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EDITORIAL

Intravenous drug abuse and tricuspid valve endocarditis: Growing trends in the Middle East Gulf region

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Core tip: It is presumed that tricuspid valve endocarditis is uncommon in the Middle East region. However, recently published global data indicate growing trends in the use of illicit drug abuse in the Middle East Gulf region. The Middle East Gulf States, currently a transit market, are also becoming a growing consumer market in view of the consumption patterns of substance abuse in the youth. This article reviews the epidemiology of illicit drug abuse in the Middle East Gulf region as well as diagnosis and treatment of tricuspid valve endocarditis.

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Abstract

Traditionally, tricuspid valve endocarditis is uncommon in the Middle East region. However, recent global data indicate growing trends in the use of illicit drug abuse, specifically injectable heroin, in the Middle East Gulf region. The presence of many transit port services in the Middle East Gulf States has led to smuggling of substance abuse drugs in the region. The Middle East Gulf States, currently a transit market, are also becoming a growing consumer market in view of the increased substance abuse in the youth. However, there is a paucity of data with respect to the prevalence or incidence of tricuspid valve endocarditis in the region, probably due to underdiagnosis or underreporting. A high index of suspicion of tricuspid valve endocarditis is essential in patients with a history of intravenous drug abuse. This article reviews the epidemiology of illicit drug abuse in the Middle East Gulf region, as well as the diagnosis and treatment of tricuspid valve endocarditis, and calls for all physicians in the region to be vigilant while dealing with intravenous drug abuse.

INTRODUCTION

Illicit drug abuse, including intravenous drug abuse (IVDA), is increasing in the Middle East Gulf region[1,2]. The existence of many transit port services in the Middle East Gulf States (Saudi Arabia, United Arab Emirates (UAE), Oman, Bahrain, Kuwait and Qatar) has contributed to smuggling of substance abuse drugs in the region[1,2]. The Middle East and Gulf, traditionally transit markets, are also increasingly becoming consumer markets in view of their geographical location and the young population of the region (60% below 15 years). As a direct consequence, this may have led to increasing correlates of drug abuse such as overdose, dependence, psychosis, suicide, road traffic accidents, cutaneous complications, thrombophlebitis of veins, myocardial infarction, pulmonary embolism, infective endocarditis

Figure 1 Map of Middle East Gulf States. UAE: United arab emirates.

(IE) specifically tricuspid valve endocarditis (TVE), pneumonia, pulmonary tuberculosis, septicemia, transmission of blood-borne infections (human immune deficiency virus (HIV)/hepatitis) and have also impacted on increased mortality due to overdose[2]. However, there is a paucity of data with respect to the incidence of tricuspid valve endocarditis in this region, probably due to underdiagnosis or underreporting. In addition, there is a lack of epidemiological studies documenting the burden of disease in terms of prevalence and related morbidity and mortality due to drug abuse in this region. This review article summarizes the epidemiology of illicit drug abuse in the Middle East Gulf Region (Figure 1) in relation to the diagnosis and treatment of TVE.

EPIDEMIOLOGY AND BURDEN OF ILLICIT DRUG ABUSE IN THE MIDDLE EAST GULF REGION

The commonly abused illicit substances can be broadly grouped as stimulants (amphetamines/methamphetamines/crystal meth/speed/captagon tablets/khat/3,4-methylenedioxy-N-methylamphetamine/ecstasy, lysergic acid diethylamide, cocaine/crack and cannabis/marijuana/ganja/hashish/bhang), hypnotics (barbiturates and methaqualones) and opiates (morphine, heroin/smack/brown sugar, opium, methadone). Among these, the most commonly injected drug is heroin[1]. However, morphine, amphetamines/methamphetamines, and cocaine are also common[1].

Globally, the United Nations Office on Drugs and Crime (UNODC), estimates that there were about 149-271 million people aged 15-64 years (3.3%-6.1%) who used an illicit drug at least once in 2009[1]. A large systematic review which included UNODC data reported 125-203 million people to be cannabis users, 15-39 million were opioid, amphetamine or cocaine users, and 11-21 million IVDAs[2]. The highest levels of use were in North America, Western Europe and Oceania. The Middle East data suggested that 6-12 million (2.4%-4.8%) were cannabis users, 2-3 million were opioid users (0.8%-1.4%), 0.4-4 million were amphetamine users (0.2%-1.7%) and 0.04-0.6 million were cocaine users[2]. Opioid use, including heroin, had an estimated 12 to 21 million users globally. The highest rates of opioid use was reported in the Middle Eastern regions, where up to 1.4% of the population aged 15 to 64 had tried the drug at least once in 2009[2].

Data from the Eastern Mediterranean Regional Office of the World Health Organization suggest a prevalence of illicit drug use disorders at the rate of 3500 per 100000 population and that of injecting drug use to be 172 per 100000 population[3]. A report from UAE estimated that about 40% of all illegal drugs in the world are sold in the Gulf region[4]. The same report noted that the mean age of new drug abusers has dropped from 17-18 years to 10 years[4]. Most of the illicit drugs destined for African and European countries transited *via* the Gulf States, with significant leakage to the Gulf States[4]. In a report from Oman, quoting the Ministry of Health, 1521 drug misuse-related cases were reported in the period 2006-2011 and the most common mode of misuse was IVDA (66%)[5].

In 2002, a report from Al-Amiri Hospital in Kuwait estimated the presence of 18000-20000 drug users in this small Gulf State, the equivalent of 1% its total population[6]. Unemployment, excess disposable income, boredom and frustration were cited as important factors for the youth to take up drugs. In addition, drug dealers easily get couriers among the thousands of expatriate laborers entering Kuwait[6]. Another survey conducted among university students in Kuwait revealed that the total lifetime prevalence of illicit drug use was 14.4% and the most frequently used illicit substance was marijuana (11%)[7]. On multivariate logistic regression analysis, drug use was significantly associated with age, poor academic performance, high family income, being an only child in the family, divorced parents and graduation from a private high school[7].

TRICUSPID VALVE ENDOCARDITIS PATHOGENESIS

Right sided endocarditis accounts for 5%-10% of all IE and predominantly affects the tricuspid valve (TV)[8-10]. TVE commonly occur among IVDAs[11,12]. The cause for the increased prevalence of TVE in IVDAs is multifactorial. Frontera *et al*[10] suggested possible mechanisms which include: (1) recurrent episodes of particulate matter bombardment (drug solutions may contain particulate matter like talc) leading to damage of TV; (2) TV intimal damage, vasospasm (cocaine induced) and thrombus formation due to injected drugs; (3) increased right sided cardiac turbulence secondary to drug-induced pulmonary hypertension (buprenorphine); (4) increased expression of matrix molecules on the TV which are capable of binding microorganisms in IVDAs; (5) injection of large

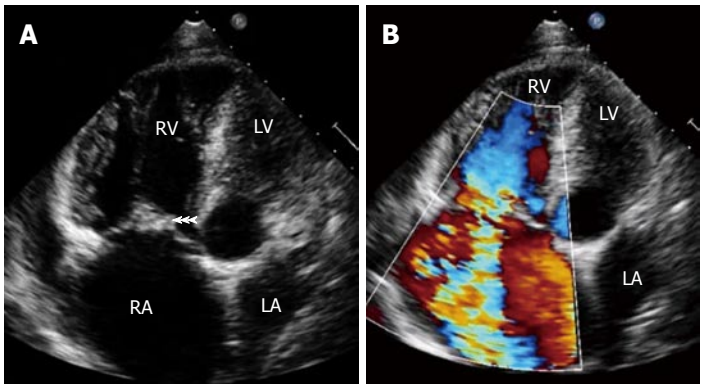

Figure 2 Transthoracic echocardiography showing (A) large vegetation attached to tricuspid valve leaflets (arrowheads) in a patient with intravenous drug abuse and septic pulmonary emboli. Note hugely dilated right atrium and right ventricle and (B) severe tricuspid regurgitation. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle.

"bacterial loads" from contaminated drug solutions causing IE; and (6) IVDA-related "immune dysregulation" with or without coexistent HIV infection. In addition, poor injection hygiene (*e.g.*, lack of skin cleaning before injecting), injecting with unsterile needles, multiple needle sharing and injecting contaminated drug solutions which tends to introduce high bacterial loads.

WORLDWIDE INCIDENCE OF TVE

Among the published reports, the overall incidence of IE among IVDAs ranges from 1.5-20 per 1000 drug user per year[10]. In the United States, the incidence is estimated at 1.5 to 3.3 cases per 1000 person-years[12]. From the Western series, acute infection is responsible for 60% of all hospital admissions among IVDAs. Among these acute infections, TVE is implicated in 5%-15% of these cases[12,13]. It is also estimated that the incidence of IE in IVDAs is 2%-5% per year and is responsible for 5% to 10% of the overall death rate[14]. In the large multinational International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) evaluating 2781 patients with IE, 10% of the patients were IVDAs[15].

INCIDENCE OF TVE IN THE MIDDLE EAST

There are few published reports of IE from Middle East Gulf States. Among these studies, IVDA is reported in only 1 study. Even although the Middle East region has the highest prevalence of IVDA among all countries in the world[2], the incidence of TVE and IVDA is reported to be very low. This may be due to either underdiagnosis or underreporting. In a study from Oman published in 2003 and involving 90 patients with IE, there were no patients with TVE or with a history of IVDA[16]. This was similar to studies from Yemen (72 patients) and Kuwait (60 patients), with no involvement of TV or history of IVDA[17,18]. However, between 2006 and 2011, 7 cases of TVE with 3 of them reporting active IVDA were reported from Oman (personal communication). In a study from Saudi Arabia among 83 patients with IE, 4 cases of native TV involvement and 1 case of prosthetic TV involvement were reported, but with no mention of IVDA[19]. In a second study from Saudi Arabia, out of 47 cases of endocarditis, TV was affected in 3 patients (6.4%), pulmonic valve in 2 patients and both pulmonic valve and TV in 1 patient (2.1%). In addition, 2 (4.3%) patients gave a history of IVDA[20]. A study from Lebanon also reported 7% (6/91) of patients with IE had TVE and no IVDA[21].

CLINICAL MANIFESTATIONS

The majority of IVDAs with TVE are young, between 20-40 years of age, and predominantly men (male:female ratio, 4 to 6:1)[12]. The most common presenting manifestations of TVE are persistent fever, bacteremia and multiple pulmonary emboli[9,11]. Respiratory symptoms are more common in TVE than left sided endocarditis. Dyspnea, pleuritic chest pain, cough and hemoptysis are the most common symptoms. Patients can present with metastatic abscesses in lungs that may lead to repeated episodes of dyspnea with hypoxemia and may mimic pulmonary embolism. However, left sided endocarditis in IVDAs is not uncommon and when any peripheral emboli or stroke occur, either left sided endocarditis or paradoxical embolism should be strongly suspected in patients with IVDA[11]. It is important to note that history and physical examination are not diagnostic of TVE in patients with IVDA. There is an absence of underlying heart disease in two-thirds of the patients. Symptoms and signs may be nonspecific. In about 65% of IVDAs with TVE, heart murmurs are not appreciated[11]. This is in view of normal or mildly elevated right ventricular pressures resulting in a low velocity less turbulent tricuspid regurgitation (TR) jet[11]. Generally, respiratory findings dominate the clinical, chest X-ray and computed tomography (CT) scan features. They can even mimic other respiratory infections like pulmonary tuberculosis[22].

DIAGNOSIS

The two most important diagnostic features of TVE in patients with IVDA are echocardiographic evidence of vegetation (Figure 2A) and the presence of septic embolic phenomena[11]. In addition, moderate to severe tricuspid regurgitation may be present (Figure 2B). In IVDAs with IE, TV is commonly involved in about 60%-80% of cases, with reported mortality of 5%-10%[9]. In a study of 105 IVDAs with IE, 86% were right sided and 14%

were left sided[11]. In IVDAs, both sides of the heart are usually involved simultaneously in 5% to 10% of cases[13]. TV vegetations generally grow to a larger size (> 2 cm) due to low pressure in right heart chambers and thus may mimic fungal endocarditis[11]. Vegetations may embolize and can be seen in the right ventricle or pulmonary artery or entrapped in the tricuspid chordal apparatus[11,22]. Transthoracic echocardiography (TTE) plays an important role in the diagnosis of TVE. Many IVDAs are young and generally have good echo windows, resulting in good high resolution images[11]. In addition, as the TV is relatively nearer to the transducer, excellent images can be obtained by TTE. TEE is indicated in patients with poor echo window or in those with initial negative TTE in whom there is high index of suspicion of TVE[11]. The diagnostic yield of TTE is comparable with that of TEE in IVDAs[23].

Duke's criteria have been predominantly applied for left sided endocarditis and have not been studied specifically in TVE. However, the two major criteria of typical echocardiographic features of TVE along with positive blood cultures with a typical organism should be regarded as diagnostic of TVE[11]. Blood culture is positive in a high proportion of TVE. When the culture is negative, it is usually due to prior antibiotic use or due to rare organisms such as Bartonella and HACEK organisms. The predominant organism of TVE in IVDAs is Staphylococcus aureus (60%-90%)[9-15]. Other organisms causing TVE are pseudomonas aeruginosa, other gram-negative bacilli, poly-microbial infections, fungi and group B streptococci[9-15]. In a study, the incidence of IE was 17% among all staphylococcal bacteremia patients and 46% among IVDAs[13]. In another study, 24% of IVDAs developed methicillin resistant staphylococcus aureus, of whom 41% developed IE[24]. Thus, in IVDAs, if patients develop staphylococcal bacteremia, nearly 50% of them go on to develop TVE. In another study among IVDAs presenting with fever to emergency departments, negative predictors of TVE were lack of skin infection, tachycardia, hyponatremia, pneumonia on chest radiograph, history of endocarditis, thrombocytopenia and heart murmur. The best criteria combination of lack of skin infection, tachycardia and cardiac murmur had a sensitivity and negative predictive value of 100%[25].

COMPLICATIONS

Septic pulmonary embolism in patients with TVE occurs in 75% to 100% of patients[26]. It may cause pulmonary infarction, pulmonary abscesses, bilateral pneumothoraces, mycotic aneurysms of pulmonary arteries, pleural effusions and empyema[9,11]. The chest X-ray may show pulmonary infiltrates or opacities in about 56% of radiographs at presentation[11]. Typical chest manifestations on CT scan due to emboli are pulmonary infiltrates, obstruction, nodules or wedge shaped opacities with or without cavitations and abscesses suggesting septic emboli, which are seen in 80% of such patients[9-14]. The use of large proximal veins (femoral veins) in IVDAs may result in life-threatening septic deep venous thrombosis and pulmonary embolism[27].

Right heart failure is common due to acute pulmonary hypertension or severe TR or TV obstruction[9,11]. Large vegetations can cause tethering of the septal and lateral valve leaflets, causing the TV to remain open throughout systole and leading to severe TR. In addition, prolapse, perforation, right ventricular dilation and flail leaflet due to disruption can all lead to severe TR. Large vegetations can even protrude through patent foramen ovale into the left atrium[28]. Paravalvar abscess formation occurs infrequently. Hypoxemia and paradoxical embolism can occur due to right to left shunting through a patent foramen ovale[11].

MANAGEMENT AND PROGNOSIS

Uncomplicated TVE is successfully treated medically in 80% of patients, with only 20% needing surgical intervention[12,29]. The reason why TVE responds well to medical therapy is that right sided heart involvement, even when severe, often allows time for medical treatment because of the greater tolerance for TR and pulmonary embolization[29]. Hence, it is recommended to wait before surgical intervention if possible until sepsis resolves with antibiotic treatment[29]. Right sided involvement, younger age and lack of pre-existing heart disease or other underlying diseases have been thought to explain the better prognosis of Staphylococcus aureus endocarditis among IVDAs than in the general population.

In methicillin-sensitive staphylococcal aureus native-valve endocarditis, beta-lactamase-resistant penicillins, like flucloxacillin, oxacillin or glycopeptides (teicoplanin or vancomycin), combined with gentamycin (for 2 wk) is recommended[9]. In uncomplicated TVE, medical treatment should be continued for 4-6 wk[12]. However, IVDAs pose a unique challenge in the treatment as they are poor or non-compliant to medication and follow-up, get early self-discharge from hospital and may go back to injecting drugs again once discharged from hospital. This naturally leads to high rates of relapse and re-infection[30]. Given the low likelihood of adherence to a 4 wk course of antimicrobials among IVDAs, shorter courses of therapy, with a combination of β-lactam with or without an aminoglycoside (for 2 wk) have become an accepted standard[12,30]. However, in a few centers in highly selected IVDA IE patients, with appropriate counseling and monitoring, it was possible to treat with outpatient parenteral antibiotic therapy using peripherally inserted central catheter lines[31]. Poly-microbial endocarditis is more frequent in IVDA, which may need long-term suppressive therapy, specifically if fungal endocarditis is present[32]. The most important organisms in poly-microbial IE in IVDAs are: Staphylococcus aureus, Streptococcus pneumonia and Pseudomonas aeruginosa, as well as mixed cultures of Candida spp. and bacteria[33].

The European Society for Cardiology guidelines made

some recommendations for operative indications for TVE in the active stage. These recommendations are: (1) refractory right heart failure secondary to severe persistent TR; (2) IE caused by organisms which are difficult to eradicate (*e.g.*, persistent fungi) or bacteremia for at least 7 d despite adequate antibiotic therapy; and (3) TV vegetations > 20 mm which persist after recurrent pulmonary emboli with or without concomitant right heart failure[9]. Surgical options include vegetectomy, valvulectomy, valve repair/reconstruction with annuloplasty ring or replacement (either mechanical or bioprosthesis valves)[29,34]. A few authors opine that in IVDAs, vegetectomy and valve repair is preferred, avoiding artificial material and thus preventing prosthetic valve endocarditis[29,35,36]. If a valve replacement is done, some authors prefer a bioprosthesis valve as it could be better in terms of prognosis than a mechanical valve[36-38]. However, in a few studies, both mechanical and bioprosthesis valves have been successfully implanted in IVDAs with a similar 15 year survival (47.8% for mechanical *vs* 46.7% for bioprosthesis valves) and re-operation free survival (53% for mechanical *vs* 52% for bioprosthesis valves)[39,40].

Prognosis in TVE is generally good and in-hospital mortality is less than 10%[9-14]. Vegetation length > 20 mm and fungal etiology were found to be the main predictors of death in right sided IE in IVDAs[41,42]. In the ICE-PCS registry, 22% of TVE patients needed surgery and in-hospital mortality was 6%[15]. In patients with IE and HIV infection, there was higher total mortality at 2 mo, specifically in those with a CD4 count below 200 per microl[43,44]. In addition, any left sided involvement and age greater than 35 years are independently associated with mortality[45-47]. In a study, IVDAs with IE admitted to intensive care unit had very high mortality (27%), mainly due to sepsis and septic embolization[48]. In patients with repeated IVDA and endocarditis, the prognosis is poor and few authors are of the opinion that these patients should be offered valve replacement only once. If they develop a second episode of endocarditis, they should not be offered another valve replacement surgery[49,50].

