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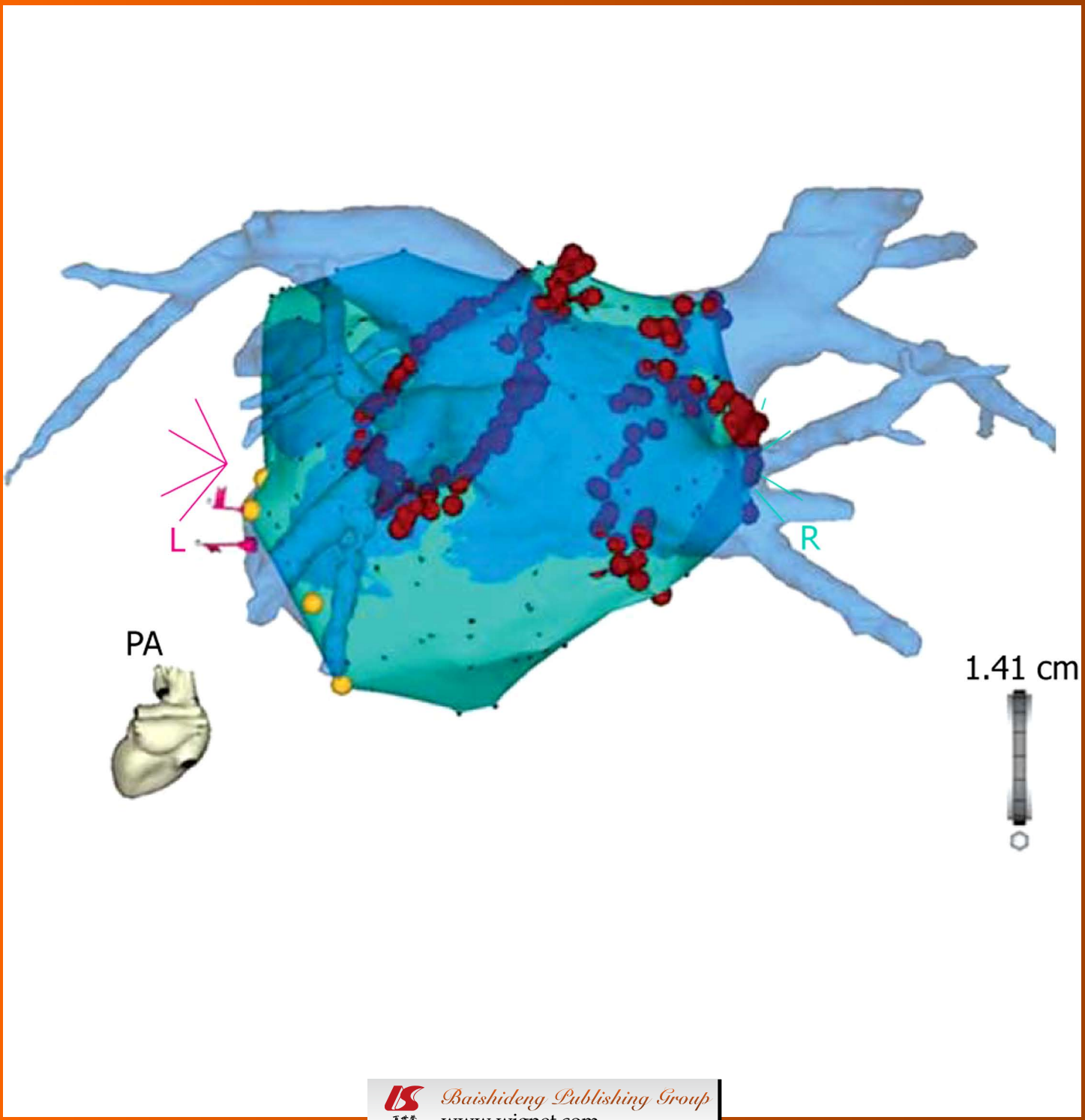

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EDITORIAL

MDCT in the diagnostic algorithm in patients with symptomatic atrial fibrillation

Christian Sohns, Dirk Vollmann, Lars Luethje, Marc Dorenkamp, Joachim Seegers, Jan D Schmitto, Markus Zabel, Silvia Obenauer

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Abstract

Atrial fibrillation (AF) is the most common supraventricular arrhythmia and a major cause of morbidity. Arrhythmogenic foci originating within the pulmonary veins (PVs) are an important cause of both paroxysmal and persistent AF. A variety of endovascular and surgical techniques have been used to electrically isolate the PV from the left atrium. Pulmonary venography for localization of the PV ostium can be difficult to perform during the ablation procedure. While the anatomy of the PV is patient-specific, non-invasive imaging techniques may provide useful diagnostic information prior to the intended intervention. In this context, multidetector computed tomography (MDCT) visualization of the left atrial and PV anatomy prior to left atrial ablation and PV isolation is becoming increasingly important. MDCT imaging provides pre-procedural information on the left atrial anatomy, including atrial size and venous attachments, and it may identify potential post-procedural complications, such as pulmonary vein stenosis or cardiac perforations. Here, we review the relevant literature and present the current "state-of-the-art" of left atrial anatomy, PV ostia as well as the clinical aspects of refractory AF with MDCT imaging protocols and procedural aspects of PV ablation.

Key words: Atrial fibrillation; Multidetector computed tomography; Pulmonary veins; Pulmonary vein ablation

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INTRODUCTION

Radiofrequency catheter ablation (RFCA) is a potentially curative treatment modality for atrial fibrillation (AF) originating in the pulmonary veins (PVs)[1]. RFCA for AF can be employed to either eliminate ectopic pulmonary venous foci or electrically isolate the PVs[2-4]. For precise application of radiofrequency lesions, accurate visualization and knowledge about the individual pulmonary vein (PV) anat-

omy is necessary. For this purpose, the value of different imaging techniques to guide RFCA procedures is increasingly recognized. However, there is still considerable debate about the ideal diagnostic imaging tool for PV isolation[5-7].

Real-time acquisition of anatomic information on left atrial and PV anatomy can be obtained by intracardiac echocardiography (ICE)[8,9]. Advantages of this imaging technique include the possibility to obtain *in vivo* information of left atrial anatomy including the PVs in relation to the position of the ablation catheter. Furthermore, ICE facilitates a save transseptal puncture, and allows monitoring for acute complications, e.g. pericardial effusion.

Alternatively, for the acquisition of anatomic information of PV anatomy before RFCA, three-dimensional (3-D) imaging techniques such as multidetector computed tomography (MDCT), cardiac MRI (CMR) and cardiac C-arm computed tomography have been applied[5,6]. MDCT has been proven to provide accurate and detailed information on PV anatomy[7]. CMR imaging has been applied to detect anomalous insertion of PVs and to evaluate PV stenosis after RFCA[10-12]. The advantage of CMR imaging is the lack of ionizing radiation exposure. Nevertheless, there are several relative contraindications of CMR. Thus, MR imaging can not generally be performed in patients with claustrophobia or pacemakers, or in patients who cannot tolerate the considerably longer imaging times of MR imaging.

Accordingly, the purpose of our review was to evaluate the current role of MDCT to provide a "road map" for subsequent RFCA (Figure 1).

