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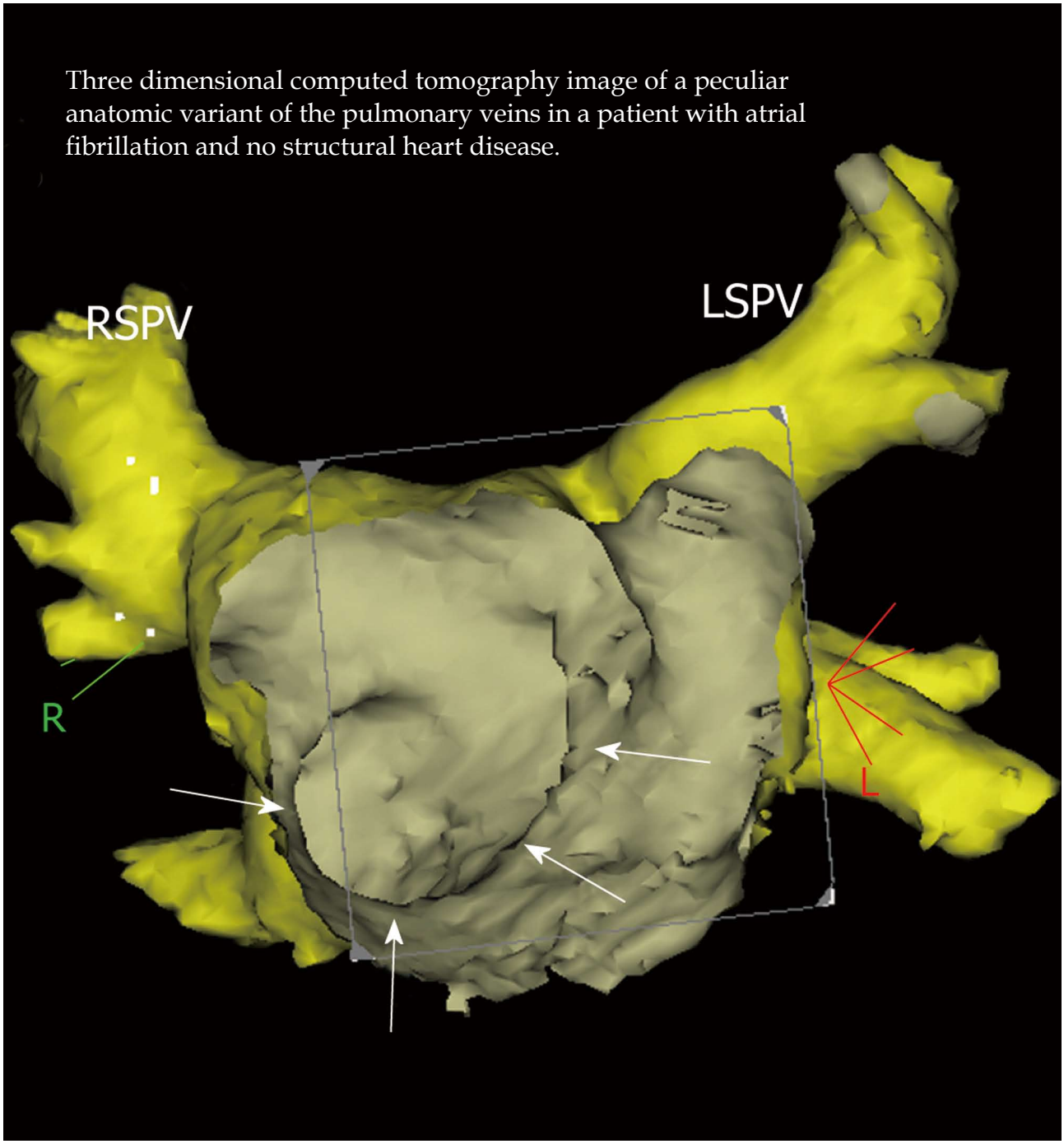

Three dimensional computed tomography image of a peculiar anatomic variant of the pulmonary veins in a patient with atrial fibrillation and no structural heart disease.

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Contents

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EDITORIAL

Role of three-dimensional imaging integration in atrial fibrillation ablation

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Abstract

Atrial fibrillation is the most common arrhythmia and in symptomatic patients with a drug-refractory form, catheter ablation aimed at electrically disconnecting the pulmonary veins (PVs) has proved more effective than use of antiarrhythmic drugs in maintaining sinus rhythm during follow-up. On the other hand, this ablation procedure is complex, requires specific training and adequate clinical experience. A main challenge is represented by the need for accurate sequential positioning of the ablation catheter around each veno-atrial junction to deliver point-by-point radiofrequency energy applications in order to achieve complete and persistent electrical disconnection of the PVs. Imaging integration is a new technology that enables guidance during this procedure by showing a three-dimensional, pre-acquired computed tomography or magnetic resonance image and the relative real-time position of the ablation catheter on the screen of the electroanatomic system. Reports in the literature suggest that imaging integration provides accurate visual information with improvement in the procedure parameters and/or clinical outcomes of the procedure.

Key words: Catheter ablation; Atrial fibrillation; Electroanatomic mapping; Multislice computed tomography; Magnetic resonance imaging

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INTRODUCTION

Over the last decade, catheter ablation has been a treatment option increasingly offered to patients with symptomatic atrial fibrillation (AF) refractory to antiarrhythmic drug therapy. In the updated survey on catheter ablation for AF[1], an almost 2-fold increase in the number of patients treated between 2003 and 2006 was observed as compared with the number between 1995 and 2002. In this survey, this treatment option shows to be effective in roughly 80% of patients after 1.3 procedures per patient, on average, with about 70% of the patients not requiring further antiarrhythmic drugs during a 10 ± 8 mo follow-up. These data are corroborated by the results of several, recently published meta-analyses on the efficacy of catheter ablation and of antiarrhythmic drug therapy for the prevention of AF[2-5]. Particularly, the most updated

meta-analysis of randomized, controlled trials comparing antiarrhythmic drug therapy *vs* catheter ablation of AF[5] showed that catheter ablation with isolation of the pulmonary veins (PVs) was associated with markedly increased odds of maintaining sinus rhythm as compared to antiarrhythmic drug therapy (77% *vs* 29%) in a patient population with predominantly paroxysmal AF (70%), refractory to 2 antiarrhythmic drugs with a mean left atrial diameter of 42 ± 3 mm. Moreover, a study performed in the United States[6] using a simulation mode showed that catheter ablation of symptomatic, drug-refractory AF with or without continuation of antiarrhythmic drug therapy during follow up appeared reasonably cost-effective compared to antiarrhythmic drug therapy alone, based on improved quality of life and avoidance of future health care costs.

In the past, different techniques and tools for catheter ablation of the PVs in patients with AF have been proposed and used. More recently, the HRS/EHRA/ECAS expert consensus statement[7] underlined that ablation of PVs with demonstration of complete electrical isolation is the cornerstone for most AF ablation procedures. Furthermore, this document stated that careful identification of the PV ostia is mandatory to avoid ablation within the PVs, which carries a significant risk of PV stenosis, which is a severe complication. Therefore, it appears mandatory that the operator should use an appropriate technology to identify the PV ostia and, more importantly, the real-time relative position of the ablation catheter.

In this review, the rationale, methods, and results of using electroanatomic mapping with imaging integration to orient catheter ablation of AF aimed at electrical disconnection of the PVs will be described in detail.

RATIONAL FOR USING ELECTROANATOMIC MAPPING WITH IMAGING INTEGRATION

Initially, to visualize the PVs during the AF ablation procedure, two methods have been reported: PV angiography and intracardiac echography. When these methods are used, different techniques and tools can be utilized to improve the quality of visualization of PV anatomy during the AF ablation procedure[7]. However, these techniques provide two-dimensional images, sometimes with suboptimal resolution and, in the case of intracardiac echography, it requires extra costs, dedicated access and personnel. Moreover, the PVs anatomy in terms of number and morphology of oses, branching and supernumerary PVs is very individual, as already reported[8-11]. This anatomic variability may influence both success and safety of the procedure, if the PV os/antrum is not adequately visualized during the procedure. In fact, if the presence of supernumerary veins is not recognized and their os not treated, the success rate can be suboptimal[7,12]. On the other hand, the ablation performed inside the PV due to mislocalization of the true ostium may affect both the complication rate, since the risk of PV stenosis may increase significantly, and the success rate, since proximal PV foci can be left untreated.

Table 1 Anatomic variants of the pulmonary veins in 147 consecutive patients with atrial fibrillation undergoing a 64-slice computed tomography scan the day before the ablation procedure

Anatomy	*n* (%)
Four distinct PV oses	81 (55)
Common os	66 (45)
Left PVs	55
Right PVs	7
Left and right PVs	1
Inferior PVs	3
Adjunctive PVs	21 (14)
Right	16
Left	2[1]
Roof	4

[1]1 patient showed an adjunctive pulmonary vein both right and left. PV: Pulmonary vein.

Based on these considerations and the experience accumulated in several centers over recent years, the best way to visualize the individual variants of PVs is three-dimensional imaging, which can be obtained before the procedure, by computed tomography (CT) scanning or magnetic resonance imaging (MRI), or during the procedure, by three-dimensional rotational angiography[13]. The latter technology provides on-line intraprocedure angiographic data of the left atrium (LA) and PVs but, so far, its availability is limited. Therefore, the most frequently used technique is CT or MRI scan of the LA and PVs, which is acquired off-line, usually the day before the procedure. MRI avoids radiation exposure, but it might be tolerated less well, especially by claustrophobic patients, and the three-dimensional rendering might be operator-dependent. On the other hand, CT obviously implies radiation exposure, which depends on the method used for imaging acquisition.

Our personal experience in 147 consecutive patients with AF undergoing a 64-slice CT scan for imaging of the LA and the PVs the day before the ablation procedure shows high individual variability, including rare forms of anatomic variants (Table 1). As shown, the most expected anatomy with four separated PV oses is observed in only 55% of the patients and in 14% of cases adjunctive PVs are present, with an os close to the right or left PVs, but independently draining or, more peculiarly, located in the medial roof of the LA. The finding of a common trunk is by far more frequently observed in the left PVs. Interestingly, the already described[14-17] presence of a common os of the left and right inferior PVs, although rare (2%), significantly distorts the LA anatomy (Figure 1). In this patient population, the radiation exposure was very much dependent on the acquisition technique. In fact, the radiation

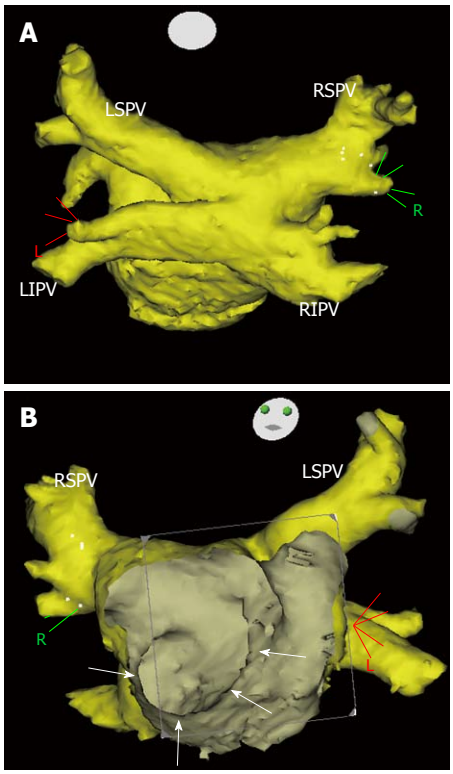

Figure 1 Three dimensional computed tomography image of a peculiar anatomic variant of the pulmonary veins in a patient with atrial fibrillation and no structural heart disease. A: The postero-anterior view of the left atrium and pulmonary veins; B: The endocardial aspect of the pulmonary vein oses after removal of the anterior wall of the left atrium. The common os of the left and right inferior pulmonary veins is evident both on the epicardial and endocardial (arrows) aspects. The oses of the right and left superior pulmonary veins are adjacent and more anterior, to the common os. LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein.

exposure was 7.6-fold higher in the first 30 patients, in whom the CT scan was performed in ECG-gated mode, as compared to the following patients, scanned in a non ECG-gated mode [23 ± 8 mSv (range 9.7-44 mSv) *vs* 3 ± 1 mSv (range 0.9-5.7 mSv), respectively, $P < 0.0001$].

The high resolution anatomical information provided by three-dimensional preprocedure imaging can be useful to the operator before the procedure. However, the best use of this imaging is obtained when, during the procedure, they are imported and integrated in the electroanatomic mapping, so that on the system screen the icon of the ablation catheter is visualized in real-time, with due accuracy, on the high resolution image of the PV os/antrum. In this way, it is possible to both accurately establish were the ablation lesion is performed and to manipulate the ablation catheter around the PV os with minimal or no use of fluoroscopy.

METHODS FOR ACCURATE IMAGING INTEGRATION OF THE LA AND PVS

For the purpose of better understanding the integration process, it can be subdivided in four different steps. First, the CT or MRI pre-acquired data set is imported in the electroanatomic system and it is "segmented" using dedicated software, so that the three-dimensional rendering of the LA and PVs is extracted. This image can be evaluated both from the epicardial and endocardial aspect, as shown in Figure 1. Second, at the beginning of the procedure, after transseptal catheterization has been accomplished, the LA is electroanatomically reconstructed by acquiring a variable number of points in this heart chamber. The third step is represented by the "registration" phase. One or more pairs of landmarks, each one positioned on the electroanatomic map and on the assumed corresponding site of the CT/MRI surface, are identified. Usually, sites easy to identify are used for this purpose (e.g. left atrial roof and os of the PVs). Then using the "landmark registration" and the "surface registration" options, each landmark on the two surfaces is superimposed and the two surfaces are superimposed as well, in such a way that the best match between the two images is obtained. In the fourth and last step, the accuracy of the superimposition of the two surfaces is checked. If imaging integration was performed accurately, the icon of the mapping/ablation catheter, visualized in real-time on the screen of the electroanatomic system, can be navigated in the high resolution anatomy image provided by the CT/MRI with optimal accuracy of localization.

As reported in Table 2, several published studies have mainly focused on the methods to integrate the CT or MRI images of the LA/PVs into an electroanatomic system and to evaluate the accuracy of this process. Overall, these studies have included more than 500 patients with a variable proportion of patients with paroxysmal AF, ranging from 31% to 83%. The CartoMerge technology and 64-slice CT have been used in the vast majority of the studies as an electroanatomic system and preprocedure three-dimensional imaging modality, respectively. Intracardiac echocardiography has been also sparingly used. In almost all cases, using the electroanatomic system, the LA and the oses of the PVs have been reconstructed as a single chamber and the number of acquired sites to reconstruct these anatomical structures varied in different studies, from 224 ± 59 to 24 ± 7 sites. Generally, all the studies reported that the integration process was successful in the majority of patients, so that the mapping/ablation catheter could be reliably navigated in the imported three-dimensional rendering of CT or MRI. The accuracy of the integration process has been evaluated by the distance between an electroanatomic point and the correspondent point on the CT/MRI, which is automatically given by the system. This value represents the average error, being the distance between the site where the catheter is shown to be on the CT/MRI image and the site where it actually is. In these reports, this value varied from 2.9 ± 0.7 mm to 1.4 ± 0.3 mm, on average, which confirms an accurate and clinically useful integration process since the catheter tip is 3.5 mm in length and every distance below

Table 2 Overview of the studies designed to evaluate the methods and accuracy of imaging integration of the left atrium/pulmonary veins in an electroanatomic mapping system during the atrial fibrillation ablation procedure

Author	No. of pts	Percentage of pts with parox. AF	System	3D-imaging (No. of pts)	ICE	Type of EA reconstruction: single/multi chamber	No. of EA points	Distance between EA and CT/MRI points (mm)		
								Mean	Maximum	Minimum
Tops *et al*[18]	16	31	CartoMerge	64-slice CT	N	Single	224 ± 59	2.1 ± 0.2	2.8 ± 1.8	1.7 ± 1.2
Dong *et al*[19]	16	62	CartoMerge	MRI (8)/ 64-slice CT (8)	N	Single	24 ± 7	2.1 ± 0.5	2.7 ± 1.8	0.9 ± 0.8
Kistler *et al*[20]	30	40	CartoMerge	8-slice CT	N	Single	39 ± 8	2.3 ± 0.4	9.3 ± 2.4	0 ± 0
Martinek *et al*[21]	40	65	CartoMerge	16-slice CT	N	Single	63 ± 14	1.6 ± 1.2	N/A	N/A
Heist *et al*[22]	61	57	CartoMerge	MRI (50)/ 64-slice CT (11)	N	Multi (LA + Ao)	LA (49 ± 25) Ao (148 ± 41)	1.9 ± 0.6	4.3 ± 3.4	1.2 ± 1.0
Fahmy *et al*[23]	124	55	CartoMerge	64-slice CT	N	N/A	59 ± 22	2.2 ± 1.7	N/A	N/A
Daccarett *et al*[24]	18	58	CartoMerge	64-slice CT	Y	Single	41 ± 8	5-10[1]	N/A	N/A
Bertaglia *et al*[25]	40	55	CartoMerge	MRI	N	Single	37 ± 10	1.3 ± 1.0	N/A	N/A
Richmond *et al*[26]	23	61	NAVx Fusion	8-slice CT	N	Single	N/A	3.2 ± 0.9	6.1 ± 1.0	2.9 ± 0.7
Brooks *et al*[27]	55	53	NAVx Fusion	64-slice CT	N	Single	N/A	2.6 ± 2.2	6.6 ± 2.8	1.9 ± 0.4
Rossillo *et al*[28]	40	45	CartoMerge	Multislice CT	Y	Single	47 ± 9	1.4 ± 0.3	N/A	N/A
Nölker *et al*[29]	38	50	CartoMerge	Rotational angiography	N	Single	104 ± 59	2.2 ± 0.4	N/A	N/A
Ejima *et al*[30]	24	83	CartoMerge	64-slice CT	N	Single	88 ± 34	1.7 ± 0.5	6.1 ± 2.7	0.04 ± 0.03

[1]Distance between an electroanatomic (EA) point and the same point localized by ICE. 3D: Three dimensional; AF: Atrial fibrillation; Ao: Aorta; CT: Computed tomography; ICE: Intra-cardiac echocardiography; LA: Left atrium; MRI: Magnetic resonance imaging; N: No; Y: Yes; N/A: Not available; Parox.: Paroxysmal; pts: Patients.