CONCLUSION

In conclusion, recent reports indicate increasing trends in IVDA in the Middle East region. However, there is lack of reports about TVE, probably due to underdiagnosis or underreporting. TVE can mimic other respiratory diseases and may mislead in obtaining early diagnosis. A high index of suspicion of TVE is essential in patients with IVDA. In addition to already prevailing regulations and strict laws against drug trafficking in the Middle East Gulf region, programs to increase public awareness about the harmful effects of drug abuse are essential. Furthermore, a de-addiction drive among the youth in this region, anti-drug campaigns and the establishment of more rehabilitation centers are the need of the hour for eradicating this menace.

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MINIREVIEWS

Taurine supplementation in spontaneously hypertensive rats: Advantages and limitations for human applications

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Abstract

Taurine (2-aminoethanesulfonic acid) is a β-amino acid found in many tissues particularly brain, myocardium, and kidney. It plays several physiological roles including cardiac contraction, antioxidation, and blunting of hypertension. Though several lines of evidence indicate that dietary taurine can reduce hypertension in humans and in animal models, evidence that taurine supplementation reduces hypertension in humans has not been conclusive. One reason for the inconclusive nature of past studies may be that taurine having both positive and negative effects on cardiovascular system depending on when it is assessed, some effects may occur early, while others only appear later. Further, other consideration may play a role, *e.g.*, taurine supplementation improves hypertension in spontaneously hypertensive rats on a low salt diet but fails to attenuate hypertension on a high salt diet. In humans, some epidemiologic studies indicate that people with high taurine and low salt diets display lower arterial pressure than those with low taurine and high salt diets. Differences in techniques for measuring arterial pressure, duration of treatment, and animal models likely affect the response in different studies. This review considers both the positive and negative effects of taurine on blood pressure in animal models and their applications for human interventions.

Key words: Arterial pressure; Circadian rhythm; Hypertension; Spontaneously hypertensive rat; NaCl; Taurine

Core tip: Many reports indicate that dietary taurine can reduce hypertension in humans and in animal models; however, the hypotensive effect of taurine supplementation depends on many factors. Taurine supplementation improves hypertension in spontaneously hypertensive rats on a low salt diet but fails to attenuate hypertension on a high salt diet. In humans, some epidemiologic studies suggest that people with high taurine and low salt diets display lower arterial pressure than those with low taurine and high salt diets. This review considers both positive and negative effects of taurine on blood pressure in animal models of hypertension to apply for human interventions.

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INTRODUCTION

Hypertension is a risk factor for both acute and chronic adverse diseases, including stroke and cardiovascular disease[1,2]. Arterial blood pressure displays a diurnal variation, *i.e.*, it is elevated during active behavior periods and decreased during quiescent periods (*e.g.*, sleep)[3]. Thus, in humans, arterial pressure typically increases during the daytime and decreases during the nighttime[4]. In contrast, rats are generally nocturnal animals, and thus their diurnal rhythm is reversed, *i.e.*, their arterial pressures are elevated at night during active behavior, and decreased during the daytime[5]. Established hypertension is associated with decreased amplitude of diurnal arterial pressure variation, in that arterial pressure fails to decrease in the non-active period (*e.g.*, sleep), especially in older adults. In contrast, during the development of hypertension, the arterial pressure amplitude is typically greater than normal. Spontaneously hypertensive rats (SHR) display a circadian rhythm that is directly correlated with activity. However, in adult SHR compared to other strains, arterial pressure declines slowly in the morning (as the animals begin to sleep) and remains in the hypertensive range throughout the sleep period (mean arterial pressure > 110 mmHg)[5,6]. Further, high NaCl diets initially increase arterial pressure in the nighttime and more slowly increase daytime arterial pressure in both SHR and Wistar Kyoto rats (WKY; a normotensive control for SHR). This is especially evident after four nights of high NaCl treatment[5]. In addition, in SHR, high NaCl diets significantly increase daytime arterial pressure after a week of feeding, but they have little effect at that time point on daytime arterial pressures of normotensive WKY[5,7]. In the SHR on either a high or basal NaCl diet, sympathetic blockade greatly decreases arterial pressure rhythm, suggesting that the sympathetic nervous system contributes significantly to SHR hypertension, especially during its development[8,9].

Taurine (2-aminoethanesulfonic acid) is a non-protein, free amino acid found in many tissues particularly brain, myocardium, liver, muscle, and kidney[10-12]. Several lines of evidence indicate that dietary taurine can reduce hypertension in humans and in animal models[13]. For examples, dietary taurine attenuates hypertension in adult SHR[14] and deoxycorticosterone acetate and high NaCl (DOCA-NaCl) rats[15]. Sugar-induced hypertension can also be greatly blunted by dietary taurine and exacerbated by taurine deficiency[16]. Epidemiological studies indicate that people consuming high taurine diets display a low incidence of hypertension and other cardiovascular diseases[17]. Taurine supplementation was also reported to decrease systolic and diastolic blood pressure in young patients with borderline hypertension[18], but not in healthy men[19]. In addition, perinatal taurine exposure affects adult susceptibility to sugar-induced hypertension in rats[20-25].

De novo taurine synthesis is limited in rats and humans; therefore, dietary taurine is needed to maintain taurine in the body, which is especially important during developmental periods[11,12]. Intestinal taurine absorption is *via* high affinity sodium chloride-dependent active transport[26]. Thus, a high luminal sodium concentration accelerates intestinal taurine absorption, and high taurine transport increases sodium absorption into the blood. This complex relation has been suggested as the reason that in previous studies, taurine supplementation did not prevent NaCl-induced hypertension in SHR[27]. There are no experiments examining the effect of taurine on 24-h arterial pressure in animal models, and such information could elucidate the mechanisms underlying the failure of taurine to reduce arterial pressure in these models. This article reviews the advantage and limitation of taurine's antihypertensive action based on 24-h arterial pressure monitoring data in SHR.

24-H ARTERIAL PRESSURE DATA

In 1978, Nara *et al*[14] demonstrated that dietary taurine decreases hypertension in SHR. This finding is later supported by both experimental and epidemiological studies[13,17]. The effective dose of taurine has been between 1%-5% in drinking water for most of animal models of hypertension, and the duration of treatment has usually been more than 2 wk. For examples, Trachtman *et al*[28] demonstrate that 1% taurine in drinking water significantly decreases arterial pressure by 4 wk of treatment and reaches a maximum antihypertensive effect by 16 wk of treatment. Although taurine supplementation prevents hypertension in DOCA-NaCl sensitive rats, it does not blunt NaCl-sensitive aspects of hypertension in stroke-prone SHR[27]. However, this finding is based on acute arterial pressure measurements that were done during the normal sleep period (daytime), when the rat's arterial pressure is typically low.

To clarify the diurnal effect of taurine on arterial pressure, we did experiments in young SHR. At 7 wk of age, rats were anesthetized with isoflurane, and the abdominal aorta was exposed *via* a midline abdominal incision. After a segment of aorta below the renal artery was cleared, the flexible tip of the pressure sensing telemetry transmitter probe was inserted and secured to the vessel with tissue adhesive. The transmitter signal was then tested and the transmitter was surgically sutured to the abdominal wall. After surgically closing the wound, all rats were caged individually in clear cages and recovered on a basal NaCl diet (0.6%) for one week. Thereafter, the rats were fed a high NaCl diet (4.0%; w/w) and given 3% taurine in the drinking water (Taurine; $n = 12$) or water alone (Control, $n = 7$) for three weeks. This high NaCl diet has been commonly used to increase arterial pressure in SHR[27], and the 3% taurine in the drinking water has been used previously to attenuate hypertension in several animal models including SHR on a basal NaCl diet[13].

On a basal (0.6%) NaCl diet, both control and taurine-fed groups displayed a similar diurnal variation of mean arterial pressure, *i.e.*, mean arterial pressures were high at night but low in daytime, and they were not significantly different between groups (Figure 1). The high NaCl intake increased daytime and nighttime arterial pressures in both

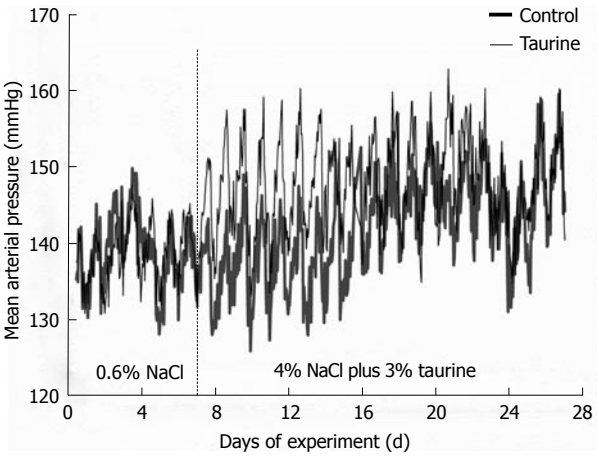

Figure 1 Group average, mean arterial pressures in control (thick line) and taurine (thin line) groups. The values were averaged from seven (control) and twelve (taurine) rats and the standard errors of means were not included to avoid confusion. Significant differences between groups ($P < 0.05$ by one-way analysis of variance and post hoc Duncan's multiple range test) were consistently observed in nighttime but not daytime mean arterial pressures from day 1 to day 9 of high salt treatment. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began.

groups, but with different time courses. Throughout the study, taurine had no effect on daytime arterial pressures (Table 1). In contrast, nighttime arterial pressures were significantly higher in the taurine (compared to control) group from the first to ninth night of treatment, but thereafter, taurine did not result in any significant difference in the high NaCl fed SHR for the remainder of the study. The arterial pressure analysis indicated that after starting a high NaCl diet, the taurine group displayed a rapid increase in mean nighttime arterial pressure within the first night, with arterial pressure approaching its maximum in the taurine-treated rats by night 2 (Figures 2 and 3). Thereafter, the nighttime mean arterial pressure of taurine group remained at nearly the same high level throughout the remainder of the study (3 wk).

These data confirm that taurine supplementation does not affect NaCl-induced daytime hypertension in the SHR, and thus, has little effect on mean average precision or on the eventual maximum level of arterial pressure in this model. Unexpectedly, the data also indicate that rather than being hypotensive or having no effect on arterial pressure in the SHR on a high NaCl diet, taurine supplementation accelerates the development of NaCl-sensitive hypertension during the nighttime.

ADVANTAGES AND LIMITATIONS OF TAURINE SUPPLEMENTATION

In most hypertensive rat and mouse models, a high (compared to basal or low) NaCl diet slowly increases nighttime arterial pressure after about 4 d of feeding, but the high dietary NaCl does not increase daytime arterial pressures until much later in these models[5,29,30]. This effect appears to be a consequence of the high dietary NaCl intake leading to Na^+ and fluid retention, especially during the active period. This may be exacerbated by taurine supplementation if the taurine increases intestinal sodium absorption, which in SHR on a high NaCl diet may lead to increased NaCl-sensitive hypertension that offsets the normal hypotensive action of taurine.

The underlining mechanism for this effect likely relates to dietary NaCl and fluid retention that leads to increased sympathetic nerve activity, resulting in increased arterial vasoconstriction and cardiac output and ulti-

Table 1 Noon and midnight mean arterial pressures in control (high salt alone, $n = 7$) and taurine (high salt plus taurine, $n = 12$) rats before and after treatment

Days of treatment	Control (mmHg)		Taurine (mmHg)	
	Noon	Midnight	Noon	Midnight
Before	128 ± 5	136 ± 4	133 ± 2	140 ± 2
1	129 ± 3	139 ± 4	136 ± 3	147 ± 2[a]
3	130 ± 3	140 ± 3	133 ± 2	150 ± 4[a]
7	138 ± 6	136 ± 4	147 ± 5	151 ± 3[a]
14	137 ± 6	143 ± 8	145 ± 2	152 ± 5
21	147 ± 5	149 ± 8	142 ± 3	148 ± 3

Data are mean ± SE; [a]$P < 0.05$ compared to midnight control by one-way analysis of variance and post hoc Duncan's multiple range test; No significant difference in noon mean arterial pressures between groups.

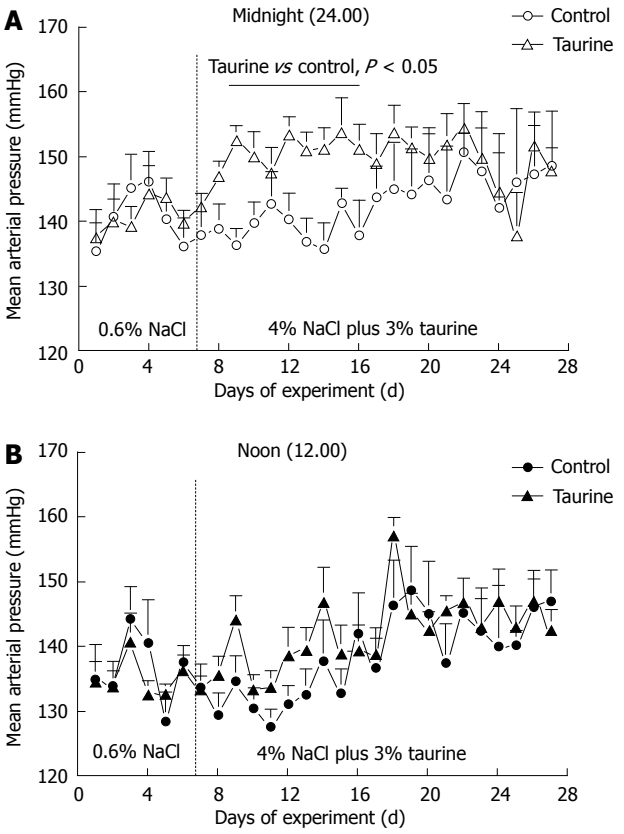

Figure 2 Group averages of mean arterial pressure in control ($n = 7$) and taurine ($n = 12$) treated groups at midnight (A) and at noon (B). The daytime mean arterial pressures were not significantly different between groups throughout the study. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began. Statistical comparisons were performed by one-way analysis of variance and post hoc Duncan's multiple range test.

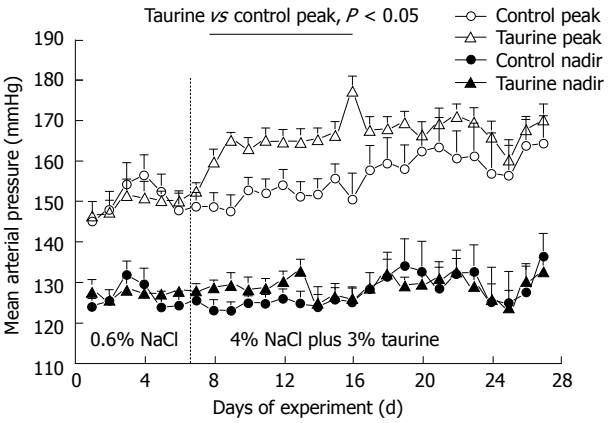

Figure 3 Peak (open symbols) and nadir (closed symbols) mean arterial pressures in control (n = 7) and taurine treated (n = 12) groups. The vertical dashed line at day 7 indicates the day that the high NaCl diet and taurine supplementation began. Statistical comparisons were performed by one-way analysis of variance and post hoc Duncan's multiple range test.

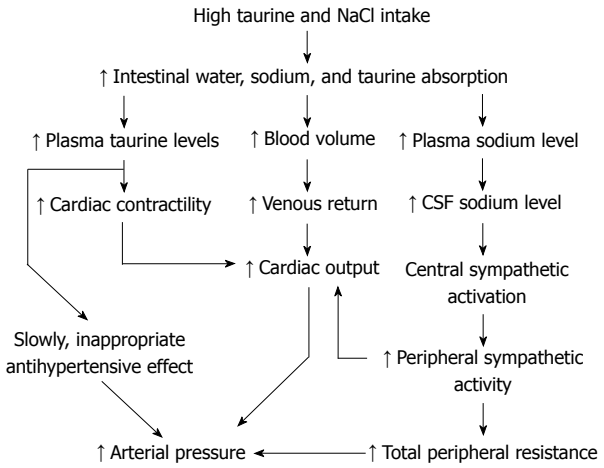

Figure 4 Possible pathways explaining the nighttime increase in arterial pressure after a combination of taurine supplementation and high salt diet in spontaneously hypertensive rats. CSF: Cerebrospinal fluid.

mately an increase in hypertension (Figure 4). Increased cardiac output significantly contributes to initial phase of essential hypertension, while increased total peripheral resistance sustains it[31,32]. In rats, 24-h measurements of plasma sodium concentration indicate that plasma Na^+ has a circadian rhythm that is opposite in phase to diurnal variation of mean arterial pressure[6]. Further, in SHR and WKY, a high NaCl diet increases daytime and nighttime plasma sodium levels, but in SHR compared to WKY on the high NaCl diet, the normal nighttime decrease in plasma sodium is greatly blunted, *i.e.*, plasma sodium remains high during the active phase[6]. This early failure of plasma Na^+ to decrease during the active period parallels the rise in nighttime arterial pressure in SHR.

Since intestinal taurine is absorbed *via* a high affinity sodium chloride-dependent active transport[26], high luminal sodium concentration can accelerate intestinal taurine absorption, and high taurine transport increases sodium absorption into the blood. This potentially causes an early increase in plasma Na^+. Further, in Dahl-NaCl sensitive rats, taurine supplementation alone increases sodium and fluid retention after a month on high NaCl diets[33]. It is likely that in the high taurine and NaCl fed SHR, taurine-facilitated Na^+ absorption and associated water absorption rapidly increase nighttime arterial pressure, which is already significantly elevated on the first night of high NaCl diet.

The increase in blood pressure in SHR on taurine and a high NaCl diet also may relate to altered brain control of sympathetic nervous system activity and a resulting increase in vasoconstriction. Huang *et al*[34] demonstrates that in SHR and Dahl-NaCl-sensitive rats, a high NaCl diet (8% NaCl) increases cerebrospinal fluid Na^+ concentration within a few days of treatment and 1-2 d before a rise in arterial pressure. This effect is not observed in WKY and Dahl-NaCl-resistance rats. Further, disruption of the hepatorenal natriuresis/diuresis pathway by hepatic denervation heightens nighttime hypertension in WKY rats[30], indicating that the nervous system normally activates the hepatorenal reflex to reduce plasma Na^+ concentration by activating renal Na^+ excretion. This is particularly effective, since the receptors in the liver very quickly monitor the concentration of Na^+ that enters through the gut. Further, an abnormality in this feedback underlies NaCl and fluid retention observed in nephrotic syndrome[35]. These studies suggest that in SHR, high NaCl intake may lead to both peripheral and/or central increases in Na^+ concentration, leading to increased sympathetic nerve activity and increased arterial pressure. At least in its developmental phase, NaCl sensitivity in SHR appears to primarily result from sympathetic nervous system overactivity and not alterations in the renin-angiotensin system[7,36].