ATRIAL FIBRILLATION

AF usually starts as a paroxysmal arrhythmia, with approximately 60% of patients converting spontaneously to sinus rhythm (SR). Approximately 40% of patients develop persistent AF requiring medical or electrical intervention to restore SR[13]. Up to 50% of patients develop recurrent AF within the first year of onset[13,14]. Patients with AF have a mortality rate twice that of control subjects and are exposed to considerable morbidity, such as stroke[13,14]. The leading symptoms associated with AF are palpitations, reduced exercise capacity and exertional dyspnoea, and are related to the rapid and irregular ventricular rate.

The major complication of AF is the formation of atrial thrombi with the risk of systemic embolization, placing these patients at considerable risk for stroke. The electrocardiographic characteristics of AF are an undulating baseline EKG with absent P waves, an atrial rate of 300-600 beats per minute, and an irregular ventricular response. Paroxysmal AF is usually found in the absence of structural heart disease. Over the years it may progress to persistent AF if substantial atrial remodelling has occurred. AF is considered persistent if it lasts for more than 7 d or if it requires cardioversion for termination. Atrial fibrillation is usually treated first with antiarrhythmic drugs. However, the use of these drugs is limited by relatively low efficacy and by the potential for proarrhythmic side effects[13]. Cardioversion has a high initial success rate for treatment of AF, especially in patients with a recent onset, but it is associated with a recurrence rate of 60% at 6 mo after treatment[14]. Thus, both pharmacologic therapy and cardioversion have demonstrated only limited success in preserving SR during long-term follow-up[14].

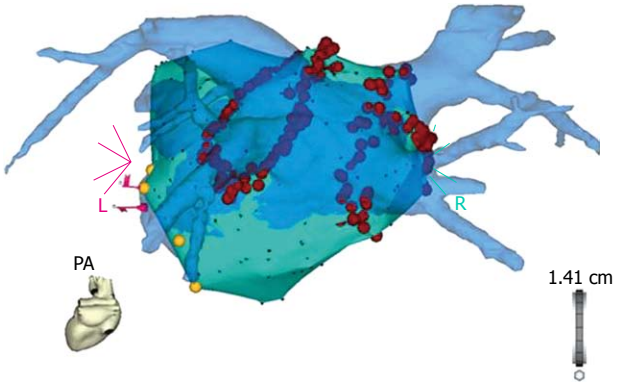

Figure 1 The blue 3D anatomical shell of the left atrium and the pulmonary veins, as acquired by pre-procedural computed tomography, is merged with the grey anatomical shell that was constructed with electro-anatomical mapping during the procedure (CARTO merge). Note the red ablation tags which mark the circumferential ablation lesions around the pulmonary vein ostia.

RELATION BETWEEN LEFT ATRIAL, PULMONARY VENOUS ANATOMY AND ATRIAL FIBRILLATION

It has been known for some time that the muscular sleeves of the distal PV are a frequent source for ectopic foci[1], with the left superior PV accounting for half of the ectopic foci initiating AF[5,6,14]. In these patients, the myocardium of the left atrium appears to extend a variable distance into the distal PV, and this is the region of interest which appears to be the origin of the ectopic discharges[14,15]. Thus, the treatment of AF is now focusing on the interruption of the conduction pathways by wide circumferential ablation around the PV ostia[16-18] (Figure 1). RFCA consists of placing a catheter with an ablation electrode at its tip into the left atrium, *via* percutaneous femoral vein access. This special catheter is forwarded through the inferior vena cava and into the right atrium under fluoroscopic monitoring. Subsequently, the catheter is advanced into the left atrium *via* a transseptal puncture. The ablation procedure itself, even in the most experienced hands, is tedious and usually lasts several hours[4].

IMAGING BEFORE RFCA

In RFCA, a significant portion of the procedural fluoroscopy time is spent imaging the PV anatomy if no other imaging technique is utilized[2-4]. Fluoroscopic imaging of the PV anatomy is achieved either by retrograde application of contrast material into the distal PVs or indirectly by positioning a circular mapping catheter within the PV. Difficulty may arise, however, in establishing all the

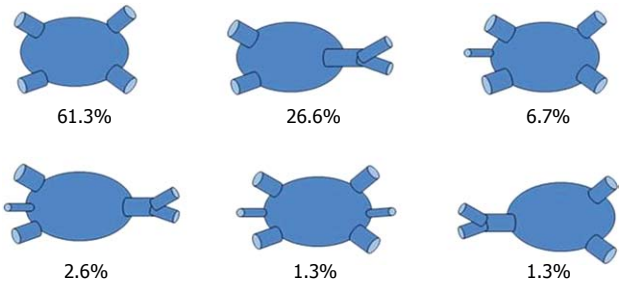

Figure 2 Variants of the left atrium and pulmonary vein-anatomy.

necessary anatomic information if only fluoroscopy is used. ICE is useful, and does not increase the radiation burden, but the echocardiographic transducer has a small field of view and this may be inadequate for visualizing the relationships between the left atrial wall and distal PV, especially when the left atrium is dilated[14]. Furthermore, ICE probes are expensive and require an invasive access[14]. Successful RFCA outcome is not only defined by elimination of AF but also by minimizing complications, and both require a precise understanding of the complex atrio-pulmonary venous anatomy. Unfortunately, the classical anatomy is found in only 70% of cases[14]. The remaining 30% of individuals have pulmonary venous anatomic variants; thus, imaging provides an important "road map" for the electrophysiologist (Figure 2). Successful pre-interventional imaging includes identification of the number, location and angulations of the PVs. In addition, exclusion of atrial or atrial appendage thrombi is mandatory, because their presence is a contraindication for the ablation procedure.

ANATOMIC CONSIDERATIONS

By application of MDCT imaging, the PV ostium needs to be identified at its juncture with the left atrium (Figure 1). The location, length and number of veins also need to be identified (Figure 2). Today, electro-anatomic mapping systems (e.g. CARTO, Biosense Webster; NavX SJM,) are utilized for real-time anatomical reconstruction of the left atrium (LA) in many centres. The technology and the technique have also been described in detail earlier[19,20]. The operator manually places the catheter tip in stable endocardial contact at multiple (at least 50) locations throughout the LA. A three-dimensional virtual shell of the mapped chamber is created by software interpolation over the coordinates of multiple endocardial points, and its volume is automatically reconstructed and "merged" with previously acquired images, e.g. a CT image of the LA (Figure 1).

Radiologists commonly divide PVs into segments, with a segment defined as the vein from the ostium to its first branch point. An ostial branch is defined as a venous branch within 5 mm of the atriopulmonary venous junction. The intervenous carina is identified as the portion of the atrial wall interposed between separate ipsilateral PVs[15]. Classically, there are four PVs with separate ostia into the left atrium. However, accessory PV can be present. A common or conjoined vein occurs when superior and inferior veins join proximal to the left atrium, resulting in a single atriopulmonary venous orifice on the involved side. In contrast, supernumerary or accessory PVs are additional veins with independent atriopulmonary venous junctions separate from the superior and inferior PVs. Conjoined veins occur more commonly on the left side, which is the side more frequently targeted for ablation[15]. Conjoined veins typically have a broad, atriopulmonary venous junction. Accessory veins occur more frequently on the right side. In this case, separate drainage of the right middle lobe or superior segment of the right lower lobe are the most frequent[15]. Accessory veins are named for the respective pulmonary lobe or segment that they drain, and these sometimes cross pulmonary lobar fissures before emptying into the left atrium. Accessory veins typically have a narrower atriopulmonary venous junction than the superior and inferior PV. Anomalous pulmonary venous drainage occurs when all or part of the PV drain into a structure other than the left atrium. If no PV drains into the left atrium, there is total anomalous PV return. Partial anomalous PV return occurs when at least one PV drains into the left atrium.

