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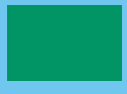

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BRIEF ARTICLE

Safety of bronchial arterial embolization with n-butyl cyanoacrylate in a swine model

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Abstract

AIM: To compare the efficacy and safety of bronchial artery embolization (BAE) with n-butyl cyanoacrylate (NBCA) and gelatin sponge particles (GSPs).

METHODS: Six healthy female swine were divided into two groups to be treated with BAE using NBCA-lipiodol (NBCA-Lp) and using GSPs. The occlusive durability, the presence of embolic materials, the response of the vessel wall, and damage to the bronchial wall and pulmonary parenchyma were compared.

RESULTS: No animals experienced any major complication. Two days later, no recanalization of the bronchial artery was observed in the NBCA-Lp group, while partial recanalization was seen in the GSP group. Embolic materials were not found in the pulmonary artery or pulmonary vein. NBCA-Lp was present as a bubble-like space in bronchial branch arteries of 127-1240 μm, and GSPs as reticular amorphous substance of 107-853 μm. These arteries were in the adventitia outside the bronchial cartilage but not in the fine vessels inside the bronchial cartilage. No damage to the bronchial wall and pulmonary parenchyma was found in either group. Red cell thrombus, stripping of endothelial cells, and infiltration of inflammatory cells was observed in vessels embolized with NBCA-Lp or GSP.

CONCLUSION: NBCA embolization is more potent than GSP with regard to bronchial artery occlusion, and both materials were present in bronchial branch arteries ⩾ 100 μm diameter.

Key words: Bronchial artery embolization; Embolic materials; N-butyl cyanoacrylate; Gelatin sponge; Lipiodol

Peer reviewer: James Chow, PhD, Radiation Physicist, Radiation Medicine Program, Princess Margaret Hospital, 610 University Avenue, Toronto, ON M5G 2M9, Canada

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INTRODUCTION

Bronchial artery embolization (BAE) for patients with massive hemoptysis has been an established treatment procedure since Rémy *et al*[1] reported the efficacy of BAE in 1974. Particles such as gelatin sponge (GS) or

polyvinyl alcohol (PVA) have been used as embolic materials[2-5]. Problems with BAE include recurrent hemoptysis, and although very rare, ischemic spinal paraplegia[6,7]. The occurrence of paraplegia is considered to be related to the anatomical anastomosis between the bronchial artery and the anterior spinal artery. Furthermore, Ivanick *et al*[8] have reported that BAE using ethanol with high occlusion potency causes bronchial wall necrosis.

Currently, BAE with n-butyl cyanoacrylate (NBCA) instead of particles is reported to enhance the potency of the occlusion, aiming to reduce the incidence of recurrent hemoptysis[9,10]. It is anticipated that peripheral occlusion with higher potency BAE causes damage to the bronchial wall and pulmonary parenchyma. Nonetheless, only one case has been found of bronchial wall damage following BAE with NBCA. We thought that it was important to establish the safety mechanism of BAE with NBCA.

The purpose of this study was to compare the efficacy and safety of BAE with NBCA and GS particles (GSPs) in a swine model.

MATERIALS AND METHODS

Approval by our Institutional Committee on Research Animal Care was obtained before the study was initiated. We used six healthy female pigs weighing 56-65 kg. The six pigs were divided into two groups with NBCA-Lp or GSPs, with three animals per group. Swine have a common trunk of the right and left bronchial arteries. Embolization of the right and left bronchial arteries was conducted using NBCA-Lp or GSPs, with six embolized lungs per group.

Pre-anesthesia was achieved with a combination of 5 mg/kg ketamine and 0.08 mg/kg atropine sulfate. General anesthesia was maintained with isoflurane gas *via* intubation. Cardiac and respiratory parameters were monitored throughout the procedures. Each pig underwent embolization of both the right and left bronchial arteries. A 4 Fr sheath (SuperSheath; Medikit, Tokyo, Japan) was inserted by direct puncture into the right femoral artery. Catheterization of the bronchial arterial trunk was performed using a 4 Fr Mikaelsson catheter (Medikit) or a 4 Fr Cobra catheter (Medikit). Selective bronchial trunk angiography was performed *via* this catheter before and after embolization. A 2.5 F microcatheter (Renegade-18; Boston Scientific, Natick, MA, United States) was coaxially inserted into the right or left bronchial artery and advanced to a peripheral site 1-2-cm from the bifurcation using a 0.014-inch micro-guidewire (Transend EX; Boston Scientific).

BAE using NBCA-Lp or GSPs was then conducted to embolize the bronchial artery. In BAE with NBCA, NBCA was prepared as a liquid embolic material by mixing 1 mL NBCA with 7 mL Lipiodol using a three-way stopcock. The ratio most commonly used for peripheral embolization in previous reports was 1 mL NBCA to 4 or 5 mL lipiodol[11-13]. We speculated that the more diluted NBCA was with Lipiodol, the more easily it should reach the more peripheral sites. Baltacioğlu *et al*[14] used and 1 to 7 ratio of NBCA-Lp for BAE. Therefore, a ratio of 0.1 mL NBCA to 0.7 mL Lipiodol was adopted in this study. Before embolization, the microcatheter was flushed with 5% glucose solution to prevent polymerization of NBCA. NBCA-Lp was slowly injected through the microcatheter under fluoroscopic control. The excessive NBCA-Lp volume was anticipated to reflux into the aorta. Based on our experiences[15], 0.2 mL NBCA-Lp volume was determined to be injected into the bronchial artery. Actually, 0.2 mL NBCA-Lp was appropriate to arrest blood flow in the bronchial artery without reflux. The microcatheter was removed after each BAE with NBCA-Lp because the lumen occluded instantly. The new microcatheter was coaxially inserted *via* a 4 Fr catheter placed in the common trunk and introduced to another bronchial artery and advanced a few centimeters peripherally beyond the origin of the bronchial artery, followed by BAE with NBCA.

In BAE with GSPs, GSP (Spongel, Astellas Pharmaceutical Inc., Tokyo, Japan) was cut into 1-mm pieces and soaked in contrast medium (Iopamidol 370; Bracco, Milan, Italy). We previously confirmed that magnified glass view of 53 GSPs revealed that GCPs was composed of four-angled-form sized 0.8-1.6 mm[16]. GSPs were slowly injected through the microcatheter under fluoroscopic control until bronchial arterial flow was arrested. The microcatheter was then introduced into another bronchial artery followed by BAE with GSP. In each group, angiography before and immediately after embolization was conducted to confirm the arrest of bronchial arterial blood flow.

