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EDITORIAL

Catheter ablation of persistent atrial fibrillation: The importance of substrate modification

Konstantinos P Letsas, Michael Efremidis, Nikolaos P Sgouros, Konstantinos Vlachos, Dimitrios Asvestas, Antonios Sideris

Konstantinos P Letsas, Michael Efremidis, Nikolaos P Sgouros, Konstantinos Vlachos, Dimitrios Asvestas, Antonios Sideris, Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, 10676 Athens, Greece

Author contributions: Efremidis M and Sgouros NP performed research; Letsas KP and Vlachos K performed research and drafted article; Asvestas D and Sideris A contributed to the critical revision of article.

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Telephone: +30-213-2041467
Fax: +30-213-2041344

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Abstract

Accumulating data have shown that elimination of atrial fibrillation (AF) sources should be the goal in persistent AF ablation. Pulmonary vein isolation, linear lesions and complex fractionated atrial electrograms (CFAEs) ablation have shown limited efficacy in patients with persistent AF. A combined approach using voltage, CFAEs and dominant frequency (DF) mapping may be helpful for the identification of AF sources and subsequent focal substrate modification. The fibrillatory activity is maintained by intramural reentry centered on fibrotic patches. Voltage mapping may assist in the identification of fibrotic areas. Stable rotors display the higher DF and possibly drive AF. Furthermore, the single rotor is usually consistent with organized AF electrograms without fractionation. It is therefore quite possible that rotors are located at relatively "healthy islands" within the patchy fibrosis. This is supported by the fact that high DF sites have been negatively correlated to the amount of fibrosis. CFAEs are located in areas adjacent to high DF. In conclusion, patchy fibrotic areas displaying the maximum DF along with high organization index and the lower fractionation index are potential targets of ablation. Prospective studies are required to validate the efficacy of substrate modification in left atrial ablation outcomes.

Key words: Ablation; Atrial fibrillation; Persistent; Substrate; Dominant frequency

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Core tip: A combined approach using voltage, complex fractionated atrial electrograms and dominant frequency mapping may be helpful for the identification of atrial fibrillation sources, and therefore for sufficient substrate modification in patients with persistent atrial fibrillation undergoing left atrial ablation.

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INTRODUCTION

Catheter ablation of atrial fibrillation (AF) is indicated in patients with symptomatic AF, refractory or intolerant to at least one class Ⅰ or Ⅲ antiarrhythmic medication[1-3]. Indications for catheter ablation of AF have expanded to include increasingly complex cases including patients with long-standing persistent AF and structural heart disease. Circumferential pulmonary vein antral isolation (PVAI) has become a standard therapy for paroxysmal AF[4]. On the contrary, PVAI displays a significantly lower success rate in patients with persistent or long-lasting persistent AF[1,2,5,6]. This difference suggests that the mechanisms underlying the maintenance of persistent AF are different in relation to paroxysmal AF. Recently, catheter ablation of stable rotors or focal sources in individuals with paroxysmal and persistent AF has given promising results[7-9]. Additional substrate modification is therefore required in the setting of persistent AF. However, the optimal ablation approach in these complex cases remains uncertain.

PATHOPHYSIOLOGY OF AF

AF represents the final common phenotype for multiple disease pathways and mechanisms that are incompletely understood. The multiple re-entrant wavelet hypothesis as a mechanism of AF was described by Moe and colleagues in 1959[10] with supportive experimental work by Alessie[11]. The "multiple re-entrant wavelet hypothesis" supports that fractionation of wavefronts propagating through the atria results in self-perpetuating "daughter wavelets". Multiple re-entrant wavelets are separated by lines of functional conduction block. The lines of the conduction block can occur around the anatomical structures within the atria with different inherent electrophysiological properties, such as scars, patchy fibrosis and myocardium, at different stages of recovery and excitability. However, this hypothesis can not easily explain why AF exhibits consistent spatial non-uniformities in rate and activation vector[12-14], how ablation may terminate AF relatively early in some cases before compartmentalization of meandering wavelets[1,6], or why extensive ablation often has little acute impact[1,15]. Alternatively, the "localised source hypothesis" is supported by elegant experiments in which localised spiral waves (rotors)[16,17] or focal sources[14] disorganise into AF. Stable microreentrant sources appears to be the most likely underlying mechanism of AF in experimental models[18,19]. Recent developments of patient-tailored and physiology-based computational mapping systems have identified localized electrical spiral waves, or rotors, and focal sources as mechanisms that may represent novel targets for therapy[7-9].

Studies have emphasised the importance of ion channel remodelling, changes in signalling pathways, oxidative stress, altered calcium handling, changes in atrial architecture, and altered connexin expression in the pathogenesis and maintenance of AF[20,21]. AF in turn causes AF-promoting abnormalities in each of these areas and enhances the vulnerability of the heart to AF induction and maintenance (AF begets AF)[21]. In particular, structural remodeling is characterized by atrial enlargement and tissue fibrosis. The presence of interstitial fibrosis leading to changes in cellular coupling results in spatial "non-uniform anisotropic" impulse propagation and is a potential cause of atrial activation abnormalities that may underlie the initiation and perpetuation of re-entrant arrhythmias including AF[22,23]. As AF progresses from paroxysmal to persistent, the atrial substrate becomes increasingly abnormal and displays a more prominent role in maintaining the arrhythmia[1,20,21]. In patients with persistent AF, a better understanding of arrhythmia mechanisms is therefore needed so that ablation approaches can be targeted to a clearly shown mechanism.

LEFT ATRIAL ABLATION

Pulmonary vein antral isolation

Despite the evolution of left atrial ablation strategies, PVAI remains the cornerstone of in both paroxysmal and persistent AF ablation procedures[1,2]. Isolation of wide circumferential areas around both ipsilateral pulmonary veins (PVs) with verification of conduction block is more effective than isolation of each individual PV using a segmental approach[4]. A lower success rate of PVAI as a stand-alone strategy has been reported in patients with persistent or long-lasting[1,2,5,6]. However, relatively new data on this topic have given contradictory results. The RASTA study have demonstrated that additional substrate modification beyond PVAI including ablation of non-PV triggers and ablation of complex fractionated electrogram sites does not improve single-procedure efficacy in patients with persistent AF[24]. The recently published STAR AF Ⅱ trial has clearly showed that additional substrate modification (fractionated atrial electrograms or linear lesions) following PVAI has no benefit in AF reduction[25]. A high incidence of PV reconnection is similarly observed in patients with and without recurrence of AF[26], suggesting that sustained PV isolation is not required for freedom from clinical recurrence of AF. This finding may be explained by the important substrate modification performed after the circumferential lines. In CONFIRM trial, AF sources were ablated coincidentally in 45% of cases after wide area circumferential ablation and left atrial roof line in persistent AF cases[8]. These data provide an alternative potential explanation for why PVAI treats AF in some patients and not others. Elimination of AF sources may explain why wide-area ablation is more

effective than ostial PV isolation, why AF may not recur in patients whose PVs have reconnected, why non-PV encircling lines or fractionated electrogram ablation may be effective and, potentially, why ablation success correlates with the extent of ablated tissue in persistent AF[8].

Linear lesions

Based on surgical MAZE procedures, linear lesions including roof and mitral isthmus lines have been also adapted in percutaneous left atrial ablation procedures providing additional substrate modification[27]. The additional benefit of linear lesions on top of ostial PV isolation has been prospectively demonstrated[28,29]. However, in these studies an ostial and not a wide circumferential PV isolation was performed. The intrapulmonary region has been also implicated as an important source of PV triggers[30]. In a randomized study, we investigated the efficacy of additional radiofrequency energy delivery in the interpulmonary isthmus following PVAI[31]. A continuous line in the interpulmonary isthmus connecting the anterior and the posterior part of the ipsilateral circumferential line creating a "theta" model (the Greek letter θ) was performed. Although patients with additional energy delivery in the interpulmonary isthmus displayed a better long-term outcome (free from arrhythmia recurrence), this was not statistically significant. Nevertheless, left atrial linear lesions remain technically challenging. Incomplete linear lesions may have a proarrhythmic effect[5,6]. Most atrial tachycardias result from gaps in the ablation lines.

DIRECT SUBSTRATE MODIFICATION STRATEGIES

Voltage mapping: Identification and modification of heterogeneous substrate and local barriers

As previously stated, interstitial fibrosis play a key-role in the pathophysiology of AF[22,23]. Delayed enhancement-cardiac magnetic resonance imaging (DE-CMRI) has demonstrated fibrosis and scarring in the left atrium of patients undergoing AF ablation[32,33]. Among patients with AF undergoing catheter ablation, atrial tissue fibrosis estimated by DE-CMRI has been independently associated with likelihood of recurrent arrhythmia[34,35]. Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities. Although, specific bipolar and unipolar voltage cut-off values have been reproducibly shown to accurately identify scar and/or fibrosis in the ventricles, data regarding voltage cut-off values in the atria are limited. In preliminary studies, the bipolar voltage cut-off value were set at < 0.05 mV for the identification of atrial scar, partly influenced by the background noise from early electroanatomic mapping systems, and < 0.5 mV for low-voltage regions[36,37]. In a recent study, the global mean left atrial bipolar and unipolar voltage amplitude in SR was 2.83 ± 2.25 and 4.12 ± 2.14 mV, respectively; 95% of all bipolar and unipolar electrograms recorded from the LA were > 0.50 and > 1.57 mV, respectively[38]. There was no difference in the segmental distribution of low-voltage areas between patients with AF and healthy controls. Jadidi *et al*[39] have demonstrated bipolar voltages of 0.63 ± 0.8 in dense DE-CMRI areas, compared with 0.86 ± 0.89 in non DE-MRI areas. These measurements were performed during AF. By using both electroanatomic mapping system and DE-MRI, Spragg *et al*[32] have demonstrated that the mean atrial voltage in areas identified as scar by DE-MRI was 0.39 ± 0.61 mV, while in areas identified as normal by DE-CMRI was 1.38 ± 1.23 mV. In a similar study, a bipolar voltage of < 0.38 ± 0.28 mV was associated with fully scarred atrial myocardium[40]. Kapa *et al*[41] using electroanatomic mapping along with DE-CMRI have shown that a bipolar voltage cut-off of 0.27 mV performed best for delineating scar (sensitivity: 90%, specificity: 83%).

Substrate mapping in patients with postinfarction cardiomyopathy and ventricular tachycardia may involve lowering the voltage cut-off that defines the scar in order to identify "channels" of relative higher voltage within the scar[42,43]. Conducting channels within the unexcitable scar areas (particularly those displaying late potentials) are considered as an appropriate ablation target[43]. In a similar way, scar homogenization may be also performed in left atrium. Rolf *et al*[44] have recently shown that catheter ablation at low voltage areas aiming to homogenize the diseased left atrium in addition to PVAI resulted in better long-term outcomes compared to PVAI alone. Catheter ablation of stable rotors in patients with paroxysmal and persistent AF has given promising results[7-9]. It is quite possible that these stable sources correlate with areas of atrial fibrosis where the site-specific micro-architecture of connective tissue fibres and the remaining myocardial fibres allows reentrant/rotor activation to occur and to sustain. The combination of localizing atrial fibrosis plus mapping of specific functional areas allowing re-entrant/rotor activation may hold promise for catheter based AF substrate modification in the future.

Mapping and ablation of complex fractionated atrial electrograms

Complex fractionated atrial electrograms (CFAEs) are seen in all forms of AF (paroxysmal and persistent). The underlying mechanisms of CFAEs remain controversial. Two leading hypothesis have been proposed for CFAEs formation. First, the "rotor hypothesis" where the rotor encounters heterogeneous substrate (*e.g.,* dispersion of refractoriness), and the CFAEs are the by-product of the reentrant rotor that breaks down at its boundary; the posterior left atrium is a histologically and

electrically complex region, in which firing from the PVs meets regions of functional block due to anisotropic conduction. The atrial signals in the area of this line of block are frequently fractionated[45]. As paroxysmal AF progresses to persistent AF, the progressive fibrotic and microarchitectural changes determine the propagation, collision, and fragmentation of the wave front as it emanates from focal triggers[46]. Second, the "autonomic hypothesis" where CFAEs indicate sites of ganglionated plexi[47,48]. Lin *et al*[48] showed in a canine model that CFAEs can be produced locally at the site where acetylcholine was topically applied. Moreover, CFAEs can be eliminated by ablating the GP at a distance, indicating that activating the "network" of the intrinsic cardiac autonomic nervous system may be a critical element in the formation of CFAEs.

The use of CFAEs has become an important tool in the clinical electrophysiology laboratory to guide catheter ablation of AF sources. However, their clinical significance is questionable. In Nademanee's original report, CFAEs were defined as (1) fractionated electrograms composed of >2 deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex; and (2) atrial electrograms with very short cycle length (< 120 milliseconds)[49]. Nademanee *et al*[49] have demonstrated 92% freedom from AF one year after CFAEs ablation without PV isolation after two procedures. This level of success has not been reproduced by other groups. Ablation of CFAE as a stand-alone ablation strategy seems insufficient for the treatment of patients with persistent AF[50,51]. In addition, there are clear data that CFAEs ablation as an adjunct therapy to PVAI does not improve the success rate of left atrial ablation[52]. As previously reported, the recently published STAR AF II trial has clearly showed that additional substrate modification (fractionated atrial electrograms or linear lesions) following PVAI has no benefit in AF reduction[25].

Whether certain subtypes of CFAE, such as those exhibiting continuous fractionation or particular types of activation gradients, are more important than others is not known[53]. Using multipolar catheters and monophasic action potentials (MAPs) to define local activation and repolarization, Narayan *et al*[54] identified four types of CFAEs in human AF: (1) CFAEs with discrete rapid MAPs and pansystolic local activation (8%); (2) CFAEs with discrete MAPs after AF acceleration (8%); (3) CFAEs pattern with distinct MAPs and dissociated superimposed signals consistent with far-field electrograms (67%); and (4) CFAEs pattern without discrete MAPs (17%), consistent with spatial disorganization. CFAEs with discrete MAPs and pansystolic activation had shorter cycle length and lower voltage and trended to have higher dominant frequency than other CFAEs sites. The majority of CFAEs were the result of superimposed far-field atrial activations from overlying atrial structures. In contrast, only a small proportion of CFAEs exhibited rapid, discrete, organized MAP recording activity consistent with an AF driver. Jadidi *et al*[39] have elegantly shown that the distribution of fractionated electrograms is highly variable, depending on direction and rate of activation. Fractionation in sinus rhythm and pacing rhythms mostly resulted from wave collision. All sites with continuous fractionation in AF displayed normal voltage in sinus rhythm, suggesting absence of structural scar[39]. Thus, many fractionated electrograms are functional in nature, and their sites dynamic. The same group of investigators has demonstrated an inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation[55]. Ninety percent of continuous CFAE sites occur at non-delayed-enhancement and patchy delayed-enhancement LA sites. Finally, there are many limitations arising from the definition of CFAEs. Lee *et al*[56] aimed to determine the prevalence and spatial correlation of CFAEs using two definitions: (1) multicomponent/continuous electrograms; and (2) AF cycle length < 120 ms. Multicomponent/continuous electrograms and sites of short CL activity (< 120 ms) identified different atrial regions.

Dominant frequency mapping

Dominant frequency (DF) mapping is aimed at identifying localized sites of high DF during AF[57]. Initial reports using optical mapping systems have identified the presence of localized regions of high-frequency activity demonstrating spatiotemporal periodicity which may act as drivers of AF[19]. Most importantly, the highest DF using spectral analysis of the biatrial electrogram correlates well with the rotor frequency observed during optical mapping[58], suggesting that this technique of signal decomposition and DF analysis may allow identification of reentrant circuits sustaining AF. Sites of high DF typically show rapid periodicity but lack significant fractionation[47]. In paroxysmal AF, the high DF sites are more prevalent within the PVs, whereas in persistent AF, the high DF sites commonly exist within the left atrium[57]. Retrospective analyses have shown that ablation at such high DF sites results in slowing and termination in a significant proportion of paroxysmal AF patients, indicating their role in AF maintenance[57,59,60]. The higher AF recurrence rate in patients with non-ablated high DF sites at the end of the procedure supports the important role of extrapulmonary sites in persistent AF maintenance[60].

Sites showing DFs that were at least 20% higher than their surrounding points were identified as primary and secondary high DF sites[57,59,60]. Two indices from fast Fourier transform (FFT) power spectrum analysis describe the degree of organization within AF: (1) the regularity index, defined as the ratio of the area under the dominant peak in the power spectrum to the total area[47]; and (2) the organization index, a ratio consisting of the sum of the areas under the dominant peak and its harmonics divided by the

total area[61].

High DF sites typically show rapid periodicity but lack significant fractionation[47]. Kumagai *et al*[62] have shown that high DF sites and continuous CFAEs sites overlap in only 14% of mapped areas after PVAI. Lee *et al*[56] have demonstrated a poor direct spatial correlation between sites of multicomponent/continuous electrograms and sites of high DF, with only 23.1% of multicomponent/continuous electrograms sites occurring at the same location as a site of high DF. Spatial analysis confirmed that the vast majority (84%) of the multicomponent/continuous electrograms sites occurred directly adjacent (< 2.5 mm) to a site of high DF[57]. If high DF identifies a focal source, then visual fractionation may represent wave front breakup at the periphery. Stiles *et al*[63] reported similar findings. Correlation between CFAEs and DF was poor. Exploration of their spatial relationship demonstrates CFAEs in areas adjacent to high DF (within 10 mm in 80% and 10-20 mm in 10%). Lin *et al*[64] demonstrated that the most consistent CFAEs activity is observed near maximum DF sites and that the core of the widely distributed continuous CFAEs is correlated with the sites of maximum DF. Maximal fractionated sites are observed in the center or the boundary region of maximum DF sites.

High DF sites have been negatively correlated to the amount of fibrosis, whereas fractionation index was positively correlated with fibrosis in the posterior left atrium[65]. Atrial fibrosis as defined by DE-CMRI have been associated with slower and more organized electrical activity but with lower voltage than healthy atrial areas[55]. As suggested by Koduri *et al*[65], the increased regularity of electrograms (indicated by increased organization index) in the presence of slower activation rates (indicated by lower DFs and higher fractionation index sites) in experimental heart failure models may indicate the presence of regions of underlying fibrosis.

Currently, there are several limitations of DF mapping as an ablation strategy. These factors include lack of high-resolution mapping to precisely locate DF sites, real-time analysis of DF, and spatiotemporal stability of DF sites[66].

HOW TO PERFORM SUBSTRATE MODIFICATION IN PERSISTENT AF ON TOP OF PVAI?

Summarizing the above data, it's clear that the additional substrate modification involving linear lesions and CFAEs sites in patients with persistent AF is debatable. Based on the recent findings by Narayan's group[7-9], elimination of AF sources (principally rotors) should be the goal in persistent AF ablation. How can we localize these AF sources with current diagnostic modalities? A combined approach using voltage, CFAEs and DF mapping may be helpful for this purpose. Voltage mapping may assist in the identification of fibrotic areas. Tanaka *et al*[67] have demonstrated that the largest fibrotic patches and the PV ostia are potential anchoring sites for "micro-anatomical" reentry. In their experiments, the fibrillatory activity is maintained by intramural reentry centered on fibrotic patches and that it appeared at the posterior left atrial wall as breakthroughs. The average area of fibrosis in the periphery is significantly larger than in the center. Differences in voltage amplitude may be important to identify relatively healthy areas within the patchy fibrotic tissue. For this purpose, upper and the lower voltage thresholds have to be decreased in decrements.

