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A pilot study of the correlation between lymph node metastasis in colorectal cancer patients found by pre-operative ^{18}FDG PET/CT scan and results of final histopathology

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Keywords:
^{18}FDG-PET/CT, colorectal cancer, lymph node metastasis

OBJECTIVE. The purpose of this research is to compare the association between the diagnostic values of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) scan (maximum standardized uptake value - SUV) for pre-operative lymph nodes status and the final histopathology report.

MATERIALS AND METHODS. This retrospective study gathered the information from patient medical records at Bangkok Hospital Medical Center. The patients were examined for colorectal cancer from May 2007 to November 2009 and received the pre-operative positron emission tomography/computed tomography (PET/CT) scan before having oncologic colorectal surgery during the time period mentioned above. The subjects in this study numbered 30 patients. Each ^{18}FDG PET/CT scan was reviewed and interpreted by one nuclear medicine professional who had no prior knowledge of patient details, including the diagnosis of any previous PET/CT scans.

RESULTS. Results demonstrated that the PET/CT scan correctly identified 24 out of 30 patients to have pre-operative lymphadenopathies. Moreover, 14 out of those 24 patients (58.3%) showed metastatic lymphadenopathies in the final histopathology. The remaining 2 out of 6 patients (33.3%) had metastatic lymphadenopathies according to final histopathology, but ^{18}FDG PET/CT did not detect them. There was a significant differentiation (p = 0.014) between the mean of the SUV in malignant lymphadenopathies (1.18 ± 0.69) and those of benign lymphadenopathies (0.59 ± 0.54) in primary colorectal cancer patients.

CONCLUSION. There was a clear association between pre-operative diagnosis of suspicious malignant lymphadenopathies by PET/CT scan and final histopathological lymphadenopathies. It will be beneficial to see further studies about the predictive role of using pre-operative ^{18}FDG PET/CT scanning in diagnosis of lymph node metastasis in colorectal cancer patients. The pre-operative PET scans of our colorectal cancer patients showed a higher uptake of ^{18}F-fluorodeoxyglucose (^{18}FDG) in malignant lymph nodes.

It is very common to use magnetic resonance imaging (MRI), computed tomography (CT) to evaluate the pre-operative lymph node status in colorectal cancer patients. However, the low sensitivity can lead to bias and incorrect evaluation.[1,2] The latest technology, which uses positron emission tomography/computed tomography. ^{18}FDG PET/CT is becoming more popular, especially with regard to using the surveillance and pre-operative staging to assess recurrence of disease and distant metastases.

Yoshiyuki's research[3] reported that the using of PET/CT scan for pre-operative diagnosis of lymph mode metastasis of colorectal cancer gives a sensitivity of around 51.2%, specificity of around 85.1% and accuracy of around 69.3% for the regional node group.The purpose of this research was to study the association between the diagnostic value of ^{18}FDG PET/CT scan (maximum standardized uptake value - SUV) for pre-operative lymph nodes status and the results shown by the final histopathology.

Materials and Methods

This was a retrospective study which gathered the information from patient medical records at Bangkok Hospital Medical Center. The patients were examined for colorectal cancer between May 2007 and November 2009; they received the pre-operative ^{18}FDG PET/CT scan before having oncologic colorectal surgery. The subjects in this study numbered 30 patients, 20 males and 10 females. The average age was 63, and 64.4 years old respectively for male and female patients. Table 1 shows the locations of primary tumors revealed in the colon of 20 patients and the rectum of 10 patients. However, in this sample, the primary tumor of one patient was not detected by ^{18}FDG PET/CT scan (post incomplete polypectomy) and the lymph node status of 6 patients was not revealed either.

Inclusion / Exclusion Criteria

The records of inpatients with carcinoma of rectum and/or colon (code ICD10), who were examined and operated on between May 2007 and November 2009, showed that every patient was examined by ^{18}FDG PET/CT scan in order to evaluate distant metastases within the 2 week period prior to their operations, and had tissue histopathology to confirm the diagnosis before surgery. Diabetic patients fasting blood sugar (FBS) should have been lower than 200 mg%, or have foregone insulin injection before having ^{18}FDG for PET/CT scan.

PET/CT scans Technique

The ^{18}FDG PET/CT, Gimini GXL was used for this study. The scintillator was gadolinium oxyorthosilicate (GSO) with a detector dimension of 4x6x30 mm. The axial field of view was 16.2 cm with sensitivity of 8.3 cps/kBq. Peak noise equivalent count rate (NECR) was 70 kcps. The transverse and axial resolutions were 5.1 and 5.5 respectively. The CT mode was used for attenuation correction. All patient fasted 6 hours; fasting blood sugar was less than 200 mg%. Patients were injected with a dosage of 0.14 mCi/Kg of ^{18}FDG. Then after resting for 1 hour, the study was begun. The field of study included the base of the skull down to the upper thighs. CT scan technique: Detector type was cadmium tungstate (CdWO4) with 16 slices; 120 kV, 250 mA.; slice thickness 5 mm. Immediately after CT scan was done, PET scan was performed with total 6 - 7 bed positions. The raw data of PET study was attenuation corrected by using the CT scan, then reformatted into trans axial, coronal and sagittal views.

Interpretations of PET/CT scan

The PET/CT scan was reviewed by one nuclear medicine professional, who had no prior patient detail such as diagnosis of any previous PET/CT scans.The report was interpreted from the SUV of lymph nodes. Moreover, we also had the report on the SUV of primary tumor(s).

Table 1: Demographic data of colorectal cancer patients.

Factor	Sample Size	
Sex	Male (20)	Female (10)
Age	46 - 83 years (mean = 63)	43 - 99 years (mean = 64.3)
Nationality	Thai (13)	Foreigner (17)
Site of primary tumor		
Ascending colon	Male (3)	Female (0)
Transverse colon	Male (2)	Female (0)
Descending colon	Male (4)	Female (2)
Sigmoid colon	Male (4)	Female (5)
Rectum	Male (7)	Female (3)

Statistical Analysis

An association between SUV of lymph node and result from final histopathology was calculated using by Student's t-test. A corrected $p < 0.05$ was considered evidence of statistical significance. Comparison of SUV between each cell types of primary tumor was done, using one-way analysis of variance (ANOVA).[4]

Results

From the review, we have found that the CT scan could identify 24 out of 30 patients with pre-operative lymphadenopathies.The final histopathology showed 14 out of 24 patients (58.3%) with metastatic lymphadenopathies (Figure 1). In addition, there were 6 out of 30 patients whereby the ^{18}FDG PET/CT scan was unable to identify pre-operative lymphadenopathies. The final histopathology showed that 2 out of those 6 patients (33.3%) did have metastatic lymphadenopathies, but the PET could not detect them (Figure 2). The imaging of CT showed no demonstrated regional node enlargement (Figure 3). The mean of the SUV in malignant lymphadenopathies (1.18 ± 0.69) together with benign lymphadenopathies (0.59 ± 0.54) in primary colorectal cancer patient had the significant differentiation ($p = 0.014$) which was shown in Table 2. The mean total of malignant lymph nodes found per patient during colorectal surgery was 13 (range 3 - 25).

The correlation between SUV and cell type of primary tumor, we found that there was no significant difference in the statistic between cell types (well, moderately and poorly differentiated) and SUV ($p = 0.304$) (Table 3). There was only one patient whose the final histopathology of primary tumor revealed lymphoma and we did not include this patient's results for the evaluation.

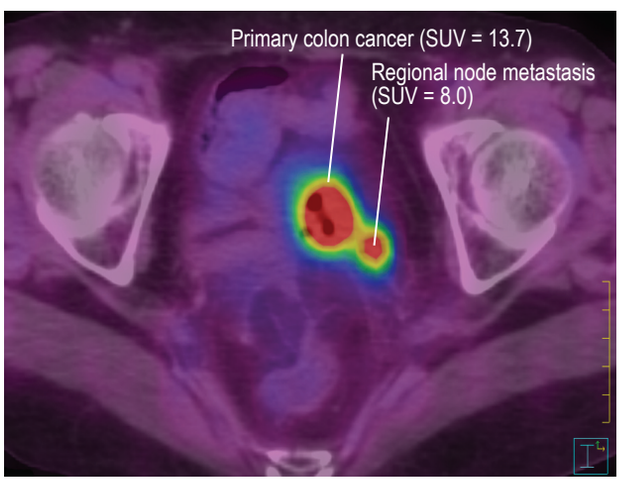

Figure 1 : *True positive PET-CT. This case of primary CA Colon with regional node metastasis SUV 8.0 at right pelvic cavity shows increased uptake.*

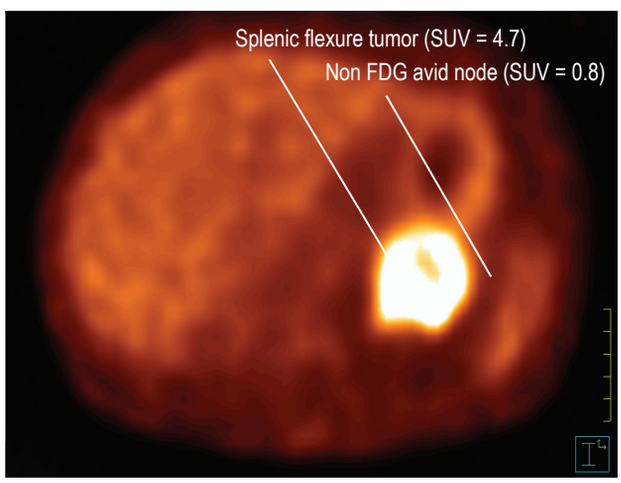

Figure 2 : *False negative PET. This case of primary CA Splenic flexor shows at primary site but regional node has not increased uptake SUV 0.8.*

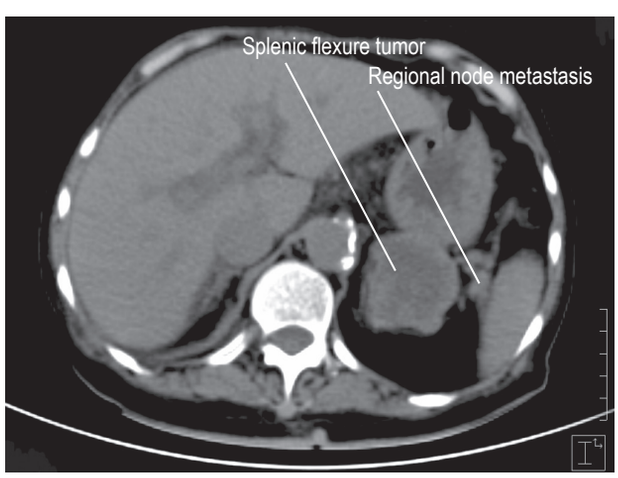

Figure 3 : *False negative CT. This case of primary CA Splenic flexor, only CT study shows no demonstrated regional node enlargement.*

Table 2: Pathological lymph nodes detected by PET/CT.

Characteristic	Malignant LN* (n = 16)	Benign LN* (n = 14)	*p* value
Range SUV	0 - 2.4	0 - 1.8	0.014
Mean ± SD	1.18 ± 0.69	0.59 ± 0.54	

Note_Data was analyzed by Student's t-test ($p < 0.05$)

*LN = Lymph node

Table 3: Comparison of standardized uptake value (SUV) between each cell type of primary tumor.

Characteristic	Pathological diagnosis of each cell type of primary tumor			
	Well differentiated (n = 6)	Moderately differentiated (n = 20)	Poorly differentiated (n = 3)	*p* value
Range SUV	0 - 2.4	0 - 1.8	3.9 - 4.6	0.304
Mean ± SD	1.18 ± 0.69	0.59 ± 0.54	4.2 ± 0.35	

Discussion

The hypothesis is that cancer cells will have a higher glycolysis metabolic rate than normal cells.[5] Given that assumption, using PET scan for ^{18}F-fluorodeoxyglucose (^{18}FDG) detection to count the glucose uptake on the cellular level will help the detection of primary tumors and metastatic lesions. However, different primary tumors have different uptakes of ^{18}FDG. It is believed that important enzymes for glucose uptake in cancer cells are hexokinase and glucose transporters (Gluts), which are located on the cell membrane.[6] Gauthier's study of mitrochondrial hexokinase found that it accounted for 75-80% of total intracellular enzyme activity.[7] Different cell types in colorectal cancer tumors-well, moderate and poorly differentiated - have different enzyme activities, meaning there is a diversity of ^{18}FDG uptake.

Our study however, did not show significant difference of ^{18}FDG uptake between cell type ($p = 0.304$ as shown in Table 3), presumably because of our small sample size. Furthermore, there are many other factors that impact on and account for the variation in ^{18}FDG uptake, which include ^{18}FDG quantity, the time period between ^{18}FDG injections and actual time of PET scan, base line blood sugar before injection of ^{18}FDG, as well as patients' weight and PET scan model used. Other enzyme activities can affect ^{18}FDG uptake, for example glucose phosphatase. Due to the abovementioned factors, it is important to set up the criteria which take these factors into account, in order to reduce the deviation on the ^{18}FDG uptake (SUV) calculation.

Yoshioka's study[8] found that the trend of ^{18}FDG uptake in histological cancer cell line (which is less differentiated in terms of using PET/CT scan to evaluate lymph node metastasis) is close to the primary tumor, if using SUV for the detection. Yoshiyuki also found that there should be more than 1.5 on cut-off point in metastatic lymph node in colorectal cancer.[3] PET/CT scan results in this study, then, also showed the trend of higher uptake of ^{18}FDG in metastatic lymph nodes, compared with non-metastatic lymph nodes. This can be confirmed by the significant result from final histopathology ($p = 0.014$). However, as study was retrospective, it still had the constraint of not being able to exactly confirm that the lymph nodes identified as positive by the ^{18}FDG PET/CT scan, actually matched those lymph nodes detailed in the final histotathology. The size of lymph node is another factor that affects the evaluation of ^{18}FDG PET/CT scan results. It was found that the lymph nodes that may cause metastasis are usually larger than 1 cm.[9, 10]

Conclusion

We show a clear correlation between ^{18}FDG PET/CT diagnoses of suspicious malignancies and final histopathological lymphadenopathies. It is therefore clearly beneficial to further document the pre-operative predictive role of the ^{18}FDG PET/CT scan in diagnosing lymph node metastasis in colorectal cancer patients. One of the constraints of this study, being retrospective, is that we could not confirm the exact correlation between the location of the malignant nodes identified by PET/CT, and those in the final histopathology report.

The pre-operative ^{18}FDG PET/CT scan shows the tendency of malignant lymph nodes to have a higher uptake of FDG than is seen in benign lymph nodes. However, due to our small sample size, the cutoff point of significant SUV could not be exactly calculated. This report will be the basis for further studies in the future.

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Original Article

Detection of Coronary Bypass Graft patency by 256-Slice Multi-detector Computed Tomography

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Keywords:
Coronary bypass graft, 256-MDCT, Invasive coronary angiography, Sensitivity, Specificity, Positive predictive value, Negative predictive value, Accuracy

OBJECTIVE. To evaluate the diagnostic accuracy of 256-slice Multi-detector Computerized Tomography (256-MDCT) in detection of coronary graft patency by comparison with the gold standard invasive coronary angiography (ICA).

MATERIALS AND METHODS. From January 2009 to April 2011, a total of 29 consecutive patients who had previously had CABG surgery were referred to us for assessment of graft patency. A total of 84 coronary bypass graft conduits (38 arterial graft conduits, 46 venous graft conduits) were studied, using 256-MDCT and ICA with iodine contrast intravenous injection. All patients underwent coronary angiography to either confirm result or PCI of graft disease. The diagnostic accuracy of the 256-MDCT for coronary bypass graft evaluation was assessed by comparing it to the ICA in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

RESULTS. A total of 84 grafts were imaged using the 256-MDCT and all grafts were visualized. There was no statistical difference in diagnostic accuracy between MDCT and ICA regardless of the age, size or type of the bypass graft conduit (p value = 0.13). The sensitivity, specificity, positive predictive value, negative predictive value of 256-MDCT in coronary artery bypass graft assessment were 100%, 97.8% , 97.5% and 100 % respectively.

CONCLUSION. The 256-MDCT provides a high accuracy, reliability and feasibility for coronary bypass graft evaluation and the diagnostic accuracy is comparable to the gold standard ICA.

Coronary artery bypass graft surgery (CABG) has been used as an alternative to medical therapy, in treating symptomatic coronary artery disease patients for over forty years as an alternative option to medical therapy.[1] The superior outcome of CABG over medical treatment in terms of survival benefit is clearly documented in patients with left main or three vessels CAD, especially when the proximal left anterior descending (LAD) artery is involved.[2] However, graft degeneration does occur which leads to graft patency reduction to 81% in one year, 75% at 5 years and less than 50% at 15 years for venous graft occlusion.[3] Therefore, verification of graft patency is vital in management of symptomatic patients who have undergone CABG. Although the invasive coronary angiography (ICA) remains the gold standard in assessing graft vessel, a recent meta-analysis study has been shown that the 64-MDCT can offer a comparable result in non-invasive fashion.[4] To date, there has been no comparative study between ICA and 256-MDCT available in Thailand, we therefore conducted a retrospective study to assess the diagnostic accuracy of this new technology by comparing with ICA.

Materials and Methods

From January 2009 to April 2011, 29 CABG patients were referred to our services with suspicious recurrent symptoms of coronary artery disease and all of them had undergone both 256-MDCT scanning and ICA. The exclusion criteria for MDCT scanning were: patients with recurrent myocardial infarction, severe allergy to seafood and iodine contrast agent or serum creatinine levels > 1.5 mg/dL. All patients underwent coronary angiography to either confirm previously indeterminate results or to correct stenotic native coronary vessel or coronary bypass graft by percutaneous coronary intervention (PCI). The bypass graft images from both studies were analyzed and compared in terms of patency and severity of luminal diameter narrowing, i.e., no stenosis (0%), < 50% stenosis, ≥ 50% stenosis or occluded (100% stenosis). Significant stenosis was defined as luminal diameter is narrower ≥ 50% by comparing to the adjacent segments.[5]

CT coronary angiography (CTA)

CT studies were performed on 256-MDCT (Brilliance ICT 256-MDCT, Philips, Netherland) scanner with a 0.27s rotation time. A bolus of iodinated contrast injection volume was calculated by the formula of scan time (5 seconds (s) for coronary artery scanning) plus post threshold delayed time (~5 seconds) and multiplied by flow rate (4.5-6 ml/s) (Phillips company protocol). A contrast bolus was injected into antecubital vein at a flow rate of 4.5-6 ml/s. (Flow rate 6 ml/s of contrast injection was preferred if the patient's body weight > 90 kg), followed by 50 ml saline solution injection. The tracking position was placed at the ascending aorta and scan started automatically at 5 seconds after reaching the threshold (100 - 120 Hounsfield units, HU). Cardiac scanning covered from the aortic arch to 2-3 centimeters below the diaphragm using the following parameters; x-ray tube potential 120-140 KV, tube current 471 MA, slice collimation 128x0.625 mm^2, table speed of 44 mm/s, and pitch 0.16. The mean coronary scan time was of 5.0 s. The retrospective electrocardiographic gating was used for cardiac phase selection. The coronary scan data was completely obtained from two to three consecutive heart beats and the axial slices were reconstructed synchronized to the electrocardiography (ECG). The administration of beta-blockades to lower the heart rate depended on the physician if there were no contraindications. The slice thickness was of 0.67 mm. The CT data was independently and blindly analyzed by three experienced cardiac CT specialists. The vessel analysis was assessed on at least two planes, one parallel and one perpendicular to the course of the vessel.

Invasive coronary angiography (ICA)

ICA was performed by standard technique via femoral approach. At least two orthogonal views were taken for assessing each epicardial artery and coronary bypass graft. The angiograms were separately analyzed by experienced interventionists without prior review of the MDCT images. The angiography results were independently compared with the MDCT results.

Statistical analysis

By using ICA as the gold standard, images from CTA and ICA were compared and analyzed. The sensitivity, specificity, positive and negative predictive values were calculated. Chi-square test was used to analyze the differences between the 256-MDCT and the ICA results and statistical difference was considered when the p value was < 0.05.

Results

Of total 29 consecutive post CABG patients (93% were male), the mean age was 61 ± 27 years old. Most patients, 27 cases (93%) had multiple bypass grafts. The mean age of coronary bypass graft was 10.33 years (ranged 3-25 years). Of total 84 graft conduits, all grafts were obtained and analyzed by 256-MDCT.

Over half of conduits (53.6%) were saphenous vein graft (SVG) and the rest were taken from arterial conduit including left internal mammary artery (LIMA) 33.3% (28/84), right internal mammary artery (RIMA) 3.5% (3/84), left radial artery (LRA) 4.7% (4/84), right radial artery (RRA) 2.4% (2/84) and the gastroepiploic artery (GEA) 1.1%(1/84) (Table 1).

Almost half of the conduits (40/84, 47.6%) had some degree of luminal stenosis. Of these, 73.3% were venous, 17.9% were arterial bypass graft conduits [(10% (4/40) were LIMA , 2.5% (1/40) were RIMA , 5.0% (2/40) were left radial arterial, 10% (1/40) were GEA)]. The diameters of arterial grafts were 2.0-5.2 mm and of the venous 2.5-6.0 mm.

By comparison with ICA, the 256-MDCT demonstrated high sensitivity (100%) and high specificity (97.7%) for coronary bypass graft assessment regardless of the age, size or type of conduit. The positive predictive value was of 97.6%, the negative predictive value was of 100% and the total accuracy was of 98.8% (p = 0.13) (Table 2, 3).

According to the type of coronary bypass graft, the 256-MDCT also demonstrated high sensitivity and high specificity for both arterial and venous grafts (100% sensitivity for both arterial and venous bypass graft, 100% specificity for arterial bypass graft and 93.3% specificity for venous bypass graft) (Table 4-7). With 84 graft conduits, 134 anastomosis sites were obtained. 4.5% (6/134) of total anastomosis sites were stenosis which was lower than the vessel body. The diagnostic accuracy of the anastomosis site assessment was 100% in sensitivity, specificity, positive predictive value and negative predictive value with the *p* value =1.0 when compared against the ICA (Table 8, 9). A further comparison between our study and other meta-analysis studies of the 16-, 64-MDCT[4] revealed no significant difference in outcomes with the exception that the accuracy of the 256-MDCT in coronary bypass graft evaluation were higher than the 16-,64-MDCT which were reported in meta-analysis study (Table 10, 11). Almost all LIMA conduit (27/28, 96.4%) were of the in situ type. In 27 patients with multiple coronary bypass grafts, the patency of the LIMA graft (24/28, 85.7%) was higher than the SVG (14/46, 30.4%) regardless of the size, type and age of graft.

Table 1: Coronary bypass graft conduit characters.

Conduit type	Number of conduits (n = 84)	Size (mm in diameter)	Disease present
LIMA	28	3.2 ± 2.9	4 (4/28 = 14.3%)
RIMA	3	3.3 ± 0.7	1 (1/3 = 33%)
LRA	4	2.6 ± 0.7	2 (2/4 = 50%)
RRA	2	2.6 ± 0.5	0 (0/2 = 0)
GEA	1	2.3	1 (1/1 = 100%)
SVG	46	3.3 ± 1.2	32 (32/46 = 69.6%)
Total	**84**		**40 (47.6%)**

LIMA = left internal mammary artery RIMA = right internal mammary artery LRA = left radial artery
RRA = right radial artery GEA = gastroepiploic artery SVG = saphenous vein graft

Table 2: Correlative findings of 84 coronary bypass graft conduits between CT coronary angiography (CTA) and invasive coronary angiography (ICA).

Test	Disease present (ICA)	Disease absent
Positive (CTA)	40	1
Negative (CTA)	0	43

Table 3: Overall diagnostic accuracy of the 256-MDCT compared to the gold standard invasive coronary angiography (ICA).

Characteristic	Diagnostic Accuracy
Sensitivity	100%
Specificity	97.7%
Positive predictive value	97.6%
Negative predictive value	100%
Accuracy	**98.8% (*p* = 0.13)**

Table 4: Correlative findings of 38 arterial bypass graft conduits between CT coronary angiography (CTA) and invasive coronary angiography (ICA).

Test	Disease present (ICA)	Disease absent
Positive (CTA)	8	0
Negative (CTA)	0	30

Table 5: Overall diagnostic accuracy of the 256-MDCT compared to the gold standard invasive coronary angiography (ICA) in arterial bypass graft assessment.

Characteristic	Diagnostic Accuracy
Sensitivity	100%
Specificity	100%
Positive predictive value	100%
Negative predictive value	100%
Total accuracy	**100% (*p* = 1.0)**

Table 6: Correlative findings of 46 venous bypass graft conduits between CT coronary angiography (CTA) and invasive coronary angiography (ICA).

Test	Disease present (ICA)	Disease absent
Positive (CTA)	31	1
Negative (CTA)	0	14

Table 7: Overall diagnostic accuracy of the 256-MDCT compared to the gold standard invasive coronary angiography (ICA) in coronary venous bypass graft assessment.

Characteristic	Diagnostic Accuracy
Sensitivity	100%
Specificity	93.3%
Positive predictive value	96.8%
Negative predictive value	100%
Accuracy	**97.8% (p = 0.90)**

Table 8: Overall diagnostic accuracy of the 256-MDCT compared to the gold standard invasive coronary angiography (ICA) in 134 anastomosis sites of the coronary bypass graft assessment.

Test	Disease present (ICA)	Disease absent
Positive (CTA)	6	0
Negative (CTA)	0	128

Table 9: Overall diagnostic accuracy of the 256-MDCT compared to the gold standard invasive coronary angiography (ICA) in 134 anastomosis sites of the coronary bypass graft assessment.

Characteristic	Diagnostic Accuracy
Sensitivity	100%
Specificity	100%
Positive predictive value	100%
Negative predictive value	100%
Accuracy	**100% (p = 1.0)**

Table 10: Comparison of the overall diagnostic accuracy of the 256-MDCT to the gold standard invasive coronary angiography (ICA) in bypass graft assessment to the meta analysis studies of the 16-, 64-MDCT.[4]

Data	Grafts	Number	Sensitivity (%)	Specificity (%)
Meta analysis	Combined	777/84	88.7/**100**	97.5/**97.7**
(Jones CM. et al, Ann Thor Surg 2007)				
VS	Arterial	245/39	90.9/**100**	98.3/**100**
Bangkok Heart Hospital				
(Jan.2009-April 2011)	Venous	348/45	85.2/**100**	97.2/**93.3**

Table 11: Comparison between the accuracy of the 256-MDCT (Bangkok Heart Hospital) with 64-MDCT in bypass graft assessment studies of the others.

Data	Patient	MDCT	Grafts	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pashka (Eur H J 2006)	31	64	96	97.8	89.3	90	87.7
Dikkers (J Cardio Imag 2006)	34	64	64	69	98.7	-	-
Meyer (J Am Coll 2007)	138	64	418	97	97	93	99
Bangkok Heart Hospital	**29**	**256**	**84**	**100**	**97.7**	**97.6**	**100**

Discussion

The emerging role of MDCT to verifying graft patency in patients non invasively

At least 30% of our new patients had CABG surgery long ago in other medical centers and presented without operative details. With no clues of sites or number of grafts taken, angiographers often use excessive amount of contrast agent in order to find or confirm the occlusion of aortocoronary bypass conduits. Therefore, acute kidney injury or CHF can be expected in patients who had impending kidney dysfunction or compromised left ventricle function. By intravenously injecting 50-70 ml of contrast, the 256-MDCT provides more complete information of the origin, number and entire length of coronary graft in one shot. In the case of post CABG patient who came with no known information about their coronary bypass graft surgeries, MDCT can provide this information. Our study showed 100% accuracy in evaluation of coronary bypass graft conduits of the 14 of 29 patients who were unable to provide us with any details of their previous coronary bypass graft operations.

A recent meta-analysis study[4] has shown comparable results between MDCT and ICA in 16 and 64 slice scanners. However, in tachycardic patients, motion artifacts do occur and beta-blockades are commonly required to reduce HR below 65 beat/min.[6-8] With shorter scan time, the 256 scanner could be used with a wider range of patients and heart rate lowering may not be required and also provides relatively higher accuracy than 16-, 64-MDCT (Table 10, 11) because of its higher temporal and spatial resolution. Our result also confirmed the role of 256-MDCT in assessing graft patency with the high accuracy (100% of sensitivity, 97.7% of specificity). Therefore, 256-MDCT can be reasonably proposed as an alternative tool using limited contrast and is comparable to the ICA in assessing graft patency.

Accuracy of severity assessment

Some artifacts can affect MDCT interpretation. The blurring of calcified arterial wall can lead to overestimation of stenotic severity. Comparing with our previous study,[9] (luminal stenosis detection by 256-MDCT between the native coronary artery and coronary bypass graft), we found that the diagnostic accuracy of coronary artery bypass graft was a bit higher than the native coronary artery. It may be due to the lesser rate of sub-intimal calcification which causes blooming artifacts in coronary bypass graft compared to the native coronary artery. Therefore, the accuracy of interpretation of graft vessel (sensitivity and specificity) was expected to be higher than for native arteries. Surgical clips also produced artifacts but to a lesser degree than calcified plaque since their scatter alignment was relatively parallel to the graft body.

By independent assessment for graft severity between ICA and MDCT, almost all agreed in 83/84 segments (98.8%) and the disparity was found only in one graft (1/84, 1.2%) since it was diagnosed as no stenosis by ICA but mild stenosis (< 40%) by MDCT. If we re-classified severity of graft stenosis into patent and occluded as aforementioned, the sensitivity, specificity, positive and negative predictive values of 256-MDCT were 100%.

Limitation

The major limitation was the relatively small patient numbers (who underwent both MDCT and ICA for coronary bypass graft evaluation). In studies with few cases, the numbers are also vulnerable to be discordant; if more than a few cases are in disagreement, this affects the statistical assessment. Also because this was a retrospective analysis, confounding factors could not entirely be excluded.

Conclusion

Our study confirms that the 256-MDCT offers a comparable result to those from the ICA in coronary bypass graft assessment. The high specificity and negative predictive value make the 256-MDCT scanner a reasonable option in excluding graft occlusion especially in patients with no operative detail. However, the fast MDCT is still not suitable for use as a screening tool because the exposure to radiation and contrast media is still an important issue of concern. No supporting data from large studies are yet available on this subject. In the near future, when techniques using dosages with the least possible radiation exposure, are better developed, it will not take long to consider the role of the fast MDCT as a screening tool in coronary bypass graft stenosis evaluation.

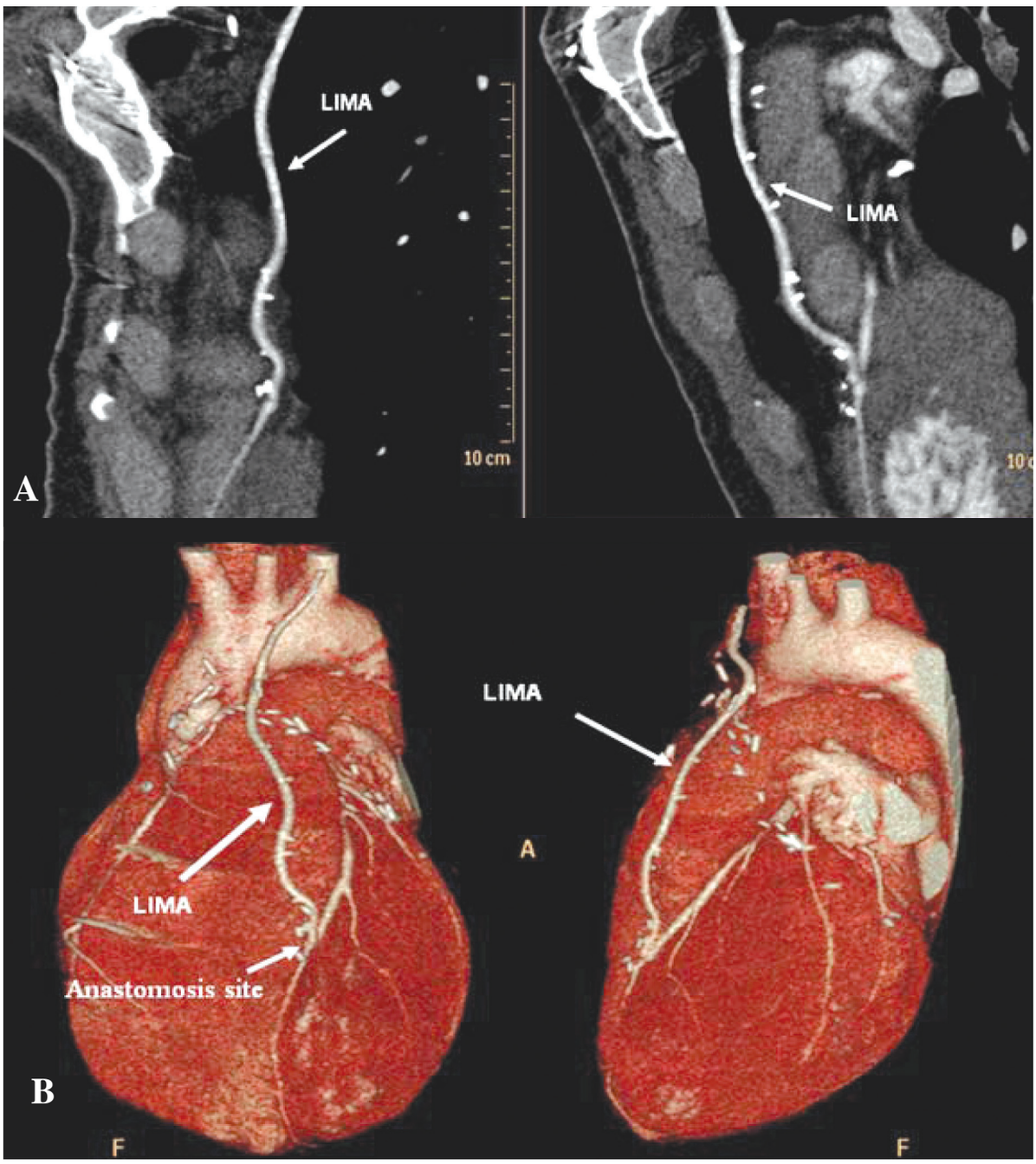

Figure 1: *Demonstration of LIMA graft to the LAD and its anastomosis site.*
A: *MPR images.*
B: *Volume rendering images.*
LIMA = left internal mammary artery
LAD = left anterior descemding
MPR = multiplanar reconstruction

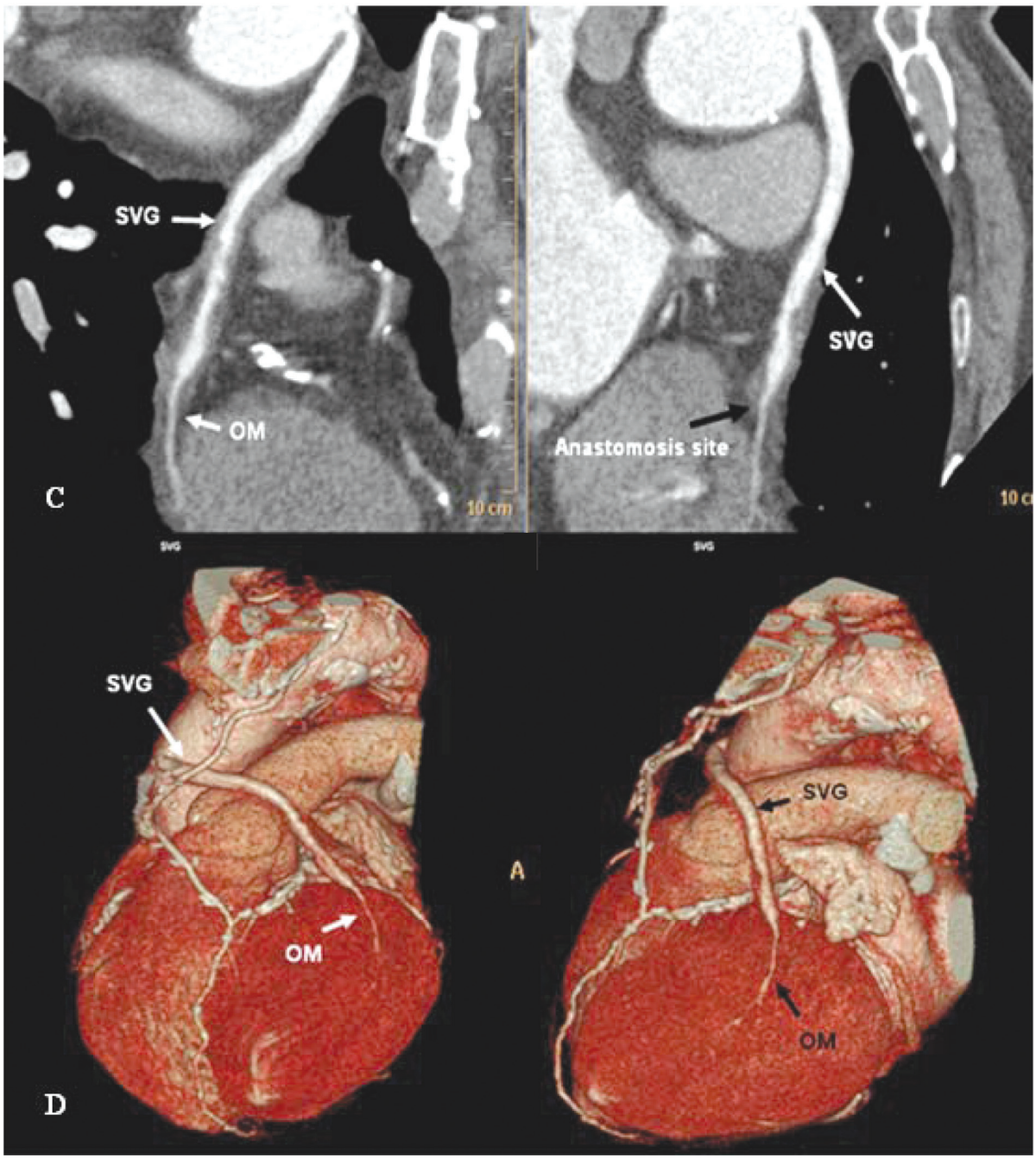

Figure 2: *Demonstration of SVG to the OM and its anastomosis site.*
C: *MPR images shows the distal stenosis of the SVG.*
D: *Volume rendering images.*
SVG = saphenous vein graft
OM = obtuse marginal branch
MPR = multiplanar reconstruction

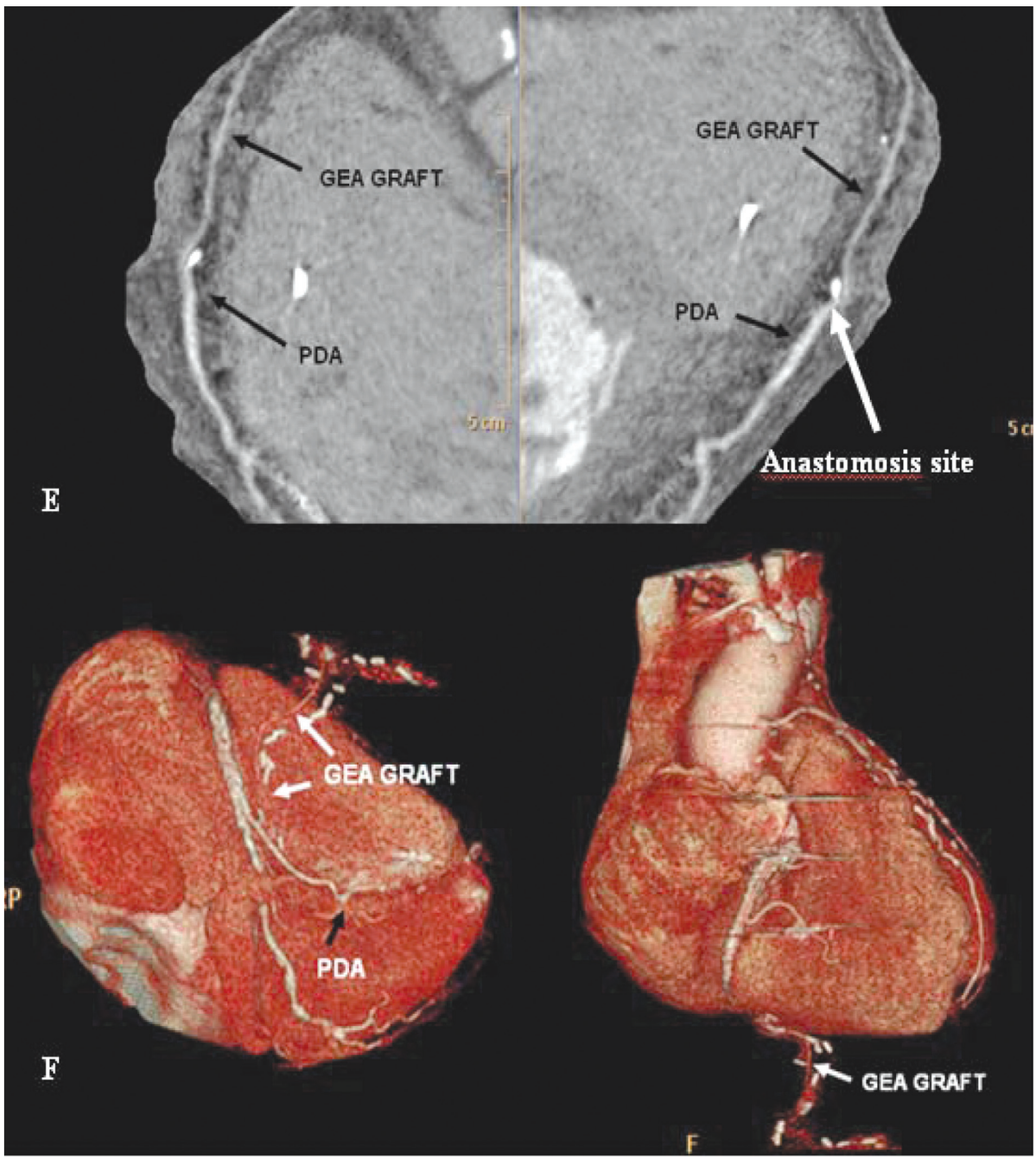

Figure 3: *Demonstration of the GEA to the PDA and its anastomosis site.*
E: *MPR images shows the patent of the GEA graft.*
F: *Volume rendering images.*
GEA = Gastroepiploic arterial graft
PDA = Posterior descending artery
MPR = multiplanar reconstruction

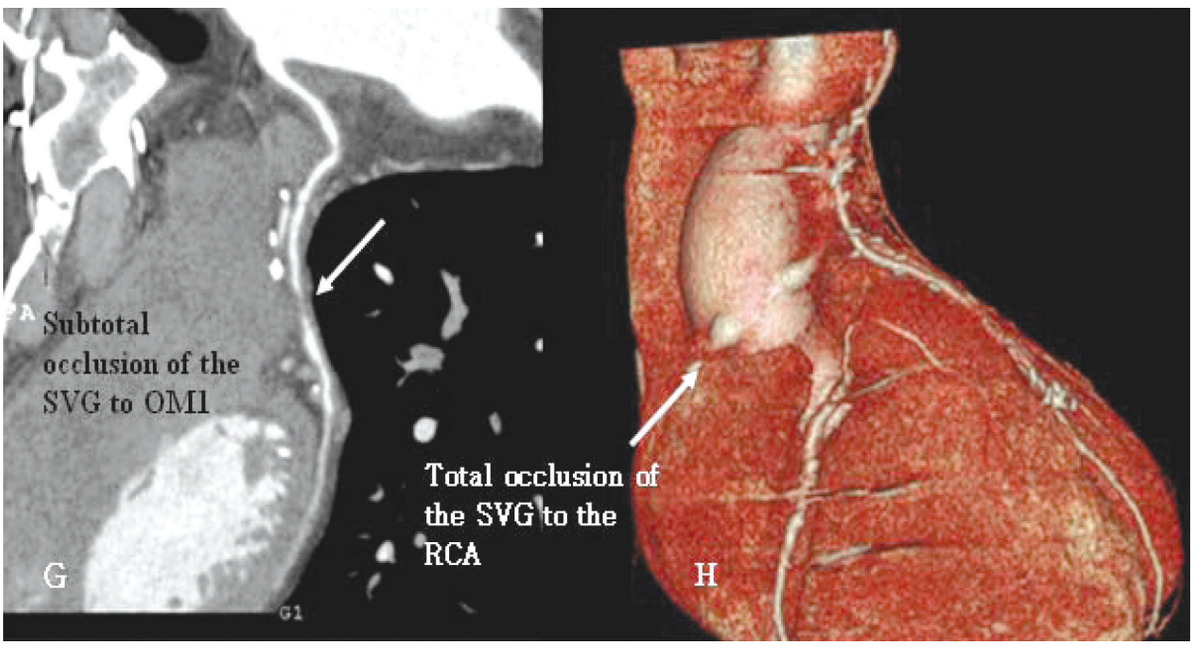

Figure 4: *Demonstration of graft vessel stenosis.*
G: *MPR images.*
H: *Volume rendering image.*
MPR = multiplanar reconstruction
SVG = saphenous vein graft
OM = obtuse marginal branch
RCA = right coronary artery

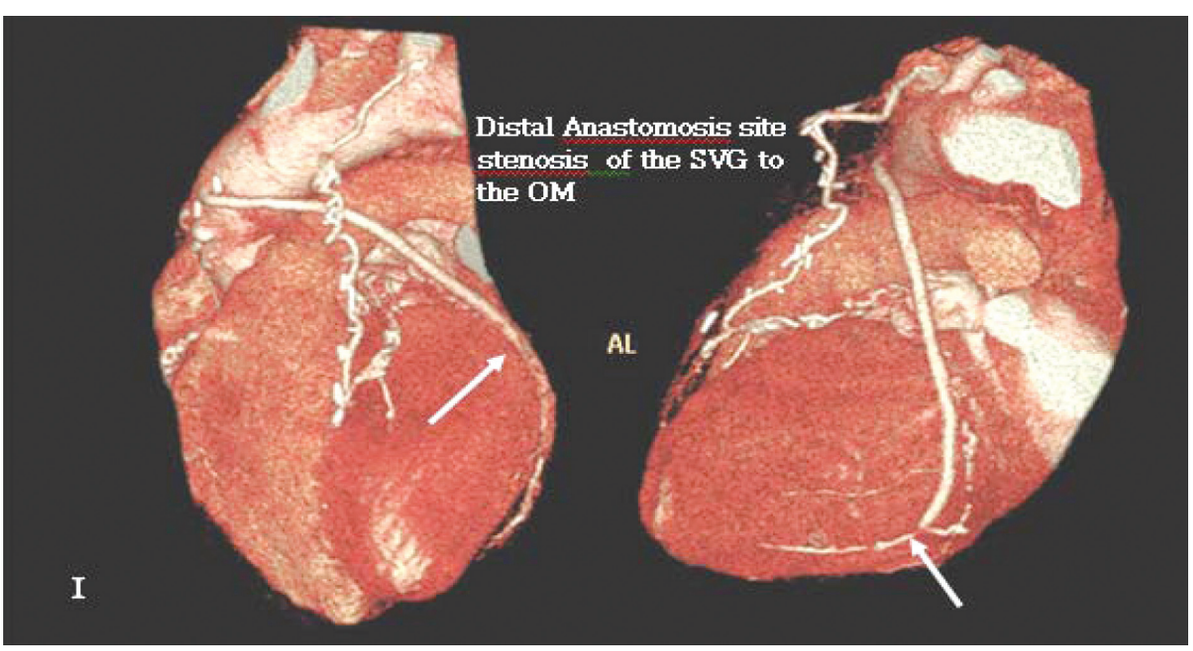

Figure 5: *Demonstration of distal anastomosis site stenosis of the SVG to the OM.*
SVG = saphenous vein graft
OM = obtuse marginal branch

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Original Article

Diagnosis of peripheral lung lesions (PPLs) by endobronchial ultrasonography, with guide sheath transbronchial biopsy

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Keywords:
Endobronchial Ultrasonography (EBUS), Guide sheath (GS), Peripheral lung lesions (PPLs)

OBJECTIVE. To study the effectiveness of Endobronchial Ultrasonography (EBUS) with Guide Sheath (GS) in detecting peripheral lung lesions.

MATERIALS AND METHODS. Between January and March 2011, 8 patients gave their informed consent to EBUS with GS being performed.

RESULTS. In 7 patients (87.5%) EBUS detected the PPLs.

CONCLUSION. EBUS is a useful and accurate tool for diagnosis of PPL.

In Thailand, which is an endemic area of tuberculosis, patients may often present with lung nodules which mimic lung cancer. Making diagnosis without requiring patients to undergo major surgery, such as an open thoracotomy has been difficult: the majority of cases are elderly and undernourished, heavy smokers, with poor pulmonary functions; they may also be under financial constraints, especially those from the northeast part of Thailand. Since the 1970's, fibreoptic bronchoscopy under fluoroscopy has become an accepted, diagnostic tool. However, if lesions are > 2 cm, the yields can be as low as 11-42%.[1-5] Whilst there is a higher accuracy rate in diagnoses of PPLs from tissue samples taken via percutaneous needle biopsy or aspiration, (76-97%),[1, 6] these techniques are not without hazards for patients; pneumothorax risks may increase, or malignant cells can be spread into the pleural cavity.[7, 8] Small calibre ultrasound probes have now been developed which can be introduced into the trachea and bronchus to assess endobronchial lesions. Kurimoto et al., demonstrated use of EBUS to differentiate between benign or malignant tumours.[9] This study intended to study the effectiveness of EBUS with GS in detecting PPLs.

Materials and Methods

Between January 1, 2011 and March 31, 2011, 8 patients, with PPLs shown by CT to be < 30 mm in mean diameter, were referred for diagnostic bronchoscopy, and were enrolled after giving their informed consent. EBUS was performed. After using EBUS to localise the lesions, biopsy forceps and a bronchial brush were introduced via the GS to conduct the cytologic examination.