Adverse effects on the lung were evaluated and blood tests were conducted. Peripheral blood was taken before embolization and 1 and 2 d after embolization to assess changes in white blood cells, red blood cells, SpO_2 and rectal temperature.. Cone beam computed tomography (CT) (Allraura, Xperfd 20; Philips, Netherlands) was performed to evaluate pulmonary infarction, damage to the bronchial wall in both groups, and the presence of NBCA-Lp, before, immediately after, and 24 h and 48 h after embolization.

Bronchial arteriography 2 d after BAE was attempted to evaluate the recanalization of the bronchial artery, and compared with the angiographic findings before BAE. When catheterization from the femoral artery approach was difficult, the carotid approach was tried. Damage of the bronchial artery was assessed according to the criteria of Maeda *et al*[17] into three grades: Grade Ⅰ, no damage or mild vessel wall irregularity; Grade Ⅱ, overt stenosis; and Grade Ⅲ, occlusion. Grade Ⅱ and Ⅲ were considered to indicate significant bronchial artery disorder.

The swine were sacrificed with intravenous injection of pentobarbital sodium 2 d after BAE and investigated for evidence of histological pulmonary infarction and/or bronchial mural necrosis. Necropsies were performed and the lungs were removed. The lungs were cut into sagittal sections of 10 mm thickness to follow the bronchial trees, and fixed in a 7.5% neutral formaldehyde

Table 1 White blood cell, red blood cell, percutaneous oxygen saturation level and rectal temperature following bronchial artery embolization

	NBCA				GSP			
	Baseline	Immediately after	1 d after	2 d after	Baseline	Immediately after	1 d after	2 d after
WBC ($\times 10^3/\mu L$)	16.5 ± 2.8	14.1 ± 0.45	15.5 ± 2.1	17.5 ± 5.3	16.3 ± 1.1	14.9 ± 0.35	17.0 ± 1.75	16.0 ± 1.6
RBC ($\times 10^6/\mu L$)	6.04 ± 0.82	5.98 ± 0.87	6.18 ± 0.10	5.69 ± 0.56	6.28 ± 0.46	6.27 ± 0.52	6.21 ± 0.19	6.30 ± 0.06
SpO_2 (%)	97.3 ± 1.25	97.7 ± 0.94	96.7 ± 0.94	97.0 ± 0.82	96.7 ± 0.47	97.3 ± 1.25	98.0 ± 0.00	97.7 ± 0.47
Rectal temperature (℃)	37.7 ± 0.45	37.8 ± 0.62	37.2 ± 0.12	37.8 ± 0.60	38.2 ± 0.41	38.4 ± 0.45	37.8 ± 0.65	37.9 ± 0.63

Values reported are mean ± range. NBCA: N-butyl cyanoacrylate; GSP: Gelatin sponge particles; WBC: White blood cells; RBC: Red blood cells; SpO_2: Percutaneous oxygen saturation.

Table 2 Presence of n-butyl cyanoacryrate on chest computed tomography two days after bronchial artery embolization

Bronchial arteries	NBCA	
	Present	Absent
Principal branch	6	0
Lobar branch	13	5
Segmental branch	12	47
Subsegmental branch	3	123

NBCA: N-butyl cyanoacrylate.

Table 3 Damage to bronchial branch arteries on angiography two days after bronchial artery embolization with gelatin sponge particles

	Grade of damage[1]		
Bronchial arteries	Grade Ⅰ	Grade Ⅱ	Grade Ⅲ
Principal branch	1	4	1
Lobar branch	3	5	6
Segmental branch	2	6	9

[1]According to the criteria of Maeda *et al*[17].

buffer. Specimens of 2 cm × 3 cm for microscopic examination were removed from the main/lobar bronchus, segmental bronchus, subsegmental bronchus, or peripheral bronchus branch arteries. The surface of the slice of interest was stained with hematoxylin-eosin (HE) to investigate damage to the bronchus and the pulmonary parenchyma, to identify embolic material in the artery, and to evaluate the vital response to the embolus. Macroscopic and microscopic studies regarding the cutting and the ischemic damage of bronchus and lung were conducted under the direction of a pathologist.

RESULTS

All pigs were able to run in the period after awakening from anesthesia until sacrifice, which implied that BAE with GSPs or NBCA did not cause ischemic damage to the spinal cord. Follow-up data revealed that all the values for white blood cells, red blood cells, SpO_2 and rectal temperature did not differ from baseline (Table 1).

Chest radiography and CT

In the NBCA-Lp group, radiography and CT immediately and 2 d after embolization revealed accumulation of NBCA-Lp in the principal, lobar, segmental and subsegmental branch arteries (Figure 1, Table 2). In both groups, radiography and CT revealed no specific changes in the pulmonary area.

Patency of bronchial artery in angiography 2 d after embolization with NBCA-Lp or GSPs

In the NBCA-Lp group, selective angiography 2 d after BAE could not be performed because it was impossible to catheterize each bronchial artery using the femoral or common carotid approach due to severe stenosis or occlusion. In the GSP group, the follow-up bronchial catheterization and angiography were possible and revealed partial recanalization of the bronchial artery with overt stenosis and/or occlusion of the bronchial branch arteries (Figure 2, Table 3).

Pathological examination of the pulmonary parenchyma and bronchial trees

Macroscopic examination revealed congestion and edema throughout the resected lungs but no coagulation necrosis in the bronchial wall and pulmonary parenchyma. Microscopy also revealed no specific changes in the pulmonary area and bronchial tree wall in either group.

Presence of NBCA-Lp or GSP in the vessels

The presence of NBCA-Lp and GSPs was investigated microscopically in 24 and 53 specimens, respectively. It was difficult to detect GSPs; probably because they were dispersed in the vessel and the number of the GSP specimens was greater than the NBCA-Lp specimens.

