

A study on dynamic monitoring, components, and risk factors of embolism during total knee arthroplasty

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Abstract

Background: Fat embolism is a common complication of orthopedic surgery. However, the exact component and risk factor responsible for this complication remains unelucidated. This study aimed to detect the origin of the pulmonary embolus and identify relevant risk factors of pulmonary embolism in total knee replacement.

Methods: A total of 40 osteoarthritis patients who underwent primary unilateral TKA were recruited into this study. Transesophageal echocardiography (TEE) was utilized to dynamically monitor the embolism. Pulmonary arterial pressure was recorded and biopsies were obtained from the medullary cavity during surgery.

Results: After tourniquet release, the arterial embolism was observed by TEE to have a peak signal at 30 seconds when pulmonary arterial pressure was increased by 25% to 40% ($P = .002$). The pathology study of the embolism revealed its bone marrow origin. Total embolus quantity was positively correlated with age ($P = .021$), body mass index (BMI, $P = .041$), and fat content of the bone marrow ($P = .003$). Logistic regression analysis revealed that the fat content of the marrow (OR: 1.432, 95% CI: 1.335–1.592), age (OR: 1.632, 95% CI: 1.445–1.832), and BMI (OR: 1.231, 95% CI: 1.032–1.381) were risk factors for pulmonary hypertension.

Conclusion: This study revealed that the embolus detected in the right atrium was derived from bone marrow tissues, and this led to pulmonary arterial pressure fluctuations after tourniquet release. Therefore, elderly patients who have high BMI or bone marrow fat content are at high-risk for pulmonary fat embolism during TKA.

Abbreviations: BMI = body mass index, FES = fat embolism syndrome, HR = heart rate, MAP = mean arterial pressure, PE = pulmonary embolism, TEE = transesophageal echocardiography, TKA = total knee arthroplasty.

Keywords: fat embolism, pulmonary embolism, total knee arthroplasty, tourniquet, transesophageal echocardiography

1. Introduction

Total knee arthroplasty (TKA) has become an effective method for treating end-stage osteoarthritis, with a long-term survival rate exceeding 90%.^[1–3] By using pneumatic tourniquets, surgeons are able to obtain good arthroscopic vision, and ensure that the interface between the bone and cement is firm. Therefore, tourniquets have become a standard operating procedure in joint surgery.^[4] Embolism is one of the common complications of joint surgery. Previous studies revealed abnormal embolus signals in the right atrium after loosening the pneumatic tourniquet using

transesophageal echocardiography (TEE)^[5] during TKA surgery. These emboli would flow into the pulmonary circulation and cause pulmonary embolism (PE), potentially leading to fatal fat embolism syndrome (FES).^[6] The incidence of postoperative FES is approximately 1% to 30%, according to previous reports. FES usually presents as a multisystem disorder that seriously affects organs, including the lungs, brain, cardiovascular system, and skin.^[7] With regard to the components of the embolus, previous researchers have considered that these components comprised of air, condensed blood clots, or bone debris.^[5] However, the study conducted by Kato et al^[8] did not reveal any solid pathological evidence of these components in blood specimens obtained from the right atrium of TKA patients, whereas the study conducted by Kim^[9] revealed a small amount of fat balls and immature cells though pathological staining. However, no immunohistochemical staining has been performed to elucidate these findings. Therefore, the present study aimed to dynamically observe the embolus during TKA, improve the pathological technique, and explore the components and origin of the embolism by immunohistochemistry.

Previous studies on risk factors have also provided evidence that patient variables were associated with higher risk for pulmonary hypertension and embolism. Genetic polymorphism,^[10] preoperational conditions,^[11] gender and body mass index (BMI)^[12] may be potential risk factors. However, the data are scarce in the Chinese population. Therefore, the present study also aimed to investigate risk factors associated with embolus volume and pulmonary hypertension.

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2. Material and methods

2.1. Patients

Patients diagnosed with osteoarthritis and underwent primary and unilateral TKA surgery between June 2014 and June 2015 in our hospital were recruited into this study. Surgical indication was fulfilled in all participants. Patients with diabetes, hyperlipidemia, rheumatoid osteoarthritis,^[13] or other diseases that may affect lipid metabolism were excluded from the study. A total of 56 patients were initially recruited into the present study. Among these patients, 16 patients were excluded. Finally, a total of 40 patients (17 males and 23 females) were included in the final analysis. All participants provided a signed informed consent. This study was approved by the Ethics Committee of our hospital (No: 2016008).

