and the inhomogeneity of the signal.

Lipomas usually have a homogenous signal with high signal intensity appearing white on T1-weighted sequence and a low signal intensity appearing dark on T2-weighted sequence. An important sequence for diagnosing lipomas is named pre- and post-fat-saturated T1-weighted Fast spin-echo sequences, which shows signal dropout on fat saturation sequence confirming the diagnosis of a fat-containing mass. It is worth mentioning that cardiac lipomas do not show delayed gadolinium enhancement. THRIVE protocol is an optimized fast T1 weighted 3-dimensional imaging technique combining sensitivity encoding, large volume coverage and uniform fat suppression for better quantification. Another incredible tool for achieving rapid and high signal-to-noise ratio imaging is balanced turbo field-echo steady-state free precession MR technique, which has been applied successfully to cardiac MRI^[14].

The role of positron emission tomography scans is to differentiate benign cardiac tumors from malignant primary tumors or metastasis with high sensitivity^[15]. It evaluates functional characteristics of soft tissue masses. Lipomas have consistently low fluorodeoxyglucose as they are hypodense and hypometabolic as demonstrated in our case. However, it is important to emphasize that lipomatous hypertrophy of the septum may be metabolically active on positron emission tomography scan as it contains brown fat. Lastly, myocardial biopsy with histopathological examination remains the definitive diagnostic method showing in our case the adipose tissue with no suspect elements of malignancy.

Benign cardiac lipomas are associated with a good long-term prognosis, and furthermore a good outcome is observed in 95% of patients after surgical excision. As cardiac lipomas are rare, no guidelines have been established to define surgical intervention indications. However, there is a consensus that surgical resection needs to be considered in symptomatic patients. The data concerning prognosis of patients treated conservatively are lacking due to the rarity of cardiac lipomas. Our patient is followed regularly with no documented abnormal clinical signs or appearance of warning symptoms necessitating surgical intervention at the present time.

CONCLUSION

Multiple imaging modalities and histopathological exam are the mainstay for confirming the diagnosis of cardiac lipomas. In most patients, surgical intervention is limited for cases with associated symptoms, life-threatening arrhythmias and flow obstruction leading to congestive heart failure or myocardial ischemia. As evidence is still lacking for cardiac lipomas, decisions should be made on a case-by-case basis.

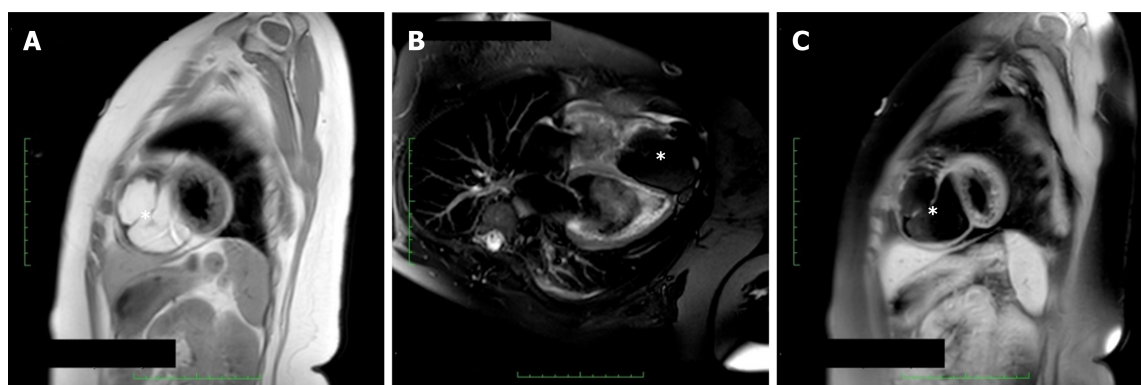


Figure 4 Cardiac magnetic resonance. A: A right ventricular mass (star) appearing white in T1-weighted sequence; B: Dark (star) in T2-weighted sequence; C: A dark signal (star) dropout in T1-weighted fast spin-echo sequences.



Figure 5 Cardiac magnetic resonance shows no delayed gadolinium enhancement.