Stable rotors display the higher DF and possibly drive AF[18,19,57,58]. Furthermore, the single rotor is usually consistent with organized AF electrograms without fractionation[68]. It is therefore quite possible that rotors are located at relatively "healthy islands" within the patchy fibrosis. This is supported by the fact that high DF sites have been negatively correlated to the amount of fibrosis[65]. This assumption also explains why CFAEs are the by-product of the reentrant rotor that breaks down at its fibrotic boundaries[67]. As previously reported, correlation between CFAEs and high DF sites is poor. CFAEs are located in areas adjacent to high DF (within 10 mm)[62]. Regularity index showed that fractionation is low within the area with the maximum DF and high within a band of approximately 3 mm at boundaries with lower-frequency domains[47]. CFAEs mapping has to be therefore performed with great caution. Only CFAEs with a discrete MAP should be targeted for ablation[53]. Of note, these are low voltage and high DF sites[53]. In conclusion, areas with relatively higher voltage compared to the surrounding tissue displaying the maximum DF along with high organization index are potential targets of ablation. Prospective studies are required to validate the efficacy of substrate modification in left atrial ablation outcomes.

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EDITORIAL

Coronary artery disease in type 2 diabetes mellitus: Recent treatment strategies and future perspectives

Ryo Naito, Takatoshi Kasai

Ryo Naito, Department of Cardiology, Juntendo University Graduate School of Medicine, Tokyo 113-8421, Japan
Takatoshi Kasai, Cardio-Respiratory Sleep Medicine, Department of Cardiology, Juntendo University Graduate School of Medicine, Tokyo 113-8421, Japan
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Correspondence to: Takatoshi Kasai, MD, Cardio-Respiratory Sleep Medicine, Department of Cardiology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo Bunkyo-ku, Tokyo 113-8421, Japan. kasai-t@mx6.nisiq.net
Telephone: +81-3-38133111
Fax: +81-3-56890627
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Abstract

Patients with type 2 diabetes mellitus (T2DM) are at a higher risk of developing coronary artery disease (CAD) than are non-T2DM patients. Moreover, the clinical outcomes in CAD with T2DM are poor despite improvements in medications and other interventions. Coronary artery bypass grafting is superior to percutaneous coronary intervention in treating multivessel coronary artery disease in diabetic patients. However, selecting a revascularization strategy depends not only on the lesion complexity but also on the patient's medical history and comorbidities. Additionally, comprehensive risk management with medical and non-pharmacological therapies is important, as is confirmation regarding whether the risk-management strategies are being appropriately achieved. Furthermore, non-pharmacological interventions using exercise and diet during the earlier stages of glucose metabolism abnormalities, such as impaired glucose tolerance, might be beneficial in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events.

Key words: Diabetes; Comprehensive risk management; Multivessel disease; Drug-eluting stents; Percutaneous coronary intervention

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Core tip: Clinical outcomes in coronary artery disease with type 2 diabetes mellitus (T2DM) are poor despite improvements in medications and other interventions. Although coronary artery bypass grafting is superior to percutaneous coronary intervention in multivessel coronary artery disease with T2DM, selecting the revascularization strategy depends not only on the lesion complexity but also on the patient's medical history and comorbidities. In these patients, comprehensive risk management with medical and non-pharmacological therapies is indispensable, and confirming whether such risk management is being appropriately achieved is also important. Furthermore, interventions with exercise and diet therapy during the early stages of glucose abnormalities might be effective in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events.

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INTRODUCTION

Patients with type 2 diabetes mellitus (T2DM) have a higher risk of developing coronary artery disease (CAD) than do patients without T2DM[1]. Additionally, 75% of T2DM patients die as a consequence of cardiovascular diseases, including CAD[2]. In patients with T2DM, CAD tends to be a more complex disease characterized by small, diffuse, calcified, multivessel involvement [multivessel disease (MVD)][3,4] and often requires coronary revascularization in addition to optimal medical therapy to control angina[5]. Regarding coronary revascularization, recent advances in the techniques and devices used during percutaneous coronary intervention (PCI) have expanded the indication of PCI to more complex lesions[6-8]. In particular, drug-eluting stents (DES) have reduced the restenosis and repeat revascularization rates[9,10]. However, the morbidity and mortality of CAD in patients with T2DM continues to be high, even in the current DES era[11]. Although most clinical trials comparing outcomes among T2DM patients with MVD have shown that coronary artery bypass grafting (CABG) was superior to PCI in terms of repeat revascularization and the incidence of myocardial infarction and mortality[12-17] (Table 1), it is not feasible to perform CABG in all diabetic patients with MVD. Because CABG is highly invasive in contrast to PCI, selecting a revascularization therapy depends not only on the lesion complexity but also on a patient's medical history and comorbidities. SYNTAX score is a reliable score to assess coronary anatomical features and lesion complexity[16]. EuroSCORE is also a useful scoring system that is based on the clinical background information of an individual patient, which might predict the operative mortality for patients undergoing cardiac surgery[18]. Recently, revised versions of these two scoring systems were proposed. Because combining the SYNTAX score and other clinical variables have been demonstrated to be more accurate in identifying the risk of patients with complex CAD compared with the SYNTAX score alone, the SYNTAX score Ⅱ was constructed, which included the original SYNTAX score and the following variables: the presence of unprotected left main CAD, female gender, chronic obstructive pulmonary disease, age and left ventricular ejection fraction[19]. Similarly, EuroSCORE Ⅱ is an updated version of the original EuroSCORE, reconstructed from a large database of 22381 consecutive patients undergoing cardiac surgery in 43 countries in 2010 using a logistic regression model[20]. These scoring systems may provide additional and reliable information to better decide revascularization strategies. In clinical trials, higher-risk surgical patients, such as the elderly and those with more comorbid diseases, have been excluded. Therefore, selecting a revascularization therapy for CAD with T2DM requires a thorough discussion of the patient's coronary anatomical features and lesion characteristics, age, and comorbid conditions.

Considering this issue, several important and as yet unresolved questions are raised including the following: (1) whether the newer DES are superior or similar in terms of repeat revascularization, incidence of myocardial infarction and mortality; (2) what can be done in conjunction with optimal medical and revascularization therapy to improve patient outcomes; and (3) whether early detection and intervention for CAD patients with undiagnosed T2DM or impaired glucose tolerance may improve mortality. In this editorial, we aim to provide novel insights into each of these specific questions and to consider the directions for future research.

REVASCULARIZATION THERAPY-THE POTENTIAL OF NEWER DRUG-ELUTING STENTS AND BIORESORBABLE VASCULAR SCAFFOLDS

First, it is essential to understand what types of outcome measures were used in clinical trials to evaluate the effectiveness of a given revascularization strategy or to determine the superiority of one revascularization therapy over another. Clinical trials for cardiovascular diseases often use a composite assessment of major adverse cardiovascular events as outcome measures including all-cause mortality, myocardial infarction, stroke and repeat revascularization. Because death and myocardial infarction are considered to be hard and preferably primary endpoints, whereas repeat revascularization is a less hard and secondary endpoint according to the severity of each case, the primary and secondary endpoints should be treated as two distinct endpoints.

Advances in PCI have prompted the selection of this procedure in more complex lesions that previously had been indicated for CABG. However, MVD in T2DM patients is associated with a high incidence of repeat revascularization after PCI with DES; therefore, CABG remains superior to PCI in such lesions. A meta-analysis has demonstrated that the superiority of CABG to PCI with balloon angioplasty or bare metal stents in terms of all-cause mortality was greater in patients with than without T2DM[21].

To date, several clinical trials have been conducted at 85 centers in the United States and Europe to compare CABG and PCI with DES. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) was a prospective randomized trial that compared the efficacy of CABG and PCI with paclitaxel-eluting stents (PES) for patients with de-novo left main

Table 1 Clinical trials of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients

Trial	Type of trial years of recruitment	Number of study population	Type of PCI	Endpoint	Main results (PCI *vs* CABG)
ARTS I [12]	Randomized 1997-1998	208	BMS	1 yr freedom from death, stroke, MI or revascularization)	63.4% *vs* 84.4% ($P < 0.001$)
MASS II [13]	Randomized 1995-2000	115	N/A	1 yr death	5.3% *vs* 6.8% ($P = 0.5$)
BARI-2D[14]	Randomized	1605	1st DES: 34.7%	5 yr freedom from death, MI, repeat revascularization	PCI *vs* medical (77.0 *vs* 78.9; $P = 0.15$)
	Comparison between revascularization and medical 2001-2005		BMS: 56.0%		CABG *vs* medical (77.6% *vs* 69.5%; $P = 0.01$)
			Others: 9.3%		P for interaction 0.002
CARDIa[15]	Randomized 2002-2007	510	1st DES: 61% BMS: 31%	1 yr death, stroke, or MI	13.0% *vs* 10.5% ($P = 0.39$)
SYNTAX[16]	Randomized 2005-2007	452	1st DES	5 yr death, stroke, MI, or revascularization	46.5% *vs* 29.0% ($P < 0.001$)
FREEDOM[17]	Randomized 2005-2010	1900	1st DES	5 yr death	16.3% *vs* 10.9% ($P = 0.049$)
				5 yr death, nonfatal MI, or nonfatal stroke	26.6% *vs* 18.7% ($P = 0.005$)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; DES: Drug-eluting stent; ARTS: Arterial revasucularization Therapies Study; BMS: Bare metal stent; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; MASS: Medicine, Angioplasty, or Surgery Study; 1st DES: First generation DES.

coronary disease, three-vessel disease or both, which were considered equally suitable for CABG or PCI by both a cardiac surgeon and an interventional cardiologist at each center[22]. In the trial, 452 (25.1%) of the study population patients were diabetic, and these patients were included in a pre-specified sub-analysis. For 3-year major adverse cardiac and cerebrovascular events in the diabetic cohort, the incidence was 37.0% in the PCI group and 22.9% in the CABG group ($P = 0.002$). The rate of revascularization was also higher in the PCI group (PCI, 28.0% and CABG, 12.9%, $P < 0.001$)[23]. In 2012, a large-scale randomized trial known as the future revascularization evaluation in patients with diabetes mellitus (FREEDOM) trial was conducted. A total of 1900 diabetic patients with MVD were randomly assigned to CABG or to PCI with mainly sirolimus-eluting stents (SES) and PES[17]. The incidence of all-cause mortality and myocardial infarction was significantly lower in the CABG group during the mean follow-up period of 5 years compared with the DES group (CABG, 18.7% *vs* DES, 26.6%). Based on these results, the latest guidelines from the European Cardiology Society for the management of T2DM patients stated that PCI for MVD was a Class IIb indication for relieving symptoms as an alternative to CABG in patients with low SYNTAX scores[24]. However, in the FREEDOM trial, almost all patients in the PCI group were treated with first-generation DES that were replaced by newer-generation DES used in current clinical practice. The newer generation DES have overcome the critical issue of stent thrombosis; in particular, the everolimus-eluting stent (EES) reduced myocardial infarction and stent thrombosis compared with other DES in a meta-analysis[25]. Recently, Bangalore and colleagues reported a meta-analysis of 68 randomized clinical trials to compare clinical outcomes in CAD patients with T2DM between those who received CABG and DES, including SES, PES and EES[26]. All-cause mortality was higher in the patients who received SES and PES compared with CABG, whereas the mortality rates in the EES group were similar to those of the CABG group (reference rate ratio to CABG, 1.31, 95%CI: 0.74-2.29). These results should be carefully interpreted because they were generated from an indirect comparison of individual clinical trials. Ongoing randomized trials in evaluation of the Xience Prime or Xience V stents *vs* coronary artery bypass surgery for the effectiveness of left main revascularization (EXCEL) and bypass surgery *vs* everolimus-eluting stent implantation for approaching multivessel disease (BEST) aim to determine the effectiveness of EES. EXCEL is a randomized trial comparing EES and CABG in patients with left main trunk lesions and SYNTAX scores of 32 or less. The BEST trial aims to compare EES and CABG in MVD. In both trials, a sub-analysis for diabetic patients is intended.

Regarding other novel devices, bioresorbable vascular scaffolds (BVS) may be a candidate treatment of CAD in diabetic patients. BVS are novel intra-coronary devices that have potential advantages over metallic DES in terms of adverse coronary events such as stent thrombosis because unlike metallic DES, no uncovered struts or polymers exist after the scaffolds are resorbed[27]. To date, only a single clinical study has reported on the efficacy of BVS in diabetic patients. Muramatsu *et al*[27] compared BVS and EES in diabetic patients using different clinical trials of each device and reported that the incidence of the clinical outcome, which was a composite of cardiac death, target vessel MI, or ischemia-driven target lesion revascularization, was similar between BVS and EES in diabetic patients (3.9% for the BVS *vs* 6.4% for EES, $P = 0.38$)[28].

As described by the authors, the data analysis was performed using different pooled data and the study population number was quite small (n = 102 in the BVS group and 172 in the EES group). Further studies in a larger cohort of diabetic patients are required to demonstrate the safety and efficacy of BVS.

COMPREHENSIVE RISK MANAGEMENT AND INTERVENTIONS

Because clinical outcomes in T2DM patients with CAD are poor, aggressive medical and non-pharmacological therapies are indispensable, regardless of the revascularization strategy pursued. The bypass angioplasty revascularization investigation in type 2 diabetes (BARI-2D) trial examined and compared long-term clinical outcomes between medical therapy alone and revascularization by PCI or CABG in T2DM patients[14]. No significant difference was observed between the PCI and CABG groups in all-cause mortality or in the event-free survival rates for cardiovascular events during the 5-year follow-up period. These data indicated the importance of comprehensive risk management with glycemic control and the administration of statins, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and antiplatelet therapy in T2DM patients with CAD[21]. Guidelines for the management of diabetes mellitus from the American Diabetes Association, the American College of Cardiology and the American Heart Association recommend the following prevention strategies for CAD: blood pressure 130/80 mmHg or less, low-density lipoprotein cholesterol (LDL-C) below 100 mg/dL (below 70 mg/dL for CAD patients) and prompt smoking cessation[29-31]. However, a previous study examining the achievement of risk management in the large-scale clinical trials of clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE), BARI-2D and FREEDOM, showed unexpectedly low achievement rates[32]. One-year risk management achievement rates (LDL-C < 100 mg/dL (70 mg/dL in the FREEDOM trial), systolic blood pressure < 130 mmHg, glycated hemoglobin < 7.0% and smoking cessation) were 18%, 23% and 8% in the COURAGE, BARI-2D and FREEDOM trials, respectively. Although the achievement rate was not originally included in the clinical trial endpoints, these results prompted us to review our clinical practices regarding not only adherence to evidence-based medical therapy but also whether risk management is being properly achieved. Furthermore, non-pharmacotherapeutic strategies including exercise, diet and smoking cessation should be pursued.

INTERVENTIONS FOR IMPAIRED GLUCOSE TOLERANCE

Considering that patients with T2DM tend to have macro- and microvascular complications and that the clinical outcomes of CAD patients are poor, interventions are desirable during the earlier stages of T2DM, such as impaired glucose tolerance (IGT). We understand that IGT is not simply an early stage of T2DM but rather an important state predisposing to T2DM. In fact, progression to diabetes was observed in 10% of IGT patients[33]. Additionally, it was suggested that IGT itself might have an impact on CAD morbidity and mortality[34]. However, it is not fully elucidated whether IGT in CAD patients might be a treatment target for secondary prevention the effects of anti-diabetic agents on reducing progression to diabetes or the incidence of cardiovascular events in such patients. Nevertheless, non-pharmacological therapies such as nutrition and exercise are important even in IGT patients. Previous studies reported that about one-third of CAD patients who had not been diagnosed with diabetes were actually diabetic[35,36]. Thus, aggressive evaluation for diabetes and IGT are required in CAD patients. In current clinical practice, although fasting blood glucose and glycated hemoglobin diabetes testing is routinely performed, the glucose tolerance test is not frequently performed in CAD patients unless the fasting blood glucose or glycated hemoglobin levels are above the upper limits of normal. To detect diabetes at an earlier stage, blood glucose, glycated hemoglobin and glucose tolerance tests for diabetes are considerably important.

CONCLUSION

When selecting revascularization strategies in diabetic patients, physicians must thoroughly consider not only a patient's coronary artery lesions but also his/her medical history. Additionally, comprehensive risk management with medical and non-pharmacological therapies should be performed and the proper achievement of risk management should be confirmed. Furthermore, non-pharmacological interventions through exercise and diet therapy during the earlier stages of glucose metabolism abnormalities such as IGT may also be beneficial in preventing the development or progression of T2DM and in reducing the occurrence of cardiovascular events by either primary or secondary prevention of CAD.

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EDITORIAL

Making cardiomyocytes with your chemistry set: Small molecule-induced cardiogenesis in somatic cells

Woong-Hee Kim, Da-Woon Jung, Darren Reece Williams

Woong-Hee Kim, Da-Woon Jung, Darren Reece Williams, New Drug Targets Laboratory, School of Life Sciences, Gwangju Institute of Science and Technology, Gwangju 500-712, South Korea

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Correspondence to: Darren Reece Williams, PhD, New Drug Targets Laboratory, School of Life Sciences, Gwangju Institute of Science and Technology, Gwangju 500-712, South Korea. darren@gist.ac.kr
Telephone: +82-62-7152509
Fax: +82-62-7152484

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Abstract

Cell transplantation is an attractive potential therapy for heart diseases. For example, myocardial infarction (MI) is a leading cause of mortality in many countries. Numerous medical interventions have been developed to stabilize patients with MI and, although this has increased survival rates, there is currently no clinically approved method to reverse the loss of cardiac muscle cells (cardiomyocytes) that accompanies this disease. Cell transplantation has been proposed as a method to replace cardiomyocytes, but a safe and reliable source of cardiogenic cells is required. An ideal source would be the patients' own somatic tissue cells, which could be converted into cardiogenic cells and transplanted into the site of MI. However, these are difficult to produce in large quantities and standardized protocols to produce cardiac cells would be advantageous for the research community. To achieve these research goals, small molecules represent attractive tools to control cell behavior. In this editorial, we introduce the use of small molecules in stem cell research and summarize their application to the induction of cardiogenesis in non-cardiac cells. Exciting new developments in this field are discussed, which we hope will encourage cardiac stem cell biologists to further consider employing small molecules in their culture protocols.

Key words: Cardiogenesis; Cell reprogramming; Somatic cells; Small molecules; Cardiovascular disease

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Core tip: There are a plethora of methods to manipulate the phenotype of somatic cells and convert them into different cell types, such as cardiac cells. The use of small molecules provides numerous advantages, such as ease of use, tight temporal control and reversible effects on target proteins. Significantly, the production of small molecules is cheap and synthesis can be readily standardized. This would allow non-specialist stem cell laboratories to readily adopt small molecule-based methods to produce functional cardiac cells from multiple

cell sources, including therapeutic applications requiring the somatic cells of patients with cardiovascular disease.

Kim WH, Jung DW, Williams DR. Making cardiomyocytes with your chemistry set: Small molecule-induced cardiogenesis in somatic cells. *World J Cardiol* 2015; 7(3): 125-133 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i3/125.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i3.125

WHY SHOULD CARDIOMYOCYTES BE PRODUCED USING NON-CARDIAC CELLS?

Heart contraction is produced by cardiomyocytes, which comprise the cardiac muscle cell population. It was thought that the heart is a refractory organ that is incapable of replacing cardiomyocytes that are lost by normal tissue damage or cardiac disease. However, over the past decade this view has been challenged by numerous studies indicating that the heart can regenerate cardiomyocytes; at least with a capacity to replace those cells lost by regular tissue turnover[1]. Unfortunately, this regenerative capacity is significantly lower compared to skeletal muscle. Thus, major disease insults, such as myocardial infarction (MI), result in an irreversible, catastrophic loss of cardiomyocytes. Typically, MI results in the death of around 20% of the total cardiomyocytes population in the heart. The ventricle is a major site of cardiomyocyte death, with billions of dead cells being eventually replaced by fibrous scar tissue[2-4]. Acute MI produces significant mortality (for example, 36% fatality in the United Kingdom, over the years 2002-2010[5]). For those patients that survive, the poor capacity of heart regeneration means that many are predisposed to eventually develop clinical heart failure[2,6,7].