2.2. Operative procedure

All operations were performed by the same surgical team. All patients received general anesthesia with tracheal intubation. No patient required patella replacement. Hence, only trimming of the edges of the patella was performed in all patients. Intramedullary instrumentation was used for distal femur resection, and extramedullary instrumentation was used to resect the proximal tibia. A medial parapatellar arthrotomy was used for exposure. Two grams of tranexamic acid was injected into the articular cavity after skin suture. An electric double limb tourniquet (2 × 500) was used for all patients (VBM Medizintechnik GmbH,

Germany), and the pressure was determined through systolic blood pressure plus 150 mm Hg (1 mm Hg=0.133 kPa). The tourniquet pressure used for the present study was based on the study conducted by Ishii and Matsuda^[14] and the experience of the investigators. The tourniquet was released before the skin suture. No drainage tube was inserted in all patients.

2.3. Vital signs and emboli monitoring

TEE was set at the right atrium from the start of the surgery. Real-time images were recorded every 5 seconds up to 60 seconds, and at 75, 90, 105, 120, and 150 seconds after tourniquet release. Images were also recorded at the beginning of the operation, at the time of the femoral intramedullary guide insertion, and at the time of the tibial and femoral prosthesis implantation. Furthermore, heart rate (HR), mean arterial pressure (MAP), blood oxygen saturation (SpO₂), and oxygen partial pressure (PaO₂) were also simultaneously recorded. Image analysis was performed using Matlab 7.0 (MathWorks), including video framing, regional calibration, and image binarization steps (Fig. 1). Then, the pixels, areas and volumes of the fat embolus were generated at each time point.^[8,15]

2.4. Pathology of blood samples obtained from the right atrium

A central venous catheter with a 1.7-mm internal diameter was placed at the tricuspid valve of the right atrium. Five milliliters of

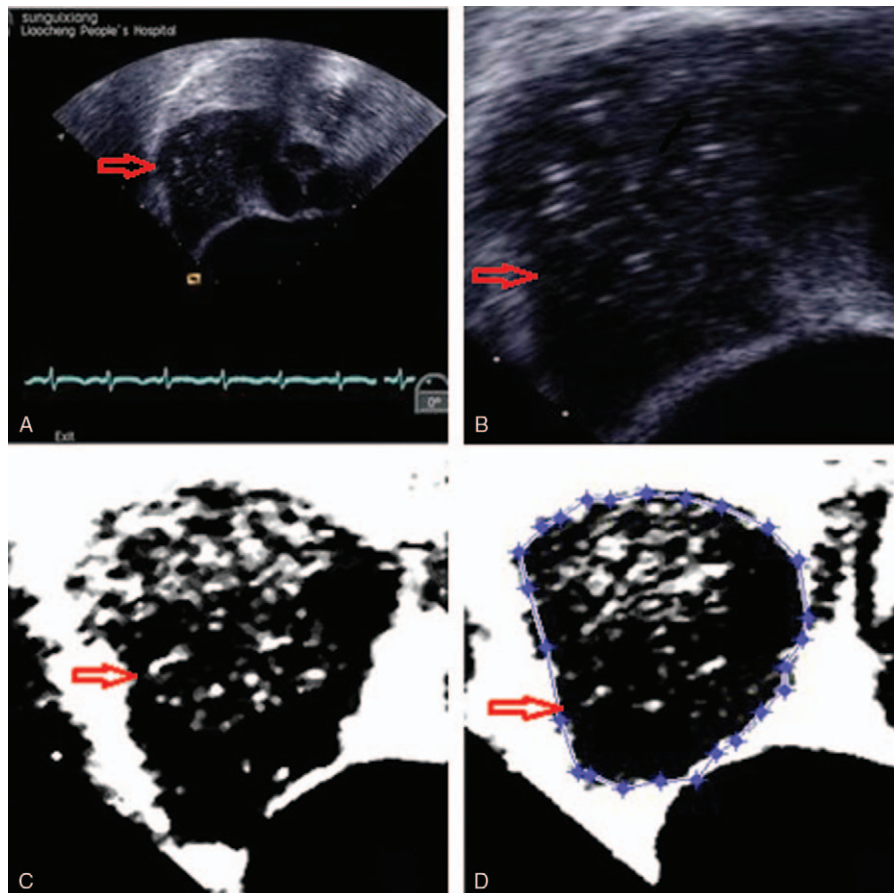


Figure 1. Processing steps of transesophageal echocardiography imaging: (A) video framing; (B) regional calibration; (C) image binarization; (D) goal area manual selection.

blood was collected when a large signal was observed by TEE. Then, the collected blood samples were centrifuged at 800 rpm for 1 minute. The supernatant and cell pellet were collected and mixed for pathological fixation and section. Staining on the embolus sample included the adipose tissue staining of Sudan III/hematoxylin and hematoxylin-eosin (H&E) staining.^[16] Immunohistochemical staining for CD34, CD99, S-100, and leukocyte cell antigen (LCA) were also performed.