Results

A total of 8 patients, consisting of 7 Thais and one Japanese (4 males) with an average age of 58.4 ± 11.3 years were examined. The mean diameter of the PPLs was 17.6 ± 7.5 mm (9-26.5 mm). Location of the PPLs was the right upper lobe in two patients, the

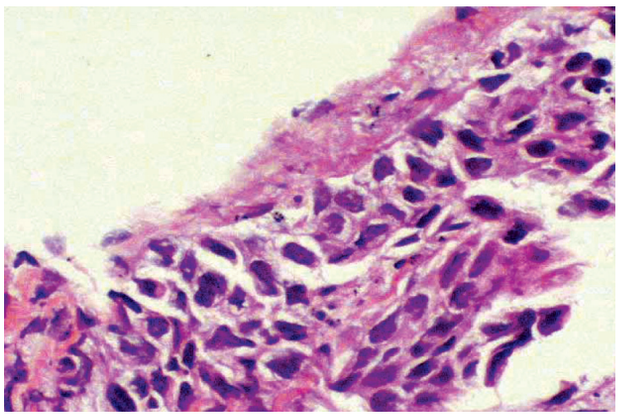

Figure 1: *Adenocarcinoma of the lung.*

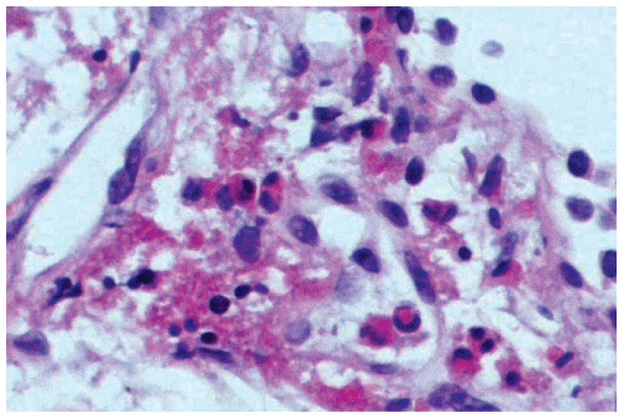

Figure 2: *Increased subepithelium eosinophil.*

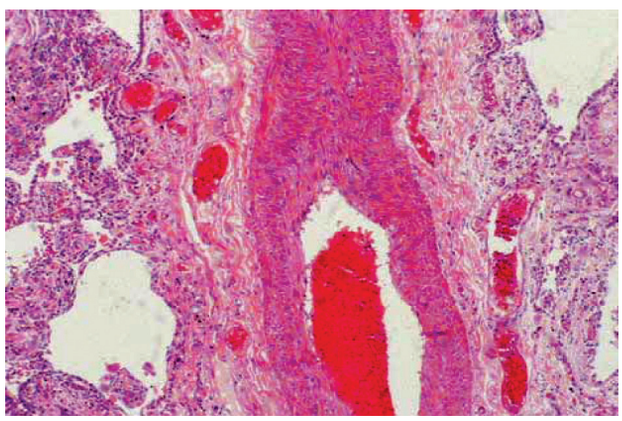

Figure 3: *Sequestration, abnormal systemic artery.*

right middle lobe in one patient, the right lower lobe in two patients, the left upper lobe in one patient and the left form lobe in two patients. In 7 patients (87.5 %) EBUS detected the PPLs; these patients accordingly underwent guide sheath-guided transbronchial biopsy (TBB) and bronchial brushing. In 6 cases (75%) diagnosis was made; there were 2 cases of primary lung cancer (Figure 1), one case of eosinophilic pneumonia (Figure 2), and 3 cases of tuberculosis. In the one patient where EBUS could not detect the lesion, surgery appeared to reveal it as sequestration of the lung (Figure 3). The pathology showed there was no connecting airway which is why the ultrasound did not detect the lesion.

We had no complications arising for the patients in this study, such as major bleeding, pneumothorax or infection. Most cases were discharged within 24 hours, with the exception of the sequestration, thoracotomy patient, and the patient with eosinophilic, interstitial pneumonia who needed treatment with intravenous steroids.

Discussion

Our small study has shown the usefulness and accuracy of endobronchial ultrasonography in identifying PPLs. It is a promising new diagnostic technique particularly suitable for areas endemic to tuberculosis, such as Thailand.

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Safety and Efficacy of Intramyocardial Implantation of Peripheral Blood Stem Cell for Cardiomyopathy

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Keywords:
Stem cells, Cell transplantation, Cardiomyopathy, Heart failure, Coronary artery bypass grafting

**Presentation at the Society of Thoracic Surgeons (STS) 47th Annual Meeting, January 31 - February 2, 2011, San Diego, California, USA*

OBJECTIVE. To determine the safety and efficacy of intramyocardial autologous blood stem cell injection for cardiomyopathy.

MATERIALS AND METHODS. Between May 2005 and February 2010, 126 consecutive patients underwent intramyocardial cell injection. Fifty two were dilated cardiomyopathy (DCM) and 74 were ischemic cardiomyopathy (ICM). Mean age was 59.2 ± 12.4 years. The stem cells are isolated from the patient's own blood and cultured. The final product is called angiogenic cell precursors (ACPs). The number of cells prior to injection was 46.1 ± 36.5 million cells. ACPs were injected into all areas of the left ventricle in DCM patients, and into the non-viable myocardium and hypokinetic segments in ICM patients. Combined coronary artery surgery and cell injection were performed in 33.8% of ICM cases.

RESULTS. There was no new ventricular arrhythmia. The 30-day mortality rate was 3.8% (2/52) and 4.1% (3/74) in DCM and ICM, respectively. New York Heart Association (NYHA) class improved from 3.0 ± 0.6 to 2.0 ± 0.9 at 485.8 ± 370.3 days ($p < 0.001$) in DCM and improved from 2.7 ± 0.6 to 1.9 ± 0.8 at 419.6 ± 345.5 days ($p < 0.001$) in ICM. Left ventricular ejection fraction (LVEF) increased from 23.3 ± 7.0% to 27.7 ± 11.3% at 409.7 ± 352.4 days ($p = 0.03$) in DCM and increased from 23.6 ± 7.7% to 31.5 ± 10.0% at 400.6 ± 350.1 days ($p < 0.001$) in ICM. Quality of life evaluated at 3 months has significantly improved for physical function, role-physical, general health and vitality domains in DCM. For ICM, physical function, role-physical, general health and social function domains were also improved.

CONCLUSION. Intramyocardial ACPs injection is feasible and safe in both DCM and ICM. NYHA, quality of life and LVEF had significantly improved in both DCM and ICM.

Cardiomyopathies represent a heterogeneous group of diseases that often lead to progressive heart failure with significant morbidity and mortality. Cardiomyopathies may be primary (i.e., genetic, mixed, or acquired) or secondary (e.g., infiltrative, toxic, inflammatory).[1] Classification was revised several times since the first use of the term *"cardiomyopathy"* in 1957, due to a rapid evolution of molecular genetics in cardiology and the emergence of ion channelopathies.[2] The American Heart Association Scientific Statement divided cardiomyopathies into 2 major groups: (1) primary cardiomyopathies and (2) secondary cardiomyopathies. This statement defines Primary cardiomyopathies (genetic, nongenetic or acquired) as those solely or predominantly confined to the heart muscle. Genetically caused primary cardiomyopathies include hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, left ventricular noncompaction, conduction system disease and ion channelopathies.

Dilated cardiomyopathy (DCM) is classified as a mixed (genetic and nongenetic) primary cardiomyopathy. DCM is characterized by ventricular chamber enlargement and systolic dysfunction with normal left ventricular wall thickness. DCM leads to progressive heart failure and a decline in left ventricular function, ventricular and supraventricular arrhythmias, conduction system abnormalities, thromboembolism, and sudden or heart failure-related death. Indeed, DCM is a common and largely irreversible form of heart muscle disease. It is the most frequent cause of heart transplantation. DCM may manifest clinically at a wide range of ages (most commonly in the third or fourth decade but also in young children) and usually is identified when associated with severe limiting symptoms and disability. Myocarditis (inflammatory cardiomyopathy), stress (*"tako-tsubo"*) cardiomyopathy and peripartum (postpartum) cardiomyopathy are examples of acquired primary cardiomyopathies. Secondary cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders such as amyloidosis, endomyocardial fibrosis and systemic lupus erythematosis. Coronary artery disease is one of the most frequent causes of heart failure (HF).[3] There is no uniform definition for ischemic cardiomyopathy (ICM). Felker GM, et al., in 2002 proposed a new definition of ischemic cardiomyopathy that reclassifies patients with single-vessel disease as nonischemic unless they have left main or proximal left anterior descending disease or a history of revascularization or myocardial infarction.[4] Despite improvements with medical treatment, the prognosis of patients with end-stage HF remains poor.[5] Myocardial viability assessments are useful tools for treatment selection. Patients with viable myocardium have a good prognosis after revascularization and medical treatment carries a higher risk of cardiac event.[6] Patients with severe ischemic cardiomyopathy (ICM) have high rates of adverse events associated with revascularization procedures. Reported perioperative mortality rates from coronary artery bypass grafting (CABG) in this patient subset range from 5% to 30%.[7] Furthermore, revascularization of nonviable myocardium has not proven to be beneficial in terms of either mortality benefit[8] or global left ventricular (LV) functional improvement.[9]

In this study, we only included patients with DCM and ICM. Although cardiomyopathy is asymptomatic in the early stages, symptoms are the same as those characteristically seen in any type of heart failure and may include shortness of breath, fatigue, cough, orthopnea, paroxysmal nocturnal dyspnea, and edema. Diagnostic studies include B-type natriuretic peptide levels, baseline serum chemistries, electrocardiography, and echocardiography.[1]

Heart transplantation is currently the best treatment option for end-stage cardiomyopathy; however it is limited by a shortage of donors.

Stem cell therapy is a rapidly growing new field that promises to improve health and quality of life by repairing or regenerating cells, tissues or organs. The angiogenic cell precursors (ACPs) used in this study were generated from autologous peripheral blood. ACPs represent a heterogenic stem/progenitor cell population of hematopoietic cells that can potentially differentiate in vivo in response to tissue signals at the site of injection and lineage specific angiogenic precursors.[10] Animal experiments demonstrated the efficacy of these cells; there was a significant reduction of myocardial scarring and increased blood vessel density in the direct intramyocardial injected areas.[11] We have previously reported on the feasibility and safety of using these cells to treat cardiomyopathy.[12]

The objectives are to determine the safety and efficacy of intramyocardial angiogenic cell precursors (ACPs) injection for dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) in a larger group of patients.

Materials and Methods

The Patients

Between May 2005 and February 2010, 126 consecutive patients underwent intramyocardial autologous peripheral blood stem cell injection. Fifty two were DCM and 74 were ICM. The study was approved by the Ethics Committee and Institutional Review Board (IRB). Informed consent was obtained before the procedure. Screening of severe contagious infections, HIV and hepatitis were done; only patients testing negative were confirmed for inclusion in the study. Malignancy within the preceding 3 years was also an exclusion criterion. All patients had a recent coronary angiogram (within 6 months) confirming the negative coronary artery disease status before the procedure. They all underwent pre-operative workups including routine chest x-ray, electrocardiography, and NT-ProB-type natriuretic peptide (NT-ProBNP). Echocardiography without stressing and/or cardiac MRI (CMR) was performed in all cases. CMR was conducted by using 3.0 Tesla MR Scanner (Achieva 3.0T systems with Philips Quasar Dual gradients, Philips Medical Systems, The Netherlands). The patients were excluded from the CMR study if they had contraindications such as metallic equipment implantation. They all undertook a six-minute walk test, New York Heart Association (NYHA) functional class evaluation and routine laboratory tests required for general anesthesia. Quality of life was evaluated at the preoperative and postoperative periods with Short Form-36 (SF-36, a multi-purpose, short-form health survey).

The SF-36 is a generic instrument consisting of 36 items or questions grouped into eight health-related aspects of the patient's life. As Ware et al explain it, *"there are eight main scales derived from the 36 questions: Physical functioning (10 items), role limitation due to physical function (4 items), role limitation due to emotional problems (3 items), social functioning (2 items), mental health (5 items), energy/vitality (4 items), pain (2 items), general health perception (5 items), and change in health (1 item). The scores for each dimension can vary from 0 -100; the higher the scores the better the quality of life"*.[13] The score of 50 was considered normal. The clinical characteristics of patients are summarized in Table 1.

The cells

The adult stem cells used in this study are *"Angiogenic Cell Precursors (ACPs)"* developed by VesCell technology (VesCell™ , TheraVitae Co. Ltd., Ness Ziona, Israel).[10] The ACPs are obtained from the patient's own blood, avoiding immunological concerns. Peripheral blood of 250 ml was collected from the patients using the same technique for general blood donation and sent for cell expansion. Blood cultures for aerobic and anaerobic bacteria were collected at the same time as blood collection and confirmed negative result during the process.

Table 1. The clinical characteristics of patients.

Clinical characteristics	Dilated Cardiomyopathy (n = 52)	Ischemic Cardiomyopathy (n = 74)
Age (years)	55.1 ± 13.0	62.1 ± 11.1
Gender - Male	38 (73.1%)	71 (95.9%)
NYHA Functional Class (Mean ± SD)	3.0 ± 0.6	2.8 ± 0.6
Diabetes	12 (23.1%)	36 (48.6%)
Hypertension	16 (30.8%)	51 (68.9%)
Dyslipidemia	22 (42.3%)	61 (82.4%)
Renal Failure	4 (7.7%)	6 (8.1%)
Chronic pulmonary obstructive disease	2 (3.8%)	5 (6.8%)
Cerebrovascular accident	7 (13.5%)	12 (16.2%)
Pulmonary hypertension	14 (26.9%)	17 (23%)
AICD/CRTD Implantation	37 (71.2%)	32 (43.2%)
Mitral regurgitation		
Trivial	5 (10.2%)	6 (8.6%)
Mild	20 (40.8%)	29 (41.4%)
Moderate	13 (26.5%)	29 (41.4%)
Severe	6 (12.2%)	1 (1.4%)
Distance walked in 6 mins. (meters)	372.8 ± 102.1	362 ± 123.1
Preoperative left ventricular ejection fraction (LVEF, %)	22.0 ± 7.3	23.2 ± 7.7
NT-ProBNP ($pg.ml^{-1}$)	3512.9 ± 3027.0	3878.1 ± 4583.3

NYHA = New York Heart Association
AICD = Automatic implantable cardioverter defibrillator
CRTD = Cardiac resynchronization therapy with defibrillator
NT-ProBNP = NT-ProB-type natriuretic peptide

The multipotent progenitor cells were isolated from the blood, rich in CD45, $CD31^{Bright}$, $CD34^{+}$ $CD45^{-/Dim}$ and $CD34^{Bright}$ cells. The cells at a concentration of 1.5-3.0 x 10^{6} cells/ml were then cultured with vascular endothelial growth factor (VEGF, R&D Systems, Minneapolis, MN, USA) and 5 IU/ml heparin (Kamada, Beit-Kama, Israel). The process of cell expansion took 5 days. Number and viability of cells were checked and passed the following quality control before their use. The product consisting of at least 1.5 ± 0.5 million autologous endothelial progenitor cells that had been isolated from the patient's blood and then expanded ex vivo under sterile conditions was suspended in 15 ml sterile cell culture medium. Acceptable culture parameters as assessed by microscopy and flow cytometry were in accordance with the following specifications: Cell viability = 75% and Morphology-spindle-shaped, large cells forming long thread-like structures (Figure 1).

Sterility tests were performed according to 21 Code Federal Regulation (CFR) 610.12. Assessment of cell culture sterility was performed on a sample of the cell fraction supernatant or phosphate buffered saline (PBS) following cell washing. Interim negative sterility results of all samples taken at different stages of the culture were compulsory for the release of the final product. The Bacterial Endotoxin test was performed according to United States Pharmacopeia (USP) 23. The Limulus Amebocyte Lysate (LAL) test was performed on a sample of supernatant taken from the cell culture. Endotoxin levels below the acceptable limits were compulsory for the release of the final product. Gram stain was used as a rapid and qualitative method for assessing bacterial contamination of tissue culture samples. Negative results of the Gram stain performed on samples taken from the washing medium of cells before vialing was compulsory for the release of the final product. Mycoplasma contamination was tested and a negative result of the test was also obtained. The product phenotype was assayed by immune staining, as well as for angiogenic potential (tube formation assay) and cytokine secretion. All cell preparations complied with pre-defined release criteria of safety and potency.

Immune Staining

Cell samples were washed in PBS and resuspended in 100 ml of PBS, stained with specific fluorochrome-conjugated anti-human antibodies or isotype-matched non-specific controls, and incubated in the dark for 30 minutes on ice. The following antibodies were used for staining:, -CD31-PE or -CD31-FITC (IQP, Groningen, The Netherlands); anti-CD34-APC (BD Bioscience, Franklin Lakes, NJ, USA), -CD117-APC (DakoCytomation, Glostrup, Denmark); anti -CD133-PE, -CD144-FITC, -KDR-PE, -Tie-2-PE (R&D Systems, Minneapolis, MN), and anti-vWF -FITC (Chemicon, Temecula, CA). Ac-LDL uptake was measured by incubating the cells with 0.8 mg/ml Ac-LDL (Alexa Fluor488 AcLDL-Invitrogen, Carlsbad, CA, or Ac-LDL-DiI-Biomedical Technologies, Inc., Stoughton, MA) for 15 minutes at 37°C. Non-viable cells were excluded by 7-Amino-Actinomycin D (7-AAD, eBioscience, San Diego, CA, USA).

Cell suspension triplicates of five hundred thousand cells each were stained, assessed by FACS (FACSCalibur, Becton Dickinson), and analyzed by CellQuest Pro software (Becton Dickinson). The percentage of each marker was determined in each test tube and the mean and % Coefficient of Variance (% CV) was calculated for each one. The results were expressed as mean ± Standard Error (SE) of the percentage of stained cells. The number of stained cells was calculated by multiplying the number of harvested cells by the staining percentages obtained using the FACS.

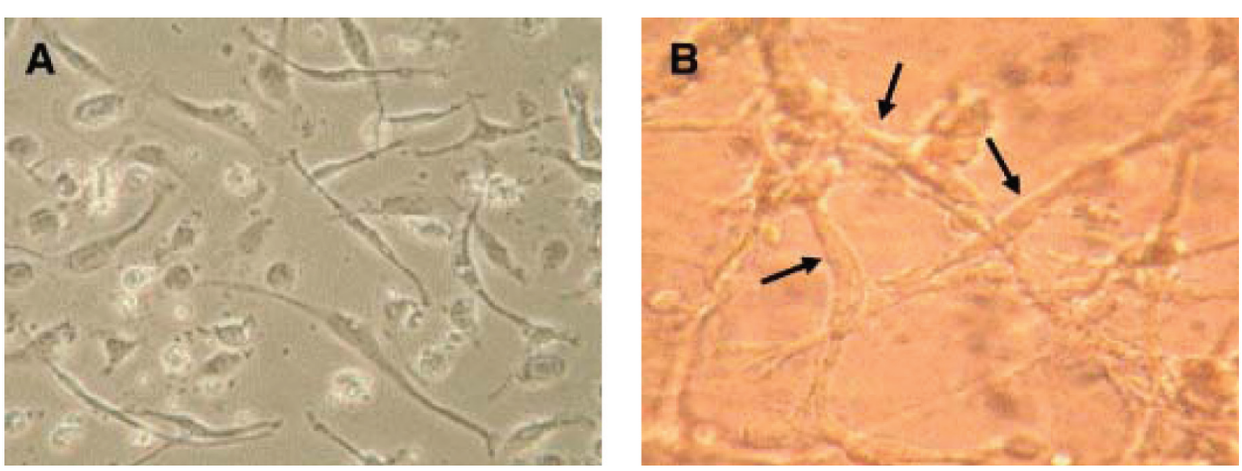

Figure 1: *In Vitro Characteristics of angiogenic cell precursors (ACPs).*
A. Photomicrographs illustrating the typical elongated, spindle-shaped morphology of cultured ACPs.
B. The angiogenic potential of ACPs indicated by organization into tube-like structures (arrows).

Tube Formation Assay

The angiogenesis potential of the cells was measured by their ability to form three-dimensional tube-like structures according to a widely-used scale using an in vitro angiogenesis assay kit (Chemicon) and scoring under an inverted light microscope (Nikon ECLIPSE TS-100).[14]

Analysis of Cytokine Secretion

Samples of the harvested cells were washed in PBS and resuspended to one million in 1 ml X-vivo15 and grown for 24 hours in 24-well plates. Cytokine secretion in the supernatant was measured as compared to that of the medium only using flow cytometry and the BD™ CBA Human Angiogenesis Kit (Becton Dickinson).

Number of cells prior to injection was 46.1 ± 36.5 million (1.6 - 200) with 96.6 ± 3.7 % viability. Cells were injected into all areas of the left ventricle in the DCM. In the ICM patients, cells were injected into non-viable myocardium including interventricular septum and hypokinetic segments of the left ventricle.

Surgical Techniques

All DCM had intramyocardial cell injection alone by thoracoscopic technique or microthoracotomy. Most patients underwent microthoracotomy approach due to better exposure, control and shorter operative time than the thoracoscopic technique. For ICM, 49 (66.2%) had ACPs injection alone and 25 (33.8%) had combined CABG plus ACPs injection.

Microthoracotomy for ACPs Injection

Under general anesthesia with one-lung ventilation, the patient was placed in the right lateral decubitus position. A 10-cm incision was made in the left chest at the 5th intercostal space on the posterior axillary line. The chest cavity was examined and the pericardium was opened longitudinally anterior to the phrenic nerve. Pericardial traction stitches were placed appropriately to assist in reaching all regions of the left ventricular wall.

The cells were injected with the 23-guage butterfly needle with home-made guard. The needle was brought to the heart and then the injections were done manually outside the chest with the extension line. There were 30 sites of injections, 0.5 ml/ injection. Cells were injected into non-viable myocardium predetermined by CMR or myocardial nuclear scan including interventricular septum and hypokinetic segments. After adequate hemostasis the microthoracotmy was closed with small chest drainage left in the 7th intercostal space opening.

Off-Pump coronary artery bypass grafting (OPCAB)

OPCAB approach was carried out and can be summarized as follow. After 1 mg/kg of heparin was given, deep pericardial traction stitches were applied to verticalize the heart. The heart was then stabilized with an Octopus III or Octopus IV stabilizer (Medtronic, Inc., Minneapolis, MN 55432) without using any cardiac positioning device. The systemic systolic blood pressure in both groups was kept above 100 mmHg and central venous pressure/pulmonary artery diastolic pressure in the 20's to maintain adequate perfusion. All operative maneuvers were carried out in routine fashion.

Anastomoses was usually performed to the left anterior descending (LAD) and diagonal arteries first; or to the highest grade or totally obstructed arteries when the LAD system had less severe obstruction. After the measuring was completed the anastomosis was performed in the usual fashion using side to side anastomosis for sequential and end to side for distal end anastomosis with 4-8 interrupted stitches of 7-0 prolene. Intra-coronary shunt was used only in the large dominant right coronary artery or when patient was unstable or exhibited significant and persisting EKG changes after the occlusion. One right ventricular temporary epicardial pacing wire was inserted in these high risk patients. Protamine was given. Normothermia was maintained with sterile warm blanket throughout the procedure. The intramyocardial cell injections were performed after protamine was given.

Statistical Analysis

Statistical analyses were carried out with SPSS™ for Windows version 10.0 (SPSS Inc, Chicago, IL). Continuous variables are expressed as the mean ± SD unless otherwise indicated. The categorical data was reported as proportion. Paired T-test was used to compare the mean difference of LVEF, NYHA class, scores of quality of life and CMR parameters between pre and post treatments. Independent sample t-test was used to compare the mean difference of the LVEF between patients who underwent OPCAB plus intramyocardial cell injection and patients who underwent intramyocardial injection alone. A p value of less than 0.05 was considered significant.

Results

There was no new ventricular arrhythmia. 30-day mortality rate was 3.8% (2/52) and 4.1% (3/74) in DCM and ICM, respectively.

New York Association Functional Class

NYHA class improved from 3.0 ± 0.6 to 2.0 ± 0.9 at 485.8 ± 370.3 days ($p < 0.001$) in DCM and improved from 2.7 ± 0.6 to 1.9 ± 0.8 at 419.6 ± 345.5 days ($p < 0.001$) in ICM (Figure 2).

Left Ventricular Ejection Fraction

LVEF increased from 23.3 ± 7.0% to 27.7 ± 11.3% at 409.7 ± 352.4 days ($p = 0.03$) in DCM and increased from 23.6 ± 7.7% to 31.5 ± 10.0% at 400.6 ± 350.1 days ($p < 0.001$) in ICM (Figure 3). For the ICM, the LVEF was improved 11.4 ± 12.2% in patients who underwent OPCAB plus intramyocardial cell injection and LVEF was improved 5.7 ± 7.5% in patients who underwent intramyocardial cell injection alone. This was no statistically significant difference ($p = 0.056$).

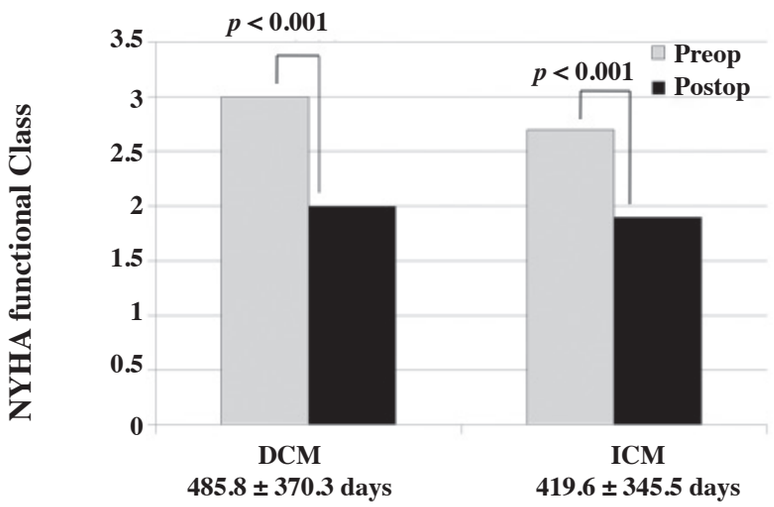

Figure 2 : *New York Heart Association (NYHA) functional class: Preoperative and postoperative periods in dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM).*

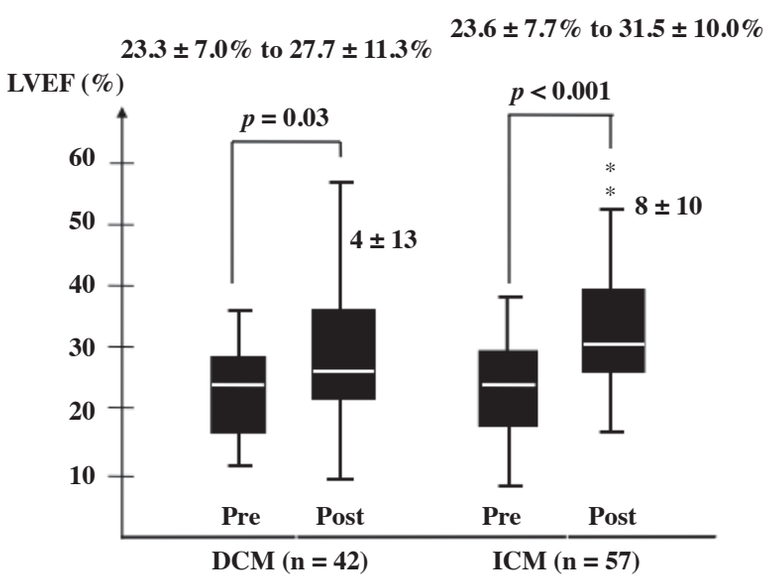

Figure 3 : *Boxplot of the left ventricular ejection fraction: before (pre) and after (post) treatment in dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM). The lower and upper edges of the "box" demonstrate the first and third quartile of the data (50% of the data lie within the box). The "median" is shown as a line inside the box. The ends of the vertical lines or "whiskers" indicate the minimum and maximum values, unless outliers are present in which case the whiskers extend to a maximum of 1.5 times the inter-quartile range. *represents outlier, LVEF = left ventricular ejection fraction.*

Cardiac Magnetic Resonance Imaging

A number of ICM had preoperative and postoperative CMR. The infarction volume, end diastolic volume and end systolic volume of the left ventricle were significantly reduced at the 474.1 ± 279.8 days follow-up (Table 2, Figure 4). Only a few patients in the DCM group had preoperative and postoperative CMR, therefore their results were not analyzed.

Quality of life

Quality of life postoperatively evaluated at 3 months has significantly improved for physical function, role-physical, general health and vitality domains ($p = 0.001$, 0.014, 0.001 and 0.002 respectively) in DCM. For ICM, physical function, role-physical, general health and social function domains ($p = 0.037$, 0.005, 0.001 and 0.026 respectively) were improved (Figure 5).

Table 2. Preoperative and postoperative cardiac MRI (CMR) results in ischemic cardiomyopathy (IMC) patients.

CMR parameters	Preoperative	Postoperative	*p* value
Infarction volume (%)	39.8 ± 29.3	25.9 ± 21.1	0.03
End-diastolic volume (ml)	269.5 ± 66.5	232.0 ± 77.9	0.03
End-systolic volume (ml)	211.5 ± 65.6	173.0 ± 72.0	0.008
Stroke volume (ml)	56.9 ± 24.4	59.0 ± 23.4	0.7
Cardiac output (l/min)	4.5 ± 1.9	3.9 ± 1.4	0.2
Left ventricular mass (g)	156.9 ± 45.6	164.1 ± 40.6	0.3

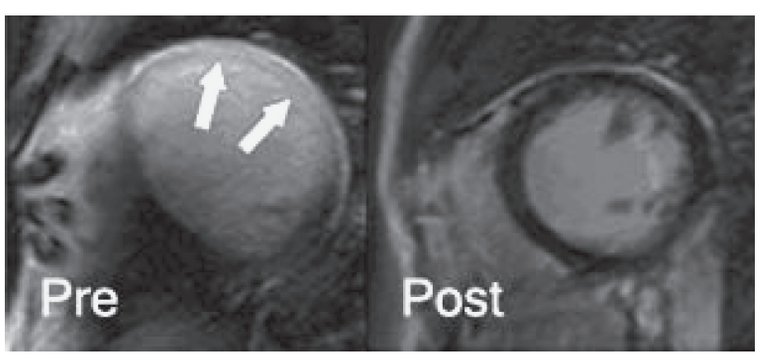

Figure 4: *Cardiac magnetic resonance imaging with gadolinium contrast;* ***Pre:*** *infarction seen as a bright signal (arrows) at the left ventricular anterior and lateral walls, before stem cell transplant. Left ventricular ejection fraction was 13.2% with end-diastolic volume of 296 ml.* ***Post:*** *3 months after stem cell transplant, there was no myocardial scar and ejection fraction was 20% with end-diastolic volume of 268 ml.*

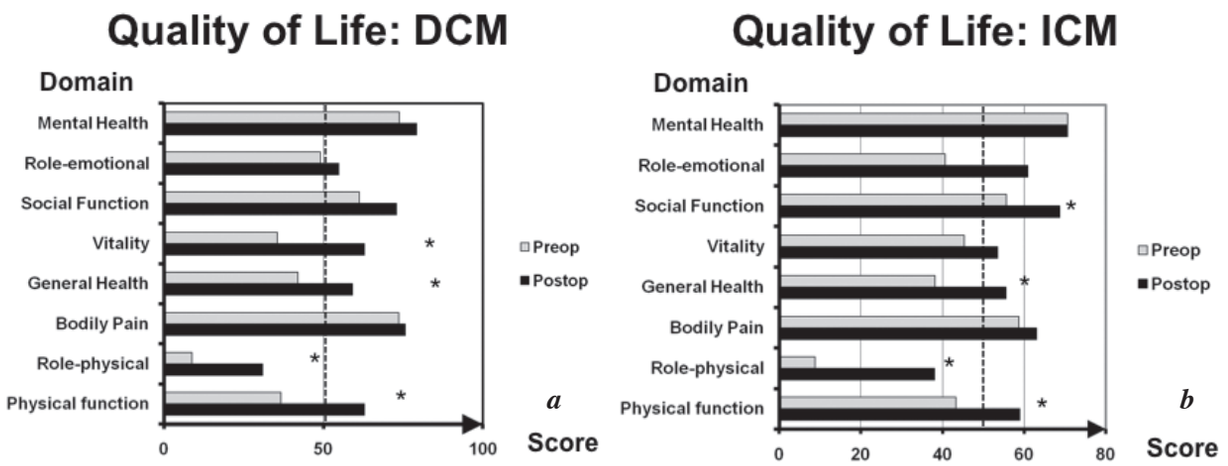

Figure 5: *Quality of life evaluated by the Short Form 36 at 3 months follow-up.*
a. Dilated cardiomyopathy (DCM). b. Ischemic cardiomyopathy (ICM).
** p value < 0.05*

Discussion

In the present study, we have demonstrated the safety of the intramyocardial peripheral blood stem cell so called *"angiogenic cell precursor (ACP)"* transplantation in patients with DCM and ICM. The 30-day mortality was about 4%. With increasing clinical experience, mortality could be lowered in both groups. The efficacy of the cell injections was demonstrated by comparing postoperative and preoperative NYHA functional class, LVEF, CMR parameters (ICM) and quality of life. NYHA functional class, LVEF and half of the domains in quality of life questionnaire were significantly improved in both DCM and ICM. Infarction volume, end diastolic volume and end systolic volume were significantly improved in the ICM patients demonstrated reverse remodeling of the left ventricle after the intramyocardial ACPs injection.

Although this study was a nonrandomized study, it did include all spectrums of the common types of heart failure patients. The data were prospectively collected and followed-up. The intention of this report is to give results of a larger group of patients than in previous reports. We did not have control group in this analysis. However we had reported our case-match studies for both DCM and ICM previously. Those patients who had undergone intramyocardial ACPs injection tended to have improvement in NYHA functional class and LVEF unlike the controls.[15, 16]

The research results on outcomes of stem cell injection for DCM were limited.[17-22] Roura S, et al., demonstrated defective vascularization and impaired vasculogenesis (the de novo vascular organization of mobilized endothelial progenitors) and angiogenesis in dilated cardiomyopathy patients. The defective vascularization was associated with reduced myocardial expression of vascular β-catenin, an important angiogenic regulator.[23] Werner L, et al., also showed that endothelial progenitor cell transfer is effective in attenuating myocardial damage in a model of dilated cardiomyopathy.[24] Chu VF, et al., demonstrated an angiogenesis effect of the mechanical puncture of myocardium. However, this was controversial.[25] These are the rationale used for intramyocardial ACPs injection in our study. Vrtovec B, et al., investigated the effects of intracoronary transplantation of $CD34^+$ cells in patients with DCM. Twenty eight patients were randomized to have intracoronary peripheral blood $CD34^+$ cells injection which were mobilized by granulocyte-colony stimulating factor and collected via apheresis compared with control. At one year, intracoronary peripheral blood $CD34^+$ cells injection was associated with an increase in LVEF (from 25.5 ± 7.5% to 30.1 ± 6.7%; $p = 0.03$), an increase in 6-minute walk distance and a decrease in NT-proBNP.[26]

Stem cells for treatment of myocardial infarction and ICM that are under-investigated clinically are mainly hematopoietic stem cells. The skeletal myoblasts injection failed to show an improvement of LVEF compared with controls in the randomized placebo-controlled myoblast autologous grafting in ICM patients (MAGIC trial).[27] There was also increased number of early postoperative arrhythmic events after myoblast implantation. The bone-marrow or peripheral blood derived stem cells have however shown positive in other clinical trials in both acute and chronic myocardial ischemia/infarction.[28-36] The range of improvement of the LVEF was 2.5-15 percentage points. There have also been some negative

studies in terms of LVEF.[37] The reasons for the disparity in results may be due to the differences in types of cells, e.g., CD34+, CD 133+ or unselected bone-marrow stem cells, dosage of cells, type of patients (acute or chronic myocardial ischemia) and delivery methods.

The advantages of using autologous peripheral blood derived stem cells in our study are as follows. Autologous cells (1) create no immunologic concern, (2) are easily harvested via blood donation, (3) have no systemic effect during the blood collection for progenitor cell selection and expansion,[38] (4) the cell populations harvested are not in the early phase of development, thus there are no tumor formation issues, and (5) ability of repeated procedure. However, the disadvantages are: (1) the cells may not be as potent as other embryonic or pluripotent stem cells to repair all the damaged areas, (2) cells had limited self-renewal process, therefore the improvement may not last forever, and (3) there was the limitation of patients with blood-borne infections such as hepatitis or patients with chronic immunosuppressant. In this current study, the reasons we delivered the cells by direct intramyocardial injection are: (1) intramyocardial injection is a simple method, (2) the target area of injection can be seen directly, (3) cell retention after implantation is maximized compared with transcatheter coronary artery infusion or retrograde coronary venous infusion,[39] and (4) do not effect coronary stents.

The proposed mechanisms of intramyocardial ACPs injection are paracrine effect, homing signal and possible transdifferentiation of ACPs to cardiomyocytes. Proving this in clinical trials has been difficult, although it was supported by basic science research.[40-42] The future researches are many: (1) the explorations of new types of cells, e.g., resident cardiac progenitor cell,[43] umbilical cord blood stem cells,[44] induced pluripotent stem cells[45] or combined stem cells, (2) non-invasive in vivo cell tracking,[46, 47] (3) pharmacologic manipulation[48] or combined gene therapy[49-51] and (4) heart tissue engineering.

Limitation of the study

This was not a randomized study. The follow-up was limited by the cardiologists and some patients came from overseas therefore they could not come for follow-up cardiac MRI. However, we received echocardiogram, NYHA functional class results and quality of life questionnaire from them.

Conclusions

Intramyocardial ACPs injection is feasible and safe in both DCM and ICM. The NYHA, quality of life and LVEF had significantly improved in both DCM and ICM. The cardiac MRI in ICM demonstrated a reversed remodeling of the left ventricle. Large-scale placebo-controlled studies are needed to confirm that use of intramyocardial ACPs injection in cardiomyopathy is efficacious.

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Disclosures and Freedom of Investigation

The *"Angiogenic Cell Precursors (ACPs)"* developed by TheraVitae Co. Ltd. Professor Michael Belkin was in the past an board member, a minor shareholder, and received a consulting fee from TheraVitae Co. However, the authors had full control of the study, methods used, outcome measurements, data analysis, and production of the written report.

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Case Report

Tuberculous Pericarditis

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Keywords:
Pericarditis, Tuberculous pericarditis

Tuberculous pericarditis, caused by Mycobacterium Tuberculosis, is found in approximately 1% of all autopsied cases of tuberculosis (TB) and in 1% to 2% of instances of pulmonary TB.[1] Pericardial involvement usually develops by the retrograde lymphatic spread of Mycobacterium Tuberculosis from peritrachial, peribronchial or mediastinal lymph nodes or by hematogenous spread from primary tuberculous infection.[2, 3] Tuberculous pericarditis presents clinically in 3 forms, consisting of pericardial effusion, constrictive pericarditis and a combination of effusion and constriction.[4]

Case Report

A 66-year-old woman presented with dyspnea, palpitations and inability to lay flat in bed since 2 months. The pertinent laboratory investigations included sputum examination which was negative. CA125 was positive. Gram stain showed no microorganism. Pleural fluid of AFB culture showed no Mycobacterium spp. isolated. Polymerase chain reaction (PCR) for TB showed negative for Mycobacterium Tuberculosis.

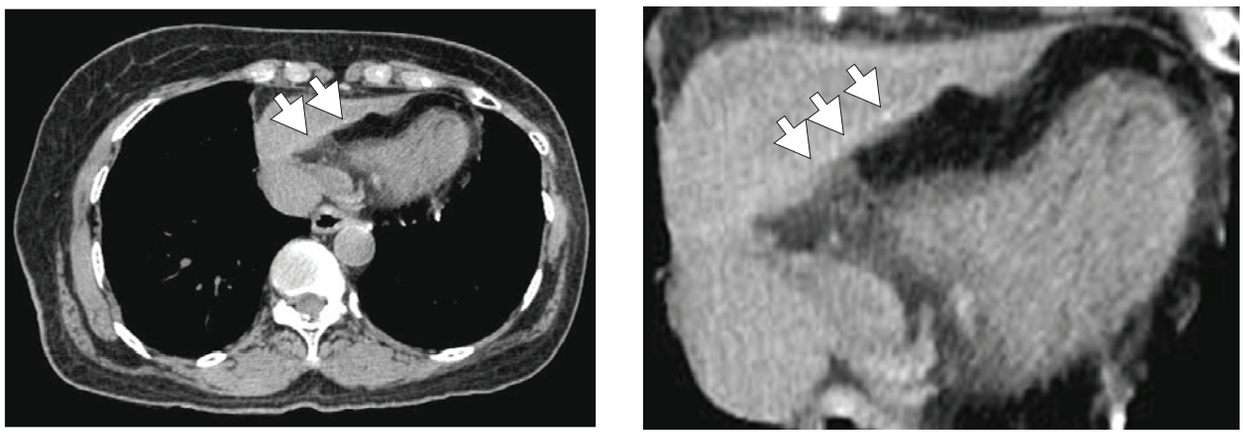
The Echocardiogram showed fluid collection in the pericardial sac. The electrocardiography (EKG) showed prolonged QT.

The CT chest (Figure 1) revealed 2.8 cm diameter, heterogeneously enhancing lesion at anteroinferior aspect of the pericardium. There was no extension into the heart chamber, multiple foci micro calcification at wall of pericardial were seen which was indicative of chronic granulomatous condition. Tuberculous pericarditis should be considered.

The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) scan (Figure 2) showed increased metabolic activity at pericardium (standardized uptake value (SUV) = 3.8). There was also increased ^{18}FDG uptake at right axillary node (SUV = 1.2) (Figure 3).

The tuberculin skin test also showed positive result (Figure 4).

The MRI study of the heart with gadolinium (Figure 5) showed localized thick wall of pericardium with rim contrast enhancement. The inner wall of pericardium was thickening and irregular fine filling defects projected into the pericardial effusion which is compatible with chronic granulomatous pericarditis. This is a classical sign of tuberculous pericarditis.



a *b*

Figure 1 a-b: *CT Chest shows thick pericardium at anteroinferior border with multiple foci microcalcification at wall of pericardium. This indicats granulomatous condition. Tuberculous pericarditis should be considered.*

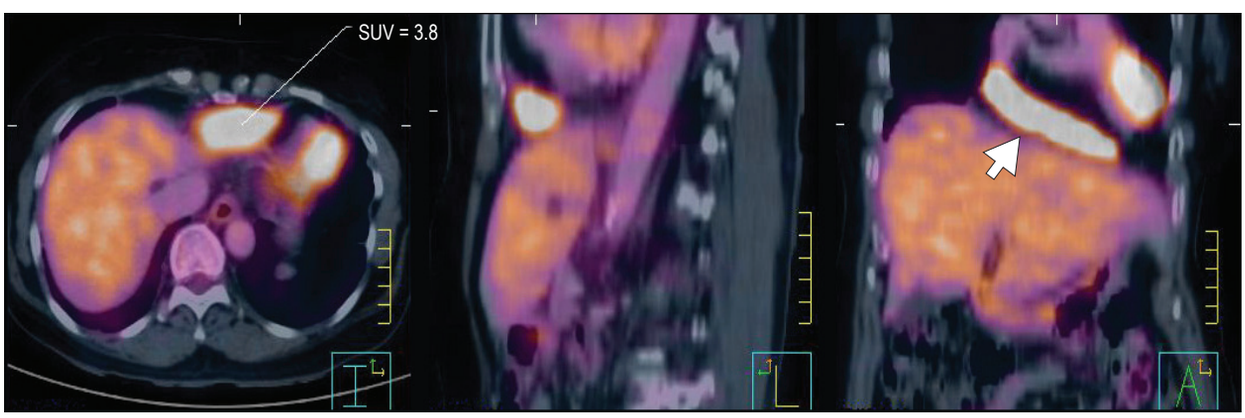


Figure 2: *The ^{18}FDG PET/CT scan shows increased metabolic activity activity at pericardium (SUV = 3.8).*

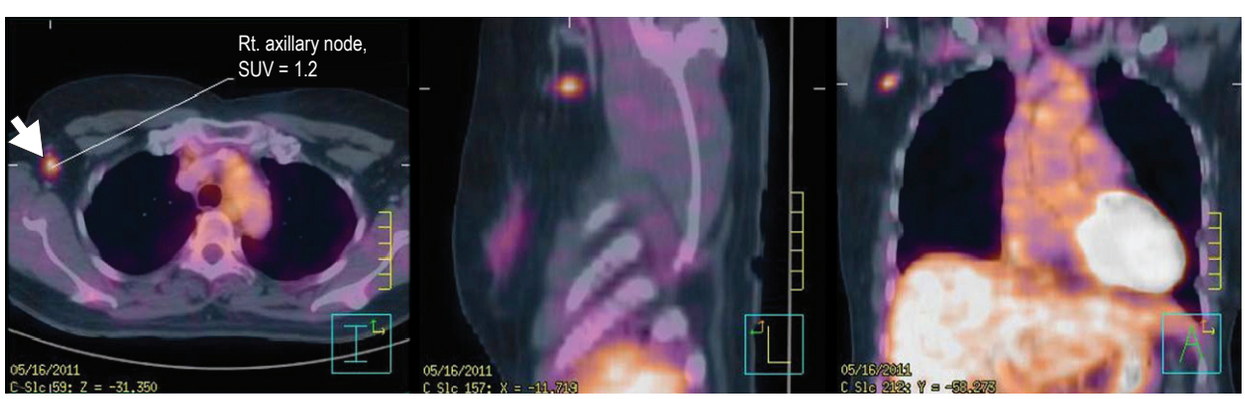


Figure 3: *The ^{18}FDG PET/CT scan shows increased ^{18}FDG uptake at right axillary node (SUV = 1.2).*

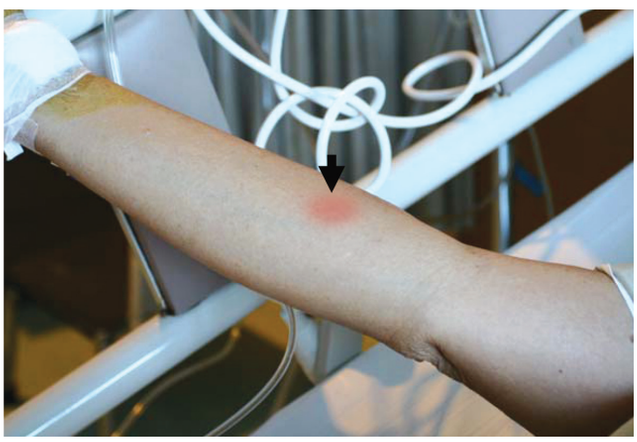


Figure 4: *The tuberculin skin test shows positive result.*

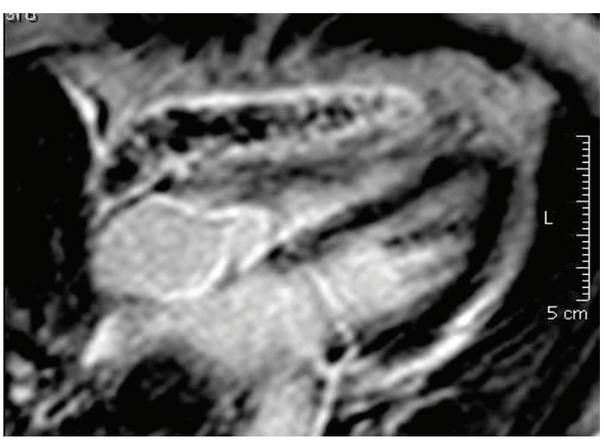


Figure 5: *The MRI study of the heart with gadolinium shows localized thick wall of pericardium with rim contrast enhancement. The inner wall of pericardium was thickening and irregular fine filling defects projected into the pericardial effusion which is compatible with chronic granulomatous pericarditis.*

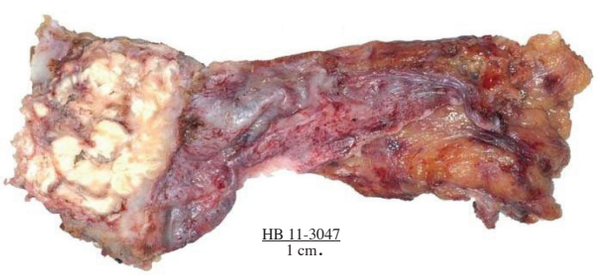


Figure 6: *The gross specimen consisted of a fibrocalcific mass size 3.5x3.5x1.8 cm. Cut section of the mass showed old and recent caseous material. The pericardium close to the mass was scarred and thick, up to 0.8 cm. The pericardium away from the mass was relatively normal.*

Discussion

Tuberculous pericarditis is responsible for approximately 4% of cases of acute pericarditis. It is a rare but life-threatening condition.[1] Tuberculosis (TB) is a serious problem in developing countries. The diagnosis is made by the identification of Mycobacterium Tuberculosis in the pericardial fluid or tissue and or the presence of caseous granulomas in the pericardium. PCR can identify DNA of Mycobacterium Tuberculosis from pericardial fluid: Pericardial biopsy provides a rapid and definite diagnosis.

Cardiac tamponade and constrictive pericarditis are two major lethal complications. In early stage patients with minimal pericardial effusion, pericardiocentesis with biopsy can be conducted to confirm the diagnosis. If cardiac tamponade develops, creation of a pericardial window should be done. If constrictive pericarditis presents, pericardiectomy is the treatment of choice.[4]

Conclusion

This case represented pericarditis identified by CT and MRI. The clue to diagnosing granular pericarditis was the thick wall of the pericardium with fine irregular border projecting into the pericardial effusion. Multiple microcalcification at the pericardium is a pathogenoic sign of chronic granulomatous disease.

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Case Report

Cardiac Tumors

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Keywords:
Cardiac tumors, Myxoma, Lipoma

Primary cardiac tumors are extremely rare. The frequency of cardiac tumor is approximately 0.02% corresponding to 200 tumors in one million autopsies.[1] The occurrence of metastatic cardiac tumors has been reported a 100-fold more commonly than primary lesions.[2] Clinical manifestations are usually determined by the location of the tumor in the heart, such as obstruction of the circulation being symptomatic of heart failure. The tumor may not only invade the myocardium but also the adjacent lung,[3] which can cause pulmonary symptoms.

We hereby present 4 cases of cardiac tumor encountered in our institution.

Case report: 1

A 33-year-old woman presented with clinical frequent embolization. The echocardiogram revealed a large floppy mass (7.3 x 2.2 cm) in the left atrium with stalk adhering to the interatrial septum. The left ventricular function with ejection fraction was about 64% and there was mild pericardial effusion. The functional class of the patient was New York Heart Association (NYHA) class I.

The patient underwent right thoracotomy: resection of left atrial myxoma, which included interatrial septum and closure defect at interatrial septum with Dacron patch.

The pathological diagnosis was myxoma.