CIRCUMFERENTIAL PULMONARY VEIN ABLATION

Circumferential pulmonary vein ablation (CPVA) is the standard procedure performed in many centres (Figure 1). The procedure is in general performed by manual catheters or remotely by soft magnetic catheters[16-18]. CPVA consists of large circumferential lesion lines to ensure a point-by-point tailored distal disconnection of all PVs (Figure 1). Accumulating data from larger studies indicate that among patients with paroxysmal or persistent AF without enlarged atria, CPVA alone is associated with an excellent outcome. Additional atrial ablation lesions may be required to achieve stable sinus rhythm in patients with long-lasting, persistent, or permanent AF and enlarged atria[16-21].

COMPLICATIONS AFTER ABLATION

Complications during or immediately after the ablation procedure include pericardial effusion and embolic events in 1%-4% of patients[14,22]. The radiologist may encounter these complications on chest radiographs or head CT scans after the procedure. Pulmonary dysfunction and bleeding resulting from anticoagulation may also occur[23-25]. Circumferential PV isolation rarely causes symptomatic PV stenosis[25]. Scharf *et al*[26] showed that 3% of patients have stenosis of up to 65% luminal diameter narrowing but remain asymptomatic. They also showed that some patients have PV dilatation after CPVA. Severe PV stenosis (Figure 3) is described in 11% of patients[22,23] and has been reported to cause pulmonary veno-occlusive disease in three patients[24,26]. Clinically, symptomatic PV stenosis may present with dyspnoea on exertion or manifest

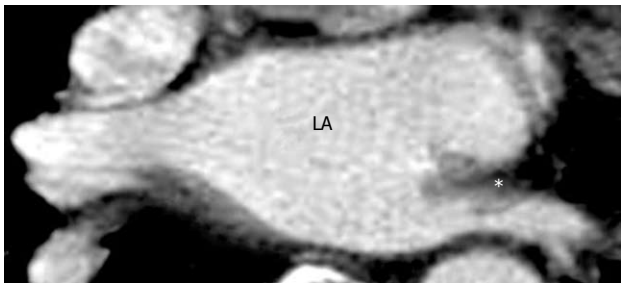

Figure 3 Axial multidetector computed tomography image of the area around a pulmonary vein stenosis (*) into the left inferior pulmonary vein in a 66-year-old male patient with dyspnea and chest discomfort 3 mo after pulmonary vein ablation. LA: Left atrium.

as focal pulmonary oedema on chest radiographs or CT scans or as PV luminal narrowing on CT images. Ablation is performed at or within 5 mm of PV ostia to reduce the risk of PV stenosis. Ablation inside the PV increases the risk of stenosis and increases the difficulty in treating stenosis. Stenosis after ablation (Figure 3) is not predicted by the initial PV size or total duration of radiofrequency energy application delivered to the vein, but instead by catheter position. The more distal the catheter from the ostium, the greater the degree of narrowing created[27]. The left inferior PV is most susceptible to the development of narrowing because of the more medial and posterior location of its ostia, therefore, projecting inside the cardiac silhouette on standard imaging and fluoroscopy. As a consequence, more energy may be delivered inside the vein distal to the ostium. CT before the procedure is helpful to clearly identify the position of the left inferior pulmonary vein ostium. Pulmonary vein stenosis may also be associated with pulmonary vein thrombosis[24]. Thrombus formation has been reported to occur from 1 d to 3 mo after RFCA, with an embolism rate of 2% despite adequate anticoagulation therapy. Therefore, patients receive anticoagulation during the procedure and post-operatively for approximately 1 mo[22]. Chest radiographs may show evidence of focal pulmonary oedema distal to the occluded vein. Recently, the optimal method for diagnosis of PV stenosis was not established[28]. In an analysis by Stavrakis *et al*[28] they came to the conclusion that in comparison with CT or MRI, TEE has a high sensitivity and specificity in detecting PV stenosis. Given its wide availability and favourable side effect profile, their data suggest that TEE is a very useful tool for the diagnosis of PV stenosis after catheter ablation of AF[28]. CT angiography or MR angiography can be used to diagnose PV occlusion noninvasively. Infarction may result in wedge-shaped parenchymal consolidation. CT may also show interlobular septal thickening and ground-glass opacity as a result of localized pulmonary venous hypertension. Reactive regional mediastinal lymph node enlargement may also occur as a result of mediastinal inflammation and fibrosis from thermal injury[29,30]. Furthermore, a detailed list of the different complications related to RFCA in AF reported with their relative incidence is shown in Table 1.

Table 1 Complications related to radiofrequency ablation in atrial fibrillation

Complication type (relative incidence)
Pulmonary veins
Pulmonary vein stenosis (1.5%-42.4%)
Pulmonary vein thrombosis
Pulmonary vein dissection
Lungs and pleura
Pulmonary hypertension (11%)
Pneumothorax (0.02%)
Hemothorax (1.3%)
Heart and pericardium
Pericarditis (3%-4.8%)
Hemopericardium, cardiac tamponade (1%-1.3%)
ST-T wave changes (3%)
Coronary artery spasm
Valvular damage (0.01%)
Other
Stroke (0.28%)
Transient ischemic attack (0.66%)
Pain or discomfort during radiofrequency energy delivery
Systemic thromboembolism (cerebral, retinal, or peripheral) (1.4%-2.6%)
Permanent diaphragmatic paralysis (0.11%)
Hematoma at puncture site (13%)
Cutaneous radiation damage
Arteriovenous fistula (1%)
Indirect
Aspiration-induced pneumonia
Sepsis (0.01%)

MULTIDETECTOR-ROW CT PROTOCOL

Contrast medium-enhanced spiral CT of the PVs ideally should be performed with a MDCT scanner and with the patient in sustained deep inspiration. Collimation of 1.5-2.5 mm is appropriate for demonstration of all PVs on axial or reformatted sections. Acquisition should begin 20 s after intravenous injection of 100 mL of 30% iodine-based contrast medium at a flow rate of 3 mL/s. A bolus test or bolus monitoring with triggering may be used to reduce the amount of contrast medium needed. Three-dimensional or multiplanar reformations are useful for analysis of the atrial-venous junction. ECG gating is not mandatory. With gated examinations, 1.25-mm collimation, 500-ms scans triggered at 50%-70% R–R interval are preferred. For non-gated examinations, images can be acquired at a collimation of 2.5 mm and a 25-cm field of view. If heart rates are rapid, drug therapy may be indicated to decrease heart rates to below 93 beats per minute to facilitate ECG gating[31-33].

The images commonly encompass an area from the top of the aortic arch through the apex during a single breath-hold. Once generated, the data are transferred to a workstation for post-processing with lung and soft-tissue algorithm displays.