NBCA-Lp and GSPs were found in the bronchial branch arteries but not in the pulmonary artery or pulmonary vein. Principal (720-1240 μm), lobar (407-700 μm), segmental (142-413 μm) and subsegmental (40-184 μm) branch arteries were observed. These arteries were in the adventitia outside the bronchial cartilage. Meanwhile, numerous fine vessels < 50 μm in diameter were observed in the submucosal and cartilage layers (Figure 3). NBCA-Lp or GSPs were found in the principal bronchus branch arteries to subsegmental branch arteries. NBCA-Lp and GSPs were present in 35 and six vessels,

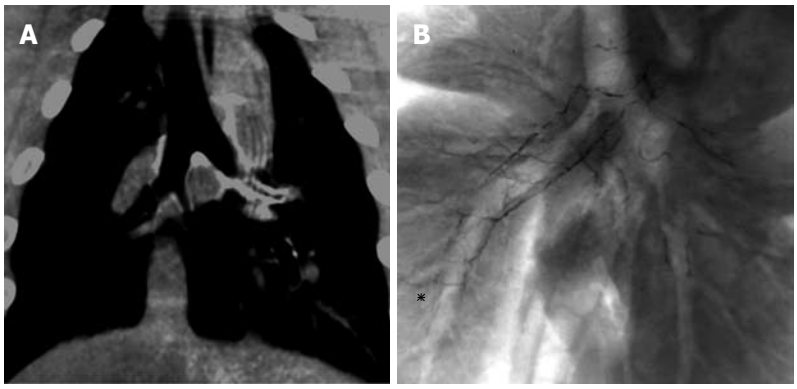

Figure 1 Embolization of right bronchial artery with n-butyl cyanoacryrate lipiodol was conducted. Two days after bronchial artery embolization (BAE) of bilateral bronchial arteries, chest computed tomography showed accumulation of n-butyl cyanoacryrate lipiodol (NBCA-Lp) alongside the bronchial trees (A). Chest radiography of the sacrificed lung two days after BAE with NBCA-Lp showed accumulation of NBCA-Lp that corresponded to the bilateral branch arteries of the main bronchus, lobar bronchus, and segmental (asterisk) bronchi (B).

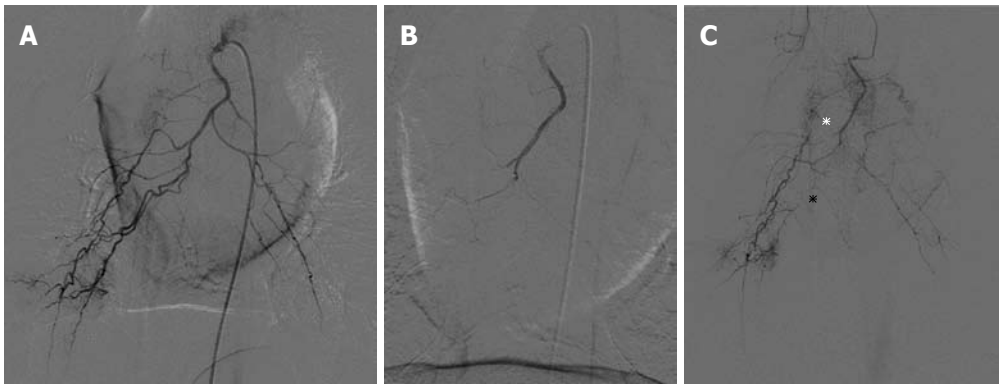

Figure 2 Common tract bronchial arteriography before (A) and immediately after (B) embolization with gelatin sponge particles. Two days after (C), common tract bronchial arteriography showed overt stenosis (black asterisk) and occlusion (white asterisk) of the bronchial branch arteries.

respectively. The diameters of NBCA-LP present in bronchial branch arteries were 127-1240 μm (Table 4), and that of GSPs were 107-853 μm. Either NBCA-Lp or GSPs were identified in bronchial branch arteries ⩾ 100 μm in the adventitia. No NBCA-Lp or GSPs were found in vessels < 100 μm, including numerous fine vessels inside the bronchial cartilage (Figure 3A).

Response to embolic materials

Arteries embolized with NBCA-Lp were dilated and NBCA-Lp was identified as a bubble-like space containing a red cell thrombus in its internal channel. The appearance of vessel wall adjacent to the bubble-like space was characterized by stripping of endothelial cells and infiltration of inflammatory cells into the vessel wall; the median membrane was thinned or totally replaced by inflammatory cells (Figure 3B). GSPs were identified as a reticular amorphous substance with a blue-purple color on HE staining. Accumulation of inflammatory cells and red cell thrombus formation were observed around GSPs and the interstices. The appearance of vessel wall adjacent to GSPs was characterized by disappearance of endothelial cells and infiltration of inflammatory cells (Figure 3C).

DISCUSSION

Boushy *et al*[18] have described that paraplegia occurred with a frequency of 60% following BAE with particles (29-200 μm), and the smaller particles induced paraplegia with a higher frequency in a canine model. The occurrence of paraplegia is related to anastomosis because of communication between the anterior spinal artery and the intercostal arteries. Liebow *et al*[19] have documented that the left or right bronchial artery in their canine models invariably came from the right intercostal artery. Meanwhile, no paraplegia occurred in our present swine model. All animals had a common trunk of the right and left bronchial arteries without anastomosis to the intercostal artery. A common tract bronchial artery is reported generally to divide from the ventral surface of thoracic aorta with least interaction with the intercostal arteries[20,21]. Then, the different frequency of paraplegia following BAE between the two species appears to depend on the different branching style of the bronchial artery. In clinical situations, when the bronchial arteries branch from the common tract with the intercostal arteries, selective catheterization of the bronchial artery is crucial.

Table 4 Distribution of embolic materials in bronchial branch arteries according to arterialdiameter

Diameter of bronchial branch artery (μm)	NBCA-Lp		GSP	
	Present	Absent	Present	Absent
1000 <	1			1
951-1000				
901-950				2
851-900			1	
801-850	1			1
751-800				
701-750	2			
651-700	2			1
601-650	1			
551-600	1		1	3
501-550	3			1
451-500	1			1
401-450	2			
351-400	4		1	2
301-350	3			
251-300	5			3
201-250	3	3	1	9
151-200	4	4		9
101-150	2	16	2	18
51-100		34		31
50 >		101		116

NBCA-Lp: N-butyl cyanoacrylate-lipiodol; GSP: Gelatin sponge particles.

In both the NBCA-Lp and GSP groups, occlusion of the bronchial artery was confirmed by angiography immediately after BAE. In the GSP group, angiography 2 d after revealed partial recanalization of the bronchial arteries, whereas in the NBCA-Lp group, catheterization of the bronchial artery was difficult because of severe stenosis or complete occlusion. Occlusion was confirmed by CT as accumulation of NBCA-Lp in the principal branch artery. The duration of occlusion of the bronchial artery was greater in the NBCA-Lp group than GSP group. In histological specimens, the presence of NBCA-Lp was fulfilled as a cast, whereas GSPs were dispersed in the vessels. These results support the clinical findings that the frequency of recurrent hemoptysis was 23%-33% after embolization with GSPs[8,22] and/or PVA particles, and 10%-16.6% after NBCA-Lp embolization[8,14].