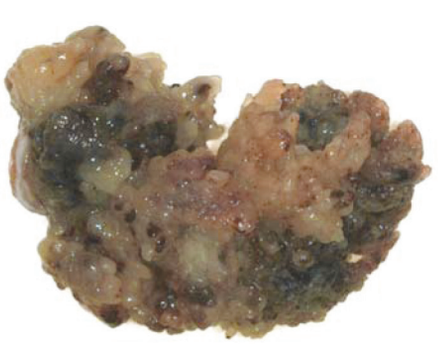
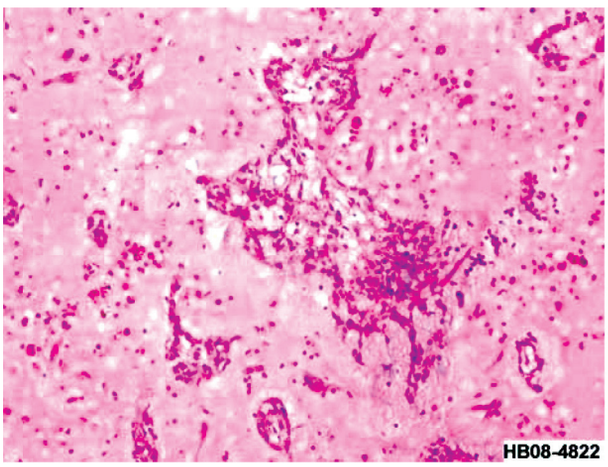
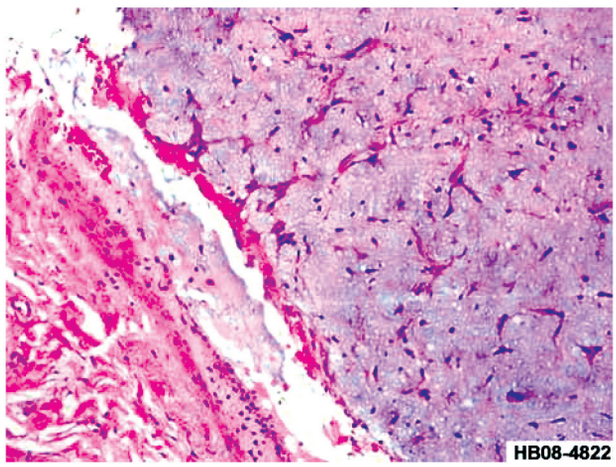


Figure 1a: *Gross examination shows a gray tan mucoid lobulated mass, measuring 7x4x2 cm.*



1b



1c

Figure 1b-c: *Microscopic examination shows mass consisting of round, polygonal and stellate cells surrounded by abundant loose mucoid and myxoid stroma, mitoses, pleomorphism or necrosis are absent.*

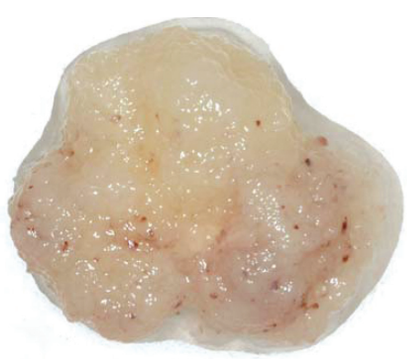
Case Report: 2

An 84-year-old man presented with progressive dyspnea. The electrocardiography (ECG) showed atrial fibrillation (AF) rhythm.

Echocardiogram revealed dilation of right atrium due to myxoma in the right atrium. The size was about 3 cm in diameter, there was fair left ventricular (LV) contractility and left ventricular ejection fraction (LVEF) was 60%. The preoperative coronary angiography revealed no abnormalities.

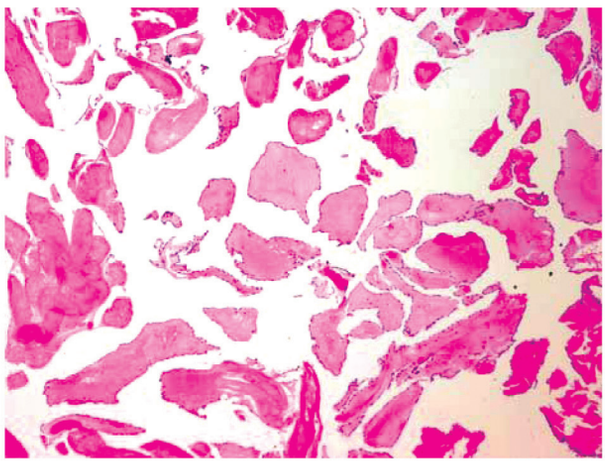
The patient underwent open cardiac surgery. The right atrium myxoma was removed from the anterior leaflet of tricuspid valve (TV). Radiofrequency ablation was applied to the left and right atrium.

The pathological diagnosis was papillary fibroelastoma.

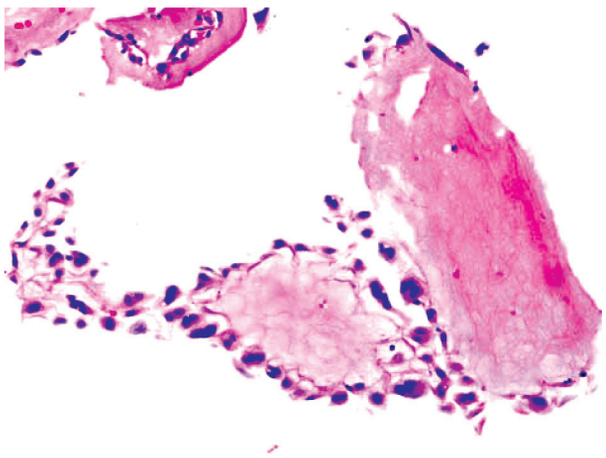


2a

Figure 2a: *Gross examination shows a sea-anemone-like light-tan soft mass, measuring 35x30x15 mm. Its base of attachment measured 10x8 mm.*



2c



2d

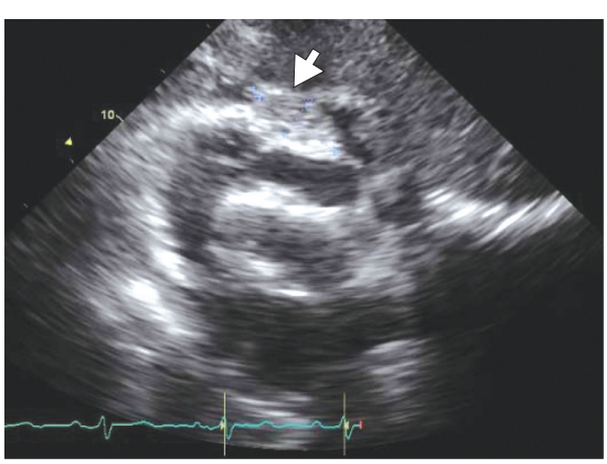
Figure 2c-d: *Microscopic examination shows long branching papillary fronds having avascular paucicellular cores of pink matrix and small round to elongated cells with eosinophilic cytoplasm, and covered with single layers of flat or plump probable endothelial cells. The base is composed of cardiac myofibers and a low cellularity of wavy slender spindle cells. No blood vessels or polygonal cells are present within the papillae.*

Case Report: 3

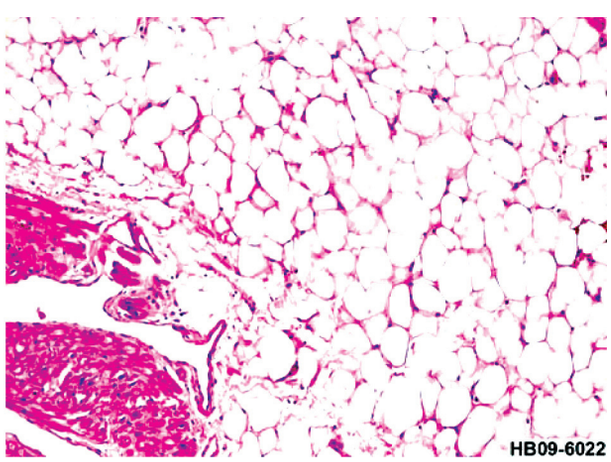
An 81-year-old woman presented with progressive dyspnea and low grade fever for 1 month, she had underlying dyslipidemia, diabetes, hypertension and was an ex-smoker. The echocardiogram (Figure 3a) revealed normal left ventricular contraction with the ejection fraction of about 73%; there was a mass-like structure of right aortic valve (AV) groove which was attached to the visceral pericardium. MRI concluded as mass like lesion of postero-superior wall of right atrium.

The patient underwent right lateral thoracotomy with the aid of cardiopulmonary bypass. The right atrium was opened. The intramural right atrial mass 1.5x0.5 cm was removed.

The pathological diagnosis was intramyocardial lipoma.



3a



3b

Figure 3a: *The echocardiogram reveals mass-liked structure of right aortic valve (AV) groove which is attached to vis-ceral pericardium.*

Figure 3b: *Microscopic examination shows presence of mass made of mature fat cells infiltrating in interstitium and between bundles of myocardial fibers.*

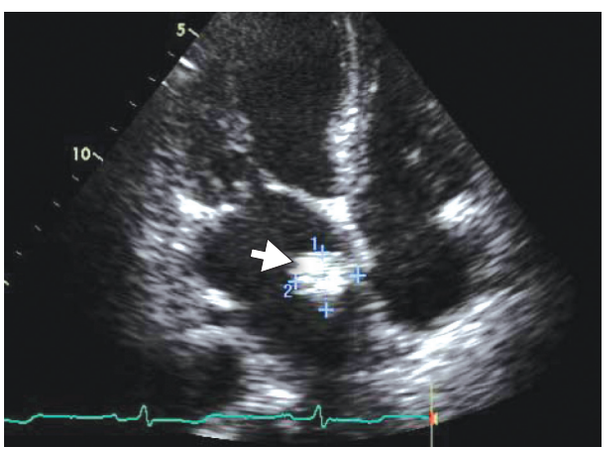
Case Report: 4

A 79-year-old woman presented with underlying history of dyslipidemia, diabetes and chronic atrial fibrillation. She was suffering from progressive dyspnea and was diagnosed as acute Non-ST Elevation Myocardial Infarction (NSTEMI) with congestive heart failure. The intra aortic balloon pump supported and inotropic medication was administered to maintain hemodynamic stability.

Echocardiogram (Figure 4a) revealed akinesia of apical inferior and anteroseptal LV wall with the left ventricular ejection about 41% and there was left atrial mass.

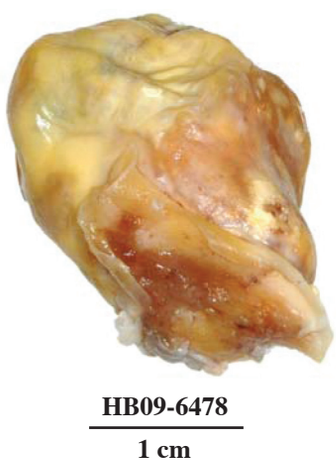
The coronary angiogram shows severe triple vessel disease. The patient thus underwent cardiopulmonary bypass, 6 coronary bypasses, and also excision of the left atrial mass 2.5 cm in diameter which had been attached to the inter-atrial septum, extending to posterior wall of left atrium.

The pathological diagnosis was calcified mesenchymal tumor (lipoma).



4a

Figure 4a: *The echocardiogram reveals left atrial mass.*



4b

Figure 4b: *Gross examination shows consists of an calcified mass measuring 3 x 3 x 2 cm.*

Discussion

Tumors of the heart remain one of the least investigated subjects in oncology, despite the improvement in both diagnostics and treatment for various cancers. Because primary cardiac tumors are quite rare, most clinicians will pay less attention.[4] The diagnoses were mostly incidentally, tumors being found due to investigations of clinical complications such as systemic embolization or the tumor invading the myocardium. The most common benign primary cardiac tumor is myxoma; about 75% of cardiac tumors are benign, with 50% of these being myxoma. Lipoma is the second most common benign cardiac tumor.[5] Sarcomas are the most common primary malignant cardiac tumors.[6] Most of these tumors occur in the left atrium of the heart.[1]

Conclusion

This report represents symptomatic cardiac tumor. Our reported 4 cases of cardiac tumors included myxoma, papillary fibroelastoma, intramyocardial lipoma and calcified mesenchymal tumor (Lipoma). Myxoma is the most common benign cardiac tumor. The result of surgery is dramatic. The total cure after surgery is high.[7]

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Prolonged Fever with Massive Hemoptysis

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Keywords:
Fever, Massive Hemoptysis, Wegener Granulomatosis

Last year in November, a 58-year-old man was referred to our hospital for further diagnosis and treatment. He presented with prolonged fever which further developed into severe haemoptysis and he subsequently died. This patient had a very interesting clinical presentation over the period of his sickness. We believe that reviewing this case will help all clinicians to be more aware of the importance of early recognition and understanding the time variable development of this disease; earlier treatment may result in a better outcome.

The patient was a middle aged man, working as a government officer, who had no known underlying disease. Around one month prior to admission, he had a low grade fever, mild coughing, anorexia, and feelings of general malaise. He sought medical treatment in his local clinic and was given the diagnosis of bronchitis. A week later, his fever still persisted and general symptoms were not improved. He was admitted in another hospital where the radiographic study of chest revealed a patchy infiltration at right lower lobe. A full septic work up was completed, but which resulted in no suggestive diagnosis and he was treated with Ceftriazone.

Intravenous antibiotic was switched to Piperacillin-Tazobactam after the sputum culture grew a few colonies of E.Coli. Even after intravenous antibiotic therapy for a week, his fever persisted. Computer tomography of chest revealed patchy infiltration or a mass like lesion at right lower lobe with minimal bilateral plural effusion. A needle biopsy from the right lower lobe revealed chronic inflammation though testing negative for organisms. The results could not yield any definite diagnosis. Therefore, the patient underwent a bronchoscopy for endobronchial biopsy of the lesion as well as bronchiolar lavage. There were no pathogens detected in clinical specimens; tests included gram stain, modified acid fast stain and acid fast stain. Pathologic study of endobronchial biopsy showed chronic granulomatous inflammation whereas the special stain for mycobacterial was negative.

Because of the prolonged course of fever, lasting more than 20 days, and the abnormal lung lesion showing granulomatous inflammation, the treating physician suspected mycobacterial infection. The patient was thus treated with anti-mycobacterial medications. Unfortunately, the medication had to cease for a week due to the patient's development of hepatitis.

One day prior to the admission of the patient to Bangkok Hospital, he developed dyspnea and hypoxia due to severe hemoptysis. He was transferred to the intensive care unit to stabilize his acute respiratory distress. Imipenem and Amphotericin B were started. The patient was then transferred to our hospital for an open lung biopsy and further

treatment. At Bangkok Hospital the initial physical examination revealed a body temperature of 38.5 °C. Blood pressure was 118/70 mmHg. Heart rate was 110/min, respiratory rate was 20/min. The patient was conscious, on endotracheal intubation with ventilation support. He had pale conjunctiva and no icterus sclera. Auscultation disclosed bilateral rhonchi. Other physical examinations were unremarkable. Chest x-ray (Figure 1) revealed infiltration at right upper lobe and left lower lobe with dense or mass like lesion infiltration at right lower lobe. Complete blood count showed white blood cells of 23,320 cells/cm^3, hemoglobin 9.1 gm/dL and hematocrit 27.4%, differential count found polymorphonuclear 92%, lymphocyte 5% and platelet 467,000 cells/mm^3. Serum creatinine 0.1 mg/dL, Total protein 5.38 gm/dL, Albumin 1.9 gm/dL, Total bilirubin 0.7 mg/dL, ALT 107 U/L, AST 189 U/L, Prothrombin time was 20.4 sec, Fibrinogen 625 mg/dL, Ferritin 17.128 ng/mL, Erythrocyte sedimentation rate (ESR) 109 mm/hr, C-reactive protein (CRP) 121.29 mg/L.

Sputum examination found bloody secretion and under the microscope, revealed numerous red blood cells with moderate white blood cells. No organism was seen.

Hospital course:

On his first hospitalization day in Bangkok Hospital, the patient had a high grade fever of 39.5°C with obvious massive hemoptysis and chest x-ray showed progressive bilateral pulmonary infiltration (Figure 2). The differential diagnoses for this patient's illness included autoimmune diseases such as vasculitis syndrome. An ENT (Ear-Nose-Throat) specialist was consulted for evaluation and found no evidence of sinusitis. Because the patient's condition was currently too critical for further invasive investigation, such as the planned open lung biopsy, we had started him on a high dose dexamethazone. Lysis of the fever thus ensued within 24 hours (Figure 3). Although we tried to control the massive hemoptysis by blood components replacement, his bleeding still continued. The patient passed away 2 days later from severe hypoxemia. The result of the blood test for c-ANCA/Anti-PR3 was positive of high titer (Table 1). This was the most important evidence for diagnosis, and we concluded that the patient's illness was caused by the autoimmune disease, vasculitis in small-medium-sized blood vessels, better known as Wegener's Granulomatosis.

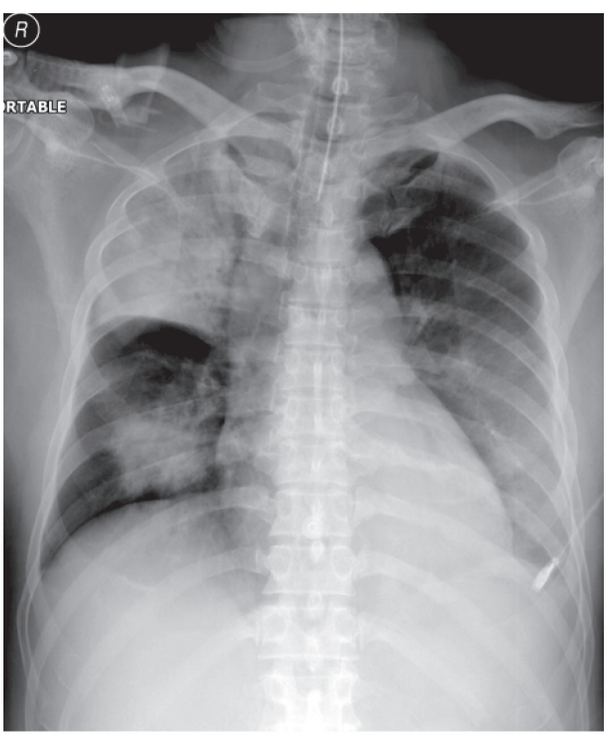

Figure 1: *Admission day, chest x-ray showed infiltration at right upper lobe and left lower lobe with dense or mass like lesion infiltration at right lower lobe.*

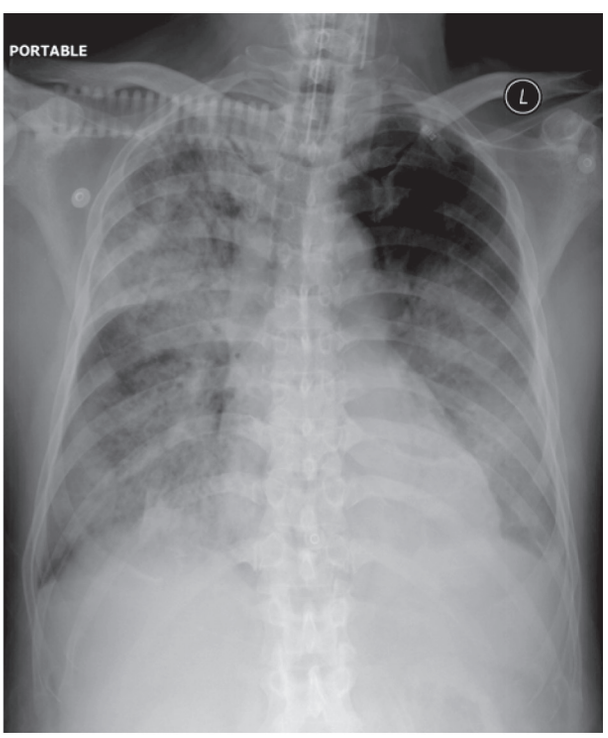

Figure 2: *On Day 2, chest x-ray showed progressive pulmonary infiltration at both lungs.*

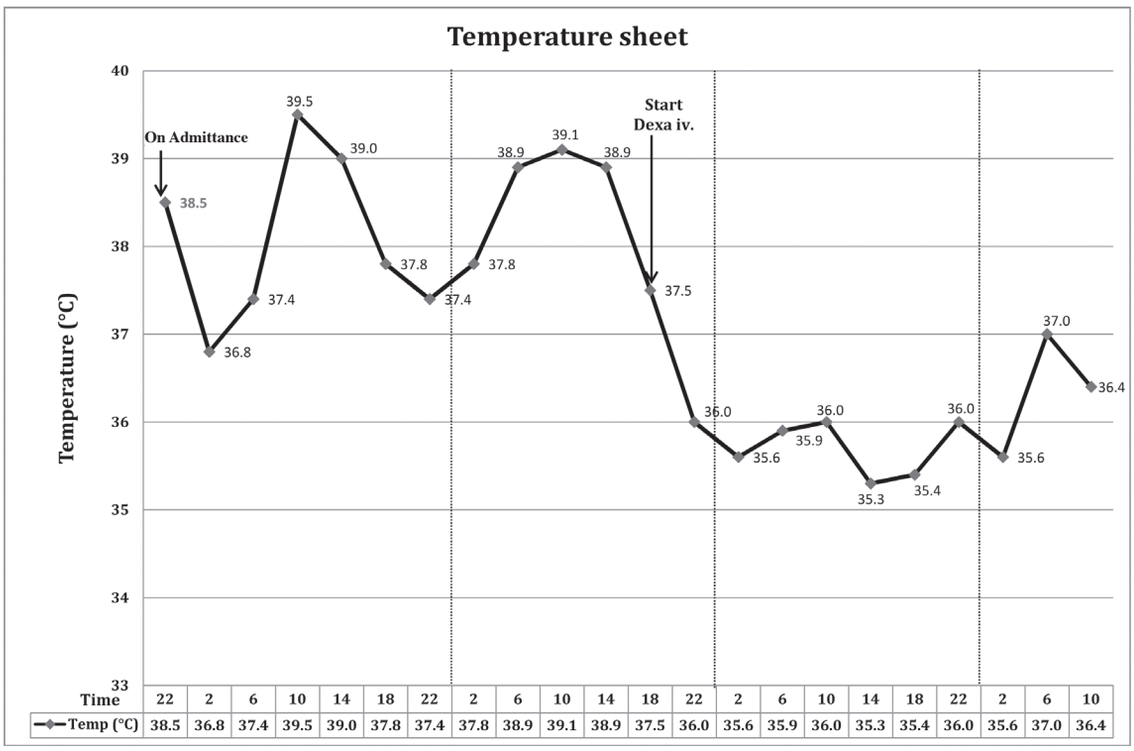

Figure 3: *Temperature sheet shows patient's high grade fever during the first 2 days of hospitalization and lysis of fever with demonstration therapy.*

Table 1: Result of the Anti-Neutrophil cytoplasmic antibody (ANCA).

Anti Neutophile Cytoplasmic Antibody (ANCA)	Valve (U/mL)	Normal (U/mL)
p-ANCA/MPO, Myeloperoxidase Antibodies	< 2.00	0.00 - 20.0
p-ANCA/MPO, Myeloperoxidase Antibodies	Negative	
c-ANCA/PR3, Proteinase 3 Antibodies	**> 200.00 H**	0.00 - 20.0
c-ANCA/PR3, Proteinase 3 Antibodies	**Positive**	

Discussion

This patient presented to our hospital with a history of prolonged fever and right lower lung lesion which had not responded to standard antibiotics. His condition had deteriorated further with the sign of hemoptysis. Taken together, the differential diagnosis needed to be reevaluated and the diagnosis of chest infection with possibility of tuberculosis was unlikely. The second most common differential diagnosis would be an autoimmune disease such as systemic vasculitis. However, the unusual presentation of a malignant tumor could not be ruled out. The treating physician approached the patient step by step from non invasive to invasive investigations. When we had reviewed all investigations, the finding of chronic granulomatous inflammation from endobronchial biopsy was of interest. Chronic granulomatous lesion in the lung along with prolonged fever would usually lead to the diagnosis of tuberculosis. However, later on, he presented with diffuse alveolar hemorrhage.

Combining all the findings together, the most intriguing diagnosis would be Wegener's Granulomatosis (WG). WG has the hall mark of necrotizing granulomatosis and pauci-immune vasculitis. We did have the ENT specialist review any evidence of chronic sinusitis with the report of negative finding although the negative result could not rule out WG. There was also no clinical finding of

renal disease that would also support a diagnosis of WG. Interestingly enough, one dosage of dexamethasone reduced the patient's fever but no definite diagnosis could be implied by this. When we discovered the c-ANCA positive in high titer in this patient, it more or less confirmed the diagnosis of WG.

Wegener Granulomatosis (WG) was first described in 1936, on the basis of clinical findings and pathological study. Around 20 years later, the pathological triad of necrotizing angiitis, granulomatous inflammation in respiratory tract and kidneys had become the main features for the diagnosis and study of this disease.[1]

At present, WG has been grouped into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) on the basis of autoantibody finding. Clinical presentation of WG is sometimes also classified into limited and severe type.[2]

Cellular and humoral immune responses are the major pathways in the pathophysiology of WG. Uncontrolled cellular immune responses contribute to granulomatous lesion along with the injury of the tissues via inflammatory cytokines. ANCA is the humoral immune response that mediates pathological process of diseases. The cytoplasmic staining pattern of ANCA or c-ANCA is specific for WG. The auto-antigen for c-ANCA has been identified as serine proteinase 3 (PR3). This antibody has no pathological role in vivo study.[3]

Patients with WG, if left untreated, suffer a mortality rate over 90%.[4] The most common cause of death includes systemic infection, respiratory, cardiovascular and renal involvement.[5] In USA and UK, the prevalence of the disease is around 1-3 cases per 100,000.[4]

The following symptoms are usual findings in patients with WG: constitutional symptoms, fevers, night sweats, fatigue, lethargy, loss of appetite and weight loss. Patients with unconventional presentation of chronic sinusitis will need to be well evaluated for other organs involvement, such as the eye. Saddle nose deformity caused by collapse of nasal support is also common and would lead to the diagnosis of WG.

Common respiratory tract findings in this disease are pulmonary infiltration (71%), cough (34%), haemoptysis (18%), chest discomfort (8%) and dyspnea (7%). Further progression of the disease in certain patients can lead to diffuse alveolar hemorrhage (DAH). Arthalgia or arthritis could be associated symptoms and signs but rarely develops into any permanent joint destruction.

Mononeuritis multiplex and cranial nerve abnormalities due to the vasculitis are not common findings in WG.[6]

Differential diagnoses for WG include: Churg-Strauss Syndrome, cocaine abuse, cryoglobulinemia, glomerulonephitis, Goodpasture syndrome, Hemolytic-uremic syndrome, Infective endocarditis, Langerhans Cell Histiocytosis, leukocytoclastic vasculitis, lung abscess, lung cancer, microscopic polyangiitis, Pneumonia, polyarteritis nodosa, sarcoidosis and systemic lupus erythematosus.

Complete blood count studied in WG often shows a mild normochromic normocytic anemia. Leukocytosis is also common, with a neutrophil predominance. The finding of eosinophilia often indicates other vasculitis syndromes, such as Churg-Strauss syndrome. Increase of inflammatory index as in ESR or CRP is common and may be used as an indicator with which to follow up response of treatment.

At present, there are two types of assays for ANCA: immunofluorescence technique (IF) and enzyme immunoassay technique (ELISA). ELISA provides the target antigen-specific character of ANCA and should be used to confirm IF findings. Autoantibody study by the above two techniques have increased the sensitivity and specificity for the diagnosis of AAV to 95% or above.

Other autoantibodies in WG may be slightly elevated as well e.g., rheumatoid factor or antinuclear antibodies (ANA).[4] Two phases of treatments need to be carried out in WG, remission induction and remission maintenance, respectively. In 1970, the introduction of cyclophosphamide in WG resulted in 75% of patients expecting complete remission. Combination therapy with oral cyclophosphamide 2 mg/kg/day and prednisolone 1 mg/kg/day has been used in induction of remission in WG. Using pulsed intravenous cyclophosphamide as opposed to giving it orally should result in less cumulative exposure to cyclophosphamide. Subsequently, standard prophylaxes of Pnuemocystis and hemorrhagic cystitis should be implemented.[7]

High doses of glucocorticoids are an important part of remission induction therapy in WG. In the case of rapid progressive glomerulonephitis and/or alveolar hemorrhage or other life threatening conditions, intravenous pulse methyprednisolone should be applied without hesitation. Plasma exchange should be considered in patients with rapidly progressive renal diseases.[8-10]

Azathiopine, methotrexate and leflunomide should be used in remission maintenance. During the treatment, glucocorticoid should be tapered according to the clinical presentation and side effect of prednisolone itself.[11]

Alternative therapies that are currently under study elsewhere are anti-CD20 immunoglobulin (IgG1) antibody,

intravenous immunoglobulin (IVIG), myclophenolate mofetil, anti-tumor mecrosis factor (TNF) antibody, 15-Desoxyspergualin, antithymocyte globulin, anti-CD52 antibody.[12-16]

The remission rate in WG ranges from 30% - 95%. However 50% of patients developed relapses within the first 5 years of treatment. Factors associated with relapse include prednisolone dosage amounts, ANCA status at diagnosis and target organs involvement.[17-19]

Poorer survival rates are associated with older age, target organs damage and involvement.

Conclusion

We reported a patient with unusual clinical manifestations of WG and an isolated lung lesion. The delays and complications in diagnosis unfortunately contributed in clinical deterioration to severe hemoptysis and the eventual death of this patient.

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Case Report

Laparoscopic Pancreaticoduodenectomy for the Treatment of Complicated Choledochal Cyst in Bangkok Hat Yai Hospital

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Keywords:
Laparoscopic surgery, Choledochalcyst, Whipple procedure, Pancreaticoduodenectomy

The Laparoscopic Whipple procedure or Laparoscopic Pancreaticoduodenectomy is the operation for treatment of pancreatic disease such as carcinoma or other benign disease involving the periampullary region or distal common bile duct. The procedure is one of the most complex surgical procedures, especially since it is conducted laparoscopically. There are many techniques to perform laparoscopic pancreaticoduodenectomy. The case report described below details our decision to use laparoscopic surgery in dissection of distal stomach, common bile duct, pancreas and duodenum and the use of small incision to remove specimen and complete anastomosis.

Case Report

A 39-year-old woman presented with fever, right side abdominal pain which radiated to her back and mild jaundice since 2-3 days. She had history of fever with chills off and on since 2-3 months and had been treated conservatively for a peptic ulcer. Her initial blood tests were normal except for the liver function test.

Bilirubin (Direct)	3.0 mg/dL	(0-1.5)
Bilirubin (Total)	3.7 mg/dL	(0-1.5)
AST (SGOT)	202 U/L	(0-40)
ALT (SGPT)	199 U/L	(0-40)
ALP (alkaline phosphatase)	589 U/L	(39-117)

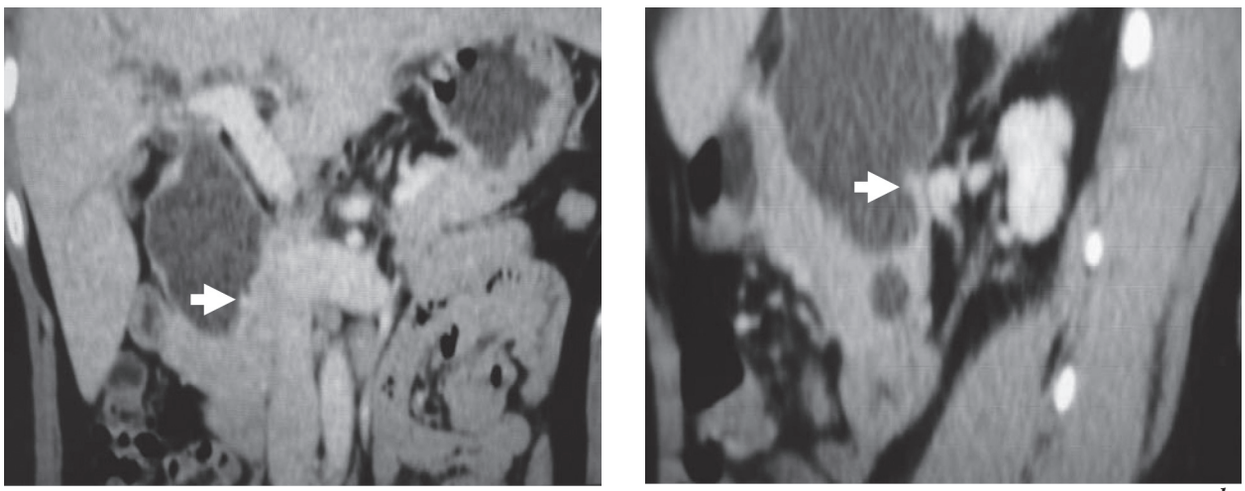
Ultrasound showed cystic mass suspected to be choledochal cyst without biliary stone.

Multi-detector Computerized Tomography (MDCT) scan (Figure 1a-b) showed fusiform dilatation of common bile duct (CBD), type 4 Todani classification[1] with enhancing nodular lesion within the dilated distal bile duct about 0.7 cm in size, just above the ampulla region that could be a tumor, such as adenoma, carcinoma of the ampulla or distal cholangiocarcinoma.

Endoscopic Retrograde Cholangiopancreatography (ERCP) (Figure 2) was performed. Findings included:

1. Type 4 choledochal cyst.
2. Two short segmental strictures 15 and 13 mm in length at distal common bile duct.
3. Anomalous pancreatobiliary junction (a long common channel found in choledochal cyst).

The treatment consisted of dilated distal CBD, brush biopsy, intraductal biopsy and insertion of biliary stent. The result of cytologic study was negative for malignancy.



a *b*

Figure 1 a-b: *MDCT scan shows enhancing nodular lesion within the dilated distal bile duct about 0.7 cm.*

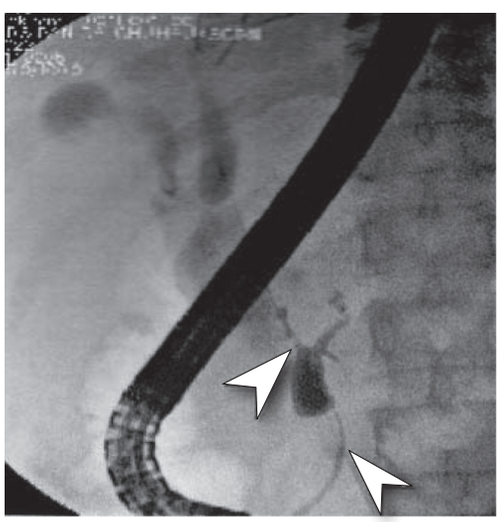


Figure 2: *ERCP shows 2 segments of stricture (white arrow) at distal CBD and anomaly of Pancreatobiliary junction.*

Treatment plan

The ultrasound, MDCT and ERCP findings showed that the problems were complicated: a multisegmental stricture of distal common bile duct at stricture site where malignancy could not be ruled out, a choledochal cyst involving the head of the pancreas, and anomaly of pancreatobiliary junction.[2-4]

We discussed with our colleagues and the patient's family about the risks and benefits of the various procedures and techniques available to correct the problem. We decided that the laparoscopic technique Whipple procedure was appropriate to handle this complicated problem. This case was the first such surgery performed in our hospital.

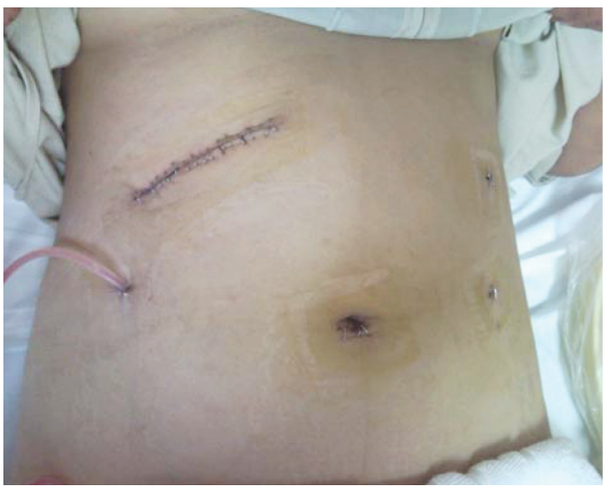


Figure 4: *Post-operative wound.*

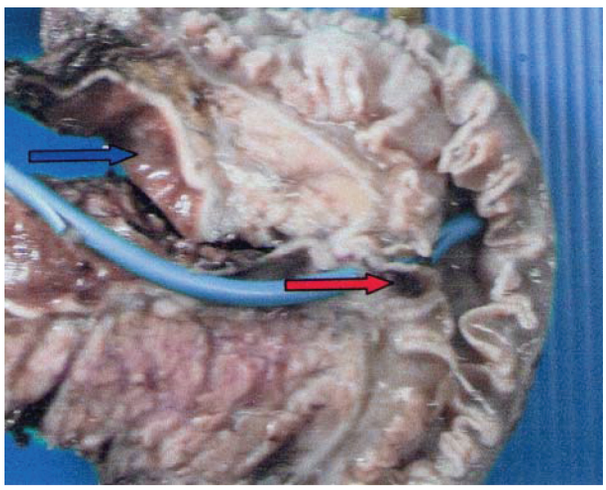


Figure 5: *Pathology specimen (stricture site-red arrow); (Choledochal cyst - blue arrow).*

Surgical Procedure: Laparoscopic pancreaticoduodenectomy was performed in two phases.[5]

Phase 1

- Laparoscopic dissection was begun to free the distal stomach and the first part of the duodenum.
- Dissection to free second and third part duodenum and cholecystectomy was performed.
- Dissection inferior border of neck pancreas to free neck of pancreas from superior mesenteric vein.
- Dissection at junction of fourth part duodenum and proximal jejunum.
- Divided distal stomach.
- Divided neck of pancreas and dissect uncinated process and head of pancreas from superior mesenteric root.
- Pulled proximal jejunum beneath superior mesenteric root and divided to prepare anastomosis.
- Dissect and remove choledochal cyst to prepare anastomosis.

Phase 2

Small right subcostal incision to remove specimen for biopsy and this incision used to created anastomosis.

- Pancreaticojejunostomy end to side anastomosis done first with catheter stent size 8 Fr. Pancreatic duct was anastomosed with mucosal tube of jejunum by 4 interrupted suture then pancreatic capsule sutured with jejunalserora by polysorb 4-0.
- Hepaticojejunostomy end to side done by creating mucosal tube for anastomosis one layer continuous suture by polysorb 4-0.
- Loop gastrojejunostomy was performed using gastrointestinal anastomosis (GIA) device and one Jackson tube drain was inserted into the subhepatic space.

The operating time was 460 minutes. Estimated blood loss was 1100 cc. Patient was given a transfusion of 2 units of packed red cells.

The patient tolerated the operative procedure well. She was able to ambulate within one hour post operatively. The patient was discharged from hospital on the 7th post operative day. She resumed regular activities within three weeks without any complications.

Discussion

The Whipple operation was performed to treat the unusual choledochal cyst that presented with 2 segments of common bile duct stricture. We could not rule out malignancy despite the cytology and needle biopsy showing no malignancy, due to the difficulty in obtaining a specimen and with the pancreatobiliary junction anomaly that caused recurrent pancreatitis. In our opinion, a total laparoscopic Whipple operation could have been done but it would have required a longer operative time. Therefore we decided to do laparoscopic dissection in the first phase and do a smaller incision to remove specimen and then create anastomosis.

The Laparoscopic procedure caused less pain and allowed an earlier recovery than the classical whipple operation technique would have done.

Laparoscopic surgery can be used for many different kinds of operation. Actually, the literature states that laparoscopic surgery is unsuitable for the surgical treatment of cancer, but no definite studies have supported that view. In the future, the trend will be to see laparoscopic substituting classical open technique because of advances in surgical instruments and a new, young generation of surgeons that are interested in laparoscopic surgery.

In our practice, laparoscopic surgery needs more operative time in learning period but decreased operative time after experience has been gained.

Conclusion

A case report of choledochal cyst, with abnormality of pancreatobiliary junction, successfully treated in Bangkok Hat Yai Hospital, by laparoscopic pancreaticoduodenectomy, a complex operation in six and a half hours.

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Case Report

Stentoplasty (Cemented kyphoplasty with Stent) Under Biplane Digital Subtraction Angiography (Biplane DSA)

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Keywords:
Kyphoplasty, Stentoplasty, Bi-plane x-ray

Vertebral body augmentation with cement such as vertebroplasty and kyphoplasty are well established minimally invasive treatment options for osteoporotic and pathological vertebral compression fracture with highly successful results. The original technique of injection of polymethylmethacrylate (PMMA) bone cement into the compressed vertebral body directly is called *"Vertebroplasty"*. This technique proved to be a useful approach that could significantly reduce back pain immediately and help the aging patient return to normal activity in a few days with less morbidity than open internal fixation. However, injecting the bone cement directly into the vertebral compression fragment "vertebroplasty" cannot well restore the height of that compressed vertebra, which can cause segmental kyphosis. Biomechanical and clinical data show that the segmental kyphosis resulting from compression fractures, leads to an increased fracture risk of the adjacent vertebral levels,[1,2] that can cause recurrent pain, deformity and disability in the future. Vertebroplasty has no intrinsic mechanical method to restore vertebral height but relies on the elasticity of the fracture itself and patient positioning to induce lordosis. Also, the directed injection of bone cement into non-homogenous space of vertebral fragments can cause a high rate of extra-vertebral leakage that can lead to tremendous complications such as cord compression, embolism, neuropathic pain, paralysis or even death. For better kyphosis correction and reducing the complication,[3] Balloon kyphoplasty (BKP) was the next step in the technological evolution of cemented vertebral body augmentation. A small, temporary "Balloon" is inflated in the vertebral body before injection of the bone cement into the space that was created by the balloon.[4,5]

Kyphoplasty is able to restore vertebral height better than vertebroplasty. However, clinical data shows 34% of kyphoplasty procedures do not result in an appreciable reduction in kyphotic angle or restoration of height.[6] One reason for inadequate height preservation in kyphoplasty is the loss of vertebral body height after balloon tamps deflation, prior to cement injection.[7,8] The next development was a new procedure called *"Vertebral body stenting"* or *"Stentoplasty"*. Vertebral body stenting uses a specially designed catheter-mounted titanium stent which can be implanted and expanded inside the vertebral body. Biomechanical tests showed no difference in stiffness and failure load between two systems. VBS (Vertebral Body Stenting) is an innovative technique which allows for the possibly complete reduction of vertebral compression fractures and helps maintain the restored height by means of a stent. The height loss after balloon deflation is significantly decreased by using stentoplasty compared to ordinary balloon kyphoplasty, thus offering a promising new option for kyphotic correction during treatment by cement augmentation.[9]

In this case, we combined *"Stentoplasty"* technique with the special x-ray equipment that can evaluate both anterior and lateral picture in the same time. "Biplanar x-ray This special x-ray equipment is widely used in interventional treatment of brain and cardiac disease, in Bangkok Medical Center. The significant benefit of using Biplanar x-ray is to be able to evaluate the position of the trocar and the injecting cement from anterior and lateral view in same time. This reduces the possibility of pedicles being broken by instruments, malpositioning of trocar or leakage of cement that are the cause of unpleasant complications. We decided to use this technique for the patient described below.

Case study

A 72-year-old man presented with lower back pain since 7 months. His extensive history included carcinoma of testis for which he had undergone orchiectomy 30 years previously. Eleven years ago, he was also diagnosed with carcinoma of the prostate and was treated by radiation. He underwent a gastrectomy to treat cancer of the stomach 5 years later. Four years ago, he developed coronary artery occlusion and was treated by cardiac catheterization and stent insertion. Eight months ago, he had a sudden back pain after minor trauma. From x-ray evaluation at that time, compression fracture of the forth lumbar spine was detected. The patient underwent a bone biopsy which showed no malignancy. The calcium paste vertebroplasty was done, but his back pain still persisted. He came to Bangkok Spine Academy 1 month later for further evaluation and proper management.

When the patient came to the Bangkok Hospital, the PET/CT scan showed no metastatic lesion. The MRI of lumbar spine (Figure 1) showed L4 compression fracture that had still not healed, the spinal canal was not compromised and neural structure showed no compression. Physical examination revealed specific points of tenderness on the back corresponding with the fourth lumbar level. Pain evaluation was 8/10 in Visual Analogue scale, Euro-quality of life was 40/100 and Oswestry Disability Index showed 53.33/100 at that time. Because his back pain significantly disturbed his quality of life, after discussion with the patient about the treatment, he allowed us to treat his un-healed osteoporotic lumbar compression fracture by injection of bone cement by using balloon kyphoplasty with stent under biplane digital subtraction angiography (Biplane DSA).

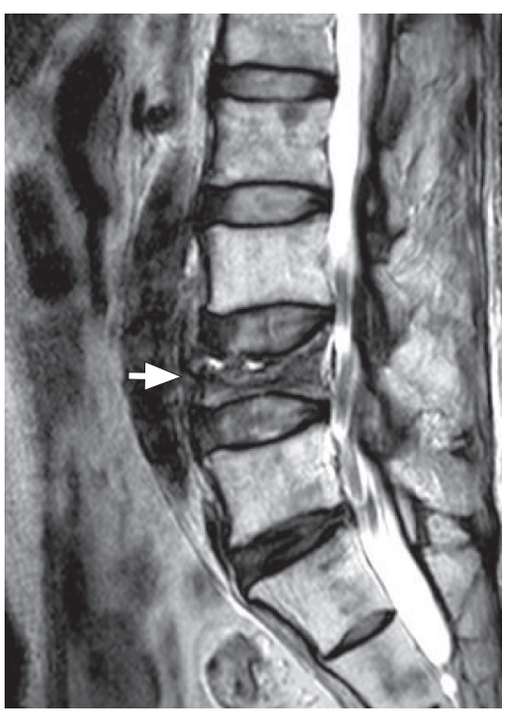


Figure 1: *The MRI of lumbar spine shows L4 compression fracture, mild central spinal stenosis, mild enhancement of bone marrow, possibly due to granulation tissue.*

Technique

The patient was placed in a prone position, and x-ray pictures were monitored by Biplane DSA equipment. The fourth lumbar vertebra was located in both AP and Lateral view. After the skin area was cleaned and draped, the trocar with the working sleeve was inserted obliquely on both sides by way of the skin, entering to the fourth lumbar pedicle, under bi-planar fluoroscopy in order to make sure there was no penetration of the trocar into the spinal canal. After the instrument assembly was deep enough and in a good position, the trocar and canula were removed, leaving the working sleeve in that corrected position in vertebral body.

After determining the appropriate length, the balloons and stents were inserted each side of the pedicles. The balloons were inflated by radio-opaque solution to 5 millimeter that reached maximum stent diameter. The balloons were removed, leaving the expanded stent on both sides. After verifying the proper position of stent, the bone cement (Polymethyl methacrelate agent) was mixed and injected into stent 5 cc each side under 2-planar radiographic real-time monitoring, to make sure there was no posterior and lateral leakage. The skin was closed by layer. The patient could turn over and lie normally within 10-15 minutes, with immediate reduction of pain.[10, 11]

Result

The patient had markedly reduced pain symptoms after this procedure. He was able to go back to his room without needing to be monitored in intensive care unit. He could move upright and walk by himself with minimal pain within a few hours. There was almost no wound pain problem because of very minimal injury at procedure site. The post-operative x-ray showed good restoration of vertebral height and that cement and stent were well placed. VAS (Visual Analogue Scale) of back pain symptom post operatively is 0/100; Euro-quality of life at sixth week showed a big improvement from 40/100 to 80/100 and ODI (Oswestry Disability Index) decreased from 53.33/100 to 2.44/100. This means that his life is now the same as normal population. At 24 weeks his Quality of life had slightly improved to 90/100 and ODI was still below at 2.44/100. No other complication occurred.