It can be envisaged that one potential therapy for preventing the progression of MI to heart failure would be the transplantation of functional cardiomyocytes to the infarction site. This cell therapy approach has been demonstrated as an achievable cure for degenerative diseases, such as the transplantation of hematopoietic multipotent stem cells to treat certain types of leukemia[8]. Cardiac cell therapy could prevent progression to heart failure by allowing functional recovery of the heart. Most cell therapy approaches involving cardiomyocyte transplantation aim to treat the consequences of MI, because of the significant impact of this disease on human health.

Cell therapy approaches have been developed to treat cardiac dysfunction, such as MI (reviewed in[9]). Multiple strategies exist for cell delivery and cell source. For example, different types of stem cells have been used for transplantation, including mesenchymal stem cells or cardiac stem cells. More differentiated cells have also been utilized, such as skeletal muscle cells and cardiomyocytes. Unfortunately, the results of clinical trials have only shown a modest improvement after MI. One approach to improve the outcome of cell therapy for MI would be the development of an ideal, optimized cell type for transplantation. This would also require the development of a rigorous, defined experimental methodology to ensure quality control for the cells prior to grafting. However, standardized protocols for culturing transplantable cells are lacking and laboratories tend to develop thief own "in house" techniques and culture media recipes.

The research field of chemical biology is ideally suited to provide reagents that can enhance cell culture and scale-up for transplantation. Chemical biology is a multidisciplinary field that uses chemical "tools" or probes provided by synthetic chemistry to understand and manipulate biological systems[10,11]. These chemical tools are usually small molecules, which are defined as organic compounds with a molecular weight below 800 Daltons. This allows diffusion across the cell membrane and is an upper limit for oral bioavailability[12,13]. A significant example of the contribution of chemical biology to cell research is the generation of induced pluripotent stem cells (iPSCs) from differentiated adult cells[14]. This was originally achieved by overexpressing four "Yamanaka" transcription factors: Oct4, Sox2, c-Myc, and Klf4. Within just a few years, the protocol to produce iPSCs was optimized and simplified by chemical biologists. It was shown that iPSCs could be generated by expressing only the Oct4 transcription factor and a two-step combination of small molecule inhibitors of cell signaling pathways and gene regulatory mechanisms[13]. This is an important example of the ability of small molecules to substitute for transcription factors that have a global influence on genes regulating cell differentiation. Small molecules also possess significant advantages compared to other technologies for controlling cell phenotype, such as genetic methods. In the following section, we briefly discuss these advantages and provide examples of the application of small molecules to the derivation of cardiogenic cells for cell therapy.

Why use small molecules to control cardiogenesis?

Small molecules allow flexibility over the manipulation of the target protein[13,15]. This is not always possible with alternative approaches, such as genetic manipulation. In addition, the effects of small molecule treatment are usually reversible. This means that the target protein can be manipulated with relatively precise timing. An additional level of control can be achieved by fine-tuning the treatment concentration. Small molecules do not always modulate a single protein target in cells; they can produce multiple effects by binding to different protein classes. An example is the molecule BIX-01294, which inhibits different histone-modifying enzymes[16]. Thus, different

small molecules can act synergistically to produce multiple effects, with the potential to produce dramatic changes in cell phenotype. The structural diversity of small molecule libraries developed exponentially in the 1990s, due to advances in chemical synthesis, such as combinatorial chemistry and diversity-orientated synthesis[17,18]. This greater diversity increases the potential to control molecular interactions with target proteins. Small molecules also provide logistical advantages for researchers. Compared to protein or nucleic acid reagents, they are cheap to produce, simple to store in the laboratory and more amenable to quality control. Small molecule-based methods do have some disadvantages, such as the potential for off-target effects on other proteins possessing similar structural elements. Notwithstanding, small molecules have become prominently used in stem cell biology and regenerative medicine, including the production of cardiomyocytes or cardiogenic stem cells[3,15,19]. Next, we discuss some prominent examples of small molecule-based strategies for cardiac cell therapy.

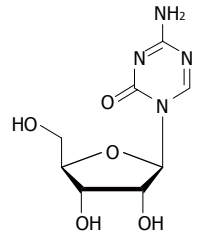
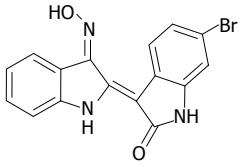
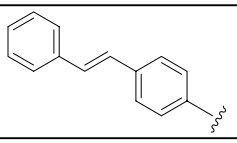
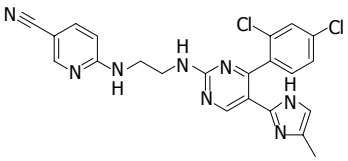
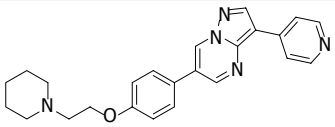
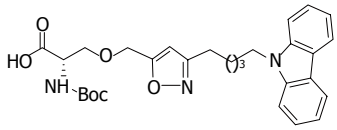
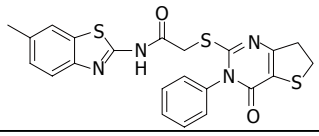
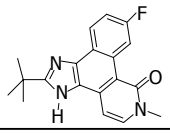
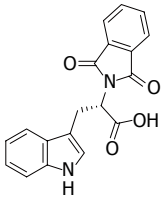
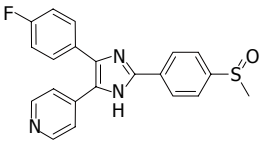
Due to the major health impact of cardiac disease, many small molecules have been developed to simplify the generation of cardiomyocytes or enhance the production of cardiogenic stem cells for potential cell therapy. A selection of these small molecules is shown in Figure 1. The use of small molecules to generate cardiomyocytes can be traced back to 1982, with the discovery that the small organic molecule, DMSO, could induce cardiomyocytes differentiation in murine teratocarcinoma-derived embryonic stem cells[20]. However, it was the development of cell therapy applications for cardiac diseases, such as MI in the 1990s[21] that spurred the discovery of bioactive compounds for enhancing cardiogenesis.

A significant advance came with the report that a small molecule inhibitor of DNA methylation, 5-azacytidine, could induce cardiomyocyte differentiation in murine bone marrow stromal cells[22]. DNA methylation is an epigenetic modification that regulates global gene expression patterns. Thus, it was demonstrated that a small molecule could modulate the epigenetic status of the cell genome to make it amenable to differentiation when exposed to a cardiogenic environment, such as transplantation into to heart or exposure to cardiomyocyte differentiation factors. A follow-up study showed that 5-azacytidine could also induce cardiomyocyte differentiation in embryonic stem cells (ESCs)[23]. Consequently, numerous studies focused on the application of small molecules to derive cardiomyocytes from ESCs. Prominent examples included the discovery of cardiogenol, which activates the Wnt cell signaling pathway and chromatin remodeling enzymes[24]; dorsomorphin, which inhibits the bone morphogenetic (BMP) signaling pathway[25]; and a series of isoxazoyl serines, which act as peroxisome activated proliferation receptor (PPAR) agonists[26] (Figure 1).

These small molecules are not only useful as tools to induce cardiomyocyte differentiation. Characterizing their biological activity also gives insights into the cellular mechanisms that regulate the differentiation process. For example, the pivotal role of the Wnt signaling pathway was confirmed in a screening study for small molecule inducers of cardiogenesis[27]. Cardiogenesis is initiated in ESCs by the formation of embryonic bodies that induce formation of the mesodermal lineage, from which cardiomyocytes are eventually derived[28]. Small molecule screening at 6 d after embryoid formation revealed that Wnt signaling inhibitors significantly enhance cardiomyocyte differentiation, confirming the important role of this signaling pathway in cardiogenesis. This finding also contrasts with the known importance of Wnt signaling for mesodermal induction at the earlier stage of cardiogenesis[28]. This was confirmed in a study which used the Wnt activating molecule, BIO (Figure 1), at the embryoid body stage to increase the number of beating cells after differentiation[29]. Another interesting finding was that inactivation of the mitogen-activated protein kinase (MAPK) signaling pathway by small molecule SB203580 (Figure 1) enhanced cardiomyocyte differentiation from ESCs[30]. SB203580 was treated to embryoid bodies at 24 h after formation, indicating the important role of the MAPK pathway in maintaining the undifferentiated cell state and inhibiting cardiogenesis.

The development of iPSCs (described above) also provided extra impetus to develop small molecule-based methods to induce cardiogenesis, because iPSCs circumvent the ethical and technical problems associated with using ESCs[31]. In addition, iPSCs can be derived from somatic cells, which offers an opportunity to derive cardiac cells from differentiated cells residing in non-cardiac tissues. An interesting example of a small molecule based approach to induce cardiac differentiation in iPSCs utilizes JAK inhibitor-1 (Figure 1), which blocks signaling by janus protein tyrosine kinase and repression of the JAK-STAT pathway (the major alternative second messenger system in cells)[32]. The usefulness of this approach is that it bypasses the need to induce fully reprogrammed iPSCs from somatic cells. Application of JAK-1 during the iPSC generation step blocked the acquisition of full "stemness" and produced a cell population that could be efficiently induced to form functional cardiomyocytes by culture in chemically defined cardiogenic media. Impressively, 100% of the treated cells underwent spontaneous contractions and the protocol was significantly faster than alternative methods, such as the forced expression of master cardiogenic transcription factors[33].

Pluripotent stem cells, such as ESCs and iPSCs, are not the only cell source that has been used for small molecule-induced cardiogenesis. Cells from a diverse range of tissues have been demonstrated to be amenable to cardiomyocyte differentiation (Figure 2). These tissue-specific stem and precursor

Name	Structure	Mechanism	Ref.
5-azacytidine		DNA methyltransferase inhibitor	[22,23]
BIO		Wnt signaling pathway activator	[29]
Cardiogenol		Wnt signaling pathway activator	[24,54]
CHIR99021		Wnt signaling pathway activator	[48]
DMSO		Unknown (possible scavenger of hydroxyl radicals or modulates protein conformation)	[20]
Dorsomorphin		BMP signaling inhibitor	[25]
Isoxazolyl serine		Peroxisome proliferator activated receptor activator	[26]
IWP2		Wnt signaling pathway inhibitor	[48]
JAK inhibitor-1		JAK-STAT pathway inhibitor	[32]
RG108		DNA methyltransferase inhibitor	[35]
SB203580		MAPK signaling pathway activator	[30]

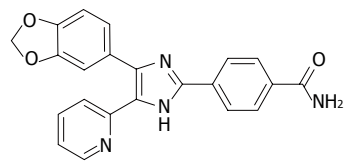
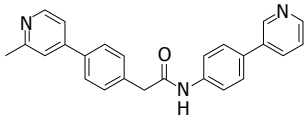
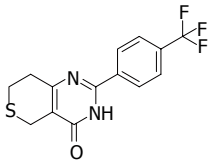
SB431542		TGF-β signaling pathway activator	[38]
Wnt C-59		Wnt signaling pathway inhibitor	[41]
XAV939		Wnt signaling pathway inhibitor	[48]

Figure 1 Selected small molecules that are used to regulate cardiogenesis (in alphabetical order). BMP: Bone morphogenetic; MAPK: Mitogen-activated protein kinase; TGF-β: Transforming growth factor-β.

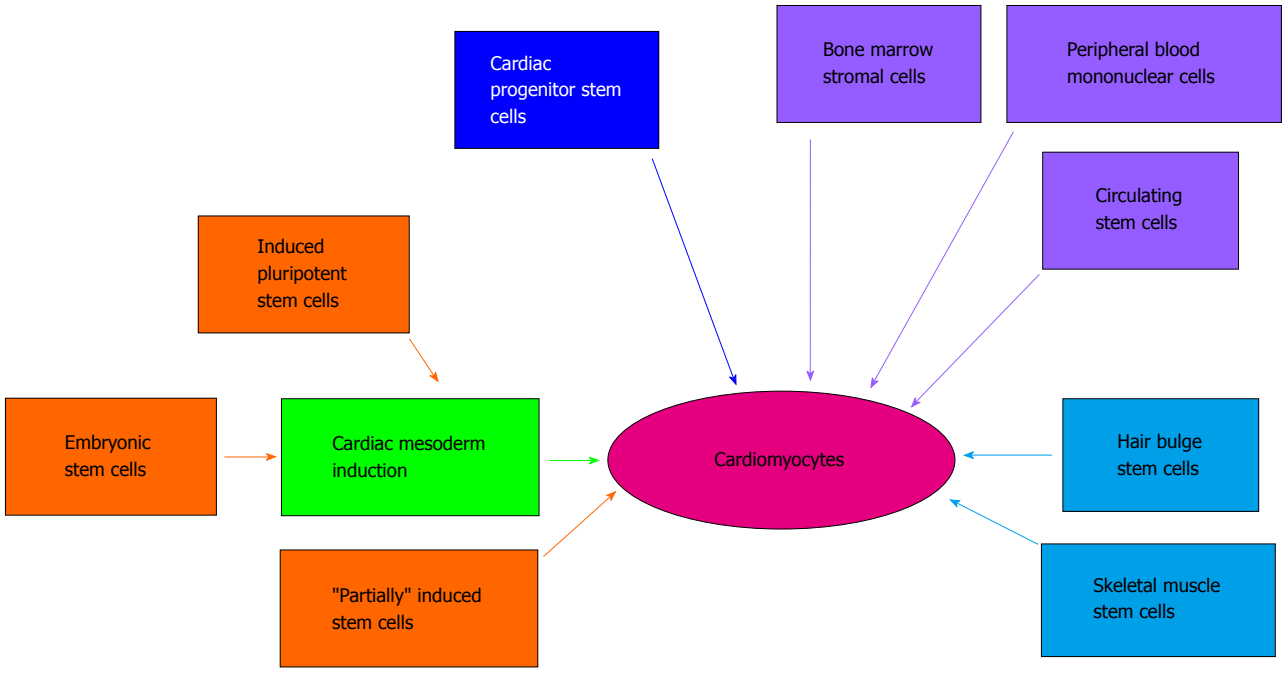


Figure 2 Pathways of small molecule-mediated cardiomyocyte production. It is now established that cardiomyocyte differentiation can be induced in multiple cells types using small molecule-based approaches. Embryonic stem cells and induced pluripotent stem cells are typically induced to undergo cardiac mesoderm differentiation before culture conditions are switched to cardiomyocyte differentiation media. "Partially" induced stem cells are somatic cells that were transfected with induced pluripotent stem cells reprogramming factors and then treated with the small molecule, JAK inhibitor-1 (as described in the text).

cells possess different levels of potency, such as skeletal muscle stems (unipotent) or bone marrow stromal cells (multipotent)[34]. These approaches may be useful for patient-specific cell therapy, because tissues such as skeletal muscle and blood are readily assessable. As an example of this small molecule-based approach, the DNA methyltransferase inhibitor RG108 was successfully used to convert skeletal muscle stem cells into a pluripotent state. These cells could then be induced to form embryoid bodies and undergo cardiogenic differentiation[35]. Significantly, transplantation of these cells could improve cardiac performance and reduce scarring in animal models of MI. Interestingly, a stem cell population has also been found to reside at the base of hair follicles (bulge stem cells)[36] and treatment with the small molecule Wnt pathway activator, cardiogenol C, induced expression of cardiomyocyte markers in these cells[37]. Thus, there are multiple "paths" to generate cardiac cells from diverse tissue types, which are facilitated by small molecule treatments (Figure 2). Moreover, small molecule methods can significantly enhance genetic-based approaches for cardiogenesis in somatic cells. For example, compound SB431542 (Figure

1), which inhibits the transforming growth factor-β (TGF-β) can produce a five-fold increase in the direct reprogramming of fibroblasts into cardiomyocytes using master cardiomyocyte transcription factors[38].

It can also be observed that, over time, these small molecule-based approaches are being optimized and simplified by the research community to allow easier derivation of cardiogenic cells. An important development in this regard is the development of chemically defined culture media for cardiogenic differentiation. This is important because serum should be eliminated from cell therapy applications. Serum supplies can suffer from batch variability and contain unspecified growth factors that may interfere with the differentiation process. Serum may also contain xenoantigens or infectious agents, which may induce an immune response in the host after transplantation[39]. To address this problem, a recently published study describes the development of a small molecule-based protocol to induce cardiomyocytes from bone marrow stem cells[40]. The development of these chemically-defined cardiogenic media cocktails are discussed in more detail below.

Latest progress in small molecule mediated cardiogenesis: Development of chemically defined induction media

A recently published study indicates the rapid progress that has been made for developing small molecule-based methods for cardiomyocyte differentiation. The study by Burridge *et al*[41] represents an impressively detailed investigation to define an optimized, chemically defined protocol for cardiomyocyte differentiation from human iPSCs. Their previous protocol for cardiomyocyte induction required the supplement B27, which is a complex mixture of 21 components. Some of these components are derived from animals, which necessitated the need to develop a chemically defined cardiogenic media. Interestingly, the iPSCs used in this study were also generated using a chemically defined methodology: human primary fibroblasts were transduced/transfected with the Yamanaka factors and cultured sequentially in the defined E8 and E7 culture media containing the small molecule histone deacetylase inhibitor, sodium butyrate. iPSC colonies could be selected after three weeks. The induction of cardiomyocyte differentiation was rigorously investigated using different combinations of small molecules and matrix scaffolds for cell attachment. Before the onset of cardiogenesis, cells were incubated with the small molecule thiazovivin, which is a selective inhibitor of Rho-associated coiled-coil containing protein kinase (ROCK) that has been shown to facilitate iPSC generation[13,42]. As mentioned above, modulation of the Wnt cell signaling pathway is a crucial aspect of the differentiation process, with positive signaling required for mesoderm specification and inhibition required for subsequent cardiomyocyte differentiation. A wide range of small molecule Wnt pathway modulators was tested to find the optimal combination for cardiac induction. Cardiomyocyte differentiation was monitored by measuring expression of the early cardiomyocyte marker gene, troponin T (TNNT)[43]. Interestingly, different small molecule Wnt pathway activators showed markedly diverse effects on cardiogenesis. Of six activators tested, only two [CHIR99021 and BIO (Figure 1)] facilitated the production of TNNT expressing cells without causing cell death. This finding emphasizes the need to compare small molecules that target identical pathways to eliminate the potential for significant off-target effects.

Further optimization of this cardiomyocyte differentiation protocol involved comparison of small molecule inhibitors of various signaling pathways (such as BMP or TGF-β) during the mesoderm induction step and Wnt signaling inhibition during the later cardiomyocyte differentiation step. Remarkably, these optimizations led to the development of a simplified induction protocol that could produce 95% TNNT positive contractile cardiomyocytes, with around 100 cells being derived from a single human iPSC. This protocol is based on the CDM3 media, which contains the chemically defined RPMI-1640 base media and is supplemented with just two reagents: l-ascorbic acid 2-phosphate and human recombinant albumin. iPSCs are cultured with CDM3 plus the Wnt pathway activator, CHIR99021 for two days, followed by two days incubation with CDM3 plus the small molecule Wnt pathway inhibitor, Wnt C-59 (Figure 1). Impressively, cardiomyocyte differentiation was observed just 96 h after this step, using additional incubation with CDM3 media alone. The cardiomyocyte phenotype was assessed by nanopillar-based microscopic observation and it was observed that the majority of cardiomyocytes (> 60%) were ventricular-like compared to atrial-like, with no nodal cardiomyocytes being observed. This observation is important, because new strategies to induce cardiomyocyte differentiation aim to produce specific, adult cardiomyocyte subtypes. The role of small molecules in these differentiation strategies are discussed in the next section.

New small molecule-based methods to induce epicardial cells for facilitating regeneration

As mentioned in the introduction for this editorial, cell therapy approaches for degenerative diseases require a high quality source of purified, functional cells for transplantation. This is also relevant for other applications, such as disease modeling, developmental studies and cell-based drug screening[44]. Early small molecule-based methods for inducing cardiogenesis, such as treatment with 5-azacytidine, were found to produce mixed populations of cells containing approximately 30% cardiomyocytes[22]. As described above, recent developments in producing chemically defined conditions for cardiogenesis from stem cells

allows the derivation of cell populations containing up to 95% cardiomyocytes[41]. However, the heart comprises multiple cell types and cardiomyocytes account for only around 30% of total cells[45]. Therefore, for applications such as modeling cardiac development or cell therapy approaches for MI, it would be useful to generate these non-cardiomyocyte cell types. This is especially relevant for the epicardial cell type, because it is known that epicardial tissue plays a pivotal role in both cardiac development and cardiomyocyte regeneration after disease[46,47]. A recently published study demonstrates that it is indeed possible to derive epicardial cells from iPSCs, with small molecules being used as "control switches" to regulate cell differentiation potential[48].