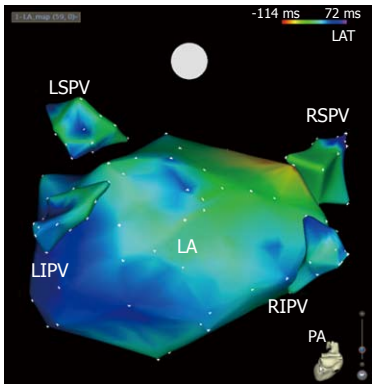

Figure 2 Postero-anterior view of the electroanatomic activation mapping of the left atrium and pulmonary veins. These have been reconstructed as five separate chambers using the Carto system and acquiring a few sites while the mapping catheter is manipulated in these anatomic structures. Colors indicate the activation sequence from the earliest in red (antero-medial part of the left atrium) to the latest in dark blue (postero-lateral part of the left atrium and distal part of the pulmonary veins). LA: Left atrium; LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; RIPV: Right inferior pulmonary vein; RSPV: Right superior pulmonary vein.

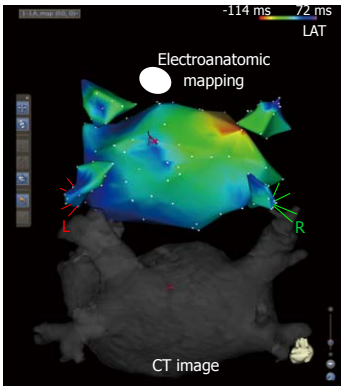

Figure 3 Postero-anterior view of the electroanatomic map shown in Figure 2 and of the three-dimensional rendering of the computed tomography scan, both in a postero-anterior view. A couple of points (small red flags on the electroanatomic mapping and computed tomography) have been identified on the left atrial roof. These two landmarks will be used to initially guide the superimposition of the two surfaces. CT: Computed tomography.

this value can be considered, with the due precautions, as acceptable.

In our experience, the method to integrate a 64-slice CT image (Aquilion 64, Toshiba Medical Systems, Tokyo, Japan) of the LA and PVs is slightly different from what has been reported in other studies. Briefly, after transseptal catheterization has been accomplished, the LA and the PVs are electroanatomically reconstructed by using the Carto 3 electroanatomic mapping system (Biosense-Webster, Diamond Bar, CA, USA) as five separate chambers, shown in Figure 2. On average, 40 sites in the body of the LA are acquired, while 20 sites and 15 sites in the proximal part of the superior and inferior PVs, respectively, are also acquired. Generally, the acquired sites are homogeneously distributed in the chamber and particular care is taken when points are acquired in the PVs, so that catheter manipulation does not distort the PV anatomy. Subsequently, as shown in Figure 3, a single site in the left atrial roof is identified, both on the CT image and the electroanatomic mapping to serve as the landmark for the first raw superimposition of the two surfaces. Afterwards, superimposition is improved by the "surface registration" option, which finds the best match between the electroanatomic maps and the CT images by rotating the two surfaces relatively. Then, an accuracy check is performed by evaluating the

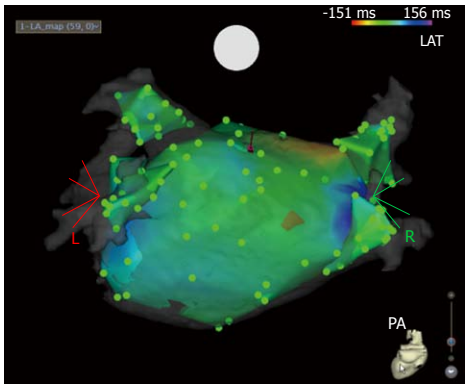

Figure 4 The two surfaces have been superimposed based on the guide provided by the two landmarks. The match of the two surfaces has been further improved with the so-called "surface registration" option, obtaining optimal integration. The accuracy of this process is then checked by verifying the distance between each electroanatomic point and the corresponding site on the computed tomography surface. In this case, all sites in the electroanatomic maps are marked by a green dot, which identifies the distance between the two surfaces as < 5 mm.

distance of each electroanatomic point from the corresponding site on the CT image. As shown in Figure 4, this can be done simply by using the software option that identifies sites with a distance < 5 mm as green dots, sites with a distance between 5 mm and 10 mm as yellow dots and sites with a distance > 10 mm as red dots. Therefore, during this final phase, sites with a distance > 5 mm should be deleted, while the catheter, visualized in real-time as an icon on the system screen, is moved in the LA and especially around the PV os/antrum to check the concordance between the actual catheter position and its display on the CT image. During this phase, other sites can be acquired to improve the quality of the integration. After the integration process has been concluded, the electroanatomic maps of the LA and PVs become transparent and the operator can manipulate the catheter looking at the projection of the catheter icon on the epicardial and endocardial aspect of the CT image, with minimal or no use of fluoroscopy, to deploy sequential radiofrequency energy lesions around the PV oses (Figure 5). In our institution, the accuracy of this integration process has been carefully evaluated in 150 consecutive patients undergoing catheter ablation of AF with electrical disconnection of the PVs. For this purpose, the distance between the actual site of radiofrequency energy application, based on different parameters (electrical signal, PV angiography, value of impedance, and three-dimensional imaging) and the corresponding site at the PV os on the CT imaging was calculated. The accuracy of integration has been defined as optimal if this distance was < 2 mm, acceptable if between 2 and 5 mm and unacceptable if > 5 mm. In this patient series, the accuracy was evaluated along the perimeter of 532 junctions between the PV and LA; in 68 patients a common os was found. An optimal imaging integration was observed in 75% of the PV-LA junctions, while it was acceptable in 16% and unacceptable in only 9%. Thus, manipulation of the ablation catheter around

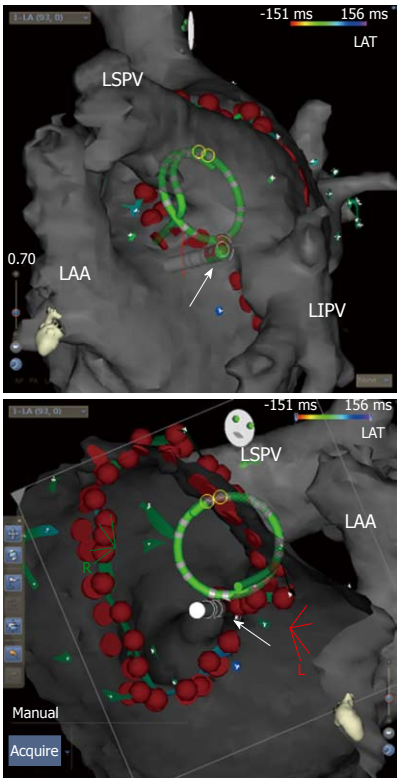

Figure 5 After completing the imaging integration process, pulmonary vein ablation is initiated. The screen of the electroanatomic system shows simultaneously the epicardial (upper) and endocardial (down) aspects of the high resolution computed tomography image of the common os of the left pulmonary veins present in this patient. The green circular icon identifies the multipolar circular mapping catheter, positioned inside the common os to verify its electrical disconnection. The icon of the ablation catheter (white arrows) is also visible, so that this catheter can be manipulated to navigate the three-dimensional computed tomography image with minimal or no use of fluoroscopy. Each red dot marks the site where radiofrequency energy has been applied along the veno-atrial junction of the left pulmonary veins to achieve their electrical disconnection. LIPV: Left inferior pulmonary vein; LSPV: Left superior pulmonary vein; LAA: Left atrial appendage.

the os of the PVs to place radiofrequency energy applications with no or minimal use of fluoroscopy was done in 91% of the cases. Both in our experience, as well as in other centers' experiences[20,21], the accuracy of integration was not affected by the difference of cardiac rhythm (sinus *vs* AF) during which the CT and the electroanatomic mapping were acquired. This is crucial, since the two images are acquired on two different days and it is likely that these patients exhibited different cardiac rhythms from 1 d to another. In fact, only 95/150 (63%) patients in our series were on the same cardiac rhythm (sinus rhythm or AF) during both (CT scan and electroanatomic mapping) imaging acquisition. In our experience, other factors that did not affect the accuracy of imaging integration were: mode of CT acquisition (ECG-gated *vs* non ECG-gated), left atrial volume, number of acquired sites in the LA and PVs and positioning of the multipolar circular mapping catheter to evaluate PV potentials during ablation. On the other hand, movements or respiratory artifacts during CT acquisition significantly altered the

Table 3 Overview of the studies designed to evaluate the impact of imaging integration for atrial fibrillation ablation on the procedure and clinical outcomes

Author	No. of pts	Type of study	Imaging	Type of evaluation	FU	Effect of imaging integration			
						Fluoroscopy time	Procedure duration	Complications	Clinical outcome
Kistler *et al*[31]	94	Non-randomized	CT	3D *vs* Merge	6 mo	↓	=	=	↑
Martinek *et al*[32]	100	Non-randomized	CT	XP *vs* Merge	6 mo	=	=	↓	↑
Kistler *et al*[33]	80	Randomized	CT	XP *vs* Merge	1 yr	=	=	=	=
Tang *et al*[34]	81	Randomized	CT	XP *vs* Merge	1 yr	↓	↓	=	=
Della Bella *et al*[35]	290	Randomized	CT	Conv *vs* Merge	> 1 yr	↑	↑	=	↑
Bertaglia *et al*[36]	573	Non-randomized	CT/MRI	Conv *vs* XP *vs* Merge	> 1 yr	=	↓	=	↑
Caponi *et al*[37]	299	Randomized	MRI	XP *vs* Merge	1 yr	↓	=	=	=

3D: Three-dimensional; Conv: Conventional; CT: Computed tomography; FU: Follow-up; Merge: CartoMerge; MRI: Magnetic resonance imaging; XP: Carto XP; ↑: Increased; ↓: Decreased; =: No difference; pts: Patients.

PV/left atrial geometry, therefore affecting the quality of imaging integration. In our experience, the quality of imaging integration was poor in a small percentage of cases (less than 10% of the PV oses), however, since quality greatly depends on respiratory or movement artifacts, great care should be taken during CT scan acquisition.

RESULTS OF IMAGING INTEGRATION IN TERM OF CLINICAL IMPACT

Using imaging integration to support AF ablation, the most important issue is whether this highly technological approach results in an improvement of the procedure parameters and the clinical outcome. Table 3 shows an overview of the results of the studies undertaken to assess the clinical usefulness of this technology[31-37]. As shown, there are three non-randomized and four randomized studies published to date. While in the early reports the number of patients included was around 100, the 2009 multicentre Italian registry[36] reported on more than 500 patients. In these studies, as well as in the studies aimed at assessing imaging integration accuracy, the most frequently used three-dimensional imaging modality was CT; the postablation follow-up was at least 1 year in most of the studies. In 5 of 7 studies[31-34,37], the impact of imaging integration was compared with the use of three-dimensional mapping without imaging integration, whereas in the two remaining studies[35,36], a comparison with the conventional technique (based only on fluoroscopy and the use of a circular mapping catheter) was made. It is evident that, apart from one study[33], all the others reported significant improvement of procedure parameters and/or clinical outcome. Specifically, the two studies[35,36] that compared imaging integration *vs* conventionally performed AF ablation reported improvement of clinical outcome with lower arrhythmia recurrences in the imaging integration group during follow-up. Among the other studies that compared an electroanatomic system with and without imaging integration, only two reported[31,32] improvement in clinical outcome. However, of the 3 remaining studies, 2 reported improvement of the procedure parameters with reduction of fluoroscopy[34,37] and procedural time[34].

Apart from the Italian registry[36], which was a non-randomized study, all the other data are from single experiences. Indeed, the best results in term of evaluation of the clinical impact of imaging integration should be obtained by multicentre randomized studies enrolling a large cohort of patients. However, such studies are difficult to design, are long-lasting and sensitive to multiple different variables in different centers and, therefore, they are at risk of being inconclusive. Data provided to date favor the use of imaging integration technology in a complex procedure, such as AF ablation, to improve the quality of patient care.

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Exercise echocardiography

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Abstract

Exercise echocardiography has been used for 30 years. It is now considered a consolidated technique for the diagnosis and risk stratification of patients with known or suspected coronary artery disease (CAD). Of the stress echocardiography techniques, it represents the first choice for patients who are able to exercise. Given that the cost-effectiveness and safety of stress echocardiography are higher than those of other imaging techniques, its use is likely to be expanded further. Recent research has also proposed this technique for the evaluation of cardiac pathology beyond CAD. Although the role of new technology is promising, the assessment of cardiac function relies on good quality black and white harmonic images.

Key words: Exercise echocardiography; Coronary artery disease; Peak imaging

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INTRODUCTION

Stress echocardiography is a useful tool for clinical decision-making, given its accuracy in the diagnosis of coronary artery disease (CAD) and its demonstrated prognostic value. Among the different stress echocardiography modalities, exercise is safer and more physiologic. Therefore, according to all current guidelines, exercise stress echocardiography (ESE) must be considered the first choice for patients who are able to exercise[1-3].

New technologies have not yet found a definitive role during stress echocardiography. Doppler tissue imaging and speckle imaging can assess myocardial velocities and deformation. However, neither of them has been demonstrated to be better than visual assessment when the latter is performed by experienced observers. Three-dimensional echocardiography (3-DE) can also be used during exercise since an image of the entire myocardium can be obtained in a few cardiac cycles.

Although ESE has long been used for the diagnosis and risk stratification of patients with known or suspected CAD[4], there has been a change in its targets, as this method has also been used in recent years as a useful tool for evaluation of dyspnea in different clinical situations[5,6].

EXERCISE ECHOCARDIOGRAPHY: 30 YEARS OF DEVELOPMENT

ESE was introduced 30 years ago when the group led by Feigenbaum first reported wall motion abnormalities (WMA) during exercise in patients with CAD[4]. Since then, a significant number of technological landmarks have been developed, including digital imaging, continuous loop quad format display for comparison of rest and exercise images, continuous imaging acquisition, broadband transducer technology, harmonic imaging, and the

use of echocardiographic contrast agents for endocardial border delineation. These are major tools currently needed for state-of-the-art performance of ESE. These tools have led to the consolidation of ESE as an accepted and established technique. Other technologies, such as myocardial Doppler imaging, myocardial perfusion, and 3-DE, although newer, have not yet found a definitive role in the ESE scenario.

A number of clinical landmarks merit mention. The first studies focused on the detection and risk stratification of patients with CAD. In the late 1990s, ESE began to be used for the functional assessment of patients with valve disease. Over the last few years ESE has been found to be useful for the evaluation of patients with dyspnea and different clinical scenarios, such as those with suspected diastolic dysfunction, those who are candidates for cardiac resynchronization therapy, and those with hypertrophic cardiomyopathy.

EXERCISE ECHOCARDIOGRAPHY: STATE OF THE ART

Common ESE modalities include treadmill ESE and semi-supine bicycle ESE. The treadmill has several advantages over the bicycle, including achievement of higher O_2 consumption and the fact that all patients able to exercise can effectively walk on a treadmill, but back-pedaling or stopping pedaling are frequent in untrained patients when a bicycle is used. Also, muscular pain or discomfort before achievement of submaximal age-predicted heart rate is a common reason for stopping exercise on a bicycle[3]. However, whatever the method we use for ESE, images should be acquired at peak exercise because peak imaging is more sensitive for the diagnosis of CAD[7-9] and because the prognostic value of peak imaging is higher than that of post-exercise imaging[10].