Histological examination of the lungs revealed no pulmonary infarction. The embolic materials of NBCA-Lp and GSPs were not observed in the pulmonary artery and pulmonary vein but in the bronchial branch arteries whose diameters were > 100 μm. Most rich bronchial-pulmonary artery anastomoses < 50 μm in diameter are reported to exist in the walls of the respiratory bronchioles and to supply the parenchyma of the lung[19,23]. NBCA-Lp and GSPs did not reach these anastomoses, and the circulation of the pulmonary parenchyma following BAE must have come from the pulmonary arterial circulation, resulting in no damage to the pulmonary parenchyma.

With regard to bronchial wall necrosis, according to the report of Boushy *et al*[18], all dogs that underwent

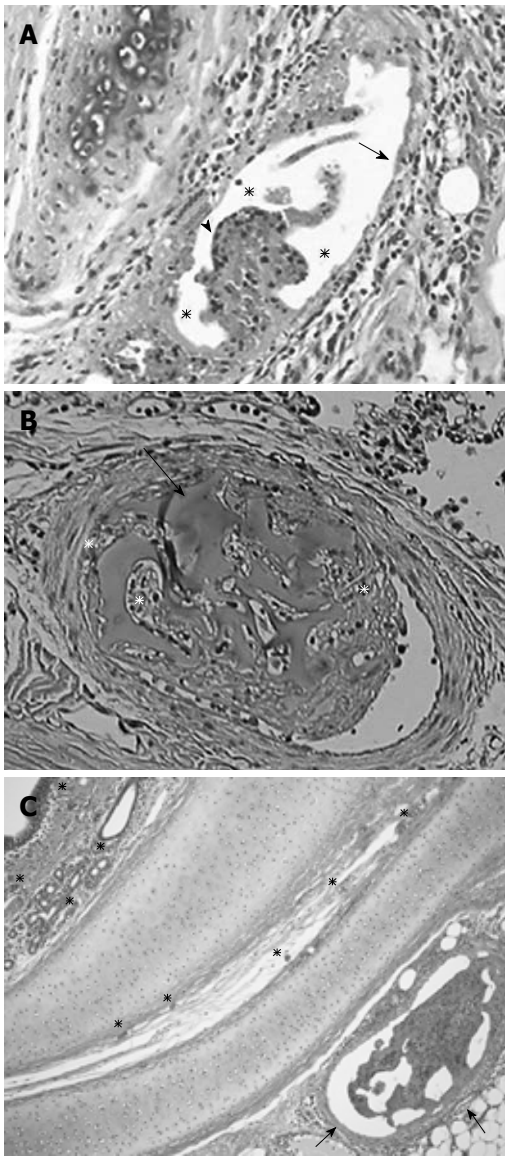

Figure 3 Microscopic study. A: The bronchial branch artery with embolization of n-butyl cyanoacrylate lipiodol (NBCA-Lp) shows that the bubble-like space corresponds to NBCA-Lp (asterisks) containing red thrombus (arrowhead), with stripping of endothelial cells (arrow) and infiltration of the inflammatory cells (hematoxylin eosin stain × 100); B: The bronchial branch artery with embolization of gelatin sponge particles (GSP) shows amorphous substance corresponding to GSP (arrow) surrounded by red thrombus with infiltration of inflammatory cells (asterisks) (hematoxylin eosin stain × 100); C: The bronchial wall revealed the bronchial branch artery (arrows) embolized with NBCA-Lp outside the cartilage and the patency of numerous fine networks (asterisks) in the submucosal and cartilage layers (hematoxylin eosin stain × 100).

BAE with glass microspheres (29 μm or 62 μm) caused bronchial wall necrosis. Ivanick *et al*[8] have reported that embolic materials < 350 μm should not be used because Pump[23] has reported two types bronchopulmonary anastomoses of 24-48 μm and 72-325 μm. Ikoma *et al*[24] have reported that histological examination of the lungs following BAE with NBCA-Lp in humans revealed no damage to the bronchial wall but they did not clarify the safety basis. Our present histological examination revealed that NBCA-Lp and GSPs were found in the bronchial branch arteries < 350 μm in diameter with a

frequency of 53% (9/17) and 50% (3/6), respectively. Then, despite both embolic materials reaching the bronchial arteries < 350 μm in diameter, no damage to the bronchial wall was found. The bronchial walls comprise endothelial, mucosal, submucosal, smooth muscle, bronchial cartilage and adventitial layers. The bronchial arteries are distributed from the adventitia to the submucosal layer and supply blood to the bronchial wall. NBCA-Lp and GSPs were found in the bronchial arteries situated outside the bronchial cartilage but not in the fine vessels in the submucosal and the cartilage layers, because the caliber of the fine vessels was too small for NBCA-Lp or GSPs to traverse. According to Pump[23,25], bronchial arteries supply the numerous fine vessels (arterioles) to the bronchi and form a rich collateral circulation with other systemic arteries present in the esophagus, pericardium and mediastinal pleura. BAE with NBCA-Lp or GSPs resulted in occlusion of the bronchial branch artery present at the adventitia, but patency was retained in the fine vessels near the internal membrane of the bronchial wall, appearing to induce no significant ischemic damage to the bronchial wall. In the clinical situation, liquid embolic material at a ratio of NBCA 1 to Lipiodol of 1 to 7 or less for BAE is considered to be least harmful.

The present study had some limitations, which is restricted to normal lung in swine but not to hemoptysis in either normal or inflammatory lung. The degree of damage of the pulmonary parenchyma and the bronchus following embolization may be greater or less in the deviation between the swine model and clinical model for patients. A further clinical study using two embolic materials is mandatory. In addition, we did not consider the negative effect of a time elapse longer than 2 d.

In conclusion, although limitations exist, NBCA embolization causes more prolonged occlusion of the bronchial artery than GSP embolization. NBCA and Lipiodol at a ratio of 1 to 7 and GSPs were present in bronchial branch arteries ⩾ 100 μm in diameter, inducing no significant harm to the bronchial wall and pulmonary parenchyma.

COMMENTS

Background

Bronchial artery embolization (BAE) with n-butyl cyanoacrylate (NBCA) instead of particles is reported to enhance the potency of the occlusion, aiming to reduce the incidence of recurrent hemoptysis, but it is anticipated that peripheral occlusion with higher potency BAE causes damage to the bronchial wall and pulmonary parenchyma.

Innovations and breakthroughs

The embolic materials of NBCA-lipiodol and gelatin sponge particles (GSPs) were not observed in the pulmonary artery and pulmonary vein but in the bronchial branch arteries whose diameters were > 100 μm. Most rich bronchial-pulmonary artery anastomoses < 50 μm in diameter are reported to exist in the walls of the respiratory bronchioles and to supply the parenchyma of the lung. NBCA-lipiodol and GSPs did not reach these anastomoses.