2.5. Pulmonary arterial pressure measurement

Pulmonary arterial pressure was measured based on the tricuspid valve regurgitation difference method, as follows: pulmonary

arterial systolic pressure = tricuspid regurgitation pressure + right atrial pressure (standard right atrial pressure = 5 mm Hg). Then, pulmonary arterial pressure was recorded before, at 30 and 150 seconds, and after tourniquet release (Fig. 2).

2.6. Medullary cavity fat content measurement

Bone marrow samples from the medullary cavity were collected by our central laboratory physician using a 5-mL syringe after opening the femoral cavity during surgery. Then, the samples were centrifuged at 3500 rpm for 10 minutes. The percentage of the supernatant was considered as the fat content proportion of each sample.

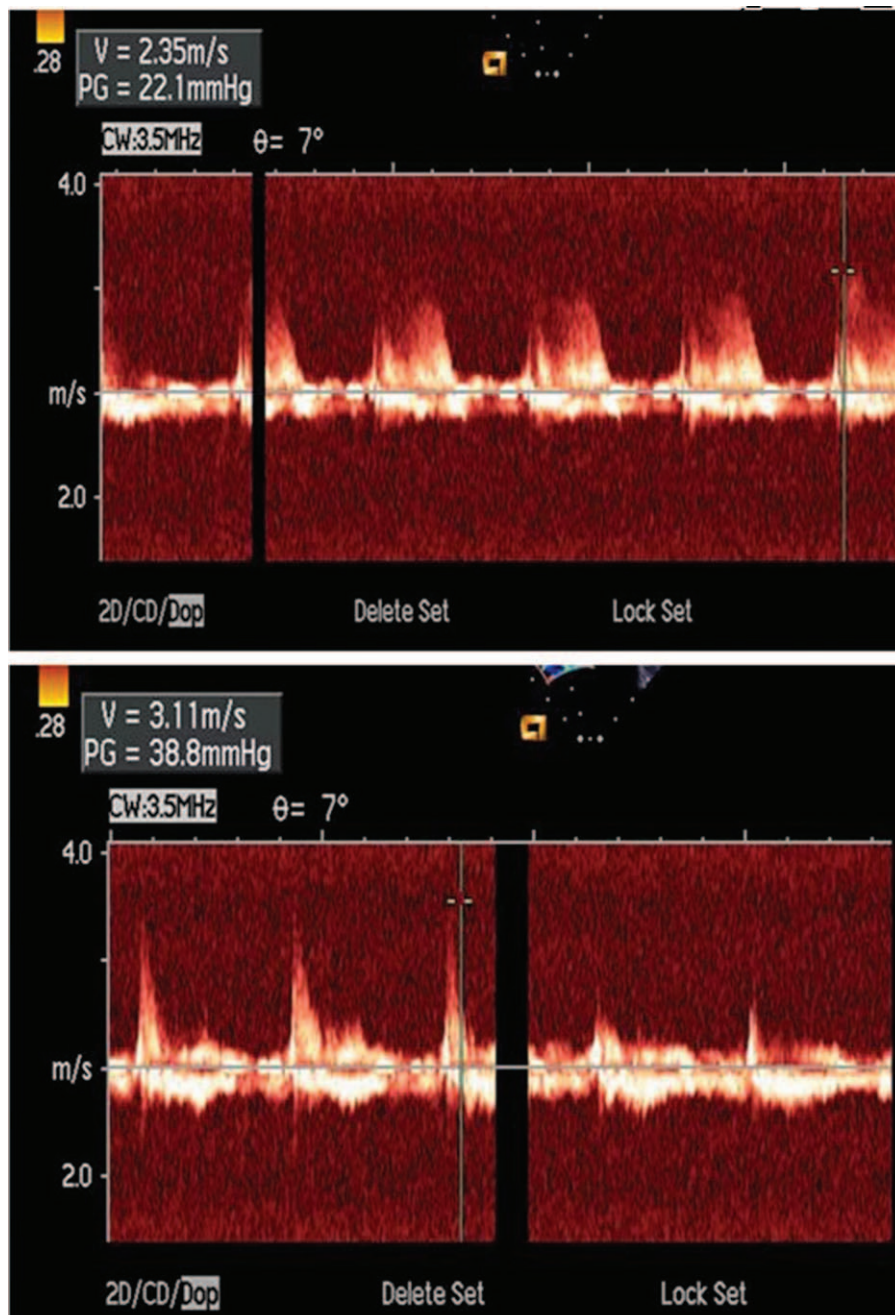


Figure 2. An example of a pulmonary arterial pressure measurement.

2.7. Statistical analysis

Quantitative data were presented as mean \pm standard deviation ($\bar{x} \pm SD$). Logarithmic transformation was performed in variables that did not distribute normally. One-way ANOVA was used to analyze the vital signs, and independent *t*-test was used for comparisons between groups. Pearson's correlation analysis was used for the association among embolus quantity, age, BMI and fat content of the medullary cavity. Multi-variable logistic regression was used to analyze the risk contribution of age, gender, BMI, and fat content of the medullary cavity. All data analyses were performed using SPSS 20.0 (SPSS Inc. Chicago, IL), and a *P*-value $<.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

The average surgical duration was 57 ± 8 minutes, and the average fat content of the bone marrow was 45% (quartile range: 25–75%). The present study included 17 male and 23 female patients. The average age of these patients was 62.4 ± 4.0 years, and their average BMI was 25.5 ± 1.4 kg/m².

3.2. Transesophageal echocardiography and vital signs monitoring