ESE consists simply of the addition of echocardiography to conventional exercise electrocardiography (ECG) testing. Thus, besides the clinical information (symptoms during exercise) and ECG information (ST segment changes), we obtain resting echocardiographic data (resting WMA suggesting scar, valvular or myocardial disease, *etc.*), and exercise echocardiography data (new WMA indicating ischemia). This is the reason for its superior sensitivity and specificity when compared to conventional exercise ECG testing. As can be inferred from above, its major advantage rests on the evaluation of patients with resting ECG abnormalities, and in the evaluation of those with an inconclusive result on exercise ECG testing. Table 1 shows the up-to-date recommendations for the performance of stress echocardiography on the management of patients with chest pain according to recent European Society of Cardiology guidelines[3]. The recommendation stating that ESE, where available, should be considered as an alternative to exercise ECG testing for diagnostic and prognostic purposes will likely lead to more widespread use of this method of stress testing. In this regard our group has recently demonstrated the prognostic value of ESE in patients with normal exercise ECG testing[11]. We have found that in 1 of every 6 patients with suspected or known CAD who had a completely normal exercise ECG test, ischemia could be detected at peak exercise by echocardiography. These patients were at double the risk of overall mortality and major cardiac events as compared with those without ischemia (5-year mortality rate of 12.1% *vs* 6.4%; 5-year major cardiac events rate of 10.1% *vs* 4.2%). Therefore, even in patients who would be considered low risk according to the absence of symptoms or ischemic ECG changes during exercise, ESE allows more accurate risk stratification. Concerns regarding cost-effectiveness are the only reason not to replace exercise ECG by ESE.

HOW TO PERFORM AN EXERCISE ECHOCARDIOGRAM

ECG and blood pressure are monitored during the test as they are during a conventional exercise ECG test. Protocols adjusted to the patient's clinical characteristics should be used, although the Bruce protocol (change in speed and slope every 3 min) is the most commonly used. We occasionally observe how the patient walks, prior to the exercise testing, to decide the most appropriate protocol for the particular patient.

When a treadmill is used, resting images are acquired on a table-bed, and peak exercise images are acquired with the patient walking or running. When a cycloergometer is used, images are acquired with the patient on the bicycle, at rest and at peak exercise. A set of 3 apical views (long-axis, 4-chamber and 2-chamber) and 2 parasternal views (long- and short-axis) is obtained. In case of non-conclusive peak images (poor quality or doubtful), images during the immediate post-exercise time are also acquired. We have previously shown that peak treadmill imaging is more sensitive than post-exercise imaging for the diagnosis of CAD, and that the quality of peak images in the apical views are similar to those acquired post-exercise[7,8]. In addition, the prognostic value of peak treadmill exercise imaging is higher because, in up to 1 in 4 patients with ischemia, the latter is limited to peak exercise, and the post-exercise study is completely normal[10]. Even in patients with post-exercise ischemia, WMA are markedly greater at peak than at post-exercise. Other authors have also demonstrated higher sensitivity for the detection of CAD with peak rather than post-exercise imaging during bicycle echocardiography[9]. Besides the superior diagnostic and prognostic capabilities of peak exercise imaging, a proper training in this approach has additional advantages: (1) patient scanning during different phases of exercise testing is feasible, and can be performed whenever there is concern about the need for termination of the test, for example in cases of doubtful symptoms or ECG changes; (2) the narrow acquisition time window we have for post-exercise imaging does not exist any more. In contrast,

Table 1 Recommendations for the use of exercise stress echocardiography testing in the initial diagnostic assessment of angina[1]

Class Ⅰ	
Ⅰ	Patients with resting ECG abnormalities, LBBB, > 1 mm ST-depression, paced rhythm, or WPW which prevent accurate interpretation of ECG changes during stress
Ⅱ	Patients with a non-conclusive exercise ECG but reasonable exercise tolerance, who do not have a high probability of significant coronary disease and in whom the diagnosis is still in doubt
Class Ⅱa	
Ⅲ	Patients with prior revascularization (PCI or CABG) in whom localization of ischemia is important
Ⅳ	As an alternative to exercise ECG in patients where facilities, costs, and personnel resources allow
Ⅴ	As an alternative to exercise ECG in patients with a low pre-test probability of disease such as women with atypical chest pain
Ⅵ	To assess functional severity of intermediate lesions on coronary angiography
Ⅶ	To localize ischemia when planning revascularization options in patients who have already had arteriography

From: ESC Guidelines on the management of stable angina pectoris: executive summary[3]. [1]Pharmacological stress echocardiography is recommended if the patient is unable to exercise adequately. ECG: Electrocardiography; WPW: Wolf-Parkinson-White syndrome; LBBB: Left bundle branch block; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft. Class Ⅰ: Benefits are greater than risks, therefore the procedure should be performed; Class Ⅱa: Benefits are greater than risks, although additional studies are required - it is reasonable to perform the procedure.

Figure 1 Exercise echocardiography. When the patient is exhausted or termination criteria appear (symptoms, significative ST changes, decrease or increase in blood pressure, *etc.*), the observer acquires images by placing the transducer in the cardiac apex, then in the parasternal region. Note the placement of the table, the treadmill and the echocardiography machine for feasible imaging evaluation at peak and post-exercise. The left lateral handlebar of the treadmill has been removed to allow for rapid post-exercise positioning of the patient on the table.

post-exercise imaging acquisition should take no longer than 45 s, otherwise WMA can rapidly recover, particularly in young patients and patients taking β-blockers. To scan the patient both during peak exercise and quickly during post-exercise requires a particular spatial disposition of the treadmill, the table and the echocardiographic machine, each one being close to the others. Figure 1 demonstrates the arrangement of these equipments in our laboratory. The transducer cable length should be adequately long, recognizing that it is not made the same length by all manufacturers; and (3) the post-exercise imaging period can be used to obtain other important information, such as mitral regurgitation (MR), diastolic function and systolic pulmonary artery pressure measurements.

Three technical requirements are mandatory to optimize peak and post-exercise imaging acquisition and also for interpretation: (1) a direct ECG wire connection between the echocardiography machine and the ergometer, which is indispensable for obtaining well registered cardiac cycles; (2) a continuous imaging acquisition system, which allows the acquisition of multiple cardiac cycles during several minutes. After the test, the interpreter only has to choose the loops with the highest quality corresponding to the different views; and (3) a quad-format screen to compare resting and exercise images. Almost all the manufacturers offer equipment with these requirements. The cost-effectiveness of a stress echocardiography laboratory may be optimized if an off-line computer is available to read the studies, as the echocardiography machine may require to be used in the meantime.

IMAGING INTERPRETATION

With stress echocardiography, CAD is considered when there are resting or stress-induced WMA (hypokinesia, akinesia, dyskinesia). When the same WMA are present at rest and during stress, the condition is defined as fixed WMA or scar. When the WMA appear only during stress, the condition is defined as induced WMA or ischemia. When there are WMA at rest that worsen with stress the condition is defined as mixed scar and ischemia. In this latter situation the WMA may develop in the same or in a different territory (ischemia at a distance). A semi-quantitative scale is used to calculate wall motion score by dividing the left ventricle (LV) into 16 or 17 segments[12] and assigning 1 to normal, 2 to hypokinetic, 3 to akinetic, and 4 to dyskinetic segments. The sum of all the scores divided by the number of visualized segments is the wall motion score index. Most laboratories also calculate resting and exercise LV ejection fraction. Figures 2 and 3 show a normal and an abnormal ESE, respectively.

ESE LIMITATIONS

The main limitation of ESE is the presence of a poor acoustic window in some patients. This percentage has dramatically diminished in recent years with the introduction of harmonic imaging. In the remaining 5%-10% of cases with a poor acoustic window, contrast agents can be used to improve myocardial border delineation. However, "excellent" visualization of LV segments is more crucial

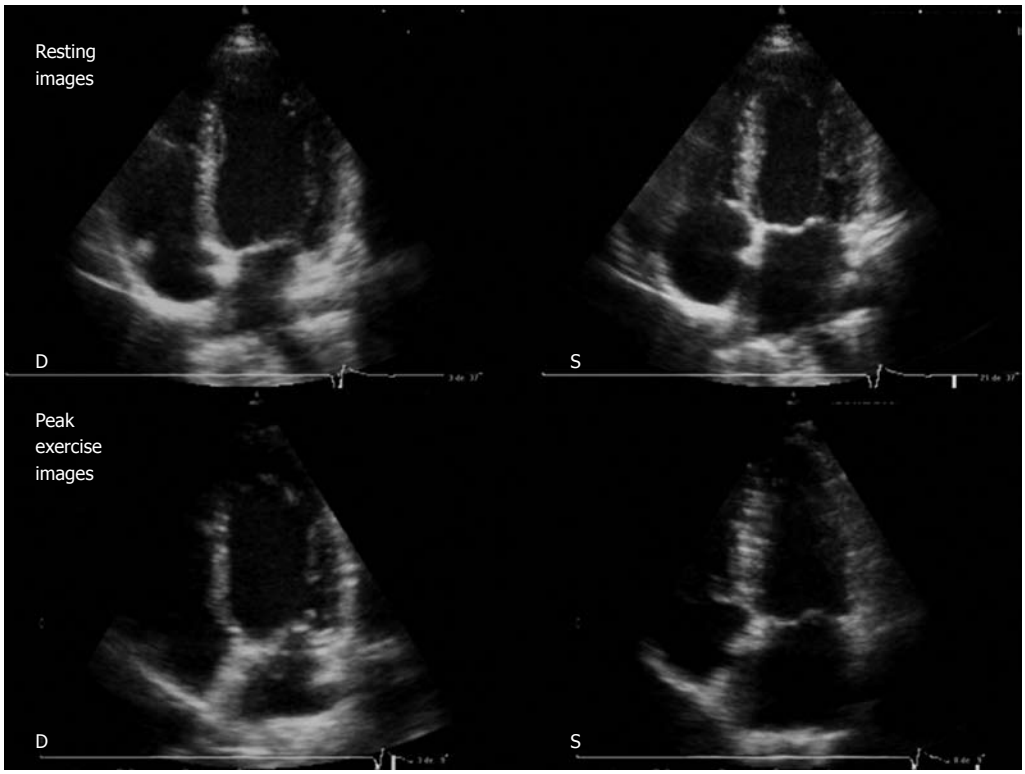

Figure 2 Resting echocardiography (top) and peak exercise echocardiography (bottom). Four-chamber apical view (diastolic frames on the left, systolic frames on the right) in a patient with normal results. Note the left ventricular (LV) cavity dimensions decrease with exercise and an increase in LV ejection fraction. D: Diastolic; S: Systolic.

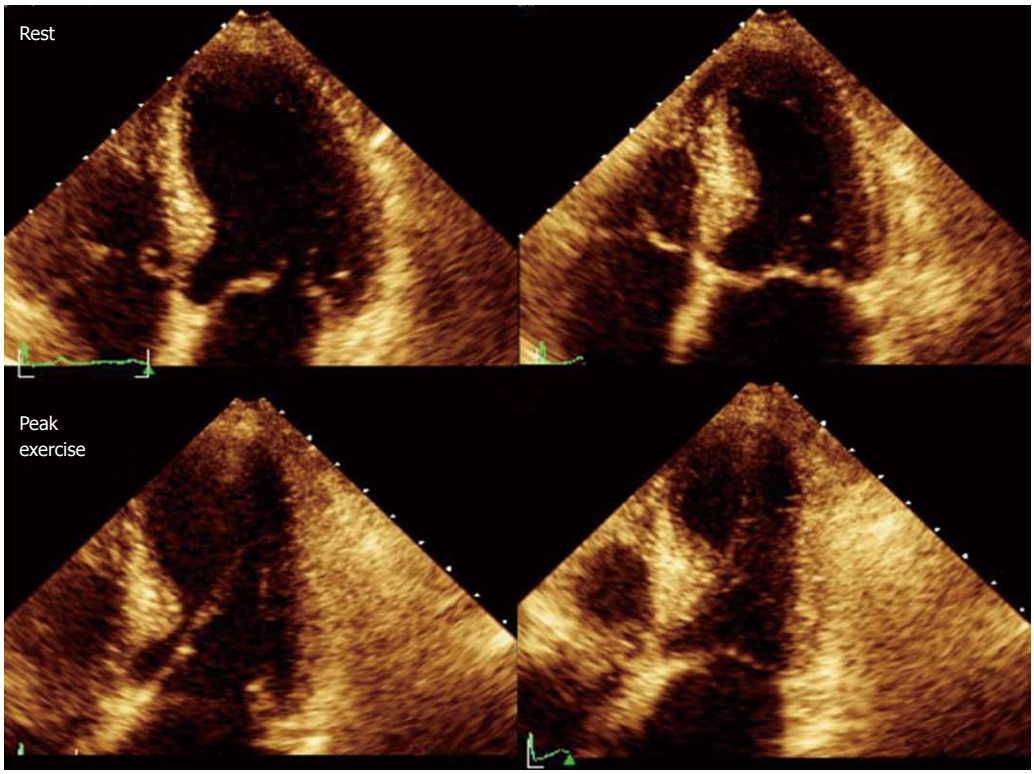

Figure 3 Resting echocardiography (top) and peak exercise echocardiography (bottom). Four-chamber apical view (diastolic frames on the left, systolic frames on the right) in a patient with significant coronary stenoses in the left anterior descending artery (99%). At rest, wall motion is normal, whereas during exercise a septoapical dyssynergia is observed with the typical 8-shaped left ventricular.

for pharmacological stress echocardiography (where diagnostic and prognostic information are almost exclusively dependent on the imaging), than for ESE, that provides diagnostic and prognostic information beyond that pro-

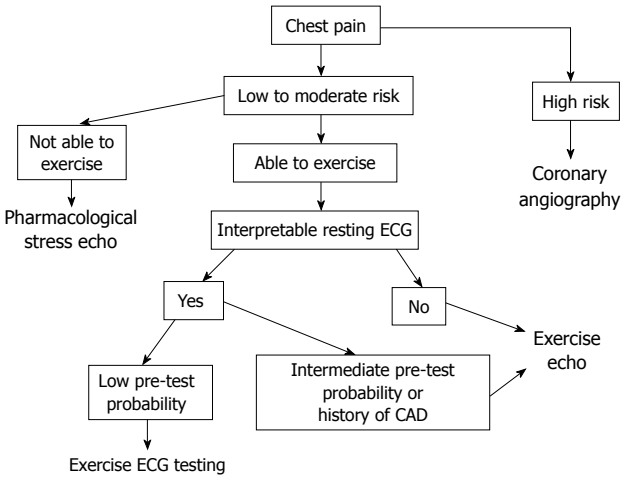

Figure 4 Algorithm used in our institution for patients with chest pain. CAD: Coronary artery disease; ECG: Electrocardiography.

vided by imaging alone (clinical symptoms, ECG changes, functional capacity). Although current guidelines recommend the use of contrast agents when at least 2 myocardial segments are non-visualized[13], it should be pointed out that the absence of visualization of 2 contiguous apical segments does not have the same significance as the absence of visualization of 2 non-contiguous basal segments.

Secondly, imaging acquisition during ESE is more difficult than during pharmacological stress, due to the greater increase in both heart and respiratory rates with exercise. Pharmacological stress echocardiography requires less skills than ESE[14]. However, subtle WMA during pharmacological stress echocardiography may be equated with more severe ischemic burden during ESE[15]. In our department, most physicians and fellows in training acquire the necessary expertise to perform peak exercise studies on a treadmill with confidence after 100 cases, although this number may vary depending on the trainee's background (i.e. previous expertise in pharmacological stress echocardiography or post-exercise imaging).

Thirdly, imaging interpretation is made by a semi-quantitative approach, which has led to only moderate agreement between observers in different studies[16,17]. However, this agreement is higher when either significant WMA or extensive CAD, as defined by angiography, is present. Interpretation of WMA may also be more challenging in certain situations such as left bundle branch block, paced rhythm, and atrial fibrillation. Among 8088 patients having a first ESE study in our institution, atrial fibrillation was present in 5.2% of the patients and left bundle branch block or paced rhythm in 7.7%. The diagnostic accuracy of WMA for the detection of CAD may be compromised in patients with these ECG abnormalities, in comparison with the overall population of patients referred for stress echocardiography[18-20]. Minor abnormalities in the septoapical region should not be considered abnormal in patients with left bundle branch block or pacemakers; instead careful assessment of the anterior wall in the 2-chamber view should be performed.

Fourthly, some patients may have limited capacity for exercising and, as 85% of the age-predicted maximal heart rate may not be achieved in up to 25%-30% of the patients, these tests are often considered as non-conclusive. This percentage can be reduced by using atropine during exercise, therefore reducing the need for pharmacological stress[21]. Atropine is particularly useful for patients with reduced resting heart rate as a result of β-blocker therapy, peripheral artery disease or arthropathies.

Finally, since in routine clinical practice not all patients can be referred for an ESE study, despite wide availability as in our case, proper selection is mandatory. In our institution, patients with either resting ECG abnormalities, known CAD, or intermediate pre-test probability of CAD are preferentially referred for ESE. Figure 4 shows the algorithm used in our center for patients referred for stress testing.