The hypertensive interactions between dietary NaCl and taurine may be mediated, in part, by taurine effects on Na^+ transport across the blood-brain barrier. As in the gut, taurine is transported across the blood-brain barrier by a Na^+-dependent, carrier-mediated mechanism[37]. SHR display low taurine content in brain[38,39] and heart[40]. In the SHR brain, taurine content is especially low in the hypothalamus and rostral ventrolateral medulla, both key areas that regulate cardiovascular function[41,42]. In SHR on a basal NaCl diet, long-term (but not short-term) taurine supplementation increases brain taurine levels to those of the WKY and decreases hypertension and related disorders, *e.g.*, cardiac hypertrophy and renal dysfunction. In SHR, the long-term taurine treatment is probably necessary because SHR display slow taurine transport across blood-brain barrier[37], thus decreasing taurine's ability to rapidly accumulate in the brain after acute treatment. In the short-term study, taurine supplementation may have increased cerebrospinal fluid Na^+ concentration in the high NaCl fed SHR before it is able to increase taurine concentration in the brain, leading to the early activation of the sympathetic nervous system[9,43].

In SHR on a basal NaCl diet, overactivity of both the sympathetic nervous system and the renin-angiotensin system contribute importantly to the development of

hypertension[7,36], and taurine supplementation reduces both mechanisms in SHR on a basal NaCl diet[13]. Sugar-induced hypertension is also maintained by overactivity of both the sympathetic nervous system and the renin-angiotensin system and is associated with mild insulin resistance[44]. Chronic treatment with taurine improves insulin sensitivity and reduces hypertension in these models of hypertension[16]. The hypotensive action of taurine in DOCA-NaCl rats is also related to inhibition of sympathetic nervous system activity[45]. In humans, taurine supplementation decreases plasma epinephrine levels in borderline hypertension, suggesting a sympathetic nervous system mechanism[18]. Further, epidemiological studies indicate an inverse relationship between taurine-rich diets and sympathetic nervous system activity in hypertension[17]. However, our 24-h arterial pressure study suggests that, while dietary taurine supplementation is antihypertensive in most hypertensive models, at least in SHR, the combination of high dietary NaCl and taurine supplementation causes an early acceleration in the development of NaCl-sensitive hypertension and does not lead to any reduction in arterial pressure at later time points. This indicates that further studies in animals and humans are needed to explore the interactions between dietary supplements and NaCl intake.

Taurine possess positive inotropic effects on cardiac muscle particularly in *in vitro* experiments (*i.e.*, an acute effect) and in taurine deficient animals[46-48]. These actions are related to taurine-increased calcium inward current and calcium release from sarcoplasmic reticulum. More taurine intake during the nighttime may increase plasma taurine (and likely cardiac taurine concentration), leading to increased cardiac contractility in the nighttime compared to the daytime. In subjects on high taurine and NaCl diets, this positive inotropic effect may increase the Starling's effect of increased venous return due to increased blood volume, leading to increased cardiac output and eventually increased arterial pressure.

CONCLUSION

Diets high in taurine prevent or decrease hypertension in many animal models of hypertension and in humans[13,17]. In SHR fed a basal NaCl diet, taurine supplementation significantly blunts the development of hypertension; however, taurine supplementation fails to decrease NaCl-induced hypertension in SHR. In contrast to our hypothesis that taurine supplementation lowers arterial pressure, taurine accelerates the hypertensive response to a high NaCl diet in this animal model. The taurine supplementation initially accelerates arterial pressure in SHR fed a high NaCl diet during the nighttime but not the daytime. After the initial 9 d of the high NaCl diet, taurine no longer increases nighttime arterial pressure above that displayed by non-treated SHR on the high NaCl diet. These data suggest that while taurine is generally beneficial to arterial pressure in hypertensive situations, dietary taurine supplementation may have early adverse effects when paired with a high NaCl diet.

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The importance of avoiding unnecessary right ventricular pacing in clinical practice

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Abstract

Symptomatic bradycardia is effectively treated with the implantation of a cardiac pacemaker. Although a highly successful therapy, during recent years there has been a focus on the negative effects associated with long-term pacing of the apex of the right ventricle (RV). It has been shown in both experimental and clinical studies that RV pacing leads to ventricular dyssynchrony, similar to that of left bundle branch block, with subsequent detrimental effects on cardiac structure and function, and in some cases adverse clinical outcomes such as atrial fibrillation, heart failure and death. There is substantial evidence that patients with reduced left ventricular function (LVEF) are at particular high risk of suffering the detrimental clinical effects of long-term RV pacing. The evidence is, however, incomplete, coming largely from subanalyses of pacemaker and implantable cardiac defibrillator studies. In this group of patients with reduced LVEF and an expected high amount of RV pacing, biventricular pacing (cardiac resynchronization therapy) devices can prevent the negative effects of RV pacing and reduce ventricular dyssynchrony. Therefore, cardiac resynchronization therapy has emerged as an attractive option with promising results and more clinical studies are underway. Furthermore, specific pacemaker algorithms, which minimize RV pacing, can also reduce the negative effects of RV stimulation on cardiac function and may prevent clinical deterioration.

Key words: Cardiac pacing; Right ventricular pacing; Heart failure; Managed ventricular pacing; Cardiac resynchronization therapy; Implantable cardioverter-defibrillator

Core tip: A high amount of long-term right ventricular (RV) pacing produces ventricular dyssynchrony and clinical deterioration in patients with reduced left ventricular ejection fraction (LVEF). In this patient group, cardiac resynchronization therapy has been shown to improve clinical outcomes and should be considered before a conventional pacemaker. In subjects with normal LVEF, the deleterious effects of RV pacing is less clear; however, specific pacemaker algorithms that minimize RV pacing may improve clinical outcomes in selected patients. Future studies will help to better identify those at risk of suffering the negative effects of RV pacing and define the correct use of preventive therapeutic strategies.

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INTRODUCTION

Cardiac pacing has greatly improved the prognosis of patients with symptomatic bradycardia, approximating that

Table 1 Summary of the major pacing and implantable cardioverter-defibrillator randomized trials that compared atrial (AAI or DDD) *vs* ventricular based pacing strategies

Ref.	Patients (*n*)	Follow-up (yr)	Pacing/ICD indication	Study groups	Endpoints	Results
Danish study[8] (1997)	225	5.5	SSS	AAI *vs* VVI	All-cause mortality, CV mortality, AF, stroke, HF, and AV block	Significant reduction in CV mortality, AF, stroke and HF in the AAI group
PASE[11] (1998)	407	1.5	SSS and AVB	DDDR *vs* VVIR	Quality of life, all-cause mortality[1], HF[1], and AF[1]	No overall difference in quality of life albeit moderate improvement in patients with SSS but not AVB in the DDDR group No difference in mortality, HF or AF
CTOPP[9] (2000)	2568	6.4	SSS and AVB	DDD/AAI *vs* VVI(R)	Stroke, CV mortality, all-cause mortality[1], AF[1], and HF[1]	No difference in stroke, CV mortality, all-cause mortality or HF Significant reduction in AF in the DDD/AAI group.
MOST[10] (2002)	2010	2.8	SSS	DDDR *vs* VVIR	All-cause mortality, stroke, AF[1], HF[1], QoL[1], pacemaker syndrome[1]	No difference in all-cause mortality, stroke Significant reduction in AF, HF, and QoL in the DDDR group 18.3% cross-over due to pacemaker syndrome in the VVIR group
UK-PACE[14] (2005)	2021	3	AVB	DDD(R) *vs* VVI(R)	All-cause mortality, AF[1], HF[1], stroke[1]	No difference in any of the endpoints
DANPACE[13] (2011)	1415	5.4	SSS	AAIR *vs* DDDR	All-cause mortality, AF[1], HF[1], stroke[1], need for pacemaker reoperation[1]	No difference in all-cause mortality, chronic AF, HF or stroke Increased risk of paroxysmal AF and need for pacemaker reoperation (development of AVB) in the AAIR group
DAVID[7] (2002)	506	0.8	Primary and secondary prevention ICD	VVI 40 *vs* DDDR 70 ICD	Composite of hospitalization for HF and mortality	Prematurely interrupted due to increased occurrences of the composite endpoint in the DDDR 70 group
MADIT Ⅱ substudy[17] (2005)	1232	1.7	Primary prevention ICD	0%-50% *vs* 51%-100% VP	Composite of HF and mortality	Nearly two-fold increase in hospitalization for HF in the 51%-100% VP group

[1]Secondary endpoints. AF: Atrial fibrillation; AVB: Atrioventricular block; CV: Cardiovascular; HF: Heart failure; ICD: Implantable cardioverter-defibrillator; QoL: Quality of life; SSS: Sick sinus syndrome; VP: Ventricular pacing; VVI: Ventricular.

of the general population. However, animal and human studies have shown that RV pacing leads to abnormal electrical and mechanical activation patterns (dyssynchrony), which leads to impaired hemodynamic parameters and myocardial remodeling[1-5]. Large pacemaker and implantable cardiac defibrillator (ICD) trials have reported an association between long-term RV pacing and deterioration of cardiac structure and function, as well as increased risk of heart failure (HF), atrial fibrillation (AF) and death[1,6,7]. This has subsequently caused concerns about the potential deleterious clinical effect of long-term right ventricular (RV) pacing. As a result, several therapeutic strategies, such as alternative RV pacing sites, cardiac resynchronization therapy (CRT) and alternative pacemaker programming options/algorithms that minimize RV pacing have emerged. This review will outline the available evidence concerning the negative effects of long-term RV pacing and comment on how to minimize RV pacing, with a focus on CRT and specific pacemaker algorithms.

THE CLINICAL EVIDENCE OF THE NEGATIVE EFFECTS OF RV PACING

Patients without baseline heart failure

The large bulk of information regarding the negative effects of RV pacing in patients without baseline HF comes from large pacemaker randomized clinical trials (RCT) of elderly patients with mainly Sick sinus syndrome (SSS) that were designed to assess the difference between atrial (AAI or DDD) and ventricular-based pacing strategies[8-14]. In the single center Danish trial, 225 patients with SSS were randomized to either single chamber atrial pacing (AAI) or single chamber ventricular pacing (VVI)[8]. After a mean of 5.5 years of follow-up, a significant increase in total and cardiovascular mortality, HF and AF in the ventricle-based pacing group was reported. The authors also found that the VVI pacing led to increased dilatation of the left atrial diameter and reduced left ventricular (LV) fractional shortening. An assumption that conserving atrioventricular (AV) synchrony is beneficial was made and because of that, several RCTs that compared dual chamber (DDD) *vs* single chamber (VVI) pacing in elderly patients with SSS only[10,12], SSS and AV block[9,11], and AV block alone[14] were carried out. To the surprise of many, DDD pacing was not associated with a decrease in mortality or hospitalization for HF, although a reduction in AF and minor improvements in quality of life were observed in the same group. These results were later confirmed in a meta-analysis[15] that included the Danish trial[8] and 4 of the recently mentioned RCTs that compared DDD *vs* VVI pacing[9-11,14] (Table 1). With atrial-based pacing, there was no significant difference in

mortality (HR = 0.95, 95%CI: 0.87-1.03) or HF (HR = 0.89, 95%CI: 0.77-1.03), but a significant reduction in AF (HR = 0.81, 95%CI: 0.72-0.89) was observed[15].

One of the previously mentioned studies is The Mode Selection Trial in Sinus Node Dysfunction (MOST), which was a multicenter randomized study that randomized a total of 2010 patients with SSS to either VVIR or DDDR pacing[10]. Unexpectedly, after 33 mo of follow-up, a small but significant increased incidence of AF and hospitalization for HF in the DDD pacing group was reported, with no difference in all cause mortality between the two groups. When analyzing 1339 patients from the same study, the DDDR group received significantly more RV pacing than the VVIR group (90% *vs* 58%, respectively) and interestingly, the amount of RV pacing was a strong predictor for AF [HR = 1.36 (95%CI: 1.09-1.69) for each 25% increase in cumulative RV pacing] and HF hospitalization [HR = 2.99 (95%CI: 1.15-7.75) for > 40% of cumulative RV pacing][6]. On the contrary, the recent Danish Multicenter Randomized Trial on Single Lead Atrial Pacing *vs* Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) trial which included 1415 patients reported no difference in mortality, HF or chronic AF between DDDR or AAIR pacing[13] or the amount of RV pacing[16] after a mean follow-up of 5.4 years. Furthermore, there was a significant increase in paroxysmal AF and need for pacemaker reoperation, mainly due to the development of AV conduction disease in the AAIR group[13].

The conflicting results of the DANPACE trial[13] and the study limitations of the subanalyses from the older pacemaker trials, like patient heterogenicity (a minority presented clinical HF) and no echocardiographic evaluation, make it difficult to estimate to what extent long-term RV pacing causes clinical deterioration in patients without baseline HF. Although with the data available, it seems likely that most patients with normal LV function tolerate some degree of RV pacing without developing HF during long-term follow up.

Patients with reduced LVEF at baseline

The Dual Chamber and VVI Implantable (DAVID) trial[7] and a subanalysis of the Multicenter Automatic Defibrillator Trial Ⅱ (MADIT Ⅱ)[17] have provided strong evidence for the negative effects of RV pacing in patients with reduced baseline LVEF (Table 1). The DAVID trial was designed to study whether DDDR pacing with a lower rate limit at 70/min (DDDR 70) would decrease total mortality and hospitalization for HF when compared against VVI backup pacing with a lower rate of 40/min (VVI 40) through increased cardiac output and allowing higher doses of β-blocker therapy[7]. A total of 506 patients with standard indication for ICD implantation as secondary prevention but without indications for antibradycardia pacing were included in the trial, with an LVEF of 28% ± 8%. After a median follow-up of 8.4 mo, the study was prematurely interrupted due to more occurrences of the composite endpoint in the DDDR 70 group, largely driven by hospitalization for HF (1 year survival free of the composite endpoint: 73.3% for DDDR 70% and 83.9% for VVI 40; P = 0.02). Like in the MOST trial[10], a subanalysis of the DAVID trial[18] reported a continuous relationship between the percentage of RV pacing and the primary endpoint, with the most significant divergence of outcomes occurring with RV pacing > 40%. The results were further supported by the DAVID Ⅱ trial[19], which randomized 600 patients with baseline characteristics similar to the DAVID trial to receive ICD implantation with either AAI pacing with a lower rate of 70/min or VVI 40. No difference in mortality or hospitalization for HF was observed after a mean follow-up of 2.7 years. Additional evidence comes from a subanalysis of the MADIT Ⅱ trial[17], which randomized 1232 patients with previous myocardial infarction and LVEF < 30% to ICD plus optimal medical therapy *vs* medical therapy alone[20]. A significant 31% reduction in mortality risk was observed in the ICD arm but there was a worrisome trend towards more hospitalizations for HF in the ICD group and the subanalysis reported a nearly two-fold increased risk of hospitalization for HF in those who received > 50% of cumulative pacing. A recent report of the 8 years of follow-up of the patients with > 50% in the MADIT Ⅱ trials reported mortality rates similar to the optimal medical therapy group, with the ICD group with a low percentage of RV pacing presenting a continued significant mortality benefit[21]. The MADIT Ⅱ trial[20] results therefore illustrate how the clinical expression of the detrimental effects of RV pacing is the result of years of a high amount of RV pacing.

THERAPEUTIC OPTIONS TO AVOID UNNECESSARY RV PACING

Alternative RV pacing sites

The purpose of RV non-apical (RVNA) pacing is to take advantage of the specialized conduction system and thereby reduce ventricular dyssynchrony. Three main anatomical sites have been evaluated: right ventricular outflow tract (RVOT), intraventricular septum (IVS) and the His bundle. Overall, evidence from several small studies suggests that dyssynchrony is reduced and that LVEF is improved with RVOT[22], IVS[23] and His bundle[24] pacing, although negative results have also been reported[25]. Nevertheless, there is conflicting evidence regarding the clinical benefit of RVNA pacing in terms of exercise capacity or quality of life scores[23,25,26]. Furthermore, only one study evaluated whether RVNA pacing would result in prolonged survival benefit and failed to find such an association, although this endpoint was not powered properly[27]. Furthermore, a recent meta-analysis reported improved LVEF with RVNA pacing but no demonstrable clinical benefit when compared with RV pacing[28]. Large RCTs with statistical power to evaluate clinical endpoints are needed in order to establish whether RVNA pacing is an effective alternative to conventional RV apical pacing.

Table 2 Pacemaker algorithms that reduce right ventricular pacing

Reverse Mode Switch/RYTHMIQ™ (Boston Scientific, St. Paul, MN, United States)
Atrial based pacing in AAI(R) with VVI backup (LRL minus 15/min) with the two modes operate independently from one another. If complete AVB occurs, ventricular paces will be delivered at backup VVI rate, asynchronous to the AAI rate. If 3 slow ventricular beats are detected in a window of 11 beats, AV conduction is considered blocked and switch to DDD (R) takes place. The algorithm will switch back to AAI if intact AV conduction is recuperated
Managed Ventricular Pacing™ (Medtronic, Minneapolis, MN, United States)
Atrial based pacing (labeled as AAI(R)+) with switch to DDD(R) if AV block is detected, defined as 2/4 absent ventricular event. The algorithm checks for AV conduction at regular intervals and if present it will switch back to AAI(R)+
Ventricular Intrinsic Preference™ (St. Jude Medical, Sylmar, CA, United States)
Intrinsic AV conduction is assessed by increasing AV delay at regular intervals (programmable AV extension of up to 200 ms; maximum AV delay 350 ms). If present, the longer AV delay will be maintained until a programmable number of cycles of absent ventricular sensed events (*i.e.*, continuous need for ventricular pacing), thus deactivating the algorithm
AV hysteresis (Biotronik, Berlin, Germany)
Similar to Ventricular Intrinsic Preference™ (St. Jude)
AAISafeR™ and AAISafeR2™ (Sorin Group, Mirandola, Italy)
Atrial based pacing in AAI (R). Abnormal AV intervals (> 350 ms if atrial sensed; > 450 ms if atrial paced) are monitored. Switch to DDD in response to any of the following:
> 6 abnormal AV intervals ("first degree AVB")
> 3/12 nonconducted atrial events ("second degree AVB")
> 2 consecutive nonconducted atrial event ("advanced AVB")
Ventricular pauses of 2–4 s (programmable)

AV: Atrioventricular; AVB: Atrioventricular block; LRL: Lower rate limit; VVI: Ventricular.