The TEE and vital sign monitoring results are presented in Table 1. There was no embolus in the right atrium at the beginning of the operation, and scattered embolus signals started to appear after opening the femoral marrow cavity. Two embolus signal peaks appeared when the guiding apparatus was inserted and the prosthesis was being installed, respectively. Ten seconds after tourniquet release, scattered small, and bright echo signals

appeared at the right atrium. These signals were big and bright, and “snowflake”-like embolus signals also appeared. Signal density peaked at 15 to 30 seconds after tourniquet release, which gradually faded away (Fig. 3). The duration of these embolus signals ranged within 1 to 3 minutes in most patients. However, embolus signals could still be observed in few patients after 3 minutes. The trend for these embolus signals are shown in Figure 4.

In addition, the vital signs of these patients were stable. The difference among monitoring indicators at each time point was not statistically significant (Table 1).

3.3. Pulmonary arterial pressure monitoring

Pulmonary arterial pressure increased to 38.5 ± 2.1 mm Hg at 30 seconds after tourniquet release (independent sample *t*-test, $P = .002$ vs before surgery; Fig. 5). Pulmonary arterial pressure returned to baseline at the end of the monitoring period (independent sample *t*-test, 150 seconds vs before surgery; $P = .914$). Pulmonary arterial pressure in 1 patient did not return to normal until 10 minutes after tourniquet release (no medication intervention). Although a large embolus signal was observed, none of the patients had any clinical manifestation such as dyspnea or subcutaneous hemorrhage.

3.4. Arterial blood sample pathology

Twenty-four of 40 blood samples revealed positive fat staining (Fig. 6). The main finding included adipocyte and lipid droplet aggregation, mixed with scattered bone marrow tissues, endothelial cells, and a large number of lymphoid hematopoietic stem cells. S100-positive mononuclear phagocytes, LCA-positive lymphocytes, CD34-positive hematopoietic stem cells, and

Table 1

Changes in MAP, HR, SaO₂, and PO₂ over time.