COST-EFFECTIVENESS

The cost-effectiveness of ESE has been explored in a few studies. Marwick *et al*[22] demonstrated that ESE was more cost-effective than exercise ECG. Due to a better risk stratification with the former, downstream costs were particularly low in patients deemed at low risk by ESE, in contrast with patients deemed at low risk by exercise ECG results. The difference in cost was mainly due to the higher rate of catheterization and revascularization procedures performed during follow-up in patients stratified as low risk by exercise ECG. The same group found ESE to be a more cost-effective strategy than exercise ECG for the decision-making process in women with suspected CAD. This approach led to a reduced number of unnecessary coronary angiograms in comparison with a pure exercise ECG only approach or with a selective ESE approach (ESE for patients with non-diagnostic exercise ECG results)[23]. Also, ESE was superior to exercise ECG in risk stratification of patients evaluated in chest pain units, resulting in less diagnostic uncertainty, fewer referrals for further unnecessary investigation, and hence, a significant cost benefit over exercise ECG testing[24].

PROGNOSTIC VALUE OF EXERCISE ECHOCARDIOGRAPHY

Resting LV function and ischemia are important prognostic markers. These indicators can be evaluated together during stress echocardiography. The independent prognostic value of stress-induced WMA, as well as the excellent outcome of patients with negative stress echocardiography (< 1% events/year)[25] have been demonstrated with each stress echocardiography modality. ESE is particularly useful for prognostic assessment because exercise parameters with well-demonstrated prognostic value (such as metabolic equivalents achieved, blood pressure response, or percentage of age-predicted maximal heart rate) may be obtained. ESE has its maximal cost-effectiveness in the assessment of patients with intermediate likelihood of events[22,26]. We have observed that ESE further catego-

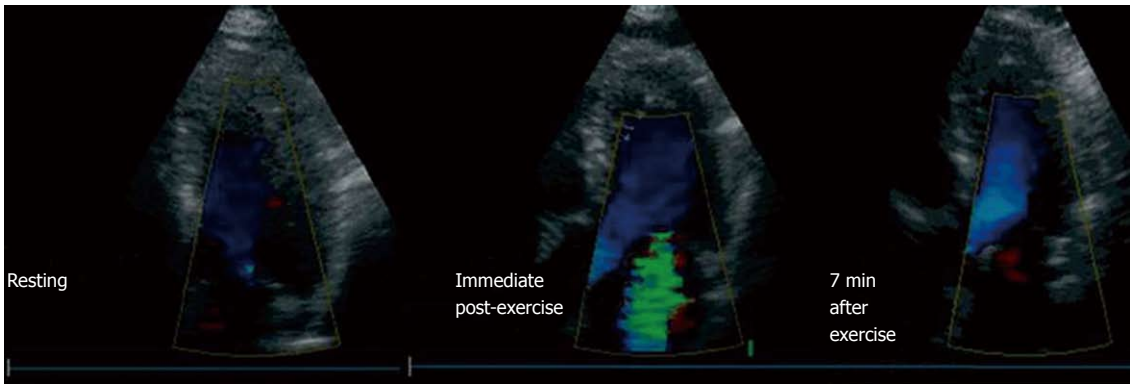

Figure 5 Example of a patient with mild ventricular dysfunction (resting left ventricle ejection fraction 49%, exercise left ventricle ejection fraction 46%) who developed severe mitral regurgitation (MR) during exercise. This patient had no MR at rest (left), severe MR developed in the immediate post-exercise period (center), which did not completely disappear until 7 min after exercise (right) (From Peteiro *et al*[32]).

rizes patients with intermediate-risk Duke treadmill score into those at higher and lower risk of events. ESE also allows a better stratification of patients with low-risk Duke treadmill score, aiding in the decision whether to perform coronary angiography[26]. Several studies have shown that gender, functional capacity, rate-pressure product, resting LV function, and ischemia are independently associated with cardiac events[26,27], and that ESE has incremental predictive value in patients with different pre-test probabilities of CAD[27]. Patients with WMA involving the territories of the 3 coronary arteries, patients with peak wall motion score index > 1.5, and patients with ischemia at a distance are at higher risk for cardiac events[28].

Furthermore, ESE can show worsening of existing MR or development of new MR during exercise[29-31], due to adverse LV remodeling (Figure 5). Assessment of functional MR is unfeasible with pharmacologic stress testing because both dobutamine and dipyridamole reduce LV preload. Our group has demonstrated that worsening of MR or development of new MR during ESE is associated with a poor outcome. In a recent study on nearly 2000 patients, those with positive ESE and worsening of MR had an event rate of 11% during a follow-up period of 4 years, as compared with 6% in those with a positive echocardiogram and no worsening of MR[30]. In addition, worsening of MR was predictive of death independent of the ESE results.

NEW TECHNOLOGY

ESE can be complemented by the addition of new modalities of imaging. As mentioned above, contrast agents may be used to improve endocardial border delineation, improve diagnostic accuracy of ESE[32] and reduce the need for additional diagnostic tests. However, its use on a routine basis may not be cost-effective[33]. Contrast agents can also be used to detect myocardial perfusion defects during stress. As perfusion defects precede WMA, assessment of myocardial perfusion may improve the sensitivity of stress (particularly pharmacologic) echocardiography for detection of ischemia, albeit at the expence of specificity[34]. It should be noted that the assessment of myocardial perfusion during ESE is not without certain technical limitations[35].

Tissue Doppler imaging and speckle imaging can assess myocardial velocities and strain, increase the agreement between observers, and also improve the accuracy of wall motion assessment by less experienced observers, but do not increase the accuracy of the visual assessment when performed by experienced observers[36,37]. Speckle imaging can be effectively used to assess the torsional movement of the myocardium, which is altered during ischemic conditions[38]. However, only one study has assessed LV torsion during stress echocardiography[39]. In this study, apical counterclockwise rotation was increased in patients with ischemia, suggesting that subendocardial ischemia might have led to a compensatory enhancement of the subepicardial counterclockwise rotation. In contrast, in previous experimental studies, more intense ischemia was associated with a reduced counterclockwise apical rotation and LV torsion[40]. Therefore the clinical applications of the assessment of LV torsion remain to be better defined.

Speckle imaging may also be used to assess tardokinesis, which is difficult to observe visually. In a recent ESE study, delayed strain was found to be more sensitive than WMA for the detection of CAD. While WMA usually recovered in less than 2 min, strain delay recovery lasted as long as 10 min[41].

Finally, 3-DE is able to acquire LV full-volume images over a few cardiac cycles. Off-line management of the obtained images (cropping) then allows evaluation of wall motion in any desired image plane at rest and at peak stress[42-44]. Although the imaging acquisition is therefore very quick, a relatively long time is necessary to crop the required images. We have demonstrated similar sensitivity and specificity with exercise 3-DE (Figure 6) and exercise 2-DE, but the feasibility of performing 3-DE was lower[44]. Present limitations are suboptimal imaging quality and low frame rate. Recent developments now allow a full-volume acquisition in only 1 cardiac cycle (i.e. 1 s) with a frame rate of around 20, which is promising for ESE.

To summarize, these features are not available in all ultrasound systems, their advantages over conventional

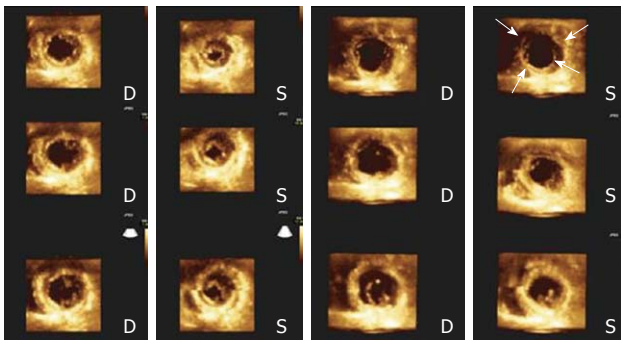

Figure 6 Cropped views obtained from a left ventricle full-volume during 3-dimensional exercise echocardiography in resting conditions (left panel) and during peak exercise (right panel) in a patient with severe 3-vessel disease. Note exercise-induced akinesia and dilation in the short axis apical views (arrows), as well as hypokinesia and dilation in the short-axis view at the papillary muscles level. 3-DE: Three-dimensional exercise; D: Diastolic; S: Systolic.

2-D imaging are not fully clear, and additional expertise is necessary for their interpretation. Although the value of these techniques, when added to traditional assessment, is currently unknown, it can be speculated that speckle tracking imaging has the potential to reduce the need for alternative tests in selected cases.

EXERCISE ECHOCARDIOGRAPHY: FROM THE EVALUATION OF CHEST PAIN TO THE ASSESSMENT OF DYSPNEA

ESE has been a useful tool for evaluation of chest pain in patients with known or suspected CAD for the last 30 years. Nevertheless, its capacity for comprehensive cardiac assessment during exercise has made this technique also valuable for evaluation of dyspnea in patients with a variety of cardiac diseases. ESE has been found to be particularly useful for functional assessment of patients with valve disease or cardiomyopathies, better prediction of response to resynchronization therapy, and identification of diastolic dysfunction as the cause of dyspnea.

Impaired LV diastolic function is associated with an adverse outcome in patients with heart disease. Among the numerous indices of diastolic function, the ratio of early transmitral flow assessed by pulsed Doppler (E) to early diastolic annulus velocity assessed by tissue Doppler (é) is closely related to LV end-diastolic pressure and can be easily measured during ESE. A higher E/é ratio index is associated with the presence of dyspnea, lower functional capacity, exercise-induced LV dysfunction and CAD[5,45]. A change to a pseudonormalized LV inflow pattern during exercise is also associated with the same poor prognostic indicators[45]. These measurements, along with the assessment of pulmonary artery pressure during exercise, may help to clarify causes of dyspnea in patients with different cardiac or noncardiac conditions. The appropriate patients for diastolic exercise testing are likely those with dyspnea of uncertain origin and absence of WMA on ESE. The additional information offered by ESE in patients suspected of having diastolic dysfunction has been recently shown by Holland *et al*[46]. These investigators performed ESE in 148 patients with the diagnosis of diastolic dysfunction based on resting conventional echo-Doppler measurements[47]. Only 24% of the patients had functional limitation to exercise and only 36% had an increased E/é ratio during exercise. It was concluded that resting measurements may not be adequate for accurate diagnosis of diastolic dysfunction because having diastolic dysfunction in the absence of exercise intolerance and an E/é increase does not seem plausible.

The assessment of dysynchrony during exercise has been found to be a better predictor of response to resynchronization therapy than resting dysynchrony (predictive value 89% *vs* 70%, $P = 0.01$)[6]. Also, exercise may change the magnitude of dysynchrony and these changes correlate with the changes in the severity of functional MR during ESE[48,49]. Finally, the appearance of a septal flash (septal movement during the isovolumic contraction period) during stress in patients with left bundle branch block and systolic dysfunction has been correlated with the response to resynchronization therapy, although it has only been studied by dobutamine stress[50].

ESE has also been used in patients with valve disease and discordant symptoms (either symptomatic patients with non-severe valve disease or asymptomatic patients with severe valve disease) helping in the decision making process. Asymptomatic patients with aortic stenosis without inotropic reserve during ESE were found to have worse prognosis during follow-up in one study[51].

In patients with hypertrophic cardiomyopathy, ESE can assess either exercise-induced LV outflow tract obstruction, MR, or LV systolic impairment. We found that patients with hypertrophic cardiomyopathy and lack of increase in LV ejection fraction with exercise have a more adverse outcome[52].

Table 2 Sensitivity and specificity of stress echocardiography and competing methodologies

	Sensitivity (%)	Specificity (%)
Exercise ECG testing[53]	50	90
Stress echocardiography[54]	80	84
Nuclear techniques[54]	84	77
Magnetic resonance[55]	89	87
Coronary computed tomography[56]	98	90

ECG: Electrocardiography.

THE COMPETITORS

Several non-invasive techniques can compete with ESE for identification of patients in need of invasive coronary angiography. These include exercise ECG testing, pharmacological stress echocardiography, nuclear myocardial perfusion imaging, coronary computed tomography and cardiac magnetic resonance imaging. Table 2 shows the sensitivity and specificity of these techniques in comparison to stress echocardiography. Although information on

the coronary anatomy might be desirable for certain patients, the outcome of CAD patients is more often related to the extent of myocardial ischemia during stress than to the number of diseased vessels assessed by the anatomic methods[57-59]. Therefore, decisions regarding revascularization procedures should not be based solely on the coronary anatomy, but should be based on the evidence that a particular coronary stenosis has an objective functional significance.

There are further advantages of ESE over these other techniques, including: safety (approximately 1 event/7000 in ESE, 1/700 in pharmacological stress echocardiography)[60,61]; relatively high diagnostic accuracy (sensitivity 80% and specificity 86%)[54], comparable to that of nuclear imaging but higher than that of exercise ECG[53]; solid prognostic data (less that 1% events/year in patients with a negative stress echocardiogram)[22,25,27,62]; and the fact that it is a green technology (compared to nuclear myocardial perfusion imaging and coronary computed tomographic angiography that may expose the patient to radiation levels equivalent to as many as 600 plain chest X-rays)[63]. In addition, the cost of stress echocardiography is lower than that of other noninvasive imaging techniques. According to the American College of Cardiology/American Heart Association guidelines, if 1 is the cost of an exercise ECG test, 2 would be that of an ESE, but 5.7 would be the cost of a nuclear imaging technique[1]. As stress echocardiography is usually performed and interpreted by cardiology staff in a quick fashion after a single procedure, the results are usually readily available. ESE in particular is the only non-invasive modality where an intravenous line is not even required.

According to the consensus statement by experts on stress echocardiography of the European Association of Echocardiography, stress echocardiography should be preferred over stress scintigraphy, because the information provided by both techniques is similar, but the latter poses a significant biological risk not only for the individual but for society[64]. Magnetic resonance might compete in the future with stress echocardiography as it is also a non-radioactive method with relatively higher sensitivity[55]. However, its availability is currently lower and most protocols are based on pharmacological stressors rather than exercise.

CONCLUSION

Because of its low cost, safety, diagnostic and prognostic capabilities, and lack of radiation exposure, ESE should be considered as a first-line technique for patients with suspected or confirmed CAD. It is the first indication for patients with resting ECG abnormalities and for those with inconclusive exercise ECG test results. In addition, ESE may be a useful alternative to conventional exercise ECG testing in centers where facilities and resources allow. The need for exhaustive training should not be a limitation for a technique that adds significantly to the decision-making process for patients with known or suspected CAD.

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REVIEW

Myocardial ischemia-reperfusion injury: Possible role of melatonin

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Abstract

Our knowledge and understanding of the pathophysiology of coronary atherosclerosis has increased enormously over the last 20 years. Reperfusion through thrombolysis or percutaneous coronary angioplasty is the standard treatment for preventing acute myocardial infarction. Early reperfusion is an absolute prerequisite for survival of the ischemic myocardium, but reperfusion itself may lead to accelerated and additional myocardial injury beyond that generated by ischemia alone. These outcomes, in a range of reperfusion-associated pathologies, are collectively termed "reperfusion injuries". Reactive oxygen species are known to be produced in large quantities in the first few minutes of the post-ischemia reperfusion process. Similarly, scientific evidence from the last 15 years has suggested that melatonin has beneficial effects on the cardiovascular system. The presence of vascular melatoninergic receptor binding sites has been demonstrated; these receptors are functionally linked to vasoconstrictor or vasodilatory effects of melatonin. It has been shown that patients with coronary heart disease have a low melatonin production rate, especially those with higher risk of cardiac infarction and/or sudden death. Melatonin attenuates molecular and cellular damage resulting from cardiac ischemia-reperfusion in which destructive free radicals are involved.

Key words: Ischemia-reperfusion injury; Melatonin; Acute myocardial infarction; Reactive oxygen species; Primary percutaneous coronary intervention

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INTRODUCTION

Acute coronary occlusion is the leading cause of morbidity and mortality in the Western world. According to the World Health Organisation, it will be the major cause of death in the world by the year 2020[1]. Despite effective reperfusion of epicardial coronary arteries by percutaneous coronary intervention or thrombolysis in acute ST-segment elevation myocardial infarction, substantial morbidity and mortality remain elevated[2]. Infarct size is an important determinant of the short- and long-term outcome after acute myocardial infarction[3].

Although beneficial in terms of myocardial salvage,

reperfusion itself may contribute to additional damage of the myocardium, due to the combined processes known as "ischemia-reperfusion injury"[4]. The pathogenesis of myocardial ischemia-reperfusion injury is a multifactorial process involving the interaction of multiple mechanisms. Partially reduced oxygen species, including the superoxide anion radical, hydroxyl radical, and hydrogen peroxide, are generated intracellularly as products of oxygen metabolism[4].

These reactive oxygen species cause peroxidation of membrane lipids, denaturation of proteins, and modification of DNA, all of which can ultimately lead to cell death. In mammals, cell damage induced by reduced oxygen species can also initiate local inflammatory responses, which then lead to further oxidant-mediated tissue injury[4]. Because there is strong evidence that free radicals contribute to postischemic injury, antioxidant therapy could be extremely effective in reducing the cellular damage. However, the usefulness of this therapy is limited by a number of factors, in particular the ability of the antioxidants to penetrate the cell membrane and to scavenge free radicals *in situ*. Recent publications present evidence that the newly discovered antioxidant melatonin has significant protective actions against the cardiac damage occurring during ischemia-reperfusion injury[5].