Applications

In the clinical situation based on this experimental study, liquid embolic material at a ratio of NBCA 1 to lipiodol of 1 to 7 or less for BAE is considered to be least harmful.

Peer review

This is a good experimental study which clarified that NBCA owned the more potency of occlusion than GSPs, and the both NBCA and GSP were present in the bronchial branch arteries of 100 μm or greater, indicating the safety of bronchial wall and pulmonary parenchyma after BAE.

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BRIEF ARTICLE

Potential of ^{18}F-FDG-PET as a valuable adjunct to clinical and response assessment in rheumatoid arthritis and seronegative spondyloarthropathies

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Abstract

AIM: To evaluate the role of fluorine-18-labeled fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in various rheumatic diseases and its potential in the early assessment of treatment response in a limited number of patients.

METHODS: This study involved 28 newly diagnosed patients, of these 17 had rheumatoid arthritis (RA) and 11 had seronegative spondyloarthropathy (SSA). In the SSA group, 7 patients had ankylosing spondylitis, 3 had psoriatic arthritis, and one had non-specific SSA. Patients with RA were selected as per the American College of Rheumatology criteria. One hour after FDG injection, a whole body PET scan was performed from the skull vertex to below the knee joints using a GE Advance dedicated PET scanner. Separate scans were acquired for both upper and lower limbs. Post-treatment scans were performed in 9 patients in the RA group (at 6-9 wk from baseline) and in 1 patient with psoriatic arthropathy. The pattern of FDG uptake was analysed visually and quantified as maximum standardized uptake value (SUVmax) in a standard region of interest. Metabolic response on the scan was assessed qualitatively and quantitatively and was correlated with clinical assessment.

RESULTS: The qualitative FDG uptake was in agreement with the clinically involved joints, erythrocyte sedimentation rate, C-reactive protein values and the clinical assessment by the rheumatologist. All 17 patients in the RA group showed the highest FDG avidity in painful/swollen/tender joints. The uptake pattern was homogeneous, intense and poly-articular in distribution. Hypermetabolism in the regional nodes (axillary nodes in the case of upper limb joint involvement and inguinal nodes in lower limb joints) was a constant feature in patients with RA. Multiple other extra-articular lesions were also observed including thyroid glands (in associated thyroiditis) and in the subcutaneous nodules. Treatment response was better appreciated using SUVmax values than visual interpretation, when compared with clinical evaluation. Four patients showed a favourable response, while 3 had stable disease and 2 showed disease progression. The resolution of regional nodal uptake (axillary or inguinal nodes based on site of joint involvement) in RA following disease modifying anti-rheumatoid drugs was noteworthy, which could be regarded as an additional parameter for identifying responding patients. In the SSA group, uptake in the affected joint was heterogeneous, low grade and non-symmetrical. In particular, there was intense tendon and muscular uptake corresponding to symptomatic joints. The patients with psoriatic arthritis showed intense FDG uptake in the joints and soft tissue.

CONCLUSION: ^{18}F-FDG PET accurately delineates the

ongoing inflammatory activity in various rheumatic diseases (both at articular and extra-articular sites) and relates well to clinical symptoms. Different metabolic patterns on FDG-PET scanning in RA and SSA can have important implications for their diagnosis and management in the future with the support of larger studies. FDG-PET molecular imaging is also a sensitive tool in the early assessment of treatment response, especially when using quantitative information. With these benefits, FDG-PET could play a pivotal clinical role in the management of inflammatory joint disorders in the future.

Key words: Rheumatoid arthritis; Ankylosing spondylitis; Psoriatic arthritis; Seronegative spondyloarthropathies; Fluorine-18-labeled fluorodeoxyglucose positron emission tomography; Axillary node; Treatment monitoring

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INTRODUCTION

With more than two decades of fluorine-18-labeled fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) use in the evaluation of oncological diseases, it is now perceived by the medical fraternity that inflammatory lesions concentrate ^{18}F-FDG to a sufficient extent to provide diagnostic and functional information on inflammatory disease activity. This observation has led several investigators to use ^{18}F-FDG PET imaging to assess various inflammatory joint disorders, particularly rheumatoid arthritis (RA). These highly morbid rheumatic disorders (RDs) affect approximately 1%-2% of the total world population[1]. Among these diseases, the incidence of RA increases with age up to about the seventh decade of life (a peak in the 5th decade)[2].

There is a paucity of tests which can be regarded as pathognomonic for RDs. Although a few serological tests have been shown to be specific for RDs, viz. rheumatoid factor (RF), anti-cyclic citrullinated protein antibodies for RA and human leukocyte antigen-B27 for spondyloarthropathies (SPA), many patients with an obvious clinical diagnosis have negative serum markers. Thus, RDs are also frequently classified grossly as "seropositive and seronegative rheumatoid diseases" referring to those with positive RF and negative RF, respectively. This also determines the treatment strategies for RDs. Radiographic examinations are routinely used for the assessment of joint erosions, and features of disease progression usually conclude that the "point of no return" has been reached in such disorders. However, this modality lacks the ability to detect early inflammation. Recently, magnetic resonance imaging (MRI), especially for finger lesions, has become important as it delineates synovial inflammation as contrast-enhanced lesions with excellent anatomical resolution. However, the tendency of RDs to involve large joints, especially in SPA (asymmetrically throughout the body), limits the application of MRI.

The usefulness of PET using FDG-PET to assess synovial inflammation, has been evaluated by a few investigators[3-7], especially in the setting of RA. Most of these studies produced promising results and were able to quantify inflammation in the joints. Despite these reports, translation into routine clinical practice requires further data including an examination of its potential to assess response to standard therapeutic regimens in RDs. To date, disease modifying anti-rheumatoid drugs (DMARDs) are the mainstay of treatment in RDs. With the advent of biological therapies (e.g., tumor necrosis factor-α), treatment strategies are changing from symptomatic relief to remission of the disease. This also demands a modality that is reliable for determining the resolution of inflammatory processes in the affected joints and possibly at extra-skeletal sites. The role of routine cross-sectional imaging modalities is substantially limited. Thus, in the present study, we endeavoured to evaluate early treatment response to DMARDs in a group of patients with RA, while assessing the whole body (WB) metabolic patterns on FDG-PET in patients with various RDs.

MATERIALS AND METHODS

Subjects

Twenty eight patients with different RDs underwent WB FDG-PET studies (Table 1), 17 of these patients had RA (seropositive) and 11 patients had seronegative spondyloarthropathy (SSA). Of the 11 patients with SSA, 7 had ankylosing spondylitis (AS), 3 had psoriatic arthritis (PsA) and 1 had non-specific SSA (nsSSA). The study protocol was approved by the Institutional Ethics Committee, and informed consent was obtained from each patient.