POST-PROCESSING

From the source images it is usually possible to identify the

primary PV, along with any associated anatomic variants, including pulmonary lobe or segmental accessory vessels. The anteroposterior diameters of the PV ostia are routinely measured. On the initial source images, it is important that the left atrium and left atrial appendage are also scrutinized for thrombi. Both epicardial and endocardial reconstructed views of the left atrium and distal PV are obtained, including surface-rendered views of the left atrium. It is also important that the reconstructed views include the entire left atrium and the distal 2 cm of the PVs, but exclude the remainder of the heart, pulmonary arteries, aorta and superior and inferior venae cavae. Sufficient views are needed to clearly depict atrial size, shape and the number and angulation of PVs, as well as the location of any ostial branches. Shaded-surface displays (SSDs) are often preferred, in order to calculate left atrial volumes and atrial dimensions. In a study by Schroeder *et al*[34] and Marom *et al*[35], it was shown that 71% of 142 patients had two ostia on the right side and 28% (56 patients) had three to five. Also, 2% (three patients) had a single right ostium. For the left side, 86% of 173 patients had two ostia and 14% had a single ostium. Individuals with an accessory ostium for the right middle lobe tended to have a higher frequency of atrial arrhythmias[34,35]. Endocardial views are needed to show the anatomy from an intra-atrial perspective and ostial measurements and the distance between ostia are important to document[15] (Figure 1). Accurate measurements are necessary, since different-sized electrodes are used for different ostial diameters. Measurements are also needed to provide baseline dimensions in the case of post-RFCA stenosis.

CMR IMAGING

Several studies demonstrated that AF is associated with electrical, contractile, and structural remodelling (SMR) in the left atrium (LA) which contributes to the persistence and sustainability of AF[1-4]. It has also been shown that the final result of this remodelling process is loss of atrial myocytes and increased collagen content, and hence fibrosis of the LA wall[36]. Delayed enhancement MRI (DE-MRI) using gadolinium contrast has been demonstrated to localize and quantify the degree of SRM and fibrosis associated with AF in the LA. Basically, DE-MRI has also been shown to be useful in localizing and quantifying scar tissue in the LA following radiofrequency ablation (RFA)[37]. Furthermore, the PV antral region can be visualized to assess circumferential PV scarring resulting from RFA lesions/ablation. In addition, the amount of scarring to the LA after catheter ablation can be quantified as a proportion of the total left atrial volume. Recently, methods for merging MR anatomical data with electrophysiological anatomic data have been introduced, motivated by the possibility that a more accurate depiction of anatomy might improve the speed, effectiveness and success rate of the ablation procedure, and to reduce procedure time[38].

CONCLUSION

The electric isolation of PVs by the application of radiofrequency energy at the veno-atrial junction is a novel technique for the treatment of paroxysmal AF. As AF is the most common cardiac arrhythmia, an increasing number of ablation procedures are performed at many centres. 3-D reformatted MDCT images of the left atrium and distal PVs provide the necessary anatomic information, including the number, location and angulation of PVs and their ostial branches. Thus, MDCT imaging can serve as a "road map" for the interventional cardiologist, as well as providing a diagnostic baseline for possible later complications, if these should occur.

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BRIEF ARTICLE

Use of carbon dioxide as negative contrast agent for magnetic resonance cholangiopancreatography

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Abstract

AIM: To evaluate the effects of using CO_2 as negative contrast agent in decreasing the overlapping on the pancreaticobiliary system from intestinal fluids.

METHODS: We evaluated the magnetic resonance cholangiopancreatography (MRCP) images in 117 patients divided into two groups (group 1, without taking gas producing crystals to produce CO_2, n = 64; group 2, with CO_2, n = 53) in a 1.5T unit using MRCP sequence. Anatomic locations of intestinal fluids distribution, overlapping with common bile duct (CBD) and pancreatic duct (PD), were evaluated.

RESULTS: In the group with CO_2, the decrease in distribution of intestinal fluids was significant in the gastric antrum (P = 0.001) and duodenal bulb (P < 0.001), but not in the gastric fundus and body and in the second portion of the duodenum (P = 1.000, P = 0.171, and P = 0.584 respectively). In the group with CO_2, the decrease in overlapping with CBD was significant (P < 0.001), but the decrease in overlapping with PD was not (P = 0.106).

CONCLUSION: MRCP with carbon dioxide as negative contrast agent would decrease intestinal fluids in the gastric antrum and duodenal bulb, thereby decreasing overlapping with the CBD.

Key words: Magnetic resonance cholangiopancreatography; Negative contrast medium; Gas-producing crystals; Carbon dioxide

Peer reviewer: Ahmed Mahmoud El-Tawil, MSc, MRCS, PhD, Department of Surgery, University Hospital of Birmingham, East Corridor, Ground Floor, Birmingham, B15 2TH, United Kingdom

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INTRODUCTION

Magnetic resonance cholangiopancreatography (MRCP) is a safe and noninvasive technique used to evaluate the pancreaticobiliary system[1-3]. With the use of thin-section single-shot fast-spin echo sequences and thick-section heavily T2-weighted sequences, MRCP can demonstrate the anatomy of the biliary tract, pancreatic duct (PD) and gallbladder, since the fluid within them serves as an intrinsic contrast medium[4]. However, high signal intensity from intestinal fluids would decrease the quality of MRCP images due to superimposition with the biliary tract[4-6]. Therefore, how to

decrease the high signal intensity from intestinal fluids has always been problematic for radiologists.

Previous researchers have used oral negative contrast agents (including blueberry and pineapple juices) to suppress the high signal of the gastrointestinal tract[4,7-9]. Although blueberry juice has been shown to be a well-tolerated and effective oral contrast agent during MRCP, pure blueberry juice is not widely available. Pineapple juice is another negative contrast medium. However, the patient has to take the 400 mL of pineapple juice 15 to 30 min before MRCP is performed, thereby limiting its clinical usage. A potential risk of loss of signal intensity of the common bile duct (CBD) caused by reflux of oral negative contrast medium agent in patients with a history of endoscopic sphincterotomy has also been reported[10].

Based on the experience of upper gastrointestinal series, we understand that CO_2 accumulates in the gastric antrum after gas-producing crystals are taken. This phenomenon will cause intestinal fluids to be retained in the gastric fundus and therefore decrease the overlapping with the CBD. There are also several advantages to using CO_2 as the negative contrast medium: it is widely available, inexpensive and easily prepared. To our knowledge, this is the first study using CO_2 as negative contrast agent for MRCP in the literature.

The purpose of our study was to evaluate the effects of using CO_2 as a negative contrast medium in decreasing the overlapping of intestinal fluids on the pancreaticobiliary system.

MATERIALS AND METHODS

Patients

From October 2007 to September 2008, a total of 117 consecutive patients (70 men, 47 women; age range, 20-82 years; mean age, 58 years), who met the inclusion criteria, were enrolled in our study. Patients were included if they were referred for evaluation of biliary tract problems. We excluded patients if they had had cholecystectomy or gastric surgery, or were unable to take gas-producing crystals. The Institutional Review Board of our hospital approved the study. Written informed consent was obtained from each patient after the purpose and protocol of the study had been fully explained.

The patients were randomly assigned to two groups: those who took and those who did not take gas-producing crystals, i.e. with CO_2 and without CO_2. Patients in the first group received 6 g of gas-producing crystals with 10 mL water orally, shortly before the MRCP examination. If there was insufficient air distension of the stomach, 3 additional grams of gas-producing crystals were given. For those who did not take gas-producing crystals, the MRCP examination was performed directly without any oral contrast.

MRCP

All patients underwent MRCP with a 1.5-T MR scanner (Achieva; Philips Medical Systems, The Netherlands) using a four-element quadrature phased-array surface coil. The MRCP was performed as per the following parameters: single shot MRCP radial sequence: repetition time (ms)/echo time (ms), 8000/800; flip angle, 90°; field of view, 350 mm; matrix, 320 × 255; echo spacing, 4.2 ms; 6 radial sections of 40 mm thickness obtained at 12 degrees of rotation.