CIRCADIAN RHYTHM AND CARDIOVASCULAR EVENTS

Almost all living organisms have developed biological rhythms linked to the day/night or light/dark cycles of the sun. The impact of these rhythms on a variety of physiological functions in humans has been recognized for a long time[6]. The internal oscillator, or control station regulating the body's circadian clock, is the suprachiasmatic nucleus, a tiny structure located in the hypothalamus above the optic chiasm[7]. The suprachiasmatic nucleus processes external signals such as ambient light, and internal signals from the brain to regulate a variety of cyclic functions, including body temperature, sleep/wake cycles, and secretion of hormones such as melatonin[6].

Evidence gathered over the past 15 years suggests that melatonin influences several functions of the cardiovascular system. Similar to other organs and systems, the cardiovascular system exhibits diurnal and seasonal rhythms in heart rate, blood pressure, and platelet and endothelial function, which are likely to be modulated by the suprachiasmatic nucleus and, possibly, by the melatoninergic system[8]. The circadian pacemaker within the suprachiasmatic nucleus stimulates the pineal gland to produce melatonin at night[6].

The amount of melatonin produced by the pineal gland of mammals changes with the age of the animal. The production of melatonin wanes with the aging process[9]. In humans, melatonin production not only diminishes with age, but it is also significantly lower in many age-related diseases, including cardiovascular disease[10,11]. Mounting evidence reveals that the rhythmicity of melatonin has a crucial role in a variety of cardiovascular pathophysiological processes including antiinflammatory, antioxidant, antihypertensive and, possibly, antilipidemic functions[12]. In addition, we have demonstrated that light/dark variations in the production of endogenous inflammatory markers in patients with coronary artery disease may be related, at least in part, to day/night fluctuations in circulating melatonin levels[13-15].

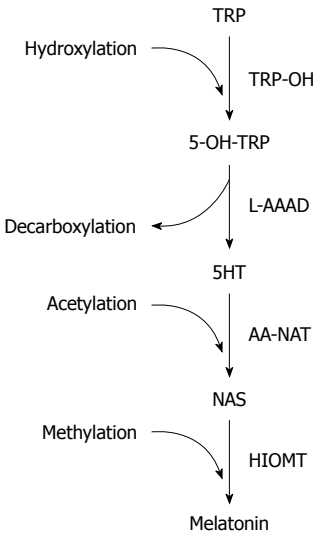

Figure 1 Biosynthetic pathways of melatonin. TRP: Tryptophan; TRP-OH: Tryptophan hydroxylase; L-AAAD: L Aromatic amino acid decarboxylase; 5HT: 5-Hydroxy tryptamine (Serotonin); AA-NAT: Aryl alkyl-amine-n-acetyl-transferase; NAS: *N*-acetyl-serotonin; HIOMT: Hydroxyindole *O*-methyltransferase.

MELATONIN SYNTHESIS

L-tryptophan circulating in the blood is taken up by pinealocytes. Via several enzymatic steps including tryptophan 5-hydroxylation, decarboxylation, *N*-acetylation and *O*-methylation, in that sequence, *N*-acetyl-5-methoxytryptamine (melatonin) is synthesized[16] (Figure 1). During melatonin synthesis, two enzymes play important roles in its production, namely arylalkylamine *N*-acetyl-transferase and hydroxyindole *O*-methyltransferase (HIOMT). The former *N*-acetylates serotonin to produce *N*-acetyl serotonin which is then *O*-methylated by HIOMT to generate *N*-acetyl-5-methoxytryptamine (melatonin)[17].

The melatonin is then secreted by the pineal gland following a circadian rhythm in response to environmental light/dark cycles. The amplitude of the diurnal melatonin cycle is attenuated by age. The diurnal/nocturnal levels of blood melatonin can range between 8 ± 2 pg/mL (light phase) and 81 ± 11 pg/mL (dark phase). The distribution of melatonin in the human being is very broad. As a result of being a non polar molecule, the melatonin is released upon biosynthesis into the extracellular fluid to the general circulation from which it easily crosses the membranes of various cells and is excreted in saliva, bile, cerebrospinal fluid, milk, urine, *etc*[18].

Melatonin mediates a variety of physiological responses through membrane and nuclear binding sites. Two mammalian receptor subtypes have been cloned and designated as MT_1 and MT_2[19]. Animal studies suggest that melatonin

has dual effects on the vasculature, depending on the specific receptor type activated[9] with vasoconstriction occurring after MT_1 activation and vasorelaxation after MT_2 activation. The likely mechanisms of melatonin's actions are *via* a modulation of the noradrenergic and/or nitric oxide effects in the system[20]. MT_1 and MT_2 receptors have also been identified in human coronary arteries from pathological samples and also from healthy controls. The functional relevance of melatonin receptors in human coronary arteries requires additional study[21-23].

MELATONIN AND REPERFUSION INJURY

The results of many publications suggest a decrease in circulating melatonin concentration at different stages of the coronary heart disease in humans. Furthermore, experimental and clinical data suggest that melatonin is involved in normal cardiovascular physiology[5]. Melatonin is known to be a powerful scavenger of the hydroxyl radical and to protect against cardiac tissue damage mediated by oxidative stress[5]. Also, metabolites of melatonin including N^1-acetyl-N^2-formyl-5-methoxykynuramine and *N*-acetyl-5-methoxykynuramine are direct free radical scavengers and also upregulate antioxidant enzymes and downregulate pro-oxidative and pro-inflammatory enzymes. In many disease states which reportedly involve reactive oxygen and/or nitrogen species, endogenous melatonin levels are significantly lower than in healthy subjects[24]. In comparison to the majority of antioxidant compounds that act on a single reactive species (Vitamin C, Vitamin E), melatonin is the most potent endogenous free radical acting on both reactive oxygen species, such as the hydroxyl radical, superoxide anion, hydrogen peroxide and singlet oxygen, and reactive nitrogen species, such as nitric oxide and the peroxynitrite anion[25]. Our group analyzed serum levels of melatonin and parameters of oxidative stress in a cohort of 25 patients diagnosed with acute myocardial infarction and 25 subjects with no evidence of coronary artery disease as controls. We demonstrated that acute myocardial infarction is associated with a nocturnal serum melatonin deficit as well as increased oxidative stress[11]. However, it is uncertain whether low melatonin levels in these patients are the result of melatonin consumption caused by scavenging of the elevated free radical production, or represent lower melatonin production, and hence less protection against oxidative stress[24].

Recently, the role of mitochondrial ATP-sensitive K^+ channel opening was further revealed by melatonin-mediated protection against heart ischemia-reperfusion injury[26]. The regulatory mechanism is related to inhibition of cardiolipin peroxidation in mitochondria and prevention of mitochondrial permeability transition and cytochrome c release[27]. Melatonin seems to have antiapoptotic actions in normal cells *via* the regulation of a permeability transition pore and cytochrome c release[28]; opposite regulation has been observed in different cell types, such as tumor cells[29]. This suggests that there exists considerable variability in the permeabilization of the outer membrane in different cell types treated with melatonin. Therefore, the role of mitochondrial ATP-sensitive K^+ channels in the regulation of cytochrome c release and reactive oxidative stress-induced cell death needs to be studied carefully[30].

In a recent study in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, we observed a relationship between melatonin concentration and ischemia-modified albumin, a marker of myocardial ischemia[31]. On the basis of this finding, our data suggested that melatonin acts as a potent antioxidant, reducing myocardial damage induced by ischemia-reperfusion[31]. We are currently assessing, in a prospective trial, The Melatonin Adjunct in acute myocaRdial Infarction treated with Angioplasty trial, whether pharmacological doses of melatonin confers cardioprotection against ischemia-reperfusion injury in ST-elevation myocardial infarction patients[32]. The importance of this study is emphasized by the fact when, exogenously administered, melatonin is quickly distributed throughout the organism. It crosses all morphophysiologic barriers and it enters cardiac cells with ease. The highest intracellular concentrations of melatonin appear to be in the mitochondria. This is especially important as the mitochondria are a major site of free radical generation and oxidative stress. Melatonin is a molecule with low toxicity. Its administration in a broad range of concentrations by oral and intravenous routes has proven to be safe in human studies[24].

CONCLUSION

Many aspects of cardiovascular physiology are subject to diurnal variations, and serious adverse cardiovascular events, including myocardial infarction and sudden cardiac death, appear to be conditioned by the time of day.

Neurohormones such as melatonin, which are particularly relevant to the cardiovascular system, exhibit a diurnal variation and they may play a role in the synchronization of molecular circadian clocks in the suprachiasmatic nucleus. Furthermore, mounting evidence indicates that the blood melatonin rhythm has a crucial role in several cardiovascular functions. Melatonin has antioxidant, anti-inflammatory, and chronobiotic regulatory functions.

We recognize that melatonin is of special interest, being an endogenous molecule that can be used in humans, and which is also safe. We will await the results of our phase Ⅱ study of melatonin with great interest.

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REVIEW

Role of cardiovascular imaging in systemic autoimmune diseases

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Abstract

Systemic autoimmune diseases are characterized by an excess of cardiovascular (CV) morbidity and mortality compared to the general population, mainly due to chronic inflammation that promotes the development of endothelial dysfunction and enhanced atherosclerosis. Early diagnosis of silent CV involvement is mandatory to improve the long term prognosis of these patients and CV imaging provides valuable information as a reliable diagnostic tool. Transthoracic echocardiography, with several applications (e.g. coronary flow reserve evaluation, tissue Doppler imaging, speckle tracking and the transesophageal approach), represents a first line evaluation, in association with biomarkers of endothelial dysfunction, such as asymmetric dimethylarginine. Nuclear medicine provides useful information on myocardial perfusion. The aim of this editorial is to provide a brief but complete review of the diagnostic tools available for screening and follow up of CV involvement in systemic autoimmune diseases.

Key words: Systemic autoimmune disease; Rheumatoid arthritis; Cardiovascular involvement; Echocardiography; Coronary flow reserve; Cardiac magnetic resonance; Computed tomography; Coronary angiography; Speckle tracking

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INTRODUCTION

Systemic autoimmune diseases represent a family of different pathologies with common pathogenetic mechanisms and occur as a consequence of the loss of physiological tolerance to self antigens. The targets of the autoantibodies are ubiquitous antigens, so that tissue damage is generalized, resulting in multiple organ involvement, including the heart. Circulating antibodies do not always play a pathogenetic role but they represent specific markers of ongoing tissue damage[1].

The most frequent systemic autoimmune diseases are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary antiphospholipid syndrome, systemic sclerosis and systemic vasculitis. Patients affected by these diseases show an increased cardiovascular (CV) morbidity and mortality, only partially related to traditional CV risk factors and mainly due to enhanced atherosclerosis[2,3]. In particular, CV disease occurs at a younger age than in the general population and often remains asymptomatic, at least in the early stages[4].

The excess of CV morbidity and mortality could be explained by specific risk factors strictly related to autoimmune diseases, such as chronic inflammation, disease duration and activity and immunosuppressive therapy [glucocorticoids, methotrexate or anti-tumor necrosis factor α (TNFα)][5]. All components of the heart can be potentially affected by several pathogenetic mechanisms involving valves, coronary arteries, conduction system, myocardium, endocardium and pericardium such that a wide spectrum of clinical manifestations can occur; e.g. pericarditis, myocarditis and myocardial fibrosis, rhythm and conduction disturbances, coronaritis with ischemic heart disease, valvular diseases, pulmonary hypertension, syncope, diastolic or systolic heart failure[6].

Several studies have shown that chronic inflammation plays an important role in the development of atherosclerotic plaque[7] and endothelial dysfunction; in particular, a reduced bioavailability of nitric oxide (NO) seems to be the primum movens in this process[8]. Asymmetric dimethylarginine (ADMA) is widely recognized as the major endogenous inhibitor of NO-synthase and is considered an emerging CV risk factor. Elevated plasma ADMA levels have been found in patients affected by systemic autoimmune diseases, for example, in RA patients[9,10].

Since CV damage in autoimmune diseases is characterized by adverse outcomes, an early identification of patients at higher risk is very important to improve long term prognosis. CV imaging techniques provide a reliable approach to CV involvement in systemic autoimmune diseases, both for screening, diagnosis and follow up. In this report, we analyze the different characteristics and applications of various imaging modalities, pointing out advantages and disadvantages.

ULTRASOUND APPLICATIONS

Ultrasound techniques are easy and useful diagnostic tools that enable detection of cardiac morphological and functional damage. Transthoracic echocardiography is a reliable, inexpensive and non-invasive technique that allows an accurate evaluation of valvular abnormalities, pericardial diseases and ventricular wall motion defects, while Doppler analysis is useful in studying left ventricular diastolic filling, valvular functioning and pulmonary pressures. Rexhepaj *et al*[11] found significant differences in early diastolic flow velocity (E), atrial flow velocity (A) and E/A ratios in RA patients compared to a control group, suggesting that a subclinical impairment of left and right ventricular function is present in RA patients, when left ventricular thickness, dimensions and myocardial performance indexes were still normal.

A new clinical application of ultrasound imaging is transthoracic dipyridamole stress echocardiography with coronary flow reserve (CFR) evaluation (Figure 1). CFR is assessed in the distal left anterior descending coronary artery defined by the ratio between peak diastolic velocity during stress and at baseline (Figure 2). It is a highly sensitive (> 90%) diagnostic marker for coronary artery disease (CAD)[12,13] and, when associated with evaluation of the regional wall motion analysis, it becomes also highly specific[14]. In literature reports, a value of CFR < 2 has been shown to accurately predict the presence of coronary stenosis[13]. In the absence of epicardial coronary stenosis, an abnormal CFR may reflect an impaired coronary microcirculation in patients with reperfused myocardial infarct, arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy and other diseases[15]. The assessment of CFR also has a prognostic value, in that a reduced CFR correlates with a negative prognosis[16]. Recently, new evidence underlined that, not only the binary (normal-abnormal) response in CFR, but the continuous spectrum of CFR values is a strong independent prognostic predictor in patients with known or suspected CAD[17].

Hirata *et al*[18] found a significant reduction of CFR in premenopausal women with SLE compared with age- and sex-matched controls. They concluded that microvascular impairment in SLE could be explained by functional alteration of the endothelium, which is responsible for the decrease in vasodilation in response to pharmacological stress. Turiel *et al*[10] detected a significant impairment of CFR in 25 early RA patients, with disease duration less than 1 year and without any anti-rheumatic therapy. The reduced CFR in the absence of wall motion abnormalities at rest and during pharmacological stress showed a coro-

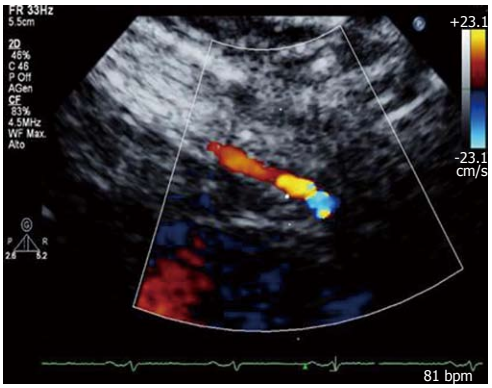

Figure 1 Color-Doppler signal in the distal left anterior descending coronary artery.

Figure 2 Example of coronary flow Doppler signal during dypiridamole-induced hyperaemia. S: Systolic flow; D: Diastolic flow.

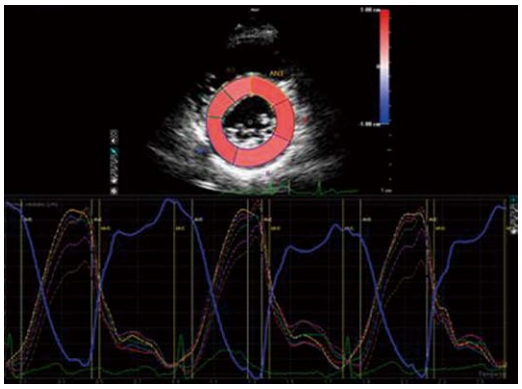

Figure 3 Speckle tracking analysis of radial strain in a left ventricle short axis view.

nary microcirculation involvement present in early RA that was associated with endothelial dysfunction.

Tissue doppler imaging (TDI) is a new imaging modality that allows the measurement of myocardial velocities. Until now, TDI has been considered a reliable tool for the assessment of myocardial deformation, but this method is limited by angle-dependency and only deformation along the ultrasound beam can be derived from velocities, while myocardium deforms simultaneously in 3 dimensions[19]. Recently, Birdane *et al*[20] demonstrated that RA patients had a significant impairment of TDI biventricular diastolic functional parameters compared to healthy controls, depending on age and use of steroids. To overcome TDI limitations, speckle tracking analysis has been introduced to evaluate myocardial strain along the longitudinal, circumferential and radial axes (Figure 3)[21].

Another very useful application of echocardiography in systemic autoimmune diseases is the echo transesophageal approach, which is widely recognized as more sensitive than a transthoracic evaluation for the detection of valvular lesions[22] and identification of intracardiac masses. In particular, Turiel *et al*[23] observed a large prevalence (61%) of valvular thickening or vegetations and/or potential embolic sources by a transesophageal echocardiographic approach in 56 patients with primary antiphospholipid syndrome followed up for 5 years. Recently, the development of 3-dimensional (3D) transesophageal echocardiography makes it possible to obtain cross-sectional visualization of the mitral, aortic and tricuspid valves, improving the diagnostic sensitivity compared to traditional 2D imaging[24]. The main advantages over conventional 2D echocardiography and the clinical applications of 3D echocardiography include more accurate and reproducible assessment of LV volumes, mass and ejection fraction, more accurate identification of wall motion abnormalities, study of the right ventricle and better understanding of valve and subvalvular apparatus abnormalities[25].