Epicardial cells can be defined by their cobblestone morphology, specific gene marker expression [Wilms tumor protein (WT1) and T-box 18 (TBX18)] and the ability to synthesize retinoic acid[49-51]. In this study, human ESCs were induced to form embryoid bodies and undergo mesoderm formation by treatment with BMP4 alone for one day, followed by treatment with combined BMP, fibroblast growth factors (FGF) and activin A (a TGF pathway stimulator). Crucially, after 96 h the TGF pathway was inhibited with the small molecule SB431542 (Figure 2). This small molecule was removed after 48 h to facilitate the derivation of cardiomyocytes. In an attempt to block this cardiomyocyte differentiation and allow epicardial cells to be generated, the authors of this study focused on manipulating the Wnt signaling pathway after the addition of BMP. Such precise manipulation of Wnt signaling within this time window of differentiation could be achieved using small molecules. The effects of small molecule Wnt inhibitors (XAV939 and IWP2) were compared with a small molecule activator (CHIR99021). The effect of BMP-mediated signaling on differentiation was assessed using the small molecule inhibitor, dorsomorphin. The use of these small molecule combinations showed that BMP signaling has no effect on the canonical Wnt signaling pathway. Most significantly, it was observed that maintaining Wnt signaling using CHIR99021 allowed the derivation of epicardial lineage cells, as assessed by gene marker expression, morphological characteristics, differentiation into vascular or smooth muscle cells and the ability to synthesize retinoic acid[48]. The population of cells expressing the epicardial marker WT1 could be expanded to account for over 95% of the differentiated cell population, with one mesodermal lineage cell at day 4 of differentiation producing 4-5 epicardial cells. This study provides a high profile example of the advantages that small molecule methodologies offer to cell biologists. In this study, small molecules were used with precise timing to derive a valuable cardiac cell population which has been of great interest to investigators of heart development and regeneration after injury.

CONCLUSION

In this editorial, we have described some prominent examples of small molecule-based methods to facilitate the production of cardiac cells from diverse cell sources. We have shown that small molecules have numerous advantages as tools to control cell differentiation. They can be viewed as cheap, simple and reliable "switches" that provide rapid and reversible control of key cell signaling pathways. Our editorial has focused on the generation of cardiomyocytes from non-cardiac cells, but small molecules are also used in many other areas of cardiac regeneration research. Examples include improving the survival of cardiac tissue grafts, inducing cardiomyocyte dedifferentiation/proliferation and activating endogenous cardiac progenitor cells[3,52]. In addition, the impact of small molecule approaches is shown in the recent demonstration that iPSCs can be derived from somatic cells using just these chemicals alone, *i.e.,* without the need for expressing reprogramming transcription factors[53]. This was achieved using a stepwise protocol requiring only seven small molecules: RepSox (a TGF signaling pathway inhibitor), PD0325901 (a MAPK pathway inhibitor), CHIR99021 (a Wnt pathway activator), TTNPB (a retinoic acid analog), 3 deazaneplanocin-A (which reduces histone methylation), valproic acid (which increases histone acetylation) and forskolin (which increases protein kinase A signaling). Remarkably, the efficiency of iPSC generation using this small molecule method was similar to that achieved using the reprogramming factors. It can be envisaged that this iPSC method could be joined with the chemically defined, small molecule method for cardiomyocyte differentiation, described above. Theoretically, this would allow the derivation of cardiac cells from almost any somatic cell source in the body.

Overall, we hope that this editorial has provided convincing evidence of the many advantages of using small molecules in biological research and cardiac regenerative medicine in particular. Chemical biologists continue to develop new bioactive small molecules or optimize the structures of existing compounds, to improve specificity and/or lower effective concentration. In concert with this research effort, cell biologists are also discovering new applications for known bioactive molecule or developing novel small molecule cocktails to manipulate cell behavior. Therefore, it seems likely that even more diverse and exciting progress is the field of cardiac regeneration can be achieved using small molecules.

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REVIEW

Role of *Helicobacter pylori* infection in pathogenesis of atherosclerosis

Rajesh Vijayvergiya, Ramalingam Vadivelu

Rajesh Vijayvergiya, Ramalingam Vadivelu, Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India
Author contributions: Both the authors have contributed equally to this review article; Vijayvergiya R has done literature search, critical review and analysis of the literature and a revision of the manuscript; and Vadivelu R has performed literature search and review, articles extraction, writing of first draft of the manuscript.
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Correspondence to: Rajesh Vijayvergiya, MD, DM, FSCAI, FISES, FACC, Additional Professor, Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. rajeshvijay999@hotmail.com
Telephone: +91-172-2756518
Fax: +91-172-2744401
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Abstract

Though a century old hypothesis, infection as a cause for atherosclerosis is still a debatable issue. Epidemiological and clinical studies had shown a possible association but inhomogeneity in the study population and study methods along with potential confounders have yielded conflicting results. Infection triggers a chronic inflammatory state which along with other mechanisms such as dyslipidemia, hyper-homocysteinemia, hypercoagulability, impaired glucose metabolism and endothelial dysfunction, contribute in pathogenesis of atherosclerosis. Studies have shown a positive relations between Cytotoxic associated gene-A positive strains of *Helicobacter pylori* and vascular diseases such as coronary artery disease and stroke. Infection mediated genetic modulation is a new emerging theory in this regard. Further large scale studies on infection and atherosclerosis focusing on multiple pathogenetic mechanisms may help in refining our knowledge in this aspect.

Key words: Atherosclerosis; Coronary artery disease; *Helicobacter pylori* ; Infection; Stroke

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Core tip: Though a century old hypothesis, infection as a cause of atherosclerosis is still a debatable issue. Clinical and epidemiological studies had shown a possible association, however in-homogeneity in the study population and methodology has yielded conflicting results. We performed a literature search on MEDLINE electronic database using keywords such as *Helicobacter pylori* (*H. pylori*), infection, atherosclerosis, coronary artery disease, myocardial infarction, stroke, cerebro-vascular disease and peripheral arterial disease using MeSH terms, to review this subject. The association between *H. pylori* and atherosclerosis is not strong and a causal role is not yet established. Large scale studies on infection and atherosclerosis focusing on multiple pathogenetic mechanisms may help in refining our knowledge in this aspect.

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INTRODUCTION

Though a century old hypothesis, infection is still debated as a cause of atherosclerosis[1]. Infection triggers a chronic inflammatory state which along with other mechanisms such as dyslipidemia, hyperhomocysteinaemia, hypercoagulability, impaired glucose metabolism and endothelial dysfunction contribute in pathogenesis of atherosclerosis. Studies have shown a positive relations between Cytotoxic associated gene-A (Cag-A) positive *Helicobacter pylori* (*H. pylori*) strains with vascular diseases such as coronary artery disease (CAD) and stroke. Infection mediated genetic modulation is a new emerging theory in this regard. Minick and Fabricant's work on infection and atherosclerosis in animal model had made the ground for revolutionary research in this field[2,3]. Chronic infection triggers T1 Helper cell (Th1) mediated inflammatory reaction, which plays a crucial role in atherosclerosis. Markers of infection and inflammation were also studied as the risk factors for atherosclerosis[4-6]. An association between infection and atherosclerosis was established following detection of infectious agents from arterial vessels, positive immunehistochemistry studies, detection of microbial DNA sequences in atherosclerotic plaques by PCR method, positive serological response with higher titres in infected patients, and a positive correlation of infection with atherosclerotic burden and dyslipidaemia[7-23]. The microbial agents that have been implicated in the etiopathogenesis of atherosclerosis are presented in Table 1, Figure 1.

This review has been divided into two parts. Part Ⅰ elucidates different mechanisms of *H. pylori* related atherosclerosis and relevant studies. Part Ⅱ reviews the literature about *H. pylori* association with atherosclerotic diseases such as CAD, stroke and peripheral arterial disease (PAD).

MECHANISMS OF *H. PYLORI* RELATED ATHEROSCLEROSIS

Development of CAD in patients without conventional risk factors suggests a possible role of an additional unexplored mechanism. The evolution of atherosclerosis in the background of chronic inflammatory milieu involves multiple pathways (Table 2, Figure 1). Some of these pathways will be discussed in following section.

H. pylori and endothelial dysfunction

Infection related chronic vascular inflammation can result in endothelial dysfunction. Tousoulis *et al*[24] first proposed an inflammatory mechanism for endothelial dysfunction. C-reactive protein (CRP) and inflammatory adhesion molecule such as intracellular adhesion molecule-1 (ICAM-1) are elevated in patients with *H. pylori* infection, suggesting a possible link between infection and endothelial dysfunction[25].

Table 1 Microbial agents associated with atherosclerosis

Bacteria	Viruses
Chlamydia pneumonia	H simplex virus type 1 and 2
Helicobacter pylori	Cytomegalovirus
Helicobacter cinaedi	Epstein- Barr virus
Hemophilus influenza	
Mycoplasma pneumonia	

Chronic infection triggers release of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α), which affects microvascular vasomotor functions, resulting into vasoconstriction and endothelial dysfunction. Coskun *et al*[26] studied a possible relation between *H. pylori* infection in children and endothelial dysfunction as a precursor for future atherosclerosis. There was no significant association between *H. pylori* seropositivity and CRP levels with flow mediated vasodilation. Another evidence is about increase prevalence of slow flow in the major epicardial coronary arteries in patients with *H. pylori* infection[27]. The possible mechanism of slow flow was endothelial dysfunction secondary to raised homocysteine levels. *H. pylori* infection causes malabsorption of vitamin B12 and folic acid and thus increases serum homocysteine levels. Evrengul *et al*[27] reported a mean TIMI frame count of coronary flow as 46.3 ± 8.7 and 24.3 ± 2.9 in patients with and without *H. pylori* infection, respectively. An association between *H. pylori* infection and functional vascular disorders such as cardiac syndrome-X, migraine and primary Reynaud phenomenon provides evidence about its role in endothelial dysfunction and atherosclerosis[28-32].

Chronic inflammation

Presence of chronic, persistent inflammation provides a vital clue for infectious theory of CAD. Chronic *H. pylori* infection induces a pro-inflammatory state, resulting into an increase in cytokines levels such as TNF-α, Interleukins (IL-1, IL-6, IL-8), gamma interferon, coagulant factors - fibrinogen, thrombin and soluble adhesion molecules such as intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1)[33-35]. Eradication of *H. pylori* infection by use of antibiotics leads to reduction in cytokines levels[34,36]. These evidences suggest that *H. pylori* induced inflammatory cascade plays an active role in atherosclerosis. Activated T lymphocytes and macrophages following cytokines release induce proliferation of smooth muscle cells and extracellular matrix, which plays a crucial role in pathogenesis of atherosclerosis. It also stimulates metalloproteinases production, which causes rupture of atheroma cap and leads to acute coronary syndromes. However, a large population based study failed to support the association between *H. pylori* and increased inflammatory cytokines[37].

Recent research has unveiled novel molecular

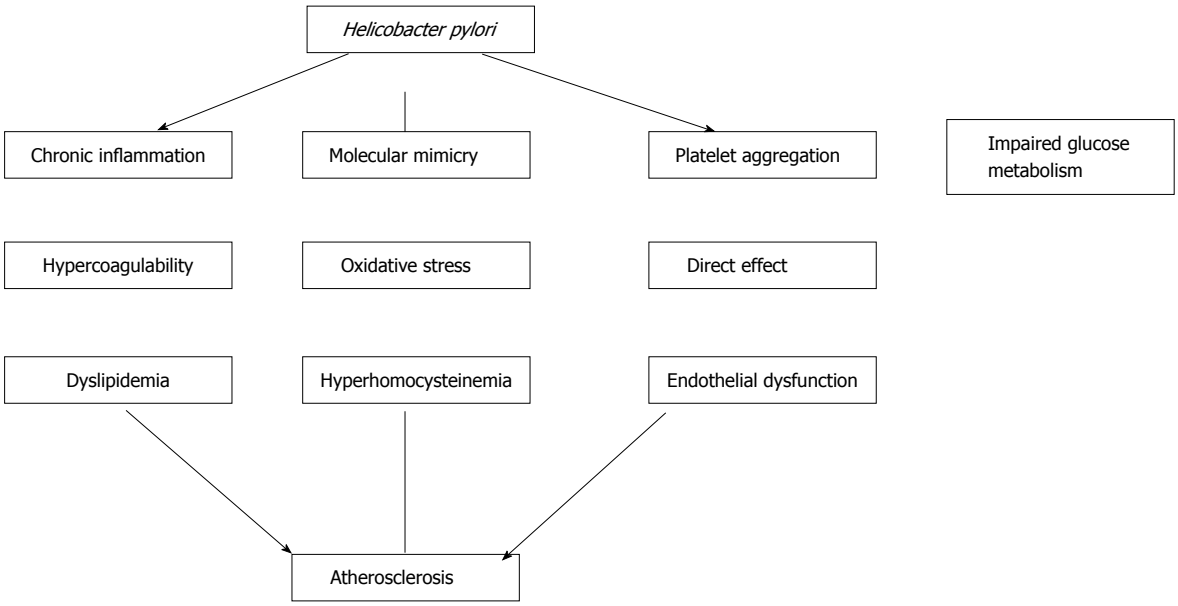

Figure 1 Theories of infection related atherosclerosis.

Table 2 Mechanisms of *Helicobacter pylori* related atherosclerosis

Induction of inflammatory response secondary to chronic infectious state
Endothelial damage
Chronic low grade activation of coagulation cascade
Dysregulation of lipid metabolism resulting in increased total cholesterol and triglyceride levels and reduced high density lipoprotein levels
Hyperhomocysteinaemia

While the proponents support the possible association[52,70,104], the opponents refute this hypothesis[46,71,105].

mechanisms of *H. pylori* mediated inflammation[38-41]. *H. pylori* infection exerts an immune-inflammatory reaction by activating cyclooxygenase enzyme-2 (COX-2), which causes increase production of prostaglandin (PGE_2) and nitric oxide (NO). *H. pylori* cell wall lipopolysaccharide (LPS) triggers toll-like receptor-4, which activates various secondary mediators such as mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase, c-Jun N-terminal kinase (JNK) and p38 kinase resulting in enhanced stimulation of *NOS* and *COX-2* gene expression[38,39]. LPS-induced activation of MAPK cascade is also associated with epidermal growth factor receptor (EGFR) transactivation which is a key protein regulating cellular proliferation, differentiation, migration and modulation of apoptosis[41]. Gherlin, a peptide hormone activates NO synthase, thereby inhibiting *H. pylori* LPS induced activation of COX-2 and other inflammatory pathways[40].

H. pylori and hyper-homocysteinaemia

H. pylori causes atrophic gastritis, which is associated with malabsorption of vitamin B12 and folic acid. Deficiency of these vitamins causes hyper-homocysteinaemia due to interruption of re-methylation pathway[42-45]. Hence, it may have a role in the pathogenesis of premature atherosclerosis[45]. In a study by Kutluana *et al*[45], carotid intima media thickness was found to be higher in patients with *H. pylori* related atrophic gastritis. In this study, *H. pylori* positive patients had significantly higher homocysteine levels compared to controls (14.17 ± 9.24 μmol/L *vs* 9.81 ± 3.42 μmol/L, $P = 0.01$). Senmaru *et al*[46] reported a higher prevalence of CAD in atrophic gastritis (5.8% *vs* 2.8%). Torisu *et al*[47] had shown an association between increased pulse wave velocity, a preclinical marker of atherosclerosis with atrophic gastritis. Apart from hyper-homocysteinaemia, other mechanisms are reduced ghrelin levels and induction of chronic pro-inflammatory cascade resulting into endothelial damage[46,47]. However, Bloemenkamp *et al*[48] did not support the hypothesis about *H. pylori* infection induced hyper-homocysteinemia and atherosclerosis.

H. pylori and dyslipidemia

H. pylori infection is associated with lower HDL cholesterol (HDL-C) and higher total cholesterol (TC), LDL cholesterol (LDL-C) and triglyceride levels. Higher apolipoprotein-B and lower apolipoprotein-A (apo-A) levels were also reported[11]. Murray *et al*[49] demonstrated that women with *H. pylori* infection had lower HDL-C ($P = 0.006$). Another study had also shown significantly lower HDL-C levels in

infected patients[11]. Niemelä *et al*[50] and Laurila *et al*[22] reported an increase triglyceride levels in *H. pylori* positive patients. These alterations in lipid homeostasis proved to be significant even after adjusting co-variables such as socioeconomic class, body weight, age and diabetic status[22,51]. de Luis *et al*[52] showed that eradication of *H. pylori* decreases apo-A and increases HDL-C. Other studies had also shown reduction in TC, LDL-C levels and increase in HDL-C, apo-AI and apo-AII levels following *H. pylori* eradication[53-55]. However, this association was not supported by few other authors[56-59].

H. pylori, impaired glucose metabolism and metabolic syndrome

Gillum *et al*[60] reported a significant association of *H. pylori* seropositivity with CAD in diabetic males. de Luis *et al*[51] showed that CAD and cerebrovascular diseases were significantly more seen in *H. pylori* infected diabetic patients. Yoshikawa *et al*[61] suggested that *H. pylori* seropositivity increases brachial-ankle pulse wave velocity, a marker of atherosclerosis, in patients with impaired glucose metabolism. Aydemir *et al*[62] reported that *H. pylori* positive subjects had higher homeostatic model assessment-insulin resistance (HOMA-IR) levels (2.56 ± 1.54 *vs* 1.73 ± 1.1, $P < 0.05$), a surrogate of insulin resistance, as compared to *H. pylori* negative controls. Aslan *et al*[63] had shown that paraoxanase, a marker of oxidative stress is well correlated with HOMA-IR levels and is significantly elevated in *H. pylori* positive patients. Regarding role of *H. pylori* eradication therapy in improvement of glucose tolerance, Gen *et al*[64] reported that HOMA-IR level significantly reduced after successful therapy, whereas Park *et al*[65] did not show any significant reduction. Polyzos *et al*[66] in his systematic review concluded that available evidences indicate a potential association between *H. pylori* infection and insulin resistance. Gunji *et al*[67] reported that *H. pylori* infection was significantly and independently associated with metabolic syndrome. A recent study by Ando *et al*[68] revealed that eradication of *H. pylori* increases circulating adiponectin levels and might be helpful in prevention of metabolic syndrome. Naja *et al*[69] suggested no association between *H. pylori* infection and metabolic syndrome or impaired glucose tolerance.

H. pylori, hypertension and arterial stiffness

Migneco *et al*[70] demonstrated a significant reduction in blood pressure after eradication of *H. pylori* in hypertensive subjects. The possible association of *H. pylori* with arterial stiffness was initially reported by Adachi and Yoshikawa. Adachi *et al*[71] reported that carotid pulse wave velocity was higher in seropositive subjects. Yoshikawa *et al*[61] similarly reported a higher brachial-ankle pulse wave velocity in seropositive patients with impaired glucose metabolism. The possible association of *H. pylori* and arterial stiffness tends to be more in younger subjects, whereas in the elderly arterial stiffness is more often due to aging[72]. Honda *et al*[73] demonstrated that *H. pylori* infection did not affect the age related progression of arteriosclerosis over a 4 years follow-up period.

EVIDENCE OF ASSOCIATION BETWEEN *H. PYLORI* AND ATHEROSCLEROSIS

H. pylori and CAD

Demonstration of an association between *H. pylori* and CAD is always challenging. Both conditions are more prevalent in the population, increases with age and are related to socioeconomic status. The following section reviews the evidence of *H. pylori* association with CAD.