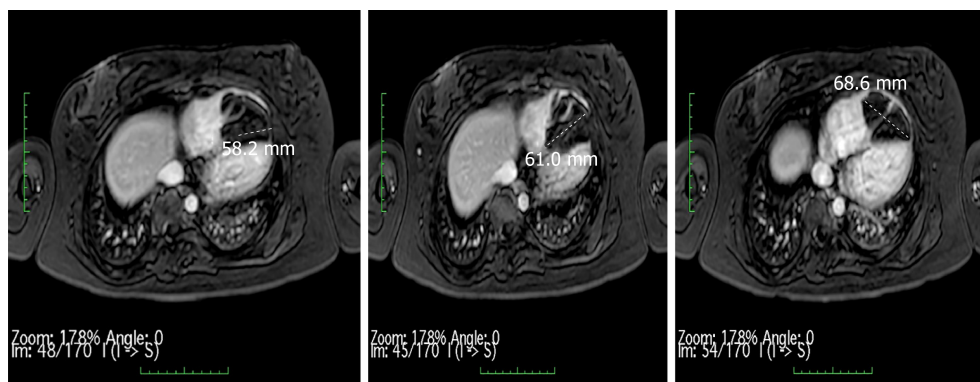


Figure 6 T1 weighted 3-dimensional imaging technique with THRIVE and uniform fat suppression.



Figure 7 Balanced turbo field-echo magnetic resonance technique shows detailed delineation of the lipoma contours (star).

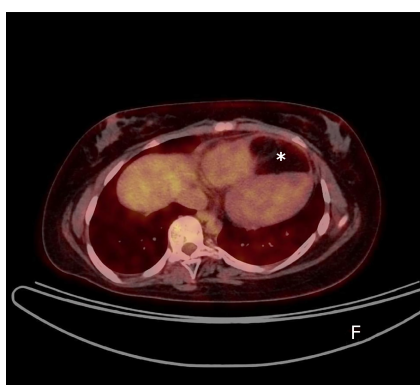


Figure 8 Positron emission tomography scan with low fluorodeoxyglucose uptake in the mass (star).

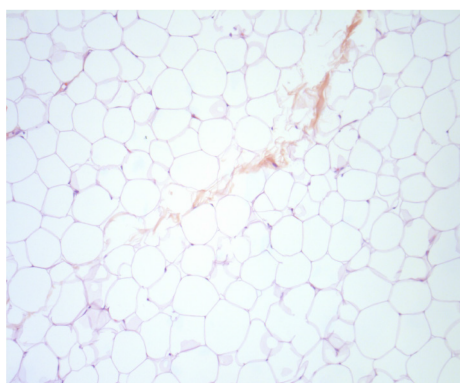


Figure 9 Histopathological examination shows adipose tissue with no suspect elements of malignancy.

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Management of hypertension in COVID-19

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Abstract

The ACE2 receptor plays a central role in severe acute respiratory syndrome coronavirus 2 host cell entry and propagation. It has therefore been postulated that angiotensin converting enzyme inhibitors and angiotensin receptor blockers may upregulate ACE2 expression and thus increase susceptibility to infection. We suggest that alternative anti-hypertensive agents should be preferred among individuals who may be exposed to this increasingly common and potentially lethal virus.

Key words: Angiotensin converting enzyme inhibitor; Angiotensin receptor blocker; Carvedilol; Coronavirus disease-19; COVID-19; SARS-CoV-2; Verapamil

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Core tip: The pathogenic mechanisms of severe acute respiratory syndrome coronavirus 2 remain under investigation, but data suggest that the ACE2 receptor plays a central role in infection. It is therefore possible that drugs known to increase ACE2 expression, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers, could promote viral proliferation. Data from animal studies have shown that carvedilol and verapamil attenuate inflammation in viral myocarditis. We are in agreement with the recommendation of major medical societies to maintain angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy in individuals who are already receiving treatment. However, in the age of coronavirus disease-19, alternative agents should be considered for patients with a new diagnosis of hypertension.

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TO THE EDITOR

Coronavirus disease-19 (COVID-19) has emerged as a major cause of morbidity and mortality worldwide. As of this writing, over half a million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been recorded. A global arms race for a vaccine or viable therapy is currently underway. However, most experts project that development of a vaccine will take at least 18 mo^[1], and an effective pharmacologic treatment has yet to be discovered. It therefore appears increasingly likely that COVID-19 will become embedded in the fabric of modern medicine for years to come.