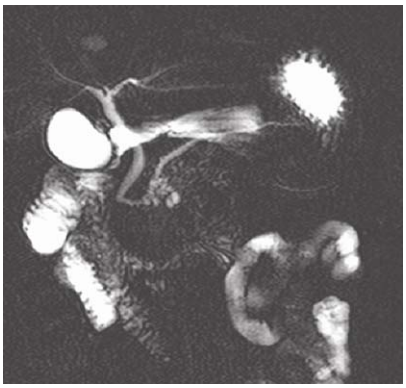

Figure 1 Magnetic resonance cholangiopancreatography image without CO_2 in a 51-year-old man shows the hyperintense intestinal fluids in the gastric antrum and duodenal bulb overlapping the common bile duct.

Imaging analysis

The MRCP images were reviewed by two gastrointestinal radiologists (HMT and MTC with 10 and 6 years of MRCP interpretation experience, respectively), who were blinded to the patients' group allocation, and who had to reach a consensus. First, the reviewers were asked to identify the presence of intestinal fluids in different anatomic locations of the stomach (fundus, body and antrum) and duodenum (bulb and 2nd portion). Then, they were asked to identify the anatomic structures of intestinal fluids overlapping the CBD. Third, the reviewers were asked to identify the anatomic structures of intestinal fluids which overlapped the PD.

Statistical analysis

Differences between the two groups of data were assessed with χ^2 test. The analyses were performed by using SPSS software (SPSS for Windows, version 11.0, 2001; SPSS, Chicago, Ill). A P value of less than 0.05 was considered to indicate a statistically significant difference for all analyses.

RESULTS

Among the 117 subjects, 53 persons took gas-producing crystals orally as negative contrast agent while 64 persons did not. Figure 1 shows hyperintense intestinal fluids in the gastric antrum and duodenal bulb overlapping the CBD. Figure 2 shows lack of overlap due to decreased hyperintense intestinal fluids in the gastric antrum and duodenal bulb. Table 1 summarizes the results of intestinal fluid distribution in different anatomic locations of the stomach and the duodenum in the two groups, i.e. with and without CO_2 as negative contrast agent. In the

Table 1 Comparison of distribution of intestinal fluids on magnetic resonance cholangiopancreatography images between the two groups without CO_2 and with CO_2 as negative contrast agent *n* (%)

Anatomic locations with intestinal fluids distribution	Patients		*P*-value
	Without CO_2 (*n* = 64)	With CO_2 (*n* = 53)	
Gastric fundus	62 (97)	52 (98)	1.000
Gastric body	25 (39)	14 (26)	0.171
Gastric antrum	24 (38)	6 (11)	0.001
Duodenal bulb	53 (83)	22 (42)	< 0.001
Duodenal 2nd portion	57 (89)	45 (85)	0.584

Table 2 Comparison of the overlap with the common bile duct and the pancreatic duct between the two groups without CO_2 and with CO_2 as negative contrast agent during magnetic resonance cholangiopancreatography *n* (%)

Overlapping structures	Patients		*P*-value
	Without CO_2 (*n* = 64)	With CO_2 (*n* = 53)	
Common bile duct	52 (81)	21 (40)	< 0.001
Pancreatic duct	12 (19)	4 (8)	0.106

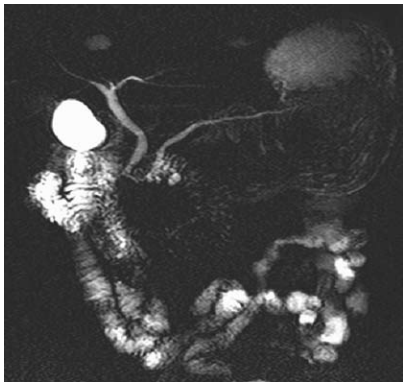

Figure 2 Magnetic resonance cholangiopancreatography image with CO_2 in a 60-year-old woman shows how the decreased hyperintense intestinal fluids in the gastric antrum and duodenal bulb do not overlap the common bile duct.

group with CO_2, the MRCP images showed significant improvement in decreased distribution of intestinal fluid in gastric antrum (P = 0.001) and duodenal bulb (P < 0.001). Nevertheless, there were no significant differences in the distribution of intestinal fluid in gastric fundus (P = 1.000), gastric body (P = 0.171) and 2nd portion of duodenum (P = 0.584) between the two groups. Table 2 shows how the overlap of the intestinal fluid on the CBD was significantly decreased in the group with CO_2 vs. that without CO_2 (P < 0.001). On the other hand, there were no significant differences in the degree of overlap on the PD between the two groups (P = 0.106) (Table 2).

DISCUSSION

MRCP is a safe and noninvasive technique used to evaluate the pancreaticobiliary system[1-3,11]. It allows obtaining images of the pancreaticobiliary similar to the endoscopic retrograde pancreatography (ERCP) without the morbidity associated with the complications resulting from diagnostic ERCP[12-14]. Although MRCP has been shown to be accurate in the diagnosis of choledocholithiasis, malignant biliary obstruction and other congenital biliary tract anomalies, awareness of several potential pitfalls is crucial to avoid inappropriate interpretation[6]. High signal intensity from the intestinal fluids superimposed on the biliary tract is one of the pitfalls that interfere with the interpretation (Figure 1).

Previous researchers have used oral negative contrast agents (including blueberry and pineapple juices) to suppress the high signal of the gastrointestinal tract[4,7-9]. However, these negative contrast agents are not appropriate for routine use. Blueberry juice, although well-tolerated and effective, as oral contrast agent for MRCP, is not widely available. Pineapple juice, another negative contrast medium, is inconvenient to administer: patients have to drink 400 mL of pineapple juice 15 to 30 min before MRCP, thereby limiting its clinical usage. A potential risk of loss of signal intensity of the CBD caused by reflux of oral negative contrast medium agent in patients with a history of endoscopic sphincterotomy has also been reported[10].

All these disadvantages led us to look for a more suitable contrast agent for MRCP that might be widely available and timesaving.

In this study, we used carbon dioxide (CO_2) as negative contrast medium produced by administering gas-producing crystals orally. There are several advantages using CO_2 as a negative contrast medium: it is widely available, inexpensive and easily prepared. After taking oral gas-producing crystals, the CO_2 will accumulate in the gastric antrum and duodenal bulb, because these areas are located upward during the supine position. The gastric antrum and duodenal bulb are also, anatomically, the nearest areas to the CBD and the PD. Therefore, the negative contrast medium effects caused by CO_2 in these areas will not influence the high signal intensity at the level of the CBD and the PD during the MRCP, thereby improving the MRCP diagnostic value.

Our results (Table 1) showed significant improvement in the distribution of intestinal fluid in gastric antrum (P = 0.001) and duodenal bulb (P < 0.001). This subsequently decreased the degree of overlap of the intestinal fluids on the CBD (P < 0.001) (Table 2 and Figure 2), hence increasing the diagnostic value. However, our results failed to show a significant difference in the degree of overlap of the intestinal fluids on the PD between the two groups of patients, i.e. those taking vs. those non taking gas-producing crystals (P = 0.106). The overlap on the PD arises from the high signal intensity of the 3rd and 4th portions of the duodenum. However, the high signal source cannot be eliminated after production of CO_2 by gas-producing crystals. A possible maneuver to decrease the overlap is the right hemi-decubitus position after taking oral gas-producing crystals. This posi-

tion would decrease the high signal intensity of the 3rd and 4th portions of the duodenum, thereby decrease the overlap with the PD.