Numerous studies have shown that CAD patients have a higher prevalence of *H. pylori* infection[74-77]. Vijayvergiya *et al*[77] demonstrated that CAD patients had higher IgG seropositivity as compared to controls (42% *vs* 23%, $P = 0.06$). Franceschi *et al*[78] found that *H. pylori* Cag-A was significantly associated with acute coronary events (OR = 1.34; 95%CI: 1.15-1.58, $P = 0.0003$). Niemelä *et al*[50] showed that the association between CAD and *H. pylori* infection was not strong. A meta-analysis revealed that there is a little association between *H. pylori* infection and stroke, but the strength of association was greater for Cag-A positive strains[79]. *H. pylori* was shown to be associated with premature CAD even in patients without conventional cardiovascular risk factors[80,81]. A number of studies had shown a negative association between *H. pylori* and CAD which include serological[82,83] and histological studies[84-86]. A negative association is even reported in long term follow-up studies[87]. The Australian Busselton health study comprising of 1612 healthy subjects demonstrated negative association between infection and CAD or stroke[88]. Danesh *et al*[89] in his meta-analysis of five prospective studies reported no significant association of *H. pylori* infection with CAD (RR = 1.13). Association of *H. pylori* infection and outcome of CAD treatment had also been studied. Schiele *et al*[90] found that *H. pylori* infection was not a risk factor for restenosis after percutaneous coronary angioplasty. Limnell *et al*[91] had shown an inverse relationship between *H. pylori* infection and coronary bypass graft occlusion. Results from Caerphilly heart disease study suggested that Cag-A seropositivity had no relations with CAD or CAD related mortality[92].

H. pylori has been associated with cardiac syndrome X, *i.e.*, angina pectoris with normal epicardial coronaries[28-30]. The proposed mechanism is chronic endothelial dysfunction. Eskandrian *et al*[28] reported a higher prevalence of *H. pylori* positivity in syndrome X patients compared to controls (95% *vs* 47.5%). Patients with syndrome X were found to be more commonly associated with *H. pylori* Cag-A positivity and elevated IL-1 and TNF-α[93]. Lanza *et al*[94] has

also described association of inflammation, infectious burden and vascular dysfunction. Assadi *et al*[30] reported 15% of patients with syndrome X had urea breath test (UBT) positivity for *H. pylori* while none of the patients with chronic stable angina or controls had UBT positivity.

H. pylori and acute myocardial infarction

H. pylori induced inflammatory reaction is possibly responsible for plaque instability and platelet aggregation in acute coronary syndrome patients. Danesh *et al*[95] demonstrated a higher prevalence of *H. pylori* infection (42% *vs* 24%, OR = 1.75) in young acute myocardial infarction (AMI) survivors. Alkout *et al*[96] showed a higher titre of *H. pylori* IgG titre in patients who died of AMI (151 ng/mL *vs* 88 ng/mL, p= 0.034). Kahan *et al*[97] reported a higher prevalence of *H. pylori* seropositivity in recent myocardial infarction patients as compared to controls (68% *vs* 53%, OR = 1.36). This remained significant even after adjusting for other CAD risk factors like age, sex, smoking and hypertension. Kinjo *et al*[98] suggested that *H. pylori* infection was significantly associated with AMI in younger patients (age < 55 years, OR = 2.7) but not in those with age of > 55 years. Frazer *et al* showed a higher prevalence of *H. pylori* infection in AMI patients compared to control (41.6% *vs* 34.5%; $P = 0.038$)[99].

Similar to CAD, negative associations is also been reported between *H. pylori* and myocardial infarction. Zhu *et al*[100] hypothesised that *H. pylori* infection could not lead to CAD or myocardial infarction. Murray *et al*[101] had shown a negative association between *H. pylori* and risk for myocardial infarction. Pellicano *et al*[102] reported a negative association between cytotoxic *H. pylori* strains and myocardial infarction, with insignificant anti-Cag-A antibody seropositivtiy between cases and controls (33.8% *vs* 26.8%).

H. pylori Cag-A positivity - Is the risk greater?

Cag-A positivity has raised a curiosity in the infectious theory of atherosclerosis. Several studies had shown a significant relationship between Cag-A strain and CAD or stroke. Carriers of Cag-A positive strains had a higher risk for stroke (OR = 2.99) and carotid plaque instability (OR = 8.42)[103]. De Bastiani *et al*[104] showed increased prevalence of Cag-A seropositivity and ischemic stroke. Rasmi *et al*[93] reported a positive relation between Cag-A seropositivity and cardiac syndrome-X. Huang *et al*[105] revealed that Cag-A positive strains enhanced atherosclerosis in CAD patients by modifying oxidised LDL levels and high sensitive C-reactive protein (hsCRP) levels. Kowalski[36] showed that Cag-A positivity was significantly associated with greater coronary artery lumen loss and restenosis after percutaneous coronary artery stenting. He also demonstrated that *H. pylori* eradication significantly attenuate reduction in coronary artery lumen after coronary artery stenting[36]. But various authors had denied the excess risk of Cag-A positive strains with atherosclerosis. Koenig *et al*[106] demonstrated a similar prevalence of Cag-A seropositivity in CAD patients and healthy subjects. Whincup *et al*[107] in his prospective study comprising of 505 patients and 1025 healthy subjects had clearly shown that there was no significant association of seropositivity with CAD. Murray *et al*[101] reported negative association between the virulent *H. pylori* Cag-A strains and acute myocardial infarction.

H. pylori and stroke

By catalysing atherosclerotic pathways, *H. pylori* infection may be a risk factor for ischemic stroke. Single infectious agent is weakly linked to stroke but cumulative chronic infectious exposures, or "infectious burden", have been associated with the risk of stroke. The adjusted hazard ratio demonstrating the risk of association between *H. pylori* and stroke was 1.13, whereas that of infectious burden and stroke was 1.39[108]. The possible mechanisms include macrophage activated plaque destabilization, increased expression of various adhesion molecules and inflammatory cytokines, localized hypercoagulability, altered gene expression, and a molecular mimicry. Markus *et al*[109] found a higher prevalence of *H. pylori* seropositivity in stroke cases compared to controls. There was an association between *H. pylori* infection and large vessel disease and lacunar stroke irrespective of other confounding factors. Another study by Grau *et al*[110] demonstrated an association between *H. pylori* seropositivity and ischemic stroke. Elkind *et al*[111] suggested that that chronic infectious burden results in increase carotid plaque thickness and stroke. A retrospective study reported higher incidence of ischemic stroke in patients with *H. pylori* infection than in non-infected group (14.8 *vs* 8.45 per 1000 person years)[112]. Diomedi *et al*[113] showed that Cag-A positive *H. pylori* infection was associated with poorer short term clinical outcomes and greater carotid intima media thickness in stroke patients. Increased risk of stroke in Cag-A positive *H. pylori* patients may be due to enhanced plaque vulnerability[103,114]. In one of the studies, the positive correlation between *H. pylori* and stroke was confounded by socioeconomic class[115]. A study on chronic bacterial infection and stroke demonstrated that elevated anti- *H. pylori* antibody was not significantly associated with ischemic stroke[116].

H. pylori and peripheral arterial disease

Studies about association of *H. pylori* infection with peripheral arterial disease (PAD) are limited. Bloemenkamp *et al*[117] demonstrated infection as a novel risk factor for PAD in young women. A case control study on infection and PAD in young women suggested that *H. pylori* infection was positively correlated with PAD only in those with high CRP levels[118]. Sawayama *et al*[119] reported a significantly higher prevalence of *H.*

pylori infection in PAD cases than in controls (79.7% *vs* 44.8%; $P < 0.01$).

CONCLUSION

Overall the association between *H. pylori* and CAD is not strong and a causal role is yet to be established. Future studies on larger scale may possibly establish a stronger link between the two. If it gets established, there can be drastic reduction in burden of CAD by managing *H. pylori* infection. Proponents of infectious theory will have a real challenge in the years to come because establishing a definite causal role of *H. pylori* in CAD will be a nightmare due to the existence of numerous confounding factors. Opponents may continue to criticise the infectious theory of CAD because of lack of strong scientific evidence.

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MINIREVIEWS

Palm oil and the heart: A review

Osaretin J Odia, Sandra Ofori, Omosivie Maduka

Osaretin J Odia, Sandra Ofori, Department of Medicine, University of Port Harcourt, Port Harcourt 500001, Nigeria
Omosivie Maduka, Department of Preventive and Social Medicine, University of Port Harcourt, Port Harcourt 500001, Nigeria
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Correspondence to: Dr. Sandra Ofori, FWACP, MSc, Department of Medicine, University of Port Harcourt, Rivers State, Port Harcourt 500001, Nigeria. sandytom77@yahoo.com
Telephone: +234-809-6598508
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Abstract

Palm oil consumption and its effects on serum lipid levels and cardiovascular disease in humans is still a subject of debate. Advocacy groups with varying agenda fuel the controversy. This update intends to identify evidence-based evaluations of the influence of palm oil on serum lipid profile and cardiovascular disease. Furthermore, it suggests a direction for future research. The sources of information were based on a PubMed, Google Scholar, African Journal online and Medline search using key words including: palm oil, palmitic acid, saturated fatty acids and heart disease. Published animal and human experiments on the association of palm oil and its constituents on the serum lipid profile and cardiovascular disease were also explored for relevant information. These papers are reviewed and the available evidence is discussed. Most of the information in mainstream literature is targeted at consumers and food companies with a view to discourage the consumption of palm oil. The main argument against the use of palm oil as an edible oil is the fact that it contains palmitic acid, which is a saturated fatty acid and by extrapolation should give rise to elevated total cholesterol and low-density lipoprotein cholesterol levels. However, there are many scientific studies, both in animals and humans that clearly show that palm oil consumption does not give rise to elevated serum cholesterol levels and that palm oil is not atherogenic. Apart from palmitic acid, palm oil consists of oleic and linoleic acids which are monounsaturated and polyunsaturated respectively. Palm oil also consists of vitamins A and E, which are powerful antioxidants. Palm oil has been scientifically shown to protect the heart and blood vessels from plaques and ischemic injuries. Palm oil consumed as a dietary fat as a part of a healthy balanced diet does not have incremental risk for cardiovascular disease. Little or no additional benefit will be obtained by replacing it with other oils rich in mono or polyunsaturated fatty acids.

Key words: Palm oil; Serum lipid profile; Heart disease; Palmitic acid; Antioxidants

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Core tip: With the increase in the prevalence of cardiovascular diseases (CVD) worldwide including developing countries, increasing attention is paid to underlying risk factors. Low-density lipoprotein (LDL) cholesterol is related to CVD in a linear and continous manner and one of the strongest risk factors for CVD. Dietary saturated fat increases LDL. Palm oil contains saturated fat and has thus been touted to be "bad for the heart". However it also contains unsaturated fats and beneficial antioxidants. This review sought to clarify the role of this important source of nutrients (to a

large part of the worlds' population) in CVD.

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INTRODUCTION

In recent times, there has been a running debate mainly in mainstream literature regarding the effects of palm oil consumption on the heart especially in the development of coronary artery disease. Advocacy groups and consumer protection groups drive most of the controversy with conflicting interests and agenda[1]. For thousands of years palm oil has been a major source of cooking oil in many communities in Asia and Africa[2-5].

In 2012, the World Heart Organization listed ischaemic cardiovascular disease (CVD) as the leading cause of death worldwide[6]. The relationship between serum cholesterol and CVD risk is linear and dose dependent with a 20%-25% reduction in the risk of death from CVD and non-fatal MI as low-density lipoprotein (LDL) cholesterol decreases by 1.0 mmol/L[7]. Palm oil consists of various fatty acids and this has been of major concern in discussing the value of palm oil vis-a-vis its relationship to cardiovascular disease[4,8]. The concern about palm oil is mainly because it contains palmitic acid, which is a saturated fatty acid and by extrapolation, using the Keys-Anderson equation which proposes that dietary intake of saturated fat increases serum cholesterol, will give rise to hypercholesterolemia when used as dietary oil[8]. However the main dietary saturated fatty acids (palmitic, stearic, lauric, and myristic acids) have varying effects on serum cholesterol. Saturated fatty acids with 12 and 14 carbon atoms (lauric and myristic acids) increase all the cholesterol fractions more than palmitic acid, and palmitic acid increases all the cholesterol fractions more than stearic acid[9]. On the other hand, oleic and linoleic acids which are unsaturated fatty acids do not have an adverse effect on serum cholesterol[9]. Palm oil has almost equal parts saturated and unsaturated fatty acids. Myristic acid (1%), stearic acid (5%) and palmitic acid (44%) make up the saturated fatty acid component in addition to monounsaturated oleic acid (39%), and polyunsaturated linoleic acid (11%)[10]. Furthermore, palm oil also contains vitamin E, carotenoids and antioxidants that do, at least in theory, protect the heart and also prevent cancer[4,5,11]. This review critically evaluates the scientific literature on palm oil in order to clearly show whether or not the consumption of palm oil indeed adversely alters the serum lipid profile and increases the prevalence of heart disease.

CHEMICAL COMPOSITION OF PALM OIL

The oil palm tree belongs to the genus Elaeis. The palm fruit has a fleshy mesocarp from which palm oil is derived and a seed from which palm kernel oil is derived[10]. These are two different types of oil and this paper is concerned with the former only.

The genus Elaeis has two species: E. guineensis and E. oleifera. The former is found mainly in West Africa, particularly in Nigeria and was propagated to Malaysia, Brazil, and Indonesia by the Portuguese in the 19th century for commercial purposes. E. oleifera originated from South America and is a dwarfish plant[5].

The major constituents of palm oil are triacylglycerols (TG). The glycerol molecule is esterified with three fatty acids. During the process of palm oil extraction from the fleshy mesocarp of the fruit, triacylglycerols attract other fat-soluble cellular components. These include phosphatives, sterols, pigments, tocopherols, tocotrienols, monoglycerols, diglycerol and free fatty acids (FFAs). The fatty acids are aliphatic acids like myristic, palmitic, stearic, linoleic acid. Palm oil also contains vitamins, antioxidants and other phytonutrients[10].

EFFECT OF PALM OIL CONSUMPTION ON SERUM LIPID PROFILE AND THE HEART

Animal studies

Onyeali *et al*[3] studied the influence of a palm oil-laced diet on the plasma lipid profile of Wister albino rats. The experimental animals were given a diet supplemented with 20% palm oil for 12 wk and compared to controls that were fed standard rat feed. They estimated the serum level of total cholesterol (TC), LDL, TG and high-density lipoprotein (HDL) at intervals of 0, 4, 8, and 12 wk. They demonstrated that although in the short term (4 wk) LDL and TC levels increased, sustained intake of the palm oil diet resulted in a significant reduction of the serum TG, TC and LDL levels compared to the control diet by 12 wk. The palm oil diet had no significant effect on HDL. The authors attributed most of these beneficial effects to the high content of antioxidants and vitamin A and E in the palm oil used. Tocotrienol and tocopherol make up 70% and 30% of the vitamin E present in red palm oil respectively[10]. The tocotrienols have been suggested to inhibit HMG CoA reductase enzyme activity and thus regulate serum cholesterol levels[12]. The findings from their study were in keeping with an earlier experiment in which Sulli *et al*[13] demonstrated that the supplementation of diet with α Tocopherol and β carotene (components of palm oil) reduced plasma cholesterol in hypercholesterolemic rabbits after 8 wk. Oluba *et al*[4] in Benin City Nigeria supplemented the diets of male albino Wister rats with palm oil and studied the effect of this on peroxidation of lipids and

activity of gluthathione peroxidase in their livers[4]. They showed clearly that as compared to the rats that were fed 5% cholesterol-diets without palm oil, those that had palm oil supplementation had a significantly reduced rate of lipid peroxidation in the liver. In addition, the activity of glutathione peroxidase increased significantly in the livers of the rats who fed on the supplemented diets. They extrapolated that in atheromatous plaques, oxidative damage induced by lipids could therefore be prevented by diets containing palm oil.

In the heart, ischemic episodes induces cell damage that can be made worse by sudden reperfusion due to the release of oxygen free radicals. Palm oil has been demonstrated to attenuate this effect in animal experiments. During reperfusion in rats that were fed diets supplemented by palm oil compared to control rats that had no supplementation, Tosaki *et al*[14] demonstrated a reduction in the level of oxidatively-modified proteins as well as an attenuation of the increase in free oxygen radicals in the heart. In a similar more recent study, Narang *et al*[15] used an isolated heart model of rats to demonstrate the effect of palm olein in the diet on ischemia reperfusion injury (IRI). Three groups of Wister rats were used. Two groups received different doses of palm olein (5% and 10% respectively). The third was the control group fed a normal diet. Thirty days later, each group was divided in two and each half was made to undergo global ischaemia for twenty minutes followed by reperfusion for 40 min. Following this, the investigators demonstrated that in the rats that were given the 5% olein-supplemented diet, there was an increase in the level of antioxidants in the myocardium but the levels of thiobabituric acid and reactive substance (TBARS) did not change. This was significant when compared to the rats fed the control diet that had significant oxidative injury with no concurrent increase in anti-oxidant activity. They however failed to observe a dose-dependent effect. Their study provided further evidence of the benefit of a palm oil supplemented diet in protecting the heart from oxidative stress and tissue injury following ischaemia-reperfusion. Furthermore, Kruger *et al*[16] clearly demonstrated a reduction in ischemia reperfusion injury in rats that were fed cholesterol rich diets when supplemented with palm oil. Many other studies have confirmed this[17-19].

Although they provide some evidence for the benefits of palm oil, they do not provide evidence of the effects of using palm oil that has been heated repeatedly on serum lipid profile and oxidant-antioxidant balance. It is well known that in parts of the world where palm oil is utilized for domestic cooking, it is reheated several times especially when used as frying oil. Adam *et al*[20] studied the influence of palm oil that had been heated repeatedly (five times) on serum lipid and homocysteine levels as well as peroxidation of lipids in rats. They found that the rats that were fed the heated palm oil had significantly increased lipid peroxidation, total cholesterol and TBARS compared to controls ($P < 0.05$).

These studies are inherently limited by the fact that they were conducted in rat models, which are not generalisable to humans as rats predominantly carry their cholesterol in HDL form[10]. Moreover the natural rat-diet is not fatty acid based further limiting the extrapolation of these results to humans.

Human studies

Palm oil especially as part of an overall low-fat diet has been shown to effectively maintain total cholesterol and lipoprotein cholesterol values. Kesteloot *et al*[21] measured serum lipids and apoproteins in 542 adults living in Nigeria. The subjects used palm oil exclusively as their source of cooking oil. The researchers reported that the subjects had lower cholesterol levels compared to values obtained from black and white Americans at the time.

Peanut oil and olive oil have 52%-60% and 65%-80% of their fatty acid composition as oleic acid respectively. Oleic acid has been demonstrated in several studies to have beneficial effects on serum lipids and cardiovascular disease[22]. These oils are thus recommended as healthier options. However, palm oil has 40% oleic acid. In addition the palmitic acid it contains, has been shown to have similar effects on the serum lipid profile as oleic acid.

Zhang *et al*[23] assessed the effect of palm oil used in Chinese diets in comparison to soya bean oil, peanut oil and lard. They showed that diets containing palm oil significantly reduced the levels of cholesterol in the serum of subjects who had normal serum cholesterol levels at baseline compared to lard but comparable to the effect of the mostly polyunsaturated soybean oil. Even among those who were hypercholesterolemic, palm oil significantly reduced the TC/HDL ratio more than peanut oil as the latter reduces HDL. It is important to note however that the Chinese diet contains less animal protein and cholesterol compared to typical "western" diets. This may have influenced their results, limiting their generalisability.