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE APPLICATIONS

Coronary artery calcification (CAC) has long been known to occur as a part of the atherosclerotic process and there is good evidence that the extent of CAC reflects the total coronary atherosclerotic burden[26]. The Agatston coronary calcium score assesses the extent and the density of calcification in the coronary tree[27]. Electron-beam computed tomography (EBCT) has been recognized as a highly sensitive tool that is able to detect small amounts of calcium in the coronary arteries. Radiation doses received during an EBCT study are much lower than invasive coronary angiography[28]. Recent studies, using multislice computed tomography (CT) with administration of iodinate contrast medium to visualize the coronary artery lumen, demonstrated accuracy in the detection of CAD[29]. This technique plays a diagnostic role not only for the detection of significant coronary artery luminal narrowing but also for the study of the atherosclerotic plaque texture. Moreover, it allows coronary calcium scanning along the coronary tree[30].

Kiani *et al*[9] evaluated coronary calcium by means of helical CT in 200 asymptomatic SLE patients and they found increased coronary calcium significantly related with plasma ADMA levels. However, while echocardiography and, mainly, stress echocardiography provide functional evaluations of the heart and the coronary tree, EBCT is limited to an anatomical and morphological description, without any functional information.

As reported above, CT requires the administration of iodinated contrast medium, which could induce intolerance symptoms or renal impairment and, moreover, patients undergo ionizing radiation exposure, which is much higher than in invasive coronary angiography. To overcome these limitations, coronary magnetic resonance (MR) angiography has been introduced in clinical practice with non-invasive visualization of the epicardial coronary arteries in the majority of subjects. It has high sensitivity, negative predictive value and overall accuracy for detecting CAD, but it is not an exercise-dependent exam[31]. Moreover, coronary MR angiography has an unsuccessful rate of 13%-14% depending on patient's features and coronary arteries with diameters less than 1.5 mm are not well visualized, so that the diagnostic accuracy of distal coronary artery lesions is inferior to multislice CT[27]. A meta-analysis of 48 studies showed that multislice CT has higher sensitivity and specificity than MR for non invasive detection of coronary artery stenosis[32]. Moreover, MR imaging protocols are variable and the imaging procedure is time-consuming[28].

Because of its non-invasiveness, MR angiography might be the most feasible imaging modality for the detection of CAD in patients with chronic kidney disease, as well as in young and asymptomatic patients. Panting *et al*[33] demonstrated the high sensitivity of myocardial perfusion MR in the detection of subendocardial hypoperfusion in patients with syndrome X, characterized by chest pain with normal coronary arteries, but these results were not supported by Vermeltfoort *et al*[34]. Pilz *et al*[35] confirmed the ability of MR to address the status of coronary microvascular impairment in the presence of normal epicardial vessels. In particular, coronary MR has been shown to be effective in detecting congenital coronary artery abnormalities[36].

Moreover, MR plays an important role in the diagnosis of myocardial inflammation that often coexists with different systemic autoimmune diseases[37,38]. Edwards *et al*[39] detected a high prevalence of late gadolinium enhancement in the left ventricular myocardium, not related to coronary artery territories in patients with SLE and Wagner granulomatosis, raising the possibility that myocardial damage is due to a combination of subclinical inflammatory and immunological processes.

Finally, coronary angiography remains the gold standard for the diagnosis and therapy of coronary epicardial stenosis and the assessment of the presence, extent and site of atheromatous lesions, but because of its invasiveness and potential high risk, should not be used as a screening tool[40].

NONINVASIVE IMAGING OF MYOCARDIAL PERFUSION

Single-photon emission CT (SPECT) is the most widely available nuclear technique to assess myocardial perfusion at rest and during stress (maximal exercise or pharmacological stress) using diffusible radiotracers[41]. While under normal conditions, myocardial blood flow during stress increases about 3 to 5 fold compared to during rest. In the presence of significant coronary stenosis, myocardial perfusion will not increase appropriately in the territory supplied by the stenotic artery, creating heterogeneous uptake. The available SPECT radiotracers are characterized by a rapid myocardial extraction and by a cardiac uptake proportional to blood flow[42]. Although SPECT is very sensitive, specificity is relatively lower[43], mainly due to the occurrence of artifacts due to soft-tissue attenuation. Disadvantages of SPECT are represented by the need to use radioactive materials. However, the diagnostic applications are based on the ability to detect a hemodynamically significant flow-limiting stenosis[44].

Positron emission tomography (PET) has higher spatial resolution than SPECT and provides absolute quantitative measurements of physiologic parameters; moreover, it has high sensitivity and specificity for detection of myocardial ischemia. Myocardial perfusion by PET is particularly useful in reducing the number of false-positive SPECT studies because of attenuation artifacts and allows a quantitative evaluation of myocardial blood flow[36].

The noninvasive study of myocardial perfusion by nuclear imaging could be a useful tool for the detection of subtle CV involvement in systemic autoimmune diseases, such as LES or RA[45], however, more study is required.

USEFULNESS OF BIOMARKERS OF ENDOTHELIAL DYSFUNCTION

In the field of systemic autoimmune disease, the new challenge for cardiology is the early diagnosis of subtle cardiac abnormalities in a preclinical stage. In addition to instrumental diagnostic tools, there is increasing evidence for a strict association between plasma levels of ADMA and CV disease in autoimmune diseases. Increased ADMA plasma levels have been demonstrated in different pathological conditions characterized by high CV risk, such as hypercholesterolemia[46], hypertrigliceridemia[47], peripheral arterial disease[48], hypertension[49], type 2 diabetes mellitus[50], acute coronary syndrome[51] and end-stage renal disease[52]. Recently, Kiani *et al*[9] described higher ADMA levels among SLE patients. In this group ADMA levels appeared to be associated with coronary calcium and poor prognosis. Recently, Turiel *et al*[10] found that increased plasma ADMA levels in early RA patients who were free of antirheumatic therapy were associated with a subclinical impairment of coronary microcirculation. Interestingly, the same authors[53] observed that after 18 mo of treatment with methotrexate or anti-TNFα agents, the improvement in inflammatory status and better control of disease activity were able to induce a significant amelioration of CFR.

Evaluation of the arterial distensibility and stiffness represents a good index of endothelial dysfunction and preclinical atherosclerosis. A reduced arterial distensibility disturbs coronary perfusion and has been related to increased CV risk[54]. Yildiz[55] reported a subclinical impairment of the aortic pulse wave velocity in chronic inflammatory rheumatic disorders, such as SLE, RA, psoriasis and systemic sclerosis, mainly due to the chronic inflammatory status.

CONCLUSION

CV involvement represents the most likely cause of morbidity and mortality in systemic autoimmune disease, with a large spectrum of clinical manifestations. However, the cardiologist should be able to make an early diagnosis of cardiac disease when it is still clinically silent. Echocardiographic techniques, with several applications, and in particular stress echocardiography with CFR evaluation, represent a first line approach for the assessment of endothelial dysfunction, such as ADMA, in addition to biomarkers. Nuclear medicine can provide a functional evaluation of myocardial perfusion, while CT and cardiac MR can be used to evaluate the morphological and anatomical integrity of coronary vessels. A careful study of CV function should be done in patients affected by systemic autoimmune diseases, early after diagnosis, to detect preclinical involvement and improve long-term prognosis.

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REVIEW

Atrial fibrillation and inflammation

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Abstract

Atrial fibrillation (AF) is the most common clinical arrhythmia. Recent investigations have suggested that inflammation might have a role in the pathophysiology of AF. In this review, the association between inflammation and AF, and the effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids, corticosteroids and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been investigated.

Key words: Atrial fibrillation; Inflammation; Statins

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EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Epidemiology

AF is the most common clinical arrhythmia and affects > 2.3 million people in the United States. Its prevalence increases with age and is as high as approximately 10% by the age of 80 years. It is associated with increased risk of stroke, heart failure and mortality[1].

Pathophysiology

Conventionally, the presence of multiple re-entrant circuits that originate in the atria and rapidly firing atrial activity in the pulmonary veins have been described as potential mechanism for atrial fibrillation (AF)[1]. Recent studies have also shown that there is an association between inflammation and AF[2]. The frequent occurrence of AF in patients with inflammatory conditions such as myocarditis and pericarditis has raised the possibility that AF is associated with local inflammation[3,4]. The finding of marked inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF, but not in control patients[5], and the presence of circulating autoantibodies against myosin heavy chain[6] supports this hypothesis. Further evidence on this issue has come from the increase in inflammatory markers such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP) and interleukin-6 in both paroxysmal and persistent AF, compared to control subjects[7-14]. In a multivariate analysis of The Cardiovascular Health Study that included 5806 individuals, CRP levels predicted both the presence of AF at baseline and the development of AF during follow-up, even after adjustment for potential confounding factors[7]. Moreover, longer duration of AF has been found to be associated with higher hs-CRP levels compared with shorter duration of AF, which indicates that there is a link between AF burden and systemic inflammation[8,15]. Similarly, hs-CRP has been found to be a significant predictor of early AF recurrence after cardioversion[11,16-20].

In this review, we focus on the evidence that supports systemic inflammatory mechanisms that might initiate and perpetuate AF. AF has been shown to be associated with inflammation, therefore, the question of whether anti-inflammatory agents can decrease AF rates has been raised. The effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids (PUFAs), corticosteroids and angiotensin-converting en-

zyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have been investigated in AF in observational and randomized studies.

STATINS AND AF

Observations

The role of inflammation on atrial electrophysiological and structural changes and the effects of atorvastatin on AF were first evaluated by Kumagai *et al*[21] in a canine sterile pericarditis model. They found that the atorvastatin group had lower CRP levels, less pronounced fibrosis in the atrial myocardium, and a shorter duration of AF.

Hypotheses

Since AF has been shown to be associated with inflammation, the question of whether anti-inflammatory agents could decrease AF rates has been raised. Therefore, the effects of statins, which have anti-inflammatory actions, have been investigated in observational and randomized studies.

Small studies

In the canine pericarditis model[21], canine rapid atrial pacing model[22] and canine ventricular tachy-pacing model[23], treatment with statins resulted in decreased inducibility and sustainability of arrhythmia. In human studies, statins have been effective in preventing AF after electrical cardioversion[24,25], in patients with stable coronary artery disease (CAD)[26], acute coronary syndrome[27,28], and pace makers[29], and in patients undergoing coronary artery bypass surgery[30-33]. In a randomized placebo-controlled study, Patti *et al*[30] have shown that atorvastatin at a dose of 40 mg significantly decreased AF rates after bypass surgery compared with placebo. Although peak CRP levels were no different between placebo and atorvastatin groups, CRP levels were higher in patients who developed AF compared to those who did not[30]. Kourliouros *et al*[34] have shown that the benefits of statins on postoperative AF are dose-related.

In contrast to these findings, several studies were unable to show any positive effects of statins on AF. Tveit *et al*[35] and García-Fernández *et al*[36] did not find any benefit of pravastatin and atorvastatin in reducing recurrence rates of AF after electrical cardioversion. Humphries *et al*[37] showed that, although there was no association with statin use and recurrence of AF, recurrence rate was significantly lower in patients who were also taking β-blockers. Richter *et al*[38] were unable to show any positive effects of statins after AF ablation in a retrospective study.

Larger studies

In a retrospective large study of 4044 patients who were undergoing coronary artery bypass grafting (CABG) surgery, Virani *et al*[39] showed that statins had no positive effects on the occurrence of AF. In analyses of two large randomized trials (PROVE IT-TIMI 22 and A to Z trial), McLean *et al*[40] demonstrated high-dose statins did not decrease AF risk. In a large retrospective study, Adabag *et al*[41] found no difference in AF incidence with statin treatment (P = 0.09) in CAD patients. However, statins decreased AF incidence in a subgroup of patients with heart failure (P = 0.04). In contrast, Hanna *et al*[42] showed that statin treatment decreased AF rates in patients with left ventricular dysfunction.

Meta-analyses

Several meta-analyses have been performed to investigate the effects of statins on AF and have indicated conflicting results depending basically on the selection of studies. Fauchier *et al*[43] have performed a meta-analysis that included six studies with 3557 patients. Three studies investigated the use of statins in patients with a history of paroxysmal AF (n = 1) or persistent AF undergoing electrical cardioversion (n = 2), and three investigated the use of statins in primary prevention of AF in patients undergoing cardiac surgery or after acute coronary syndrome. Overall, the use of statins was significantly associated with a decreased risk of AF compared with controls (OR = 0.39). The benefit of statins was more marked in secondary prevention of AF (OR = 0.33) than for new-onset or postoperative AF (OR = 0.60). In the meta-analysis of Liu *et al*[44], six randomized and 10 observational studies with 7041 patients were analyzed. The analysis of randomized controlled trials showed no significant effect of statins on AF development, and significant heterogeneity between individual studies. Subgroup analysis revealed that differences in AF detection methodology might have been the cause of heterogeneity. The analysis of observational studies demonstrated that statin use reduced the relative risk for AF significantly without significant differences between the trials. This favorable effect was greatest in the postoperative patients. A more recent meta-analysis of seven hypothesis-generating trials with 3609 patients and 15 hypothesis-testing trials with 68 504 patients showed a 30% reduction in relative risk of AF in the hypothesis-generating trials and no effect in the hypothesis-testing trials. There was no difference in the effects of statins on primary or secondary prevention of AF[45]. Patel *et al*[46] included 14 trials with 7402 patients in their meta-analysis and showed that statins decreased AF rates by 45%, new-onset AF by 32%, recurrent AF by 57%, recurrent AF after cardioversion by 42%, and postoperative AF by 58%.

Conclusion

The studies that have evaluated the benefits of statins on AF were mainly retrospective and observational, and the results are controversial. The results of meta-analyses are also controversial, depending on the selection of the studies that included different patient populations and different agents at different doses. The data are not yet sufficient to recommend these agents for the treatment of AF outside their approved indications.

Table 1 Statins and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Kumagai *et al*[21]	Prospective	Interventional canine sterile pericarditis model; atorvastatin	Atorvastatin group had lower CRP, shorter duration of AF, less inflammation in atrial tissues
Siu *et al*[25]	Retrospective	62 lone persistent AF, statin *vs* control	Lower recurrence rate in the statin group
Tveit *et al*[35]	Prospective	114 patients undergoing electrical cardioversion; pravastatin *vs* none	Pravastatin did not reduce the recurrence rate of AF
Young-Xu *et al*[26]	Prospective	449 patients with CAD were followed for 5 yr	Development of AF was lower in statin group
Ozaydin *et al*[24]	Prospective	48 patients undergoing cardioversion; atorvastatin *vs* none	81% relative risk reduction in AF recurrence
Ozaydin *et al*[31]	Observational	264 patients undergoing CABG surgery; any statin	Statin group had lower AF rates
Patti *et al*[30] (ARMYDA-3)	Prospective	200 patients undergoing CABG surgery; atorvastatin *vs* placebo	61% reduction in the odds of AF
García-Fernández *et al*[36]	Prospective	52 patients undergoing cardioversion; atorvastatin *vs* none	No significant difference in recurrence rate of AF
Ramani *et al*[27]	Retrospective	1526 patients with ACS; various statins	43% reduction in the odds
Humphries *et al*[37]	Prospective, observational	625 patiens undergoing cardioversion; any statin	74% reduction in the odds of AF with β-blocker; no effect alone
Hanna *et al*[42]	Data from a multicenter registry	25 268 patients with LVEF ⩽ 40%	Lipid-lowering drug use was associated with reduced odds of AF
Fauchier *et al*[43]	Meta-analysis	Six studies with 3557 patients	Statins were significantly associated with a decreased risk of AF (P = 0.02) Benefit of statins was more marked in secondary prevention of AF
Liu *et al*[44]	Meta-analysis	Six randomized and 10 observational studies with 7041 patients	No significant effect of statins on AF development (P = 0.09). Observational studies showed that statin use decrease the relative risk for AF by 23%. This effect was greatest in the postoperative patients
Patel *et al*[46]	Meta-analysis	14 trials with 7402 patients	Statin decreased AF rates by 45%. Decrease was most prominent in postoperative AF
Marín *et al*[32]	Prospective, observational	234 patients undergoing CABG surgery; any statin	48% reduction in the odds of AF
McLean *et al*[40]	Two large, randomized trials: PROVE IT-TIMI 22 and A to Z trial	8659 patients with ACS; low- *vs* high-dose statin therapy	Neither study showed decreased AF risk with high-dose statin therapy
Lertsburapa *et al*[33]	Observational	555 patients undergoing CABG surgery; any statin	40% reduction in the odds of AF
Kourliouros *et al*[34]	Retrospective	680 patients undergoing CABG surgery; atorvastatin and simvastatin	Improving benefits with higher dose
Virani *et al*[39]	Retrospective	4044 patients undergoing CABG surgery; any statin	No effect
Adabag *et al*[41]	Cohort	13 783 CAD patients	No difference in AF incidence with statin treatment (P = 0.09). However, AF was reduced in a subgroup of patients with congestive heart failure (P = 0.04)

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CRP: C-reactive protein; ACS: Acute coronary syndrome; LVEF: Left ventricular ejection fraction.