Management of chronic illnesses in patients with COVID-19 should be considered a priority. Hypertension affects over 1.4 billion individuals worldwide^[2] and has been associated with markedly increased morbidity and mortality in the setting of COVID-19^[3,4]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are among the most frequently prescribed antihypertensive agents throughout most of the developed world^[5]. These drugs are safe, well-tolerated, and effective as a first-line therapy. However, emerging evidence suggests that ACEIs and ARBs may increase patient susceptibility to SARS-CoV-2 host cell entry and propagation by upregulation of the angiotensin-converting enzyme 2 (ACE2) viral binding site^[6-8].

There is insufficient data to recommend withdrawal of ACEIs and ARBs among individuals who have been diagnosed with COVID-19. Indeed, most major medical organizations – including the American Heart Association and European Society of Cardiology – recommend maintaining ACEI or ARB therapy in all hypertensive patients with COVID-19. However, we propose that an alternative agent should be considered in patients presenting with COVID-19 and a new diagnosis of hypertension.

Verapamil is a non-dihydropyridine calcium channel blocker that was once used for the management of hypertension. It has largely been supplanted by ACEIs, ARBs, and dihydropyridine calcium channel blockers; in the modern era, verapamil is primarily used for rate control in supraventricular tachycardia, migraine prophylaxis, and hypertension with co-morbid atrial fibrillation. We believe that this drug may be appropriate as a first-line agent for the management of hypertension in patients with COVID-19. Preliminary data from animal studies have demonstrated that verapamil has no effect on ACE2 expression. Furthermore, it has been shown to ameliorate the clinical and pathological course of viral myocarditis in murine models. Indeed, in a study of mice inoculated with encephalomyocarditis virus, investigators found that those treated with verapamil before and/or during infection exhibited markedly less cardiac inflammation and necrosis as compared to an untreated group^[9]. Cardiac involvement – and, specifically, SARS-CoV-2-associated myocarditis – represents a serious and potentially fatal manifestation of COVID-19^[10]. Management of hypertension with a drug that may reduce inflammation in viral myocarditis and does not pose a theoretical risk of promoting COVID-19 proliferation would appear to be a rational strategy to optimize patient outcomes.

Carvedilol, a nonselective β -adrenoreceptor antagonist with additional α_1 -adrenergic blocking properties, represents another promising antihypertensive agent in the setting of COVID-19. Similar to verapamil, carvedilol attenuates inflammation in murine models of acute viral myocarditis. In a study of mice infected with coxsackie B3 virus, those receiving carvedilol exhibited superior survival as compared to an untreated group and those treated with metoprolol^[11]. The mechanism of action is unclear, but it has been postulated that carvedilol exerts anti-inflammatory effects via inhibition of peroxidants in the myocardium. Carvedilol also has the added benefit of reducing heart rate, which may reduce myocyte injury and ventricular remodeling in the setting of myocarditis^[12].

Notably, there are demonstrable anti-inflammatory effects associated with upregulation of ACE2. Indeed, lung function improvement with ACEI or ARB treatment has been described in the setting of COVID-19^[13]. However, irrespective of the purported benefits of ACEIs and ARBs, the potential of these agents to facilitate

viral disease remains under investigation.

In conclusion, we believe that verapamil or carvedilol should be considered for the management of hypertension in patients at risk of COVID-19. The pathogenic mechanisms of SARS-CoV-2 remain under investigation, but data suggest that the ACE2 receptor plays a central role in infection. It is therefore theoretically possible that drugs known to increase ACE2 expression, such as ACEIs and ARBs, could promote COVID-19 proliferation. We are in agreement with the recommendation of major medical societies to maintain ACEI or ARB therapy in individuals who are already receiving treatment. However, patients with a new diagnosis of hypertension who are at risk of COVID-19 would likely benefit from verapamil or carvedilol, as these agents effectively control blood pressure and may conceivably attenuate inflammation and necrosis in SARS-CoV-2 myocarditis.

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