The selected RA patients fulfilled the American College of Rheumatology revised criteria[8-10] for the diagnosis of RA. The diagnosis of SSA was purely based on clinical assessment. Treatment response was focused only on RA patients, with one PsA patient undergoing response evaluation (RE). The detailed clinical and laboratory parameters undertaken by the rheumatologist are shown in Table 2.

Methods

Imaging was performed after ensuring more than 6 h

Table 1 Characteristics of patients included in the study

No.	Characterstics	Ankylosing spondylitis	Psoariatic arthritis	Non specific SSA	Rheumatoid arthritis
1	Total number of patients	7	3	1	17
2	Male: female ratio	All male	2:1	Male	All female
3	Age range	17-40 yr (mean = 28.6 yr)	34-53 yr (mean = 42 yr)	19 yr	27-60 yr (mean = 40 yr)

SSA: Seronegative spondyloarthropathy; M: Male; F: Female.

Table 2 Clinical and laboratory parameters adjudged for inclusion and exclusion of each patient and designating them to a particular group

Inclusion criteria
Positive ACR criteria[8-10] (at least 4 out of 7) for designating RA
Clinical diagnosis of specific seronegative spondyloarthropathy[1]
Positive or negative RA factor
Classical symptoms with raised ESR (> 30 mm/h)
Classical symptoms with raised C-reactive protein (> 20 mg/L)
HLA-B27 positive with supportive clinical diagnosis[1]
Newly diagnosed and not received any form of treatment.
Exclusion criteria
Had been treated with any DMARD/steroids earlier.
Uncontrolled diabetics

[1]Clinical diagnosis was based upon thorough clinical assessment. ACR: American College of Rheumatology; RA: Rheumatoid arthritis; ESR: Erythrocyte sedimentation rate; HLA: Human leukocyte antigen; DMARD: Disease modifying anti-rheumatoid drugs.

Table 3 The erythrocyte sedimentation rate and C-reactive protein characteristics of studied patients

Type of RD	No. of patients	ESR range (mm/h)	CRP levels (mg/L)
RA	17	< 10 to 640	< 5 to 46.14
AS	7	30 to 92	< 5 to 20
PsA	3	27 to 30	20 to 29
nsSSA	1	31	23.1

RD: Rheumatic disorder; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RA: Rheumatoid arthritis; AS: Ankylosing spondylitis; PsA: Psoriatic arthritis; nsSSA: Non-specific seronegative spondyloarthropathy.

fasting and blood glucose levels below 150 mg/dL. Approximately 10 mCi of ^{18}F-FDG was injected intravenously through a secure IV line. One hour after FDG injection, WB PET scanning was performed from the skull vertex to below the knee joints using a GE Advance dedicated PET scanner. Separate scans were acquired for upper limbs (elbow, wrist and hands) and leg (ankle and feet). The PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (2 iterations, 8 subsets). Standard axial, coronal, sagittal and maximum intensity projection images were generated. Post-treatment scans were performed in 9 patients in the RA group at 6-9 wk after initiating therapy, with protocols maintaining the same standards as an earlier study (i.e. blood glucose < 150, waiting duration of 60 min, and similar reconstruction algorithms).

The pattern of FDG uptake was analysed in the small joints of hands and feet, wrists, elbows, shoulders and sacroiliac (SI) joints, knees, hips and ankle joints as well as the atlanto-axial joint (total of 21 joints). The small joints of the hands and feet (interphalangeal, metacarpo/tarso-phalangeal and carpal/tarsal joints) were collectively considered as single units for the ease of quantitation. A dedicated work station was used to draw circular regions of interest covering each joint and to calculate the maximum standardized uptake value (SUVmax) of each joint. FDG uptake in extra-articular sites such as lymph nodes, tendons, soft tissue nodules was also noted and SUVmax was measured. FDG uptake in affected joints was also evaluated qualitatively and categorised as follows; no uptake (same as background); mild uptake if more than background, but less than liver; moderate uptake (same as in liver); high uptake if higher than in liver, but less than brain, and intense uptake if equal to or more than brain. The method was based on the scoring system by Kubota *et al*[7] with modifications.

The number of painful/swollen joints, the white blood cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were evaluated within 5 d of the PET examination during pre- and post-treatment scans. The patients who were evaluated for response received standard regimens of DMARDs either as monotherapy or a combination of two drugs with or without steroids.

RESULTS

This study included 28 newly diagnosed patients with either RA or SSA. Of these patients, 17 had RA (all RF positive) and 11 had SSA (7-AS, 3-PsA, 1-nsSSA) (Figures 1-4). The clinical and serological details of the patients are shown in Tables 1 and 3. Female predominance was noted in the RA group, while males predominated in the SSA group.

Visual assessment in the RA group

FDG-PET imaging features in the joints of RA patients: Seventeen patients with newly diagnosed RA were studied in this group of which 9 were evaluated for RE following therapy. Eight patients were lost to follow up. FDG uptake was in agreement with clinical presentation and symptoms; as all the painful and/or swollen and/or tender joints showed considerable FDG avidity (in the high to intense category). Metabolically, the wrist joint was the most common and predominantly affected (13/17) followed by the ankle joints. Although RA is

Table 4 Response details in patients with rheumatoid arthritis: Fluorodeoxyglucose positron emission tomography *vs* clinical assessment

Sr. No.	No. of joints involved	Clinical assessment	% change in SUVmax
1	10	Mixed symptoms	Knee = 64% ↓ Ankle = no change Wrist = 51.7% ↑ Elbow = 47% ↓
2	4	Progressive disease	Knee = 44% ↑ Ankle = 33% ↑
3	2	Improvement	Wrists = 62% ↓
4	6	Improvement	Ankle = 23% ↓ Wrist = 45.2% ↓
5	4	Improvement	Wrist = 73 % ↓ SJH* = 34% ↓
6	6	Improvement	Ankle = 43.3% ↓ Wrists = 23 % ↓ SJF* = 24.5% ↓
7		No response	No change
8		No response	No change
9	2	Progressive disease	Wrists = 48% ↑

SUVmax: Maximum standardized uptake value.