Future directions

Future large randomized, placebo-controlled clinical trials are required to clarify the effect of statins on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 1.

PUFAs AND AF

Observations

The observation that PUFAs reduce asynchronous contractile activity in rats suggests that they have antiarrhythmic effects on atrial muscle[47].

Hypotheses

The effects of PUFAs that have anti-inflammatory actions have been investigated in several studies.

Small studies

The reports about the effects of PUFAs on AF are more controversial. Calò *et al*[48] showed that pretreatment of 160 patients with fish oil capsules for 5 d before bypass surgery reduced the occurrence of postoperative AF. Saravanan *et al*[49] showed that fish oil 2 g/d did not reduce postoperative AF burden. PUFA supplementation in a randomized fashion in patients with implantable cardioverter defibrillators did not demonstrate any significant beneficial effect on ventricular tachyarrhythmias[50].

Larger studies

Two epidemiological studies have shown that PUFAs decrease the risk of AF[51,52]. Mozaffarian *et al*[51] reported that there was a negative correlation between the consumption of fish oil and risk of AF in a prospective study of 4815

Table 2 Polyunsaturated fatty acids and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Physicians' Health Study[54]	Prospective	17679 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Danish study[53]	Prospective	47949 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Rotterdam study[55]	Prospective	5184 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Mozaffarian *et al*[51]	Prospective	4815 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in fried fish/fish sandwich group Significantly, AF risk is lower in broiled/baked fish group
Calò *et al*[48]	Prospective	160 patients undergoing CABG surgery	AF risk is significantly lower in PUFAs group
Saravanan *et al*[49]	Prospective	Patients undergoing CABG surgery	AF risk is significantly lower in PUFAs group

PUFAs: Polyunsaturated fatty acids; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting.

adults aged ⩾ 65 years. The study of Macchia *et al*[52] supported these findings and showed that n-3 PUFA reduced the risk of hospitalization for AF. In contrast to these findings, the Danish Diet, Health and Cancer Study[53], Physicians' Health Study[54] and Rotterdam study[55] were unable to show any beneficial effects of fish consumption on AF.

Conclusion
The question of whether PUFAs have beneficial effects on AF development cannot be answered with the current evidence. Therefore, the use of PUFAs in the prevention of AF cannot be supported.

Future directions
More research is needed in this area to yield clearer evidence. A summary of the studies that have been performed on the effects of PUFAs on AF is given in Table 2.

CORTICOSTEROIDS AND AF

Observations
The first observation of the possible relationship between corticosteroids and AF rates came from the study of Ueda *et al*[56].

Hypotheses
The effects of corticosteroids that have anti-inflammatory actions on AF have been investigated in several studies.

Small studies
Chaney *et al*[57] found no difference in the incidence of postoperative AF between the those treated and untreated with methylprednisolone. Yared *et al*[58] have shown that dexamethasone decreases the incidence of new-onset AF in patients undergoing heart surgery. Similarly, in a small study, low-dose methylprednisolone decreased plasma CRP levels and AF recurrence after electrical cardioversion[17]. On the other hand, a randomized double-blind study did not show any beneficial effects of corticosteroids on postoperative AF and inflammation[59]. However, in a randomized study, Halonen *et al*[60] showed that corticosteroids decreased the incidence of postoperative AF and serum CRP levels. In a canine sterile pericarditis model, Goldstein *et al*[61] found that prednisone significantly attenuated the increase in CRP, reduced neutrophil infiltration, and eliminated atrial arrhythmia inducibility.

Meta-analyses
A meta-analysis of nine randomized controlled trials has suggested positive effects of perioperative corticosteroid use on AF occurrence and on length of stay after cardiac surgery[62].

Conclusion
Data are not yet sufficient to recommend corticosteroids for the treatment of AF.

Future directions
Large randomized studies are required to clarify this issue of corticosteroid treatment of AF. A summary of the studies that have been performed on the effects of corticosteroids on AF is given in Table 3.

ACEIs AND ARBs

Observations
In an animal study, it has been shown that angiotensin Ⅱ inhibitors might prevent atrial electrical remodeling[63].

Hypotheses
The effects of ACEIs and ARBs that have anti-inflammatory actions on AF have been investigated in observational and randomized studies.

Small studies
ACEIs or ARBs have been shown to decrease AF in left ventricular dysfunction[64,65] and left ventricular hypertrophy[66], and after cardiac surgery[67-70] and cardioversion[71-73]. In contrast, two previous studies were unable to show any beneficial effect of ACEIs and ARBs on postoperative AF[74,75] and patients in AF rhythm control strategy[76].

Larger studies
In larger studies, ACEIs or ARBs were effective in reducing AF incidence in left ventricular dysfunction or heart failure[77-79]. In a retrospective large study of 10023 con-

Table 3 Corticosteroids and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Chaney *et al*[57]	Prospective	60 patients undergoing CABG surgery; methylprednisolone	No effects of steroids on in the incidence of AF
Yared *et al*[58]	Randomized	235 patients undergoing CABG or valve surgery	Dexamethasone decreased incidence of new-onset AF
Yared *et al*[59]	Randomized	78 patients undergoing CABG or valve surgery	Dexamethasone did not decrease incidence of new-onset AF and inflammation
Dernellis *et al*[17]	Randomized	104 patients undergoing electrical cardioversion	Methylprednisolone decreased plasma CRP levels and AF recurrence
Goldstein *et al*[61]	Animal study	Canine sterile pericarditis model	Prednisone treatment decreased inflammation, and eliminated atrial arrhythmia inducibility
Halonen *et al*[60]	Randomized	241 patients undergoing CABG or valve surgery	Corticosteroids decreased the incidence of postoperative AF and serum CRP levels
Baker *et al*[62]	Meta-analysis	Nine studies with 990 patients undergoing CABG or valve surgery	Positive effects of perioperative corticosteroid use on AF occurrence

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CRP: C-reactive protein.

Table 4 Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Murray *et al*[76]	Prospective study, retrospective analysis	732 patients; AF rhythm control	No difference in AF recurrence
Madrid *et al*[71]	Prospective (electrical cardioversion)	154 patients; amiodarone only *vs* amiodarone + irbesartan	Recurrence of AF lower in irbesartan group
Zaman *et al*[73]	Prospective (electrical cardioversion)	47 patients; ACEI *vs* no ACEI group	Number of defibrillation attempts required for successful cardioversion was less in ACEI group
Ueng *et al*[72]	Prospective (electrical cardioversion)	125 patients; amiodarone only *vs* amiodarone + enalapril	Enalapril group had decreased rate of recurrence
Pedersen *et al*[65]	Prospective (post-MI)	1577 patients with LV dysfunction post-MI; trandolapril *vs* control	Trandolapril reduces AF
SOLVD[66]	Prospective study, but retrospective analysis (heart failure)	374 patients with depressed LV function; enalapril *vs* control	AF rate lower in ACEI group
Val-HeFT[78]	Prospective study, retrospective analysis (heart failure)	4409 patients with; valsartan *vs* control	ARB lower incidence of AF
CHARM[77]	Prospective study, retrospective analysis (heart failure)	5518 patients; candesartan *vs* control	ARB lowers incidence of AF in both normal and depressed ejection fraction
L'Allier *et al*[79]	Retrospective (hypertension)	5463 patients receiving ACEI *vs* 5463 patients receiving CCB	The incidence of AF was lower in ACEI group
Miceli *et al*[80]	Retrospective (post-CABG)	10023 patients undergoing isolated CABG; ACEI *vs* non-ACEI	ACEI treatment is associated with an increased risk of post-operative AF
Madrid *et al*[81]	Meta-analysis	Seven trials involving a total of 24849 patients	There was a significant statistical difference in the development AF with ACEI/ARB treatment
Kalus *et al*[82]	Meta-analysis	Four trials	There was a significant statistical difference in the development AF with ACEI/ARB treatment
Anand *et al*[83]	Meta-analysis	Nine randomized controlled trials	The use of ACEIs and ARBs had an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with heart failure
Jibrini *et al*[84]	Meta-analysis	11 randomized trials	Overall, inhibition of the RAAS reduced the RR of AF by 19%. Reduction in AF was greatest in patients after electrical cardioversion and in patients with heart failure
Healey *et al*[85]	Meta-analysis	11 randomized trials	Overall, ACEIs and ARBs reduced the relative risk of AF by 28%. Reduction in AF was similar between ACEI and ARB and was greatest in patients with heart failure. Overall, there was no significant reduction in AF in patients with hypertension

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MI: Myocardial infarction; CCB: Calcium channel blocker; LV: Left ventricle; RAAS: Renin angiotensin aldosterone system; RR: Relative risk.

secutive patients undergoing isolated CABG (3052 of whom received preoperative ACEI), Miceli *et al*[80] showed that the risk of new-onset postoperative AF ($P < 0.0001$) increased in patients treated with ACEI. They have stated that preoperative administration of ACEI in patients undergoing CABG might lower systemic vascular resistance and vasoplegia in the early postoperative phase, which results in hypotension and requires administration of more

fluids and inotropic and/or vasoconstrictor drugs that might increase the risk of AF.

Meta-analyses

Meta-analyses that have evaluated the benefits of ACEIs and ARBs have shown that, although their use is associated with low AF rates, efficacy rates differ between subgroups of patients mainly due to inclusion of different studies[81-85].

Conclusion

Both ACEIs and ARBs decrease AF incidence. However, the evidence is not sufficient to recommend these agents for the treatment of AF.

Future directions

Large randomized studies are still required to clarify the beneficial effects of ACEIs and ARBs on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 4.

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BRIEF ARTICLE

Hypertension and obstructive sleep apnea in Caucasian children

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Abstract

AIM: To evaluate the prevalence of hypertension and/or left ventricular hypertrophy (LVH) in children with a diagnosis of obstructive sleep apnea (OSA).

METHODS: A cross-sectional case series of consecutive, otherwise healthy children aged > 4 years, with polysomnography-proven OSA [apnea hypopnea index (AHI) > 1.5/h] is described. Echocardiography was performed on all subjects and left ventricular mass was calculated. Study subjects underwent additional investigation with 24-h ambulatory blood pressure (BP) monitoring.

RESULTS: Thirty children (21 males) were studied. Mean age was 8.9 years. Mean body mass index was 19.87 kg/cm^2. Mean AHI was 14.3/h. 10/30 (33%) of the study population met criteria for pre-hypertension (n = 3) or masked hypertension (n = 7) based on standard ambulatory monitoring criteria. All 10 children had systolic hypertension throughout the night with 5 of these also having elevated daytime systolic readings. There was a relationship between AHI and BP showing an increase of 1.162 percentile units in mean diastolic night BP (age, gender and height specific) per unit increase in AHI (P = 0.018). There were no subjects with LVH and/or right ventricular hypertrophy.

CONCLUSION: In our population of otherwise healthy Caucasian children, there was a high prevalence of hypertension that would not have been identified using standard office/clinic protocols.

Key words: Blood pressure; Sleep apnea; Cardiovascular complications; Pediatrics

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INTRODUCTION

It has been well established that obstructive sleep apnea (OSA) causes increased mortality and significant cardiovascular complications such as pulmonary hypertension, systemic hypertension, and cerebral and coronary artery disease in adults[1,2]. Importantly, Davies *et al*[3] reported a

significant decrease in nocturnal systolic blood pressure (SBP) following treatment of OSA with nasal continuous positive airway pressure in a group of adults with hypertension compared to untreated matched control subjects. These associations have not yet been fully studied in the pediatric population but there are several earlier reports describing pulmonary hypertension, cardiorespiratory failure, coma, and even sudden death associated with adenotonsillar hypertrophy and upper airway obstruction in children[4-6]. More recently, Marcus *et al*[7] reported elevated diastolic BP during both wakefulness and sleep in a group of 41 children with OSA compared to a control group of 26 with primary snoring. The degree of BP elevation was related to the severity of OSA. Subsequent pediatric studies have reported variable effects of OSA on BP in children, including elevation in either diastolic or systolic pressure alone, in part due to the variability in methodology and patient population studied[2,8,9]. Recently, O'Driscoll *et al*[10] described minute to minute increases in both heart rate and BP occurring with individual apneic events in children undergoing polysomnography (PSG). Finger photoplethysmography, a surrogate measure of BP, revealed that obstructive events during non-rapid eye movement sleep were associated with the largest increase in mean arterial pressure, particularly when associated with an arousal.

In adults, left ventricular mass (LVM), a surrogate measure of left ventricular hypertrophy (LVH), is a sensitive and specific predictor of clinical events attributed to cardiovascular diseases and it can be accurately measured by echocardiography[11,12]. Recently, Amin *et al*[8] reported that OSA in children is associated with structural changes of the heart, including increased LVM. They studied 28 children with OSA and identified abnormalities of LVM in 39% (*vs* 15% in snoring controls). They concluded that the increased LVM was not related to systemic hypertension, as few subjects had evidence of the latter condition. However, only a single BP measurement was obtained on all subjects, and it was recorded during wakefulness[8]. Subsequent papers by the same investigator have reported elevated SBP as measured by ambulatory monitoring as well as some evidence of diastolic dysfunction, both of which were associated with the severity of OSA[2,13]. Only one group to date has reported BP changes consistent with a diagnosis of pediatric hypertension related to OSA in children[9]. Our aim was to confirm a relationship between OSA and hypertension in children and to evaluate the effect of increasing severity of OSA on BP. Our paper adds to the current body of knowledge by confirming a high prevalence of hypertension in otherwise healthy children with PSG-proven OSA that appears to be related to the severity of OSA.

MATERIALS AND METHODS

A cross-sectional case series of consecutive, otherwise healthy children aged > 4 years with PSG-proven OSA is described. Children with cardiac or renal disease and those with known risk factors for hypertension were excluded. Eligible subjects were identified by the principal investigator (VK) following confirmation of OSA by PSG. Families were invited to participate when PSG results were discussed with them *via* telephone. Those indicating an interest in the study were then contacted by one of the study coordinators (AA, PR) and consent was obtained at that time from parents of subjects < 8 years. Both parental and subject consent was obtained in those aged 12 years and older. Assent was obtained in all children aged 8 to 12 years. Echocardiography was performed on all subjects, as per our routine clinical care. Study subjects underwent additional investigation with 24-h ambulatory BP monitoring (see below). Medical charts were reviewed for demographic and medical information in order to confirm that subjects met inclusion criteria. Ethics approval was obtained by the University of Calgary prior to enrollment of the first subject.

Laboratory PSG

Computerized laboratory PSG (Sandman® NT), (Nellcor Puritan Bennett, Ottawa, ON) was performed according to American Thoracic Society guidelines at the Alberta Children's Hospital sleep laboratory[14]. Monitoring included electroencephalogram (C4-A1, C3-A2, O1-A2, O2-A1), electrooculogram, submental electromyogram, electrocardiogram, oxygen saturation monitoring, chest, abdominal wall, and sum channel movements using respiratory inductance plethysmography, bilateral tibial electromyograms, nasal/oral airflow using a thermistor device, nasal pressure, end-tidal carbon dioxide monitoring, and transcutaneous carbon dioxide monitoring. Sleep architecture was determined using standard criteria[15]. A registered sleep technologist scored sleep architecture and respiratory events using standard scoring criteria. Obstructive apnea was defined as a reduction in airflow of > 80% associated with continued abdominal and chest wall motion lasting 2-3 breaths in duration, obstructive hypopnea was defined as a reduction in airflow of > 50% but < 80% associated with continued abdominal and chest wall motion associated with EEG arousal and/or > 3% drop in oxygen saturation, and central apnea was defined as a reduction in airflow of > 80% associated with no evidence of abdominal or chest wall motion lasting 20 s in duration, or shorter, if associated with > 3% drop in oxygen saturation. Central apneas occurring in association with body movements or sighs were not included in the overall apnea hypopnea index (AHI). Mixed apnea, consisting of both central and obstructive components, was scored using the same criteria as obstructive apneas. OSA was defined as an overall apnea hypopnea index of > 1.5/h of total sleep time[14,16-19].

Echocardiography

2D mode echocardiography was used to assess the LVM using the methodology of Devereux *et al*[20]. Measurements were made with the subject in a supine, resting state for at least 5 min in a quiet, darkened examination room.

All studies were interpreted by a blinded study cardiologist (MG). As per the de Simone *et al*[21] protocol, a LVM index was calculated. This calculation takes into consideration the impact of body size on heart size and improves the accuracy of the measurements. LVM index was calculated by dividing the measured LVM by subject height raised to the power 2.7.