Table 3 Clinical studies of pacemaker algorithms that minimize right ventricular pacing

Study	Design	Pacing indication	Patients (*n*)	Follow-up (mo)	Outcomes
Sweeney *et al*[30]	Randomized, crossover MVP *vs* DDD(R)	SSS	181	1	Amount of pacing: MVP™: 4.1%; DDD(R): 73.8%
Murakami *et al*[29]	Randomized, crossover MVP *vs* Search AV+	SSS and AVB	127	1	Amount of pacing: MVP: 66.1%; Search AV+: 54.3% (patients with %RVP < 40) MVP: 57.5%; Search AV+: 38.6% (patients with %RVP < 10)
Olshansky *et al*[32]	RCT DDD(R) AVSH 60/min *vs* VVI 40/min (non-inferiority)	ICD[1]	1530	10.4	Trend towards a lower rate of death and hospitalization for HF in the DDD(R) AVSH group
Sweeney *et al*[33]	RCT Search AV+/MVP *vs* DDD(R)	SSS	1065	12	Amount of pacing: DDD(R): 99%; Search AV+/MVP: 9.1% Reduction in time to development of AF (primary endpoint) in the search AV+/MVP group No difference in hospitalization for HF or death (secondary endpoints)
Sweeney *et al*[36]	RCT MVP 60/min *vs* VVI 40/min (non-inferiority)	ICD[1]	1030	29	Prematurely interrupted due slightly more deaths and hospitalization for HF in MVP group

[1]Patients with an implantable cardiac defibrillator indication were included in the trial; AVB: Atrioventricular block; AVSH: AV Search Hysteresis (Medtronic); MVP: Managed Ventricular Pacing (Medtronic, Minneapolis, MS, United States); ICD: Implantable cardiac defibrillator; RCT: Randomized control trial; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; VVI: Ventricular.

Pacemaker algorithms to reduce RV pacing

There are several pacemaker algorithms that permit prolonged AV intervals, all potentially capable of reducing RV pacing, and they can be divided into two large groups: (1) algorithms which periodically prolong the AV interval to search for, and if present, allow intrinsic AV conduction (AV hysteresis); and (2) algorithms that operate in a primary atrial pacing mode, with mode switch to secondary mode ventricular pacing (DDD) in case of significant loss of AV conduction[29-31] (Table 2). The most studied algorithm is probably the Managed Ventricular Pacing™ (MVP) (Medtronic, Minneapolis, MN, United States) that operates in primary atrial based mode labeled (AAI[R]+) with switch to secondary DDD[R] mode in the case of loss of AV conduction occurring in 2 out of 4 atrial-atrial intervals[30]. In a short-term study without clinical endpoints with patients with SSS and various degrees of AV block, the MVP algorithm was reported to be significantly more effective in reducing the amount of RV pacing when compared to one AV hysteresis algorithm (66.1% *vs* 54.3% had < 40% of RV pacing, respectively)[29].

In terms of the potential clinical benefits associated with algorithms that minimize RV pacing, this has been evaluated by a few RCTs (Table 3). The Inhibition of Unnecessary RV Pacing With AVSH in ICDs (INTRINSIC RV) Study[32] was a multicenter non-inferiority trial which included 1530 patients with conventional indication for ICD implantation to dual chamber pacing

(DDDR mode with lower rate of 60) with AV Search Hysteresis™ (DDDR 60 AVSH) (Boston Scientific, St. Paul, MN, USA) or backup VVI 40 pacing. However, due to the worrisome results of the DAVID trial[7], eventually only 988 patients with < 20% RV pacing at 1 wk with DDDR 60 AVSH were randomized to the two programming modes. After a mean follow-up of 10.4 mo, non-inferiority of the primary endpoint, hospitalization for HF or total mortality had been met with a trend towards superiority for the primary endpoint in the DDDR 60 AVSH group. The DDDR AVSH 60 and VVI 40 groups presented with a mean RV pacing percentage of 10% and 3%, respectively. The results of the INTRISC RV study are reassuring since they suggests that in ICD recipients with a need for dual chamber pacing (*e.g.,* SSS and various degrees of AV block), the deleterious effects of long-term RV pacing as observed in the DAVID trial[7] can be avoided by the use of the AV hysteresis algorithm. However, since only those with < 20% of RV pacing were included in the trial, one should only consider the pacing algorithm in this patient profile and not in patients with high grade AV block who would expect to receive a significant amount of RV pacing (> 20%) despite the use of the algorithm. The Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial[33] assessed whether dual chamber pacing, using the Search AV+™ or MVP algorithms (Medtronic), decreases time to development of persistent AF compared with conventional dual chamber pacing (AV interval 120-180 ms) in patients with SSS and normal LVEF. After a follow-up of a mean of 1.7 years, significantly less patients in the minimal pacing group developed persistent AF (7.9% *vs* 12.7%, respectively, $P = 0.004$). However, no difference in the secondary endpoints, hospitalization for HF or mortality was found. As expected, the median percentage of atrial pacing was similar between the two groups but the amount of RV pacing in the conventional group was markedly increased when compared to the minimal pacing group (99.0% *vs* 9.1%). For the first time, a prospective association between a reduction in RV pacing and clinical benefit (freedom from AF) was reported. The results therefore support the use of algorithms that minimize RV pacing in patients with SSS.

Although the results are promising, the algorithms that minimize RV pacing may not be suitable in some patients. No large long-term trials with clinical endpoints have evaluated these algorithms in patients with high-degree AV block (although there is evidence that supports their short-term safety and effectiveness in reducing RV pacing)[34]. Furthermore, allowing severely prolonged AV intervals may lead to compromised cardiac output resulting from inefficient atrial systole and various degrees of diastolic mitral regurgitation[35]. The Managed Ventricular Pacing Versus VVI 40 Pacing Trial[36] compared dual chamber pacing with the MVP algorithm (with a lower rate of 60) and backup VVI 40 pacing in ICD patients. The trial was unexpectedly terminated early since non-inferiority for the primary combined endpoint of HF events or total mortality could not be demonstrated, with a trend towards more primary endpoint events in the MVP. Interestingly, the subgroup analysis found that the increase in HF and mortality was largely contributed to by patients with a PR interval of ⩾ 230 ms. Moreover, a subanalysis of the INTRINSIC RV study[37] reported on a J-shaped relationship between amount of RV pacing and the clinical event rate, with the best outcome for those with RV pacing between 10% and 19%. It therefore seems that a certain amount of RV pacing in those with impaired baseline AV conduction is necessary, although the equilibrium between low amounts RV pacing and preserved AV synchrony is not fully known. However, patients with normal or near normal AV conduction and the need for antibradycardia pacing are likely to benefit from the use of algorithms that minimize RV pacing.

Finally, sometimes pacemaker algorithms, like the ones previously discussed, may not work as expected. We recently evaluated the performance of the reverse mode switch™ (RMS) algorithm (Boston Scientific) which offers, like the MVP algorithm, primary atrial pacing AAI(R) mode with switch to DDD(R) secondary mode in the case of AV conduction loss, in a small retrospective study of 21 patients[38]. A large majority (84%) of the RMS episodes analyzed revealed an inappropriate switch to DDD(R) mode, mainly triggered by premature ventricular contractions (PVC). Therefore, our results suggest that patients with the RMS algorithm and high amounts of PVCs are paradoxically subject to an increased risk of unnecessary RV pacing through inappropriate RMS episodes. The results are also transferable to the newer but similar algorithm RYTHMIQ™ (Boston Scientific), given that the only difference between the two algorithms is the availability of the atrial tachycardia response feature in AAI(R) mode in RYTHMIQ.

Cardiac resynchronization therapy

It is well established that CRT improves ventricular dyssynchrony, LVEF, hospitalization for HF and mortality in patients with HF, prolonged QRS interval and NYHA class Ⅱ-Ⅳ and it has become a part of standard HF treatment[39,40]. Until recently, there was little data on the benefit of CRT in patients with a conventional indication for antibradycardia pacing; however, the results from the Biventricular Versus Right Ventricular Pacing in Patients with AV block (BLOCK HF) study[41] were recently published. It constitutes the first large scale RCT that assesses the clinical benefits of CRT compared to RV pacing in patients with LV systolic dysfunction (LVEF ⩽ 50%) and AV conduction loss with a standard pacemaker indication but without conventional indication for CRT. A total of 691 patients, with mean QRS of 125 ms and 121 ms and mean LVEF 43% ± 7% and 33% ± 8% (CRT pacing and CRT-ICD groups, respectively) were randomized to RV pacing and CRT. The patients presented with first (19%), second (33%) and third degree (48%) AV block. After a mean of 37 mo of follow-up, CRT was

Table 4 Clinical studies of right ventricular pacing *vs* cardiac resynchronization therapy

Study	Design	Patient characteristics	Patients (*n*)	Follow-up (mo)	Baseline LVEF	LVEF in RV pacing	LVEF in CRT	Clinical benefit from CRT
Martinelli *et al*[42]	RCT multicenter	AVB	60	5 (crossover)	30.1% ± 9.2%	22.5% ± 8.1%	29.3% ± 6.9%[a]	Improved NYHA class and QoL
Yu *et al*[45]	RCT multicenter	AVB and SSS	177	12	61.6% ± 6.6%	54.8% ± 9.1%	62.2% ± 7%[b]	No difference in hospitalization for HF, exercise capacity or QoL
Curtis *et al*[41]	RCT multicenter	AVB	691	37	43% ± 7% (CRT-P) 33% ± 8% (DRT-D)	-	-	Reduction in composite endpoint (mortality, HF urgent care and LVESI)
Brignole *et al*[47]	RCT multicenter	AVN ablation	186	20	38% ± 14%	Increasing from baseline + 4.7%	Increasing from baseline +6.6% (NS)	Reduction in composite endpoint (death from HF, hospitalization for HF or worsened HF)
Doshi *et al*[49]	RCT multicenter	AVN ablation	184	6	46% ± 16%	41.1% ± 13%	46% ± 13%[a]	Improved exercise capacity No difference in QoL
Orlov *et al*[51]	RCT multicenter	AVN ablation	127	6	56.1% ± 9.4% (CRT group) 57.2% ± 7.5% (RVP group)	54.6% ± 11.5%	59.3% ± 7.7%[a]	No difference in NYHA class, exercise capacity or QoL

[a]$P < 0.05$; [b]$P < 0.001$ *vs* left ventricular function in right ventricle pacing; AVB: Atrioventricular block; AVN: Atrioventricular node; CRT-D: Cardiac resynchronization with implantable cardiac defibrillator; CRT-P: Cardiac resynchronization therapy pacing; NS: Non-significant; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; QoL: Quality of life; LVEF: Left ventricular function; RV: Right ventricle; LVESI: Left ventricular end-systolic index; HF: Heart failure; RCT: Randomized controlled trial.

associated with a 26% risk reduction in the primary composite endpoint of all-cause mortality, HF-related urgent care and LV end-systolic index [HR = 0.74 (95% credible interval 0.60-0.90)] and a 27% risk reduction in all-cause mortality and HF-related urgent care [HR = 0.73 (95% credible interval 0.57-0.92)]. The findings from the BLOCK study therefore confirm the results from previous small studies[42] that CRT in patients with a pacemaker indication for AV block and a high degree of expected RV pacing and LV systolic dysfunction improves LV function and clinical outcomes. Furthermore, there is also data suggesting that patients with reduced LVEF and a reported high amount of long-term RV pacing may benefit from a device upgrade to CRT. For example, in a retrospective study, Fröhlich *et al*[43] reported inverse LV remodeling (LVEF and LV end-systolic and end-diastolic diameters) and improved NYHA functional class in patients with chronic RV pacing and reduced LVEF who received a CRT upgrade. A recent small RCT that included 50 patients with LV systolic dysfunction listed for routine pacemaker generator replacement with > 80% RV pacing in the preceding 12 mo found that an CRT upgrade was associated with improved LVEF, reduced N-terminal pro-B-type natriuretic peptide levels, exercise capacity and quality of life[44].

There is less evidence in favor of CRT in patients with normal LVEF. The Pacing to Avoid Cardiac Enlargement (PACE) study[45], which was a multicenter, double blind trial, randomized 177 patients with SSS or AV advanced block to receive either RV pacing (DDDR mode) or CRT. After 1 year of follow-up, the authors reported maintained LVEF and LV end-systolic volume (primary endpoints) in the CRT group but a reduction in these parameters in the RV pacing group. However, CRT did not improve the secondary clinical endpoints: 6 min walking test, hospitalization for HF or quality of life. It should be noted that no increased procedure-related complications were reported in the discussed studies, indicating that CRT is also a safe alternative to conventional RV pacing.

In AF patients with rapid ventricular rates who undergo catheter ablation of the AV node to create complete AV block due to irresponsiveness to pharmacological treatment, there is a high risk of suffering the detrimental effects associated with prolonged high density RV pacing, such as LV dyssynchrony, reduced LVEF and worsened HF symptoms[46]. Five small short-term RCTs studied the potential benefit of CRT compared to RV pacing in patients with AF and AV node ablation[47-51] and found improved LVEF and in some instances a reduction in hospitalization for HF. Thus, there is evidence that this group of patients would also benefit from CRT. Nevertheless, in asymptomatic individuals with AV node ablation for AF and normal LV function there is currently no evidence to support CRT. A list of some of the major clinical studies that compared CRT *vs* RV pacing is shown in Table 4.

A PRACTICAL APPROACH TO MINIMIZE UNNECESSARY RIGHT VENTRICULAR PACING IN CERTAIN PATIENT GROUPS

Data from subanalyses of ICD trials, including patients with reduced LVEF, suggests that > 40%-50% of RV pacing is associated with adverse clinical outcomes[17,18]. In addition, patients with reduced LVEF are at a significantly higher risk of suffering the negative clinical effects of RV pacing when compared to those with a normal cardiac function and most patients with normal LVEF

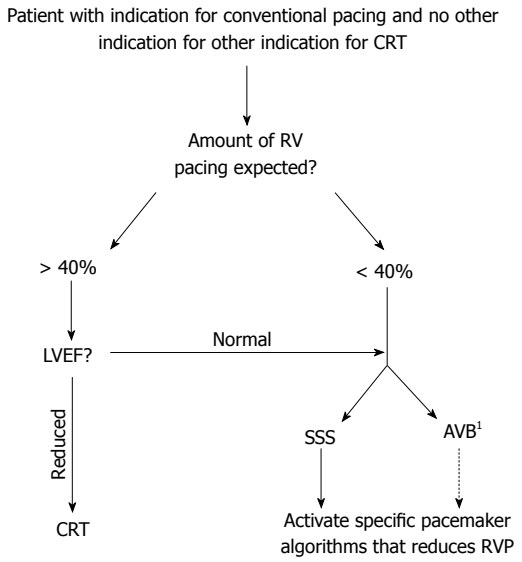

Figure 1 A schematic management plan of how to avoid unnecessary right ventricle pacing in a patient with an indication for conventional pacing and no other indication for cardiac resynchronization therapy. [1]No large scale trials have assessed the benefits and safety of the managed ventricular pacing algorithm in patients with high-grade AV block. AVB: Atrioventricular block; LVEF: Left ventricular ejection fraction; RVP: Right ventricular pacing; SSS: Sick sinus syndrome; CRT: Cardiac resynchronization therapy; RV: Right ventricle.

appear to tolerate some degree of chronic RV pacing[16,52]. It is therefore useful to stratify the patient with an indication for permanent cardiac pacing according to LVEF (reduced or conserved) and the likelihood of a high amount of RV pacing (high or low) (Figure 1). However, it may sometimes be difficult to estimate the latter although some more clear-cut scenarios also exist, such as patients with complete AV block (high risk) and patients with SSS and intact AV conduction (low risk).

Considering the available evidence, in a patient with a normal LVEF, a conventional pacemaker is currently the best option and unnecessary RV pacing should be avoided through appropriate device programming. This includes the correct selection of the pacing mode and also the lower rate limits (*e.g.,* VVI mode at 40 ppm in a patient with infrequent paroxysmal AV block), AV interval (*e.g.,* long AV intervals or AV hysteresis if there is no significant AV conduction loss) and the use of special algorithms aimed at minimizing RV pacing (if available). As discussed, several algorithms that all reduce the amount of RV pacing exists, although the MVP algorithm is the most studied with results indicating improvement in LV mechanics and also some clinical benefit[33,53]. However, there is currently insufficient evidence on the use of the MVP algorithm in patients with high grade AV block and in addition it may have a neutral or even negative effect when the PR interval is prolonged (> 230 ms)[36,54]. We therefore suggest that the MVP algorithm should only be used in those with SSS with no significant AV conduction disease (narrow QRS and PR interval < 230 ms).

If a patient presents with a reduced LVEF, with the results from the BLOCK HF study[41], there is now strong evidence that CRT should be chosen over a conventional pacemaker in order to improve both LV reverse remodeling as well as clinical outcomes[41,42]. The recently published European guidelines on cardiac pacing and CRT thus recommend *de novo* CRT in patients with HF, reduced LVEF (≤ 50%), bradycardia indication for pacing and an expected high percentage of RV pacing[39]. Furthermore, patients with reduced LVEF and planned AV node ablation for AF are likely to benefit from CRT[55]. Also, an important group of patients with indication for antibradycardia pacing also have a conventional indication for CRT and should obviously be offered this therapy[40]. Finally, there is presently not enough evidence to support the use of alternative RV pacing sites, such as RVOT, IVS and His bundle[28].

FUTURE DIRECTIONS AND UNSOLVED QUESTIONS

Despite the publication of a significant amount of evidence that has made us aware of the adverse pathophysiological mechanisms and clinical effects of prolonged RV pacing, as well as on the use of different strategies to overcome them, several questions remain unresolved. There is currently a lack of specifically designed studies that evaluate the potentially negative effect of long-term RV pacing in patients with normal LVEF. Most of the available information comes from old pacemaker trials aimed at evaluating atrial *vs* ventricular based pacing strategies in which echocardiography evaluation of LV function or percent RV stimulation was not always reported[8-11,14]. The conflicting results of the recent DANPACE trial[13], in which no association between the amount of RV pacing and clinical outcome was observed in patients with normal LVEF, further complicates the matter. Therefore, the extent of the negative effects of RV pacing in patients with normal LVEF and whether this is clinically relevant is at present debatable and future studies in this area are subsequently warranted. Other areas of future research include the indications and potential benefits of therapeutic strategies aimed at minimizing RV pacing such as specific algorithms, alternative pacing sites and CRT; however, several large scale trials are ongoing and the results will provide guidance for future clinical practice. The Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BIOPACE) study[56] is an international large randomized prospective mortality-driven trial that is comparing CRT *vs* conventional RV pacing in patients without a standard indication for CRT. Since patients with severely depressed to normal LVEF are being included, the results will not only help in defining the role of CRT in a wide range of patient characteristics but also provide information on the detrimental effects of RV pacing in those with normal LVEF. Finally, future large RCTs with long-term follow-up and clinical endpoints are currently evaluating the MVP algorithm and should provide important new information on its potential benefits[57,58].

CONCLUSION

In a significant number of patients, chronic RV pacing leads to negative effects such as reduced LV function and adverse cardiac remodeling, as well as increased incidence of HF, AF and death. Those with reduced LVEF and long-term high amount of RV pacing are at particular risk and there is now solid evidence that CRT improves LV function and clinical outcomes in this group. However, patients with normal LVEF seem to tolerate some degree of long-term RV pacing and thus the clinical relevance of the detrimental effects of RV pacing is less certain in these individuals. Appropriate pacemaker programming and the use of different pacemaker algorithms represent important methods to avoid unnecessary RV pacing in this patient group.