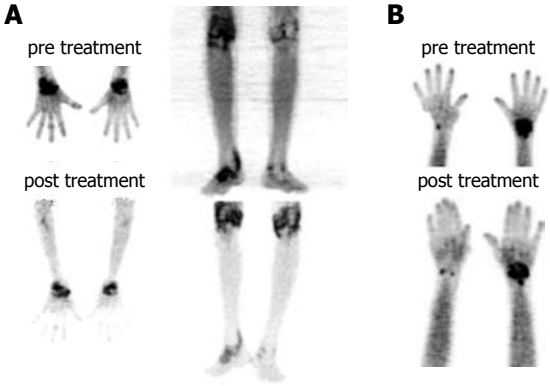

Figure 1 Images of response assessment in rheumatoid arthritis. The patient on the left side was a responder and right side was a non-responder. A: A good response to the hydroxyquinone, methotrexate and prednisolone treatment (at 6 wk) on follow up scan. The pre treatment maximum standardized uptake value (SUVmax) values were 10.6 in right wrist which fell to 4.0 on post treatment scan; B: An example of non-responder. The pre treatment SUVmax value was 2.9 while that of post treatment with hydroxyquinolone, methotrexate and prednisolone was 4.3. The similarity of the uptake in pre and post treatment scan made it difficult to interpret progression on visual basis. The patient had no symptomatic relief clinically.

known to involve multiple joints, 4 patients showed intense uptake in only one joint, predominantly (3) in the wrists. Only one patient showed uptake in the small joints of the feet.

Extra-articular FDG uptake pattern in RA: Different areas of extra-articular soft tissue FDG uptake were found in 10 patients. The most common sites were axillary lymph nodes (9 patients), epitrochlear lymph node (1 patient), cervical lymph nodes (2 patients), thyroid gland (3 patients) and subcutaneous (possibly rheumatoid) nodules (2 patients). Only 2 patients with RA showed mild FDG uptake in the tendons associated with inflamed joints. One patient, who was anaemic, also showed increased FDG avidity in the bone marrow.

Quantitative FDG-PET parameters in the RA group

SUVmax values in the inflamed joints ranged from 3.1 to 11.5. During the RE scan, clinical evaluation in 9 patients showed symptomatic improvement in 4, mixed relief in 1, persistent symptoms but no progression in 2 and progressive disease in 2 patients. The SUVmax values on RE scans ranged from 2.2 to 9.3. Good correlation was observed between SUVmax values and clinical response to therapy. The detailed data of response assessments are shown in Table 4. However, on visual analysis of response, the uptake pattern in most of the joints remained in the high to intense category, although patients who had improved showed reduced joint FDG avidity, as measured by SUV estimation. Significant intra-observer and inter-observer variation was noted when comparing pre- and post-treatment scans in the visual assessment. Thus, SUVmax values were considered appropriate for the assessment of treatment response.

Results in patients with SSA

The FDG uptake pattern observed in SSA patients was different from that observed in RA patients. A total of 11 WB scans were acquired which predominantly included patients with AS (n = 7). FDG uptake in the affected joints was heterogeneous and of varying intensity (from mild to high). Interestingly, FDG uptake in patients with AS was not observed and uptake in the SI joints or the spine typically ranged from 2.66 to 3.703 (mean SUVmax 3.1), which were the predominant sites of pain in these patients. Enhanced FDG uptake was more asymmetrical than that observed in RA patients. FDG hypermetabolism was noted in the bilateral SI joints, and asymmetrical uptake was observed in the sternoclavicular, shoulders, hip and facet joints. There was significant evidence of tendon and muscular uptake corresponding to the symptomatic joints. A few patients also showed abnormal FDG uptake in the interosseous membranes of the legs (Figure 4A). This favours enthesitis as the proposed pathogenesis of SPA[11,12]. The most common tendons with abnormal FDG uptake were the calcaneal tendons (Figure 4B).

The patients with psoriatic arthritis showed high to intense FDG uptake, predominantly in the distal phalangeal joints. The SUVmax values depicting tendon or soft tissue uptake were obvious on visual assessment.

DISCUSSION

In this study, a varying pattern of articular and extra-articular activity was observed in various rheumatic diseases detected by WB PET scans. FDG PET delineated a varying pattern of inflammatory activity in the affected joints and extra-articular sites that could also be quanti-

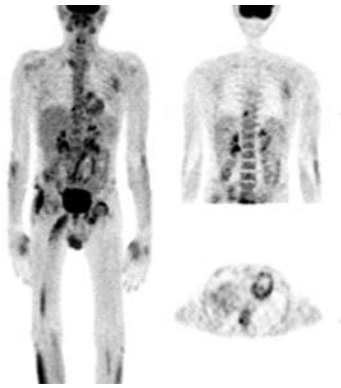

Figure 2 The asymmetrical fluorodeoxyglucose uptake pattern in a newly diagnosed patient with ankylosing spondylitis. The asymmetrical heterogeneous fluorodeoxyglucose (FDG) uptake is noted right sternoclavicular, left hip and a solitary facetal joint in dorsal spine. High to intense FDG uptake is seen in soft tissue of right thigh (probably fascia lata) and right lower limb muscles. Even one could notice the soft tissue FDG activity in tendons of small joints of hands.

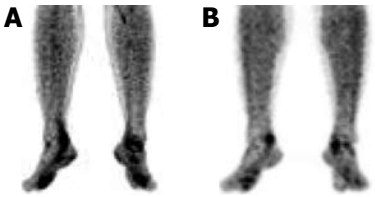

Figure 4 Assessment of treatment response in a patient of psoriatic arthritis. A: Pre treatment; B: Post treatment. The fluorodeoxyglucose-positron emission tomography lower-limb scan of a patient with psoriatic arthritis. Rest of the whole body survey was unremarkable. Same patient was followed and a response evaluation scan was performed 6 wk after specific treatment for psoriatic arthropathy. There was significant fall in maximum standardized uptake value values correlating to the clinical improvement in the patient.

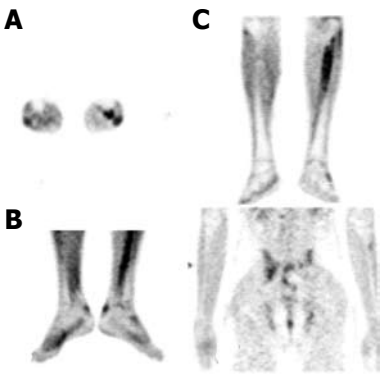

Figure 3 Soft tissue uptake in patient with seronegative spondyloarthropathy. A: The fibrous tissue uptake in the interosseous membrane of left leg; B: The bilateral calcaneal tendonal tracer activity; C: Fluorodeoxyglucose (FDG)-positron emission tomography in another patient with ankylosing spondylitis demonstraing the heterogeneous FDG uptake in the bilateral sacroiliac joints.

fied using SUV values. The FDG uptake patterns were in agreement with the clinically inflamed/tender/swollen joints, the acute phase reactants (ESR, CRP) and the clinical assessment and diagnosis by the rheumatologist. The WB scan provided an assessment of disease extent by showing the variable intensity of metabolic activity in the inflamed synovial joints in RA and the enthesitis in SSA which correlated with the patient's symptoms. The successful assessment of small as well as large joints in the present study supported the results of previous studies which specifically assessed either small[5] or large[7] joints. The efficacy of WB FDG-PET in RDs in this study was similar to that in these previous studies and suggests that WB FDG uptake represents disease activity in joints affected by RDs.