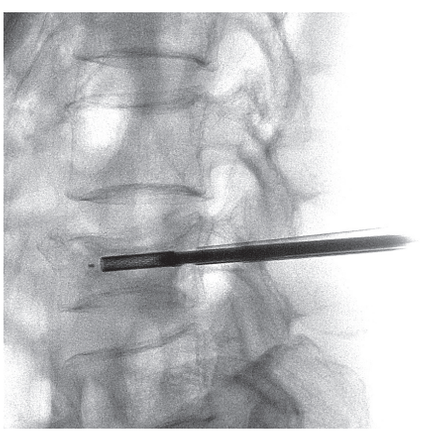


Figure 2: *Shows stent before inflation.*

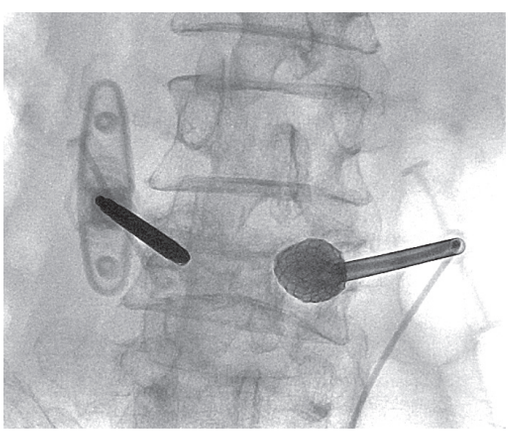


Figure 3: *Shows stent start inflation.*

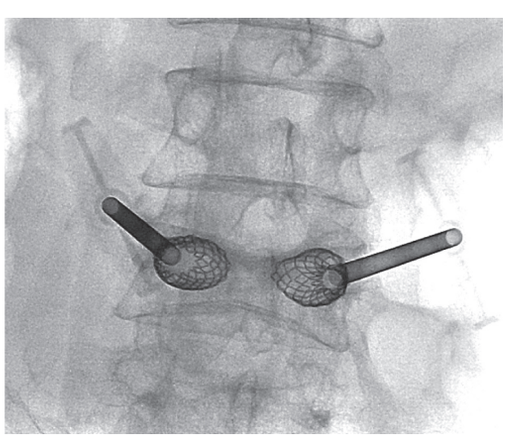


Figure 4: *Shows stent final inflation.*

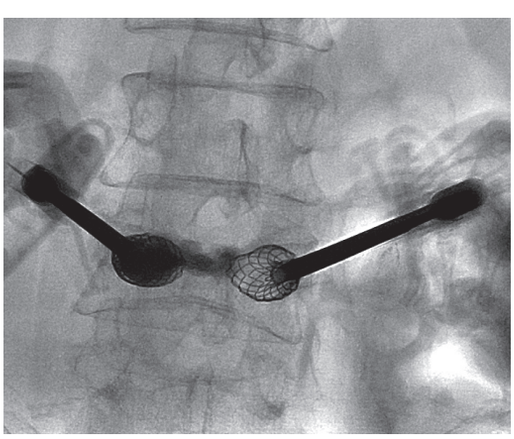


Figure 5: *Shows stent during cement injection.*

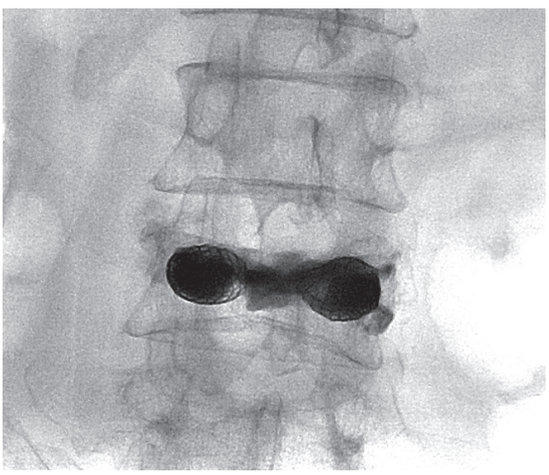


Figure 6: *Antero-posterior views shows stent after cement injection.*

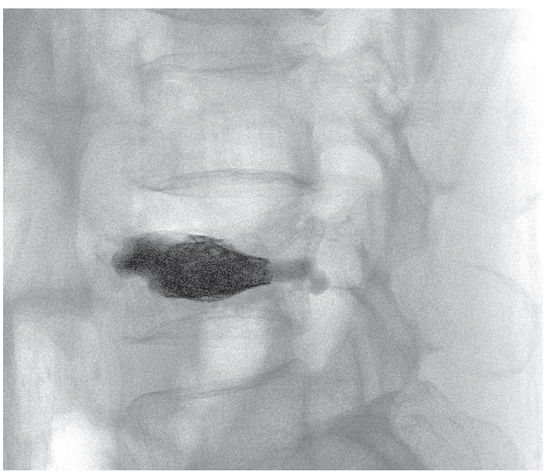
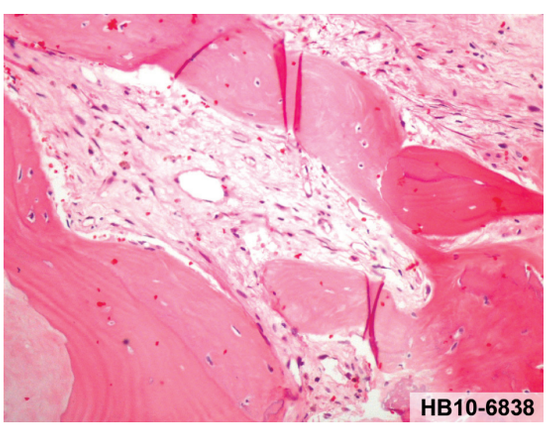
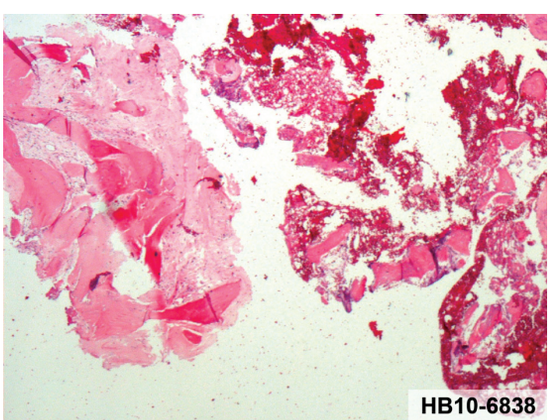


Figure 7: *Lateral views shows stent after cement injection.*



a



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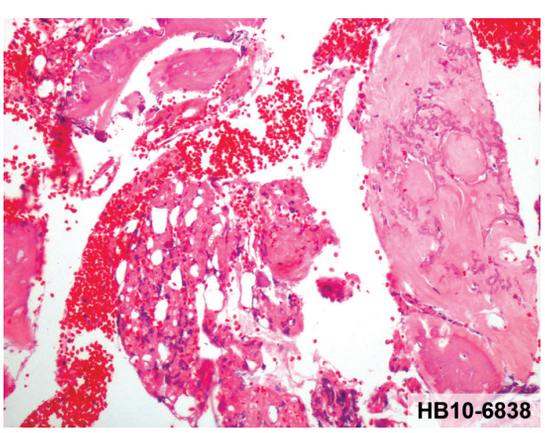

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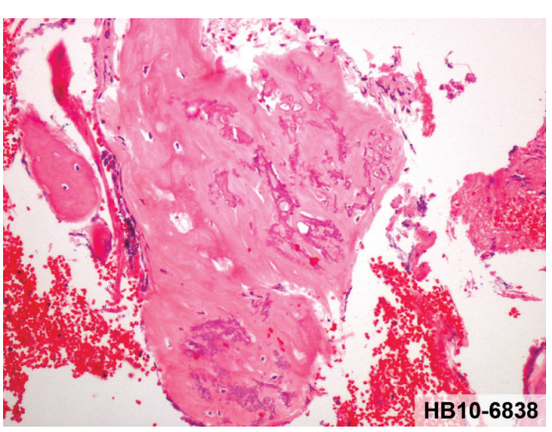

d

Figure 8 a-d : *Microscopic Sections reveal 4 irregular fragments of bone, 2 pieces show large foci of bone degeneration with amorphous areas and necrosis. A few reactive macrophages are noted. No identified or viable malignant cells. Residual tissue is congested bony trabeculae with fibrotendinous tissue.*

Discussion

Vertebral Augmentation with Cement is an interventional procedure whose indications, advantages, and results have caused controversial discussions. [1, 2, 4-8] Vertebroplasty, Kyphoplasty, and the newest Stentoplasty are all techniques whereby cement is injected in to the compressed vertebral body, thus immediately stabilizing the fracture fragment and decreasing back pain. This interventional technique has proven to be effective in elderly patients who have pathological fractures due to osteoporosis or tumorous condition. Kyphoplasty with or without Stent is proven to be more effective and safer than Vertebroplasty. Anyway, the most serious complications are cement leakage that can cause castratrophic morbidity. Cement leakage is more likely to occur due to poor visualization of needle placement in the correct position. Therefore, operators should use the highest quality fluoroscopy available to them and avoid poor-quality imaging systems such as older bedside units. Although kyphoplasty can be performed by using a single plane unit, biplane monitoring of fluoroscopic images decreases procedural time. The availability of digital subtraction angiography allows documentation of needle placement and evaluation of the trabecular space and epidural veins. Regardless of the modality used for needle placement, the injection of polymethylmethacrylate should always be performed with direct fluoroscopic control. We initially injected with biplane x-ray but did not feel confident that polymethylmethacrylate distribution was adequately and completely visualized. Cement may flow in a cranial or caudal direction, which may be difficult to monitor using CT.[12]

This method appears to be useful especially for monitoring the difficult steps of the procedure, such as an insertion of the osteointroducer, the balloon inflation and cemented injection. Vogl et al., have demonstrated that combined guidance improves accuracy of needle positioning in vertebroplasty. Potential cement leakages were detected earlier than with fluoroscopy alone.[13]

Conclusion

Vertebral Body Augmentation with Stent or *"Stentoplasty"* is an innovative technique for treatment of elderly patients presenting with pain from vertebral compression fracture. This technique is proven cost-effective, resulting in rapid return to normal life of the patient. The challenge of this procedure is to prevent the complication of leakage of cement. The combined use of Balloon-Stent and Bi-planar x-ray real-time in this procedure significantly increase the safety margins of this interventional treatment.

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When Baby's giggles are not funny: seven years overlooked diagnosis in a case of gelastic seizures

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Keywords:
Giggles, Pathologic laughter, Ictal laughing, Gelastic seizures, Hypothalamic hamartoma, Tuber cinereum

Laughter actually has positive emotional effect. However, it could be pathologic when laughter is not related to emotion and occurs independent of a stimulus in the environment. We reported a 7-year-6-month old Thai boy who presented with *'early giggles'* since the age of 2 months. Despite parental concerns, the symptoms were overlooked until seven years of age, when he developed complex partial seizures. An MRI study of the brain revealed a small ill defined lesion within the tuber cinereum that was compatible with hypothalamic hamartoma. We also reviewed and emphasized the characteristics of the pathologic laughing in infancy that should not have been ignored. Early diagnosis leads to appropriate counseling and proper seizure management. Common comorbidity such as precocious puberty and cognitive impairment or behavioral impediment should be followed up closely in long-term care.

A baby's giggling or laughing is always adorable and most parents do not have any cause to be concerned. However, pathologic laughter is different, particularly when it happens at an inappropriate age, or occurs without specific stimuli. It can cause hesitation in the observer, as to whether or not this is in line with the normal development of the child. Laughing seizures, known as gelastic seizures or ictal laughing, are epileptic events characterized by bouts of laughter as an isolated event, commonly lasting less than 30 seconds but frequently are accompanied by other seizure types.[1,2] According to the International League Against Epilepsy (ILAE) classification, gelastic seizures were classified into *"localization-related epilepsy"*. Criteria for diagnosis of gelastic seizures include stereotyped recurrent bouts of laughter, absence of external precipitants, concomitant additional paroxysmal events considered epileptic, presence of ictal or interictal epileptiform discharges on the electroencephalogram, and the absence of other conditions in which pathologic laughter may occur.[1] Gelastic seizures have been associated classically to hypothalamic hamartomas (HH) that are rare congenital lesions presenting with the classic triad of gelastic epilepsy, precocious puberty and developmental delay.[3,4] This report detailed an interesting case of gelastic seizures in infancy, caused by hypothalamic hamartoma, in a Thai boy in whom diagnosis had been overlooked for seven years. We also reviewed the clinical characteristics that should have caused earlier suspicion about pathologic laughing.

Case Report

A 7-year-6-month old, right handed Thai boy was brought to the emergency department due to brief but intense staring during his doing a jigsaw puzzle followed by a 10 minute generalized tonic-clonic seizure which precipitated a loss of consciousness. At the emergency room, he developed seizures twice and was treated as status epilepticus.

Two weeks prior to admission, according to his parents, he was noticed to have episodes of standing still, eyes turning upward and wetting himself without collapse or convulsive seizure. Past history revealed that he had had spontaneous bouts of giggles a couple times a week since 2 months of age. They were described as brief moments of the child giggling to himself, lasting for 30 to 60 seconds, without any precipitants and these symptoms frightened his mother. Because of maternal concern, he was evaluated by many pediatricians but due to his physical examination developmental milestones being unremarkable, the parents were advised to wait and see. Birth history revealed that he was a first baby, born full-term, to non-consanguineous Thai parents with a birth weight of 3,150 grams. Pre-, peri-, and post-natal period were uneventful. Developmental milestones were age appropriate although he showed exceptional academic performance. He did not have any underlying disease. Family history was unremarkable for neurologic disorders.

On physical examination, he was drowsy due to being post-ictal. BP 120/60 mmHg, HR 110 /min, T 37.2 ^{o}C, RR 22/min. Weight was 23 kg (50th centile). Height was 122 cm (50th centile). Heart, lungs and abdomen were normal. There were no dysmorphic features or neurocutaneous lesions. Neurological examination after he fully regained wakefulness, revealed a delightful boy with good orientation to time, place and person. Other neurological signs including cranial nerves, motor system, sensory system, gait and coordination were normal. Genitalia showed normal male phenotype without sign of precocious puberty.

Hematologic and biochemical laboratory tests including CBC, electrolytes, calcium, magnesium, phosphate, liver function, BUN, creatinine, thyroid function were normal. The 30 minutes, video electroencephalogram (vEEG), during wakefulness and natural sleep, using standard 10-20 system displayed normal background activity for age and no evidence of epileptiform discharge.

MRI of the brain with gadolinium revealed a small ill defined lesion at left side of hypothalamus (tuber cinereum) about 1.23 x 1.21 x 0.87 cm, which has slightly decreased T1, slightly increased T2 signal intensity without definite enhancement (Figure 1). These findings were consistent with sessile type, hypothalamic hamartoma. The pituitary stalk and suprasellar sellar region were within normal range. The cerebral parenchyma, brain stem and cerebellum showed normal signal intensity and appearance without definite space taking lesion. No infarction or hemorrhage was seen. MRA study of the brain showed normal vascularity without stenosis (Figure 2).

Seizures were well controlled by using topiramate at dosage of 3 mg/kg/day. Clinical seizures, developmental milestones, and signs of precocious puberty have been followed up in long term care.

Discussion

Pathologic laughter is defined as inappropriate laughter. The criteria, first proposed by Poeck in 1969, included laughter as response to non specific stimuli, no corresponding change in affect, no voluntary control of expression and no relief after the laughter.[5] This condition frequently is part of an associated syndrome of disease particularly in Angelman's syndrome. However, it has copious etiologies such as acquired neurologic damage, metabolic defects, and epilepsy known as gelastic seizures.[6] Gelastic seizures or ictal laughing, classifiedinto *"localization-related epilepsy"* according to the ILAE classification, are epileptic events characterized by bouts of laughter that are commonly deemed a hallmark of the evolution of hypothalamic hamartomas (HH).[1, 7] However, several studies have also reported that other conditions could cause laughing seizures such as focal cortical dysplasia, pituitary tumors, astrocytomas of mamillarybodies, third ventricular papillomas, lesion of the temporal lobes, frontal lobes, etc.[8]

Early detection and prevention of HH are important. Gelastic seizures are rarely diagnosed at their onset and may be misinterpreted as normal laughter or misdiagnosed as *'parental overconcern'* or even as infantile colic.[9] The clinical course of patients with gelastic seizures associated with HH is progressive, beginning with gelastic seizures in infancy and progressing to other seizure patterns in childhood and adulthood. Delay in diagnosis worsens seizure response leading to increases in both severity and frequency of seizures that directly cause cognitive impairment and behavioral hindrance.[10-13]

Our case of HH was diagnosed at age of seven years old because of overt convulsive seizures. His history of uncommon giggles during infancy was retrospectively discovered after detection of HH from MRI study of the brain. It is difficult to know whether or not the small lesion (less than one centimeter) of tuber cinereum found at the age of diagnosis (seven years of age) could have been detected in infancy. The size of HH reportedly correlates to the severity of the cognitive dysfunction, particularly in patients with large HH.[14-16] The cognitive function of our reported case is as yet, intact, perhaps his pathologic lesion in MRI is rather small. The location and anatomical features of HH have shown correlation with the clinical presentation. HH is classified into 2 types: pedunculated or type I, and sessile or type II. Pedunculated HH, clinically associating with precocious puberty, divide into type Ia that attach to the tuber cinereum and type Ib that attach to the angle between the tuber cinereum. Sessile HH, correlating to gelastic seizures, have a broad attachment to the floor of the third ventricle and the mamillary bodies.[17, 18] For our case, HH was compatible with sessile type, his first clinical manifestation was gelastic seizures.

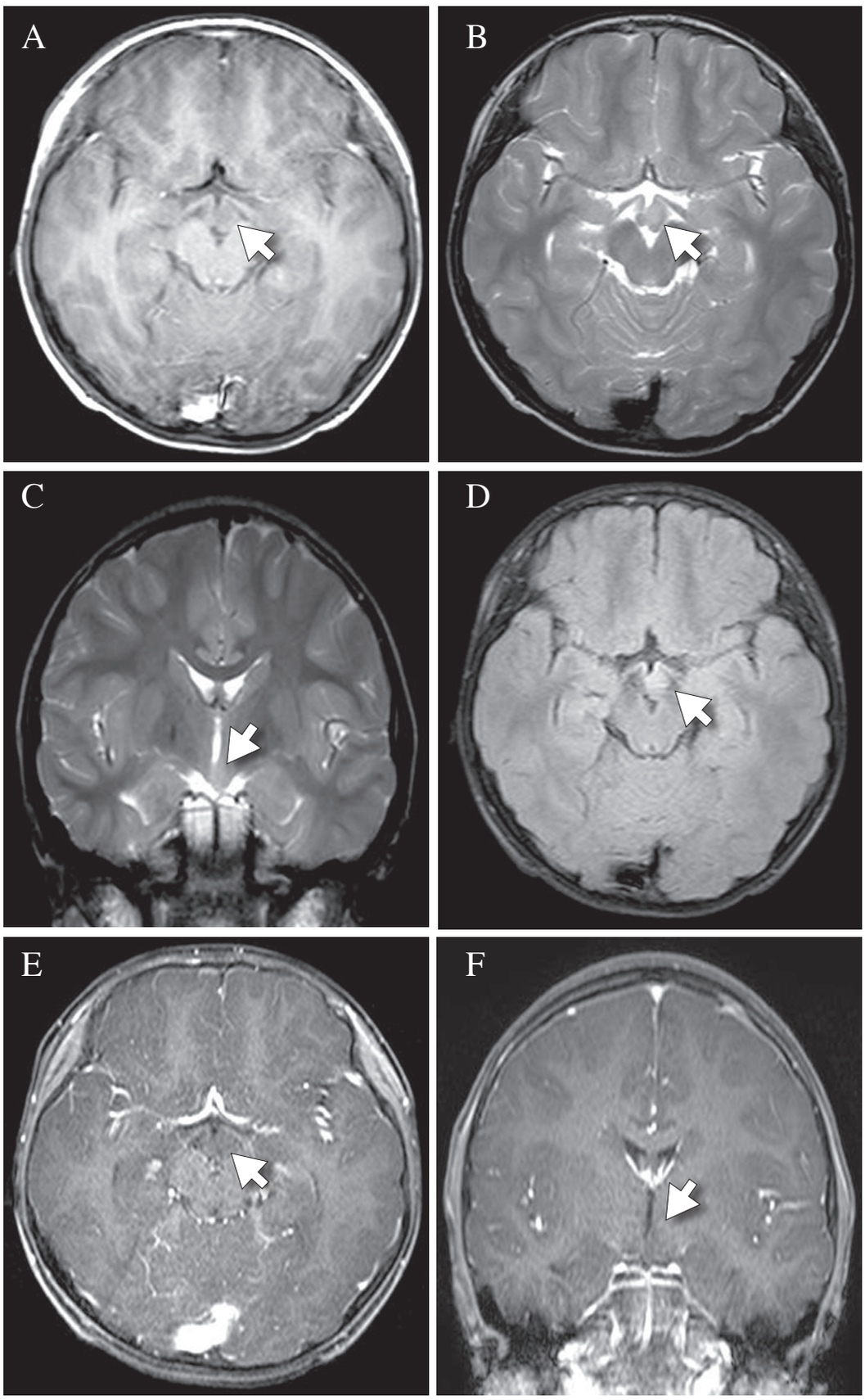

Figure 1: *MRI scan of the brain demonstrated small ill defined lesion at left side of hypothalamus (tuber cinereum) about 1.23 x 1.21 x 0.87 cm (white arrow), which had slightly decreased signal intensity in T1W (A, axial view), and slightly increased signal intensity in T2W (B, axial; C, coronal view) and FLAIR (D) without definite enhancement (E, axial; F, coronal view).*

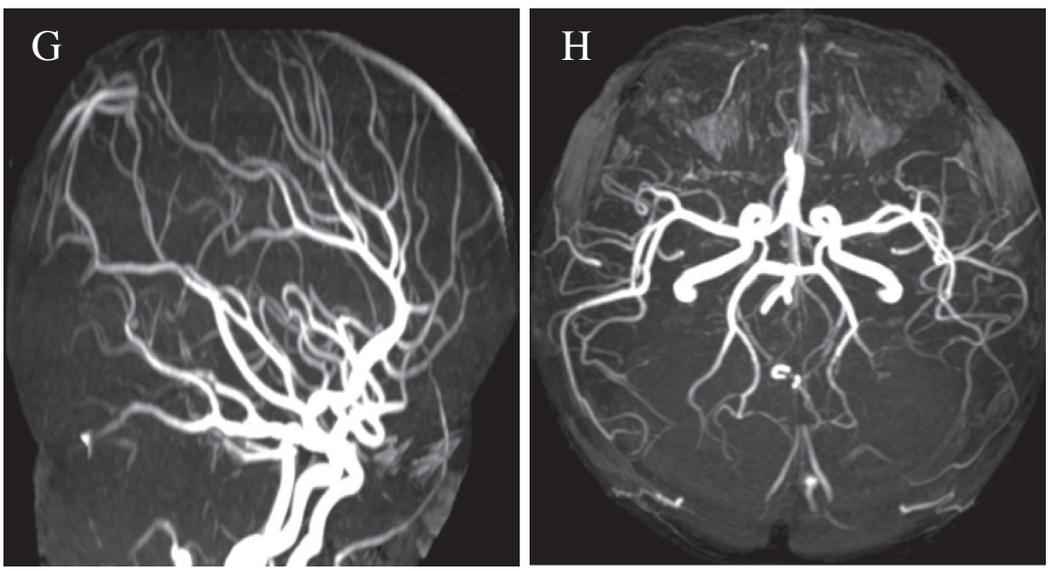

Figure 2: *MRA study of the brain demonstrated normal study without sign of vascular stenosis. The vascularity was normal (G, lateral view; H, top view).*

Precocious puberty, defined as the occurrence of puberty in girls aged less than 8 years and in boys aged less than 9.5 years, is a clinical finding that has been reported commonly in patients with gelastic seizures associated with HH which cause of 75% of precocious children aged between 1 and 3 years old.[19, 20] Even though this symptom has not shown up in our case, clinical observation of this aspect should not be forgotten in long term care.

Treatments of HH include both medical management for epilepsy and precocious puberty, and surgical interventions for those with medical failure or having intracranial hypertension caused by HH. A review of the literature illustrates that gelastic seizures are typically refractory to antiepileptic agents and these progressive symptoms will eventually deteriorate intellection and behavioral function.[21-24] Currently the best treatment for those with intractable seizures is the ablation of the HH that can be done with different procedures including surgery and nonsurgical treatments e.g. radiosurgery.[25] The nonconventional surgeries e.g. radiofrequency coagulation, stereotactic implantation of 125I radioactive seeds, and gamma-knife radiosurgery in particular seem to be safe and effective treatments even in children.[26] Stereotactic radiosurgery is generally used for emergency and suits for small intrahypothalamic hamartomas or the postoperative residue lesion.[27]

In Thailand, Bunyaratavej et al. applied transcallosal subchoroidal approach for resection of HH to a patient with intractable gelastic seizures and had a successful outcome without interfering with patient's memory function.[28]

For our case, gelastic seizures and complex partial seizures were well controlled by using topiramate (5 mg/kg/day). After 12 months follow up, developmental milestones were uneventful and there were no clinical signs of precocious puberty.

Conclusion

Pediatricians should remain aware of and pay attention to patients where there is parental concern about abnormal laughter. Pathologic laughter is not related to emotion but independent of a stimulus in the environment. An interview about seizure history, the child's developmental history and a complete physical examination are very important and absolutely necessary. MRI is the best investigation for confirmation the diagnosis of HH. The best treatment for patients with failed medical control is the ablation of the HH. This can be done with different procedures including surgery and nonsurgical treatments. The patients should have long term follow up to evaluate about seizure control, cognitive ability, development and precocious puberty.

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Review Article

Cerebral complications in conventional coronary bypass graft surgery

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Four decades ago, after on-pump coronary artery bypass graft surgery (CABG) was introduced for treating symptomatic coronary artery disease (CAD), operative mortality had continuously declined to below 5%.[1-3] While the mortality had fallen, the operative morbidity had been rising as CABG gradually enrolled more complicated elderly cases with advanced CAD and co-morbidities.[1-4] Among surgical morbidity, cerebral complications were the most devastating events, since they increased the length of stay, medical expense as well as hospital mortality.[5-19] Although the available data showed the declining incidence of peri-operative CNS injury, the incidence of overt cases still varied from 2-7%.[20, 21]

Post-operative cerebral events were formally categorized in three groups: ***1. stroke*** (focal motor, sensory or visual deficit), ***2. diffuse encephalopathy syndrome or DES,*** (obtunded, stupor and coma) and ***3. neuropsychological impairment or cognitive dysfunction*** (changes in behavior, intellectual or thinking process).[8] In Thailand, on-pump conventional CABG remains the standard operation in most cardiac centers but its cerebral complications are less known. Therefore, it was our purpose to address the causes and consequences of these serious complications and to review the alternative options for reducing cerebral complication.

Prevalence, etiologies and outcomes of post-CABG cerebral complications:

1. Strokes

Prevalence: The prevalence of post-CABG stroke varied from 0.6-5%, depending on timing and method of evaluation.[7, 9-11] In a retrospective analysis of a total of 3,279 post-CABG patients, Gardner et al., reported the increasing stroke rate from 0.6 % in 1979, to 2.4% in 1983.[9] Shaw and colleagues prospectively performed neurological evaluation in 312 post-CABG cases and found a much higher post-CABG stroke rate, up to 5%.[12] They further detected other neurological complications such as prolonged encephalopathy (3%), ophthalmic abnormalities (25%), peripheral nerve damage (12%) and primitive reflexes (39%). The post-CABG stroke rate also increased with age and its prevalence rose from 1% in patients aged between 51-60 years to ≥ 9% in patients aged over 80 years.[9]

Etiology: Intra-operative embolization remained a major cause of post-CABG stroke.[23-35] Two-third of strokes resulted from numerous small atheroemboli that predominantly affected the occipital lobe and the area lying between the supply of middle cerebral and posterior cerebral arteries.[8] In one-third of cases, infarct lesion was single and involved the area supplied by the middle cerebral, vertebral and basilar arteries.[8]

Prognosis: Post-CABG stroke increased mortality, the length of stay and cost of treatment.[5-7] In a multicenter prospective study from 24 US institutions involving 2,108 patients, Roach and coworkers categorized adverse, cerebral outcomes into two subsets, **type I** (death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack or stupor, coma at the time of discharge) and **type II** cerebral complications (a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit or seizure without focal injury). Although both groups were equally detected in about 3%, patients with type I complication had a significant higher hospital mortality (21 % vs. 10% vs. 2%, $p < 0.001$) and had a longer hospital stay (25 days vs. 21 days vs. 10 days, $p < 0.001$) when compared with those of type II and the uncomplicated group respectively.[7]

2. Diffuse encephalopathy syndrome (DES)

Prevalence and prognosis: The manifestation of DES widely ranged from post-operative somnolence, decreased alertness and activity, confusion, agitation and disorientation, to irreversible coma. Among those symptoms, decreased alertness and changes in mental function were quite common and the prognosis was fairly favorable. In the Newcastle study, Shaw and coworkers found that only 3% of post-CABG patients did not regain consciousness to the normal level within 24 hours, although most of them recovered within 12 days.[12] Since most of DES was transient and reversible, it was rather difficult to detect the true prevalence.

Etiology: In contrast to stroke, no definite cerebral CT finding was found in DES and multi-factorial causes had been proposed. Typical DES patients were elderly, having a history of alcoholic consumption and/or renal disease. It was believed that several medications used during or after surgery such as sedatives, narcotics (especially morphine) and psychotropic drugs became the key contributing factors of DES.[8]

3. Neuro-psychological deficits or cognitive dysfunction

Prevalence and prognosis: Cognitive dysfunction generally manifested as inappropriate perception, new memory deficits, deterioration in concentration or attention and delay in response. It was more common than stroke or DES with the prevalence varying from 2.6% - 43% in some prospective reports.[7, 13-17, 22, 35] For example, Roach, et al., found only 55 cases (2.6%) that had deterioration of intellectual function and 8 cases of seizure with no focal injury.[7] This wide range of prevalence suggested the variation in time and methods of neuropsychological assessment. Unlike the DES, cognitive dysfunction lasted longer, from several months to years or even persisted. Venn and colleagues reported persisting cognitive abnormalities in 35% of cases at 12 months after CABG surgery.[17] At three years, Martzke, et al., reported 20% of post CABG cases still had cognitive dysfunction.[18] McKhann, et al., studied 60 post-CABG cases and found rapid decline in memory, psychomotor speed and constructional abilities within 5 years.[19]

Etiology: Microembolization was the major cause of cognitive dysfunction.[8, 32, 33] Multiple small infarctions were usually found in cortical area of frontal, parietal and temporal regions.[8] The prevalence of cognitive dysfunction increased with age and the amount of embolism.[32, 33] By using a transcranial doppler ultrasound, Clark and colleagues found that the neuropsychological complications increased from 2.4% in patients who had less than 30 emboli to 35% in those who had more than 60 emboli.[32] Pugsley, et al., noted that the rate of cognitive dysfunction (at 8 weeks after surgery) rose from 8.6% in patients who had less than 200 emboli to 43% of cases with > 1,000 microembolization.[33] Other contributing factors of impaired cognitive function included pre-existing diseases such as Alzheimer's, diabetes mellitus and the effects of psychotropic drugs used during and after surgery.[8, 22] Kadoi, et al., reported a significant higher incidence of peri-CABG cognitive impairment in patients with type 2 diabetes mellitus at 7 days and the difference still persisted at 6-months.[22]

Clinical risk factors to predict post-CABG cerebral outcomes:

Roach identified 8 clinical risk factors for developing stroke (type I neurologic adverse outcome) and 6 other factors for impaired intellectual function (type II neurologic adverse outcome) (Table 1).[7] The presence of ascending aortic atheroma, prior neurological disease, the use of intraaortic balloon pump (IABP) and diabetes mellitus were strong predictors of developing stroke with the odd ratio (OR) of 4.52, 3.19, 2.60 and 2.59 respectively. For intellectual dysfunction, advancing age, hypertension and history of alcoholic intake were significant predictors (Table 1).

A large observational study by Khan, et al., involving 1,000 patients who underwent isolated CABG, demonstrated the presence of increased age, diabetes mellitus, aortic disease and intramural thrombi were in favor of adverse cerebral outcomes.[6] The influence of diabetes mellitus for developing cognitive disorders was further studied by Kadoi and colleagues in 180 post-CABG type 2 diabetic patients by matching age, sex and educational level.[22]

Table 1: Factors predicted the CABG related cerebral complications.[7]

Risk factors	Odd Ratio (95% CI)
A. Risk factors for stroke	
a. Proximal aortic atherosclerosis	4.52 (2.50-8.09)
b. History of neurological disease	3.19 (1.65-6.15)
c. Use of intra-aortic balloon pump	2.60 (1.21-5.58)
d. Diabetes mellitus	2.59 (1.46-4.60)
e. History of hypertension	2.31 (1.20-4.47)
f. History of pulmonary disease	2.09 (1.14-3.85)
g. History of unstable angina	1.83 (1.03-3.27)
h. Age	1.75 (1.27-2.43)
B. Risk factors for decreased intellectual capacity	
a. Age	2.20 (1.60-3.02)
b. Admission systolic BP > 180 mmHg	3.47 (1.41-8.55)
c. History of excess alcohol consumption	2.64 (1.27-5.47)
d. History of prior CABG	2.18 (1.14-4.17)
e. Dysrhythmias on day of surgery	1.97 (1.12-3.46)
f. Antihypertensive therapy	1.78 (1.02-3.10)

Six risk factors were significantly associated with cognitive dysfunction at 7 post-operative days including advanced age (OR 1.5, CI 1.3-1.8), hypertension (OR 1.8, CI 1.3-2.0), jugular venous oxygen saturation < 50% (OR 1.5, CI 1.1-2.6), ascending atherosclerosis (OR 1.5, CI 1.1-2.6), diabetic retinopathy (OR 2.0, CI 1.3-3.0) and insulin use (OR 2.0, CI 1.3-3.0). At 6 months, only insulin treatment (OR 2.0, CI 1.3-3.8), diabetic retinopathy (OR 1.3, CI 1.2-2.9) and high HbA1C (OR 1.9, CI 1.3-3.1) were the predictors of persisting cognitive disorders.[22]

To minimize the peri-operative cerebral complications, the associated risk factors mentioned above and high risk candidates should be identified before surgery. The details of pathophysiologic mechanisms and how to reduce complications are discussed below.

Pathophysiologic mechanisms of post-CABG cerebral complications:

1. Embolization from proximal aortic atherosclerosis and aortic clamping:

The most common cause of post-CABG stroke was embolization of atherothrombotic plaque from aortic arch.[23, 25-30] McKhann, et al., found that the prevalence of atheroembolism increased from 2% (in patients with no significant aortic disease) to 37% in those who had severe atheromatous disease.[19] Clamping, releasing and canulating the diseased aorta potentially dislodged atheromatous plaque and caused ischemic stroke.[23-26, 35] (Figure 1a-b)

2. Embolization due to pre-existing mural thrombi from cardiac chamber and intra-cardiac operation:

Most single cerebral infarction occurring after CABG were usually caused by emboli originating from intra-cardiac chambers.[8] Mural thrombi from prior myocardial infarctions (Figure 1d), cardiomyopathies, valvular calcification, vegetation and atrial fibrillation were all possible sources of embolization.[8] In a multi-center study involving 2,264 post-CABG patients, Wolman, et al., found that neurological complications increased by almost twice in patients who underwent CABG combined with other intracardiac surgery.[34]

3. Embolization from pre-existing thrombus in the left atrium in patients with atrial fibrillation:

Atrial fibrillation (AF) was the most common complication after cardiac operation and its prevalence ranged from 25-50%.[36-38] AF was associated with an increase in mortality, morbidity, cost of care and doubled the incidence of post operative stroke.[38] The preexisting atrial fibrillation (AF) in CABG patients was independently associated with increased late mortality, morbidity and poor long-term outcome.[39, 40] Most embolic stroke in AF solely originated from thrombus in left atrial appendage.[41]

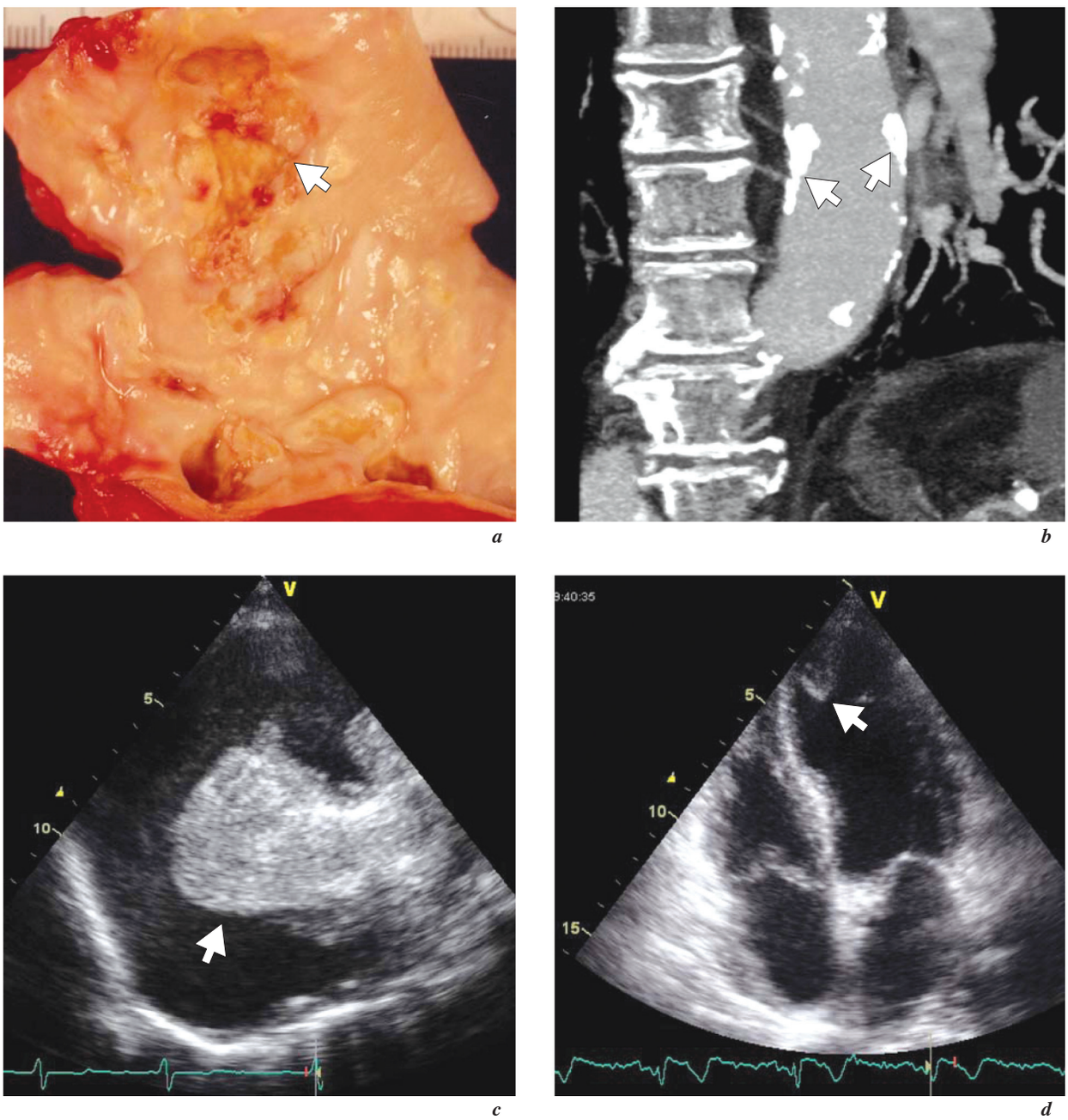

Figure 1: *Arrow head above elucidated the potential sources of coronary artery bypass graft surgery (CABG) related cerebral embolism and stroke.*
a. *Complicated atheromatous plaque in aortic arch.*
b. *Calcified aortic atheroma detected by multi-slice CT scan.*
c. *Large left atrial thrombus.*
d. *Apical thrombus in left ventricle.*

Figures courtesy of Forensic department of Denver General hospital (a), Cardiac imaging unit, Bangkok Heart hospital (b) and Cardiovascular Research and Prevention Center, Bhumibol Adulyadej hospital (c, d)

Risk factors of developing AF included advanced age, chronic obstructive pulmonary disease, preoperative arrhythmia, use of digoxin within two weeks before surgery, low resting pulse rate, high resting systolic blood pressure and intra-operative procedures i.e., cardiac venting via right superior pulmonary vein, mitral valve repair or replacement, the use of inotropic agents for greater than 30 minutes, prolonged ventilation > 24 hours, and CPB.[38, 41]

4. Hemodynamically significant carotid stenosis:

Carotid bifurcation disease is a marker of global atherosclerotic burden and is associated with aortic atheroma and CAD.[41] Significant carotid stenosis reduced cerebral blood flow and increased risk of stroke during cardiopulmonary bypass operation.[31] The risk of peri-operative stroke rose along with the degree of carotid luminal narrowing i.e., from 2% in patients with no significant carotid stenosis (< 50% luminal narrowing) to 10% and up to 18.8% in those patients who had 50-80% and > 80% carotid stenosis respectively.[42]

5. Air embolization during open heart operation:

A significant amount of air could be introduced to the cardiac chambers during open heart operation through CPB machine and might be difficult to remove.[8] The gaseous micro-emboli that potentially cause neurological damage could be visualized by transesophageal echocardiogram.[43, 44]

6. Combined effects of transient cerebral hypoperfusion, increased coagulation in the presence of prior cerbrovascular disease:

Prior history of cerebrovascular diseases i.e., stroke or TIA indicated an impaired cerebral auto-regulation, inadequate cerebral blood flow and underlying atherosclerosis.[7] Transient hypotension during bypass operations further decreased brain perfusion and increased neurological deficits.[8, 45, 46] Tufo and colleagues studied the mean arterial pressure (MAP) during CPB and found that neurological deficits rose from 27% in patients whom MAP was maintained above 60 mmHg to 78% in patients with MAP below 40 mmHg.[45] In a prospective randomized controlled study of 248 cases, Gold and colleagues found that the stroke rate was low, only 2.4%, in the group that had MAP ranging from 80 to100 mmHg, but it increased to 7.2% in patients who had lower MAP, in the range of 50-60 mmHg.[46] In addition, the intraaortic balloon counter pulsation (IABP) that is commonly used in hemodynamically unstable cases was also associated with dislodgement of pre-existing aortic atheroma.[7]

Procedures which potentially reduce adverse cerebral outcomes:

1. Pre-detection of atheroma in ascending aorta by ultrasound sonography, magnetic resonance imaging and CT scan.

Identification of aortic atheroma and thus minimizing the risk of embolization remained in class 1C recommendation by AHA/ACC.[55] Detection included manual palpation by surgeons or ultrasound sonogram.[27, 30] Using an 8 MHz epi-aortic transducer enhanced detection of non-palpable atheroma in 17% of cases and it changed the plan of surgery.[27] Transesophageal echocardiogram has been used to locate aortic calcification and monitor emboli during bypass operation.[29, 30] Currently magnetic resonance imaging (MRI) technique and multi-slice CT scan have been applied to delineate amount and severity of aortic atheroma (Figure 1b). The result of in vivo MRI study of human aorta is closely related with the findings from transesophageal echocardiogram.[28]

2. Avoid aortic clamping and cardio-pulmonary bypass, by MIDCAB and off-pump CABG.

In 70% of operation centers worldwide, CABG are still performed with extracorporeal circulation system (CPB) and partial or total aortic clamping was required to allow proximal anatomosis.[41] Manipulation of atheromatous ascending aorta by clamping, releasing and cannulation potentially dislodged atheromatous plaque and caused embolic stroke.[23-26] Current guidelines recommend minimizing aortic manipulation or avoiding touching atheromatous aorta whenever possible.[41] In addition, the CPB machine used in conventional CABG only provided a non-pulsatile blood flow that further compromised vital organ perfusion and enhanced cerebral ischemia. To avoid aortic clamping and CPB, surgery on beating heart (Off-pump CABG, OPCAB) and a minimally invasive direct coronary artery bypass (MIDCAB) surgery had been successfully performed in 1990's.[47-50]

By avoiding CPB machine, OPCAB potentially offered further advantages such as reduced inflammatory response created by contact of blood and artificial surface of CPB, decreased myocardial injuries, less inotropic drugs used and less blood transfusion. The benefit of an OPCAB in lowering mortality, renal, respiratory, neurological and bleeding complications, had been demonstrated in many studies.[48-50] The large observational study in 2001 to 2004, involving 13,889 OPCAB and 35,941 on-pump CABG patients, the matched analysis showed the benefit of OPCAB by decreasing in-hospital mortality (OR 0.81) and reducing neurological and respiratory complications (OR 0.7 and 0.8 respectively).[51] However, the long term result of OPCAB was of concern. At 3 years, although there was no mortality difference between the two groups, the OPCAB patients had higher revascularization rate (Hazard Ratio (HR) 1.55).[51]

The randomized trials between off-pump CABG vs. conventional procedures showed no clear benefit of OPCAB in terms of operative mortality and neurologic complications.[52-54] In a recent large randomized trial enrolling 1,104 OPCAB patients and 1,099 on-pump CABG cases, there was no statistical difference of the 30 day composite outcome (death or complication, coma, stroke, renal failure, cardiac arrest, reoperation and new mechanical support) between two groups.[54] At one-year, OPCAB patients had higher composite outcome (9.9% vs. 7.4%, $p = 0.04$) and had lower graft patency (82.6% vs. 87.8%, $p < 0.01$) on follow-up angiogram.[54] These conflicting data also suggested that the surgical skill was of great importance: performing OPCAB requires a longer learning curve than the on-pump CABG.

Despite the existing controversies, the current AHA/ACC 2009 and ESC guideline 2010 still recommend off-pump surgery and/or hybrid percutaneous coronary intervention (PCI) as an alternative option for patients with severe atheromatous disease of ascending aorta and aortic arch.[41, 55]

3. Percutaneous transluminal coronary intervention (PCI) alone or combining with OPCAB as hybrid operation.

Unlike the conventional CABG, there was no aortic manipulation involved in PCI therefore, cerebrovascular complications were relatively low, in the range of 0.07-0.23%.[53, 54] Long-term data over 16 years, from one PCI center showed a steady incidence of PCI related cerebrovascular events (CVE) with the total CVE rate of 0.37%.[55] In multi-vessel CAD, meta-analysis of ten randomized controlled clinical trials which compared PCI and CABG favored surgery in terms of 5-fold reduction in revascularization rate.[59]

Although CABG offered either no or only a modest survival benefit overall, surgery was still better than PCI in selected cases i.e., in elderly at age > 65 years old (HR 0.82) and in diabetic patients (HR 0.7).[59] It should be noted that most of the randomized patients had normal LV function with single or double vessel but had no proximal left anterior descending (LAD) disease.[41]

In isolated proximal LAD disease, two meta-analysis studies enrolling over 1,000 patients showed no significant differences in mortality, myocardial infarction or cerebrovascular accidents between PCI and CABG but PCI group carried a three-fold higher incidence of recurrent angina and a five-fold increase in repeat target vessel revascularization at 5 years follow-up.[60, 61]

In patients who had extensive aortic sclerosis, alternative options including OPCAB and hybrid procedures were recommended by current guidelines from ESC and AHA/ACC.[41, 55] The hybrid revascularization referred to a planned combination of minimally invasive surgery (MIDCAB) by grafting the internal mammary artery to the left anterior descending artery with PCI of other vessels during the same hospital stay.[62] Both procedures could be performed consecutively in a hybrid operating room or sequentially on separate occasions.[63]

4. Carotid artery stenosis detection and revascularization before CABG.

The risk of stroke after CABG was quite high in patients with carotid stenosis (50-99%), so it is recommended by current European guidelines to perform duplex ultrasound scanning of carotid artery in patients with a prior history of TIA/nondisabling stroke or carotid bruit on auscultation (class I, C).[41] This suggestion was extended to patients with left main disease, severe peripheral arterial disease or age ≥ 75 years as class IIa, C. In patients with significant carotid stenosis (≥ 70%) by ultrasound, further evaluation with MRA, CT or digital angiography is also recommended (class IIb, C). It remains unclear whether the timing of carotid and coronary revascularization should be synchronous or staged.[41] The choice of carotid revascularization should be individualized after discussion by a multidisciplinary team including a neurologist (class I, C). The most recent data indicates that carotid endarterectomy (CEA) remains the procedure of choice but selection of CEA versus carotid stenting (CAS) depended on multidisciplinary assessment (class I, B).[63, 65] In a meta-analysis study comparing CEA versus CAS, stented group had a significant higher chance of 30 day mortality or stroke (OR 1.6, CI 1.26-2.01) than those of surgical cases.[66]

In the International Carotid Stent study involving over 1,600 cases randomized to CAS and CEA, CAS group was associated with a higher rate of death, stroke, myocardial infarction, HR 1.69, $p = 0.006$.[64] In the substudy analysis, CAS had more new postprocedural brain lesions detected by MRI when compared with those of CEA patients (OR 5.2, $p < 0.0001$).[67]

5. Reduction of atrial fibrillation and its complication.

Post-operative atrial fibrillation (AF) could be reduced by administration of beta-blockers, sotalol and amiodarone.[68-71] The efficacy and safety of beta-blockers in reducing post-operative AF had been documented in the meta-analytic studies with the odd ratio of 0.36 (CI 0.28-0.47).[69] Amiodarone was also effective in AF prevention as shown in several randomized controlled trials and meta-analytic studies.[69-71] In one large randomized placebo controlled trial, amiodarone significantly reduced atrial arrhythmia by 13.4% with hazard ratio of 0.52 (CI 0.34-0.69).[71]

Among the multiple risk factors of developing AF, systemic inflammatory response created by CPB machine remained of interest. Administration of systemic steroids to prevent AF had been shown in two randomized trials. By giving methylprednisolone 1 gm before operation and dexamethasone 4 mg every 6 hours for 24 hours, AF was significantly reduced but higher post-operative complications were also noted in steroid treated group.[72, 73] Pre-treatment with statin drugs effectively prevented AF, as shown in the two randomized trials with the OR of 0.57 (CI 0.42-0.77).[74, 75]

Conclusion

CABG related cerebral complications are devastating events and increase in elderly patients who have advanced atherosclerosis and co-morbid diseases. The degree of cerebral adverse outcomes widely ranges from vivid irreversible coma, peri-operative stroke to transient disorientation and long-term memory deficit which might not be detected. Routine neurological examination, before and after surgery, therefore has been recommended to identify these events early. Prevention of cerebral disorders may be achieved by identifying high-risk cases (i.e., elderly who had preexisting neurological disease, carotid stenosis etc.) and their associated risk factors such as aortic atheroma, use of IABP, diabetes mellitus and atrial fibrillation etc. Several preventive procedures are recommended by current revascularization guidelines, such as hybrid operation with MIDCAB and PCI in patients with advanced aortic atheroma, revascularization of significant carotid stenosis and prevention of AF with beta-blockers, amiodarone and statin.

Finally, we hope that this review will ensure Thai physicians increase attention to identifying post-CABG cerebral complications, since conventional, on-pump CABG remains as yet the standard of care in Thailand.

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Mapping of Complex Fractionated Atrial Electrograms (CFAE) as Target Sites for AF Ablation

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Keywords:
CFAE, Cardiac ganglionic plexi, AF ablation

The myriad pathologies leading to and resulting from atrial fibrillation (AF) have led to many theories regarding how substrate should be defined and how to reconcile substrate ablation with trigger ablation. The identification of spatiotemporally stable areas of very low amplitude short cycle length CFAE, in a sea of otherwise discrete normal amplitude and relatively longer cycle length electrograms, led to ablate the CFAE as a marker of abnormal substrate.[1] This pure substrate-based ablation strategy has resulted in remarkable success with great benefits, which include stroke and mortality reduction in high-risk patients with very long standing persistent AF. In this review, we discuss the prevailing mechanisms underlying CFAE, how to map and ablate CFAE sites, correlation of CFAE areas to those of ganglionic plexi, clinical outcomes of the approach, and the controversy surrounding targeting CFAE as substrate sites for AF ablation.

I. Characteristics of atrial electrograms during atrial fibrillation

Over the past decade, several important observations were made during mapping studies in human AF. First, atrial electrograms during sustained AF have three distinct patterns: single potential, double potential, and complex fractionated potential (CFAEs).[1-6] Second, during AF, these atrial electrograms tend to localize in specific areas of the atria and do not meander, exhibiting surprisingly remarkable temporal and spatial stability.[1, 7, 8] Third, the CFAE areas represent the AF substrate sites, which have become important target sites for AF ablation.[1-3] By ablating such areas that have a persistent CFAE recording, one eliminates AF and usually renders AF non-inducible. Thus, CFAE mapping has become a novel approach for guiding a successful ablation of AF substrate, yielding excellent long-term outcomes. CFAEs are defined as low voltage atrial electrograms (Figure 1), ranging from 0.04 - 0.25 mV, that have fractionated electrograms composed of two deflections or more, and/or have a perturbation of the baseline with continuous deflection of a prolonged activation complex. CFAE have a very short cycle length (≤ 120 ms) with or without multiple potentials (Figure 1: 4th tracing, RIPV antrum); however, when compared to the rest of the atria, this site has the shortest cycle length.