Surgical time points	MAP, mm Hg	HR	SaO ₂ , %	PaO ₂ , mm Hg
Beginning of operation	109 \pm 2.1	72 \pm 3.6	99	342 \pm 6.5
Open the marrow cavity	106 \pm 3.2	78 \pm 2.3	99	335 \pm 9.5
Femoral prosthesis implanted	109 \pm 2.4	77 \pm 4.2	99	351 \pm 7.5
Tibia prosthesis implanted	110 \pm 1.8	79 \pm 2.3	99	341 \pm 8.5
0 s after a tourniquet releasing	105 \pm 2.5	81 \pm 4.2	99	354 \pm 9.5
5 s	108 \pm 1.3	81 \pm 3.4	99	351 \pm 10.5
10 s	107 \pm 2.2	79 \pm 2.4	99	349 \pm 9.5
15 s	109 \pm 3.2	78 \pm 1.9	99	344 \pm 5.5
25 s	105 \pm 2.5	80 \pm 2.2	99	338 \pm 7.5
25 s	107 \pm 3.8	78 \pm 3.1	99	339 \pm 11.5
30 s	104 \pm 2.9	78 \pm 4.2	99	339 \pm 9.4
35 s	106 \pm 2.4	79 \pm 3.2	99	346 \pm 7.5
40 s	107 \pm 4.2	80 \pm 2.5	99	351 \pm 6.5
45 s	107 \pm 2.8	81 \pm 1.4	99	347 \pm 8.5
50 s	109 \pm 2.2	79 \pm 2.6	99	338 \pm 13.5
55 s	108 \pm 3.1	78 \pm 3.1	99	343 \pm 9.5
60 s	106 \pm 2.7	79 \pm 2.6	99	354 \pm 10.5
75 s	109 \pm 3.6	81 \pm 2.3	99	345 \pm 7.5
90 s	108 \pm 2.5	80 \pm 1.8	99	349 \pm 11.5
105 s	109 \pm 3.2	79 \pm 2.4	99	353 \pm 8.5
120 s	110 \pm 2.8	80 \pm 2.6	99	343 \pm 13.5
150 s	107 \pm 4.5	79 \pm 2.7	99	352 \pm 10.5
<i>F</i> -value	<i>F</i> = 4.121	<i>F</i> = 7.231	–	<i>F</i> = 9.231
<i>P</i> -value	<i>P</i> = .121	<i>P</i> = .062	–	<i>P</i> = .231

HR = heart rate, MAP = mean arterial pressure, PO₂ = oxygen partial pressure, SaO₂ = oxygen saturation.

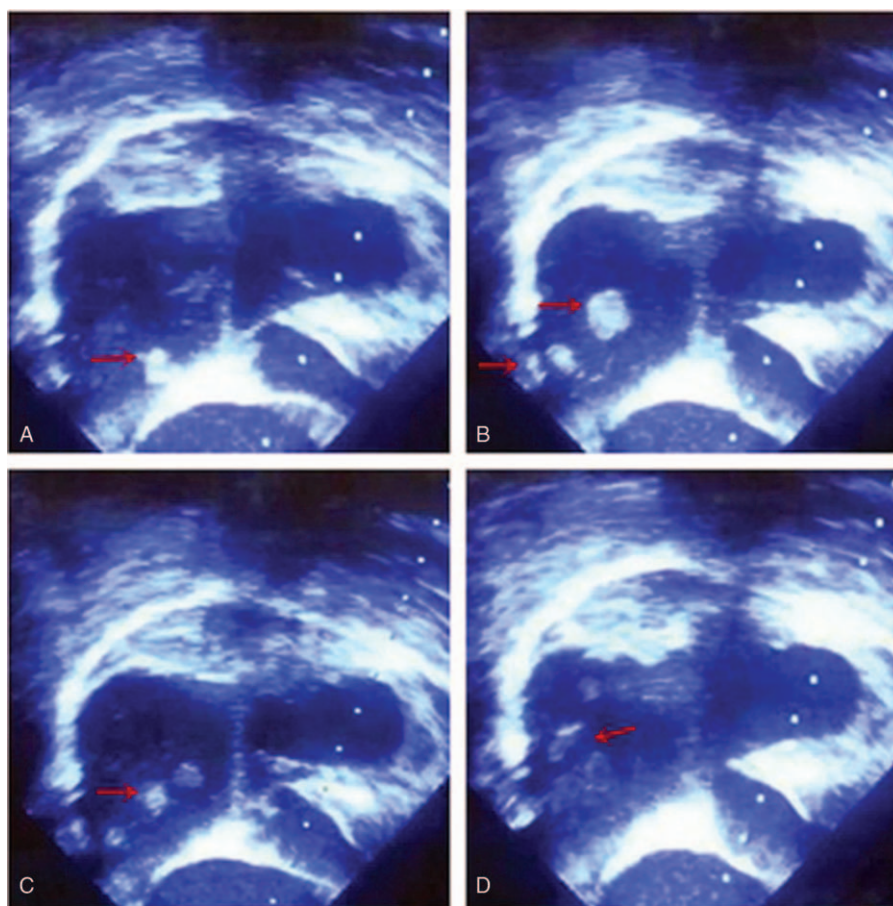


Figure 3. “Snowflake”-like pattern of the embolus in the right atrium after tourniquet release. The red arrow reveals the sporadic embolus in the right atrium.