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BRIEF ARTICLE

Trend in prevalence of uncontrolled total serum cholesterol for cardio-cerebro-vascular disease in a mediterranean area, 1988/89-2008/09

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Abstract

AIM: To examine trends of uncontrolled total serum cholesterol, treatment and control in a Mediterranean region (Campania).

METHODS: We considered and compared the data collected as part of "Montecorvino Rovella Project" 1988-1989 and cross-sectional data from the two phases of the "VIP Project-Valle dell'Irno Prevenzione": 1998-1999 (1st phase) and 2008-2009 (2nd phase), in the 35-74-year-old-population.

RESULTS: Data show a reduction of mean cholesterolemia in the last twenty years of 7.3 mg/dL for men and unchanged values for women. In the three surveys the mean values for serum cholesterol are in men: 205.2 ± 47.1 mg/dL (1988/89), 200 ± 38.9 mg/dL (1998/99) and 197.9 ± 40.2 mg/dL (2008/09); in the women: 203.1 ± 42.5 mg/dL (1988/89), 198.9 ± 37.9 mg/dL (1998/99) and 203.3 ± 39.3 mg/dL (2008/09). Prevalence of uncontrolled high cholesterol ⩾ 240 mg/dL for men decreased from 20.8% (1988/89) to 14.3% (1998/99) and 13.9% (2008/9), P = 0.002; for women the values decreased from 19.9% (1988/89), to 18.2% (1998/99) and 18.1% (2008/09), P = 0.007. Is statistically increased the number of patients treated and those treated to target.

CONCLUSION: Encouraging increases in awareness, treatment, and control of hypercholesterolemia occurred from 1988 through 2008. Nevertheless, control of hypercholesterolemia remains poor.

Key words: Mediterranean diet; Hypercholesterolemia; Drug; Heart disease; Southern Italy

Core tip: Risk of cardiovascular disease (CVD) is directly related to blood cholesterol levels. CVD due to atherosclerosis is the foremost cause of premature mortality and of disability-adjusted life years in Europe, and is also increasingly common in developing countries. The objective of this study was to examine trends of high cholesterol, treatment and control in a Mediterranean region (Campania). Data show a reduction of mean cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for women. Encouraging increases in treatment and control of hypercholesterolemia occurred from 1988 through 2008. However, control of hypercholesterolemia remains poor.

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Notari E, Iannone AG, Marchese F, Sonderegger M, Capuano Ed. Trend in prevalence of uncontrolled total serum cholesterol for cardio-cerebro-vascular disease in a mediterranean area, 1988/89-2008/09. *World J Cardiol* 2013; 5(11): 420-425 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i11/420.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i11.420

INTRODUCTION

Coronary heart disease (CHD) is now the leading cause of death worldwide. It remains the major cause of premature death in Europe, even though CHD mortality has fallen considerably over recent decades in many European countries[1,2].

Raised serum total cholesterol is an important cardiovascular risk factor, which causes an estimated 4.4 million deaths every year worldwide[3,4]. Research from the World Health Organization highlights the importance of raised blood cholesterol as a risk factor for CHD. The World Health Report 2002[5] estimates that around 8% of all disease burden in developed countries is caused by raised blood cholesterol and that over 60% of CHD and around 40% of ischaemic stroke in developed countries is due to total blood cholesterol levels in excess of the theoretical minimum (3.8 mmol/L). Variations in diet, especially consumption of animal-based *vs* plant-based fats, adiposity, and use of drugs to lower cholesterol have led to differences in serum cholesterol concentrations across populations and over time[6-8]. Therefore, the focus on cardiovascular prevention must remain high. Our aim was to estimate trend in total serum cholesterol, in a Mediterranean area of southern Italy, in the last twenty years.

MATERIALS AND METHODS

We compared the results of three epidemiological surveys as far as cardiovascular risk factors are concerned, performed in Southern Italy, in a Mediterranean region (Campania), in two areas near the city of Salerno.

In particular we considered and compared the data collected as part of "Montecorvino Rovella Project"[9] (PMR) 1988-1989 and cross-sectional data from the two phases of the " VIP Project-Valle dell'Irno Prevenzione": 1988-1989 (first phase)[10] and 2008-09 (second phase).

In three investigations, a sample taken from people between 25-74 years (divided into 5 classes of age: 25-34, 35-44, 45-54, 55-64, 65-74) was studied. People were enlisted at random from the electoral rolls and subjected to blood tests after an overnight fast.

The methodology of data collection and conducting tests to which the population underwent during the three phases are standardized and comparable, they have been fully described in some other publications[9-11].

PMR and VIP were conducted by the same working group and the same coordinator. Areas over district level, are similar for geographic position, they both are about 20 km far from Salerno. Moreover the socio-economic status of the rural populations and their recent industrial development are similar.

PMR project design

PMR project had the following aims: to analyze the prevalence of cardiovascular risk factors in an area of the Campania region at the end of 1980s. This study was conducted between 1988 and 1989, inviting a randomized statistical sample to represent the area. Randomized samples included 1500 subjects, 300 (150 males and 150 females) for each decade. Only 1091 subjects (569 females and 522 males) were examined with a total participation of 72.7% (75.9% for females and 69.6% for males).

VIP project design

VIP project has the following aims: to conduct a program of cardiovascular prevention in a population of the Irno Valley controlled by Mercato S. Severino's Hospital, to know the physiological limits and biohumoral parameters of the resident population, to know the trend of the main cardiovascular risk factors in the area near Salerno. This study has collected epidemiological data on cardiovascular risk factors in two phases: 1998/99 and 2008/09. The "VIP Project" is a part of CINDI program, WHO study[12,13] and has contributed to the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group[14]. Both surveys include 1200 subjects, 600 males and 600 females, age ranging from 25 to 74 years, randomized from the electoral rolls of the towns of Mercato S Severino and Baronissi, near Salerno, in Southern Italy. In a randomized way, we compiled three lists, each one of 120 subjects divided into decades of sex and age. The recruitment from the first list was realized by letter of invitation, in the case of impossibility or refusal, the subject was replaced by a person of the same age and sex from the second list and in the case of failure, someone from the third list. This type of procedure for the recruitment was suggested by the manual of the rules of monica project-monica cardiovascular diseases[15]. During all phases the subjects underwent to: (1) General examination; (2) Ecording of blood pressure; (3) Anthropometric measurements (weight, height, waist-hip ratio); (4) Electrocardiogram; and (5) Laboratory tests (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, blood glucose, blood count, platelets, plasma insulin, fibrinogen, creatinine, C3).

Fasting venous blood was taken in the seated position without stasis after an overnight fast. The laboratory has always made use of quality control: Biorad (in 1988/89 and 1998/99) and VEQ (University Hospital of Bologna, Policlinico S. Orsola Malpighi) in 2008/09.

In particular, with regard to the parameters analyzed, cholesterol, HDL cholesterol, triglycerides were determined through an enzymatic method (Fixed-time to 500 nanometer) installed on Cobas-ABX (Roche, Milan Italy) automatic line.

A history, with a focus on cardiovascular disease, was performed by a physician who, through a questionnaire,

Table 1 Mean ± SD of cholesterol, high density-cholesterol, low density lipoprotein-cholesterol and triglycerides

	Age (yr)	Cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	Triglycerides (mg/dL)
Male	25-34	191.9 ± 41.6	45.1 ± 10.1	125.2 ± 35.5	114.6 ± 78.9
	35-44	206.8 ± 39.7	48.4 ± 12.5	131.3 ± 35	136.7 ± 77.3
	45-54	197.9 ± 40	55.7 ± 13.9	117.8 ± 34.6	122.2 ± 70.9
	55-64	195.6 ± 31.6	49.4 ± 12.6	120.2 ± 31.9	130.2 ± 62.7
	65-74	196 ± 45.5	52.4 ± 12.4	119.5 ± 39	118.9 ± 69.9
	25-74[1]	197.9 ± 40.2	50 ± 12.3	123.3 ± 34.9	124.9 ± 72.6
Female	25-34	201.1 ± 37.6	47.8 ± 11.4	131.0 ± 34.7	111.5 ± 71.7
	35-44	206.7 ± 41.4	52.5 ± 14.9	130.3 ± 37.7	119.6 ± 65.3
	45-54	203.7 ± 38.3	59.7 ± 13.7	120.9 ± 33.1	115.8 ± 72.7
	55-64	206.2 ± 38.8	52.4 ± 12.7	125.3 ± 34.2	142.6 ± 74.7
	65-74	195.6 ± 41.4	51.9 ± 12.4	119.8 ± 34.7	119.2 ± 67.1
	25-74[1]	203.3 ± 39.3	53.0 ± 13.1	126.1 ± 34.9	121.0 ± 70.5

[1]Data standardized to the European population. VIP Study 2008/09 (120 subjects by age group). HDL: High density lipoprotein; LDL: Low density lipoprotein.

Table 2 Percentiles of cholesterol, high density-cholesterol, low density lipoprotein-cholesterol and triglycerides (mg/dL) for both sexes

Percentiles	Cholesterol		LDL-C		HDL-C		Triglycerides	
	M	F	M	F	M	F	M	F
5°	136	137	70	70	32	34	47	49
25°	169	175	98	101	40	43	75.5	76
50°	196.5	201	121	123.5	49	52	105.5	104.5
75°	222	229.5	143	146.5	57	60	151	145
95°	267	270	189.5	182.5	72.5	79.5	256	235

M: Male; F: Female. HDL: High density lipoprotein; LDL: Low density lipoprotein.

also evaluated: the habit of cigarette smoking, physical activity, occupation, and level of education, the educational qualification of the partners, civil status, and regular use of pharmacological therapy.

Statistical analysis

Results are expressed as mean ± SD for continuous variables and as frequency distributions for the categorical ones. The data have been standardized using the direct method considering the European population standards of reference. To compare the means among the three groups, we used one-way analysis of variance and Bonferroni's test for the differences among the groups. χ^2 analysis was used to compare prevalences. $P < 0.05$ was considered significant.

RESULTS

Table 1 show age-specific levels of lipid pattern in the VIP Study 2008/09. The data from the previous surveys were published in a previous work[16]. Mean values of cholesterolaemia are higher in women, with a statistically significant difference ($P = 0.02$). The values of HDL are, in all decades, higher in females (except in the 65-74 years), with more marked differences for age groups 35-44 and 45-54 years.

The values of LDL cholesterol are similar between men and women: 123.3 ± 34.9 and 126.1 ± 34.9 (P = NS) whereas for the age groups 25-34 and 55-64 years, are higher in women. Regarding triglycerides mean values were found to be higher for men in the first three age groups but less in the last two decades. The highest values are recorded in the 35-44 years for male and in the 55-64 years for women. Table 2 shows the percentiles of lipidic pattern.

Figure 1 show age-specific levels of total serum cholesterol for PMR (1988/89) and two phases of VIP studies (1998/99 and 2008/09). The mean values (standardized to the European population) are in the male: 205.2 ± 47.1 (1988/89), 200 ± 38.9 (1998/99) and 197.9 ± 40.2 (2008/09); in the female: 203.1 ± 42.5 (1988/89), 198.9 ± 37.9 (1998/99) and 203.3 ± 39.3 (2008/09). Is evident a reduction of cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for female. In both of sexes it is clear a reduction in cholesterol values after 45 years.

Table 3 shows prevalence of uncontrolled high cholesterol. The trend is decreasing for both men and women. The decrease was greater in men. Table 3 also shows the percentage of patients treated to target. The hypercholesterolemic to target increased, statistically significant, in both sexes.

DISCUSSION

Hypercholesterolemia is undoubtedly one of the major risk factors of cardiovascular disease. Knowing its trend is particularly important for prevention strategies and to

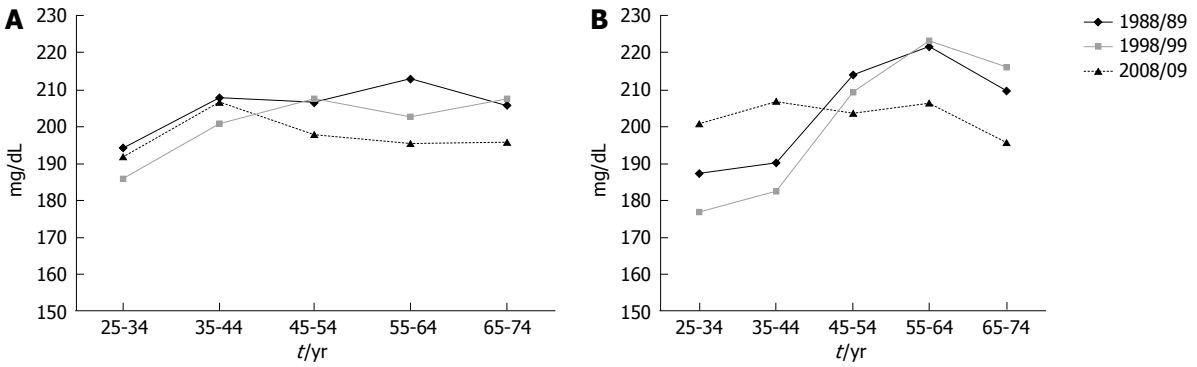

Figure 1 Cholesterolaemia between 25-74 years: 1988/89-2008/09. A: Male; B: Female.

Table 3 Prevalence of ipercholesterolaemia

	Group1 1988-89 (*n* = 522)	Group2 1998-99 (*n* = 600)	Group3 2008-09 (*n* = 600)	*P* value	1 *vs* 3	1 *vs* 2	2 *vs* 3
Male							
Uncontrolled high cholesterol (≥ 240 mg/dL)	20.80%	14.30%	13.9%	0.002	< 0.05	< 0.05	NS
Hypercholesterolemia	20.80%	16.40%	21.1%	NS			
Treated hypercholesterolaemia	-	2.50%	40.8%	0.000			
Treated to target	-	84%	91.0%	0.000			
Hypercholesterolaemia to target	-	12.80%	37%	0.000			
Female							
Uncontrolled high cholesterol (≥ 240 mg/dL)	19.90%	18.20%	18.1%	0.007	< 0.05	< 0.05	NS
Hypercholesterolemia	19.90%	18.90%	25.8%	NS			
Treated hypercholesterolaemia	-	7.90%	39.1%	0.000			
Treated to target	-	46.70%	80.2%	0.000			
Hypercholesterolaemia to target	-	3.70%	37%	0.000			

Data standardized to the European population; Men and women. Uncontrolled high cholesterol (≥ 240 mg/dL): Subjects with Cholesterolaemia ≥ 240 mg/dL, may or may not have been taking medication; Hypercholesterolemia: Subjects with cholesterol ≥ 240 + cholesterol-lowering therapy subjects; Treated hypercholesterolaemia: Treated/Hypercholesterolemia; Treated to target: Treated to target (cholesterol < 240 mg/dL)/all subjects treated; Hypercholesterolaemia to target: (Hypercholesterolemia < 240 mg/dL/subject with hypercholesterolemia). NS: Non-significant.

evaluate the effectiveness of interventions.

In Southern Italy, the cholesterol value, in the years between 1950 and 1960, was one of the lowest in the world[17]. Our country is the place where the practice of the Mediterranean Diet was born and developed. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990[18]. In those years, a greater attention to risk factors, the return to a more balanced nutrition, and use of statins have led to important change in the trend. Our data show a favorable trend, similar to that registered in other parts of the world, including North America and Western European countries[7,14,19,20]. We have observed a more favorable trend in the male population, consequence of a difference between the two sexes in percentage of treated hypercholesterolemic (48% in male and 39.1% in female) and in reaching an acceptable target (91% in male and 80.2% in female). This can be explained probably by considering a more direct drug intervention in the male population than in the female one. A therapeutic attitude more aggressive in men than in women is clearly described in the literature[21,22].

Another interesting observation is that, in the period before the statins, the cholesterol curves showed a reduction only after 65 years, due to the fact that subjects with high cholesterol die more easily[9]. Today, with statins, the distribution of cholesterol is reduced already after 45 years to stay then essentially unchanged.

Recently, the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group has published the trend at national, regional and global cholesterol[14].

These data provide an interesting point of comparison to analyze the data of our study. Globally, mean total cholesterol changed little between 1980 and 2008, falling by less than 3.9 mg/dL per decade in both sexes. In our population the mean cholesterol was steadily declining in men (7.3 mg/dL) while substantially constant in women, with a decrease in the survey of the 1998/99 before recovering to the initial values. An exception is the age group 64-75 years, where there is a decrease of over 20 years, 14 mg/dL, and this is probably related to the increased use of statins in the population more adult. Doing an analysis for areas, total cholesterol decreased among high-income territories formed by Australia, North America, Western Europe, Central and Eastern Europe regional. The decreases were approximately 7.7 mg/dL per decade in both sexes. In the population of

the VIP Project we find a smaller reduction: 3.7 mg/dL per decade in men and non-reduction for women. Despite this, serum total cholesterol in 2008 was higher in high-income countries; the regional mean was 202.2 mg/dL for men (in our population are slightly lower: 197 mg/dL) and 201.8 mg/dL for female (the values of the VIP project are slightly higher: 203.3 mg/dL). It was lowest in sub-Saharan Africa at 157.45 mg/dL in men and 164.8 mg/dL for female. Thus, there is evidence of a trend in the reduction of cholesterol levels in many areas of the world, as confirmed by our data, but we must undoubtedly increase interventions (particularly in women) because this result could be more obvious. The intervention must be conducted in two directions: encourage healthy diets, with unsaturated fats and extending and optimizing therapy with statins in the population at greatest risk[23-25].

COMMENTS

Background

Coronary heart disease (CHD) is now the leading cause of death worldwide. Raised serum total cholesterol is an important cardiovascular risk factor, which causes an estimated 4.4 million deaths every year worldwide. Therefore, the focus on cardiovascular prevention must remain high. The aim was to estimate trend in total serum cholesterol, in a Mediterranean area of southern Italy, in the last twenty years. In particular the authors considered and compared the data collected as part of "Montecorvino Rovella Project " 1988-1989 and cross-sectional data from the two phases of the "VIP Project-Valle dell Irno Prevenzione": 1988-1989 (1st phase) and 2008-2009 (2nd phase). Data show a reduction of mean cholesterol in the last twenty years of 7.3 mg/dL for men and unchanged values for women. Is statistically increased the number of patients treated and those treated to target.

Research frontiers

Research from the World Health Organization highlights the importance of raised blood cholesterol as a risk factor for CHD. In Southern Italy, the cholesterol value, in the years between 1950 and 1960, was one of the lowest in the world. The authors' country is the place where the practice of the Mediterranean Diet was born and developed. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990. Successively, high consumption of saturated fats and low use of vegetable fibres that had as a consequence an increase of cholesterol until the beginning of 1990. In those years, a greater attention to risk factors, the return to a more balanced nutrition, and use of statins have led to important change in the trend. The data show a favorable trend, similar to that registered in other parts of the world, including North America and Western European countries.