II. Electrophysiologic mechanisms underlying CFAEs

The underlying etiology of CFAE has not yet been elucidated, but several theories are being investigated. During intraoperative studies in patients with WPW syndrome, Konings et al.,[5] identified mechanisms of propagation of the above three types of electrograms during AF:

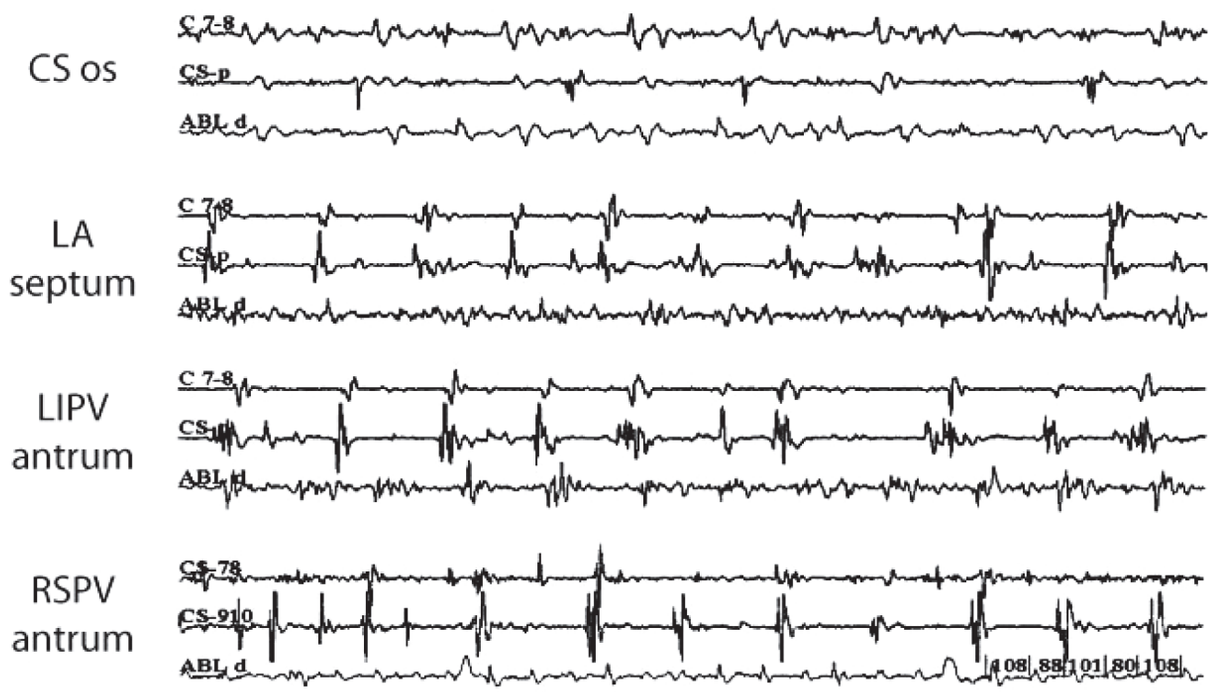

Figure 1: *Various examples of CFAE that were recorded from the ablation catheter (ABL d) from different sites. Four trace panels show CFAE recorded from CS ostium (CS os), LA septum, LIPV antrum and RIPV antrum, Each panel also shows recordings from reference site in the proximal CS (CS-7, 8 and CS-9, 10 [CSp]). The most highly fractionated electrograms can be seen in this example to exist on the LA septal wall, LIPV antrum and at the RSPV antrum.*
CS = coronary sinus *LA = left atrium*
LIPV = left anterior pulmonary vein *RSPV = right superior pulmonary vein*

- *Type I* that exhibits discrete complexes separated by an isoelectric baseline free of perturbation. These electrograms were caused by single broad-wave fronts propagating without significant conduction delay, exhibiting only short arcs of conduction block or small areas of slow conduction not disturbing the main course of propagation.
- *Type II* that exhibits discrete complexes, but with perturbations of the baseline between complexes. These electrograms were recorded during activation patterns characterized either by single waves associated with a considerable amount of conduction block and/or slow conduction or the presence of two wavelets.
- *Type III* that exhibits CFAE. Konings and colleagues found that CFAE represented the presence of three or more wavelets associated with areas of slow conduction (10 cm/s) and multiple arcs of conduction block.

On the other hand, Kalifa et al. identified a key relationship between areas of dominant frequency and areas of fractionation in sheep.[9] The investigators were able to localize areas with regular, fast, spatiotemporally organized activity and map the regions around them.

Waves propagating from these areas were found to break and change direction recurrently at a boundary zone, and demonstrate fractionation of local electrograms. Their findings suggested that one of the possible electrophysiologic mechanisms, by which fractionation occurred during AF, was due to high-frequency reentry at the boundary zones of the dominant frequency areas.

The most prominent theory underlying the occurrence of CFAE involves the complex interplay of the intrinsic cardiac nervous system on atrial tissues. The cardiac ganglionic plexi (GP) are a collection of autonomic nervous tissues with afferent and efferent sympathetic and parasympathetic fibers.[7,8] Six major GPs (Figure 2) that may exert influence on the atria are: (1) Superior LA; (2) Posterolateral LA; (3) Posteromedial LA; (4) Anterior descending LA; (5) Posterior RA; (6) Superior RA. In animal models, the stimulation of parasympathetic fibers within the GP has been shown to decrease atrial effective refractory periods and allow AF to perpetuate. Simultaneously, stimulation of sympathetic fibers may occur in similar areas, which can initiate PV ectopy. Unfortunately, mapping and ablating the GP is time consuming and difficult.

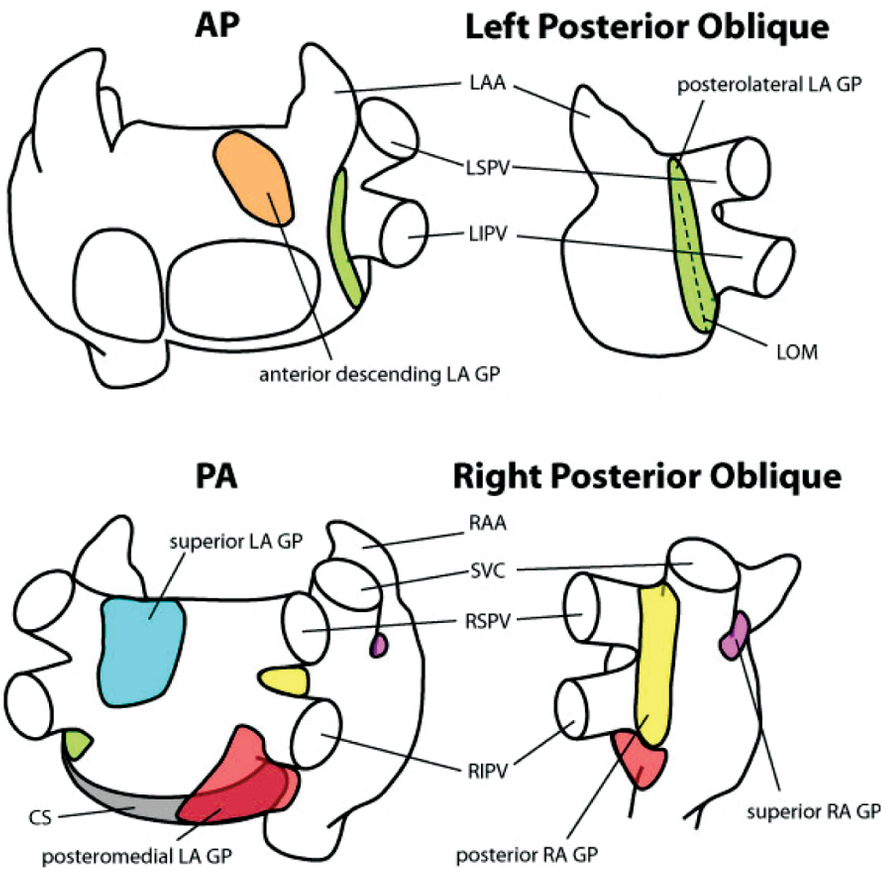

Figure 2: *Six cardiac ganglionic plexi (GP) are located on or near the left and right atria and have been shown to exhibit influence on the initiation and perpetuation of AF: superior left atrial GP, posterolateral left atrial GP, posteromedial left atrial GP, left anterior descending GP, posterior right atrial GP, and superior right atrial GP.*

AP = anteroposterior *PA = posterior-anterior* *LAA = left atrial appendage*
RAA = right atrial appendage *CS = coronary sinus* *LOM = ligament of Marshall*
SVC = superior vena cava *LSPV = left superior pulmonary vein*
LIPV = left inferior pulmonary vein *RSPV = right superior pulmonary vein*
RIPV = right inferior pulmonary vein

Ongoing research has identified a close relationship between the location of CFAE and the GP in animal models.[7,8] CFAE-targeted ablation may provide a surrogate for modification of the GP if this relationship can be confirmed in humans. Certainly, ablation in areas that have resulted in a vagal response has shown excellent results in the treatment of AF.[9]

III. Regional distributions of CFAE

Each individual has temporal and special stability of CFAE, which facilitates accurate mapping. These regions are not symmetrically located within the atria, but can be predictably sought in certain places during mapping.[7] The following key areas have demonstrated a predominance of CFAE within our cohort: (1) the proximal coronary sinus; (2) superior vena cava-RA junction; (3) septal wall anterior to the right superior and inferior PVs; (4) anterior wall medial to the LA appendage; (5) area between the LA appendage and left superior PV; and (6) posterosuperior wall medial to the left superior PV (Figure 3). Typically, patients with persistent or long-lasting AF have greater numbers and locations of sites with CFAE than those with paroxysmal AF.[1,8]

The distribution of CFAEs in the right and left atria is vastly different from one area to another. Despite regional differences in the distribution of these atrial electrograms, CFAEs are surprisingly stationary, exhibiting relatively spatial and temporal stability. Thus, one can perform point-to-point mapping of these CFAE areas and associate them into an electroanatomical map.

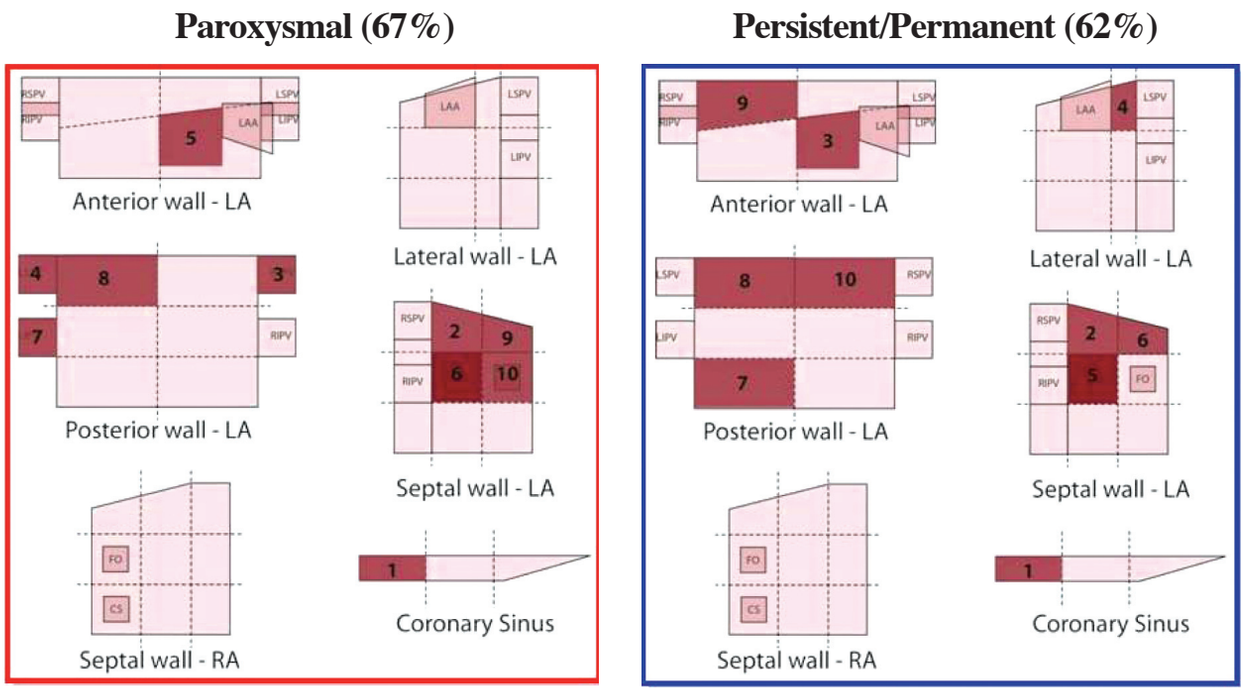

Figure 3: *The most common locations of CFAE were identified (darkest shading) on a grid representing the regions of the right and left atria.*
LA = left atrium *LAA = left atrial appendage* *RA = right atrium*
CS = coronary sinus *FO = fossa ovalis* *LSPV = left superior pulmonary vein*
LIPV = left inferior pulmonary vein *RSPV = right superior pulmonary vein*
RIPV = right inferior pulmonary vein

IV. CFAE Mapping to guide substrate ablation

Mapping is always performed during AF by point-to-point mapping, although detailed mapping of the LA, coronary sinus, and occasionally RA is also required. The spatial and temporal stability of CFAE allows the precise localization of these electrograms.

A map with a minimum of 100 data points is usually created, especially in high-density areas commonly known to have CFAE. Additionally, we usually create a detailed map of the proximal coronary sinus, and occasionally the RA. We identify locations with stable electrograms, and these are *"tagged"* to create targets for ablation. Areas with fleeting CFAE are not sought as a primary target. A highly reliable map allows for minimal use of fluoroscopy. We routinely use less than 10 minutes during average procedure duration of 113-27 minutes.

A customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA, USA) was produced.[3] The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-second recording window and interprets it according to two variables: (1) shortest complex interval (SCL) minus the shortest interval found (in milliseconds), out of all intervals identified between consecutive CFAE complexes; and (2) interval confidence level (ICL) minus the number of intervals identified between consecutive complexes identified as CFAE, where the assumption is that the more complex intervals that are recorded - that is, the more repetitions in a given time duration - the more confident the categorization of CFAE. Information from these variables is projected on a three dimensional electroanatomic shell according to a color coded scale. This allows targeting and retargeting of areas of significant CFAE.

V. Evidence that CFAE areas represent AF substrates

Our recent study results support the hypothesis that CFAE areas are critical in perpetuating AF and RF ablations over these areas, resulting in the termination of AF and rendering the atria no longer able to sustain AF.[1] The findings are summarized as follows.

The study population included 121 patients (29 females; mean age, 63 years) with refractory AF (57 paroxysmal, 64 chronic). All patients underwent non-fluoroscopic electroanatomic mapping (CARTO) during AF. Using CARTO, the bi-atrial replica, displayed in a 3-D color-coded voltage map, was created during AF, and areas associated with CFAEs were identified.

RF ablation of the area with CFAEs was performed to the closest anatomic barrier. We found CFAE in seven different regions, but mainly confined to the interatrial septum, PVs, roof of LA, and left posteroseptal mitral annulus and coronary sinus ostium. Ablations of the areas associated with CFAEs resulted in termination of AF without external cardioversion in 115 of the 121 patients (95%); 32 (28%) required concomitant ibutilide treatment. At 1-year follow up, 110 (91%) patients were free of arrhythmia and symptoms, 92 after one ablation (76%), and 18 after two.

In virtually all patients, after RF applications over the CFAE areas, most atrial electrograms either disappeared or were reduced drastically in amplitude, resulting in complete elimination of CFAEs, often associated with organization of atrial electrograms in the areas adjacent to the ablated ones. The elimination of CFAEs always uniformly increased tachycardia cycle lengths before AF termination, even though the cycle lengths were measured from the electrical reference of the area remote from the ablation sites. The overall tachycardia cycle length increased from 172 ± 26 ms at baseline to 237 ± 42 ms ($p < 0.05$).

Clearly, the preceding findings suggest that CFAE areas are indeed the substrates that perpetuate AF. Furthermore, we followed the above initial study with a larger study[2] that included 674 high-risk AF patients (mean age 67 years). This study confirmed that our ablation approach is very effective and yields excellent long-term outcomes. More importantly, sinus rhythm after our ablative procedure is associated with a lower mortality rate and stroke risk.

VI. Other studies and Controversy

Our introduction of CFAE mapping to guide AF ablation as an alternative to anatomical approach of PVI spurred other investigators to follow our approach. However, our results were not fully reproduced by others.[10,11] While it is unclear what exactly are the factors underlying the differences in both acute and long-term outcomes between our studies and others, it seems more likely that one or more of the following key variables may help explain the differences between these studies[4]:

1) *Right atrial ablation*. Other investigators often did not map and ablate the right atrium. We found that 15% of our patients required right atrial ablation; the common sites are right postero-septum, Cavo-tricuspid isthmus, tricuspid annulus, and rarely posterior wall of the right atrium and SVC-right atrial junction.
2) *Power and duration of RF energy applications*. Our power of RF applications was significantly higher than those of others: we used RF power up to 50 watts over the anterior and septal wall and 30-40 watts in the posterior wall that is not close to the esophagus but titrated down to about 20-30 watts in the areas close to the esophagus.
3) *Ablation endpoint*. Perhaps this variable is the most significant factor influencing the differences among these studies. CFAE are low voltage atrial signals usually ranging from 0.05-0.25 mV and the areas with the very low voltage signals (between 0.05-0.1 mV) are often the most desirable. By contrast, other investigators defined successful lesion creation as a voltage reduction to < 0.1 mV or by decreased by ≤ 80% reduction. This single factor may explain why the investigators did not have a high success rate of acute termination. In our experience, the ablation sites where AF terminated are often the sites that we had applied RF before and often the voltage of atrial signals at these successful sites were in the range of 0.5-0.8 mV.
4) *Procedure endpoint*. The procedure endpoint in our study was sinus rhythm and/or complete elimination of CFAE target sites, we deliberately attempted to ablate all *"new"* arrhythmias, including pleomorphic forms of atrial tachyarrhythmias, whereas others often did not and elected to just merely perform cardioversion to revert the arrhythmias to sinus rhythm.
5) *Comprehensive mapping*. Lastly, the electroanatomic map for CFAE should have a high density of evenly spread mapping points. It was unclear whether other investigators were committed to a detailed mapping of the CFAE. There is, however, no question that the key to the success of AF ablation guided by CFAE is exploring all areas of the atria and coronary sinus.

VII. Future Development

Signal processing of low amplitude CFAE needs further improvement; many recording systems have great difficulty in separating such signals and noises. That poses an even greater difficulty for the software to accurately measure electrogram intervals, which are crucial for evaluating cycle lengths of CFAE and/or for dominant frequency analysis. Since excellent CFAE targets have distinct morphologies and electrogram patterns, one should have programmed pattern recognition built into the software package for an automated display of CFAE target sites.

Clearly more research studies need to be done to find the best algorithm with which to differentiate between CFAE sites that represent AF substrate that perpetuate the arrhythmia and those that are just merely passive bystanders. Finally, new tools such as robotic navigation of catheters, which are being introduced at an impressive pace, will undoubtedly help improving the efficacy and lowering the risks of AF ablation.

VIII. Conclusions

Substrate ablation guided by CFAE mapping is effective in both acute termination of AF and maintaining sinus rhythm. This highlights the fact that CFAE probably does represent the AF substrate that perpetuates the arrhythmias. Controversy remains as to what are the underlying electrophysiologic mechanisms of CFAE; however, several prevailing proposed mechanisms suggest that CFAE are either arrhythmogenic sites or hyperactive ganglionic plexi, both of which play a significant role in AF genesis. More clinical studies need to be performed to delineate the values and limitations of CFAE mapping in guiding ablation and resolve debates over its usefulness. Advances in technologies and development to improve signal processing and to incorporate CFAE pattern recognition are necessary to help electrophysiologists to be more proficient in performing the technique of CFAE mapping. Similarly, it is imperative that the AF ablation procedures be done in centers that are well equipped with an advanced electrophysiology mapping system and ancillary equipment, along with an experienced team, to ensure the best possible patient outcomes.

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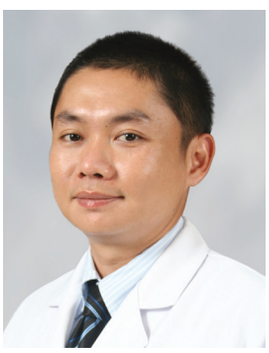
Resurgence of Unicompartmental Knee Arthroplasty



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During the 1970's and 1980's, Orthopaedic Surgeons began developing and using unicondylar knee arthroplasty (UKA) for treatment of unicompartmental osteoarthritis (OA) of the knee.[1] High failure rates were reported, due to poor design (mostly due to the cement loosening and plastic wear), poor surgical technique, and improper patient selection.[2-5]

In contrast, high promising results of total knee arthroplasty (TKA) were reported from many studies.[6-11] When UKA results were compared to TKA, the UKA fell out of favor with many surgeons. By the 1990's TKA was considered to have become the standard treatment of knee osteoarthritis.

However, UKA continued to be used. There has been a renewal of interest in UKA, due to emerging minimally invasive techniques, improvement of instrumentation and design rationales together with increased understanding of biomechanics, and proper patient selection.

Recently there have been many comparative studies between TKA and UKA. Most results report UKA provides better functional outcomes, earlier recovery, ease of revision and lower costs.[12-17]

The Concept and Philosophy

The philosophy behind UKA is much different to that of TKA. In osteoarthritis of the knee, the knee malalignment (from either varus or valgus deformities) is due to articular cartilage loss and ligament laxity. Using the TKA technique, alignment is corrected by cutting the bone, which changes the knee anatomy to achieve mechanical axis of the lower limb.

UKA will not cut the bone to achieve mechanical axis but uses instead the composite thickness of the prosthetic unicompartmental components (thickness of polyethelene) to correct limb alignment (Figure 1).

The advantages for UKA are a less invasive surgery and shorter hospital stay. The range of motion is usually better than for total knee arthroplasties and proprioception is not impaired. Other benefits include better kinematics, quicker recovery and the bone stock is preserved, thus making revision easier.[18] Newman, et al., showed in a randomized study that UKA had less perioperative morbidity, patients both recovered faster, and gained more flexion; however the loosening rate was similar to TKA.[19] The Oxford Group has shown similar results in studies in which UKA was compared with TKA; furthermore, their results showed that recovery was even faster if a small incision was used.[20, 21] Results from the Swedish Knee Registry showed that the UKA procedure was more

cost-effective than TKA, even taking into account the increased risk for revisions.[22]

Considering the factors which cases are amenable to surgery, according to Deschamps's statement: *"there are five types of indications to take into account. These are the age of the patient, the patient's activity level, weight, and ligamentous status (particularly the central pivot), and lastly, the severity of the deformity. The ideal indication for a UKR is a low demand patient over 60 years of age; the UKR is particularly recommended in old or sedentary patients. The patient should weigh less than 85 kg, but the Body Mass Index (BMI) should also be taken into account. The central pivot should be intact. The deformity should be moderate and, above all, reducible without overcorrection (varus-valgus shift when taking stress views). The residual deformity (if any) after correction should not exceed 5 degree varus in a varus knee and 5 degree valgus in a valgus knee"* [23]

Design

Presently, two designs of UKA are available, fixed bearing and mobile bearing UKA but there is controversy over which design provides superior results. The first design of UKA, with more than 30 years of clinical use, was fixed bearing. The first implant was Mammor prosthesis.

Fixed bearing prosthetics come in two types: metal backing design (Figure 1) and all polyethelene (Figure 2). The metal back design provides better load distribution and load transfer to the bone but it needs more cutting. The all polyethelene tibial component design requires less bone to be cut which means a greater remaining bone stock. Although this has the potential for good results, the literature suggests there may be a higher rate of early loosening and failure due to the thin cement mantle needed to fix the component in place.[24]

A report by Small, et al., showed all polyethelene designs significantly increased tibial strain which led to tibial subsidence. An in vitro biomechanical model was established to measure strain on tibial bone surface. The results showed implantation with all polyethylene tibial components resulted in higher strain measurements across the medial surface of the proximal tibia. Statistically significant increases in maximum shear strain ranged from 57% to 223% ($p < 0$ .05).[25] Although many studies show promising results over the long term, there are still aspects to be concerned about with the mobile bearing designs, such as the frequency of radiolucenct lines in metal back tibial components, or the more frequent need for gap balancing techniques or the risk of bearing dislocation.[26, 27]

Mobile Bearing Design

Much of the recent literature reports excellent long term results with specific mobile bearing UKA design (Oxford; Biomet, Warsaw, Figure 3) with increasing use of mobile bearing knee. The polyethelene bearing is not fixed to the metal back; instead it acts like the meniscus and can move along the metal back. The mobile meniscal bearing allows contact over a large area, which ought to then minimize contact stresses, shear forces, and proably polyethylene wear.

Figure 1: *Metal-Back Design.*

Figure 2: *All Polyethelene design.*

Figure 3: *The tibial components are made from cobalt chromium molybdenum alloy. Six sizes are available for both the left and right side, for maximum coverage on tibial bone cut and to avoid anteriomedial overhang, which sometimes caused postoperative pain in the Phase 2 design.*

Figure 4: *The femoral components (single radius design) are made of cast cobalt chromium molybdenum alloy for strength, wear resistance and biocompatibility. The design is available in 5 sizes.*

Figure 5: *The articulating surface of the femoral component is spherical and polished to a very high tolerance.*

Retrieval analysis suggests that the edge loading effect of flat on flat articulation of most fixed bearing designs is the cause of polyethelene wear. Therefore some designs of fixed bearing UKA tried to increase conformity of articulation. However these attempts led to an increased, loosening rate of femoral and tibial components; more conformity actually caused additional strain to implants and the bone interface. The mobile bearing design by comparison reduces the strain on the bone interface.

Changing Indications for UKA

Kozinn and Scott described the classic indications for UKA in 1989. Using these stringent criteria, results improved significantly, although these criteria actually excluded 90-95% of patients with knee arthritis[28] With improvements in surgical technique, (such as minimally invasive methods)and better designs of UKA with enhanced longevity and durability, recovery time was significantly reduced. Hospitalization is now often reduced to 1-2 days, and recovery time to 2-4 weeks. [29-33] UKA indications could be expanded to include use as a temporizing procedure in younger patients with unicompartmental arthritis.[31, 34, 35] (Table 1). Some treatment centers claim that up to 30% of their knee arthritis patients now receive UKAs.[36]

A UKA may be appropriate for younger patients as a temporizing procedure. The option for conversion to a TKA is reasonable due to reduced bone loss making revision easier.[37] As Carlson and Albrektson pointed out, *"UKA yields results comparable with TKA. Because of the high level of patient satisfaction and the lower incidence of complications and morbidity compared with TKA, UKA is an attractive alternative for patients with predominantly unicompartmental, noninflammatory arthritis. Patient interest in UKA is enhanced by the adaptation of the operative procedure to a minimally invasive incision with the possibility of outpatient surgery".*[18]

Table 1: UKA indications.

Characteristics	Classic indications	Evolving indications
Age (years)	> 60	> 50 as temporizing measure > 60 as definitive procedure
Weight (kg)	< 82	Yet undefined
Activity level	Low demand	Non-laborers
Arthritis location	Purely medial or lateral	Purely medial or lateral
Diagnosis	Non-inflammatory, non-crystalline	Non-inflammatory, non-crystalline; Ahback stage 1,2 or 3 (not 4) osteoarthritis
Range of motion		
Flexion	> 90°	> 90°
Flexion contracture	< 5°	< 15°
Deformity		
Varus	< 10°	Passively correctible to within 5° of neutral mechanical axis
Valgus	< 15°	
ACL	Intact without mediolateral subluxation	OK if attenuated or absent due to attrition; no gross clinical instability
Patellofemoral joint	No symptoms; minimal chondromalacia	Minimal symptoms; no sclerosis of patellar facet; mild/moderate degenerative changes OK if a symptomatic
Symptoms	Unicompartmental; abate with rest	Unicompartmental

Results of Unicompartmental Arthroplasty

Although early to midterm studies cited a high rate of satisfactory results after UKA, long-term survivorship and outcomes continue to be a concern.[38] Many recent studies have reported good long term results after improvements in UKA design and more rigorous attention being given to patient selection criteria and improved surgical techniques.

Price AJ, et al.,[39] reported the survival rate at 20 years of Oxford knee design; 510 Oxford UKA was enrolled in the study. The 10 and 20 year survival rates were 94% and 91% respectively. They reported 29 revision procedures were performed: 10 for lateral arthrosis, nine for component loosening, five for infection, two bearing dislocations, and three for unexplained pain. No failure rate from patellofemoral problem was seen, which implies that patellofemoral arthritis was not a contraindication for UKA. It was also noted that there were very low rates of revision due to polyethylene wear related complications, which suggested low wear from fully congruent mobile designs of UKA.

Keblish and Briard [40] conducted a nonblinded review of 177 patients with LCS mobile bearing knee (DEPUY) from two centers, 137 from USA, and 44 from France, which were followed up over 11 years. All patients and radiographics were evaluated preoperatively, immediately post operative, then at 6 months and yearly until complications occurred. They reported overall good and excellent results in 82% of cases and fair/poor results in 18% of cases using the Hospital for Special Surgery Knee Rating Scale. Thirty two complications were found in this series. The most common failures in this study were bearing failures, which occurred in first generation polyethelene with design errors. Fifteen cases were revised by polyethelene exchange. Polyethylene wear with oxidative changes and varying degrees of splits/cracks of the articulating surface were noted in all cases. The authors suggested periodic x-rays were necessary in order to detect polyethelene failure at an earlier stage, especially for first generation designs (made between 1985 and the late 1990's), because the polyethelene exchange procedure was easier and more cost effective than revision of all components.

Several comparative studies of TKA and UKA have looked at the short and long term results with regard to aspects such as patient satisfaction, survival rate and cost. Most studies show better functional outcomes faster recovery, ease of revision and lower cost for UKA.

A recent study from Lombardi AV, et al.,[41] did a matching comparison (in terms of incidence of complication and manipulation, postoperative function and time needed for return to work) between 103 (115 patients) Mobile bearing UKA performed with minimally invasive technique and 103 (115 patients) cruciate retaining TKA. Post hoc power analysis revealed sufficient power to detect the variables studied at 80%. The UKA group had better range of motion at discharge and shorter hospital stay than TKA group (77 versus 67 and 1.4 versus 2.2 days). At 6 weeks, Knee Society functional scores and range of motion were higher for UKA than TKA (63 versus 55 and 115 degrees versus 110 degrees). The conclusion was that minimally invasive UKA demonstrated better early ROM, shorter hospital stays, and improved functional scores.

Recently, numerous reports detail the advantages of minimally invasive technique for UKA. This approach is performed with a small incision, but without dislocation of the patella, leaving the quadriceps tendon intact, and is therefore conducive to a faster recovery. Muller PE, et al.,[42] performed a comparative study between 30 minimal invasive approach and 30 standard approaches for UKA in terms of implant position and functional results. The mobile bearing oxford knee was implanted in all cases. Data from the study shows better functional outcome with significant higher score of HSS scores in the minimally invasive group; the minimally invasive technique did not show negative effect for implant positioning. So, they recommended minimally invasive technique should be the method of choice. Price et al.,[43] compared recovery rates by the time it took for patients to be able to do straight leg raising, and ability to climb stairs between 40 Oxford UKA with minimally invasive approach and 20 Oxford UKA with standard UKA; both groups were then compared to 40 of Anatomic Graduated Component (AGC) TKA. The results show average rate of recovery after minimal invasive UKA was twice as fast as after standard UKA and 3 times as fast as after total knee arthroplasty. All postoperative radiographic tests in minimal invasive UKA group show similar accuracyof implantation. This demonstrates that the minimally invasive technique can achieve both good short and long term results after UKA.

Potential Problems

There are many potential factors related to the longevity of UKA, such as patient activity levels, body habitus, intact cruciate ligaments, postoperative alignment, soft tissue balancing, implant positioning and design.[43-48] These factors can lead to many complications.

Fracture of Medial Tibial Plateau

Berger RA, et al., [49] reported complications due to tibial fractures in 51 knees after UKA at minimum 6 years follow up. All UKAs were performed using the Miller-Galante fixed bearing design (Zimmer Warsaw). His series had 4 fractures of medial tibial fracture, 3 cases which occurred intraoperatively and one case occurring 6 weeks post op.Vince and Cyran[50] noted that some fractures *"may require more extensive open reduction and intenal fixation and others revision by arthroplasty. These fractures might be avoidable by limiting the number and location of pin holes that are created in securing cutting instruments to the proximaltibia"*

Yang, et al.,[51] reported a case of a 63-year-old woman (Figure 6 A-B) with medial compartment osteoarthritis who initially had limited deformity. Within 3 months of surgery, medial tibial plateau fracture had displaced. Considerable amounts of bone were missing and there was the possibility of extensive avascular necrosis. Revision arthroplasty would have been difficult. Figure 6 B shows open reduction and internal fixation has been performed. This procedure is extensive, surgical, and involves wide exposure.

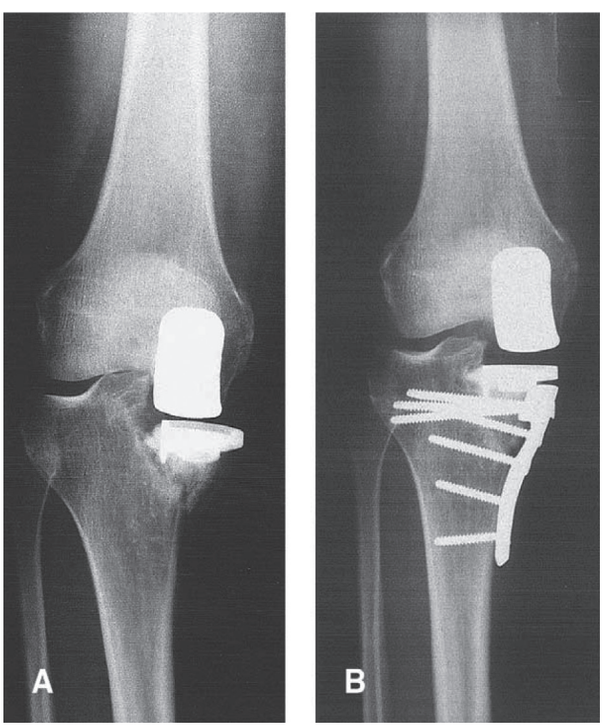

Figure 6 A-B: *Demonstrates a case of OA which underwent open reduction and internd fixation due to excessive bone loss.*

Brumby SA, et al.,[52] reported the 4 cases of medial tibial plateau fracture after UKA. Tibial cutting jig was fixed to the bone by 4 guide pins, which reduced compressive strength and caused stress fracture in all 4 cases. They recommended *"avoiding multiple guide pin holes in the proximal tibia for UKA. This can be achieved by using one centrally placed pin in association with another form of stabilization such as a clamp at the ankle. Furthermore, a tibial cutting jig that can be adjusted to take a thicker cut using the same guide pins should be used. If 3 or more pin holes are deemed necessary for UKA, surgeons must be aware of the potential for tibial stress"*.

Bearing Dislocation

The Oxford mobile bearing UKA has a 10% bearing dislocation rate as reported by the center where it was developed. Moo-Ho Song, et al.,[53] retrospectively reviewed the first 100 consecutive minimally invasive mobile-bearing UKA using Oxford knee design, with mean follow up time of 24 months: all surgeries used the minimally invasive medial parapatella approach. Four cases of bearing dislocation were reported, which were corrected by changing to a thicker polyethelene bearing. They suggested the main cause of bearing dislocation was inequality of flexion and extension gap, another potential cause was delayed elongation of MCL and osteophyte impingement.

A multicenter review identified performed by the Swedish Orthopaedics Society, the failure pattern was identified in 699 cases with Oxford Knee.[54] The results show the main reasons for revision surgery were *"dislocating meniscus in 16 cases, loosening of the femoral component in 6, tibia component in 4, both components in 4, contralateral arthrosis in 10, infection in 4, and technical failure with instability, pain, and/or impingement of the meniscal bearing anterior in the femoral condyle in 6"*. The authors reported dislocation of the menisci was caused mainly by thin components and/or malposition of the implants which may occur ventrally in the femoral condyle by the menisci.

Lateral compartment progression

Much of the literature reported one common cause of revision in UKA was progression of disease to contra-lateral side, mostly due to surgical technique.

Price AJ, et al.,[42] reviewed the long term results of 510 Oxford mobile bearing UKA's performed during 1983-2005; the survival rate at 10 years was 94% and at 20 years was 91%. The most common cause of failure was the progression of arthritis of lateral compartment (10 patients or 1.5%). They reported that the cause of rapid deterioration of lateral compartment was over correction of alignment. The reason for lower reported rates of lateral progression, reflects successful surgical techniques that did not attempt to overcorrect alignment.

Bert JM[55] studied ten year survival rates of medial UKA performed with Fixed bearing design (Biomet, Warsaw) between 1985-1987. The survival rate at ten years was 87.4% in 95 UKAs. The most common cause of failure in this series was lateral compartment disease after 5 years (Figure 7). Ten cases were revised due to lateral disease progression; eight of these cases had tibiofemoral angles greater than 5 degree valgus, but only two cases had tibiofemoral angles of less than 4.5 degrees. In cases with overcorrection, there was a higher rate of progression of lateral compartment.

Hernigou P and Deschamps G[56] did a retrospective radiographic review of 156 medial UKA performed with Lotus (Mark 1). They divided the patients in three groups depending on their HIP-KNEE-ANKLE angle.

Group I had an angle of more than 180 degrees, group II's angle was between 170-180 degree and group III's angle less than 170 degrees. A higher than average rate of cartilage wear was found in group I (0.23 mm/year). However in group III, a significant high rate of polyethelene wear was also found (0.21 mm/year). They confirmed significant rapid OA change on lateral compartment can occur where there has been overcorrection alignment of preexisting varus deformity and advise to avoid overcorrection more than 180 degree on HIP-KNEE-ANKLE angle.

Summary

Renewed interest in UKA is the result of improving minimally invasive techniques and implant designs, as well as improvement of instrumentation. The literature clearly shows the benefits of minimally invasive UKA: rapid recovery time, less blood loss, less disruption of soft tissue, shorter hospital stay, faster return range of motion and function, and without any impairment effect on implant alignment.

In well selected patients, with isolated medial compartment knee arthritis, minimally invasive UKA can be the procedure of choice when performed with meticulous technique by a well trained surgeon.

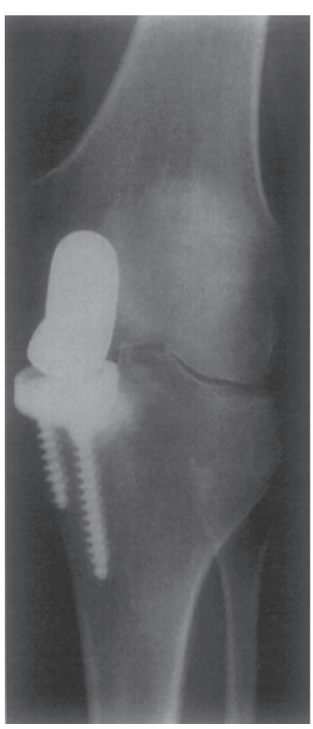

Figure 7: *Progressive increased lateral compartment pain. Femoral tibial angle increased to 12° at 6.5 years after surgery.*

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Review Article

Writing a Mammography Report

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Keywords:
Mammography, Report, Breast cancer

A mammography report is a key component of the breast cancer diagnostic process. Although mammographic findings were not clearly differentiated between benign and malignant lesion, the radiologist must assess the findings for chance of malignancy and guide the clinician for appropriate management. The report must be clear, concise and standardized for clinicians to understand.

For screening studies, the following questions need to be answered:
- Is the examination normal?
- Is there an area of concern requiring further evaluation?

Diagnostic Studies:

- If based on screening study, is anything confirmed? Are these findings consistent with breast cancer? What is the next step? Following complete work up, assessment categories 1 to 5 are used.[1]
- The impression should consist of conclusion and specific recommendations rather than mammographic findings.
- Guidelines for writing such reports, based on the Breast Imaging Reporting and Data System (BI-RADS), developed by the American College of Radiology should be used. This will standardize mammography reporting so that the report is clear, understandable and decisive.[2]
- BI-RADS consists of a lexicon of terminology with definitions to provide standardized language, as described below.

Breast Imaging Reporting and Data system[3]

Assessment is incomplete

BI-RADS 0: Needs additional imaging evaluation and/or comparison to prior mammograms is needed.

- This means a possible abnormality may not be clearly seen or defined and more tests are needed, such as the use of spot compression (applying compression to a smaller area), magnified views, special mammogram views, or ultrasound. This also suggests that the mammogram should be compared with older ones to see if there have been changes in the area over time.

Assessment is complete

BI-RADS 1: Negative

- In this case, there is no significant abnormality to report. The breasts look the same with no masses, distorted structure, or calcifications. In this case, negative means nothing bad was found.

BI-RADS 2: Benign finding

- This describes a finding known to be benign, such as benign calcifications, intra-mammary lymph nodes, calcified fibroadenoma, fat containing lesion, implants, architectural distortion clearly related to prior surgery. This finding is recorded in the mammogram report to help compare with future mammograms.

BI-RADS 3: Probably benign findings-Short interval follow up

- The findings in this category have a good chance (greater than 98%) of being benign. The findings are not expected to change over time. Follow up with repeat imaging is usually done in 6 months and regularly thereafter until the finding is known to be stable (usually at least 2 years). This approach helps avoid unnecessary biopsy but allows for early diagnosis of a cancer should the suspicious area change over time.

BI-RADS 4: Suspicious abnormality-Biopsy should be considered.

- Findings do not definitely look like cancer but could be cancer. The radiologist is concerned enough to recommend a biopsy. The findings in this category can have a wide range of suspicion levels. For this reason, some radiologists may divide this category further:
  - 4A: finding with a low suspicious of being cancer, such as a palpable, partially circumscribed solid mass with ultrasound suspected fibro adenoma, a palpable complicated cyst and probable abscess
  - 4B: intermediate suspicion of malignancy
  - 4C: moderate suspicion, but no classic for malignancy

BI-RADS 5: Highly suggestive of malignancy- Appropriate action should be taken.

- The findings look like cancer and have a high chance more than 95% of being cancer. Biopsy is very strongly recommended, i.e.,
  - A spiculated with irregular high-density mass
  - A segmental or linear arrangement of fine linear calcification
  - An irregular spiculated mass with pleomorphic microcalcification

BI-RADS 6: Known biopsy proven malignancy but prior to definite therapies such as surgical excision, radiotherapy, chemotherapy.

- A full diagnostic work up should be completed, which would include additional views, ultrasonography, and comparison with previous studies, before categorizing into category 1 to 5.

The Sections of a Mammogram Report[4]

The format for mammography report should consist of:

1. Pertinent Information: Usually appears at the top of the report and typically includes the patient's name, age and the reason for the mammogram (i.e., annual screening mammogram, referred by physician to evaluate new breast lump)
2. Clinical history: The patient's medical and family history of breast cancer or other breast conditions. It may also include relevant medications the patient is taking, such as hormone replacement therapy.
3. Procedure: May explain what types of mammogram views were taken. Typical views for screening mammogram included the cranio-caudal view (CC) and the medio lateral oblique view (MLO). Typical views for diagnostic mammograms included CC, MLO and supplemental views tailored to the specific problem i.e., magnification views, spot compression and others.
4. Notation about comparison with previous studies.
5. A description of overall breast composition provided information about the accuracy of mammography for the breast being evaluated.
6. Significant findings and modifiers are described according to standardized terminology that has relevance in terms of potential for malignancy.

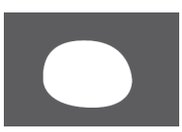
Findings that are of significance in patient management should be reported. Overall density is significant in that small cancers can be missed. The terms fibrocystic disease, fibrocystic changes, fibrocystic tissues, dysplasia, and hyperplasia are inappropriate and should be eliminated from image interpretation. Histopathologic terms should be reserved for the pathologist.[5]

Terminology section for described mammographic findings:

Breast Composition

- Almost entirely fat (less than 25% glandular)
- Scatter fibrograndular densities (25% to 50% glandular)
- Heterogeneous dense (51% to 75% glandular)
- Extremely dense (>75% glandular)

Mass

- Shaped
  - Round 
  - Oval 
  - Lobular 
  - Irregular 
- Margin
  - Circumscribed 
  - Microlobulated 
  - Obscured 
  - Indistinct 
  - Spiculated 

Density

- Fat containing radiolucent: i.e., oil cyst, lipoma or galactocele
- Mixed lesion: i.e., Hamartoma or fibroadenolipoma

Calcifications

- Benign Calcification
  - Skin calcification 
  - Vascular calcification 
  - Coarse calcification 
  - Large rod-like 
  - Round: punctate < 0.5 mm 
  - Lucent centered 
  - Eggshell (< 1 mm in thickness): Fat necrosis, calcified cyst 
  - Milk of calcium 
  - Suture 
  - Dystrophic 

• Intermediate

Amorphous or indistinct
Coarse heterogeneous

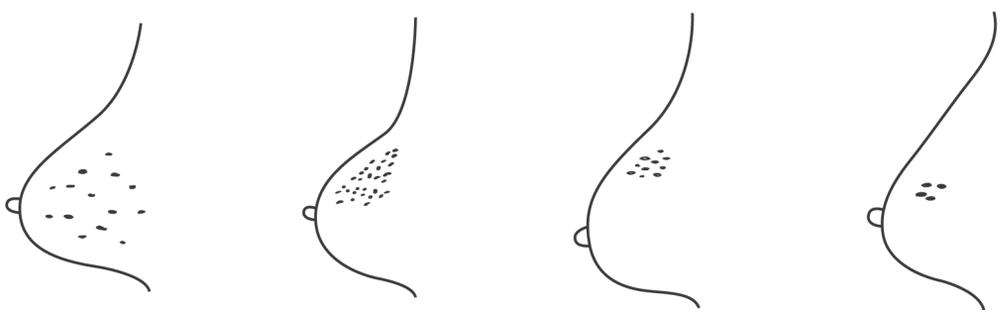
• Higher probability of malignancy

Fine pleomorphic

Fine linear branching

Distribution of breast calcifications

- Diffuse distributed calcifications are scattered randomly throughout the breast.
- Regionally distributed calcifications are most likely due to benign processes. These calcifications are scattered in a large volume of the breast and do not necessarily conform to a ductal distribution. This term use to describe calcifications that occupy > 2 cc of tissue.
- Group or clustered should be used to describe calcifications that occupy a small volume < 1 cc of tissue
- Linear: Calcification that is linearly distributed is arranged in a line and may have branch points.
- Segmental distributed calcification suggests deposition of calcification in a duct and its branches. This type of calcification may be secondary to benign or malignant process



Diffuse Regional Segmental Clustered

7. The report concludes with an overall assessment into a classification of the mammogram using the BI-RADS system developed by the American College Radiology (ACR).
8. Recommendation: Radiologists should give specific instructions on what actions should be taken next. For example, no action necessary, a six month follow-up mammogram, spot views, breast ultrasound, biopsy. etc.
9. Disclaimer: Radiologists should use disclaimer to communicate with clinician about the limitation of mammography and the meaning of a normal report.

For example

- Not all breast abnormalities show up on mammography.The false negative rate of mammography is approximately 10-15%.
- The management of a palpable abnormality must be based on clinical grounds.
- If you detect a lump or any other change in your breast before your next screening mammogram, consult your doctor immediately.

Example: Mammogram Report at the Bangkok Hospital

Mammogram and Ultrasound Breasts Report

Date:

Name: **Age:** **Sex:**

HN: **Department:**

Request Doctor:

Report By:

Patient Order: Mammogram and Ultrasound Breasts

MAMMOGRAM AND ULTRASOUND BREASTS

Clinical:	Screening

Mammography:

Technique:	CC and MLO views
Breast tissue	Heterogeneously dense breast tissue, may lower the sensitivity of mammography
Mass	Not detectable
Calcifications	Not detectable
Architectural distortion	Not detectable
Focal/breast asymmetry	Not detectable
Skin thickening	Not detectable
Others	

ULTRASOUND:

Cystic mass	Not detectable
Solid mass	Not detectable
Abnormal vessels	Not detectable
Other	

IMPRESSION: No mammographic evidence of malignancy
BI-RADS 1 (Negative)

SUGGESTION: Self breast exam monthly and follow up study yearly

Note: The false negative rate of mammography is approximately 10%
Dense breast may obscure underlying neoplasm
Management of a palpable abnormality must be based on clinical assessment.

BI-RADS 0: Need additional image
BI-RADS 1: Negative
BI-RADS 2: Benign Finding
BI-RADS 3: Probably Benign
BI-RADS 4: Suspicious Abnormality (4A: low, 4B intermediate, 4C moderate suspicious)
BI-RADS 5: Highly suggestive of malignancy
BI-RADS 6: Known malignancy

Conclusion

The use of mammographic screening to detect cancer at a preclinical stage is increasing rapidly. High quality imaging and accurate interpretation are critical elements for successful mortality reduction. The communication of the interpretation is being scrutinized in an effort to eliminate ambiguity and confusion. This can be accomplished by an organized approach to interpretation and a structure analysis of significant findings. These can grouped into BI-RADS by ACR to suggest a probability of malignancy.[8]

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Design of digital radiographic rooms for general diagnostic purposes

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Keywords:
Wireless digital radiography, DR wireless

Many changes have taken place in the radiographic field as technology gradually changes from analog to computed radiography (CR) system and the digital radiography (DR) system. Developing countries such as Thailand, Vietnam, Cambodia and Myanmar have not been able to easily keep up with the rapid advances in radiographic technology.

If a hospital is growing from less than 300 out patients per day to over 3,000 patients daily and hospital bed occupancy rises from 150 beds to 250-350 beds, such as happened at Bangkok Hospital over the last ten years, then the X-ray department necessarily has to accelerate all processes in order to prevent *"long wait times for outpatient procedures, due to backlogs."*[1]

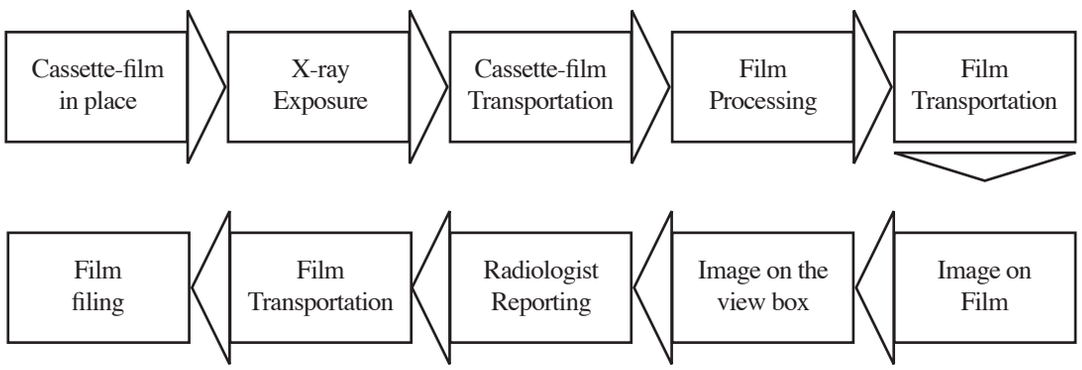
According to Professor Hermann, we compare CR and DR, *"each type of system offers relative advantages, but DR may represent a better option for some facilities with a larger patient load due to the greater ease of use and elimination of cassette handling with DR. The ability to streamline workflow is a major advantage to DR systems, especially in facilities that regularly encounter a high patient volume. Even those imaging centers that do not currently have substantial scheduling constraints may see increased challenges in the future with the aging population and an anticipated dwindling of healthcare workers. Meanwhile, facilities could also be drawn to CR and DR systems as images are increasingly managed through PACS. While a CR image may take approximately 60 to 90 seconds to be processed and available for viewing, a DR image can be available"* just 3 seconds after exposure.[2]

In this article we compare the different systems, and outline some possible design solutions for converting to DR (Table 1).