CD99-positive endothelial cells were also found in 15 samples (Fig. 7). This evidence confirms that the embolus came from bone marrow tissues.

3.5. Correlations between the variables of patients and embolus quantity

Pearson’s correlation analysis revealed that total embolus quantity was positively correlated with age ($r=0.209, P=.021$), BMI ($r=.331, P=.041$), and the fat content of the bone marrow ($r=0.242, P=.003$). However, fat content was not correlated with either age or BMI (Table 2, Fig. 8).

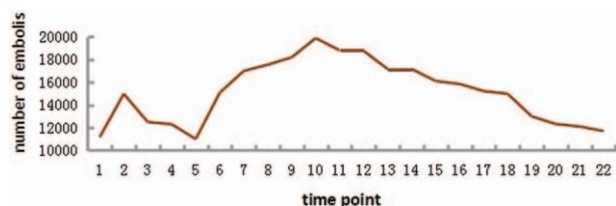


Figure 4. Embolus quantity changes over time: time-point 1: start of the operation; time-point 2: opening of the marrow cavity; time-point 3: implantation of the femoral prosthesis; time-point 4: implantation of the tibial prosthesis, time-points 5–22: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, and 150seconds after tourniquet release.

3.6. Risk factors for pulmonary hypertension

In the present study, pulmonary hypertension was defined as having a pulmonary pressure higher than the median value of 30 seconds after tourniquet release (34 mm Hg). Multivariable logistic regression analysis revealed that fat content was independently associated with higher risk for pulmonary hypertension (OR: 1.432, 95%CI: 1.335–1.592; $P=.006$). Other risk factors included age (OR: 1.632, 95% CI: 1.445–1.832) and BMI (OR: 1.231, 95% CI: 1.032–1.381).

4. Discussion

The present study revealed that the embolus occurred during TKA, which was essentially adipose tissues or lipids derived from bone marrow tissues (Table 3). Pulmonary arterial pressure was in accordance with the release of the tourniquet. More importantly, these fat emboli could result in pulmonary hypertension, which was also significantly associated with age and BMI. A more detailed discussion is presented below.

4.1. Application of transesophageal echocardiography

Previous studies have confirmed the usage of TEE to monitor emboli in the right artery during TKA surgery.^[17,18] In recent years, studies have also used TEE to observe abnormal embolus signals.^[19] It was inaccurate to use grey values and the ultrasound embolus area ratio as a quantitative index of the embolus. More