Innovations and breakthroughs

The authors have observed a more favorable trend in the male population, consequence of a difference between the two sexes in percentage of treated hypercholesterolemics (48% in male and 39.1% in female) and in reaching an acceptable target (91% in male and 80.2% in female). This can be explained probably by considering a more direct drug intervention in the male population than in the female one. A therapeutic attitude more aggressive in men than in women is clearly described in the literature. Another interesting observation is that, in the period before the statins, the cholesterol curves showed a reduction only after 65 years, due to the fact that subjects with high cholesterol die more easily. Today, with statins, the distribution of cholesterol is reduced already after 45 years to stay then essentially unchanged.

Applications

There is evidence of a trend in the reduction of cholesterol levels in many areas of the world, as confirmed by our data, but the authors must undoubtedly increase interventions (particularly in women) because this result could be more obvious. The intervention must be conducted in two directions: encourage healthy diets, with unsaturated fats and extending and optimizing therapy with statins in the population at greatest risk.

Terminology

The World Health Report 2002 estimates that around 8% of all disease burdens in developed countries is caused by raised blood cholesterol and that over 60% of CHD and around 40% of ischaemic stroke in developed countries is due to total blood cholesterol levels in excess of the theoretical minimum (3.8 mmol/L). Variations in diet, especially consumption of animal-based *vs* plant-based fats, adiposity, and use of drugs to lower cholesterol have led to differences in serum cholesterol concentrations across populations and over time.

Peer review

The authors are dealing with an interesting topic, as the regulation of risk factors and the related communities planning are the best way to fight cardiovascular disease. The objective of this study was to examine trends of uncontrolled serum total cholesterol, treatment and control in a Mediterranean region (Campania). Data show a reduction of mean cholesterol in the last 20 years of 7.3 mg/dL for men and unchanged valves for women. Encouraging increases in awareness, treatment, and control of hypercholesterolemia occurred from 1988 through 2008.

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BRIEF ARTICLE

Positive influence of aspirin on coronary endothelial function: Importance of the dose

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Abstract

AIM: To investigate the effects of different doses of aspirin on coronary endothelial function.

METHODS: The study included 139 Japanese subjects (mean age, 60 years; 53 women) with angiographically normal coronary arteries. Patients were distributed into Group Ⅰ (n = 63), who was administered aspirin and Group Ⅱ (n = 76), the control, who were not administered aspirin. Group Ⅰ was further divided into Group Ⅰa (n = 50, low-dose aspirin, 100 mg) and Group Ⅰb (n = 13, high-dose aspirin, 500 mg). After a routine coronary angiography, acetylcholine (ACh; 3 and 30 μg/min successively) and nitroglycerin (NTG) were infused into the left coronary ostium over 2 min. The change in the diameter of the coronary artery in response to each drug was expressed as the percentage change from baseline values.

RESULTS: The patient characteristics did not differ between the two groups. The change in coronary diameter in response to ACh was greater in Group Ⅰ than in Group Ⅱ (P = 0.0043), although the NTG-induced coronary vasodilation was similar between groups. ACh-induced dilation was greater in Group Ⅰa than in Group Ⅰb (P = 0.0231). Multivariate regression analysis showed that a low-dose of aspirin (P = 0.0004) was one of the factors associated with ACh-induced dilation at 30 μg/min.

CONCLUSION: In subjects with angiographically normal coronary arteries, aspirin only had a positive influence on coronary endothelial function at the low dose of 100 mg. This improvement of coronary endothelial function may be involved in the preventive effect of aspirin against future coronary events.

Key words: Acetylcholine; Aspirin; Coronary endothelial function; Quantitative coronary angiography

Core tip: We investigated the effect of aspirin on coronary endothelial function. Patients were distributed into Group Ⅰ, who were administered aspirin and Group Ⅱ, which was the control group. Group Ⅰ was divided into Group Ⅰa (low-dose aspirin) and Group Ⅰb (high-dose aspirin). Acetylcholine (ACh)-induced coronary dilation was greater in Group Ⅰ than in Group Ⅱ and was greater in Group Ⅰa than in Group Ⅰb. Multivariate regression analysis showed that a low-dose of aspirin was associated with ACh-induced coronary dilation. A Low dose of aspirin has a positive influence on coronary endothelial function.

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INTRODUCTION

Aspirin, an inhibitor of cyclooxygenase-1, helps prevent cardiovascular disease. However, its efficacy with respect to primary prevention of cardiovascular events remains controversial[1-6]. Although several studies have shown that primary prevention with aspirin has a positive effect on cardiovascular disease[1-3], others have not shown any such relationship[4-6]. Aspirin increases the risk of bleeding, particularly gastrointestinal bleeding[7]. In addition, the discrepancies in the effect of primary prevention with aspirin may depend on the cardiovascular risk of individual patients. These factors may contribute to the study findings reported for this population; therefore, aspirin may be effective in the primary prevention of cardiovascular disease if the degree of risk for cardiovascular burdens and gastrointestinal bleeding are appropriately assessed. The efficacy of aspirin in the secondary prevention of cardiovascular disease is, however, well established[8,9], and aspirin reduces reoccurrence in patients with established cardiovascular disease.

The dose of aspirin used to prevent cardiovascular disease ranges from 75 to 325 mg/d[8,10]. Aspirin inhibits the synthesis of thromboxane A2 in platelets and prostaglandin I2 in endothelial cells. Low-dose aspirin only inhibits thromboxane A2 in platelets, whereas high-dose aspirin inhibits both thromboxane A2 and prostaglandin I2[11]. Low-dose aspirin (approximately 81-162 mg) has been widely used as a preventive therapy against cardiovascular disease[10]. This preventive effect of aspirin may be primarily due to its prevention of thrombus formation, which is mediated by inhibition of platelet aggregation[11]. However, several studies have shown a favorable effect of aspirin on endothelial function[12-16], and there is some interest in the relationship between aspirin and endothelial function. To investigate the existence of such a relationship in the coronary arteries, and if one exists, to confirm whether this relationship depends on the dose of aspirin used, we investigated the effects of different doses of aspirin on coronary endothelial function in patients with angiographically normal coronary arteries.

MATERIALS AND METHODS

Study population

One hundred and thirty-nine Japanese patients who underwent coronary angiography to evaluate chest pain were included in this study. All had angiographically normal epicardial coronary arteries, normal left ventricular function (contrast ventriculographic ejection fraction; LVEF, ≥ 60%), and normal coronary flow reserve (CFR; > 2.0). We excluded patients with vasospastic angina, previous myocardial infarction, left ventricular hypertrophy, moderate-severe valvular disease detected using echocardiography, heart failure, or other serious diseases.

The patients were divided into two groups based on their aspirin intake: Group I consisted of 63 patients who took aspirin and Group Ⅱ consisted of 76 patients who did not. The 63 patients in Group I were subdivided into Group I a, consisting of 50 patients who took aspirin 100 mg/d, and Group I b, consisting of 13 patients who took aspirin 500 mg/d in Group I a, 32 patients had taken aspirin for a possible coronary artery disease before admission. The remaining 18 patients in Group I a and 13 patients in Group I b began taking aspirin on admission. All patients in Group I took aspirin for at least 2 d. Written informed consent was obtained from all patients before their entry into the study. The protocol was approved by the Ethics Committee of our institution.

Study protocol

All anti-anginal agents were discontinued at least 48 h before catheterization, except for sublingual nitroglycerin, which was withheld for 1 h before catheterization but was otherwise unrestricted. Diagnostic left heart catheterization and coronary angiography were performed using a standard percutaneous brachial approach. A 6F-guide catheter was introduced into the left main coronary artery. A 0.0014-inch Doppler flow guidewire (Volcano FloWire; Volcano Therapeutics Inc., Rancho Cordova, CA) was subsequently advanced through the guide catheter into the proximal segment of the left anterior descending coronary artery. The wire tip was positioned in a straight segment of the vessel to obtain a reliable flow-velocity signal.

After baseline control conditions were established, incremental doses of acetylcholine (ACh) were infused into the left coronary artery (3 and 30 μg/min) for 2 min with 5-min intervals between consecutive doses. After re-establishment of control conditions, nitroglycerin was intracoronarily infused at a rate of 200 μg/min for 1 min. Finally, adenosine triphosphate (20 μg) was infused. ACh and nitroglycerin (NTG) were directly infused into the left coronary ostium using an infusion pump (TE-311; Terumo, Tokyo, Japan) at a rate of 1 mL/min.

Coronary angiography was performed under controlled conditions and at the end of each drug infusion. Coronary blood flow (CBF) velocity was continuously monitored using a 12-MHz pulsed Doppler velocimeter (FloMap; Volcano Therapeutics Inc.). Arterial pressure, heart rate, and electrocardiogram were continuously monitored and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

Quantitative coronary angiography

The method used for measuring the coronary diameter was previously described in detail[17-20]. The coronary segment 2 mm distal to the Doppler wire tip was selected for quantitative analysis. In each patient, the luminal diameters of selected segments of the left anterior descending coronary artery were measured by a single investigator blinded to angiographic and clinical data to determine the effects of the different drugs on epicardial coronary diameter. The luminal diameters were measured on an end-diastolic frame using a computer-assisted coronary angiographic analysis system (CAAS Ⅱ /QUANTCOR; Siemens, Berlin and Munich, Germany).

Means of triplicate measurements of luminal diameter were used for analysis. Changes in coronary diameter in response to ACh and NTG infusions are expressed as the percentage change from the baseline measurement on the angiogram obtained before infusion. Intra- and inter-observer variability have previously been reported to be excellent[17].

Estimation of CBF and CFR

CBF was calculated as the product of CBF velocity and vessel diameter using the following formula: $\pi \times$ average peak velocity $\times 0.125 \times$ diameter^2. For CBF calculations, the internal diameter of the vessel at the location of the flow measurements (2 mm distal to the wire tip) was measured using the method described above. CFR was calculated as the ratio of CBF velocity after adenosine triphosphate infusion relative to baseline velocity.

Definition of coronary vascular function

As described previously[17,18,21-23], in the present study, we adopted the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of conduit vessels. When the ACh-induced changes in coronary diameter is reduced despite of preserved NTG-induced dilation, it is accepted that coronary endothelial dysfunction at the level of conduit vessel is present. In addition, we adopted the percent change in CBF in response to ACh infusion and CFR as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of resistance vessels. When the ACh-induced increase in CBF is reduced despite of preserved CFR, it is accepted that coronary endothelial dysfunction at the level of resistance vessel is present.

Other parameters

Blood samples were drawn from each patient on the same day as coronary angiography after fasting. Total cholesterol, triglyceride, high-density lipoprotein -cholesterol, low-density lipoprotein -cholesterol, glucose, hemoglobin A1C, high-sensitive C-reactive protein (CRP), and fibrinogen levels were subsequently measured.

Statistical analysis

All data are expressed as mean ± SEM. Baseline characteristics of the two groups were compared using Student's unpaired *t* test or χ^2 analysis, as appropriate. Serial changes in hemodynamic variables and changes in coronary vasoreactivity in response to drug infusion were compared using a one-way analysis of variance. If the analysis of variance showed a significant difference between means, the level of significance was determined by contrast analysis. Serial percentage changes in the coronary vascular response to ACh infusion were compared between groups using a two-way analysis of variance. Univariate and multivariate regression analyses were also performed to identify factors associated with percent changes in coronary artery diameter induced by ACh. A P value < 0.05 was defined as indicative of statistical significance.

Table 1 Characteristics of the patients (mean ± SE) *n* (%)

	Group Ⅰ (*n* = 63)	Group Ⅱ (*n* = 76)	*P* value
Age	60 ± 1	59 ± 1	NS
Men/women	40/23	46/30	NS
Body mass index (kg/m^2)	24.6 ± 0.3	24.2 ± 0.3	NS
Coronary risk factors			
Smoking (%)	22 (35)	19 (25)	NS
Hypertension (%)	29 (46)	29 (38)	NS
Hypercholesterolemia (%)	23 (37)	30 (39)	NS
Diabetes mellitus (%)	9 (14)	6 (8)	NS
Medications			
Statins (%)	11 (17)	13 (17)	NS
ACI and/or ARB (%)	8 (13)	11 (14)	NS
LV ejection fraction (%)	70 ± 1	71 ± 1	NS

ACI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin Ⅱ receptor blocker; LV: Left ventricular; NS: Not significant.

Table 2 Biochemical parameters (mean ± SE)

	Group Ⅰ	Group Ⅱ	*p* value
Total cholesterol (mg/dL)	210 ± 5	206 ± 5	NS
Triglyceride (mg/dL)	155 ± 10	144 ± 9	NS
HDL-cholesterol (mg/dL)	54 ± 2	52 ± 2	NS
LDL-cholesterol (mg/dL)	125 ± 5	125 ± 4	NS
Fasting blood sugar (mg/dL)	100 ± 2	98 ± 2	NS
Hemoglobin A1C (%)	5.5 ± 0.1	5.4 ± 0.1	NS
C-reactive protein (mg/L)	1.4 ± 0.4	2.1 ± 0.4	NS
Fibrinogen (mg/dL)	340 ± 21	350 ± 22	NS

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NS: Not significant.

RESULTS

Patient characteristics and biochemical parameters

The patient characteristics are detailed in Table 1. Age, sex, body mass index, frequency of coronary risk factors, medications, and LVEF were similar between the two groups. The patient characteristics between Groups Ⅰ a and Ⅰ b were also similar.

Data on the biochemical parameters are detailed in Table 2. The biochemical parameters did not differ between Group Ⅰ and Group Ⅱ; the parameters were also similar between Group Ⅰa and Group Ⅰ b.

Results of coronary vasoreactivity

The hemodynamic and coronary vasoreactivity findings are shown in Table 3. Hemodynamics were similar between the two groups, as were the baseline coronary artery diameter and CBF. Changes in coronary artery diameter in response to ACh infusion were reduced in Group Ⅱ compared with those in Group Ⅰ ($P = 0.0043$), whereas NTG-induced coronary dilation did not differ between the two groups (Figure 1 and Table 3). The increase in CBF in response to ACh infusion and CFR did

Table 3 Hemodynamics and angiographic results between groups Ⅰ and Ⅱ (mean ± SE)

	Group Ⅰ	Group Ⅱ	*P* value
Baseline mean BP(mmHg)	107 ± 2	104 ± 1	NS
Baseline heart rate (/min)	66 ± 1	67 ± 1	NS
Coronary diameter			
Baseline (mm)	3.22 ± 0.07	3.07 ± 0.06	NS
ACh at 3 μg/min (mm)	3.28 ± 0.07	3.07 ± 0.07	NS
(% change)	1.8 ± 0.9	0.1 ± 0.8	NS
ACh at 30 μg/min (mm)	3.26 ± 0.08	2.95 ± 0.07	0.0030
(% change)	1.2 ± 1.1	-3.9 ± 1.0	0.0008
Nitroglycerin (mm)	3.67 ± 0.07	3.51 ± 0.07	NS
(% change)	14.0 ± 1.1	15.1 ± 1.0	NS
Coronary blood flow			
Baseline (mL/min)	88.1 ± 3.7	81.9 ± 3.3	NS
ACh at 3 μg/min (mL/min)	131.3 ± 7.8	123.3 ± 7.1	NS
(% change)	50.0 ± 6.3	52.1 ± 5.7	NS
ACh at 30 μg/min (mm)	219.9 ± 21.4	194.8 ± 19.5	NS
(% change)	172.8 ± 33.2	142.6 ± 30.3	NS
Coronary flow reserve	3.4 ± 0.2	3.4 ± 0.1	NS

BP: Blood pressure; ACh: Acetylcholine; NS: Not significant.

Table 4 Hemodynamics and angiographic results between groups Ⅰa and Ⅰb (mean ± SE)

	Group Ⅰa (*n* =50)	Group Ⅰb (*n* = 13)	*P* value
Baseline mean BP (mmHg)	108 ± 2	105 ± 3	NS
Baseline heart rate (/min)	67 ± 2	65 ± 3	NS
Coronary diameter			
Baseline (mm)	3.23 ± 0.08	3.14 ± 0.16	NS
ACh at 3 μg/min (mm)	3.32 ± 0.08	3.05 ± 0.17	NS
(% change)	2.4 ± 0.9	-0.6 ± 1.8	NS
ACh at 30 μg/min (mm)	3.32 ± 0.08	3.05 ± 0.17	NS
(% change)	2.6 ± 1.1	-3.8 ± 2.9	0.0123
Nitroglycerin (mm)	3.67 ± 0.08	3.65 ± 0.16	NS
(% change)	13.6 ± 1.1	15.4 ± 2.2	NS
Coronary blood flow			
Baseline (mL/min)	91.0 ± 4.6	76.8 ± 9.1	NS
ACh at 3 μg/min (mL/min)	137.7 ± 9.5	106.8 ± 18.7	NS
(% change)	53.4 ± 6.8	37.0 ± 13.4	NS
ACh at 30 μg/min (mm)	195.2 ± 15.9	188.6 ± 31.1	NS
(% change)	125.3 ± 16.2	141.9 ± 31.7	NS
Coronary flow reserve	3.4 ± 0.2	3.7 ± 0.3	NS

BP: Blood pressure; ACh: Acetylcholine; NS: Not significant.

not differ between the two groups (Table 3).

The hemodynamic and coronary vasoactivity findings for the subgroups of Group I are shown in Table 4. Hemodynamics, coronary artery diameter, and CBF at baseline did not differ between Group I a and Group I b (Table 4). However, changes in coronary artery diameter in response to ACh infusion were reduced in Group Ib compared with those in Group I a (P = 0.0231). NTG-induced coronary dilation did not differ between the two groups (Table 4, Figure 2). The increase in CBF in response to ACh infusions or CFR did not differ between the two groups (Table 4). Statistically significant differences were observed in the percentage change in coronary diameter induced by ACh infusion at a dose of 30 μg/min, and the subsequent analyses were performed using this value.

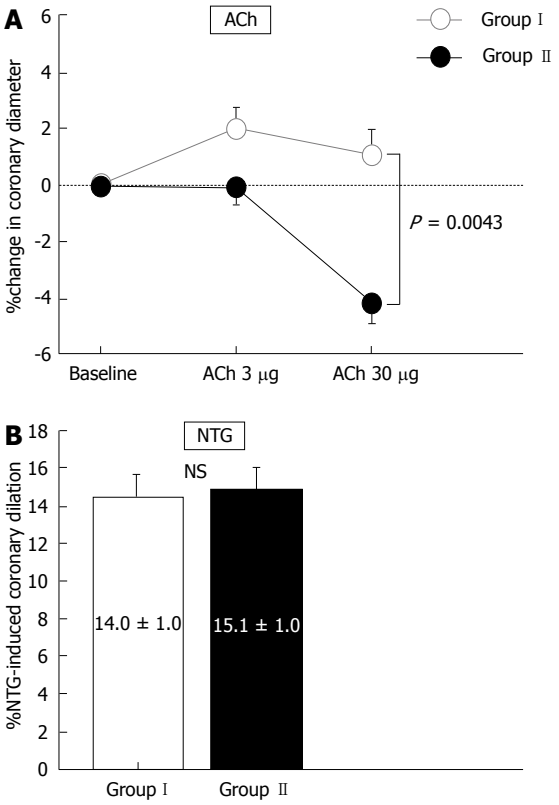

Figure 1 Percentage changes in epicardial coronary artery diameter in response to acetylcholine infusion and nitroglycerin in Groups Ⅰ and Ⅱ. A: Greater changes in coronary artery diameter in response to acetylcholine infusion were observed in Group Ⅰ (open circles) compared with Group Ⅱ (black circles); B: Nitroglycerin-induced coronary dilation was similar between Groups Ⅰ and Ⅱ. Vertical bars represent SEM. ACh: Acetylcholine; NS: Not significant; NTG: Nitroglycerin.