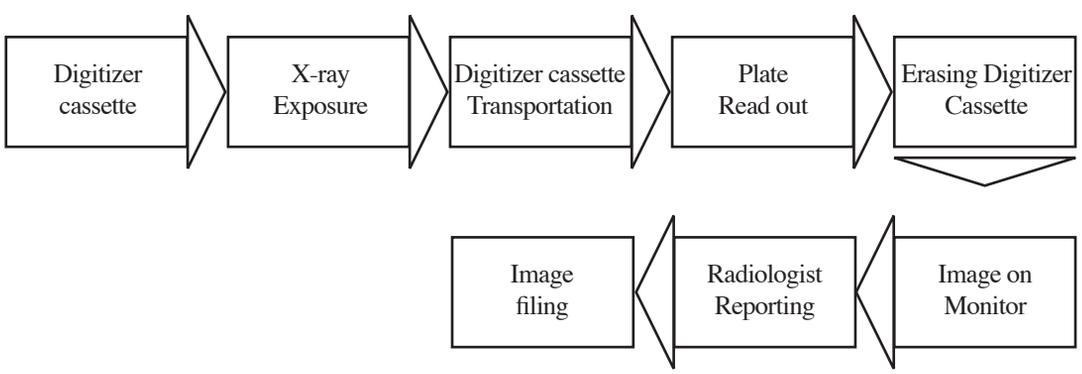
We look into 4 different scenarios of design for DR rooms which may be suitable for different hospitals, depending on the budget available for the x-ray department. Some of the newer DR technology today allows for DR plates to be used with bucky trays using wireless remote technology to transfer the image data.

Table 1 : Comparison of operations and workflow for Screen-film, CR and DR system.

Screen-film

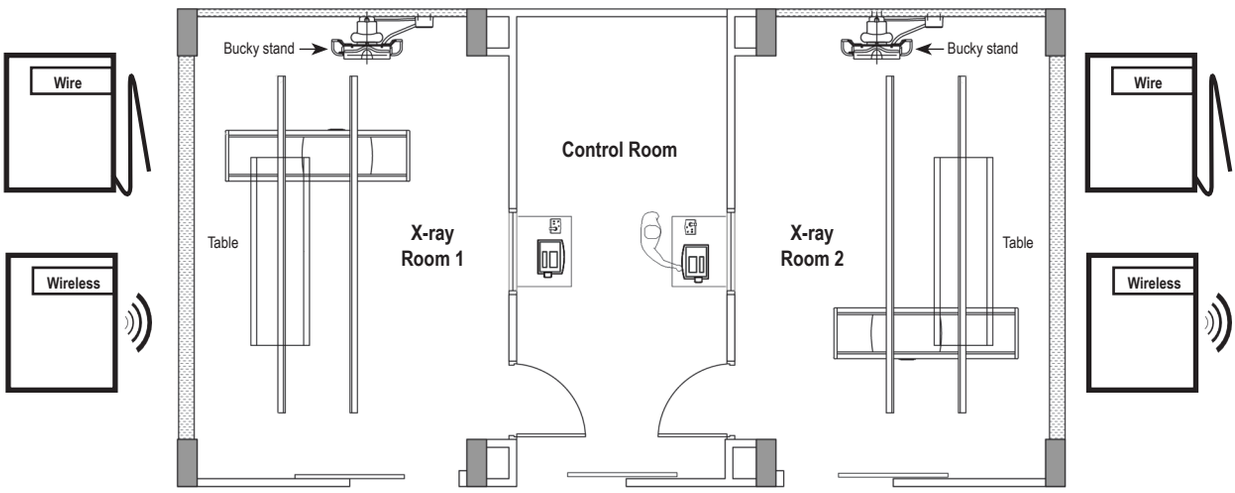


Computed Radiography (CR)



Digital Radiography (DR)

Scenario 1: Ideal DR System for 2 rooms with 2 wires and 2 wireless.



Equipments

1. 2 X-Ray machines.
2. Bucky stand 17x17 inches or 14x17 inches for 2 pieces wired system.
3. Flat detector 14x17 inches 2 pieces for wireless.
4. Control personal computer 2 sets.

Advantage:

- Complete for general radiographic service including large size patients.

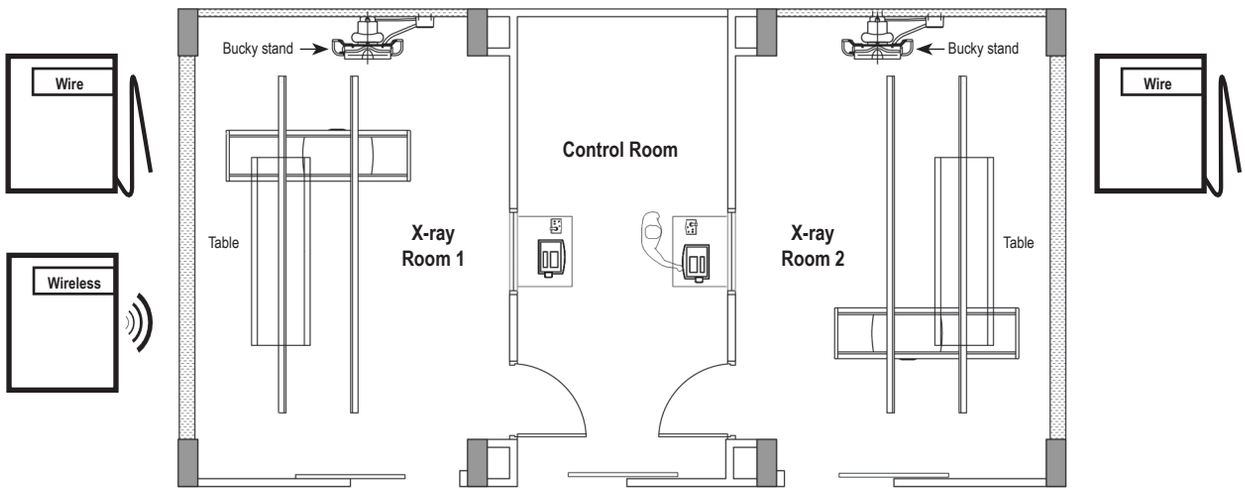
Disadvantage:

- Highest cost of investment.

	Patient Volume per Day	Patient Volume per Year	DR Cost (Approximate / Baht)	ROI* (Calculate over 5 years)
4 Detectors (2 X-Ray Rooms)	300	109,500	16,000,000.-	29.22 Baht / Image

Remark: *Case volume assumption*
**ROI = Return on investment*

Scenario 2: DR system for 2 rooms with 2 wires and 1 wireless.



Equipments

1. 2 X-Ray machines.
2. Bucky stand 17x17 inches or 14x17 inches for 2 pieces wired system.
3. Flat detector 14x17 inches 1 piece for wireless.
4. Control personal computer 2 sets.

Advantage:

- Good for check ups of general patients and larger patients.
- Service flow is convenient.
- Cost of investment 25% less than Scenario 1.

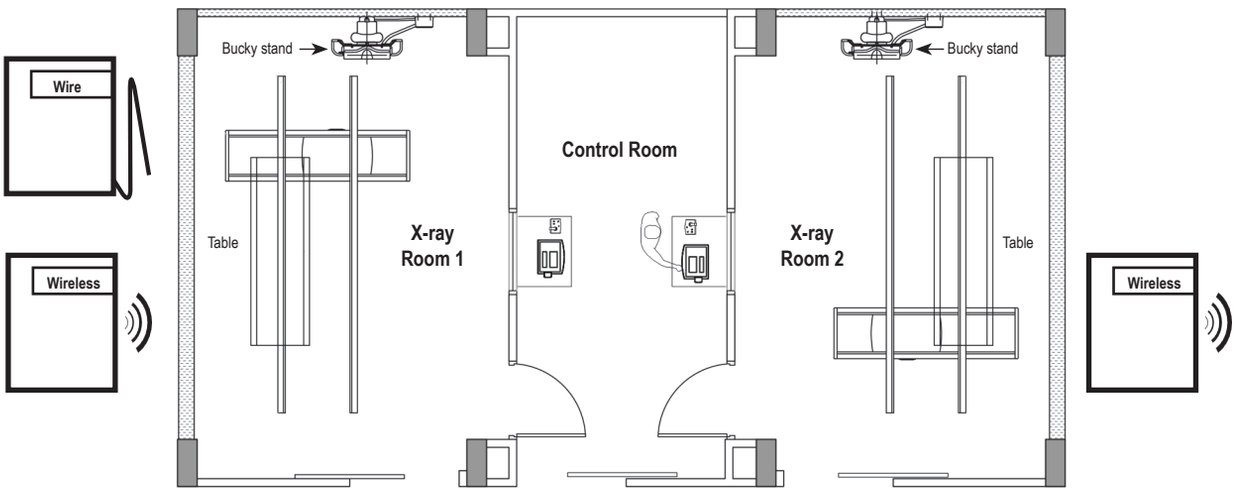
Disadvantage:

- Because there is only one wireless device, service and patient flow might sometimes be slower, due to technicians only being able to do multiple positioning with a patient in one room at a time.

	Patient Volume per Day	Patient Volume per Year	DR Cost (Approximate / Baht)	ROI* (Calculate over 5 years)
3 Detectors (2 X-Ray Rooms)	300	109,500	12,000,000.-	21.92 Baht / Image

Remark: *Case volume assumption*
**ROI = Return on investment*

Scenario 3: DR system for 2 rooms with 1 wire and 2 wirelesses.



Equipments

1. 2 X-Ray machines.
2. Bucky stand 17 x 17 inches for 1 device wired system.
3. Flat detector 14 x 17 inches 2 wirelesses devices serving 2 rooms.
4. Control personal computer 2 sets.

Advantage:

- Good for check ups, can cater for both general and larger patients.
- Service flow more flexible and convenient than Scenario 2.
- Cost of investment: 25% cheaper than Scenario 1.

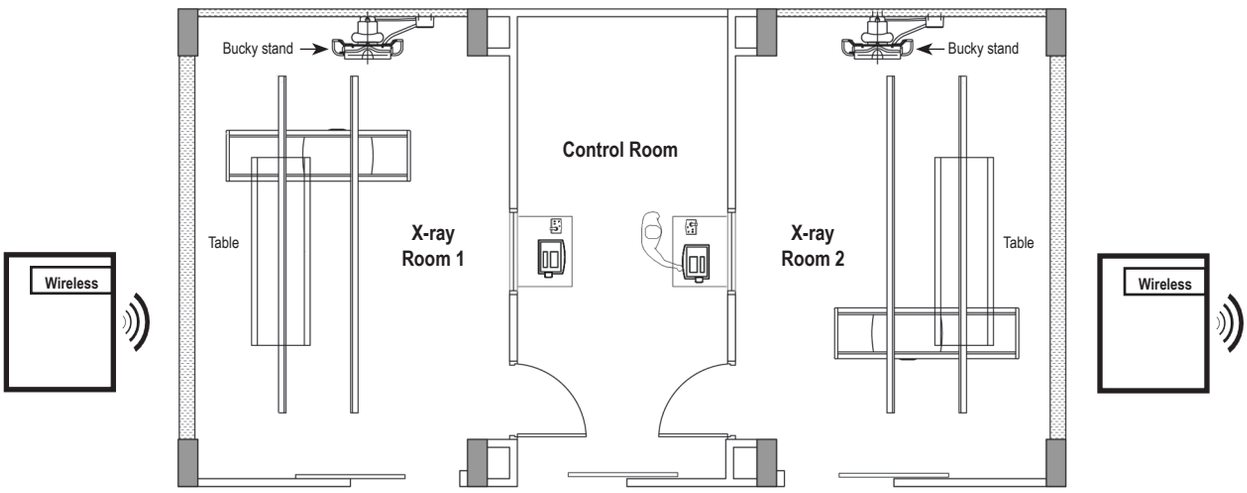
Disadvantage:

- None

	Patient Volume per Day	Patient Volume per Year	DR Cost (Approximate / Baht)	ROI* (Calculate over 5 years)
3 Detectors (2 X-Ray Rooms)	300	109,500	12,000,000.-	21.92 Baht / Image

Remark: *Case volume assumption*
**ROI = Return on investment*

Scenario 4: DR System for 2 rooms with 2 wirelesses.



Equipments

1. 2 X-Ray machines.
2. Flat detector 14 x 17 inches 2 wirelesses devices serving 2 rooms.
3. Control personal computer 2 sets.

Advantage:

- Lowest cost.
- Service flow still flexible and convenient for patients.
- Cost of investment 50% less than Scenario 1.

Disadvantage:

- Unable to cater for larger size patients for chest examination.

	Patient Volume per Day	Patient Volume per Year	DR Cost (Approximate / Baht)	*ROI (Calculate over 5 years)
2 Detectors (2 X-Ray Rooms)	300	109,500	8,000,000.-	14.61 Baht / Image

Remark: *Case volume assumption*
**ROI =Return on investment*

Summary of differences

Scenario 1: Ideal Prototype.
Scenario 2: We can reduce 1 wireless DR plate.
Scenario 3: We can reduce by 1 wired DR plate, but service and patient flow remains flexible and convenient.
Scenario 4: We can exclude wired devices, thus reducing the DR plate from 4 pieces to 2; patient flow is still convenient. However, this scenario cannot cater for images of larger patients, because the flat detector plate for wireless devices is not fixed to the bucky tray.

Analysis

Scenario 1 is the most expensive investment. Scenario 2 or 3 will cost approximately 25% less than Scenario 1. Scenario 4 will cost about 50% less than Scenario 1. The choice of set up will of course depend on available budget.

Discussion

The ideal DR system should be:

1. As cost effective as possible.
2. Effective in terms of speed of use per patient.
3. Easy for technicians to operate.
4. Able to ensure patient comfort.

Hermann reminds us that *"initial cost investment is the primary disadvantage of DR as compared to CR. CR can be easily integrated into an existing room structure whereas DR requires new radiographic equipment. Although an entire system overhaul to DR may offer greater streamlining of workflow, the costs of this upgrade could still be prohibitive to some facilities. In response to the high costs of upgrading the entire x-ray room or suite to DR, some vendors are offering DR tools that can be integrated into an existing CR platform. Now DR detectors have been developed that fit into a conventional cassette and bucky tray. A wireless transmission of images to the PACS allows facilities to take advantage of DR technology without upgrading the entire room."*[1]

Conclusion

A DR combination of wire and wireless system is the ideal for general diagnostic purposes, and the investment needed of course depends on patient numbers and their requirements. As Selbert explains:

"Today, there are many types of digital radiography devices, including CR and several types of directdisplay digital radiography (DR). The challenge for users is to determine what best fits their imaging requirements. While upfront costs are important, you must also consider patient throughput, system maintenance costs, positioning capabilities, and other factors that contribute to overall operational expenses. This means there is no single ***"best"*** *system for everyone."*[3]

It also needs to be noted that not only is it expensive to convert to DR, but there is a time lag before benefits can be reaped. Radiology staff will need to be re-trained and there is a steep learning curve, not only with regard to operating the new technology, but because of work flow changes.

We would like to express our appreciation to Thai GL Co. Ltd for helping to provide us with data which we used in this paper. We hope that our summary provides a useful guide for other hospitals about converting to DR.

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Migraine Headaches : Acute treatment in Thailand

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Migraine headache is a very common, chronic neurovascular disorder with a prevalence of 11.7% in the United States of America, and 29.1% in Thailand. Females tend to experience migraine more often than males. The common age group is between 30 and 39 years of age.[1, 2] Migraine is characterized by episodes of unilateral, pulsating or throbbing pain which is moderate to severe in its intensity and is often debilitating. It is also associated with nausea, vomiting and hypersensitivity to either light, sound, or smell. Headaches are usually aggravated by routine physical activity and are often alleviated by sleep within appropriate surroundings, such as in a dark, silent and cool place. If untreated or unsuccessfully treated, symptoms can persist from 4 to 72 hours.[3] Approximately 90% of the migraineurs have moderate or severe pain. Approximately 75% of cases said their routine functions deteriorated whilst 53% reported serious impairment or required bed rest during attacks.[2, 4] At least one half migraineurs complained of decreased productivity and one third missed at least one day of work or school in the previous year.[5-7]

Pathophysiology

The pathophysiology of migraine is not fully understood. Copious studies suggest a link between the pathogenesis of migraine and cortical spreading depression (CSD), neurogenic inflammation and vasodilatation.[8, 9] Moreover, surveys in twin populations strongly imply that migraine is a disorder which is the result of a combination between genetic mutations and environmental factors. This is particularly so in sufferers with familial hemiplegic migraine, which involves the voltage-gated calcium channel mutation (CACNA1A), voltage-gated sodium channel mutation (SCN1A), and sodium-potassium pump mutation (ATP1A2).[10-16] These channelopathies produce cerebral hyperexcitability and lower CSD threshold from a variety of triggers.[17] CSD can activate the trigeminovascular system. Several neuropeptides such as calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide (VIP), and nitric oxide (NO) are released from nerve terminals which led to meningeal neurogenic inflammation, plasma extravasations, and vasodilatation. These peripheral pain mechanisms activate nociceptive afferents in trigeminal nerve and upper cervical dorsal root (C2-C3) and then turn back to activate the central pain pathway including trigeminal ganglion, trigeminal nucleus caudalis in brain stem, thalamus, and finally in the sensory cortex.[18,19]

Clinical features of migraine attack

Migraine attack consists of four phases: (i) prodrome phase (e.g., irritability, food craving), (ii) aura phase (e.g., visual, sensory, language, or motor symptoms that often precede the headache),

(iii) headache phase (usually unilateral, pulsating), and (iv) postdrome phase (e.g., tiredness, head pain).[3, 20, 21]

The prodrome or premonitory phase may occur for hours or up to one day prior to the onset of headache in 70% of migraineurs.[22] It is composed of symptoms which may be psychological (depression, euphoria, irritability, restlessness, hyperactivity, hypoactivity, fatigue, drowsiness); neurological (photophobia, phonophobia, hyperosmia) or general (stiff neck, increased thirst, anorexia, diarrhea, constipation, fluid retention, craving for particular foods, repetitive yawning); there are also other less typical symptoms reported by some patients.[23-25]

Aura symptoms occur in one fifth of migraineurs. Typical aura is characterized by fully reversible focal neurological disturbances such as visual symptoms, sensory symptoms or dysphasia / aphasia that gradually develop over ≥ 5 minutes and last for ≤ 60 minutes.[3] Visual aura is the commonest aura found in 99% of cases, followed by a sensory aura (54%), and aphasic aura (32%).[26, 27] Headaches could start simultaneously or after aura onset. However, most migraineurs (80%) usually developed the headache within 60 minutes after the end of aura.[28]

In 20% of patients, headaches can consistently occur at the same side. However, in 40% of cases headaches may develop bilaterally. Head pain could be aggravated by routine physical activities such as walking or climbing stairs. Headache symptoms usually occur gradually, any sudden onset of headache should raise suspicions of secondary headache.[29-31]

Postdrome phase is reported in 68% of migraineurs. Symptoms include tiredness (71.8%), head pain (33.1%), cognitive difficulties (11.7%), hangover (10.7%), gastrointestinal symptoms (8.4%), mood change (6.8%), and weakness (6.2%). Postdrome is frequently found in females (69.1%) and is associated with a full-blown migraine attack.[32]

The International Classification of Headache Disorders (ICHD-2) criteria were introduced in 2004 for standard diagnosis and research. Migraine was classified into six major categories. Two major sub-types were recognized; (1) Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms, and (2) Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or sometimes accompany the headache. ICHD-2 criteria for diagnosis of the two major types of migraine are shown in Table 1.

Strategies in migraine treatment

There are two approaches in migraine treatment: step care and stratified care.[33] Step care starts treating the attack with general pain-killer medications e.g., acetaminophen, NSAIDs, or combination of simple analgesics. If headaches are not responsive within two hours, migraine-specific medication such as triptan or ergot should be commenced.

In the other approach, known as stratified care, the person with migraine is firstly evaluated for severity of disability by using the Migraine Disability Assessment (MIDAS).[34, 35] This is a 5-item questionnaires which assesses lost time caused by headache over 3 months. A MIDAS score of more than *'10'* indicates moderate to severe disability that requires migraine-specific treatment. Another validated disability tool is the Headache Impact Test (HIT-6). A HIT-6 score more than 60 indicates severe impact from migraine.[36] The Disability in Strategies of Care (DISC) study showed stratified care is superior to step care, resulting in better patient outcomes, and also reduced time loss.[37, 38] Stratified care is recommended in current guidelines for migraine treatment.[33, 39]

Nonspecific acute migraine treatment

Analgesics

NSAIDs inhibit cyclooxygenase (COX) and reduce prostaglandin within the central nervous system (CNS) and outside the blood-brain-barrier. Selective cyclooxygenase - 2 (COX-2) inhibitors, refecoxib and valdecoxib, have been studied and demonstrated their efficacy in acute migraine treatment but they were withdrawn from the market because of increase in cardiovascular risk. Celecoxib, an available selective COX-2 inhibitor, could be used for acute migraine attack with doses between 100 and 400 mg. Since it causes less gastrointestinal side effects, it should be considered in people with gastrointestinal intolerance.[40, 41]

Analgesics such asacetylsalicylic acid (ASA) up to 1000 mg,[42-44] naproxen 500 - 1000 mg,[45] ibuprofen 200-800 mg,[46] diclofenac potassium 50 - 100 mg,[47] and paracetamol 1000 mg[48] are the first medications for mild to moderate migraine. A combination of *"Aspirin-acetaminophen-caffeine (AAC)"* elucidates higher efficacy for acute treatment in those with mild or no disability migraines, when compared to treatment with placebo or other individual analgesic.[49-51] The United States Headache Consortium recommended that NSAIDs and AAC can be effective for non-disabling migraine (Level A).[39, 52]

Table 1 : ICHD-2 criteria for migraine headache.[3]

Migraine

1.1 Migraine without aura
1.2 Migraine with aura
- 1.2.1 Typical aura with migraine headache
- 1.2.2 Typical aura with non-migraine headache
- 1.2.3 Typical aura without headache
- 1.2.4 Familial hemiplegic migraine (FHM)
- 1.2.5 Sporadic hemiplegic migraine
- 1.2.6 Basilar-type migraine

1.3 Childhood periodic syndromes that are commonly precursors of migraine
- 1.3.1 Cyclical vomiting
- 1.3.2 Abdominal migraine
- 1.3.3 Benign paroxysmal vertigo of childhood

1.4 Retinal migraine
1.5 Complications of migraine
- 1.5.1 Chronic migraine
- 1.5.2 Status migrainosus
- 1.5.3 Persistent aura without infarction
- 1.5.4 Migrainous infarction
- 1.5.5 Migraine-triggered seizures

1.6 Probable migraine
- 1.6.1 Probable migraine without aura
- 1.6.2 Probable migraine with aura
- 1.6.3 Probable chronic migraine

Migraine without aura

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not attributed to another disorder

Migraine with aura (Typical aura with migraine headache)

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
   1. fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
   2. fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
   3. fully reversible dysphasic speech disturbance
C. At least two of the following:
   1. homonymous visual symptoms and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
   3. each symptom lasts ≥ 5 and ≤ 60 minutes
D. Headache fulfilling criteria B-D for begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

Table 2 : Medications for acute treatment of migraine (Available in Thailand).[39, 52, 76]

Medications	Dose/Route	Level of recommendation*	Comment
Non-Specific Medications			
- Acetylsalicylic acid (ASA)	1000 mg PO	A	Gastrointestinal side effects.
- Ibuprofen	200-800 mg PO	A	Gastrointestinal side effects.
- Naproxen	500-1000 mg PO	A	Gastrointestinal side effects.
- Diclofenac-K	50-100 mg PO	A	Gastrointestinal side effects.
- Paracetamol	1000 mg PO	A	Caution in liver and kidney.
- Ergotamine tartrate and Caffeine	1 mg, 100 mg PO	B	Caution in cardiovascular, liver and kidney diseases.
Specific Medications			
- Sumatriptan	50-100 mg PO	A	Caution in cardiovascular diseases.
- Eletriptan	20-80 mg PO	A	Caution in cardiovascular diseases.
Parenteral Medications			
- Metoclopramide	10 mg IV	A	Risk for extrapyramidal effects and mild sedation. Contraindicated in childhood and in pregnancy; also have analgesic efficacy.
- Chlorpromazine	0.1 mg/kg IV	B	Risk for extrapyramidal effects and mild sedation.
- Ketorolac	15-30 mg IV 60 mg IM	A	Non-sedating, risk for gastrointestinal (GI) bleeding.

Classification of Recommendations.[39, 52]

Level A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies)

Level B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies)

Level C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

Medications for acute migraine treatment

Ketorolac, a parenteral NSAIDs, has not yet been researched in placebo-controlled study to assess it in acute migraine treatment. The efficacy of ketorolac in acute migraine treatment was similar to meperidine and led to headache resolution similar as antiemetic medications.[53, 54] Ketorolac can be administrated intravenously at a dosage of 15 to 30 mg or intramuscularly at 30 to 60 mg per dose. The U.S. Headache Consortium recommended that intravenous or intramuscular ketorolac injection should be considered for acute treatment of migraine for whom requiring parenteral therapy (Level B).[52] Opioid use in acute migraine is generally ineffective.[55-57] The U.S. Headache Consortium stated that enteral and parenteral opioid may be added for acute migraine should the sedative effect not put patients at risk: moreover the risk for abusive use of opioids has been addressed (Level B).[52] Opioid should be limited and reserved for some particular circumstances such as pregnancy, lactation, contraindication to triptans or NSIDs (Level U).[52] Parenteral opioid should be used as a back up for acute migraine when sedation side effects will not increase patient risk and when the risk of abuse has been addressed (Level B).[52]

Antiemetics and Neuroleptics

Nausea and vomiting are common associated symptoms of migraine and can be as disabling as the headache. Antiemetic in acute migraine is recommended to treat these symptoms. It increases gastric emptying times resulting in optimizing absorption and effectiveness of oral medications. However, large prospective, placebo-controlled randomized trials are still lacking.

Intravenous metoclopramide showed superiority over placebo and ibuprofen in acute migraine treatment.[58, 59] Repeated doses of metoclopramide plus intramuscular dimenhydrinate were found to have an effectiveness similar to subcutaneous sumatriptan.[60] However, using oral metoclopramide alone, as monotherapy, is not effective for acute migraine treatment (Level A) but it can still be considered as an adjunctive therapy to NSAIDs or triptans (Level B).[52] Intravenous 10 to 20 mg metoclopramide is recommended for adults and adolescents (Level A).[39, 52]

Intravenous chlorpromazine demonstrated a higher efficacy than meperidine and lidocaine.[61] Dose of 0.1 mg/kg chlorpromazine intravenously achieved a pain free response within 30 minutes compared with placebo.[62] Chlorpromazine should be used for patients requiring parenteral therapy (Level A).[52]

Both metoclopramide and chlorpromazine share common side effects which include drowsiness, sedation, and hypotension. Extrapyramidal side effects such as acute dystonic reaction and akathisia are uncommon.[63]

Specific acute migraine treatment

Triptans

Triptans are selective 5-hydroxytryptamine (5-HT) 1B/1D-agonists and ameliorate headache without sedative effect. Agonist of serotonin-1D receptors inhibit CGRP and inflammatory neuropeptide release in the meninges that cause extravasation of dural plasma protein, and block pain transmission from peripheral trigeminal pathway to the centrally trigeminal nucleus caudalis in brain stem. They also work via the 5HT1B receptor to constrict vessels dilated by CGRP. On the present market, there are seven types of triptans: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan. In Thailand, however, only two triptans are available, sumatriptan and eletriptan. Non-oral routes are also not available in Thailand. The efficacy of triptans has been proven in large placebo-controlled trials of which meta-analyses have been published.[64-67] Triptans can be effective at any time during a migraine attack. However, there is evidence that the earlier triptans are taken, the better their efficacy. Triptans should be taken when the headache is mild, ideally within less than 30 minutes from onset.[74, 75] Triptans are also effective in about 60% of NSAIDs non-responder. All triptans should be used for acute treatment of mild, moderate, and severe migraine unless contraindicated (Level A).[39, 52]

Sumatriptan was the first triptan to be introduced in 1991. Sumatriptan 100 mg (oral form) is significantly more effective than placebo for complete headache relief at 2 and 4 hours. Doses of 50 mg and 100 mg sumatriptan are more effective than dose of 25 mg. Dose of 50 mg is associated with a lower incident of adverse events than the dose of 100 mg.[62, 68] Sumatriptan is extensively metabolized in liver by monamine oxidase-A (MAO-A) and therefore it should not be used in patients who take MAO-A inhibitors.

Eletriptan is rapidly absorbed and has a higher bioavailability (50% vs. 14%) with longer half-life (5.5 hours vs. 2 hours) than sumatriptan.[69] Eletriptan 20, 40, and 80 mg have been studied in double blind, placebo-controlled trials which revealed that eletriptan provided higher favorable outcome compared with placebo. Eletriptan 40 mg is more effective than 20 mg and causes lower side effect than 80 mg dose.[66, 70-73]

Table 3 : Pharmagology and efficacy of triptans in Thailand.[65, 66, 69, 76]

Pharmacokinetics	Sumatriptan	Eletriptan	
Onset of Efficacy (minutes)	45-60	60	
Bioavailability (%)	14	50	
Elimination Routes	Hepatic, MAO	Hepatic (active metabolite) CYP3A4	
Maximum Daily Doses (mg)	200	80	
Efficacy	Sumatriptan	Eletriptan 40 mg	80 mg
Headache response at 2 hours (%)	50-61	65	65-80
Complete relief of pain at 2 hours (%)	29-36	22-41	30-53
Recurrence rate at 24 hours (%)	29-34	19-23	21-33

Active metabolism of eletriptan, N-desmethyl eletriptan, is catalyzed by cytochrome P-450 system (CYP3A4). Thus eletriptan should not be used with potent CYP3A4 inhibitors such as ketoconazole and clarithromycin.

Triptans are contraindicated in those with coronary artery disease, high risk for occult cardiac disease, cerebrovascular disease, peripheral vascular disease, uncontrolled hypertension, and pregnant woman. The most common adverse effects are fatigue, dizziness, asthenia and nausea. Known as triptans sensations, sensation of flushing, chest pain or chest pressure can occur in some cases and those symptoms are mild and usually transient.[64-66]

Contraindication of Triptans

1. Ischemic stroke.
2. Ischemic heart disease.
3. Prinzmetal's angina.
4. Raynaud's disease.
5. Uncontrolled high blood pressure.
6. Severe liver or renal failure.
7. Familial hemiplegic migraine.
8. Basilar type migraine.
9. Pregnancy and lactation.
10. Ergotic alkaloid used.
11. Monoamine oxidase inhibitors used.
12. Caution in selective serotonin reuptake inhiditos (SSRIs) or serotonin/norepinephrine reuptake inhiditos (SNRIs) used.

Conclusion

Migraine is a common, chronic and mostly debilitating neurovascular disorder, which impairs quality of life. Its pathophysiology is still not fully discovered but cerebral hyperexcitability either from genetic mutation or environmental factors can trigger central and peripheral pain pathway. Stratified care is recommended for migraine treatment. Persons with headaches should establish the correct diagnosis and evaluate their level of disability together with impact of migraine, prior to treatment. NSAIDS and ACC are the drugs of choice for those with mild to moderate migraine headaches. Ketorolac is a solely parenteral NSAID recommended for acute migraine treatment. Opioid should be avoided due to sedative side effect and risk of abuse. Intravenous metoclopramide and chlorpromazine can be used in patients with nausea/vomiting and who require parenteral therapy. Triptans are specific treatment for acute migraine headache and should be used in disabling migraineurs in the absence of vascular contraindications.

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Questions of Migraine Headaches

Q1. Which of the following is not a feature of migraine prodrome?

a. Fatigue
b. Muscle aching
c. Increased thirst
d. Visual blurring
e. Irritability

Q2. Which of the following is not true of migraine aura?

a. Aura can occur in isolation without headache phase.
b. Aura phase can occur suddenly.
c. Visual aura is the commonest symptom of aura phase.
d. Unilateral motor weakness is a part of migraine aura.
e. Aura in migraine can be suppressed by antiepileptic medications.

Q3. Which is the best tool for assessing the severity of a migraine attack that occurred in the last month?

a. MIDAS (Migraine Disability Assessment)
b. HIT-6 (Headache Impact Test)
c. Migraine-ACT (Migraine Assessment of Current Therapy)
d. HART (Headache and Assessment of Response to Treatment)
e. PHQ-9 (Patient Health Questionnaire)

Q4. What is the most appropriate oral medication for patient with acute severe migraine attack that interferes with his or her daily activities?

a. Naproxen sodium (Synflex®)
b. Combination of ergotamine, and caffeine (Cafergot®)
c. Eletriptan (Relpax®)
d. Domperidone (Motilium®)
e. Haloperidol (Hadol®)

Q5. What is the most appropriate intravenous medication for acute migraine attack (rescue therapy)?

a. Metoclopramide (Plasil®)
b. Ketorolac (Acular®)
c. Parecoxib (Dynastat®)
d. Meperidine (Pethidine®)
e. Tramadol (Tramol®)

Answers of Migraine Headaches

Answer 1: d. Prodrome includes symptoms which are: psychological (depression, euphoria, irritability, restlessness, hyperactivity, hypoactivity, fatigue, drowsiness), neurological (photophobia, phonophobia, hyperosmia) or general (stiff neck, increased thirst, anorexia, diarrhea, constipation, fluid retention, craving for particular foods, repetitive yawning), and other less typical symptoms. The most common aura symptoms in migraine are visual symptoms including positive (flickering, zig zag line, bright dot, blurring) and negative (scotoma).

Answer 2: b. Acute onset of aura should cause suspicion of causes other than migraine, such as transient ischemic attack (TIA) or seizure aura. Migraine aura is characterized by gradual onset of symptoms in more than 5 minutes. Visual, sensory, aphasic and motor aura are recognized as transient neurological dysfunction in migraine. Aura can occur in isolation without headache. Cortical spreading depression that clinically represented aura can be suppressed by antiepileptic medications.

Answer 3: b. HIT-6 is an easy and reliable tool with which to assess severity and impact of migraineurs in the last month. MIDAS is another tool for assessing severity and impact in migraineurs in the 3 month follow up period.

Answer 4: c. Triptans (Eletriptan, sumatriptan) are recommended in debilitating migraine, according to stratified strategy (level of evidence A). NSAIDs and combination of ergotamine, and caffeine (Cafergot®) can be used in non-disabling migraine attack.

Answer 5: b. Ketorolac is the only parenteral NSAIDs that is approved for acute migraine treatment. Metoclopramide can be used in acute migraine attack because it is binding in a non-selective fashion on dopamine receptors. However, it can cause dystonic reaction, and akathisia. Opioids, such as meperidine, tramadol should be avoided in migraine and other headache treatment because they can induce central sensitization and also have addictive effect.

Neuro -Vascular Intervention

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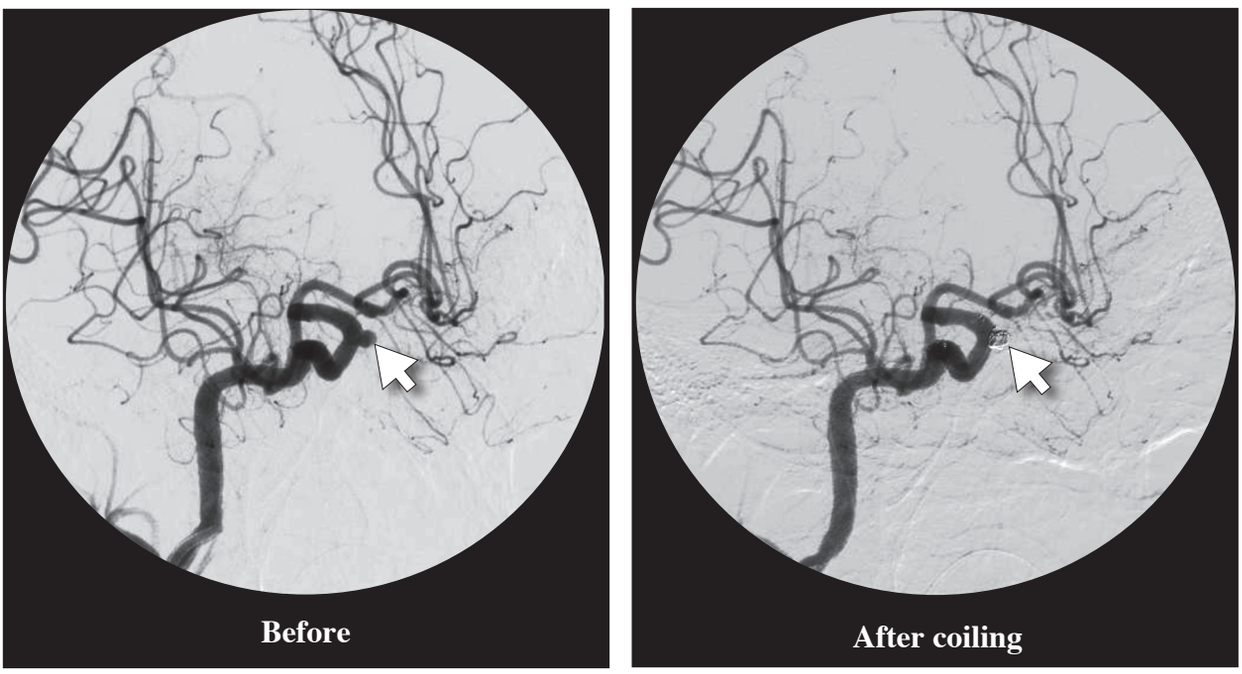
Case 1 : Aneurysm at carotid siphon



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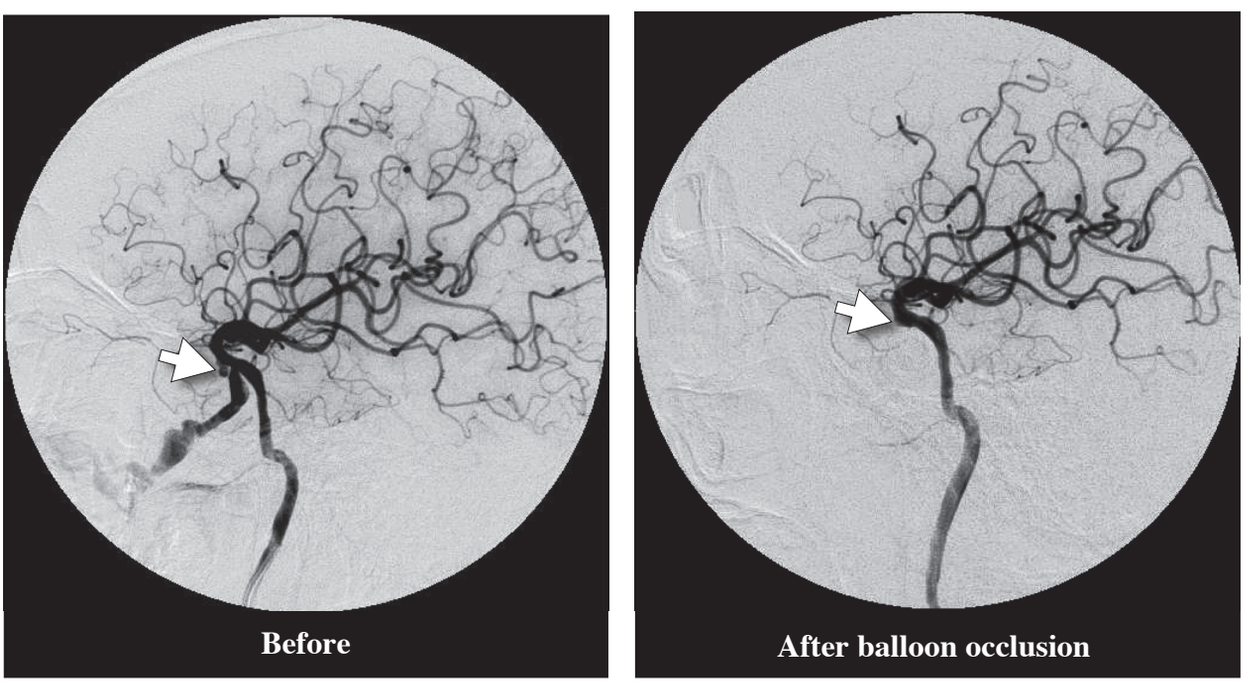

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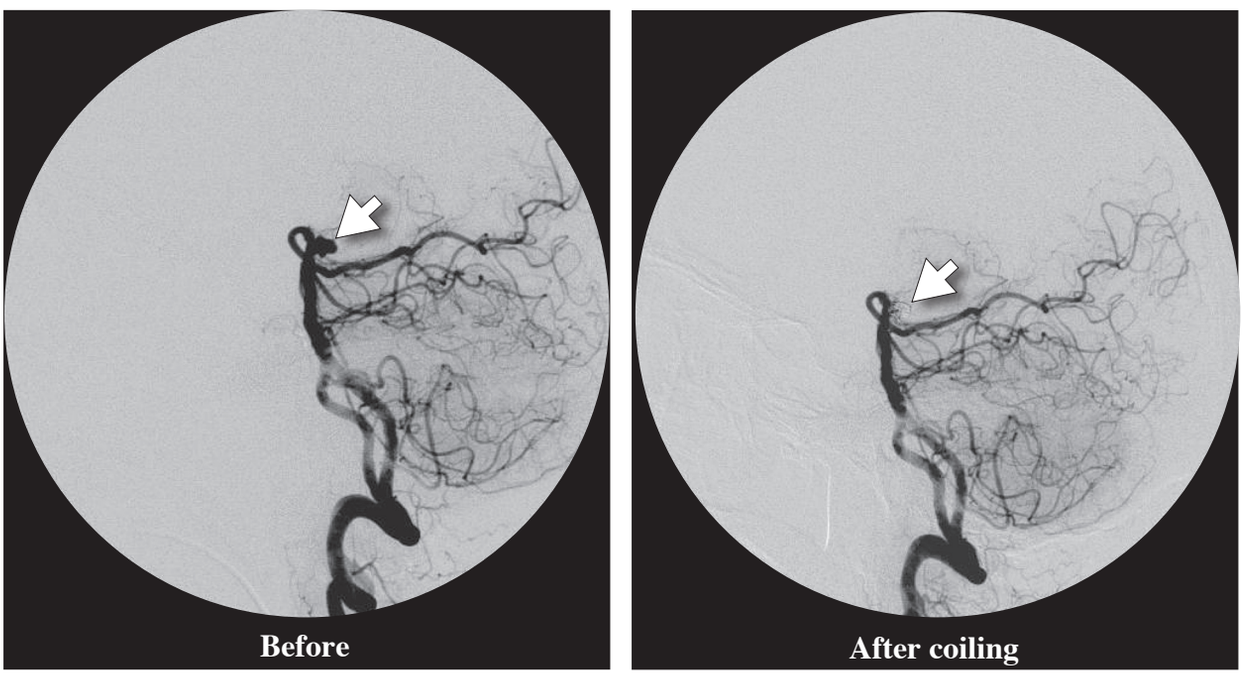

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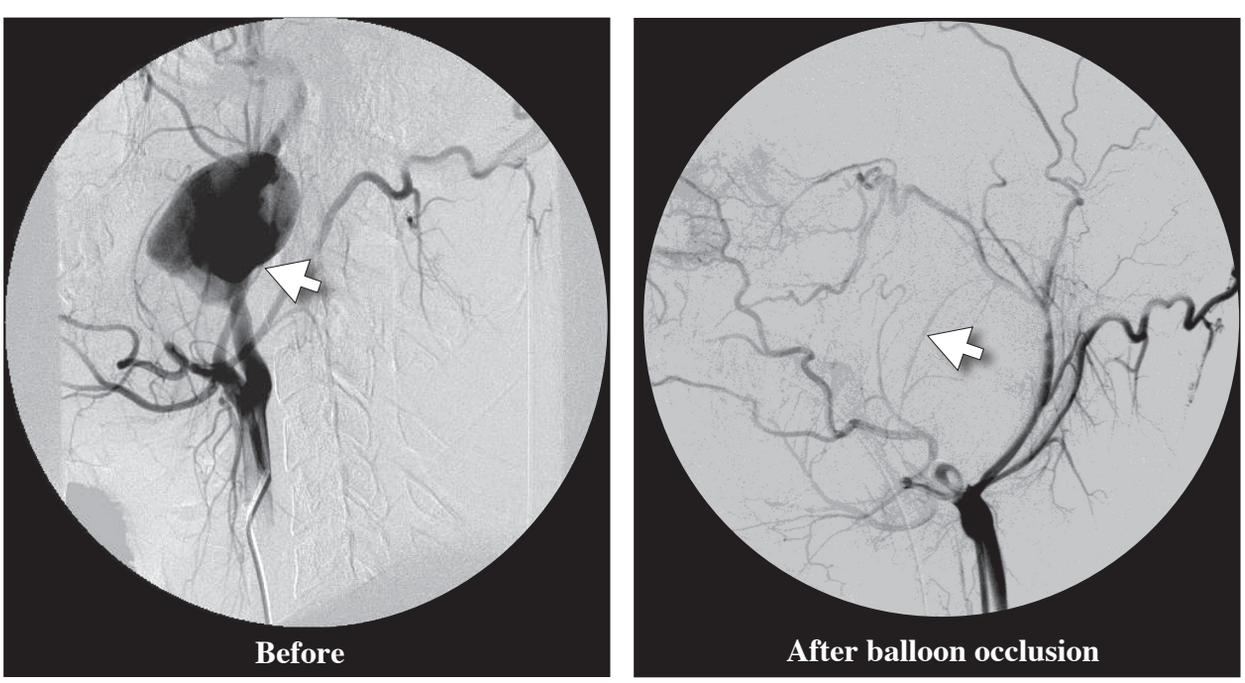
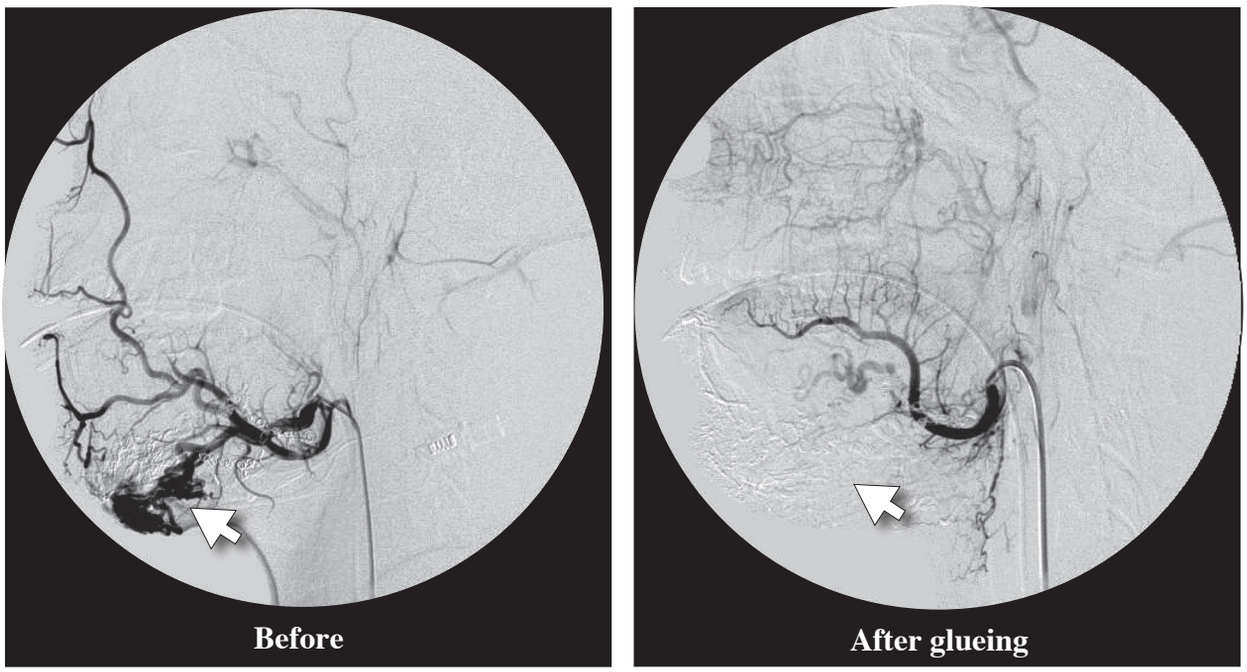
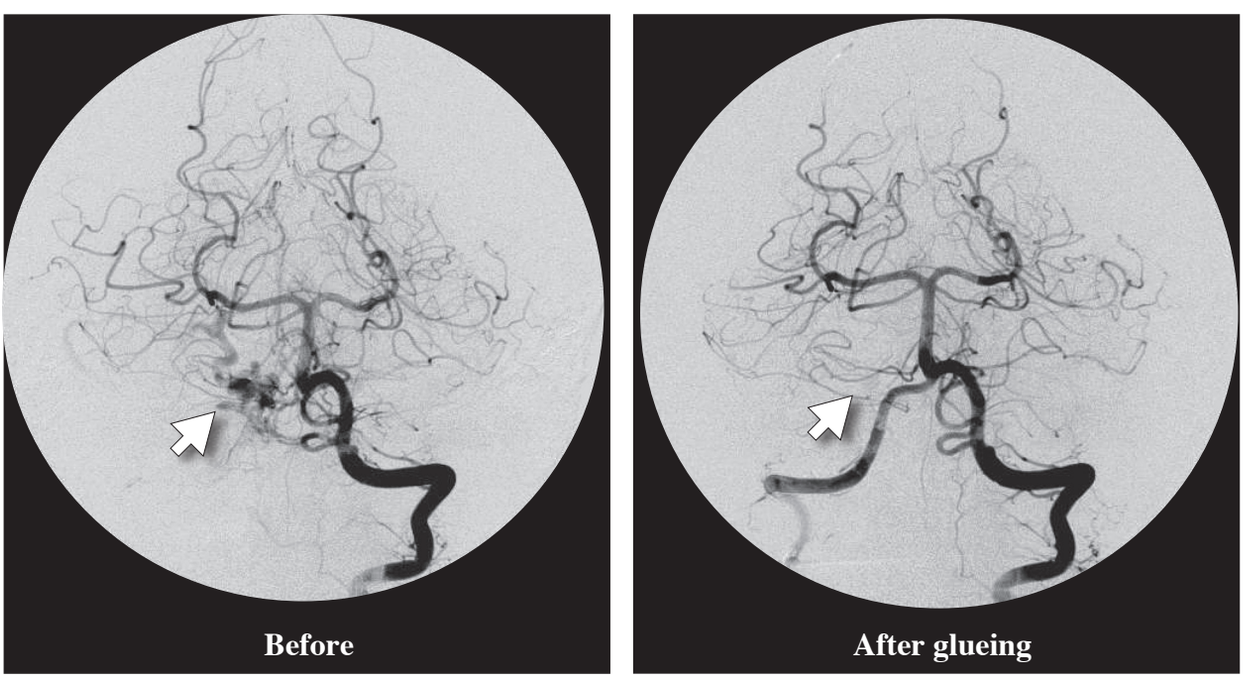