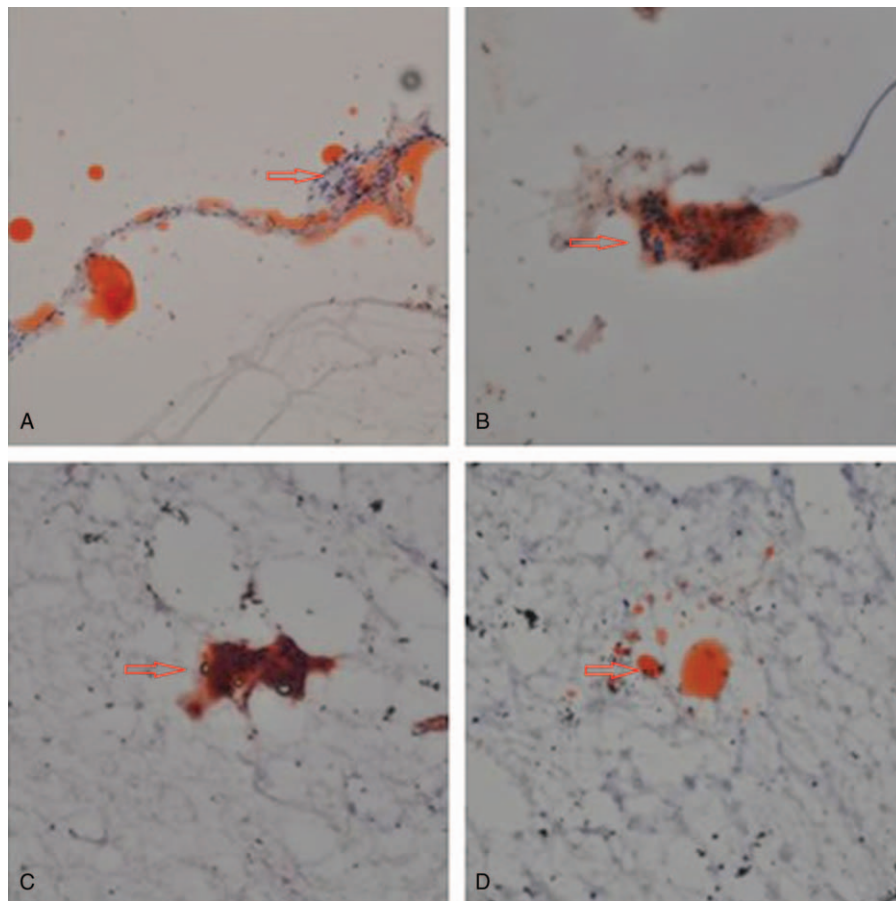


Figure 5. Pulmonary arterial pressure before and after tourniquet release.

importantly, in the present study, we improved the TEE image processing method by using the median filter instruction during image processing, which reduced interference and increased sensitivity. This approach has not been applied in previous studies. The application of TEE during joint surgery can be considered as a standard method for embolus monitoring.

4.2. Pathologic composition of the embolus

The pathologic composition of right arterial emboli during orthopedic surgery remains under debate. A previous hypothesis included air or cold blood clots.^[5] However, there is no evidence to confirm this hypothesis. A present study revealed that it was difficult for air embolus to be flushed by blood flow, and it would not be shown as “snowflake”-like signals on TEE.^[20] Moreover, Burhop et al^[21] and Giachino et al^[16] reported in their studies that heparin administration did not reduce these emboli. Therefore, right arterial emboli are not likely to be blood clots. In the present study, we collected blood samples from the right atrium, and processed these samples to allow both supernatant and cell fractions to be used for pathology. Therefore, we demonstrated that the embolus was mainly composed of bone marrow tissues.

After entering the pulmonary vascular bed, the embolus would first block the blood vessels, which is recognized as the mechanical effect stage. However, previous evidence have pointed out that pulmonary arterial pressure would not change until the dispersed and small embolism was over 40%.^[18,22]

We infer that when emboli passes into the atrium, they would be dispersed by high blood flow velocities and diffuse into the pulmonary vascular bed, cause transient pulmonary hypertension, and finally be cleared by pulmonary capillaries.^[20,23] Since lung tissue pathology was not performed in the present study due to ethic considerations, we were not able to elucidate the mechanism of the pulmonary arterial pressure caused by the embolus. Therefore, future studies are warranted. In addition, in a previous hypothesis of pulmonary capillary contraction raised by Gurewich et al^[24] and Smulders^[25] present evidence from animal models suggests that localized inflammation at the pulmonary capillary bed caused by lipid deposition could finally lead to pulmonary edema.^[20,23,26] However, in the present clinical study, there were no symptoms of pulmonary edema in any of the patients. Therefore, more clinical evidence is warranted to verify the inflammation reaction caused by fat embolism.

4.3. Obesity and advanced age increased emboli quantity after tourniquet release

The present study also demonstrated that the total amount of emboli was positively associated with BMI, suggesting that obesity might be a risk factor for fat embolism post-operation. Previous studies have suggested potential associations between higher BMI and embolism risk after orthopedic surgery.^[27,28] However, the underlying mechanism remains unclear. Furthermore, the present results also revealed that age was a significant risk factor for fat embolus, which may be explained by the