Our study has limitations. Firstly, although gas-producing crystals can produce carbon dioxide in the stomach, there were still 22 (41.5%) subjects in our study whose MRCP images were characterized by an insufficient amount of air. The possible reason was the fact of having taken just one pack of gas-producing crystals. This would have been improved simply by taking another pack. However, some patients might feel uncomfortable about the smell of the gas-producing crystals and hesitate to take another pack. Secondly, some patients took the gas-producing crystals too slowly, which may negatively influence the desired effects. This problem may be overcome by assuming the crystals faster. However, the physician should be aware of possible complications, such as choking. For those patients with nasogastric tube placement, the oral gas-producing crystal method could be replaced by manually injected air from the nasogastric tube. Thirdly, some patients had hiccups after they took the crystals. This would undoubtedly influence the results of the MRCP. Lastly, the CO_2 might enter the papilla of Vater in patients with incompetent papilla. This would subsequently lead to pneumobilia which may mimic choledocholithiasis[6].

In conclusion, MRCP with carbon dioxide as negative contrast medium may decrease intestinal fluids in gastric antrum and duodenum, thereby decreasing their overlapping with the CBD.

COMMENTS

Background

MR cholangiopancreatography (MRCP) is a useful and noninvasive method to evaluate the normal anatomy and various pathologies of the pancreaticobiliary system. However, bile within the common bile duct (CBD) serving as an intrinsic bright contrast medium could be superimposed by hyperintensity from intestinal fluids on MRCP.

Research frontiers

Several oral negative contrast agents (such as blueberry and pineapple juices) have been used to decrease the hyperintensity from intestinal fluids.

Innovations and breakthroughs

Carbon dioxide, a widely available, inexpensive and easily prepared contrast agent, used as a negative contrast agent during MRCP would accumulate in the gastric antrum, displace the intestinal fluids into the gastric fundus and therefore decrease the overlap with the CBD. This would greatly improve the diagnostic value of MRCP.

Applications

Administration of carbon dioxide as a negative contrast agent for MRCP is a practical method to decrease the overlap of intestinal fluids on the CBD.

Terminology

MRCP is a noninvasive method by using thin-section single-shot fast-spin-echo sequence to enhance the bile juice and help clinician understand the normal anatomy and various pathologies of the pancreaticobiliary system. Cholodocholithiasis within the pancreaticobiliary system would appear as hypointense filling defects on MRCP.

Peer review

The manuscript addressed a novel procedure to improve the visualization of CBD or pancreatic duct during MRCP.

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CASE REPORT

Miliary nodules due to secondary pulmonary hemosiderosis in rheumatic heart disease

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Abstract

Pulmonary hemosiderosis is defined as the clinical and functional consequence of iron overload of the lungs, which usually occurs due to recurrent intra-alveolar bleeding. It can manifest as miliary mottling and should be entertained in the differential diagnosis of patients presenting with miliary nodules on chest radiography, especially those with mitral stenosis. The management of secondary pulmonary hemosiderosis secondary to valvular heart disease includes valvuloplasty and/or valve replacement. The radiological opacities may disappear with successful treatment of the underlying valvular disease in many patients. However, they may persist with no physiological impairment to the patient. Here, we present a 32-year-old man with mitral stenosis who presented with fever and miliary shadows on chest radiography, which was ultimately diagnosed as secondary pulmonary hemosiderosis.

Key words: Miliary nodules; Mitral stenosis; Tuberculosis: Hemosiderosis

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INTRODUCTION

Pulmonary hemosiderosis is a rare pulmonary disease that manifests as a triad of hemoptysis, anemia and diffuse parenchymal infiltrates on chest radiography. This condition occurs due to the deposition of hemosiderin-laden macrophages in lungs as a result of repeated alveolar hemorrhage that subsequently leads to the development of pulmonary fibrosis[1]. Hemosiderin is formed by the breakdown of red blood cells and release of iron in heme. It reflects an alveolar abnormality, which may be a primary condition or secondary to a systemic disease. In general, primary pulmonary hemosiderosis is more common than secondary types[2]. The common secondary causes are collagen vascular diseases, coagulation disorders and cardiovascular disorders, especially mitral stenosis[1,3-5].

Mitral stenosis typically results from rheumatic heart disease, although it may be congenital. The increased left ventricular filling pressure in mitral stenosis leads to pulmonary venous hypertension, and, eventually, post-

capillary pulmonary arterial hypertension. Recurrent bleeding from the anastomoses between pulmonary arterioles and bronchial vessels results in pulmonary hemosiderosis. Radiologically, hemosiderosis may present as diffuse reticular or miliary nodular opacities, and is seen in 10%-25% of patients with mitral stenosis[6]. Diagnosis is confirmed by the demonstration of hemosiderin-laden macrophages in bronchoalveolar lavage and lung biopsy. This condition is also called "brown lung induration" and is characterized histologically by alveolar hemorrhage, hemosiderin-laden macrophages in the alveoli and, to a lesser extent in the interstitium, and mild interstitial thickening that can become prominent in long-standing cases, leading to septal fibrosis[7]. Here, we present the case of a 32-year-old patient who presented with miliary opacities and was ultimately diagnosed with pulmonary hemosiderosis secondary to mitral stenosis. Being a high-prevalence country for tuberculosis (TB), a diagnosis of miliary TB was initially considered in the differential diagnosis of this patient.

CASE REPORT

A 32-year-old man was admitted with complaints of fever, dry cough and worsening breathlessness of 3 d duration. There was no history of chest pain, hemoptysis or leg edema. In the past, there was a history of fever and joint pains at the age of 5 years, for which he was admitted to hospital, and since then, the patient has been receiving injections of benzathine penicillin every 3 wk. The patient also had a history of progressive dyspnea on exertion over the past 12 years, and before this current hospitalization, his dyspnea was severe enough to limit his daily activities. There was no previous history of cough, chest pain or hemoptysis. For the present illness, he first visited his general practitioner who performed a chest radiograph (Figure 1), which revealed cardiomegaly with straightening of the left heart border, and diffusely distributed miliary (approximately 3 mm) nodular opacities. The patient was subsequently referred to this institute for work-up of fever and the radiological opacities.

Upon examination, the patient was conscious and afebrile with a pulse rate of 96 beats/min, blood pressure of 130/70 mm Hg, and respiratory rate of 20 breaths/min. Jugular venous pulse showed prominent a waves; examination of the cardiovascular system showed the apex to be located at the sixth intercostal space in the anterior axillary line, and a palpable diastolic thrill. Auscultation revealed a loud first heart sound, a loud pulmonic component of the second heart sound, and a mid-diastolic murmur with a presystolic accentuation. Examination of the respiratory system was normal. There were no joint deformities or joint tenderness. The rest of the physical examination was unremarkable.

Complete blood count revealed hemoglobin of 102 g/L, total leukocyte count of 10 800/μL and platelet count of 206 000/μL. Peripheral blood film showed microcytosis and hypochromia. The coagulation profile, serum

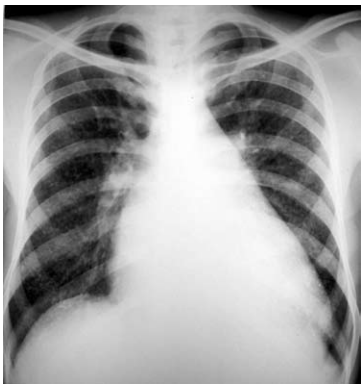

Figure 1 Chest radiography showed cardiomegaly with straightening of the left heart border. In addition, there were diffusely scattered miliary nodular opacities (approximately 3 mm).