Factors responsible for coronary endothelial dysfunction

As noted above, statistically significant differences between the two groups were observed in the percentage change in coronary diameter induced by ACh infusion at a dose of 30 μg/min. Univariate analysis revealed that the presence or absence of aspirin (P = 0.0002), NTG-induced coronary dilation (P = 0.0142), and the increase in CBF in response to ACh infusion at a dose of 3 μg/min were associated with the change in coronary artery diameter response induced by ACh infusion at 30 μg/min; the mean blood pressure at baseline also showed a trend toward a positive association with the change in coronary artery diameter associated with ACh infusion at 30 μg/min (P = 0.0888). Multivariate regression analysis using these parameters demonstrated that low-dose aspirin (P = 0.0004), NTG-induced coronary dilation (P = 0.0077), and the increase in CBF induced by ACh infusion at a dose of 3 μg/min (P = 0.0344) were positively associated with the change in coronary artery diameter induced by ACh infusion at 30 μg/min, and that not taking aspirin (P = 0.0387) was negatively associated with this change (r^2 = 0.212; Table 5).

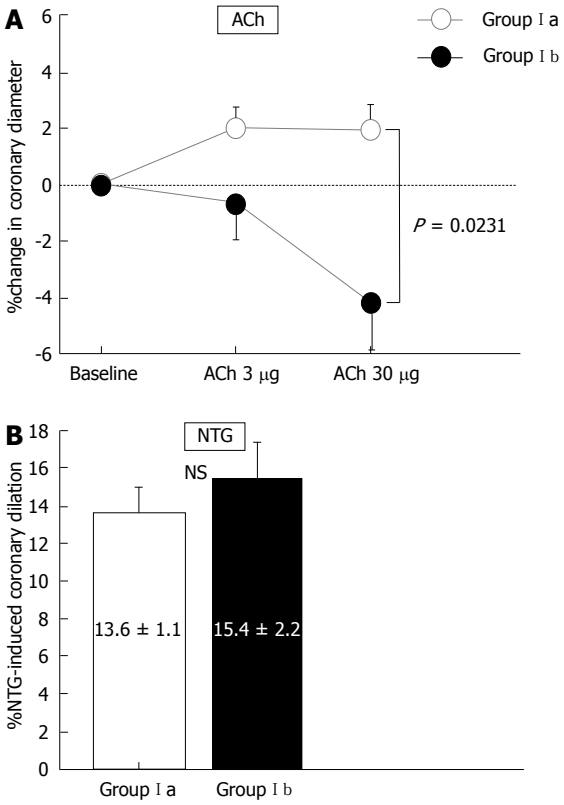

Figure 2 Percentage changes in epicardial coronary artery diameter in response to acetylcholine infusion and nitroglycerin in Groups I a and I b. A: Greater changes in coronary artery diameter in response to acetylcholine (ACh infusion were observed in Group I a (open circles) than those in Group I b (gray circles); B: Nitroglycerin -induced coronary dilation was similar between Groups I a and I b. Vertical bars represent SEM. ACh: Acetylcholine; NTG: Nitroglycerin; NS: Not significant.

DISCUSSION

In the present study, we investigated the effects of different doses of aspirin on coronary endothelial function in patients with angiographically normal coronary arteries. We showed that the change in coronary artery diameter in response to ACh infusion was higher in patients who took aspirin than in those who did not take aspirin. However, NTG-induced coronary dilation, the increase in CBF in response to ACh infusion, and CFR were not significantly different between the two groups. In addition, among patients who took aspirin, the change in coronary artery diameter in response to ACh infusion was higher in those who took a low dose of aspirin (100 mg/d) than in those who took a higher dose of aspirin (500 mg/d). Multivariate regression analysis demonstrated that taking a low dose of aspirin was positively associated with ACh-induced coronary artery dilation and not taking aspirin was negatively associated with such dilation. These findings suggest that taking a low dose of aspirin has a positive influence on coronary endothelial function in patients with angiographically normal coronary arteries.

The preventive effect of aspirin against cardiovascular disease is mainly because of its inhibition of platelet aggregation, which is mediated by the inhibition of thromboxane A2 in platelets and prevention of thrombus formation[11]. However, there has been some interest in the relationship between aspirin and endothelial function[12-16]. Husain *et al*[12] reported that intra-arterial co-infusion of aspirin (1000 mg) restored ACh-induced microvascular endothelial dysfunction of the femoral vasculature in patients with coronary atherosclerosis and atherosclerotic burdens. In addition, Noon *et al*[13] showed that intra-arterial co-infusion of aspirin (600 mg) restored ACh-induced microvascular endothelial dysfunction of the forearm in hypercholesterolemic patients but not in control subjects. Monobe *et al*[14], Magen *et al*[15], and Furuno *et al*[16] have reported a relationship between aspirin and endothelial function using flow-mediated dilation (FMD) of the brachial artery. Monobe *et al*[14] reported that FMD was higher in hypercholesterolemic patients who took a low dose of aspirin (100 mg). Magen *et al*[15] reported that FMD was higher in hypertensive patients who took a low dose of aspirin (100 mg). Furuno *et al*[16] investigated the effects of various doses of aspirin on FMD in healthy male subjects and showed that aspirin had a positive influence even in healthy volunteers. Taking these studies into consideration, the effect of aspirin on endothelial function may, in part, depend on the severity of the atherosclerotic burden or on the dose of aspirin.

In the present study, we showed that aspirin has a positive influence on coronary endothelial function in patients with chest pain who have angiographically normal coronary arteries. When assessing coronary endothelial function, it is advantageous to simultaneously assess endothelial function at the level of both the conduit and resistance vessels[21,22]. In this study, aspirin only had a positive effect on coronary endothelial function at the level of the conduit vessels. In general, endothelium-derived nitric oxide (NO) and prostaglandin I 2 act as an endothelium-derived vasodilators, primarily in large vessels[24-26]; this may account for the effect of aspirin on coronary endothelial function being limited to the level of the conduit vessels.

With regard to the dose of aspirin administered, 75-325 mg/d and particularly, 75-162 mg/dare widely used in the clinical setting[8,10]. Although a high dose of aspirin is effective in preventing cardiovascular disease[8], bleeding increases as the dose of aspirin increases[27], and this may explain the widespread use of low-dose of aspirin. Theoretically, a high dose of aspirin inhibits both

Table 5 Multivariate analysis of variables influencing %change in coronary diameter induced by acetylcholine infusion

Variables	%change in coronary diameter induced by ACh 30 mg/min	
	t value	*P* value
Taking aspirin		
(+) at the low dose	3.61	0.0004
(-)	-2.09	0.0387
Nitroglycerin-induced dilation	2.71	0.0077
%increase in CBF at ACh 3 mg/min	2.14	0.0344
Mean blood pressure at baseline	1.79	0.0765

r^2 = 0.212. ACh: Acetylcholine; CBF: Coronary blood flow.

thromboxane A2 in the platelets and prostaglandin I 2 in endothelial cells; therefore, it is not unexpected that a high dose of aspirin has a negative influence on endothelial function. However, only one study has shown the relationship between the dose of aspirin administered and endothelial function[16]. Furuno *et al*[16] reported that the maximum effect of aspirin on endothelial function was observed at 162 mg/d, whereas the minimum effect was observed at 660 mg/d. In the present study, because a small number of patients took a high dose of aspirin, the multivariate regression analysis did not show that taking a high dose of aspirin led to a deterioration in endothelial function. However, in the subgroup analysis, the coronary endothelial function of patients who took a high dose of aspirin was significantly lower than that of patients who took a low dose. These results suggest that a low dose of aspirin is superior to a high dose of aspirin for improving endothelial function.

Several studies have examined possible mechanisms associated with the positive effect of aspirin on endothelial function[12,28-31]. Theoretically, a low dose of aspirin inhibits only thromboxane A2, which is an endothelium-derived, cyclooxygenase-dependent constricting factor, leading to vasodilation[12]. Furthermore, aspirin has a positive effect on endothelium-derived NO. Aspirin directly enhances NO synthesis in endothelial cells[28,29]; it delays the onset of endothelial senescence[30] and reduces oxidative stress[31]. These factors may contribute to aspirin-induced improvement of endothelial function. It is possible that vascular inflammation causes endothelial dysfunction[18], but aspirin has not been observed to have any influence on the assessment of high-sensitive CRP. Therefore, the anti-inflammatory effect of aspirin may not be involved in the mechanism through which aspirin exerts its positive effect on endothelial function.

The present study demonstrated that a low dose of aspirin had a positive effect on coronary endothelial function in patients with angiographically normal coronary arteries. However, this does not always imply that a low dose of aspirin should be administered for the primary prevention of cardiovascular disease. As mentioned above, there is no doubt that aspirin frequently causes gastrointestinal bleeding[27]; therefore, despite the positive effect of aspirin on coronary endothelial function, a low dose of aspirin should be used, particularly for primary prevention in consideration of the balance of atherosclerotic burden and bleeding risks.

There are several limitations to the present study. First, all patients in our study had chest symptoms and had undergone coronary angiography; thus, they may represent a specific group. Therefore, the results of the present study may not be representative of endothelial function in all patients. Second, the duration of aspirin intake was not consistent between the patients who took aspirin. This difference may have influenced the results, such as the high-sensitive CRP level. Third, the number of patients who took a high dose of aspirin was small, and this may also have influenced the results. However, it was not ethically possible to increase the number of patients in this subgroup. Finally, we did not measure biochemical parameters and platelet function associated with aspirin. Therefore, we cannot report on the precise mechanisms by which aspirin had a positive influence on coronary endothelial function in the present study.

In conclusion, our findings suggest that only low-dose aspirin has a positive effect on coronary endothelial function in patients who have chest pain but angiographically normal coronary arteries. The favorable effect of aspirin on coronary endothelial function as well as the prevention of thrombus formation may be involved in the mechanisms responsible for the preventive effects of aspirin against cardiovascular disease.

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COMMENTS

Background

Aspirin, an inhibitor of cyclooxygenase-1, helps prevent cardiovascular disease. This preventive effect of aspirin may be primarily due to its prevention of thrombus formation. In addition, several studies have reported a relationship between aspirin and endothelial function. However, it has not been fully elucidated whether aspirin has a positive influence on coronary endothelial function.

Research frontiers

Aspirin has a preventive effect against cardiovascular disease, mainly mediated by its anti-platelet effect. Clarifying the relationship between aspirin and endothelial function may reveal other mechanisms responsible for the preventive effect of aspirin against cardiovascular diseases.

Innovations and breakthroughs

The results showed that acetylcholine (ACh)-induced coronary artery dilation was higher in patients who took aspirin compared with patients who did not take aspirin, whereas nitroglycerin (NTG)-induced coronary artery dilatation and coronary blood flow increase in response to ACh or coronary flow reserve did not differ significantly between the 2 groups. Furthermore, aspirin-induced coronary artery dilation in response to ACh was higher in patients who took low-dose aspirin, compared with patients who took high-dose aspirin. These findings suggest that only low-dose aspirin has a positive effect on coronary endothelial function in such patients.

Applications

Aspirin should be used in primary prevention, but in consideration of the balance between atherosclerotic burden and bleeding risks because it can cause gastrointestinal bleedings. However, if taking aspirin, a low dose should be recommended for improving endothelial function.

Terminology

There are two components of coronary vascular functions: at the level of conduit vessels (epicardial coronary artery) and at the level of resistance vessels (microvascular coronary artery). In addition, there are two factors of coronary artery vasodilation: endothelium-dependent and -independent. In the present study, using quantitative coronary angiography and Doppler velocity measurements, the authors defined the percent changes in epicardial coronary diameter in response to ACh and NTG infusions as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of conduit vessels, and the authors defined the percent change in coronary blood flow in response to ACh infusion and coronary flow reserve as the endothelium-dependent and -independent functions, respectively, of the coronary artery at the level of resistance vessels.

Peer review

The research is important in that it provides new evidence of aspirin effect on the endothelial function of the coronary artery. The experiments are well designed with good controls matched with age, gender, body mass index, coronary risk factors, medications, left ventricular function, as well as many biochemical parameters. The study also excluded many apparent heart diseases, making the sampled population more homogenous. Paper is well organized.

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BRIEF ARTICLE

Myocardial bridging analysis by coronary computed tomographic angiography in a Saudi population

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Abstract

AIM: To assess the incidence, location, morphology and clinical association of myocardial bridging in a Saudi population using coronary computed tomographic angiography (CCTA).

METHODS: A total of 350 CCTA of Saudi patients were included in this study (236 men, 114 women) with a mean age of 56.3 years. All patients were examined for appropriateness criteria of CCTA indications (typical chest pain, recent onset cardiomyopathy, left bundle branch block, *etc.*). The scans were retrospectively reviewed for the presence of myocardial bridging and any other pathological association.

RESULTS: Myocardial bridging was found in 89 of 350 (22.5%) patients. Most of the intramuscular segments were of the superficial type and found in the mid left anterior descending (LAD) (24.6%), followed by distal LAD (3.7%), diagonal branches (2%), ramus intermedius artery (1.4%) and obtuse marginal artery (0.8%). No myocardial bridging was detected in the right coronary or circumflex arteries. No significant differences were found between males and females (P = 0.14). Coronary artery atherosclerosis was found in 51 of 89 (57.3%) patients with MB. Atherosclerotic plaques were not detected in the intramuscular or distal segment of bridging arteries. Dynamic compression was observed in 35 (94.5%) patients with full encasement. No evidence of myocardial hypoperfusion was found in the territories supplied by the bridging arteries.

CONCLUSION: CCTA is excellent in analyzing myocardial bridging in a Saudi population and the results are comparable to other populations. However, finding the real incidence may need a large multicenter study.

Key words: Coronary heart disease; Myocardial bridging; Coronary computed tomographic angiography; Coronary arteries anatomy; Coronary atherosclerosis

Core tip: A great revolution has happened in imaging of coronary arteries with multi-detector computed tomography. Myocardial bridging is considered a benign anomaly, but in exceptional incidences, it is associated with clinical manifestations. By reviewing the current literature, there is no research studying the prevalence of myocardial bridging (MB) in a Saudi population. This study is considered the first to investigate the prevalence of MB in a Saudi population and its clinical significance in 350 patients. The study highlighted that coronary computed tomographic angiography offers an excellent way to detect and characterize MB and the national prevalence of MB and its anatomical and clinical findings in Saudi Arabia is comparable to worldwide prevalence.

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INTRODUCTION

Myocardial bridging (MB) is an inborn abnormality. It occurs when a segment of a coronary artery or its major branch travels through the myocardium instead of on the surface of the myocardium, resulting in a tunneled arterial segment[1]. In an autopsy study, Ferreira *et al*[2] distinguished two types of MB: superficial bridges crossing the artery perpendicularly or at an acute angle towards the apex and deep bridges characterized by muscle bundles arising from the right ventricular apical trabeculae that cross the affected artery transversely, obliquely or helically before terminating in the interventricular septum[2]. The clinical outcome of patients with MBs has been considered benign when it is not associated with hemodynamic changes[3]. However, the relationship of MB and ischemia remains controversial. Myocardial bridging is considered clinically significant when it is associated with regional hemodynamic compression.

Atherosclerotic changes usually affect the segment immediately proximal to the myocardial bridge, whereas its occurrence in the tunneled coronary segment is still controversial[3-5].

Coronary angiography was considered the gold standard for the diagnosis of myocardial bridging[6,7]. However, it is an invasive procedure and requires a great deal of experience for its interpretation. Also, a superficial type of myocardial bridges may be missed on angiography.

Recently, coronary computed tomographic angiography (CCTA) has been introduced as a noninvasive imaging of the coronary arteries. CCTA is able to visualize the lumens of coronary arteries as well as their walls and the neighboring myocardium in any plane. The depiction rate of MB is greater with 64-section multi-detector computed tomography (MDCT) than with conventional coronary angiography; the higher prevalence of MB on MDCT is considered to be due to the inclusion of partial and full encasement on CCTA, the use of short-axis images obtained perpendicular to the long axis of the left anterior descending (LAD) for all analysis and measurement, and the consistently high image quality of MDCT. Coronary CT Angiography is able to visualize myocardial bridging in a more sensitive and comprehensive way than conventional coronary angiography, in which the diagnosis is not made by the direct visualization of the intramuscular course but the indirect finding of systolic compression of the coronary artery indicated by the milking effect[8,9]. Based on CCTA, Kim *et al*[9] classified myocardial bridging of LAD into three types. Type I is myocardial bridging with partial encasement with the artery within the interventricular gorge and in direct contact with left ventricular myocardium. Type Ⅱ is myocardial bridging with full encasement of LAD by myocardium but without measurable overlying myocardium. Type Ⅲ is myocardial bridging with full encasement of LAD by myocardium but with measurable overlying myocardium (> 0.7 mm)[9].

Table 1 Clinical presentations of the patients *n* (%)

	Total patients	MB patients
Typical chest pain	32 (9.1)	6 (6.8)
Atypical chest pain	138 (39.4)	44 (49.5)
Known coronary artery disease	21 (6)	4 (4.5)
Valvular lesions	16 (4.5)	2 (2.3)
New onset of heart failure symptoms	39 (11.2)	8 (8.9)
Presence of risk factors	104 (29.8)	25 (28)

MB: Myocardial bridging.

The objective of the present study is to assess the incidence of myocardial bridging, as well as their location and morphology, in Saudi patients by using CCTA and comparing the national results to the international worldwide published studies. The clinical association and pathological changes in relationship to myocardial bridging will be also assessed.

MATERIALS AND METHODS

The study was designed to be a retrospective observational study. A total of 350 Saudi Caucasian subjects were included in this study. Patients of other ethnic groups were excluded from the study. The patients included 236 men and 114 women, with an average age of 56.3 ± 11 years. The patients were examined for different clinical cardiac conditions (Table 1). All CCTA studies were done between January 2010 and February 2013. Written informed consent was taken from all patients included in the study. The ethics committee in the hospital approved the use of the clinical and imaging data.