Ng *et al*[24] demonstrated that the main saturated fat in palm oil, palmitic acid was comparable to oleic acid in terms of its effect on cholesterol and lipoprotein levels in serum, as well as eicosanoids. Oleic acid is the major component of olive oil that is recognized as "heart-healthy" oil[24]. They achieved this by challenging 33 subjects (whose ages ranged between 22 and 41 years) that had normal serum levels of cholesterol with a diet rich in coconut oil for four weeks. Following this, they were given diets rich in palm olein or olive oil with a subsequent crossover after 6 wk. During this time, the only oil the subjects were allowed to use was the test oil group to which they were assigned. The coconut oil containing lauric and myristic fatty acids elevated all the lipoprotein and lipid parameters in

serum significantly. During the crossover periods, the olive oil and palm olein diets did not differ significantly in their effects on all measured lipid parameters. They concluded that in healthy humans with normal serum cholesterol levels, olive oil could be substituted with palm oil without significant changes in lipid profile. Similarly Sundram conducted a cross over study that was double blinded and demonstrated that palm olein and oleic acid were similar in their ability to lower cholesterol levels in serum[25]. An Indian study by Chafoorunissa *et al*[26] reported that groundnut oil and palm olein also have similar effects on cholesterol levels. They both maintain comparatively normal serum cholesterol levels.

In a systematic review and meta-analysis of 51 human dietary intervention trials, the authors compared trials in which palm oil was substituted for diets rich in polyunsaturated fatty acids (PUFAs), stearic acid and monounsaturated fatty acids (MUFAs)[27]. Although serum lipid profile (TC, HDL and LDL cholesterol, apolipoprotein A-I and apolipoprotein B) was beneficially altered with diets containing palm oil compared to myristic and lauric acid, the same was not the case when compared to PUFAs and MUFAs. In young people and those subjects that had overall lower energy intake from fat, this latter finding was not significant. The diets rich in palm oil did not significantly change the TC/HDL or LDL/HDL cholesterol ratios. On the other hand, the palm oil rich diets significantly increased the levels of apolipoprotein A-I and HDL cholesterol and reduced the levels of TC/HDL, triacylglycerols and apolipoprotein B when compared to trans fatty acid-rich diets. They concluded that with regards to usual dietary sources of fat, palm oil was not much different except when it was substituted for trans fat where it proved beneficial. Considering that majority of global fat consumption is in the form of solid fats and the process of converting liquid oils to solid fats involves hydrogenation, which produces trans fats, palm oil has a distinct advantage; it does not require hydrogenation to turn it to solid fats. In this way solid fats made from palm oil are free from trans fats[28].

Dietary fats influence on coronary heart disease risk has traditionally been estimated from their effects on total and LDL cholesterol. Following large epidemiologic studies in the 50's and 60's saturated fats gained a bad reputation in terms of being significantly associated with cardiovascular disease especially coronary heart disease (CHD) and cardiovascular mortality[8,9,22]. Furthermore several meta-analysis and systematic reviews of randomised controlled trials and cohort studies recommended that polyunsaturated fatty acids should substitute saturated fatty acids. This was based on the supposition that this reduces the risk of CHD events and fatal CHD despite the fact that they demonstrated no direct link between saturated fatty acids and CHD death[29-31]. This informed various guideline recommendations to reduce total dietary energy intake from saturated fats in a bid to decrease the prevalence of coronary heart disease[32-34]. A recent meta-analysis has countered this theory as the authors found that a significant relationship did not exist between saturated fat intake and cardiovascular disease (coronary heart disease and stroke)[35]. In patients with established CHD, secondary prevention by means of a reduced fat or modified fat diet (in which saturated fat is substituted by mono- or poly unsaturated fat) is also recommended[34]. However, another recent meta-analysis by Schwingshackl and Hoffmann has shown that this had no significant effect on all-cause mortality and cardiovascular mortality, combined cardiovascular events and myocardial infarction[36]. Furthermore multivariate meta-regression in their study did not reveal significant relationships between changes in saturated fatty acids, monounsaturated and polyunsaturated fatty acids and risk of all-cause or cardiovascular mortality, myocardial infarction and cardiovascular events. It remains important to note however that this meta-analysis included studies that differed in various ways including the protocols of the studies resulting in some heterogeneity. In addition there was publication bias and the quality of evidence was graded as moderate.

CONCLUSION

Taking all the above into consideration, it is known that saturated fat adversely affects lipid profile and raised serum total and low-density lipoprotein cholesterol is associated with cardiovascular risk. However not all saturated fats have this adverse effect. Palmitic acid the main saturated fat in palm oil has a similar effect on lipid profile as the monounsaturated fat oleic acid that is currently recommended. In addition palm oil also contains oleic and linoleic acids, and vitamin E tocotrienols that are powerful antioxidants and inhibit cholesterol synthesis as well[37].

Therefore, in conclusion it is the opinion of the authors that palm oil consumed as a dietary fat as part of a healthy balanced diet does not have incremental risk for cardiovascular disease. Little or no additional benefit will be obtained by replacing it with other oils rich in mono or polyunsaturated fatty acids. We recognize that more longitudinal population-based studies are needed to fully characterize the impact of the consumption of diets, which utilize palm oil compared to other accepted "heart healthy" oils like olive oil on the future risk of heart disease using lipid parameters as intermediate markers of risk.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous closure of secundum type atrial septal defects: More than 5-year follow-up

Roel JR Snijder, Maarten J Suttorp, Jurriën M Ten Berg, Martijn C Post

Roel JR Snijder, Maarten J Suttorp, Jurriën M Ten Berg, Martijn C Post, Department of Cardiology, St. Antonius Hospital, 3435 CM Nieuwegein, The Netherlands
Author contributions: Snijder RJ, Suttorp MJ, Ten Berg JM and Post MC had substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; Snijder RJ drafted the article; Suttorp MJ, Ten Berg JM and Post MC revised the article critically for important intellectual content; all authors gave final approval for publication.
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Correspondence to: Martijn C Post, MD, PhD, Department of Cardiology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands. m.post@antoniusziekenhuis.nl
Telephone: +31-88-3203000
Fax: +31-30-6034420
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Abstract

AIM: To investigate long-term efficacy of two different devices more than five years after percutaneous atrial septal defect (ASD) closure in adults.

METHODS: All patients who underwent percutaneous closure of an ASD in the St. Antonius Hospital, Nieuwegein, The Netherlands, between February 1998 and December 2006 were included. Percutaneous closure took place under general anaesthesia and transesophageal echocardiographic monitoring. Transthoracic echocardiography (TTE) was performed 24 h post-procedure to visualize the device position and to look for residual shunting using color Doppler. All complications were registered. All patients were invited for an outpatient visit and contrast TTE more than 5-years after closure. Efficacy was based on the presence of a residual right-to-left shunt (RLS), graded as minimal, moderate or severe. The presence of a residual left-to-right shunt (LRS) was diagnosed using color Doppler, and was not graded. Descriptive statistics were used for patients' characteristics. Univariate analysis was used to identify predictors for residual shunting.

RESULTS: In total, 104 patients (mean age 45.5 ± 17.1 years) underwent percutaneous ASD closure using an Amplatzer device (ASO) in 76 patients and a Cardioseal/Starflex device (CS/SF) in 28 patients. The mean follow-up was 6.4 ± 3.4 years. Device migration occurred in 4 patients of whom two cases occurred during the index hospitalization (1 ASO, 1 CS/SF). The other 2 cases of device migration occurred during the first 6 mo of follow-up (2 CS/SF). The recurrent thrombo-embolic event rate was similar in both groups: 0.4% per follow-up year. More than 12 mo post-ASD closure and latest follow-up, new-onset supraventricular tachyarrhythmia's occurred in 3.9% and 0% for the ASO and CS/SF group, respectively. The RLS rate at latest follow-up was 17.4% (minimal 10.9%, moderate 2.2%, severe 4.3%) and 45.5% (minimal 27.3%, moderate 18.2%, severe 0%) for the ASO- and CS/SF groups, respectively. There was no residual LRS in both

groups.

CONCLUSION: Percutaneous ASD closure has good long-term safety and efficacy profiles. The residual RLS rate seems to be high more than 5 years after closure, especially in the CS/SF. Residual LRS was not observed.

Key words: Percutaneous intervention; Atrial septal defect; Closure device; Right-to-left interatrial shunt; Left-to-right interatrial shunt; Echocardiography

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Core tip: Several atrial septal defect (ASD) closing devices have been proven safe and effective for percutaneous ASD closure. We evaluated long-term (*i.e.*, more than 5-year of follow-up) efficacy of two different devices used in adults. Percutaneous ASD closure seems to be relatively safe using the Amplatzer device. Though, the right-to-left shunt (RLS) rate is high, a residual left-to-right shunt was absent at latest follow up. The Cardioseal/Starflex device appears to be associated with a higher complication- and residual RLS rate. The importance of a residual RLS is unclear. Therefore, long-term follow up might be necessary.

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INTRODUCTION

An atrial septal defect (ASD) is a common cardiac defect and accounts for one third of all congenital heart diseases detected in adults[1,2]. The diagnosis in adults is often made when complications of the shunt occur, such as pulmonary hypertension, heart failure, arrhythmias, or paradoxical embolism. Most of these complications might be prevented by closure.

Since the first description of the transcatheter closure device for an ASD in 1976 by King *et al*[3], percutaneous ASD closure has been practiced and described extensively. Other studies evaluated various ASD closure devices and showed good mid-term (up to 2 years) safety and efficacy profiles[4-7]. However, long-term (*i.e.*, more than 5-year after closure) safety and efficacy data on percutaneous closure devices has not been available yet. We report long-term efficacy and safety of two types of ASD closure devices.

MATERIALS AND METHODS

Population

All patients who underwent a percutaneous closure of an ASD in the St. Antonius Hospital, Nieuwegein, The Netherlands, between February 1998 and December 2006 were included in this study. All patients were invited for an outpatient visit and transthoracic echocardiography (TTE).

Closing procedure

As reported earlier, percutaneous closure took place under general anaesthesia and transesophageal echocardiographic (TEE) monitoring according to standard techniques[4]. TTE was performed 24 h post-procedure to visualize the device position and to look for residual shunting using color Doppler.

Follow-up and complications

Follow-up information was obtained at the outpatient clinic or by a telephone interview. All complications were documented, and divided into major and minor as described by Khairy *et al*[8]. Major complications included procedure related events such as haemorrhage requiring blood transfusion, occurrence of cardiac tamponade, need for procedure-related surgical intervention, massive fatal pulmonary emboli, occurrence of new thrombo-embolic events and death[8].

New-onset supraventricular tachycardia's were diagnosed by routine ECG when patients visited the outpatient clinic or when patients visited the emergency department because of symptoms.

Efficacy

The efficacy of the ASD closure was based on the presence of residual shunting using contrast TTE (cTTE) with Valsalva manoeuvre, and color Doppler. A residual right-to-left shunt (RLS) was present if microbubbles appeared in the left atrium. Opacification of the left ventricle and shunt grade were classified as minimal (maximum of 30 micro-bubbles in left ventricle), moderate (between 30 and 100 bubbles in left ventricle), and large (> 100 micro-bubbles in the left ventricle). This division was based on the maximum number of microbubbles counted in one still frame, as previously reported[9]. The presence of a left-to-right shunt (LRS) was based color Doppler imaging at the atrial septum. The LRS was not graded.

Statistical analysis

Descriptive statistics were used for patients' characteristics. Continuous variables with normal distribution are presented as mean ± SD or median with range if normal distribution was absent. Univariate analysis was used to identify predictors for residual shunting. All statistical analyses were performed using SPSS software (version 22.0 for Windows).

RESULTS

Study population

Percutaneous ASD closure was performed in 104

Table 1 Basline characteristics

Number	104
Age (yr)	45.5 ± 17.1
Female, *n* (%)	78 (75.0)
Weight (kg)	73.1 ± 15.1
Risk factors and co-morbidities (%)	
Arterial hypertension	18.4
Hypercholesterolemia	3.9
Diabetes	1.9
Smoking	18.4
CAD	4.9
History of SVT	26.2
Antithrombotic treatment, *n* (%)	
None	59 (56.7)
Aspirin	20 (19.2)
Dipyridamol	1 (1.0)
Oral anticoagulants	21 (20.2)
Unknown	3 (2.9)
Indication for closure, *n* (%)	
RV volume overload	72 (69.2)
Cryptogenic TIA/stroke	21 (20.2)
Asymptomatic	11 (10.6)
RVSP + CVP (mmHg)[1]	34.6 ± 10.5
ASD diameter (mm)[2]	18.3 ± 6.3
Follow up (yr)	6.4 ± 3.4

Data are presented as mean ± SD. [1]On transthoracic echocardiography; [2]On transesophageal echocardiography. CAD: Coronary artery disease; SVT: Supraventricular arrhythmia; TIA: Transient ischemic attack; RVSP: Right ventricular systolic pressure; CVP: Central venous pressure; ASD: Atrial septal defect.

consecutive patients (75% women; mean age, 45.5 ± 17.1 years). Baseline characteristics, risk factors, co-morbidity and indication for closure are summarized in Table 1.

Less than 12-mo follow-up: Safety and efficacy

Device implantation was initially uneventful in 102 patients (98.1%). In 76 patients (73.1%) an Amplatzer (ASO), and in 28 patients (26.9%) a Cardioseal/Starflex (CS/SF) was used for closure. In total, 4 major complications occurred within the first 6 mo. Two patients (1.9%, 1 ASO, 1 CS/SF) suffered from embolization of the device during the index hospitalization and two (1.9%, 2 CS/SF) within the first 6 mo after closure. All underwent surgical device extraction; the ASD was closed using a patch during the same operation. All patients recovered well. Procedural characteristics are shown in Table 2.

Between 6- and 12 mo, another two patients (1.9%, 2 CS/SF) underwent surgical extraction of the device and the ASD was closed with a patch during the same operation. One patient had a large residual shunt, which could not be closed with a second device. The other patient needed rhythm surgery, therefore, device extraction was performed.

Within the first 12-mo, recurrent thrombo-embolic events occurred in 1 patient (0.9%, 1 CS/SF). This 58-year-old patient suffered a transient ischemic attack (TIA). Because of a history of supraventricular tachyarrhythmia's (SVT) the patient was already using oral anticoagulation. cTTE showed no residual RLS.

Table 2 Procedural characteristics *n* (%)

Devices	
Amplatzer	76 (73.1)
Diameter, mm[1]	25 (12-38)
Cardioseal/starflex	28 (26.9)
Diameter, mm[1]	33 (20-40)
General anaesthesia	104 (100)
TEE guiding	104 (100)
In-hospital complications	
Device embolization	2 (1.9)
New-onset SVT	3 (2.9)
Allergic reaction	1 (1.0)
Fever	1 (1.0)
Groin hematoma	1 (1.0)
Tamponade	1 (1.0)
Shunt by TTE[2]	
Color Doppler	9 (11.4)
Hospital stay, d[1]	2 (2-7)

[1]Data presented as median (range); [2]Data available in 79 patients. TEE: Transesophageal echocardiography; SVT: Supraventricular tachycardia; TTE: Transthoracic echocardiography.

New-onset SVT's occurred in 6.6% of the ASO group and in 17.9% of the CS/SF group.

More than 12-mo follow-up: Efficacy and complications

Contrast TTE was performed in 57 patients (54.8%, 46 ASO and 11 CF/SF). Median follow-up time for the ASO group was 6.6 years (5.0-11.1 years) and the CS/SF group 9.9 years (6.3-13.4 years). Though, cTTE could only be performed in 57 patients, follow-up information was available in a total of 81 patients.

Long-term follow-up data could not be retrieved (interview or cTTE) in 23 patients of which 6 were surgically closed, 4 died (no device related cause was suspected) and 13 were lost to follow-up.

Contrast TTE showed a RLS shunt in eight patients (17.4%) who received an ASO. Of these, five patients (10.9%) had a minimal, one patient (2.2%) a moderate and two patients (4.3%) a severe residual shunt. Five patients who received a CS/SF device (45.5%) had a residual RLS of which three patients (27.3%) had a minimal and two patients (18.2%) a moderate residual RLS. When minimal shunts were excluded, the closure rate was 93.5% for ASO and 81.8% for the CS/SF device, respectively. There was no recurrent LRS at latest follow up. Our analyses showed no significant differences in the diameters of the ASD or the device used between the patients with or without a residual shunt. Secondly, no predictors for a right-to-left shunt at long-term follow-up could be found using univariate analysis.

Recurrent thrombo-embolic events after more than 12 mo of follow-up occurred in two patients (1.9%, 2 ASO). One 40-year-old patient suffered a cerebrovascular accident 2.5 years after ASD closure, while on aspirin because of coronary artery disease.

Table 3 Five years follow-up

	Amplatzer	Cardioseal/STARflex
5 yr follow-up available, *n* (%)	58 (76.3)	23 (82.1)
New-onset SVT		
0-1 yr	5 (6.6)	5 (17.9)
> 1 yr	3 (3.9)	0
Reoccurrence TIA/stroke		
0-1 yr	0	1 (3.6)
> 1 yr	2 (2.6)	0
TTE > 5 yr FU available, *n*	46	11
RLS		
No shunt	38 (82.6)	6 (54.5)
Minimal	5 (10.9)	3 (27.3)
Moderate	1 (2.2)	2 (18.2)
Severe	2 (4.3)	0
LRS	0	0
Follow up (yr)	6.6 (5.0-11.1)	9.9 (6.3-13.4)

SVT: Supraventricular arrhythmia; TIA: Transient ischaemic attack; TTE: Transthoracic echocardiography; FU: Follow-up; RLS: Right-to-left shunt; LRS: Left-to-right shunt.

Although there was no history of SVT or device thrombus, oral anticoagulation was initiated after this event. At long-term follow up, a minimal residual RLS was found. The other patient (48-year-old) was known with a history of multiple TIA's prior to closure and was therefore treated with Aspirin. Despite closure of the ASD and optimal medical treatment, the patient suffered from another TIA more than 5 years after ASD closure. At the long-term follow-up visit no residual shunt or thrombus formation on the device was found. This patient had no history of SVT. In total, 3 patients suffered a recurrent neurological event during a mean follow up of 6.4 years (0.5% per year follow up).

During long-term follow-up, new-onset SVT occurred in 3 patients (3.9%) who received an ASO and in none of the patients who received a CS/SF device.

Long-term residual shunt rate, recurrent thrombo-embolic event rate and new-onset SVT rate are presented in Table 3. Figure 1 shows the percentage of patients with residual right-to-left shunt at more than 5-year follow-up after percutaneous ASD closure.

A flow-chart showing the results of this study during follow-up is presented in Figure 2.

DISCUSSION

Percutaneous ASD closure has relatively good long-term safety- and efficacy profiles, especially using the ASO device. A high residual RLS was present in CS/SF. Residual LRS was not observed in either the ASO- or the CS/SF group.

Complications

Device embolization and dislocation is a well-known complication after percutaneous ASD closure[10,11]. The CS/SF is related to a relatively high embolization rate compared to the ASO[12]. In literature, embolization of the CS/SF has been described between 1.4% and 2.5% and for the ASO between 0.1% and 2.4%[7,10,13,14]. In all studies, embolization occurred during the procedure or the index hospitalization. Kefer *et al*[15] and Masura *et al*[16], described 112 and 151 patients with a mean follow-up of 5 and 6.5 years, respectively, and showed no device embolization using the ASO device.

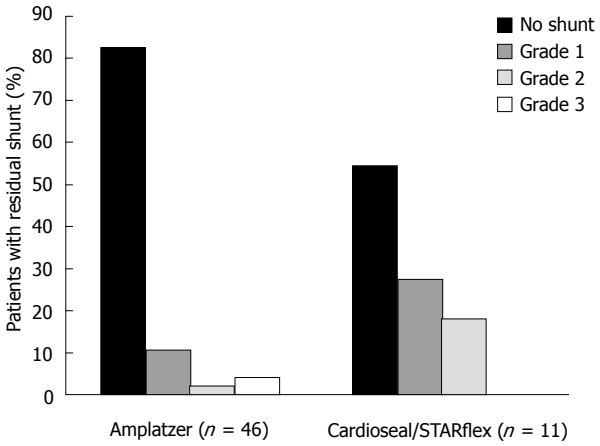

Figure 1 Percentage of patients with residual right-to-left shunt at more than 5-year follow-up after percutaneous atrial septal defect closure.