Ambulatory BP monitoring

Ambulatory cuff BP was measured using the QuietTrack® instrument (manufacturer Welch Allyn). Measurements were obtained using the right arm and the appropriate cuff size, based on standard criteria[22]. Calibration was performed prior to recording of BP values. Measurements were obtained every 20 min during the day (start at usual wake time) and every 30 min during the night (start at usual bedtime). All subjects were asked to maintain their usual activity but to remain still during daytime measurements. Using the software provided by Welch Allyn, average systolic and diastolic BP and BP load (percentage of BP measurements > 95th percentile) were calculated for each subject and compared to standard normative data for ambulatory BP monitoring (ABPM) in children adjusted for age, gender and height percentiles[22]. Nocturnal, daytime, systolic and diastolic hypertension were defined using standard age, gender and height criteria for children[22]. Briefly, children with a SBP load greater than 25% met criteria for hypertension. If associated with a normal mean SBP but high clinic BP, they were classified as prehypertensive. If the mean ambulatory SBP was greater than the 95th percentile, they were classified as having either masked hypertension (normal clinic BP) or hypertension (clinic BP also greater than the 95th percentile)[18]. BP data was also analyzed by converting mean daytime and night-time measurements to body mass index (BMI) and height specific percentiles according to published standards[23,24]. All ambulatory monitoring data were analyzed by the study nephrologist (JM).

Statistical analysis

A convenience sample size of 30 children with OSA was studied. Based on previous reports[8], we anticipated a prevalence of LVH in children with OSA of approximately 5%. Based on these predictions, 2 study subjects with evidence of LVH were needed to provide an exact binomial confidence interval of 0.8% to 22.1%.

To describe the relationship between hypertension and apnea AHI, apnea arousal index (AAI), BMI, and BMI percentile, logistic regression coefficients were estimated for the slopes and intercept to examine whether there was a relationship between the variables. The relationship between BP as a numerical value (age, gender and height specific percentiles) and simultaneous polysomnographic data (AHI, AAI, and hypoxemia index) were examined *via* multiple linear regression. Multiple regression was used to examine each of the responses separately (mean systolic day/night BP, mean diastolic day/night BP as age and gender percentiles) *vs* AHI, AAI and BMI percentiles, hence a conservative significance level of 0.0125 (Bonferroni correction) for the slopes should be considered when interpreting their significance. All BP parameters were analyzed separately for day and night results.

Table 1 Demographic and polysomnographic data on subjects with (n = 10) and without (n = 20) any form of hypertension

	Hypertension, OSA (n = 10)	OSA, no hypertension (n = 20)	95% CI for difference
Age (yr)	8.61	9.01	-1.65, 2.46
Male, n (%)	8 (80)	13 (65)	-54.93, 24.93
Body mass index (kg/cm^2)	19.16	20.23	-2.89, 5.03
Desaturation index (%)	1.09	1.36	-2.68, 3.22
Oxygen saturation mean (%)	96.4	96.1	-1.30, 0.71
Oxygen saturation minimum (%)	87.3	85.6	-6.36, 3.02
Spontaneous arousal index (/h)	3.5	3.7	-1.20, 1.67
Apnea arousal index (/h)	10.8	3.7	-24.52, 10.25
Apnea hypopnea index (/h)	21.5	10.6	-39.13, 17.25

Means shown for all numerical variables. Number and percentage for categorical. OSA: Obstructive sleep apnea.

RESULTS

A total of 43 children met inclusion criteria between April 1, 2004 and January 31, 2006. Of these, 30 (21 males) agreed to participate. Children were aged on average 8.9 years (range 4 years and 1 mo to 15 years and 1 mo). The mean BMI was 19.87 kg/cm^2 (range 13.6-44.1 kg/cm^2). Nine of 30 (26%) subjects were obese based on a BMI percentile > 95. The mean AHI value for the group was 14.3/h (range 1.5-125.2/h). The mean hypoxemia index (percent of total sleep time with oxygen saturation < 90%) was 1.3% (range 0%-19.9%).

10/30 (33%) of the subjects had systolic hypertension (> 25% measurements > 95th percentile for age and height percentiles) with the vast majority (90%) of high measurements occurring during the night. Four of the 10 also had elevated daytime systolic readings and 2 of the 10 had elevated diastolic readings in the night. As per our current protocol, manual BP with ABPM was not done at the same time as clinic baseline BP measurements. Of the polysomnographic variables, there were no significant relationships between the AHI, hypoxemia index or AAI variables and BP status overall (Table 1). A logistic regression of hypertension status on AAI, BMI and AHI was performed. All showed a coefficient of positive numerical value, which suggests an indication of positive relationship with hypertension, but none reached statistical significance.

The relationship between AHI and hypertension was also analyzed as categorical; that is, for each of the day/night BPs using the variable "percentage of time with systolic (diastolic) BP greater the 95th percentile for day (night)". Abnormal was defined as > 25%. Although inspection of the dot plots suggested a trend towards higher AHI in those with nocturnal systemic hyperten-

Table 2 Relationship between mean blood pressure (age and gender percentiles) and apnea hypopnea index in children with obstructive sleep apnea (adjusted for body mass index percentile)

BP (percentile)	Severity of OSA	Coefficient (increase of BP in percentual points)	*P* value
Diastolic day	AHI increase of 1/h	1.211	0.046
Systolic night	AHI increase of 1/h	1.964	0.025
Diastolic night	AHI increase of 1/h	1.162	0.018

OSA: Obstructive sleep apnea; AHI: Apnea hypopnea index; BP: Blood pressure.

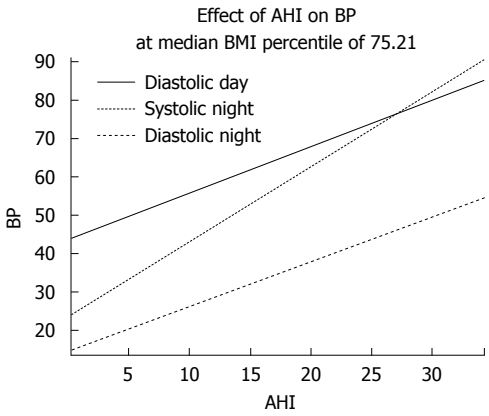

Figure 1 Graphical illustration showing the relationship between apnea hypopnea index and blood pressure. AHI: Apnea hypopnea index; BP: Blood pressure; BMI: Body mass index.

sion, they did not meet statistical significance. There were two outliers whose extreme AHI and AAI values set them clinically apart from the rest of the data. We elected to exclude these and re-analyze in the event that they were affecting the results of the others. The conclusions were unchanged.

A regression analysis on this subset of 28 subjects, using mean BP values, revealed a linear relationship between AHI and mean daytime diastolic BP, as well as mean systolic night and mean diastolic night BP (Table 2). BMI percentile was identified as a confounder only. The effect of AHI on BP was adjusted for this. As seen in Table 2, for every unit change in AHI, mean systolic night BP (as an age and gender specific percentile) increased by 1.964 percentile points ($P = 0.025$). The interpretations of the other coefficients shown were similar. This relationship is shown in graphical form in Figure 1.

LVM was within normal limits (less than the 95th percentile for age) in all subjects and there was no evidence of LVH in any of the children. Right ventricular pressures were less than one-third systemic pressures in all subjects, indicating absence of right ventricular hypertrophy.

DISCUSSION

This study provides strong support that Caucasian children with OSA have a significantly increased prevalence of hypertension. We were able to show a linear relationship between the AHI and both nocturnal systolic and diastolic mean BP as well as daytime mean diastolic BP in children with OSA (Table 2). This confirms the recent report of Li *et al*[9] concluding that OSA in children is an independent risk factor for nocturnal hypertension. Although evidence of target organ damage due to hypertension is most correlated with night time SBP in children[22], we did not identify evidence of increased LVM in any of our 30 subjects. This is not in keeping with previous reports and may be due to differences in demographics. Prior reports have included evaluation of obese and non-Caucasian children. These factors were controlled for in the overall statistical analysis but perhaps they contributed something to the findings of LVH in those populations[8,13]. We did not specifically study mitral valve inflow as part of our protocol for this study but plan to study diastolic dysfunction in a prospective future analysis to verify the previous report by Amin *et al*[2,13] and to further describe the relationships between OSA, BP and cardiac function.

Our findings are in contrast to a recently published meta-analysis concluding there was no relationship between OSA in childhood and elevated BPs[25]. This analysis included only 5 papers with the vast majority of BP measurements performed during wakefulness. Additionally, as noted above, the populations studied included a significant proportion of obese (12%-29%) and/or African American/Hispanic children (up to 51%). Race and obesity are independent risk factors for hypertension and may act as confounders when specific relationships between OSA and BP are being examined.

Previous pediatric studies using ABPM also failed to show this relationship. Amin *et al*[26] evaluated 60 snoring children and did not find any evidence of hypertension in the group. However, the normative references used for their analysis were not specific for ambulatory BP measurements, which could have resulted in inappropriate interpretations. A subsequent and more recent publication by the same investigators[13] evaluating morning BP surge (nocturnal dip) and BP load by ABPM reported an independent association between elevation of all these parameters and increasing AHI (2).

The majority (70%) of children with abnormal BP findings in our study met criteria for masked hypertension, defined as normal day time clinic BP but elevated ambulatory levels. The estimated prevalence of masked hypertension in the general pediatric population is approximately 6%[27] and is associated with progression to sustained clinical hypertension and higher LVM[28]. In adults, masked hypertension has been associated with an increased cardiovascular risk[29] and with progression of chronic kidney disease[30]. The greatly increased prevalence of masked hypertension in our study population is a remarkable finding. Ten percent of the children studied had pre-hypertension [elevated clinic BP and BP load (SBP > 95th percentile for 25%-50% of ABPM readings) with a normal mean ambulatory BP]. Pre-hypertension is an in-

dicator of increased BP variability, which is also associated with target organ damage, at least in adults[31].

In summary, 30% of otherwise healthy Caucasian children with a new diagnosis of OSA had evidence of nocturnal systolic hypertension. This study adds further support to the hypothesis that hypertension due to OSA may begin at a much younger age than previously thought suggesting a potentially powerful role in the prevention of adult hypertension and cardiovascular disease. Currently, ABPM is not part of the standard clinical evaluation of children with OSA. Such measurements during a sleep study may, in fact, cause some sleep disruption and affect the overall PSG results. Further evaluation of the effect of ABPM on sleep architecture is warranted, and if shown to not skew PSG results, consideration should be given for inclusion of BP monitoring during PSG in children as part of the standard testing regimen. Alternatively, surrogate measures of BP, such as finger photoplethysmography, could be further studied to identify how the data obtained minute to minute relates to overall BP status. In the interim, ABPM should be considered following PSG diagnosis of OSA in children as part of the evaluation for end-organ involvement.

COMMENTS

Background

Obstructive sleep apnea (OSA) is well established as a cause of hypertension and cardiovascular disease in adults. The pediatric literature related to these issues is preliminary and mixed. We were able to show that blood pressure (BP), but not ventricular geometry or function, is influenced by the severity of OSA in otherwise healthy, Caucasian children.

Research frontiers

Marcus *et al* reported elevated diastolic BP during both wakefulness and sleep in children that was related to the severity of OSA. Amin *et al* reported structural changes of the heart in children with OSA that did not appear to be BP, based on one measurement obtained while awake. Subsequent papers by the same investigator have reported elevated systolic BP, as measured by ambulatory monitoring, as well as some evidence of diastolic dysfunction, both of which were associated with the severity of OSA. Only one previous group to date has reported BP changes consistent with a diagnosis of pediatric hypertension related to OSA in children.

Innovations and breakthroughs

More recent publications have included data related to both wake and sleeping BP measurements in homogeneous groups of children and may be more helpful in identifying true relationships. The inclusion of obese and/or mixed race children in study populations adds complexity to the interpretation of findings related to risk attributed to OSA on BP and cardiac geometry and function.

Applications

The relationship between OSA and cardiovascular disease may begin at a very young age. Learning more about the specifics in children will potentially allow for prevention of a significant proportion of adult cardiovascular disease and/or hypertension and related morbidities.

Peer review

This article on the relation of sleep apnea to hypertension is of great interest. It is unfortunate that there were no subjects with left ventricular hypertrophy, but it is significant that there is a high prevalence of hypertension in the nighttime using 24 h ambulatory BP monitoring.

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Meetings

Events Calendar 2010

January 12-13
Riyadh, Saudi Arabia
1st International Cardiovascular Pharmacotherapy Conference

January 17-21
Hollywood, United States
22nd Annual International Symposium on Endovascular Therapy

January 20-23
Sao Paulo, Brazil
World Cardiology, Metabolism and Thrombosis Congress

January 21-24
Phoenix, United States
13th Society for Cardiovascular Magnetic Resonance Annual Scientific Sessions

January 28-30
Brussels, Belgium
29th Belgian Society of Cardiology Annual Scientific Meeting

January 28-31
Nashville, United States
31st Annual Meeting of The American Academy of Cardiovascular Perfusion

February 3-6
Snowbird, United States
35th Annual Cardiovascular Conference at Snowbird

February 4-5
Leuven, Belgium
Leuven Symposium on Myocardial Velocity and Deformation Imaging

February 6-9
St. Petersburg, United States
10th Annual International Symposium on Congenital Heart Disease

February 8-10
Tel Aviv, Israel
10th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy

February 11-12
London, United Kingdom
2nd National Chronic Heart Failure and Hypertension

February 18-21
Istanbul, Turkey
The 2nd World Congress on Controversies in Cardiovascular Disease (C-Care)

February 22-25
Maui, United States
Arrhythmias & the Heart Symposium

February 22-26
Cancun, Mexico
15th Annual Cardiology at Cancun-Advances in Clinical Cardiology and Multi-Modality Imaging

February 25-28
Valencia, Spain
First International Meeting on Cardiac Problems in Pregnancy

February 26-28
Hong Kong, China
International Congress of Cardiology

February 28-March 4
Scottsdale, United States
International Congress XXIII on Endovascular Interventions

February 28-March 5
Keystone, United States
Keystone Symposia: Cardiovascular Development and Repair (X2)

March 3-5
Kish Island, Iran
Islamic Republic of 4th Middle East Cardiovascular Congress

March 4-7
Newport Beach, United States
30th Annual CREF: Cardiothoracic Surgery Symposium

March 7-12
Snowmass Village, United States
Interventional Cardiology 2010: 25th Annual International Symposium

March 14-16
Atlanta, United States
American College of Cardiology 59th Annual Scientific Session

March 18-20
Rome, Italy
VIII Congress of the Italian Society of Cardiovascular Prevention

March 18-20
Prague, Czech Republic
XI International Forum for the Evaluation of Cardiovascular Care

March 24-25
Jeddah, Saudi Arabia
12th KFAFH Cardiovascular Conference: A balanced approach to treatment of cardiovascular diseases

April 8-11
Guangzhou, China
The 12th South China International Congress of Cardiology

April 14-15
Tel Aviv, Israel
The 57th Annual Congress of the Israel Heart Society in Association with The Israel Society of Cardiothoracic Surgery

April 15-18
Izmir, Turkey
59th European Society for Cardiovascular Surgery International Congress

May 5-7
Prague, Czech Republic
EuroPRevent 2010-Cardiovascular Prevention: a Lifelong Challenge

May 8-9
St. Paul, United States
Controversies in Cardiovascular Disease: Practical Approaches to Complex Problems: Medical and Surgical

May 12-16
Marrakesh, Morocco
7th Metabolic Syndrome, type II Diabetes and Atherosclerosis Congress

May 17-20
Whistler, Canada
6th IAS-Sponsored HDL Workshop on High Density Lipoproteins

May 21-22
Sydney, Australia
3rd Cardiovascular CT, Concord Conference 2010

May 29-June 1
Berlin, Germany
Heart Failure Congress 2010

June 1-4
Seoul, Korea, Republic of
9th Asian-Pacific Congress of Cardiovascular & Interventional Radiology (APCCVIR 2010)

June 16-19
Beijing, China
World Congress of Cardiology Scientific Sessions

June 17-19
Port El Kantaoui, Tunisia
The 7th Tunisian and Europeans Days of Cardiology Practice

July 1-3
Singapore, Singapore
6th Asian Interventional Cardiovascular Therapeutics Congress

July 16-19
Berlin, Germany
Frontiers in CardioVascular Biology 2010-1st Meeting of the CBCS of the ESC

July 24-27
Vancouver, Canada
15th World Congress on Heart Disease, Annual Scientific Sessions 2010

August 13-15
Krabi, Thailand
East Meets West Cardiology 2010

September 16-18
Athens, Greece
5th International Meeting of the Onassis Cardiac Surgery Center

September 25-29
Belo Horizonte, Brazil
65th Brazilian Congress of Cardiology

September 30-October 2
Berlin, Germany
5th International Symposium on Integrated Biomarkers in Cardiovascular Diseases

October 10-13
Rochester, United States
26th Annual Echocardiography in Pediatric and Adult Congenital Heart Disease Symposium

October 16-19
Copenhagen, Denmark
Acute Cardiac Care 2010

October 20-23
Boston, United States
2010 Cardiometabolic Health Congress

November 25-26
London, United Kingdom
13th British Society for Heart Failure Annual Meeting

December 9-11
Lisbon, Portugal
Heart, Vessels & Diabetes-The European Conference

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Acknowledgments

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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

Volume with supplement

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Issue with no volume

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

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

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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

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

Patent (list all authors)

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

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Write as mean ± SD or mean ± SE.

Statistical expression

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