Machines used for CCTA are dual-source 128-slice scanners (Siemens Definition Flash, Forchheim, Germany) and 64-slice CT scanners (Light Speed VCT, GE Healthcare, Waukesha, Wisconsin, United States). Briefly, the technique used for CCTA is as follows. Volumetric data set for the coronary arteries is acquired; the data set covers the entire heart from the proximal ascending aorta (approximately 1-2 cm below the carina) to the diaphragmatic surface of the heart. The scan is acquired in a single breath-hold during inspiration and starts with the injection of a nonionic contrast agent with a concentration of 300-400 mg I/mL at a flow rate of 4-6 mL/s. The total volume of contrast agent depends on the scan length, but typically 60-80 mL is injected, followed by a saline bolus (40-70 mL at 4-6 mL/s). Scanning delay was determined according to the test bolus technique and the region of interest was placed on the ascending aorta. The subjects were instructed to maintain an inspiratory breath-hold during which the CT data and ECG trace were acquired. Retrospective ECG-gated reconstructions were generated at best systolic and diastolic phases

Table 2 Location and incidence of myocardial bridge in different coronary arteries in Saudi patients *n* (%)

Coronary artery	Patients
Mid LAD	68 (24.6)
Distal LAD	13 (3.7)
Diagonal	7 (2)
Ramus intermedius	5 (1.4)
Obtuse marginal artery	3 (0.8)
Left circumflex	0 (0)
Right coronary	0 (0)

LAD: Left anterior descending.

or any other phase of the R-R interval according to the situation. All patients included in this study were in sinus rhythm and were always pre-medicated with nitroglycerin (5 mg sublingually 1 min before the examination) to dilate the coronary arteries. The heart rate ranged between 50 and 78 BPM with a mean of 65 BPM. Most patients received beta-blockers to control their heart rate within this range, as metoprolol tartarate (5 mg/mL Ⅳ bolus) can be repeated according to HR (Beloc ampule, AstraZeneca).

Image reconstruction and interpretation

Two experienced readers certified with level Ⅲ CCTA blindly interpreted the CCTA images for all patients. Interpretation started with the axial resource images, then other multiplanar reconstructions. If myocardial bridging was detected, the depth and length of the tunneled segment were measured. Myocardial bridge was defined as a segment of a coronary artery that courses through the myocardium. Coronary artery disease (CAD) was defined as coronary wall atheromatous change (calcified and non-calcified plaque) with or without luminal reduction. Hemodynamically significant stenosis was defined as equal or greater than 50% reduction of the lumen diameter[10].

Each involved coronary artery was assessed for the presence of atherosclerotic changes and the location of those changes in relationship to the tunneled segment. The exact anatomy of a normal coronary artery or a tunneled segment was identified in both axial and reformatted images in all planes. The tunneled segment is considered superficial or deep if the depth of the covering myocardium is ≤ 1 or > 1 mm respectively[11].

Superficial MB was further subdivided into complete and incomplete based on the full or partial encasement of the LAD within the left ventricular myocardium[9].

The relationship between length, thickness of the bridge, and severity of the stenosis in the coronary artery proximal to the bridge was studied. The coronary CTA findings were classified as the following: no atheromatous changes or luminal narrowing as normal; atheromatous changes without luminal narrowing as mild disease; atheromatous changes with insignificant stenosis as moderate disease; and atheromatous changes with significant stenosis as severe disease. Because the LAD is the most common artery involved with MB, we compared coronary CTA findings in subjects with myocardial bridge with other patients without bridging.

Statistical analysis

The SPSS software package was used for the statistical data analysis. In the descriptive statistical analysis, quantitative variables were expressed as mean ± SDs, whereas categorical variables were expressed as a percentage. Statistical significance was set at P value < 0.05.

RESULTS

All CCTA scans interpreted in this study were of a good image quality and all involved tunneled segments were assessable. Myocardial bridging was found in 89 of 350 (22.5%) patients. No significant differences were found between males and females (P = 0.14). The total intramuscular segment was 96; thus, in 7 patients, more than 1 intramuscular segment was found. Most of the intramuscular segments were in the LAD artery. No myocardial bridging was detected in the right coronary artery or proximal LAD. The coronary arteries involved are presented in Table 2.

The length of the intramuscular segments ranged from 6 to 24 mm (average 15 ± 7 mm). The mean diameter of the intramuscular segments was 3 ± 3 mm and 1.6 ± 0.5 mm for LAD and the remaining arteries, respectively. The diameter of the proximal segments was significantly larger than that of the intramuscular segment, 2.8 ± 0.5 mm for the LAD and 1.8 ± 0.6 mm for the remaining arteries (P > 0.001). The depth of the intramuscular segments ranged from 1 to 6.2 mm and the mean thickness was 2.3 ± 3.9 mm.

Two anatomical patterns of intramuscular segments were identified according to the depth and the course of the intramuscular segment of LAD: the superficial type [46 segments (61.3%)] in which the intramuscular artery had a superficial course along the interventricular septum (Figure 1) and was covered by a thin layer of tissue (< 1 mm thick) and the deep type [29 segments (38.6%)] in which the intramuscular segment penetrated the interventricular septum at a depth between 1 and 6.2 mm (Figure 2).

Imaging evidence of coronary artery atherosclerosis was found in 51 of 89 (57.3%) patients and in 41 of 261 (15.7%) patients without bridging. Atherosclerotic plaques were not detected in the tunneled or distal segment to myocardial bridging in any case. No evidence of myocardial hypoperfusion was found in the myocardial territories subtended by the tunneled coronary arteries.

In 81 patients with a LAD-myocardial bridge, atherosclerotic changes were found in 37 subjects (45.7%) and were consistently localized in the coronary segment proximal to the bridge. Dynamic compression was observed in two patients with partial encasement (5.5%) and 35 patients with full encasement (94.5%). The results indicated that dynamic compression occurred almost exclusively in myocardial bridging with full encasement. In patients with MB of other coronary arteries, significant atherosclerotic

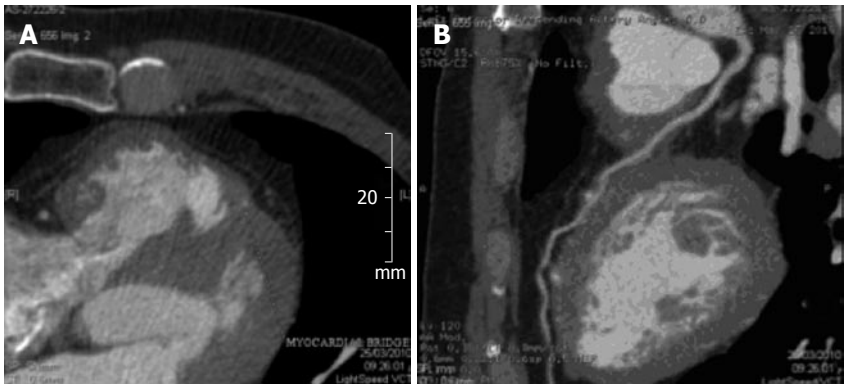

Figure 1 Coronary computed tomographic angiography in transverse axis (A) and long axis (B) show a thin layer of myocardium covering mid-left anterior descending (superficial myocardial bridging).

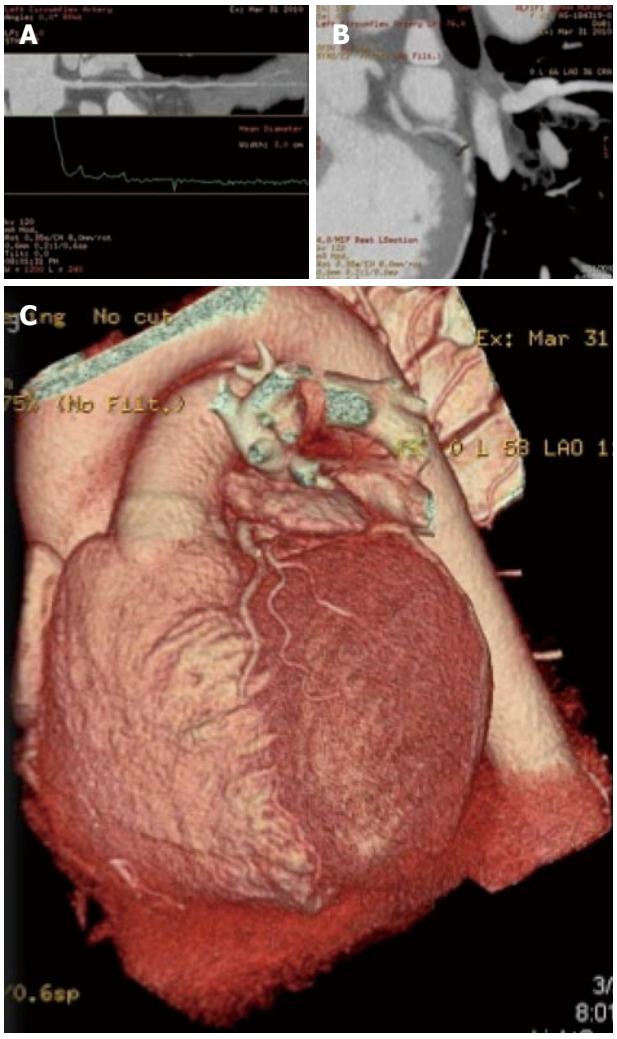

Figure 2 Curved multiplanar reconstruction (A), Sagittal image (B) and 3D- coronary computed tomographic angiography image (C) show thick myocardium covering mid-left anterior descending associated with luminal narrowing of the involved segment (deep myocardial bridging).

changes were detected in three with diagonal artery MB, in two patients with ramus intermediate artery MB, and in one patient with obtuse marginal artery MB.

DISCUSSION

Myocardial bridging is generally considered a benign anomaly but in exceptional cases, it is associated with clinical manifestations. Coronary angiography was considered the gold standard for the diagnosis of myocardial bridging[6,7]. With the introduction of MDCT into clinical practice, a great revolution has happened in the imaging of coronary arteries and their diseases. By reviewing the current literature, there is no research studying the prevalence of MB in a Saudi population. This study is considered the first to investigate the prevalence of MB in a Saudi population and its clinical significance in a relatively big sample size (350 patients). There is a wide discrepancy in the reported prevalence of myocardial bridging between autopsy findings (average 33%, range 15% to 85%)[12,13] and those of conventional angiography (average 5%, range 0.5% to 16%)[14-23]. This discordance occurs because most patients with MB have unrelated overt symptoms that are rarely referred for CCA. Also, CCA is not sensitive enough to detect a milking effect (temporary occlusion of artery during systole) with superficial MB[16]. Recently with an apparent increase in the detection rates of MB, a prevalence as high as 44% has been found[23].

Multiple studies have reported myocardial bridging by coronary CTA, showing a wide range of frequencies. With the use of 16 slice CT frequencies of MB, 18.9% of 228 patients[24], 48.7% of 235 patients[25], 15.8% of 148 patients[26] and 8.7% of 276 patients[27] had MB , while frequencies of MB with 64 slice CT were 6.42%, 30%, 22.5%, 5.8%, 10.4%, 17%, 18.6%, 50%, 37%, 58%, 23%, 44% and 30.5%[9,11,28-38]. On the other hand, by dual source MDCT, Ou[39] detected 5.4% of 2530 patients with MB and the results by Hwang *et al*[7] showed 46% of 1275 patients with MB. The worldwide prevalence of MB (if we exclude the lower and higher results) ranges from 17%-40%[37]. In this study, the incidence of MB in Saudi patients is 22.5%, which lies within the worldwide prevalence range near its lower limit. Also, in the current study, there is no difference in prevalence of MB between male and female subjects. This observation is in agreement with other studies[40,41].

The exact course of the coronary arteries was easily recognized on reformatted MDCT in all our cases together with the consequences of myocardial bridging making it possible for the clinician to see the problem and start the management plan. The length and depth of myocardial bridging in the current study are in agreement

with the results of many studies[7,42]. In the vast majority of cases, angiographic localization of myocardial bridges is in the LAD[43]. Localization other than the LAD is extremely rare[14].

This study shows that the intramuscular course of coronary arteries most commonly involves the middle segment of LAD, followed by its distal segment, and no cases were reported to have MB of the proximal LAD, circumflex or right coronary arteries. These results are in contrast with Loukas *et al*[44] who demonstrated that the presence of myocardial bridges appeared to be related to coronary dominance and it goes with their results in detecting MB in LAD, diagonals, OM and RCA in descending order. On the other hand, Arjomand *et al*[45] reported the first case of myocardial bridging of the circumflex artery (mid-portion) association with acute myocardial infarction.

Also, Tuncer *et al*[46] reported a 63-year-old man with myocardial bridging of the left circumflex coronary artery with significant systolic narrowing at the mid segment after the first obtuse marginal branch.

The length of the intramuscular segments and their mean diameters were clearly determined by CCTA in the current study. The diameter of the proximal segments and the depth of the intramuscular segments were also evaluated. The results revealed a significant decrease in the diameter of the intramuscular segment compared with the adjacent proximal segment. Similar observations were reported in other literature[26,47]. These structural differences between intramuscular and epicardial segments and the reduced diameter of the intramuscular segments have been associated with the detection of atherosclerotic changes detected in our cases.

Depth criteria is not clear cut for the classification of MB into superficial or deep types depicted on CT. However, some research classified MB as superficial or deep depending on the thickness of the covering muscular layer, either $\leqslant$ 1 mm or $\geqslant$ 1 mm respectively[11]. In addition, superficial MB can be classified as complete or incomplete in accordance with the extent of the vessel encasement by the myocardium[9]. This subdivision of superficial MB into complete and incomplete types based on the full or partial encasement is in our study. The incidence of superficial MB (61.3%) was higher than that of the deep type (38.6%). Nearly the same results were illustrated by Hwang *et al*[7] as they found that the prevalence of superficial MB (66%) was higher than that of deep MB (34%). This study illustrated that dynamic compression was detected in two patients with partial encasement (5.5%) and 35 patients with full encasement (94.5%). The results indicated that dynamic compression occurred almost exclusively in myocardial bridging with full encasement, which is in concordance with Kim *et al*[9] who reported that dynamic compression occurred almost exclusively (97.5%) in patients with full encasement of the LAD coronary artery regardless of the presence of overlying muscle[9].

Atherosclerotic changes detected in our series are limited exclusively to the arteries proximal to the deep-tunneled segments. No atherosclerotic changes were found in the superficial type of bridging, which can be explained by the lower shear stress that may contribute to atherosclerosis at proximal segment of MB, whereas higher shear stress may protect it from atherosclerosis at the tunneled segment of MB[48]. Another explanation is that due to the high-pressure gradient at the proximal segment, the local wall tension and subsequent endothelial dysfunction will enhance atherosclerotic changes in that segment[49]. This observation was in agreement with other investigators who reported that the tunneled segments are free of atheroma[50].

Duygu *et al*[51] found a significant positive correlation between hs-CRP and the percentage of atherosclerotic stenosis on the IVUS study of patients with stable angina pectoris and detected MB in LAD. They concluded that their results indicate the presence of low-grade inflammation in patients with an atherosclerotic lesion in bridged segments.

On the other hand, Duygu *et al*[52] studied 71 patients with MB diagnosed by coronary angiography and they concluded that a myocardial bridge may initiate the development of an atherosclerotic lesion or may facilitate progression of atherosclerosis in the proximal segment of the vessel. The risk of acute coronary syndrome rises when atherosclerosis is superimposed on MB.

Zoghi *et al*[53] studied 50 patients with MB in LAD on coronary angiography. All coronary artery segments were evaluated by IVUS and endothelial function was assessed with measurement of flow mediated dilatation in the brachial artery. They concluded that endothelial function is impaired in patients with MB and there is an increased tendency for atherosclerosis proximal to the bridge in MB patients.

However, our results do not agree with other studies showing that the atherosclerotic process occurs in the tunneled coronary segment with the same severity and frequency as the epicardial coronary segments[54].

Some studies showed that such instances of myocardial bridging are linked to clinical complications that include ischemia, acute coronary syndrome, coronary spasm, arrhythmia and sudden death, although in the vast majority of cases, myocardial bridging remains clinically silent[3,4,15,16]. Because dynamic compression occurs almost exclusively in myocardial bridging with full encasement, the incidence of myocardial bridging with full encasement is considered to be more meaningful in the clinical setting[55].

Finally, our results support the classic belief that myocardial bridging is a normal variant and has no clinical consequences as none of our patients required specific medical or invasive treatment for MB. These findings are supported by Kramer *et al*[56] and Nakanishi *et al*[23] who demonstrated that MB is an incidental finding associated with an excellent survival rate of 97% at 5 years. They postulated that the clinical significance of a MB appears to be related to the anatomic properties of a tunneled

segment of coronary artery, the presence of associated myocardial ischemia, and the presence of proximal and distal atherosclerotic disease. They concluded that medical treatment is the choice for symptomatic patients. Coronary stenting and surgery should be kept for resistant cases that have not responded well to medical therapy. Preoperative mapping of MB allows the surgeon to be ready to deal with myocardial bridging and this will shorten the surgery time and operative risks significantly.

Limitations of the study

This study is the first to investigate such a relatively large patient group in Saudi Arabia. However, this study has a few limitations, including that it is just a descriptive study; we do not compare CCTA with other techniques like coronary angiography for a radiation dose. Also, we did not correlate our results with the clinical outcome after treatment. These limitations can be avoided by including a wide spectrum of patients from different provinces of the country. Also, multicenter clinical studies of larger groups are required to determine the degree to which myocardial bridging is responsible for symptoms such as angina, myocardial infarction and life-threatening arrhythmias. Prospective multicenter studies of larger groups are definitely still required to determine the true national prevalence and whether myocardial bridging is responsible for cardiac symptoms or not.

In conclusion, the study shows clearly that CCTA offers an excellent non-invasive way to detect and characterize myocardial bridging. The national prevalence of MB in Saudi Arabia is comparable to worldwide prevalence. Also the anatomical and associated pathological findings of the tunneled arteries are similar to many other studies. However, multicenter clinical studies of larger groups are required to determine the real national incidence of MB, as well as the true clinical and physiological significance of myocardial bridging. However, it is still remains unclear which patients require further testing after the detection of myocardial bridging.

COMMENTS

Background

Myocardial bridging occurs when a segment of a coronary artery or its major branch travels through the myocardium instead of on the surface of the myocardium. Coronary computed tomographic angiography (CCTA) is able to visualize myocardial bridging in a more sensitive and comprehensive way than conventional coronary angiography. The prevalence of myocardial bridging varies widely between different studies.

Research frontiers

The current study assessed the incidence, location and morphology of myocardial bridging in Saudi patients by using CCTA and comparing the results to other international studies. The clinical association and pathological changes in relationship to myocardial bridging was also assessed.

Innovations and breakthroughs

This study highlighted the usefulness of CCTA as a non-invasive method to detect and characterize myocardial bridging. The incidence, location and clinical significance of myocardial bridging (MB) in Saudi patients do not differ from most of other populations.

Applications

CCTA is an excellent imaging modality to assess the real incidence and clinical significance of myocardial bridging in Saudi patients.

Terminology

MB is an inborn abnormality. It occurs when a segment of a coronary artery or its major branch travels through the myocardium. CCTA is the use of CT imaging to visualize the courses, lumens and relationships of the coronary arteries.

Peer review

In this study, the authors retrospectively examined the incidence of myocardial bridges in Saudi people, as well as their location and morphology from 350 individuals with coronary CT angiography. This paper is the first to describe the prevalence and clinical significance of MB in Saudi patients.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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