In our study 4 major complications (3.8%) occurred within the first six months after closure. Device migration occurred in 10.7% of the patients with a CS/SF device and in 1.3% using an ASO device. All devices were surgically extracted and the ASD was closed with a patch. Compared to the literature our CS/SF subgroup had a higher complication rate, while the ASO subgroup was similar. Hence, the CS/SF devices are no longer available for ASD closure. However, long-term follow-up of patients who received a CS/SF device is recommended.

Because device embolization occurred more often in patients with a Cardioseal/Startflex device, we analysed potential reasons/risk factors only for this device. Post *et al*[5] showed that the initial ASD and the device diameter were significantly higher in the patients in whom the device was embolized. However, due to the small sample size of this study it is difficult to make any conclusions.

Recurrent thrombo-embolic events

Kefer *et al*[15] described a recurrent stroke rate of 0% after percutaneous ASD closure with similar devices and follow-up time as in our study. Masura *et al*[16] described no thrombo-embolisms during the entire follow-up period. One patient (0.6% per follow-up year) with an ASO device in the study of Spies *et al*[7] suffered a thrombo-embolic event, which could not be related to a residual shunt or device related thrombus formation.

In our study, the recurrent thrombo-embolic event rate during long-term follow-up was 0.4% per

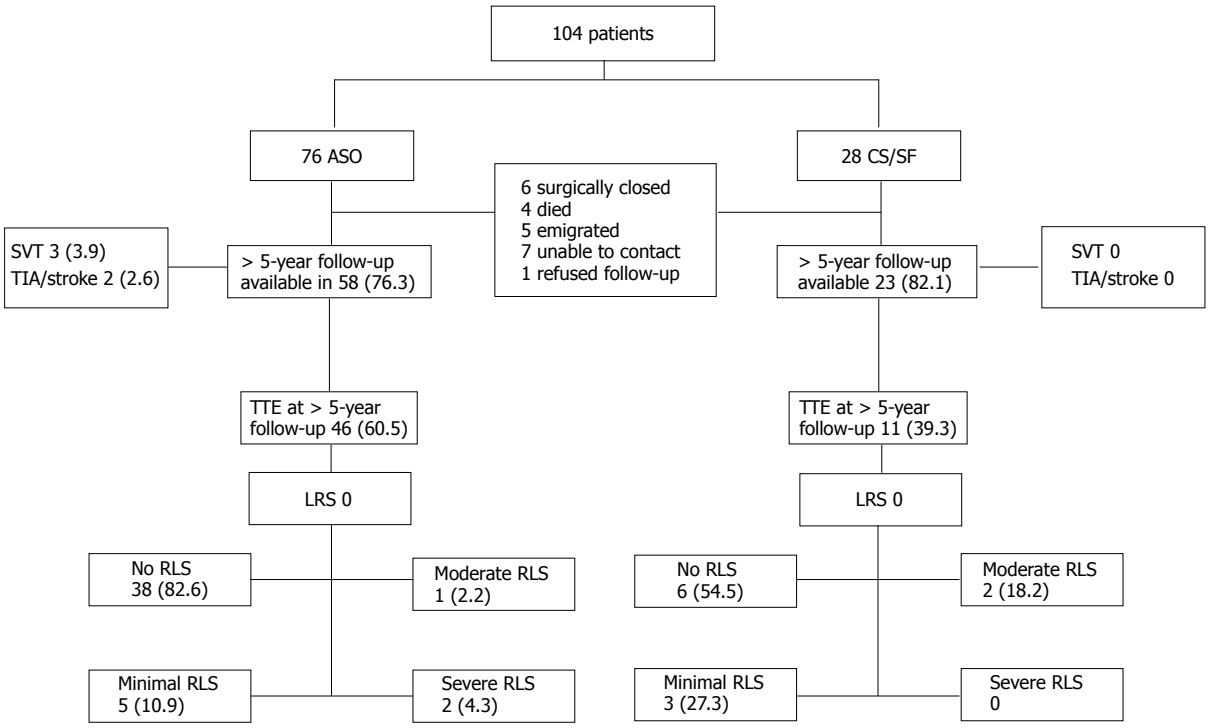

Figure 2 Flow-chart showing the results of this study during follow-up. Data is presented as number of patients (%). ASO: Amplatzer; CS/SF: Cardioseal/Starflex; SVT: Supraventricular arrhythmia; TIA: Transient ischemic attack; TTE: Transthoracic echocardiography; LRS: Left-to-right shunt; RLS: Right-to-left shunt.

follow-up year for both devices, which is similar when compared to the literature. As described above, all patients were treated with anti-platelet therapy or oral anticoagulation and a minimal residual RLS was found in only one patient.

Arrhythmias

arrhythmias early after ASO or other devices implantation are common and extensively described[10,17,18]. Masura *et al*[16] also mentioned SVT's at early follow-up, but none during long-term follow-up. Chessa *et al*[10] noted that arrhythmias are the second most common complication in their study (2.6%) early after the procedure using both the ASO and the CS/SF. Tomar *et al*[19] described peri-procedural arrhythmias but none were seen during long-term follow-up (median 56 mo). At 2-year follow-up, Spies *et al*[18] found an annual incidence of new-onset atrial fibrillation of 4.1%. Butera *et al*[13] described 274 patients (153 ASO, 121 CS/SF) and showed no arrhythmias at follow-up (respectively 16- and 24-mo).

In our study, 3.9% of the patients with an ASO device had new-onset SVT without any abnormalities during cTTE at long-term follow up.

Residual shunting

Residual LRS rates for the ASO has previously been described in several studies and ranged between 0%-12.5% at long-term follow up[13-16,19,20]. Kefer *et al*[15] described a residual LRS rate of 4%. However, only 2 patients (1.8%) with a residual LRS had received an ASO. At 3-year follow-up, Masura *et al*[16] showed no residual shunt using color-Doppler. Butera *et al*[20] described 165 patients with a residual LRS rate of 2% in patients suffering multiple ASD's. At 24-mo follow-up, a non-significant difference between the ASO and CS/SF was found (respectively 0% *vs* 4.4%). In a study by Nugent *et al*[14], 72 patients received a CS/SF device with a total residual LRS of 12.5% between 12- and 24-mo of follow-up.

Our study showed no residual LRS for both devices at more than 5-year of follow-up. However, the prevalence of a RLS is relatively high. Earlier, Luermans *et al*[12] described a residual RLS rate of 14% 3.4 years after closure in 29 patients who received a CS/SF device.

In our study, the RLS rate for the ASO was 17.4% and 45.5% for the CS/SF device more than five years after closure. When excluding the minimal shunts, the ASO had a RLS rate of 6.5% and the CS/SF of 18.2%. The importance of this relatively high rate of RLS is unclear, as the reason for closure was mainly related to the presence of a LRS. Therefore, the fact that we did not notice residual LRS is an important observation. Moreover, to assess the clinical importance of the presence of a RLS, long-term follow-up might be necessary.

The difference in RLS rate after percutaneous ASD closure might be due to the different closing mechanisms; the ASO has a "stent-like" mechanism and consists of Nitinol metal with rounded disks with a polyester fabric sewn inside the meshed disks. The CS/SF device has a "double patch" mechanism and

the fabric is directly exposed to blood[13,21]. The latter might delay the endothelialisation of the devices, which is important for complete closure of the ASD. Why endothelialisation happens in some patients better than others is unclear.

Limitations

Firstly, it is a single-centre design with a small sample-size. Secondly, we used cTTE at follow-up for residual shunt classification while the gold standard is contrast TEE. Though, we did not use contrast TEE, literature describes mostly studies where only color Doppler is used for the assessment of residual shunts. Thirdly, an independent core lab did not review the TTE's. Fourthly, the long-term follow up data was available in about 80% of patients; this might lead to an under- or overestimation.

Percutaneous closure of a secundum-type atrial septal defect seems to be safe using the ASO. Though, the RLS rate is relatively high, a residual LRS is absent more than 5-year after closure. The CS/SF appears to be associated with a relatively high complication- and residual RLS rate. Because of the unclear importance of a RLS after percutaneous ASD closure, long-term follow-up might be necessary.

COMMENTS

Background

An atrial septal defect (ASD) is a common cardiac defect and accounts for one third of all congenital heart diseases detected in adults. The diagnosis in adults is often made when complications of the shunt occur, such as pulmonary hypertension, heart failure, arrhythmias, or paradoxical embolism. Most of these complications might be prevented by closure.

Research frontiers

Since the first description of transcatheter device closure of an ASD in 1976, percutaneous closure of an ASD has been practiced and described extensively. Other studies showed the efficacy and safety of percutaneous closure of ASD's with different devices, mainly during mid-term follow up. Little is known about follow-up more than 5 years after percutaneous ASD closure in adults. We report the efficacy of ASD device closure at more than 5 years follow-up (long-term follow-up).

Innovations and breakthroughs

Previous studies showed that a percutaneous closed ASD using a Cardioseal/Startflex (CS/SF) is associated with a high residual right-to-left shunt (RLS) at mid-term follow-up. This study confirmed that a high residual RLS is still present during long-term follow-up. However, no left-to-right shunt (LRS) was present. Percutaneous closure using a Amplatzer device (ASO) has proven to be efficient at mid-term follow-up. During long-term follow-up no LRS was found. However, a relatively high RLS was present. The importance of RLS at follow-up is unclear. The safety for both devices is similar when compared to literature.

Applications

During long-term follow-up, percutaneous closure of ASD's seems to be safe using different devices, especially using the ASO device. A high residual RLS is present in CS/SF, however there was no residual LRS observed using both the ASO- and the CS/SF device.

Terminology

An ASD is an opening in the septum between the right- and left atrium. It is a congenital heart disease and therefore present at birth. An ASD can cause symptoms due to heart failure, arrhythmia's, paradoxical embolism and pulmonary hypertension. Percutaneous closure of an ASD is a relatively simple procedure where a Nitinol device is placed in the opening between the right- and left atrium. Tansthoracic ultrasound of the heart is used to check whether there is a residual opening in the atrial septum.

Peer-review

The paper by Dr. Snijder *et al* reports the experience in percutaneous closure of atrial septal defects in 104 patients using two devices. Interestingly, in a long-term follow-up a residual left-to-right shunt is absent, although the rate of a residual right-to-left shunt is relatively high.

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CASE REPORT

9.1 cm abdominal aortic aneurysm in a 69-year-old male patient

Celine Saade, Bhavi Pandya, Muhammad Raza, Mustafain Meghani, Deepak Asti, Foad Ghavami

Celine Saade, Bhavi Pandya, Muhammad Raza, Mustafain Meghani, Deepak Asti, Foad Ghavami, Department of Internal Medicine, Staten Island University Hospital, Staten Island, NY 10304, United States

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Correspondence to: Bhavi Pandya, MD, Department of Internal Medicine, Staten Island University Hospital, 475 Seaview Avenue, State Island, NY 10304, United States. dr.bhavipandya@gmail.com
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Abstract

We are presenting a case of one of the largest unruptured abdominal aortic aneurysm ever reported. Presented here is a rare case of a 69-year-old active smoker male with history of hypertension and incidental diagnosis of abdominal aortic aneurysm of 6.2 cm in 2003, who refused surgical intervention at the time of diagnosis with continued smoking habit and was managed medically. Patient was subsequently admitted in 2012 to the hospital due to unresponsiveness secondary to hypoglycemia along with diagnosis of massive symptomatic pulmonary embolism and non-ST elevation myocardial infarction. With the further inpatient workup along with known history of abdominal aortic aneurysm, subsequent computed tomography scan of abdomen pelvis revealed increased in size of infrarenal abdominal aortic aneurysm to 9.1 cm of without any signs of rupture. Patient was unable to undergo any surgical intervention this time because of his medical instability and was eventually passed away under hospice care.

Key words: Abdominal aortic aneurysm; Unruptured; Elderly male; Active smoking

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Core tip: Regular screening of patients with abdominal aortic aneurysm with abdominal ultrasound to prevent catastrophic complication of aortic rupture and early aggressive surgical intervention when indicated.

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INTRODUCTION

Abdominal aortic aneurysm is one of the most common conditions seen in elderly hypertensive male with active smoking. Aortic rupture is seen to be the

commonest catastrophic complication associated with the condition[1-3]. Purpose of our case report is to illustrate importance of regular screening and timely intervention of abdominal aortic aneurysm along with one of the largest reported image of un-ruptured aortic aneurysm.

CASE REPORT

A 69-year-old man was brought to the emergency department by emergency medical services (EMS) after being found unresponsive by his partner's mother. Initially he was detected to be hypoglycemic with blood glucose of less then 30 mg/dL, which was managed by Ⅳ dextrose administered by EMS prior to arriving at the hospital.

The patient was diagnosed 6.2 cm infra renal artery aneurysm in 2003. He also had a 3.4 cm saccular aneurysm of the descending thoracic aorta, an aneurysm of 1.9 cm in the common iliac artery, and an aneurysm of the left renal artery. At that time, he decided to receive medical treatment. His past medical history is also significant for systolic congestive heart failure (CHF) mitral regurgitation, myocardial infarction, hypertension, type 2 diabetes mellitus, peripheral vascular disease, smoking (40 packs per year), lower gastrointestinal bleeding and depression. His medications included Aspirin, Carvedilol, Digoxin, Lasix, spironolactone, Lantus insulin, Dexilant, Lorazepam, Gabapentin, and Percocet. Upon arrival to the emergency room in October 2012, the physical exam was characterized by an altered mental status, and he was barely responsive to painful stimuli. He was tachypneic and tachycardic with bilateral rhonchi and rales in respiratory exam, but had stable blood pressure. The rest of his physical exam was unremarkable.

Electrocardiogram showed sinus rhythm with premature ventricular complexes, right bundle branch block, and ST segment depression in inferior leads. Chest X-Ray revealed cardiomegaly and a right lower lobe infiltrate. Computed tomography (CT) scan of the chest with contrast revealed a segmental pulmonary embolism in the right lower lobe consistent with a small infarction, a new 1.0 cm × 0.8 cm × 1 cm marginated left upper lobe pulmonary nodule suspicious for neoplasm, a moderate centrilobular emphysema, small bilateral pleural effusions and a new filling defect within a dilated left ventricle which is suggestive of left ventricular thrombus. CT scan of the abdomen and pelvis with contrast was significant for an increase in size of the descending thoracic aortic aneurysm to 4.2 cm × 3.6 cm, an infrarenal abdominal aorta measuring 9.1 cm × 8.7 cm and right common iliac artery at about 2.4 cm × 2.6 cm. Left renal artery was stable at 3.1 cm × 2.7 cm. There was no evidence of rupture in the abdominal aortic aneurysm.

The patient had elevated troponins level possibly due to a NSTEMI. He received Ⅳ heparin to manage pulmonary embolism and possible NSTEMI. Considering his extensive medical history, poor medical management outcome and deteriorating mental condition, his family decided to place the patient in hospice care on 10/10/12. The patient died on 10/12/12.

DISCUSSION

Aortic aneurismal disease is defined as a focal dilation of the aorta with a diameter greater than 3.5 cm. Thoracic aneurysms are located above the diaphragm. The abdominal aneurysm is more common and is located below the diaphragm with a prevalence of 1.4% in the United States population age 50 to 84[2]. Aortic rupture is the most common complication of these aneurysms with a mortality rate as high as 75% for the abdominal aneurysm[3]. The profile of a patient that might have an aneurysm and eventually may benefit from a screening test would be a man between 65 and 75 with a history of smoking or a younger patient with a family history of a genetic disease associated with aneurysms[1,4]. The 2005 United States Preventive Services Task Force (USPSTF) report recommended ultrasonography as the screening test for the abdominal aneurysm with a sensitivity rate as high as 100%. Multiple risk predictors for the growth and rupture of an AAA were determined and included: continuous smoking which is the major risk factor, female gender, diastolic hypertension, maximum transverse diameter > 5.5 cm, and dyslipidemia[1,4-9]. On the other hand, other factors were found to decrease the growth rate and subsequently the risk of rupture of abdominal aortic aneurysm (AAA). The use of statins in a recent metanalysis[10] has been shown to reduce by 0.63 mm/year the growth rate of the AAA. Both macrolides and tetracyclines[11-13] were associated with a lower expansion rate of the AAA. However, propanolol use hasn't been beneficial in preventing the growth rate of AAA in a double-blind randomized study[14]. When it comes to surgical management, the threshold recognized currently is 5.5 cm or above. This was demonstrated in two trials conducted in the United Kingdom and United States[6,7]. A CT scan is warranted as part of the preoperative planning because it can help characterizing the AAA for a better surgical approach.

Our patient had both thoracic and abdominal aneurysms with the latter measuring 9.1 cm as a maximum diameter at the time of his death. To our knowledge, this is the largest unruptured AAA to be diagnosed. The patient was incidentally diagnosed to have an AAA of 6.6 cm on CT scan (Figure 1). The incidental finding of an AAA is as high as 0.5% on CT scan as reported in Al-Tahani study[15]. Even though the patient was eligible for surgical reparation of the AAA, he refused the operation knowing the risks of his decision. Between 2003 and 2012, the patient

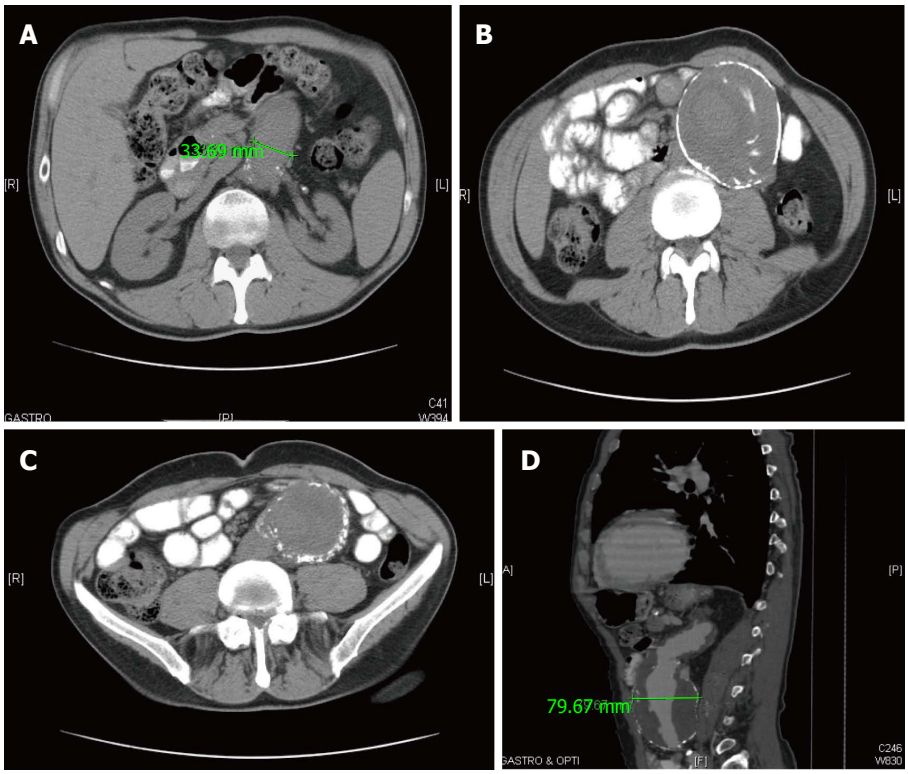

Figure 1 Computed tomography scan. A: Showing aortic abdominal aneurysm at the level of renal arteries; B: Showing massive unruptured abdominal aortic aneurysm along with loops of small intestine; C: Showing continuation of abdominal aortic aneurysm along with plaques of calcification surrounding it; D: Showing longitudinal section of contrast filled abdominal aortic aneurysm with bilateral mural thrombus.

continued to smoke and was taking medications for his hypertension and CHF. He had thus 2 major risk factors for the growth of his AAA considering that his hypertension was medically controlled. In 2012, the size of his AAA increased to 9.1 cm thus at a rate of 0.32 cm/year. At this point, the patient was inoperable because of his worsening CHF and his massive pulmonary embolism. The CT scan also showed the continuous growth of the thoracic aneurysm and the right common iliac artery aneurysm. As per Brown et al study[9], this male patient with an AAA greater than 6 cm had a 14.1% risk per year of having a ruptured AAA. The Helsinki study[16] showed that in 154 cases excluded from the surgical repair of AAA due to severe co morbidities in the patients, 43% eventually died because of a ruptured AAA. Therefore, it can be postulated that the patient had an imminent risk for AAA rupture. No autopsy was done as per the request of the family but it might be speculated that the patient's death was due to ruptured AAA especially that he had to be started on therapeutic heparin for his massive symptomatic PE.