In RA patients, the uptake pattern was diffuse and homogeneous, and intense metabolic activity corresponding to the joint space was poly-articular in distribution. This in turn, correlated with the pathology of cytokine-induced hyperactive and hyperplastic inflamed synovial membrane ("pannus") laden with macrophages. Macrophages are known to use glucose as a major metabolic substrate[13]. In contrast, the FDG uptake was mild to moderate in the affected joints of SSA patients. This also signifies the major difference between RA and SSA, where the latter lacks the "pannus". However in SSA, increased metabolic activity was noted in fibrous tissue such as tendons, osseous membranes and muscle (fascia) corresponding to the affected joints. The primary pathology of SPA is "enthesitis" with chronic inflammation. Cytokines and other inflammatory markers are also important in the inflammatory process which ultimately leads to fibrosis and ossification at sites of enthesitis. Early lesions including subchondral granulation tissue erode the joint and is gradually replaced by fibrocartilage and then ossification[11,12]. This pathogenesis is proposed to lack the presence of a large population of inflammatory cells at the affected joints, which could be the reason for our observation of low grade metabolic activity in affected joints in this group of patients. The inflamed fibrous tissue in the peri-articular region showed high metabolic activity.

We found a different metabolic pattern in patients with RA and SSA (especially AS) which correlated with their pathogenesis. Such uptake patterns can have implications for differentiating RA and SSA from degenerative diseases (e.g., osteoarthritis) involving major joints such as knee, hip and SI regions in challenging situations. This will be particularly useful in elderly patients where it is difficult to differentiate between SSA and osteoarthritis. SSA also lacks the specific inflammatory markers associated with RA, therefore, FDG-PET may be useful in such cases. Further studies are required to assess the potential efficacy of FDG PET in this area.

In the RE in a small group of RA patients and a patient with PsA, our study showed a variation in SUVmax values in inflamed joints which correlated with clinical assessment. The visual assessment of FDG uptake in inflamed joints was not found to be useful as major intra- and inter-observer variability was observed. This finding is in contrast to the response assessment performed by Elzinga *et al*[14], who studied WB FDG-PET in patients

with RA using a visual evaluation score, and concluded that FDG uptake was significantly correlated with clinical evaluations of disease activity in patients with RA before and after treatment with infliximab. Our findings are in agreement with those of Kubota *et al*[7] and Goerres *et al*[6] who also recommend the use of a FDG uptake scoring system as a useful tool in the assessment of joint inflammation. The difference between the results of Elzinga *et al*[14] and the other studies could be due to the use of different treatment modalities (biological *vs* cytoreductive) and duration of the RE scan. However, based on our findings, we recommend the use SUVmax values as quantitative parameters for the assessment of treatment response in RDs. The additional evaluation using visual scoring methods may also be beneficial. The finding of regional lymph node hypermetabolism in RA patients (based on the involved joints) is in agreement with previous reports[15,16]. In patients with RA, we also observed resolution of regional nodal uptake (axillary or inguinal nodes based on the site of joint involvement) following DMARD therapy, which can be regarded as an additional parameter for identifying responding patients. The clinical implications of this observation require to be explored further. The limitations of this study include (1) small sample size and (2) low percentage of patients who took part in the post-treatment study. Therefore, further well-powered prospective studies would help to determine more definitive conclusions. In addition, the use of SUV values requires careful attention to the PET imaging protocol, patient preparation, measurement of blood glucose levels, waiting period, scan duration, reconstruction techniques and methods of SUV calculation.

Thus, we conclude that FDG-PET demonstrates varying patterns of metabolic activity in articular and extra-articular sites in various inflammatory joint disorders. Different metabolic patterns on FDG-PET studies in RA and SSA patients may play a diagnostic role in the future with the support of larger studies. FDG PET can also serve as an objective tool in the early assessment of treatment response in affected patients, especially with the use of quantitative information. With these benefits, FDG-PET could play a significant clinical role in the management of a wide spectrum of inflammatory joint disorders.

COMMENTS

Background

The potential of metabolic imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) is being increasingly explored in several inflammatory disorders. The advantage of evaluating the whole body in a single examination is a major advantage of this modality which is preferable in systemic inflammatory disorders.

Innovations and breakthroughs

It is postulated that under the influence of cytokines and growth factors, activated inflammatory cells demonstrate enhanced FDG due to increased expression of glucose transporters. Recent reports have highlighted the increasing importance of FDG-PET in assessing various infective and inflammatory disorders such as osteomyelitis, pyrexia of unknown origin, painful joint prosthesis, vasculitis and sarcoidosis, and thus have demonstrated the potential of this technique in becoming the radionuclide imaging procedure of choice in many of these inflammatory conditions. However, there is a paucity of data on its usefulness in inflammatory joint disorders, the majority of which are systemic in nature. In the present study, the authors explored the usefulness of FDG-PET-based molecular imaging in depicting inflammatory activity at various skeletal and extra-skeletal sites.

Applications

Understanding the various metabolic patterns depicted by FDG-PET both at the articular and extra-articular sites can have important implications for their diagnosis and evolving therapeutic strategies in patients with inflammatory joint disorders. FDG-PET molecular imaging using quantitative methods may also prove to be an important diagnostic tool in the early assessment of treatment response. If similar findings are obtained in larger studies in the near future, FDG-PET could play a pivotal role in management of inflammatory joint disorders.

Peer review

This is a good study which clarified that ^{18}F-FDG PET accurately delineates the ongoing inflammatory activity in various rheumatic diseases (both at articular and extra-articular sites) and relates well to clinical symptoms.

NBCA owned the more potency of occlusion than GSPs, and the both NBCA and GSP were present in the bronchial branch arteries of 100 mm or greater, indicating the safety of bronchial wall and pulmonary parenchyma after BAE.

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2012 35th Annual Meeting
Miami, FL 33169, United States

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2012
Rome, Italy

February 13-16, 2012
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Palm Beach, FL 33480, United States

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ASSR 2012 Annual Symposium
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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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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