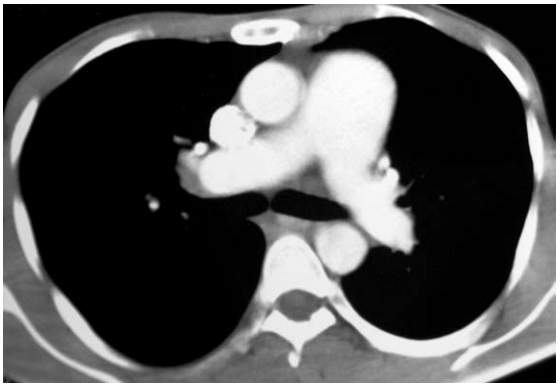

Figure 2 Chest computed tomography (mediastinal sections) showed an enlarged main pulmonary arterial trunk.

electrolytes, and renal and liver function tests were normal. Routine urine examination was normal. Electrocardiography revealed right axis deviation, P-pulmonale and voltage criteria for right and left ventricular hypertrophy. Echocardiography was performed, which showed evidence of severe mitral stenosis (mitral valve area: 0.7 cm^2), moderate aortic regurgitation with associated pulmonary hypertension, and mild tricuspid regurgitation. Blood cultures and urine cultures were sterile. Computed tomography (CT) of the chest showed an enlarged pulmonary artery (Figure 2), and the corresponding lung windows showed randomly scattered nodular opacities 2-3 mm in size (Figure 3). Fiberoptic bronchoscopy was done subsequently, and transbronchial lung biopsies were performed, which showed characteristic histological findings of numerous hemosiderin-laden macrophages within the alveolar spaces (Figure 4). A final diagnosis of rheumatic heart disease with severe mitral stenosis with moderate aortic regurgitation with secondary pulmonary hemosiderosis was made. The patient was managed conservatively and his fever remitted with oral paracetamol. A balloon mitral valvuloplasty was done, following which, dyspnea improved and the mitral valve surface area increased to 1.3 cm^2. The cause of the radiological abnormalities was explained to the patient, and he was advised to undergo dual valve replacement.

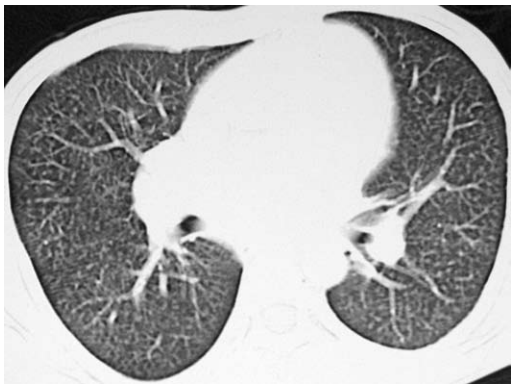

Figure 3 Chest computed tomography (lung windows) showed randomly scattered miliary nodules.

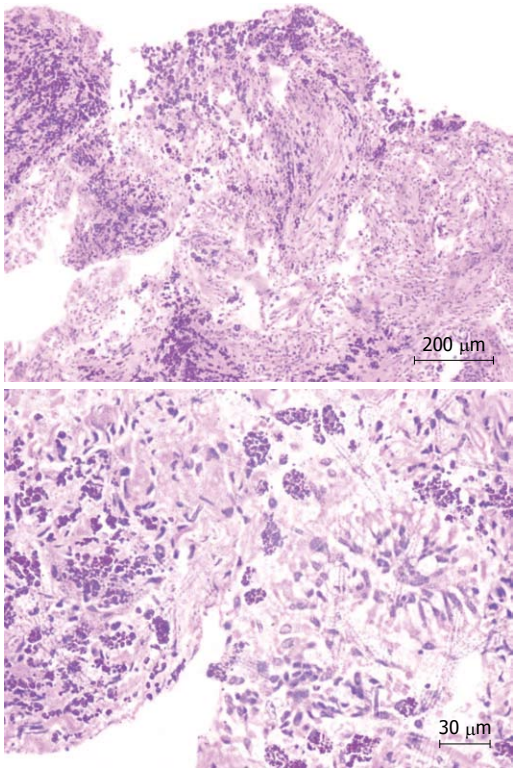

Figure 4 Bronchoscopic lung biopsy (upper) showed alveoli filled with coarse pigment-laden macrophages with sparse lymphocytic infiltrate in the interstitial septa. The figure on the bottom reveals the same findings at a higher magnification.

DISCUSSION

The term hemosiderosis is derived from the Greek words, hemo (blood) and sideros (iron), and is characterized by the focal or generalized accumulation of iron in the form of hemosiderin[3]. Hemosiderin is an intracellular storage form of iron (> 33% iron by weight) and contains ferric hydroxides, polysaccharides, and proteins. The main source of iron in the lungs is from the red blood cells and is metabolized during episodes of alveolar hemorrhage. After 48-72 h of acute bleeding, the alveolar macrophages convert hemoglobin iron into hemosiderin, hence the term hemosiderosis.

Table 1 Differential diagnosis of miliary pattern on computed tomography

Infections	Miliary tuberculosis
	Fungal infections: histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis,
	Varicella pneumonia
Pneumoconiosis	Coal worker's pneumoconiosis, silicosis, berylliosis
Inflammatory	Sarcoidosis
Malignancy	Metastasis (thyroid carcinoma, osteosarcoma)
Others	Alveolar microlithiasis, amyloidosis

Pulmonary hemosiderosis is the clinical and functional consequence of iron overload of the lungs. The deposition of hemosiderin in the lung was first commented upon by Virchow in 1858, but it was in 1928 that Rosenhagen described the occurrence of pulmonary hemosiderosis in association with valvular heart disease[8]. The term pulmonary hemosiderosis is reserved for recurrent intra-alveolar bleeding because hemosiderin-laden macrophages reside for up to 4-8 wk in the lungs. Pulmonary hemosiderosis is considered idiopathic (also known as Ceelen-Gellerstedt's syndrome) if no other cause is identified, and if the lung biopsy excludes capillaritis, granulomas, or other immune depositions. It can also occur due to various other causes of recurrent alveolar hemorrhage, including mitral stenosis[2]. The diagnosis is often missed because the bleeding can be covert, and hemoptysis is often missing, as in the present case[1].

Mitral stenosis is characterized by left atrial outflow obstruction with resultant pulmonary venous and capillary hypertension, and finally, frank pulmonary arterial hypertension. Pulmonary hemosiderosis has been reported to occur in up to 16% of patients with mitral stenosis[1]. The deposition of hemosiderin results from pulmonary capillary hypertension, which results in the formation of anastomoses between pulmonary arterioles and bronchial vessels; these varicose anastomoses repeatedly rupture with resultant recurrent intra-alveolar hemorrhages and formation of pulmonary hemosiderin[5]. The clinical presentation of focal pulmonary hemosiderosis is probably more common than the presentation of miliary opacities on chest radiography, as seen in the present case, which are quite often mistaken for other conditions[9]. Other factors also play a role in the pathogenesis of pulmonary hemosiderosis resulting from mitral stenosis, because hemoptysis and pulmonary capillary hypertension is common, but diffuse pulmonary hemosiderosis is uncommon[4]. However, one caveat is that diffusely scattered hemosiderin collections of < 1 mm do not cast an appreciable shadow on chest radiography, and therefore, pulmonary hemosiderosis can be missed. Chest CT is more sensitive than radiography for detection of small nodular opacities, which has a wide range of differential diagnosis (Table 1).