COMMENTS

Case characteristics

A 69-year-old male presented with hypoglycemia found to have 9.1 cm × 8.7 cm unruptured AAA.

Clinical diagnosis

Patient was found to have subsequent pulmonary embolism and Non ST elevation Myocardial infarction.

Imaging diagnosis

CT scan of the abdomen and pelvis with contrast was significant for an increase in size of the descending thoracic aortic aneurysm to 4.2 cm × 3.6 cm, an infrarenal abdominal aorta measuring 9.1 cm × 8.7 cm and right common iliac artery at about 2.4 cm × 2.6 cm.

Treatment

Due to patient's medical instability, he was not a surgical candidate.

Related reports

So far reported cases in literatures are either ruptured abdominal aortic aneurysm or not significantly enlarged. Reported here is case of unruptured largest abdominal aortic aneurysm, which can be managed successfully with timely intervention.

Experiences and lessons

Regular screening of patients with abdominal aortic aneurysm with abdominal ultrasound helps prevent catastrophic complication of aortic rupture and early aggressive surgical intervention when indicated.

Peer-review

This is a well-written clinical case report regarding to the large un-ruptured abdominal aortic aneurysm. The case is interesting and illustrates importance of regular screening and timely intervention of abdominal aortic aneurysm, which will gather the great interests from the readers.

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CASE REPORT

Trauma and syncope-evidence for further sleep study? A case report

Erik Skobel, Andreas Bell, Dang Quan Nguyen, Holger Woehrle, Michael Dreher

Erik Skobel, Clinic for Cardiac and Pulmonary Rehabilitation, "An der Rosenquelle", 52077 Aachen, Germany
Andreas Bell, Department of Surgery, Marienhospital, 52077 Aachen, Germany
Dang Quan Nguyen, Department of Internal Medicine, Marienhospital, 52077 Aachen, Germany
Holger Woehrle, Sleep and Ventilation Center Blaubeuren, Respiratory Center Ulm, 89073 Ulm, Germany
Michael Dreher, Department of Cardiology, Pneumology, Angiology and Intensive Care Medicine, University Hospital, 52077 Aachen, Germany
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Correspondence to: Erik Skobel, MD, Head of Department, Clinic for Cardiac and Pulmonary Rehabilitation, "An der Rosenquelle", Kurbrunnenstraße 5, 52077 Aachen, Germany. erik.skobel@rosenquelle.de
Telephone: +49-241-6007501
Fax: +49-241-6007502
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Abstract

We report on an 83-year-old male with traumatic brain injury after syncope with a fall in the morning. He had a history of seizures, coronary artery disease and paroxysmal atrial fibrillation (AF). No medical cause for seizures and syncope was determined. During rehabilitation, the patient still complained of seizures, and also reported sleepiness and snoring. Sleep apnea diagnostics revealed obstructive sleep apnea (SA) with an apnea-hypopnoea index of 35/h, and sudden onset of tachycardia with variations of heart rate based on paroxysmal atrial fibrillation. Additional tests showed nocturnal AF which spontaneously converted to sinus rhythm mid-morning with an arrest of 5 s (sick sinus syndrome) and seizures. A DDD-pacer was implanted and no further seizures occurred. SA therapy with nasal continuous positive airway pressure was refused by the patient. Our findings suggests that screening for SA may offer the possibility to reveal causes of syncope and may introduce additional therapeutic options as arrhythmia and SA often occur together which in turn might be responsible for trauma due to syncope episodes.

Key words: Sleep apnea; Syncope; Atrial fibrillation; Trauma

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Core tip: Arrhythmias and sleep apnea should be considered as relevant factors resulting in syncope and trauma in the elderly. This case report applies screening for sleep apnea to detect arrhythmia as a common cause of syncope. Screening for sleep apnea may offer the possibility of additional therapeutic options and diagnostic in trauma and syncope after performing standard diagnostics.

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INTRODUCTION

Sleep apnea (SA) has been shown to be an independent risk factor for cardiovascular diseases[1-4]. Obstructive sleep apnea (OSA) is the most prevalent type of SA. It is defined as repetitive episodes of partial or complete cessation of airflow in the upper airways during sleep. The number of people in the United States estimated to be affected by OSA is 3%-7%[5,6] and, according to US National Commission of Sleep Disorders Research, OSA contributes to 38000 cardiovascular deaths annually[7]. In Europe, a Spanish study reported that 7% of women and 15% of men aged 30-70 years had OSA, defined as an apnea-hypopnoea index (AHI) of $\geqslant$ 15/h[8].

Patients with OSA typically present with symptoms such as disruptive snoring, witnessed apneas or gasping, excessive daytime sleepiness, morning headache, sleep disturbance and cognitive dysfunction[9,10]. OSA is associated with higher prevalence of diabetes and hypertension[11,12], coronary artery disease and myocardial infarction[13], heart failure[14] and arrhythmias such as bradycardia or atrial fibrillation or flutter (AF)[15]. Traumatic brain injury (TBI) is often associated with SA and sleep disturbances[16,17]. Although the incidence of arrhythmia in the presence of SA is high[15,18,19], the influence of SA on traumatic loss of consciousness (syncope) and TBI have rarely been evaluated[20-22].

Syncope is the most common cause of TBI in the elderly and it often has an underlying cardiovascular aetiology (*e.g.*, bradycardia, tachycardia, myocardial infarction or valvular disease)[23]. The incidence of syncope is 5-11 events per 1000 person years[23]. Different forms of disease sometimes make the diagnosis difficult and different approaches may be needed. Screening for sleep apnea is not standard practice in the evaluation of syncope[20].

This case report describes a male patient with frequent syncope and seizures with SA related arrhythmia.

CASE REPORT

An 82-year-old male (BMI: 26 kg/m^2) was transferred to our rehabilitation facility after experiencing syncope 3 wk previously. He reported a history of seizures mostly in the morning hours at rest and on the day of the most recent syncope episode he fell down without warning soon after breakfast and was transferred to an emergency unit with a frontal head laceration. The patient also had a history of hypertension, dyslipidaemia, coronary artery disease (CAD) without infarction, bypass surgery (14 years ago) and paroxysmal AF. The patient was taking warfarin, ACE inhibitors, β-blockers, statins and diuretics. In the emergency department, the patient was awake without neurologic impairment. Paroxysmal AF was documented on ECG, without evidence of ischemia or myocardial infarction, and troponin testing was negative. Pulmonary embolism was ruled out. A computed tomographic (CT) scan revealed frontal cerebral haemorrhage, which was treated conservatively and warfarin therapy was stopped. Magnetic resonance (MR) imaging one week later showed that the haemorrhage was resolving.

Some further cardiac evaluation of syncope showed no abnormalities. Twenty four hours blood pressure monitoring was normal. Holter 24-h monitoring revealed sinus rhythm without bradycardia, or tachycardia, or paroxysmal AF. Two-dimensional echocardiography showed normal left ventricular function without valve disease, but no carotid sinus massage, tilting test or electrophysiological studies were performed.

At the rehabilitation facility, the patient was assessed as being well without neurologic disorders. The patient reported snoring and hypersomnia (Epworth Sleepiness Scale score of 9 points, with normal being < 5) and complained of intermediate seizures without falling. Sinus rhythm was present on 12-lead ECG.

The patient was screened for SA using 2-channel polygraphy (Figure 1), which showed intermittent nocturnal oxygen desaturations and recurrent apneas with an AHI of 35/h. Heart rate data from polygraphy revealed an increase in the morning hours (Figure 1) with arrhythmic pulse curve based on onset of paroxysmal AF during sleep apnea. A second period of 24-h Holter monitoring was performed the following day to evaluate the incidence of paroxysmal AF. Nocturnal paroxysmal AF was seen with onset in the early morning hours, which spontaneously converted to sinus rhythm mid-morning with an arrest of 5 s (sick sinus syndrome) and the patient reported a seizure at the time of the arrest (Figures 2 and 3). The patient was transferred to the cardiac department for pacer implantation (DDD) and then transferred back to the rehabilitation facility for further rehabilitation. Seizures fully resolved after pacemaker implantation and an increase in β-blocker therapy eliminated paroxysmal AF. A further performed polysomnography for SA diagnostics conformed severe OSA (Table 1).

Treatment of sleep with nasal continuous positive airway pressure (nCPAP) therapy was discussed with the patient but he refused this treatment.

DISCUSSION

In this case report, sleep apnea screening revealed the nocturnal onset of arrhythmia and facilitated further evaluation of syncope. The temporal relationship between the documented pause in the ECG and seizures in our patient means that this was highly likely to be the underlying cause of the repeated

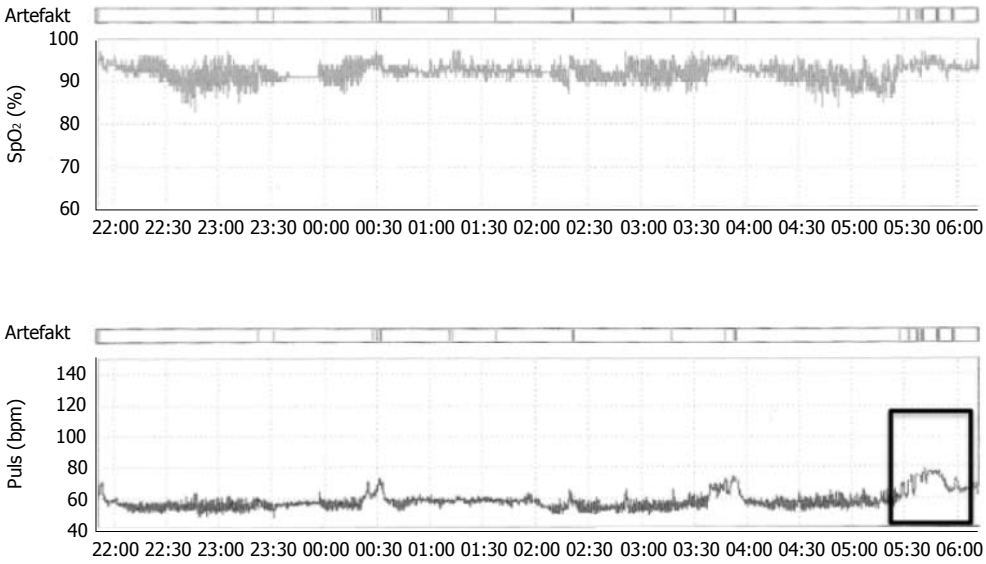

Figure 1 Overnight polygraph recording showing recurrent desaturations at night (above), increased heart rate in the morning hours (down) and arrhythmia onset due to changes in heart rate (see marker box).

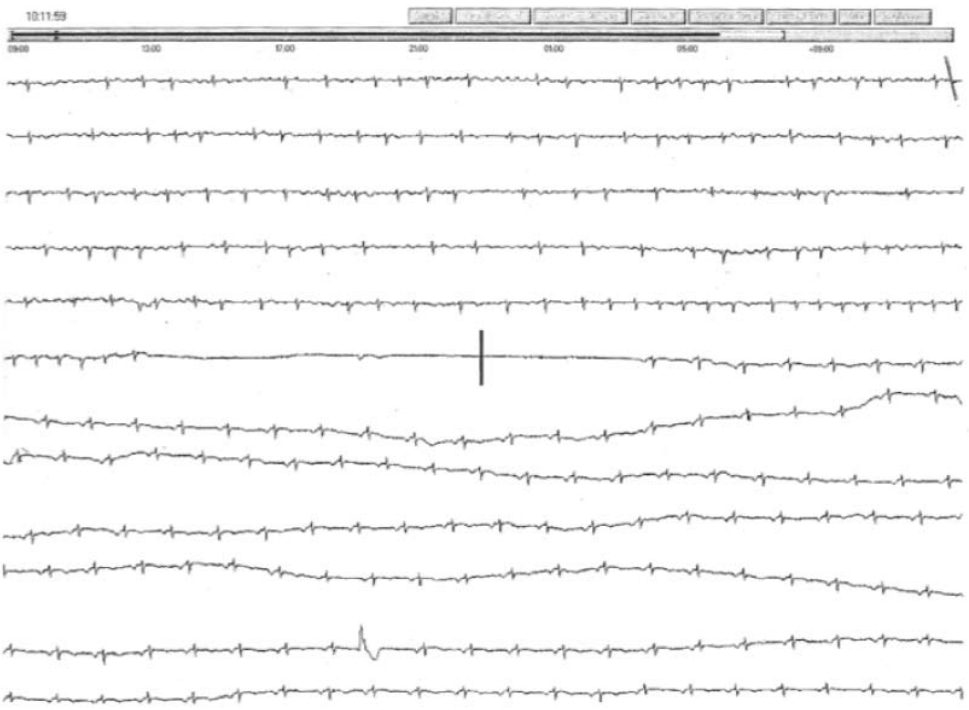

Figure 2 Twenty-hour Holter monitor recording showing atrial fibrillation in the morning with arrest of 5 s (marker) followed by sinus rhythm.

seizures and falls, and ultimately the traumatic injury he sustained. A limitation in this case report is the lack of standard diagnostic for syncope, *e.g*., carotid sinus massage, tilting test or electrophysiological studies before the rehabilitation setting.

The indication for pacing in our patient was based on syncope with trauma and documentation of sick sinus syndrome in the morning hours after onset of paroxysmal AF. After pacemaker implantation the patient had no further seizures, providing further evidence that sick sinus syndrome was the cause of syncope.

AF and nocturnal bradycardia are often triggered by sleep apnea[24]. This is based on nocturnal hypoxemia and its effects on the cardiac autonomic nerve system[25,26]. Accordingly, our patient was offered, but refused, nCPAP therapy. However, there is evidence to show that CPAP not only effectively treats SA but also reduces nocturnal arrhythmias[27,28]. Although nCPAP therapy can reduce arrhythmia burden and possibly reduce the incidence of paroxysmal AF[24], it is not clear whether nCPAP therapy can prevent

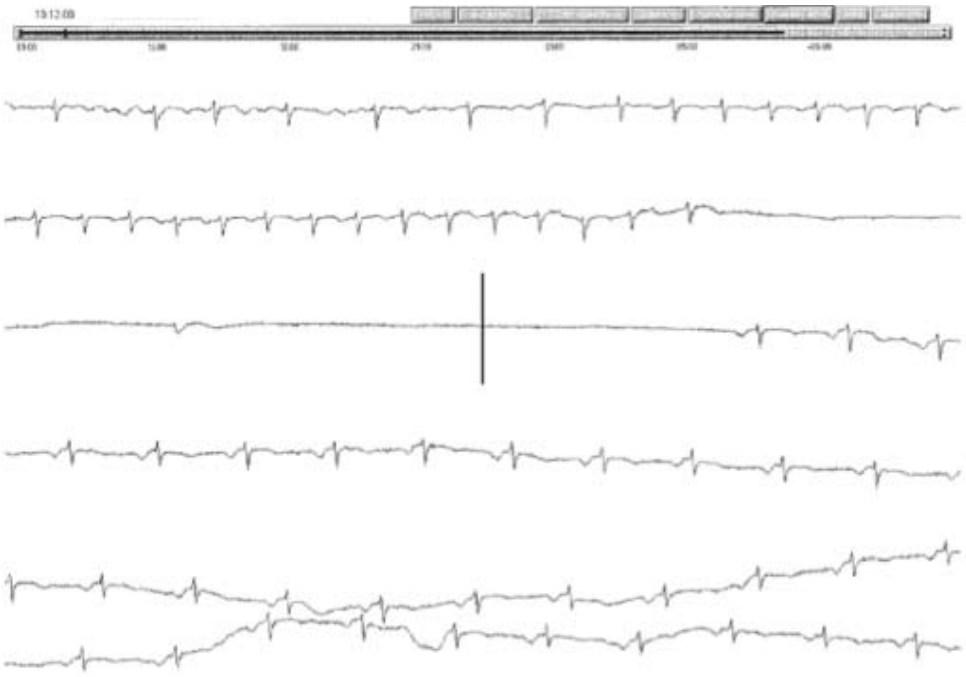

Figure 3 Twenty-hour Holter monitor recording showing atrial fibrillation in the morning with arrest of 5 s (marker) followed by sinus rhythm (enlargement of Figure 2).

Table 1 Polysomnographic data revealing obstructive sleep apnea

Polysomnographic parameter	Value
AHI (h)	33
Obstructive apnoea index (h)	31.4
Central apnoea index (h)	0
Mixed apnoea index (h)	0
Hypopnoea index (h)	1.6
Snoring, min	9
Mean oxygen saturation (%)	91
Minimum oxygen saturation (%)	85
Oxygen desaturation index (h)	18

all arrhythmias and arrests, justifying the use of a pacemaker in this case. In addition, compliance with nCPAP is necessary for the benefits of therapy to be realised, which is another justification for pacemaker implantation. However, it has been shown that patients with a pacemaker and ongoing syncope have a high incidence of SA[19], indicating that screening for SA in patients with pacemaker implement and syncope would be appropriate.

Sleep disorders are common in TBI and develop in 12%-36 % of patients[16,17,29]. For example, Verma *et al*[29] found that 50% of patients with TBI reported daytime hypersomnia and 30% were diagnosed with OSA. TBI can result in sleep/wake disturbances, sleep fragmentation, and insomnia or hypersomnia. However, the mechanism of sleep disorders in the setting of TBI is not clear. On one hand the mechanism of injury could trigger sleep disorders such as posttraumatic insomnia or hypersomnia with sleep fragmentation[30,31]. On the other hand, the underlying cause of the accident resulting in TBI may be hypersomnia as a result of nocturnal OSA or, as in this case, nocturnal arrhythmia with syncope and following TBI. Further studies are needed to evaluate the incidence of sleep-related arrhythmias and traumatic injury with the goal of determining whether screening for SA is appropriate in this setting.

Arrhythmias and SA should be considered relevant factors resulting in syncope and trauma. Screening for SA may offer the possibility of additional therapeutic options and diagnostic in trauma and syncope.

COMMENTS

Case characteristics

An 83-year-old male with traumatic brain injury after syncope of unknown origin in the morning and seizures.

Clinical diagnosis

2-channel polygraphy showed intermittent nocturnal oxygen desaturations and recurrent apneas with an apnoea-hypopnoea index (AHI) of 35/h. Heart rate data from polygraphy revealed an increase in the morning hours with arrhythmic pulse curve based on onset of atrial fibrillation (AF) during sleep apnea.

Imaging diagnosis

Nocturnal paroxysmal AF was seen with onset in the early morning hours, which spontaneously converted to sinus rhythm mid-morning with an arrest of 5 s (sick sinus syndrome) and the patient reported a seizure at the time of the arrest.

Pathological diagnosis

Diagnostic of severe obstructive sleep apnea, AHI 33/h.

Treatment

Pacer implantation (DDD). Treatment of sleep with nasal continuous positive airway pressure therapy was discussed but refused.

Related reports

Syncope is the most common cause of traumatic brain injury in the elderly and it often has an underlying cardiovascular aetiology. Arrhythmias and sleep apnea (SA) should be considered relevant factors resulting in syncope and

trauma as SA is one trigger of sudden onset of arrhythmia.

Experience and lessons

Further studies are needed to evaluate the incidence of sleep-related arrhythmias and traumatic injury with the goal of determining whether screening for SA is appropriate in this setting.

Peer-review

This manuscript reports a typical case of sick sinus syndrome in an 83-year-old male, with paroxysmal atrial fibrillation and sinus arrest, presenting clinically with syncope.

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