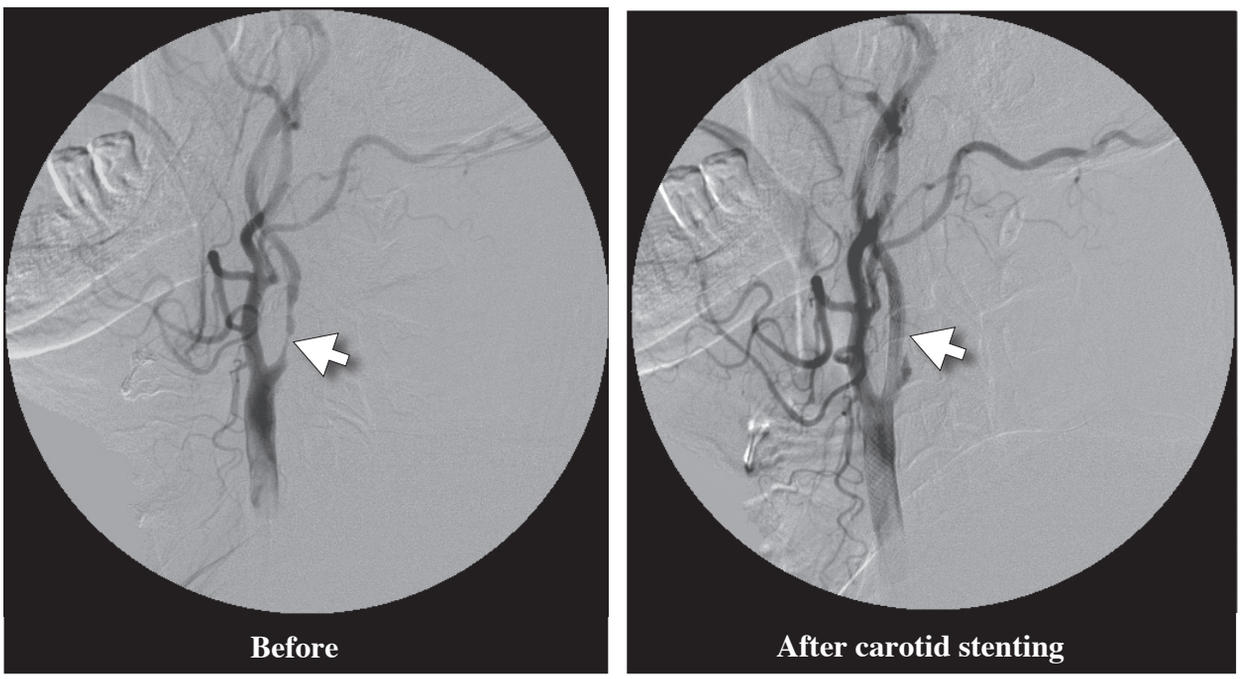
Case 5 : Arteriovemous malformation (AVM) at inferior alveolar artery



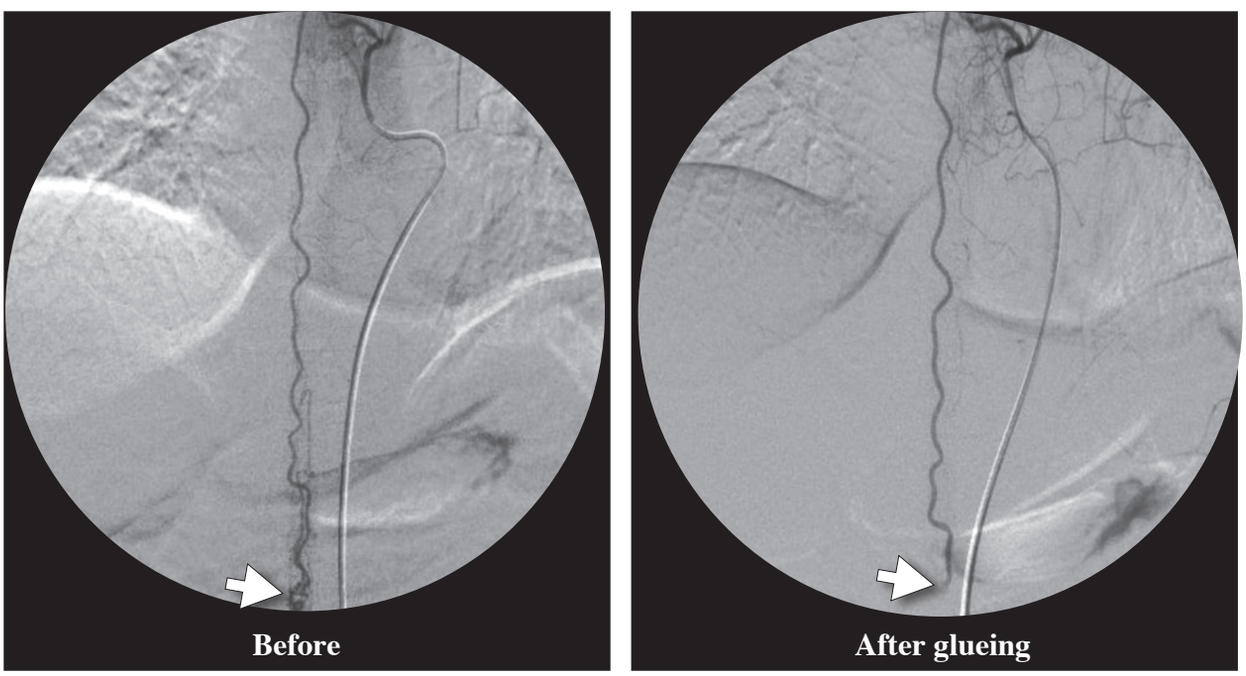
Case 6 : Arteriovemous malformation (AVM) at right antero-inferior cerebellar artery



Case 7 : Internal carotid stenosis



Case 8 : Arteriovemous malformation (AVM) at anterior spinal artery



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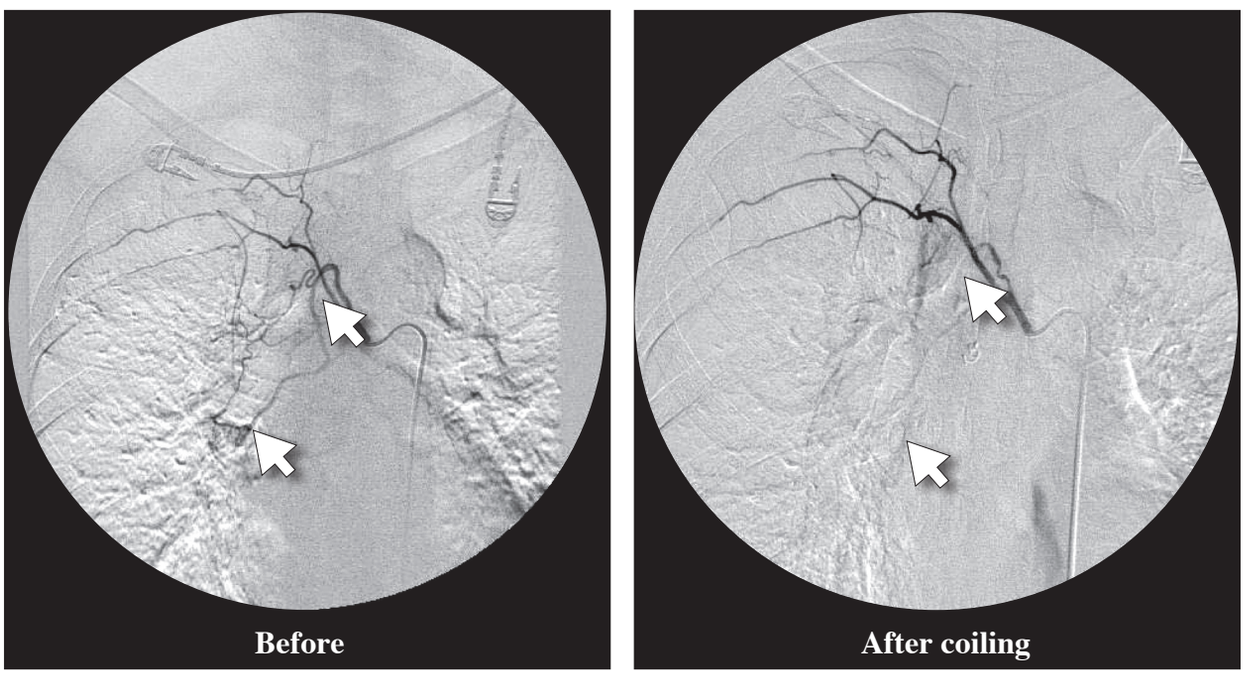

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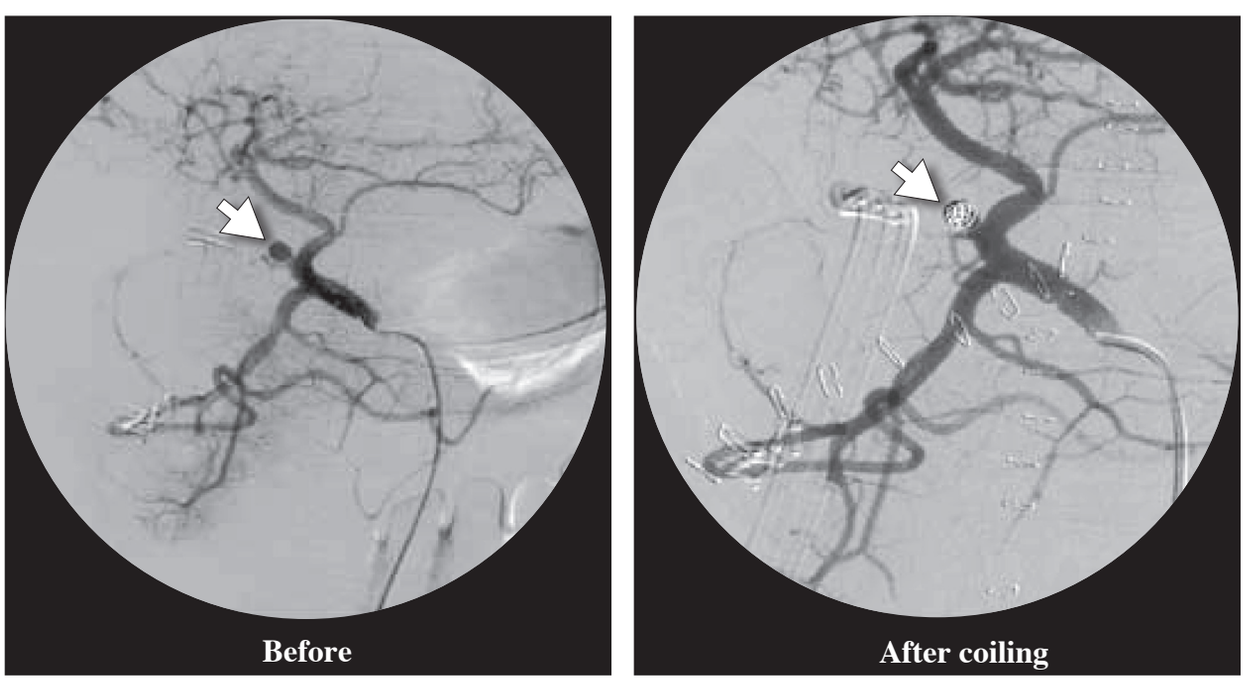

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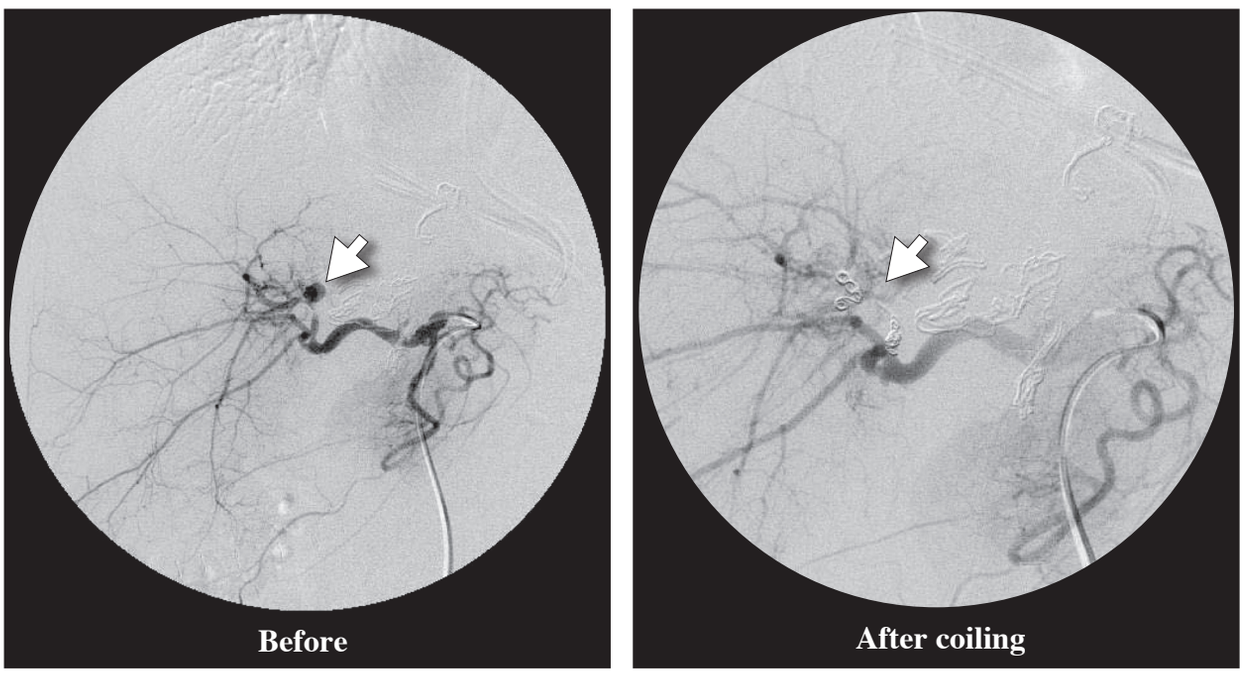

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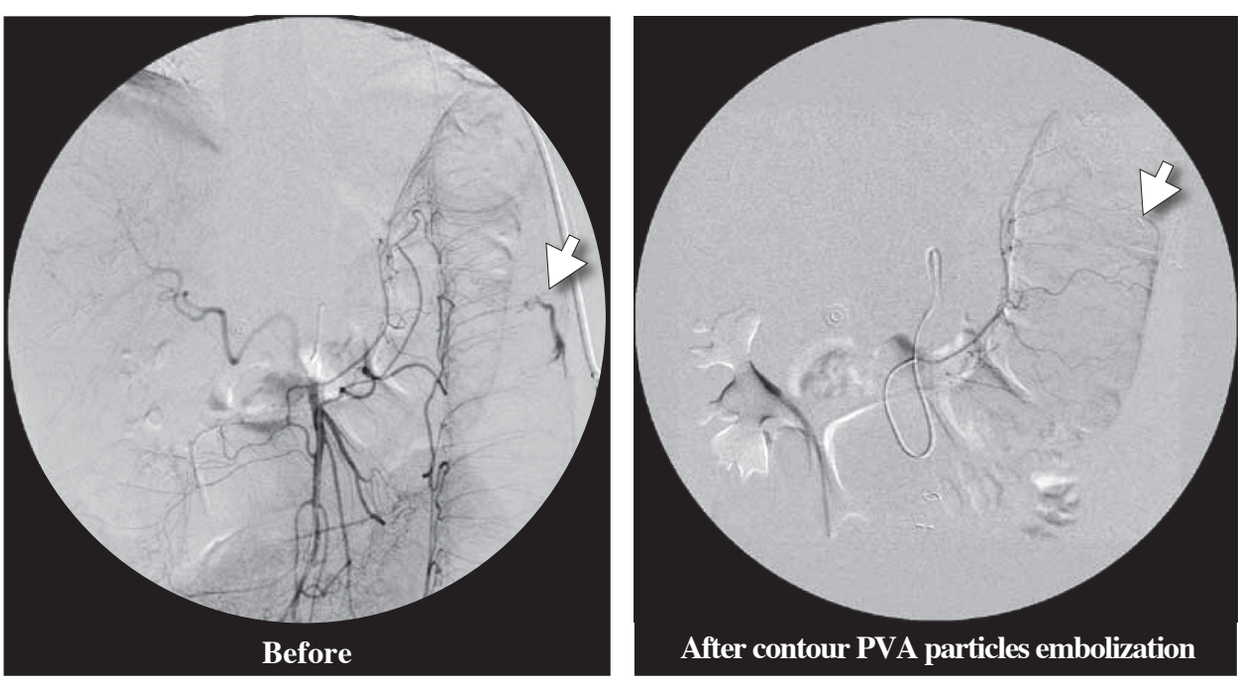

PVA = polyvinyl alcohol embolic

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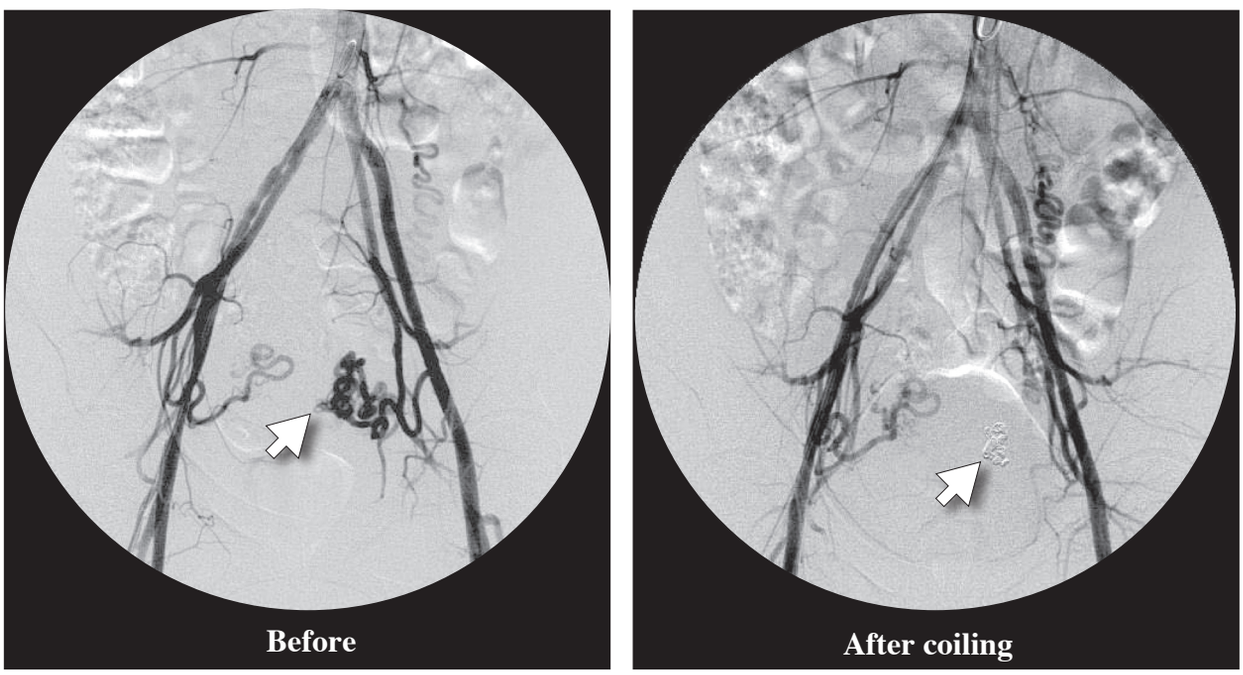

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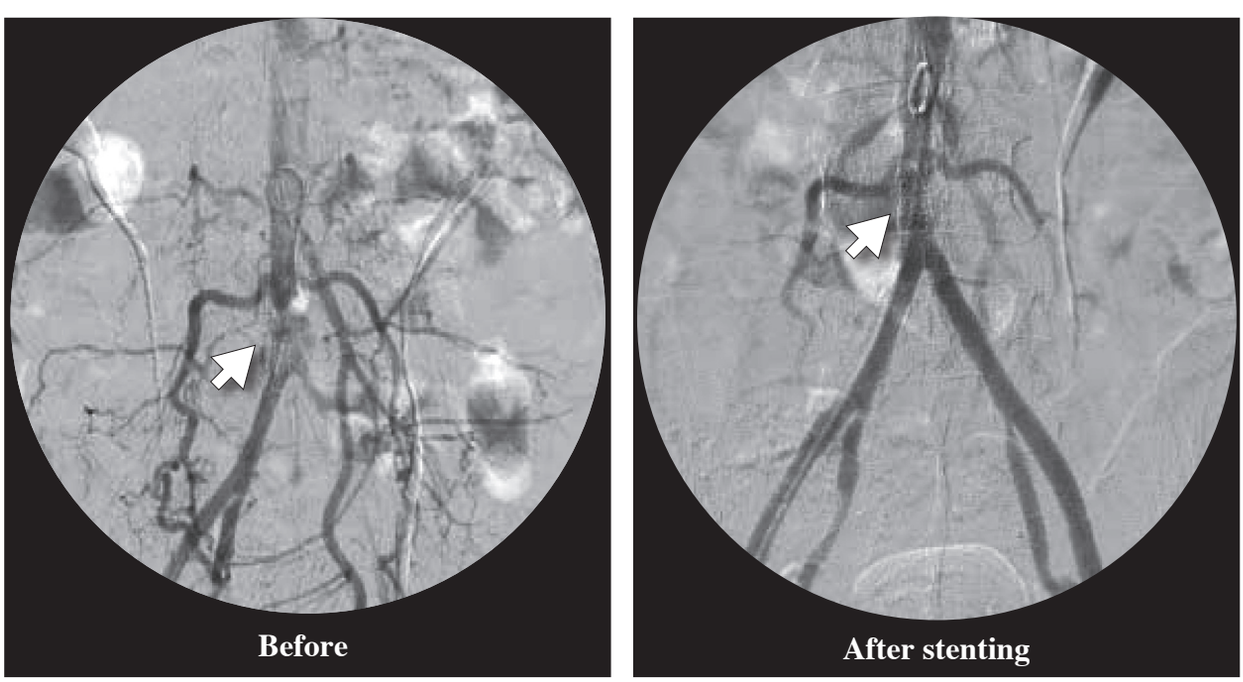

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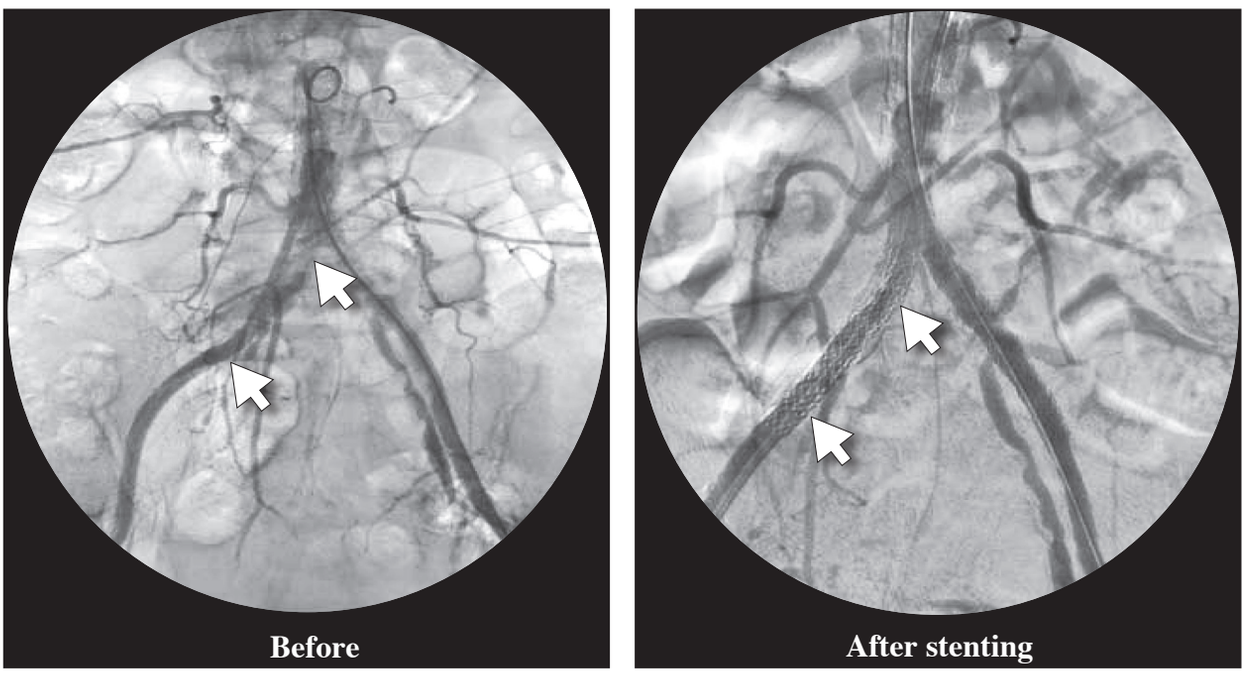

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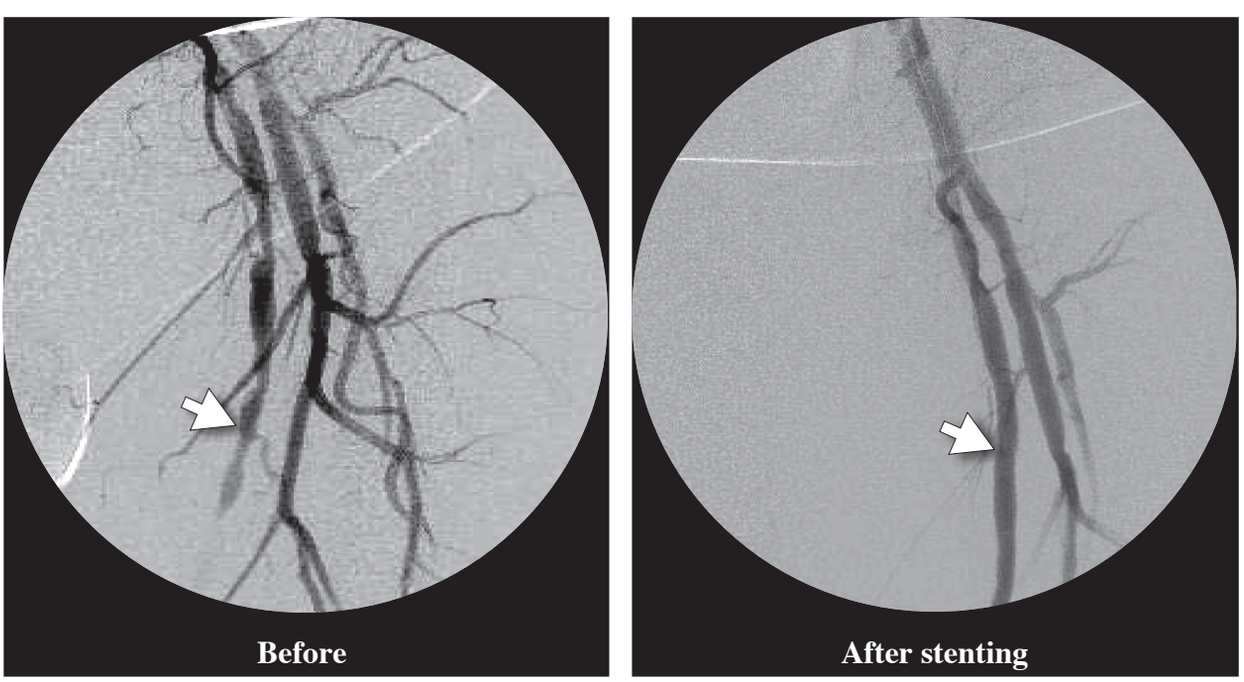

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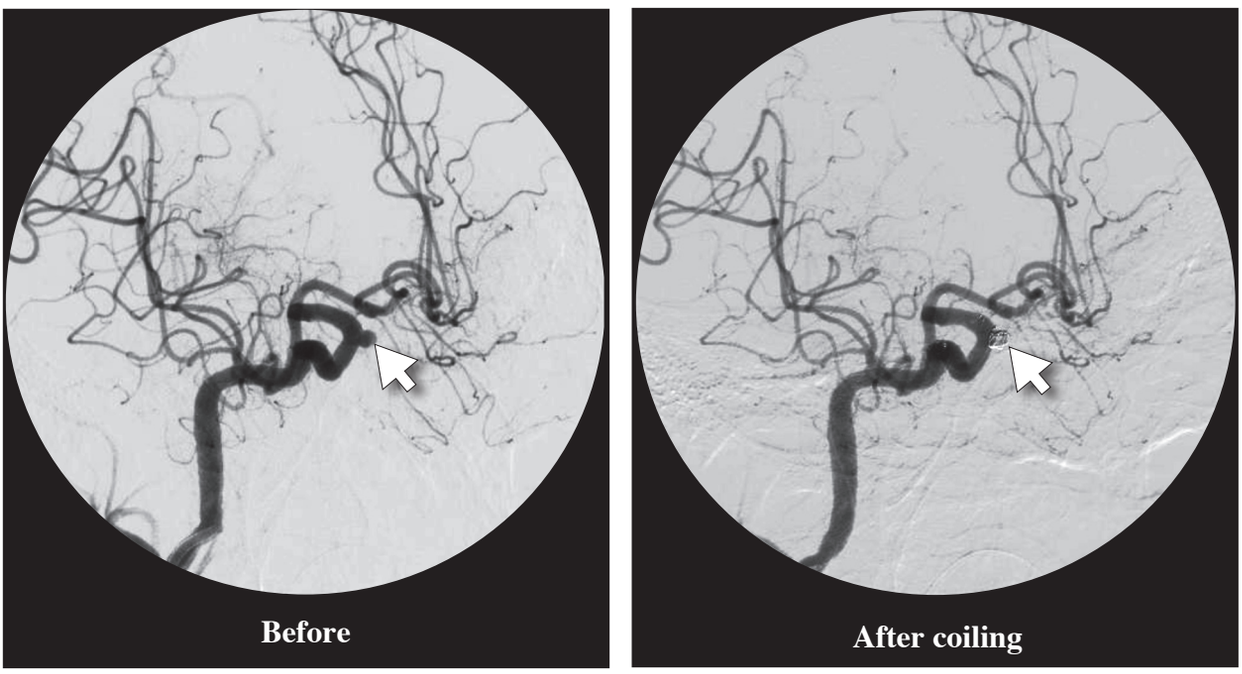

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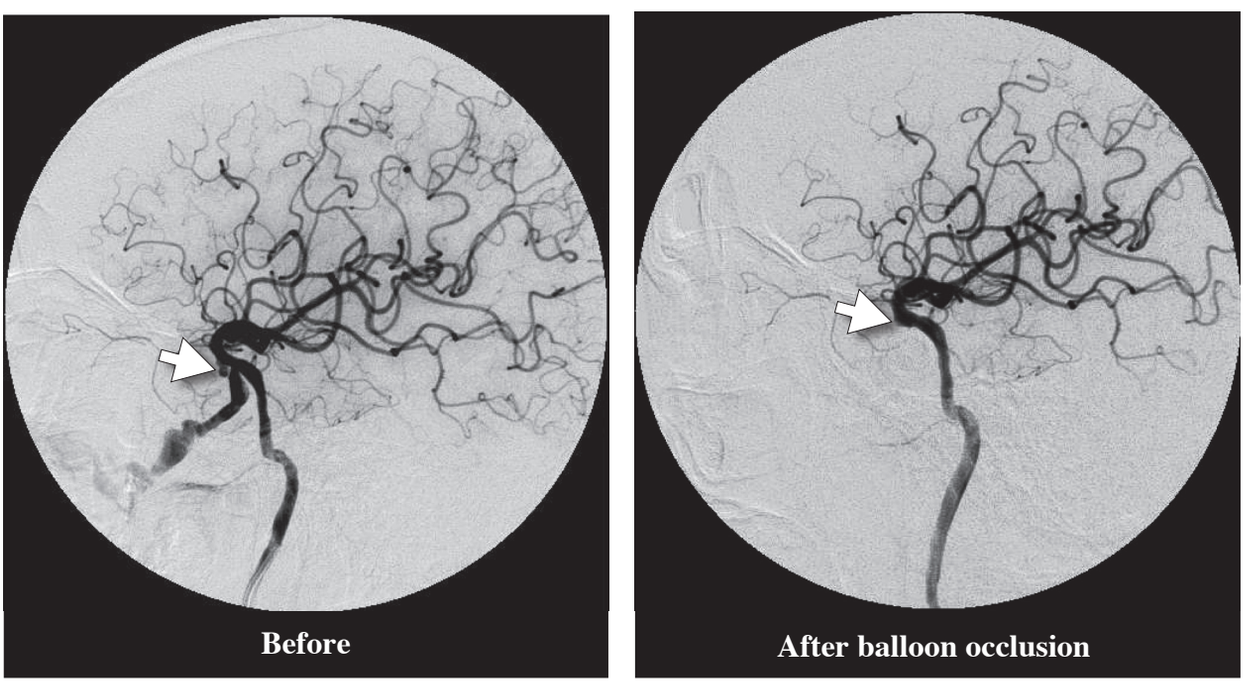

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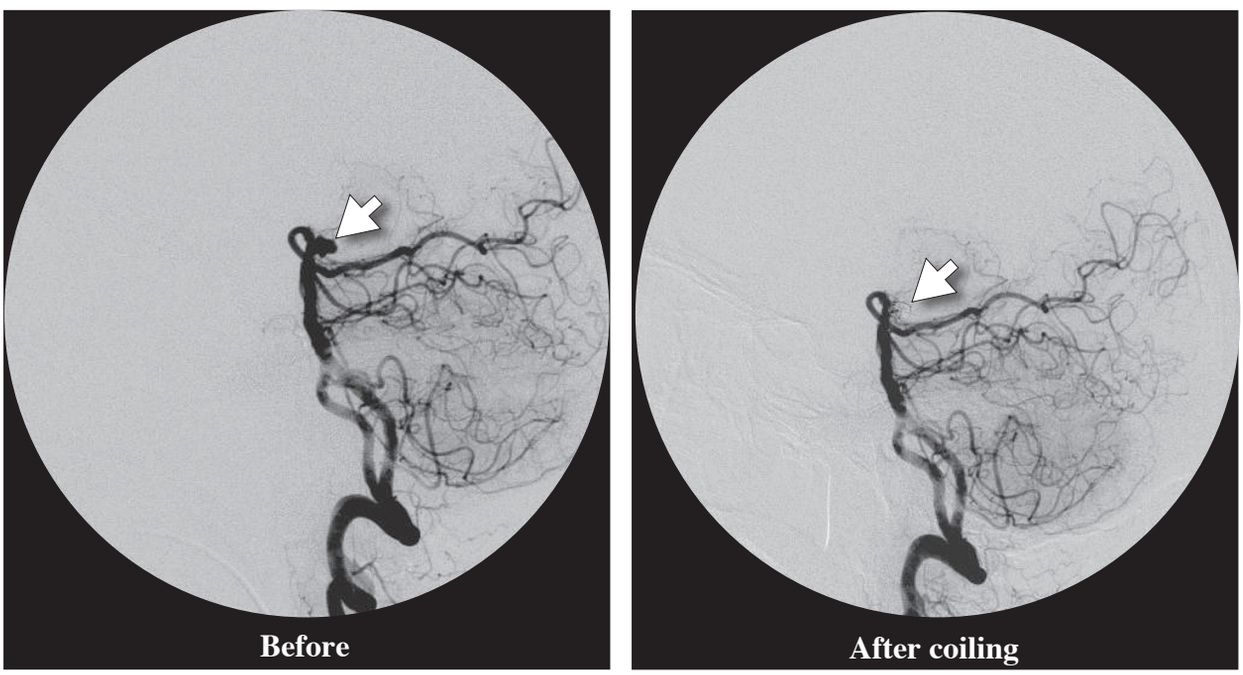

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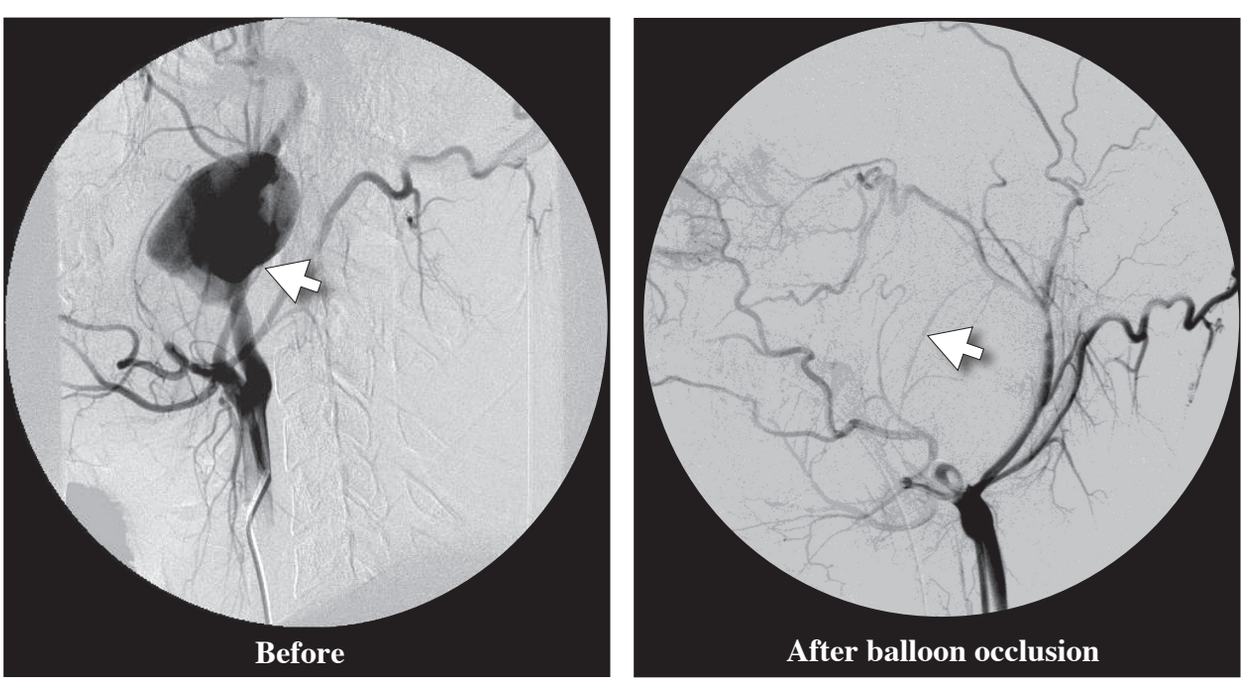

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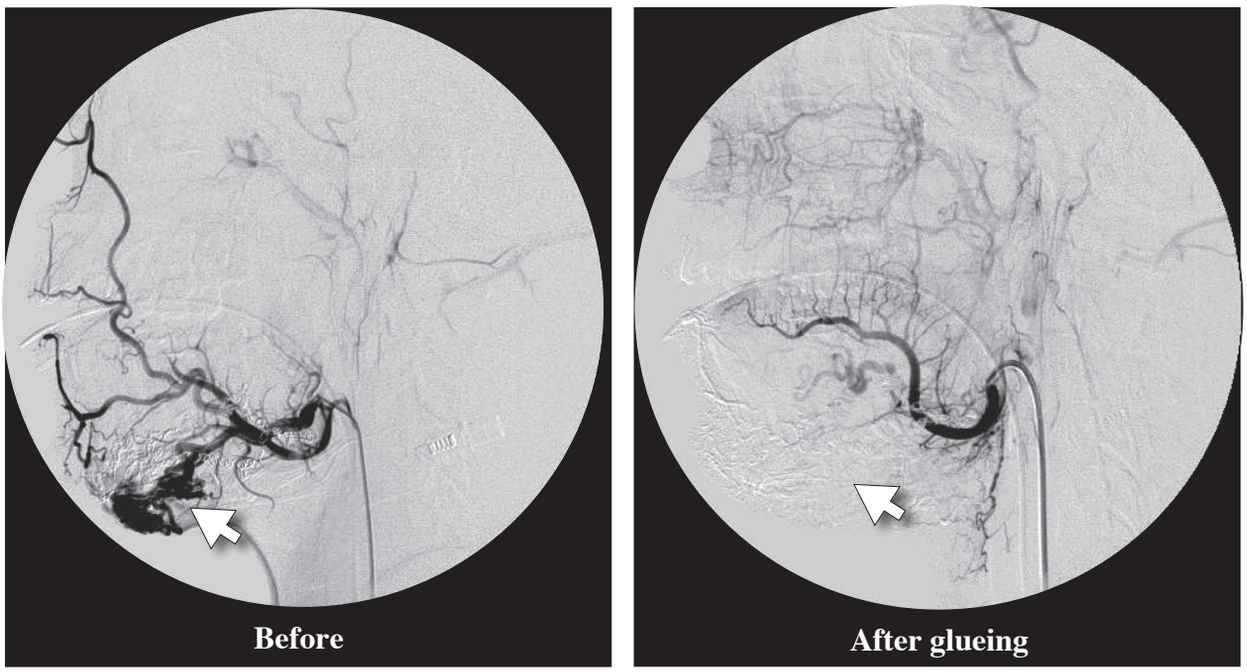

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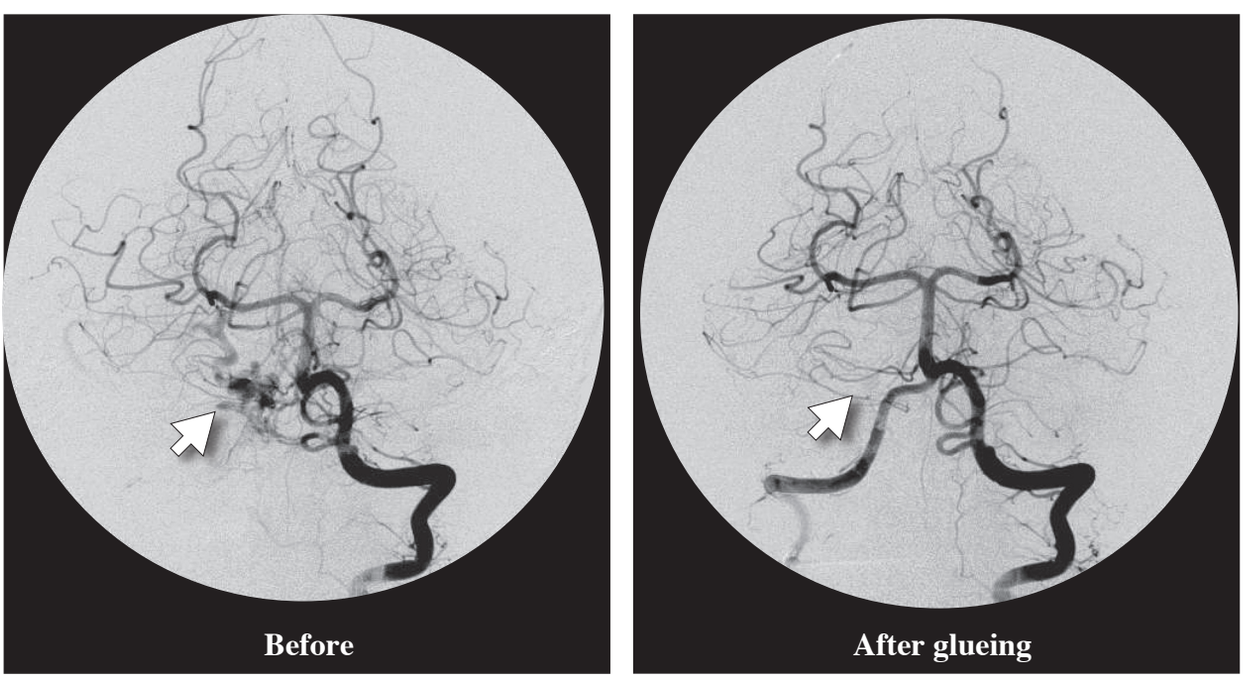

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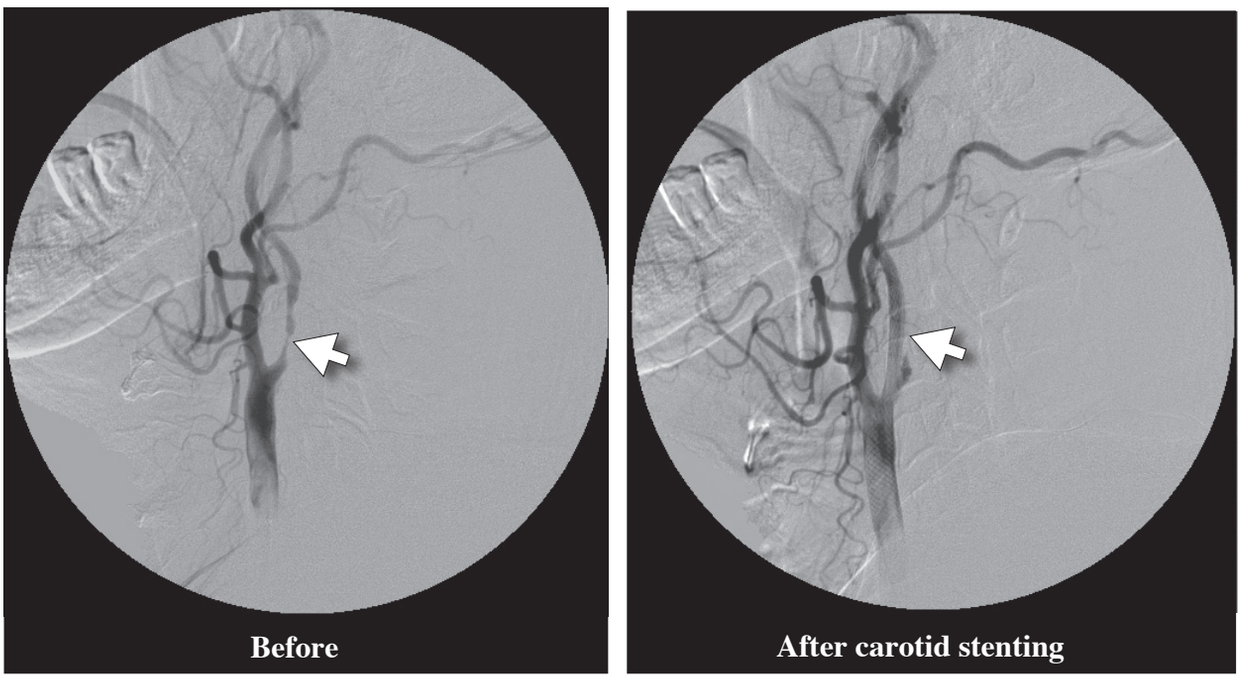

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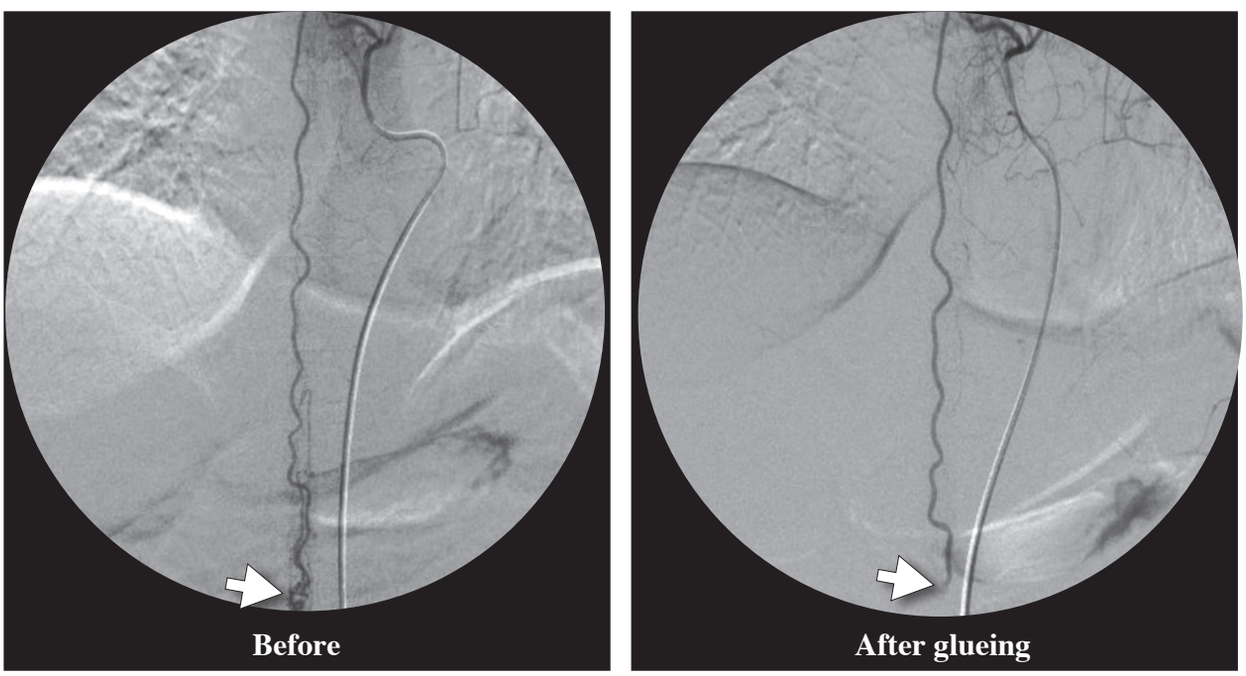