Iron exerts a toxic effect, partially through its capacity to produce highly reactive hydroxyl radicals from less toxic oxygen superoxide and hydrogen peroxide (Haber-Weiss and Fenton reactions), which in turn, cause lipid

layer peroxidation, protein and carbohydrate degradation, and subsequent fibrogenesis[3]. Within the pulmonary macrophages, iron is removed from hemoglobin by the enzyme heme oxygenase, however, the capacity of alveolar macrophages to metabolize iron is easily exhaustible, and the presence of free iron in the alveoli can cause local injury and fibrosis.

Management of secondary pulmonary hemosiderosis secondary to valvular heart disease includes valvuloplasty and/or valve replacement. There are cases on record where there is gradual clearance of the pulmonary opacities after treatment of mitral stenosis[1]. On the other hand, there are cases where there is little fibrotic reaction in spite of radiological (as in our patient) and autopsy evidence of heavy pulmonary hemosiderosis[1,6-8,10].

In conclusion, pulmonary hemosiderosis secondary to mitral stenosis can present as miliary nodules on chest radiography, and this fact should be kept in mind when managing such patients. Although in many cases the radiological opacities may disappear with successful treatment of the underlying valvular disease, in others, the radiological opacities may persist with no physiological impairment to the patient.

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Meetings

Events Calendar 2011

January 23-27
Radiology at Snowbird
San Diego, Mexico

January 24-28
Neuro/ENT at the Beach
Palm Beach, FL, United States

February 28-29
MIAD 2011 - 2nd International Workshop on Medical Image Analysis and Description for Diagnosis System
Rome, Italy

February 5-6
Washington Neuroradiology Review
Arlington, VA, United States

February 12-17
MI11 - SPIE Medical Imaging 2011
Lake Buena Vista, FL, United States

February 17-18
2nd National Conference Diagnostic and Interventional Radiology 2011
London, United Kingdom

Februrary 17-18
VII National Neuroradiology Course
Lleida, Spain

February 18
Radiology in child protection
Nottingham, United Kingdom

Februrary 19-22
COMPREHENSIVE REVIEW OF MUSCULOSKELETAL MRI
Lake Buena Vista, FL, United States

March 2-5
2011 Abdominal Radiology Course
Carlsbad, CA, United States

March 3-7
European Congress of Radiology Meeting ECR 2011
Vienna, Austria

March 6-9
World Congress Thoracic Imaging - IV
Bonita Springs, FL, United States

March 14-18
9th Annual NYU Radiology Alpine Imaging Symposium at Beaver Creek
Beaver Creek, CO, United States

March 20-25
Abdominal Radiology Course 2011
Carlsbad, CA, United States

March 26-31
2011 SIR Annual Meeting
Chicago, IL, United States

March 28-April 1
University of Utah Neuroradiology 2nd Intensive Interactive Brain & Spine Imaging Conference
Salt Lake City, UT, United States

April 3-8
1st Annual Ottawa Radiology Resident Review
Ottawa, Canada

April 3-8
43rd International Diagnostic Course Davos on Diagnostic Imaging and Interventional Techniques
Davos, Switzerland

April 6-9
Image-Based Neurodiagnosis: Intensive Clinical and Radiologic Review, CAQ Preparation
Cincinnati, OH, United States

April 28-May 1
74th Annual Scientific Meeting of the Canadian Association of Radiologists CAR
Montreal, Canada

May 5-8
EMBL Conference-Sixth International Congress on Electron Tomography
Heidelberg, Germany

May 10-13
27th Iranian Congress of Radiology
Tehran, Iran

May 14-21
Radiology in Marrakech
Marrakech, Morocco

May 21-24
European Society of Gastrointestinal and Abdominal Radiology 2011 Annual Meeting
Venice, Italy

May 23-25
Sports Medicine Imaging State of the Art: A Collaborative Course for Radiologists and Sports Medicine Specialists
New York, NY, United States

May 24-26
Russian Congress of Radiology
Moscow, Russia

May 28-31
International Congress of Pediatric Radiology (IPR)
London, United Kingdom

June 4-8
58th Annual Meeting of the Society of Nuclear Medicine
San Antonio, TX, United States

June 6-8
UKRC 2011 - UK Radiological Congress
Manchester, United Kingdom

June 8-11
CIRA 2011 - Canadian Internventinal Radiology Association Meeting
Montreal, QC, Canada

June 9-10
8th ESGAR Liver Imaging Workshop
Dublin, Ireland

June 17-19
ASCI 2011 - 5th Congress of Asian Society of Cardiovascular Imaging
Hong Kong, China

June 22-25
CARS 2011 - Computer Assisted Radiology and Surgery - 25th International Congress and Exhibition
Berlin, Germany

June 27-July 1
NYU Summer Radiology Symposium at The Sagamore
Lake George, NY, United States

July 18-22
Clinical Case-Based Radiology Update in Iceland
Reykjavik, Iceland

August 1-5
NYU Clinical Imaging Symposium in Santa Fe
Santa Fe, NM, United States

September 22-25
European Society of Neuroradiology (ESNR) XXXV Congress and 19th Advanced Course
Antwerp, Belgium

October 12-14
International Conference Vipimage 2011 - Computational Vision and Medical Image Processing
Algarve, Portugal

October 15-16
Essentials of Emergency and Trauma Radiology
Ottawa, Canada

October 23-29
2011 IEEE NSS - 2011 IEEE Nuclear Science Symposium and Medical Imaging Conference
Valencia, Spain

October 25-28
NYU Radiology in Scottsdale - Fall Radiology Symposium in Scottsdale
Scottsdale, AZ, United States

October 28-30
Fourth National Congress of Professionals of Radiological Techniques
Florianópolis, Brazil

October 28-30
Multi-Modality Gynecological & Obstetric Imaging
Ottawa, Canada

November 3-4
9th ESGAR Liver Imaging Workshop
Taormina, Italy

November 15-19
EANM 2011 - Annual Congress of the European Association of Nuclear Medicine
Birmingham, United Kingdom

November 22-29
NSS/MIC - Nuclear Science Symposium and Medical Imaging Conference 2011
Valencia, Spain

November 26-28
8th Asia Oceaninan Congress of Neuro-Radiology
Bangkok, Thailand

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Instructions to authors

GENERAL INFORMATION

World Journal of Radiology (*World J Radiol*, *WJR*, online ISSN 1949-8470, DOI: 10.4329), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 319 experts in Radiology from 40 countries.

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Maximization of personal benefits

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The major task of *WJR* is to rapidly report the most recent improvement in the research of medical imaging and radiation therapy by the radiologists. *WJR* accepts papers on the following aspects related to radiology: Abdominal radiology, women health radiology, cardiovascular radiology, chest radiology, genitourinary radiology, neuroradiology, head and neck radiology, interventional radiology, musculoskeletal radiology, molecular imaging, pediatric radiology, experimental radiology, radiological technology, nuclear medicine, PACS and radiology informatics, and ultrasound. We also encourage papers that cover all other areas of radiology as well as basic research.

Columns

The columns in the issues of *WJR* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in radiology; (9) Brief Articles: To briefly report the novel and innovative findings in radiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJR*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of radiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in radiology.

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

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

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

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

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

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

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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