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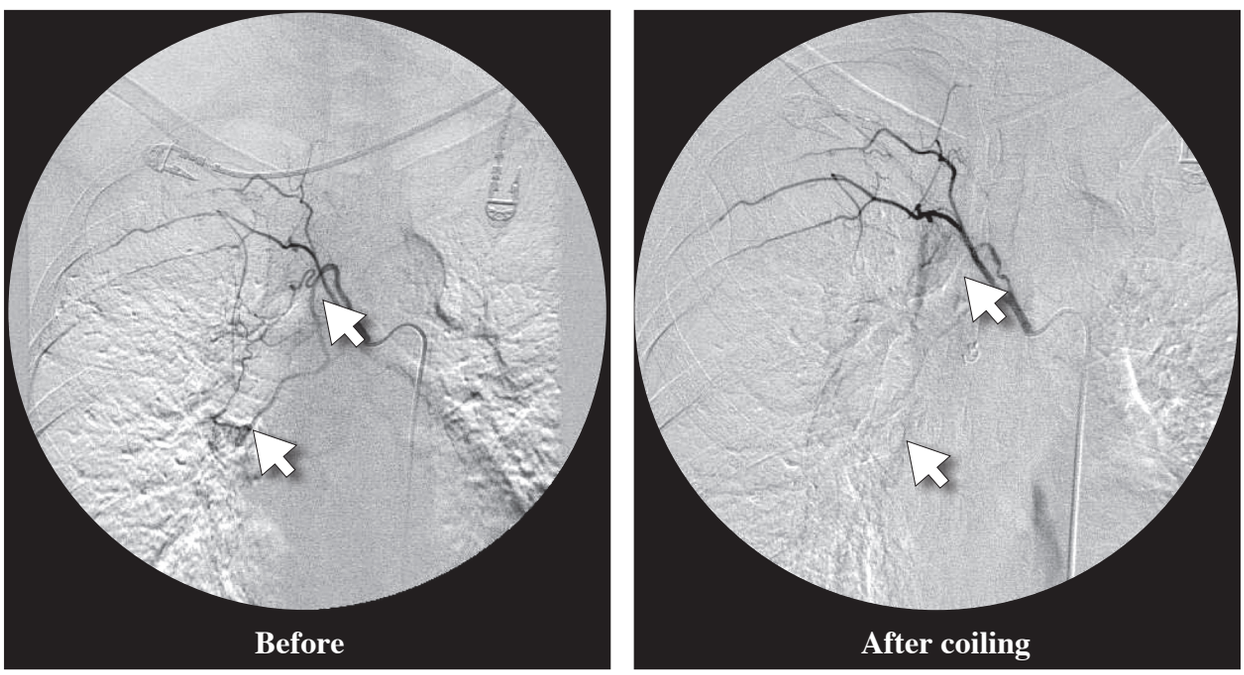

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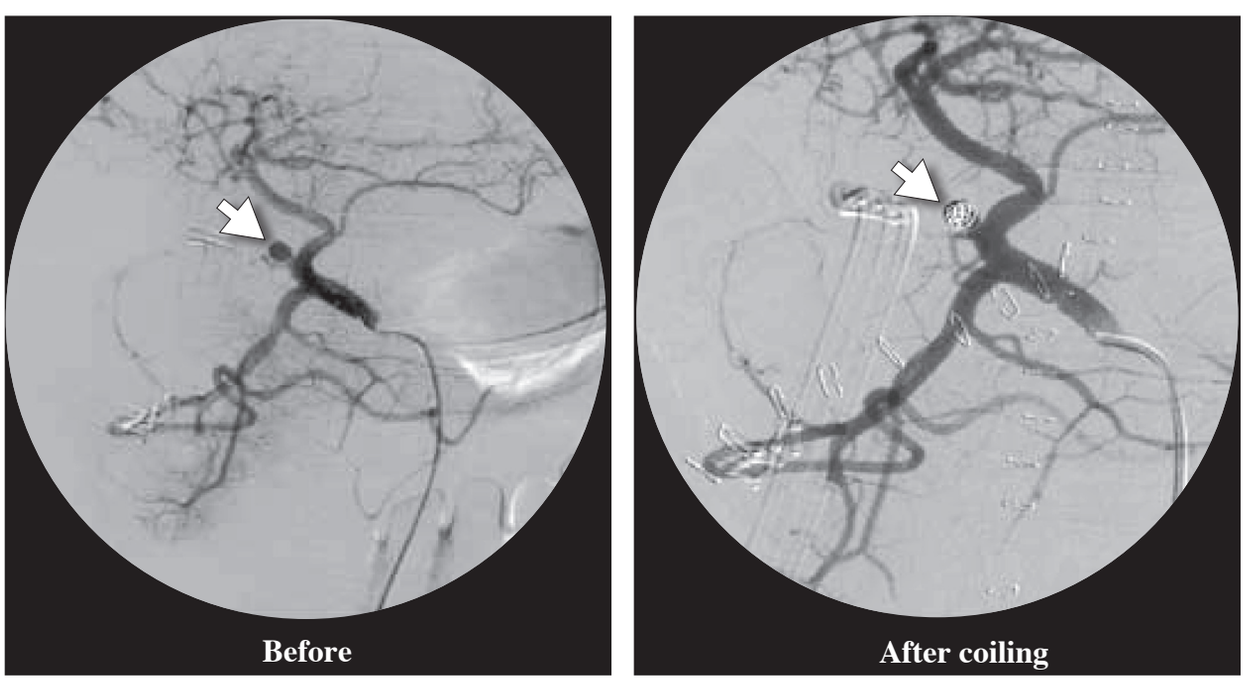

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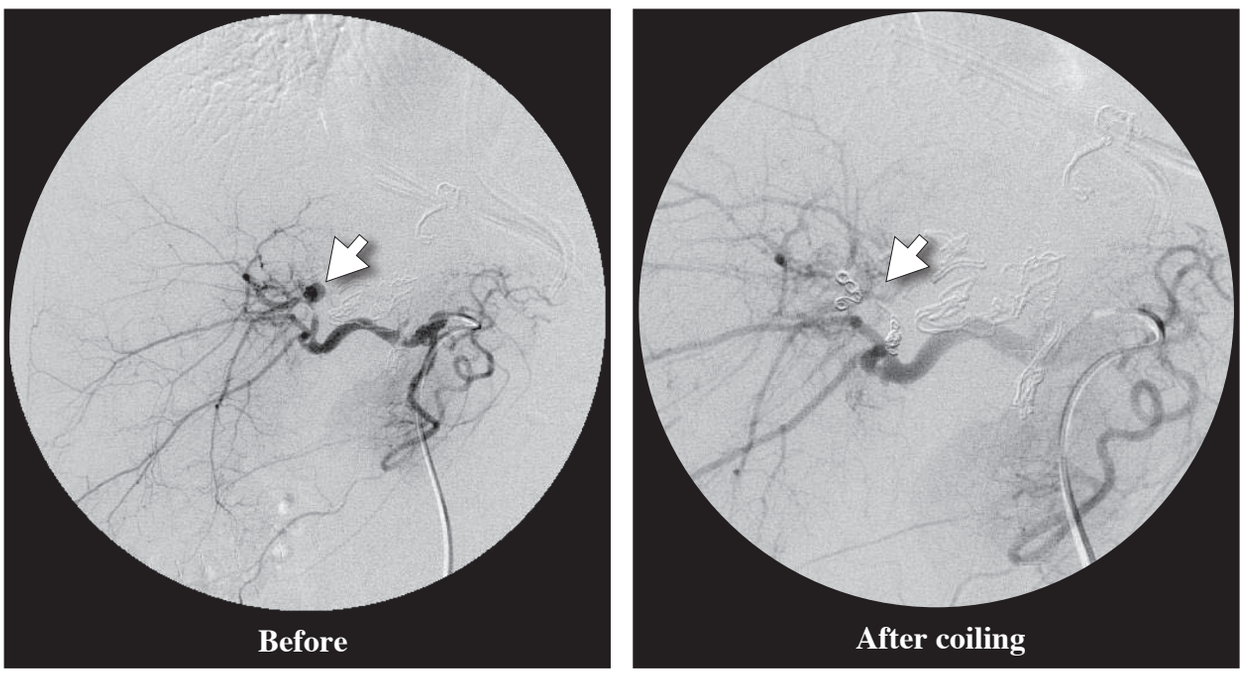

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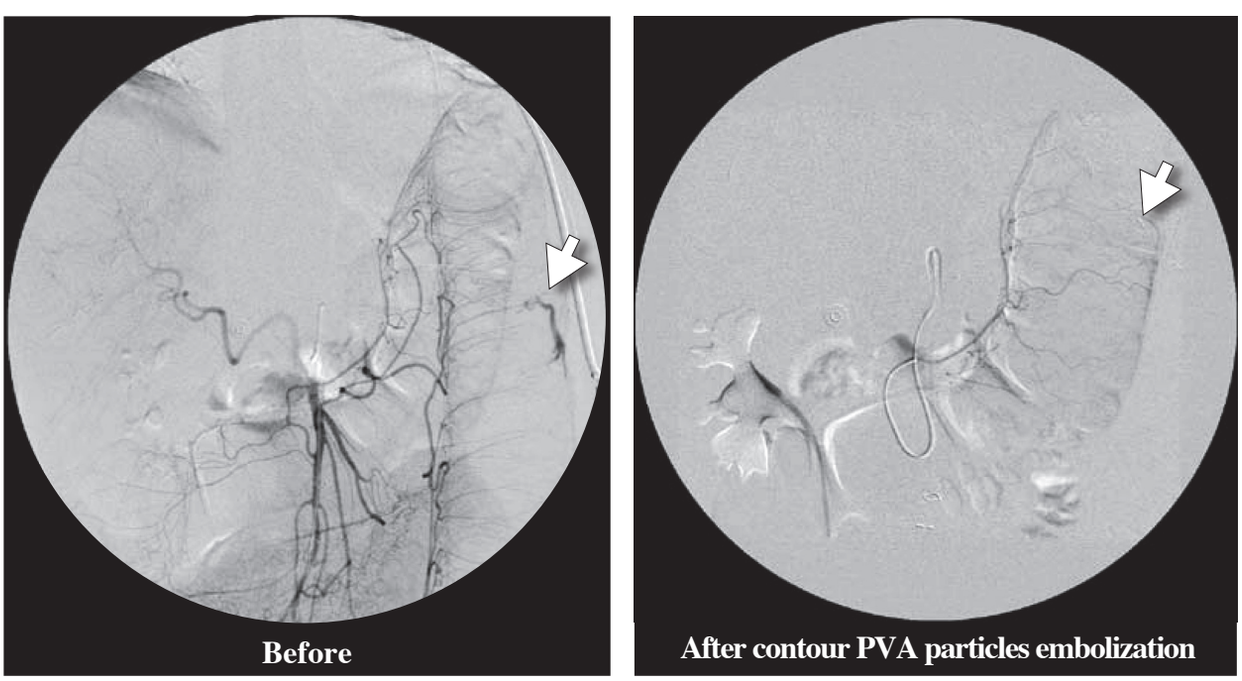

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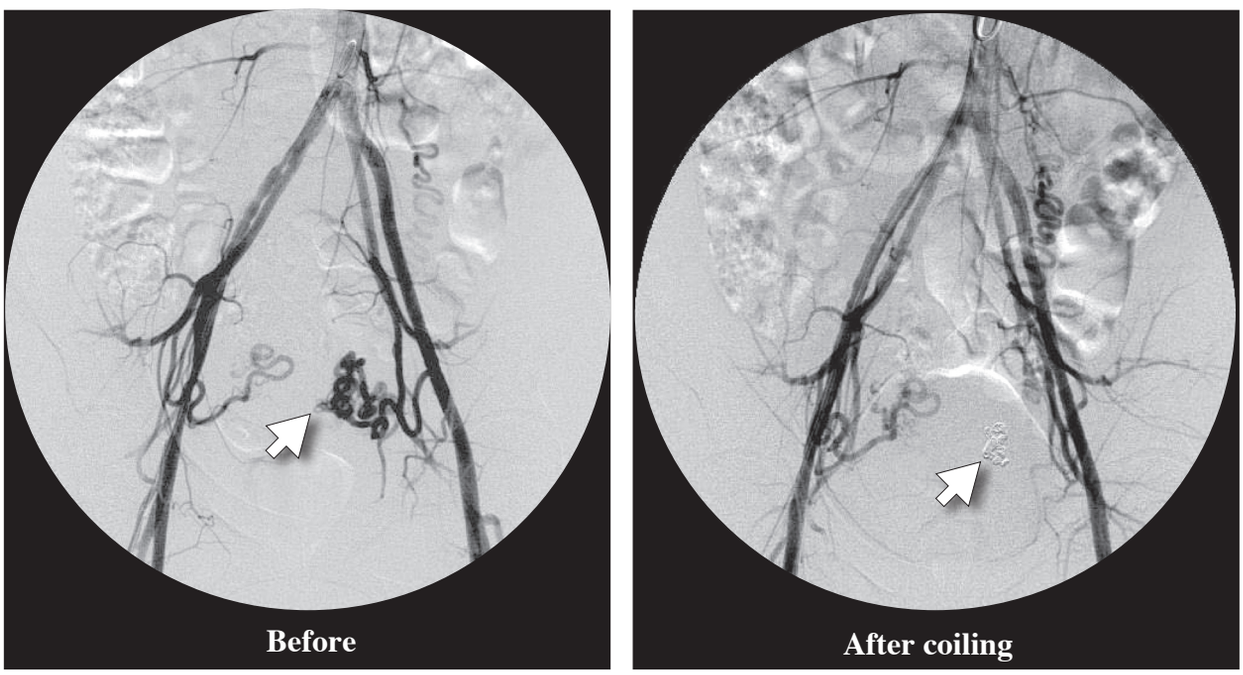

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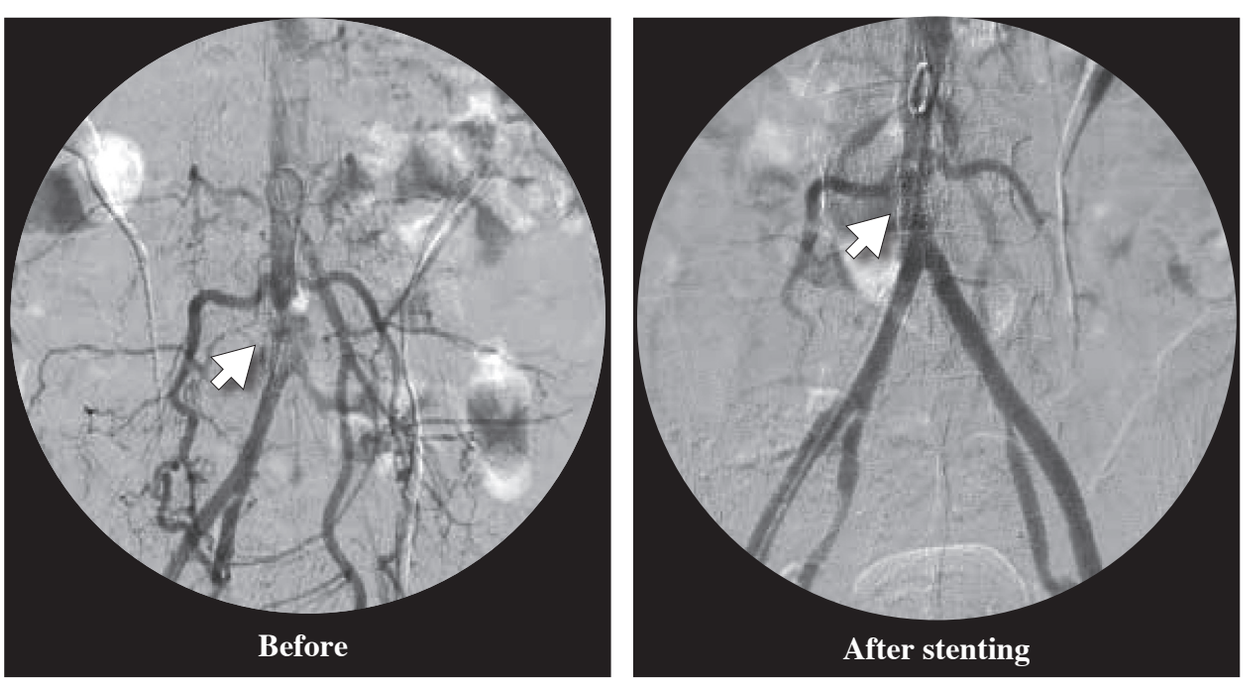

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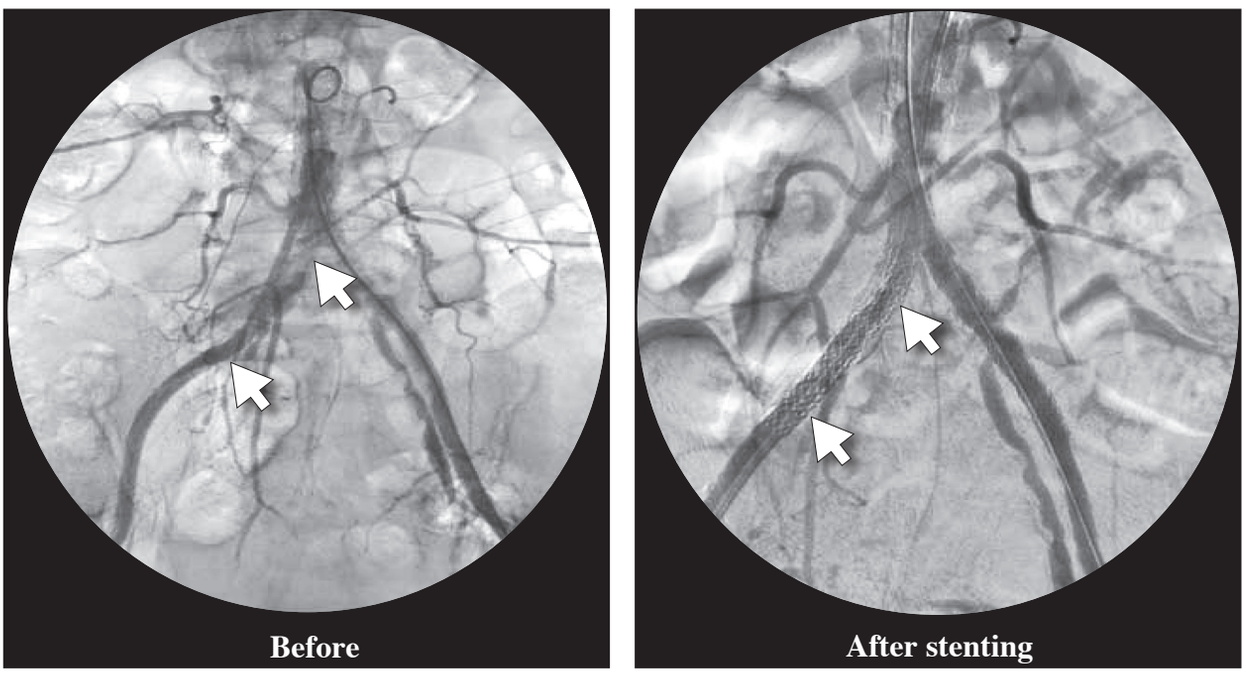

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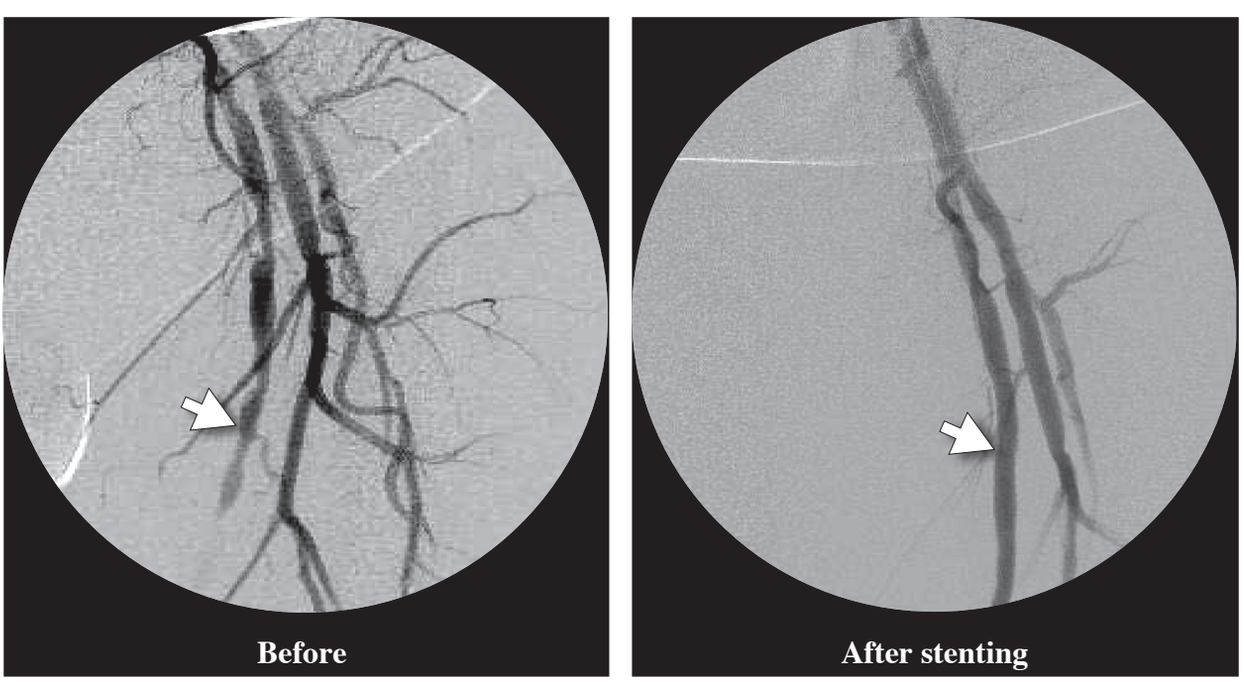


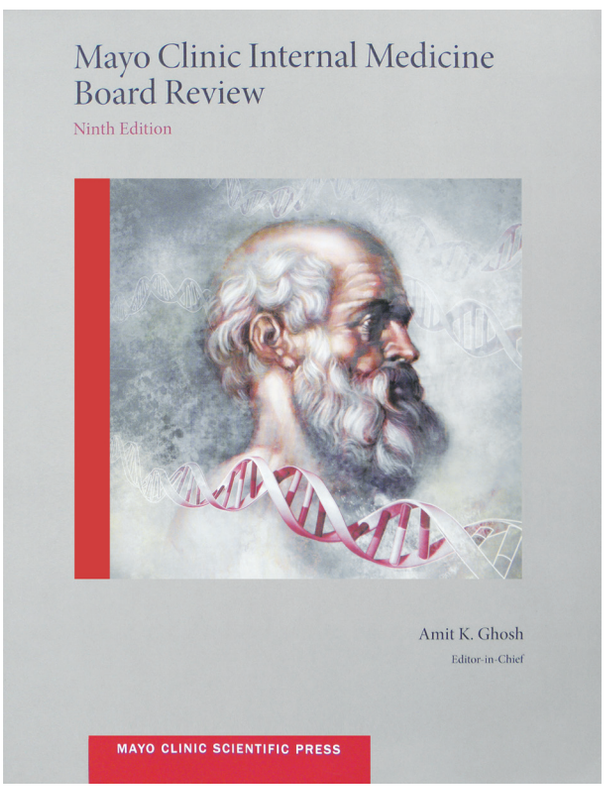
Mayo Clinic Internal Medicine Board Review, 9th Edition 2010

Amit K. Ghosh, MD: College of Medicine, Mayo Clinic, New York.

Publisher: Oxford University Press, Inc.,

Reviewer: Sonchai Hiranniramol, MD[1]

[1] Intensive Care Unit, Bangkok Hospital, Bangkok Hospiatl Group, Bangkok, Thailand.



The Mayo Clinic has once again revised its time-honored, *"Mayo Clinic Internal Medicine Board Review"*. Since its first publication in 1994, it has been used as a course syllabus for the popular Mayo Clinic Board review course. It is also a book that is frequently used by Internal Medicine third year residents as an overall review for preparation for the American Board of Internal Medicine (ABIM) examination. However, other medical students, family medicine residents, or any physician who wants to have a broad knowledge of Internal Medicine would benefit from it. The practicing internists or doctors with subspecialties in Internal Medicine will find this book particularly useful; it helps keep one up to date with general internal medicine concepts.

This ninth edition was published in 2010. As all internists would expect, it contains updates in Clinical medicine pertinent to the ABIM Certification examination. There are 26 chapters starting from the introduction to Board examination. Then a chapter for each specific organ systems and certain subjects emphasized by the ABIM, such as Critical Care medicine, Men's health or Geriatrics receive a chapter of their own. This edition also includes up to date pharmacy reviews that detail current information about medications in each subspecialty.

The special characteristic of this book is that it provides extensive knowledge about Internal Medicine, in a format that particularly facilitates the reader's retention of information. The chapters have been revised to include new treatment guidelines, evidence based recommendations and recent advances in medicine. What I find very helpful is the bullet points, which remind the readers of the important issues for each topic. Practicing internists who are short on time may use it the opposite way; reading the bullet points as a quick reference and returning to absorb the details in more leisure later. Those who prefer to learn by challenging themselves first before acquiring the information may do so since there are self assessment questions at the end of each chapter. Overall, there are more than 450 questions and their answers; this allows the exam takers to evaluate themselves before reading the syllabus or practice before taking the real exam.

However, this book is unbelievably heavy, weighing 8.3 kg. To my knowledge, there is no e-book format yet. The weight of this book is a major obstacle to its usefulness. You need an extra bag and strong muscles to carry it to and from the hospital, if you want to read it often, especially when the exams are getting close. Some readers may want to rip it apart into chapters which will allow them to go light weight and read as much as they want, without incurring wrist strain. However, this is not something book lovers would want to do. Many people have also complained that the font size in this edition is too small, suggesting that the book is indeed more valuable to younger internists with better eyesight, than as a reference for mature physicians.

Despite the ways in which the book's weight make it hazardous to health, I would nevertheless rate this book an overall 9.3/10. That is, 10/10 for the knowledge all authors put in the book, 10/10 for the format that the editor made and 8/10 for the printing quality from publisher. I do believe that it is a must-read book for ABIM exam takers and should be read and assimilated cover to cover, if one wants to get a good score.

The Vejdusit Foundation's Scholarship - promoting research and development in medicine, nursing, and public health

The Vejdusit Foundation, under the Royal patronage of H.R.H. Princess Kalayaniwatana Kromluangnaradhiwasrajnagarindra, is delighted to offer THB 1,000,000 (one million Baht) for 10 scholarships, for medical research, which can be applied in the field of public health by nurses or doctors. The program's main objective is to promote medical research and magnify the research outcomes, in order to increase the knowledge of doctors and nurses and disseminate this knowledge for the benefit of public health, within the Kingdom of Thailand.

Interested candidates may submit their research proposals by hand or post to:

The Vejdusit Foundation
2. Soi Soonvijai 7, New Petchburi Road,
Huay Khwang, Bangkapi,
Bangkok 10310.

Objectives:

- To promote valuable and salutary medical research and magnify the development outcomes of such research and utilize its benefits toward the medical, nursing, and public health.
- To offer good opportunities for Thai physicians, nurses and other medical staff in order to build a worldwide reputation with their research.
- To relieve the burden on the government sector, with regard to budget allocation for research and development.

Scholarship Quota:

- Not more than 10 scholarships, under the limited budget of 1 million Baht.

Scholarship's Requirement:

- The researcher is required to submit the research proposal and appropriate documentation as herein detailed.

Research Criteria:

- The study should be an innovative research topic in the field of medicine which may include nursing or public health issues.
- The study should conform to medical theory and ethics.
- The results of the study should generate public benefit and value.
- In case the research topic had previously been in vestigated, the researcher should clarify the reason for the repetition of, or the contiguity of the proposed research to the prior study.

Applicant's Qualification:

- The scholarship is open only to Thai physicians, Thai nurses, or other Thai medical professionals.
- There is no limitation of gender and age.
- The applicant(s) may apply individually or collectively.

Research Duration:

- Each project should be completed within one year.

Registration Time Frame:

- Application submission: 1st September 2011 to 15th December 2011.
- Result announcement: 15th January 2012.
- Granting of the scholarship: 15th Febuary 2012.

Guidelines for submission of Research Proposal:

Research Proposal should contain the following:

1. Name of the study in both Thai and English
2. Name and surname of the project leader, and his/her qualifications, affiliations, contract address, telephone and facsimile number(s), email. (In case of collective research, the researchers need to provide all contact details, as aforementioned, for all members).
   - Researchers should also provide their curriculumvitae, and 5 examples of their latest research (if any).
3. The principle of the study.
4. The objectives of the study.
5. Research methodology.
6. Project duration.
7. Action plan.
8. Research location or plan for data collection.
9. Necessary Equipment & instruments to be used in the study.
10. Budgeting plan, classified into groups.
11. The expected outcome or the value of the study.
12. Research reference(s).
13. Other explanations (if any)
14. The signature of the project leader including the certified letter from their supervisor, and signature of all co-researchers.
15. In case the research is studying on human, the informed consent forms of the volunteers or patients who join the study is required.

Previous Scholarship Winners:

Project Study in 2011

Project	Researcher
1] Prevalence survey, health risk behavior of helminthic infections and implement the control of parasites to school children by their creation and participation at Hui-Tom school, Li District, Lumphun Province Thailand.	*Teera Kusolsuk, MD* Department of Helminthology, Mahidol University, Bangkok, Thailand.
2] A descriptive study of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.	*Somporn Srifuengfung, PhD* Department of Microbiology, Siriraj Hospital, Bangkok, Thailand.
3] Development of Exercise Model Using Wand Stick with Modified Nan Mong Serng Dance for Older Adults.	*Kattika Thanakwang, PhD* Nursing Unit, Pua Crown Prince Hospital. Nan, Thailand.
4] Effect of Torvoside on cholesterol synthesis in "HepG2 cells."	*Anong Kitjareontharm* Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
5] Cervical cancer prevention by HPV vaccination: Predictor of vaccine acceptability among young adult woman in upper Northern Thailand.	*Dr. Phanida Juntasopeepun, PhD* Faculty of Nursing, Chiang Mai University, Chiang Mai, Thailand.
6] Detection and characterization of genes encoding betalactamase in final effluents of a hospital wastewater treatment plant.	*Pornphan Diraphat, PhD* Department of Microbiology, Mahidol University, Bangkok, Thailand.
7] Effects of Acute Ethanol Exposure on K+Current of Human Coronary Artery Endothelial Cells.	*Wattana Watanapa, MD, PhD* Department of Physiology, Mahidol University, Bangkok, Thailand.
8] Effects of sFlt-1on Potassium Channels of Human Umbilical vein Endothelial cells.	*Wattana Watanapa, MD, PhD* Department of Physiology, Mahidol University, Bangkok, Thailand.

Project Study in 2010

Project	Researcher
1] The study of the immunostimulation on Purified Vero-Cell Rabies Vaccine (PVRV) by administering 4-site intraderma method at 0.1 ml per intradermal injection site (one time) to the volunteers who had ever applied pre-exposure vaccine regimen (intrademal dose, 0.1 ml, one time) 8 years ago.	*Pakamatz Khawplod, PhD* *Somchai Tangsupachai, MD* *Pongpisanu Srithammanusarn* *Atikaya Sawangwaree* Queen Saovabha Memmorial Institute, The Thai Red Cross Society, Bangkok, Thailand.
2] Phase I-II clinical trial of therapeutic angiogenesis for diffuse coronary artery disease by sustained release of basic fibroblast growth factor gelatin hydrogel.	*Permyos Ruengsakulrach, MD, PhD* *Masashi Komeda, MD, PhD* *Yasuhiko Tabata, PhD* *Masaya Tabata, PhD* Bangkok Heart Hospital, Bangkok, Thailand.
3] The comparative study between radial artery graftand internal artery graft on coronary artery bypass surgery (CABG).	*Permyos Ruengsakulrach, MD, PhD* *Vibul Jotisakulratana, MD* *Chockchai Suwankitborihan, MD* *Pivapan Pamornsing, MD* *Chayanin Vatcharasiritham, MD* *Montip Tiensuwan, PhD* Bangkok Heart Hospital, Bangkok, Thailand.
4] Effects of the smoking cessation program on smoking cessation behavior in patients admitted to hospital for open heart surgery.	*Pannee Kaewduang* *Sucheela Ungtrakul* *Sasikorn Pimjaisai* *Tadsanewan Gantagad* Central Chest Institute of Thailand, Bangkok, Thailand.
5] The role of cytokine signaling (SOCS) in the immuno-pathogenesis of Dengue Hemorrhagic Fever.	*Natthanej Luplertlop, MD* *Pannamas Maneekan* *Soontri Saengmukdanum* Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
6] Exploring Transcriptional factor-Nuclear factor kappa B (NF-KB) as a prognostic factor in developing acute renal failure in Plasmodium falciparum patients.	*Parnpen Viriyavejakul, MD, PhD* *Urai Chaisri, PhD* *Chuchard Punsawad* Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Project Study in 2009

Project	Researcher
1] Serial ultrasonography for Early Detection of Plasma Leakage in Dengue Hemorrhagic Fever.	*Kanokwan Sriraksa, MD* Pediatric Unit, Khon Kaen Hospital, Khon Kaen, Thailand.
2] A Cohort of breastfeed preterm infants to evaluate for iron deficiency anemia and growth.	*Sopapan Ngerncham, MD, PhD* Department of Pediatric, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
3] A study of using family counseling program adaptation of schizophrenic patients. Amphawa district, Samutsongkram province.	*Siripan Puangkaew* Bang Chang Health Station, Samutsongkram, Thailand.
4] Effect of pre-germinated brown brown rice extracts with enhanced levels of GABA on anti-apoptotic activity in neuonal cell culture.	*Rungtip Soiampornkul, PhD* Department of Biochemistry, Siriraj Hospital, Mahidol University, Thailand.
5] Microtensile bond strength of surface treated fiber post bonded to root canal dentin.	*Wisit Piyawattanathavorn, DDS* Burriram Public Health Office, Burriram, Thailand.
6] Factors Influencing mental health and behavior problems of adolescents who have lived under unrested situation in three border provinces in southern Thailand.	*Muslin Tohkani* Faculty of Nursing, Princess of Naradhiwas University, Naradhiwas, Thailand.
7] The development of the community cooperation for health promotion in piscatorial community.	*Chutarat Sathirapanya, MD* Health and Sports Science, Thaksin University, Songkla, Thailand.
8] Nursing ethic committee: Opinion of nurse administrators and staff nurses in university hospital-college of medicine.	*Kosoom Mookhajornphan* Department of Nursing, Songklanagarind Hospital, Songkla, Thailand.
9] Detection and identification of Mycobacterium tuberculosis and non Mycobacterium tuberculous Mycobacteria by polymerase chain reaction-restriction enzyme analysis.	*Sirilak Teeraputon* Faculty of Allied Health Sciences, Naresuan University, Phitsanulok, Thailand.

Project Study in 2008

Project	Researcher
1] Prevalence of coronary artery calcium on hemodialysis and Sodium Thiosulfate Therapy patient.	*Sinee Disthabanchong, MD, PhD* Division of Kidney, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.
2] The study of cancerous neoplasm on osteosacroma for indicating the biomarker.	*Suradej Hongeng, MD, PhD* Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.
3] Development of a strip test for the detection of rabies virus.	*Songsri Kasempimolporn, PhD* Division of Research & Development, Queen Saovabha Memmorial Institute, The Thai Red Cross Society, Bangkok, Thailand.
4] Development of Thalassemia diagnosis by Melt Curve.	*M.L. Saovaros Svasti, PhD* Institute of Science and Technology for Research and Development, Mahidol University, Bangkok, Thailand.
5] School Violence Problem among adolescents in Bangkok Metropolitan.	*Rooja Phuphabool, PhD* Department of Nursing, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Project Study in 2007

Project	Researcher
1] Who benefits from the roll out of national antiretroviral therapy program in Thailand?	*Thammasorn Piriyasupong, MD* Khon Kaen Hospital, Khon Kaen, Thailand.
2] Diagnostic performance of Squat test for mensical injured detection compare to arthroscopic examination in knee injured patients.	*Pakorn Narakol, MD* Khon Kaen Hospital, Khon Kaen, Thailand.
3] The method of tracking and evaluating the child nutrition in the community: The benefits of child growth charts.	*Penpak Sornchai, MD* Nakornping Hospital, Chiengmai, Thailand.
4] The involvement of collagen-binding integrin on MMP-2 activation mechanism in type I collagen stimulation in.	*Kulrut Borrirukwanit* Phetchabun Hospital, Phetchabun, Thailand.

Project Study in 2005-2006

Project	Researcher
1] Relationship between the level of omega-3 fatty acids in cardiac tissues and the cardiac mortality in Thai cadavers.	*Nipon Chattipakorn, MD, PhD* Chiangmai University, Chiengmai, Thailand.
2] Proteomic analysis of Altered Proteins in Distal Renal Tubular Cells during Potassium Depletion: Implication to Hypokalemic Nephropathy.	*Visit Thongboonkerd, MD* Mahidol University, Bangkok, Thailand.
3] Association between genetic polymorphism of b-cell differentiation and Insulin sensitivity and ß-cell dysfunction in childhood acute lymphoblastic leukemia.	*Suradej Hongeng, MD, PhD* Ramathibodi Hospital, Bangkok, Thailand.
4] Antimicrobial susceptibility of streptococcus pneumonia and preliminary epidemiological study by penicillin binding protein genotyping.	*Somporn Srifuengfung, PhD* Mahidol University, Bangkok, Thailand.

Project Study in 2004

Project	Researcher
1] Study the membrane protein antigen of Leptspira that react with patient serum of Leptospirosis.	*Thareerat Kalambaheti, PhD* Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
2] The prognosis on the Hepatpcellular carcinoma by measuring the vascular endothelial growth factor (VEGF) in the serum of patients who had been applied Transcatheter arterial chemoembolization (TACE) treatment.	*Kawin Keekawat, MD* Rajavithi Hospital, Bangkok, Thailand.
3] Correlation between the complete blood coun- coagulogram, fibrinogen and D-dimer with the clinical severity of dengue infection in Thai children.	*Panya Seksarn, PhD* Chulalongkorn University, Bangkok, Thailand.
4] Development of diagnostic kit for hamatotoxic snake venom.	*Narumol Pakmanee* R&D Department, Queen Saovabha Memmorial Institute, Thai Red Cross, Bangkok, Thailand.
5] Development of Specific immunoassay for diagnosis and follow up of lymphatic Filariasis.	*Surang Nuchprayoon, MD, PhD* Chulalongkorn University, Bangkok, Thailand.
6] Value of the abdominal ultrasound screening in check-up program.	*Kaewalin Rungsinapron, MD* Bangkok Hospital, Bangkok, Thailand.
7] Comparative Study of Direct-Measured and Calculated LDL in Clinical Use.	*Surachai Roongtanapirom, MD* Bangkok Hospital, Bangkok, Thailand.
8] Improve catheter related bloodstream infection in Bangkok Hospital.	*Paithoon Boonma, MD* Bangkok Hospital, Bangkok, Thailand.

Project Study in 2003

Project	Researcher
1] The evaluation of obstructive sleep apnea therapy	*Somsak Wankijcharoen, MD* Bangkok Hospital, Bangkok, Thailand.
2] The determination of Photon-Electron radiation exposure of the skin cancer on the head.	*Chawalit Lertbutsayanukul, MD* Chulalongkorn University, Bangkok, Thailand.
3] The study of antibody of the angiostrongylus cantonensis in the serum by Dot-blot ELISA methodon the eosinophilic meningoencephalitis patients.	*Kanchana Tomanakan* Khon Kaen Hospital, Khon Kaen, Thailand.
4] The study of antioxidant activities in Thai traditional herbals.	*Klai-Upsorn Pongrapeeporn, PhD* Mahidol University, Bangkok, Thailand.

Project Study in 2002

Project	Researcher
1] The comparative study of the effectiveness and efficiency between Intensive Phototherapy and Conventional Phototherapy in the treatment of neonatal hyperbilirubinemia in newborn.	*Santi Punnahitanonda, MD* Chulalongkorn University, Bangkok, Thailand.
2] The study of cardiac function in healthy newborns and Hydrops Fetalis.	*Vachara Jamjureeruk, MD* Bangkok Hospital, Bangkok, Thailand.
3] The role of the antioxidant therapy in the treatment of oxidative stress on the thalassemia patient who has contributed iron overload from blood transfusion.	*Piyaratana Tosukhowong, PhD* Chulalongkorn University, Bangkok, Thailand.
4] The effects of human immune response on the different rabies vaccination programs.	*Pakamatz Khawplod, PhD* Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand.

In Memorial - Dr. Kitipan Visudharom

Dr. Kitipan Visudharom can be best described as a dedicated and untiring cardiovascular surgeon, scientist, humanitarian, advisor, teacher, and innovator, who truly loved releasing his patients from their suffering. He passed away on Sunday 30th May, 2010 at Bangkok Hospital, Bangkok, Thailand after a 20 month battle with pancreatic cancer. He was 72 years old.

He was born on 28th May, 1939 in Thailand. His father, Mr. Kong Visudharom, was a director-general of the Department of Physical Education of Thailand and a pioneer of the worldwide scout movement in Thailand.

Dr. Kitipan started his elementary education at Rajini Elementary School - a place where he started learning embroidery, decorating the edges of a handkerchief with lovely stitching. The apparently insignificant needlework of that 10 year old boy can be seen in a different, almost miraculous light, when we consider what he was destined to become, a successful cardiothoracic surgeon.

The primary medical education of Dr. Kitipan began at Siriraj Medical School, Bangkok. With the fervent desire to achieve the Doctor of Philosophy degree, he decided to do his internship at the University of Kentucky and completed residencies in General Surgery and Cardiovascular Surgery at the University of Minnesota. After 10 years in the United States of America, he accomplished not only his PhD in surgery from the University of Minnesota but also became a Diplomate of the American Board of Surgery and the American Board of Thoracic Surgery. Up until now, he was the first and only Thai doctor to have achieved a doctoral degree in thoracic surgery from the United States. During his long stay in the U.S, Dr. Kitipan Visudharom decided to shorten his name to Dr. Kit Arom. *"No one could pronounce it otherwise"*, was his wry comment on this decision.

In 1964, Dr. Kit began his medical career in Minnesota. Following his tenure at the University of Minnesota, he went to the University of Texas Health Sciences Center in San Antonio and helped develop a strong Thoracic Surgery Residency Program. In 1979, he returned to Minnesota. During this time, he was the Chair of Cardiothoracic Surgery and a co-founder of the Minneapolis Heart Institute, Chair of Cardiovascular Surgery at United Hospital, Chair of Cardiovascular Surgery at St. Joseph's Hospital Health East Care System and Head of Cardiovascular Surgery at the John Nasseff Heart Hospital. This made him the busiest heart surgeon in the state of Minnesota. A prime recognition of his dedication was being the recipient of the Humanitarian Award, the public acknowledgement that Minnesota City bestows on people who have contributed valuable benefits to Minnesota City.

The primary factor that influenced Dr. Kitipan's return to Thailand was to join the *"72 heart valves replacement program"* that was dedicated to honoring the 72nd birthday of His Majesty King Bhumibol Adulyadej. Bangkok Hospital sponsored all medical expenses incurred for the treatment of selected outreach patients who lived in rural areas and suffered from valvular heart disease. Dr. Prasert Prasartthong-Osoth, his former medical student and Senior Resident at Siriraj Medical School, invited him to join Bangkok Hospital, with the intention that Dr. Kit would help develop the heart clinic to become a premier hospital dedicated to curing heart disease.

Finally, in the year 2000, he returned to Bangkok and established the Bangkok Heart Hospital, which is the first specialized heart hospital in Thailand. He was appointed as the Chief Cardiothoracic Surgeon, Cardiothoracic Director, and worked as Hospital Director of Bangkok Heart Hospital until the end of his life. He also served on several boards and took various leadership positions in Bangkok Hospital and Thailand.

With an impressive work ethic that showed him consistently demonstrating his best efforts, Dr. Kitipan helped turn Bangkok Heart Hospital into an institute of advanced technology and innovative techniques for relieving patients from heart disease. Bangkok Heart Hospital's innovations include the minimally invasive cardiac surgery technique which reduces pain in patients having heart valve replacement, the bypass surgery with off pump technique, da Vinci Robotic Surgery and stem cell technique which treated end-state heart failure patients. More than 150 patients were given stem cell treatments, the results of which have been presented to over 25 scientific conferences including prestigious surgical conferences in USA and Europe such as The American Heart Association, The American Association for Thoracic Surgery (AATS), The Society of Thoracic Surgeons (STS), USA and The European Association for Cardio-Thoracic Surgery (EACTS). Moreover, Dr. Kitipan led the Bangkok Heart Hospital to be accredited by the Joint Commission International's Disease-Specific Care Certification Program for BHH's Acute Coronary Syndrome and Heart Failure Program. In addition, he also extended his attention towards charity.

He created a health project for Buddhist monks, which included outdoor health education, a mobile check up service, and cardiovascular risk calculation for 585 monks from 40 temples in Bangkok.

Dr. Kitipan was known and loved for his outstanding ability, his affability and tireless work ethic by friends and colleagues from all over the world during his years of practice and work. The satisfaction and enjoyment of his life was enhanced by his beloved family. He was married to Khunying Sumonda Veravaidhaya and had two sons, Mr. Kan Mach Visudharom and Mr. Dan Monte Visudharom. His family also rejoiced in the 3 sweet grandchildren, Luke Kit Visudh Arom, Ava Pimalai Visudh Arom, and Olivia Juil Visudh Arom.

Dr. Kitipan truly enjoyed American football, especially the Vikings team from Minnesota. He also loved music, traveling, Joan Miro paintings, and cars. Collecting exotic cars was his favorite hobby; he was extremely fascinated with speed. Despite cars bringing much happiness to him and his family, they were also the cause of grievous sorrow, since his father, mother, and cousin died in a car accident. This painful misery was repeated, when his son, Mr. Kan Mach Visudharom, also died in Rwanda.

Dr. Kitipan is sincerely mourned, and his loss is regretted by all his family members, friends, patients and colleagues in Bangkok Hospital, and other medical organizations with which he was associated. Everyone however, takes great comfort in remembering the valuable contributions he made in the cardiology field during his lifetime, both in his home country and abroad. His memory remains an inspiring example for the next generation of Cardiothoracic surgeons and specialists at Bangkok Heart Hospital.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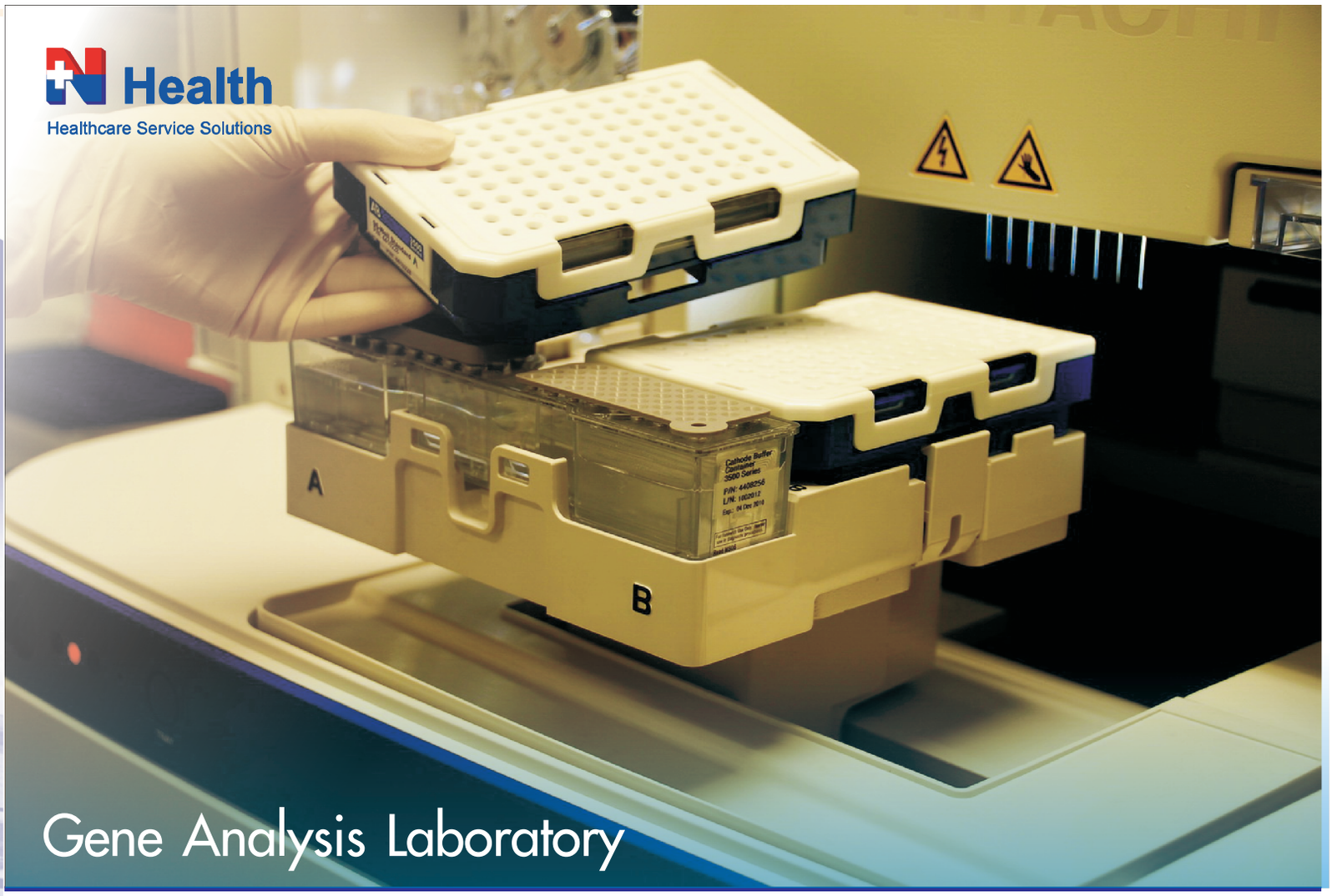
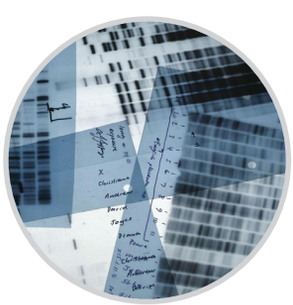
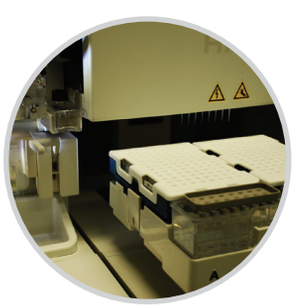


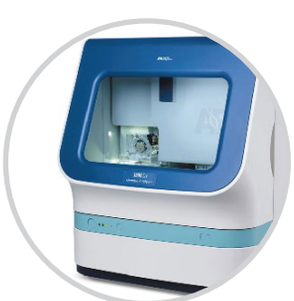
Gene Analysis Laboratory

Gene Sequencing

Gene Sequencing is a process in which the individual base nucleotides (DNA are characterized) in genome. The process can be used to identify genetic variations across multiple individuals, investigate specific area of interest and concern to analyze drug responsiveness. It is also supported to targeted therapy drugs consideration in malignant patients such as *K-RAS gene mutation testing** for Colorectal cancer patients or *EGFR gene mutation testing** for non-small cells Lung cancer patients. N Health Healthcare Advanced Diagnostics is the first private laboratory who provides testing for K-RAS gene mutation and EGFR gene mutation by using Gene Sequencing Technique.







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