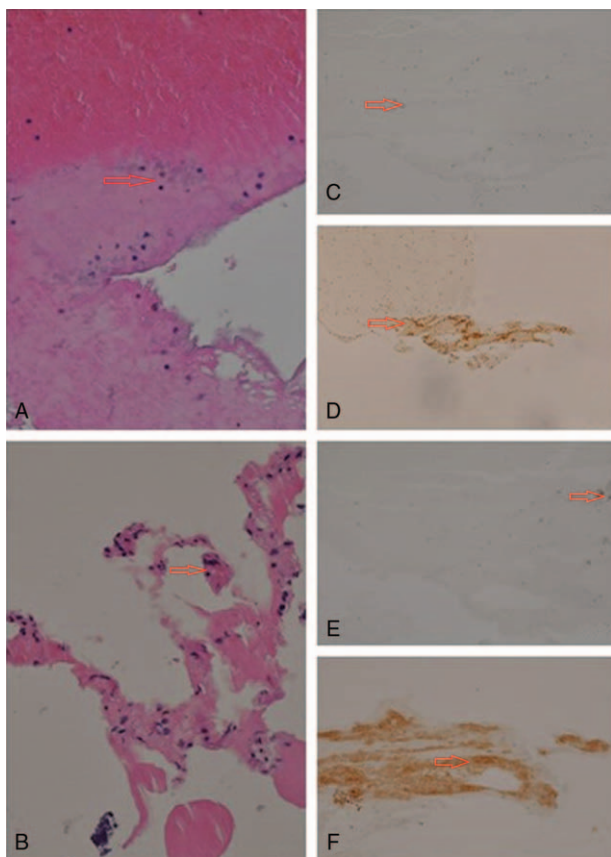


Figure 6. Adipose tissue or lipid from the right arterial blood sample by Sudan III/hematoxylin staining. (A) Adipose tissue surrounding broken blood vessels; (B and C) fat group surrounding the lymphocyte; (D) fat droplets; microscopic scale, $\times 400$.

decrease in vascular compliance along with ageing.^[29] Elder patients would experience more compression on the superficial vein at the lower extremities under the same pressure by the tourniquet, as compared to younger patients. Taken together, the relationship we found among BMI, age, the total amount of fat

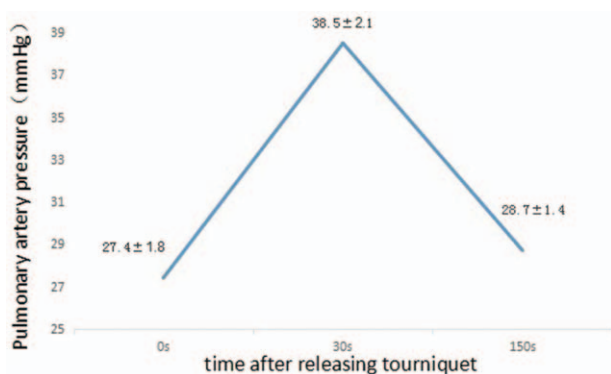


Figure 7. Hematoxylin-eosin and immunohistochemical staining of the right arterial blood sample. (A and B) A large number of nucleated cells; (C) S100-marked mononuclear phagocytes; (D) LCA marked lymphocytes; (E) CD34-marked hematopoietic stem cells; (F) CD99-marked endothelial cells; the yellow stains represented the immunohistochemical positive area; microscopic scale, $\times 400$. LCA = leukocyte cell antigen.

Table 2
Correlation analysis of the total amount of embolus and relevant variables.

Variables	The total amount of embolus		Bone marrow fat percentage, %	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.209	.021	0.091	.058
Bone marrow fat percentage, %	0.242	.003	–	–
BMI, kg/m ²	0.331	.041	0.439	.241
Pulmonary artery pressure at 30 s	0.421	.032	0.331	.031

Data are shown as correlation coefficients (*r*) and *P* values. BMI = body mass index.

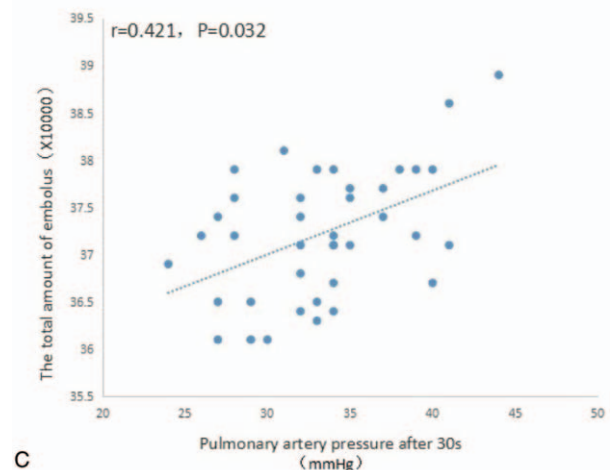
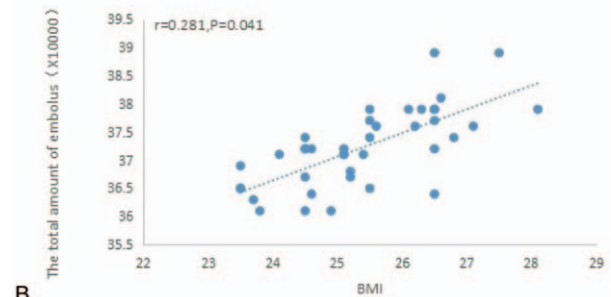
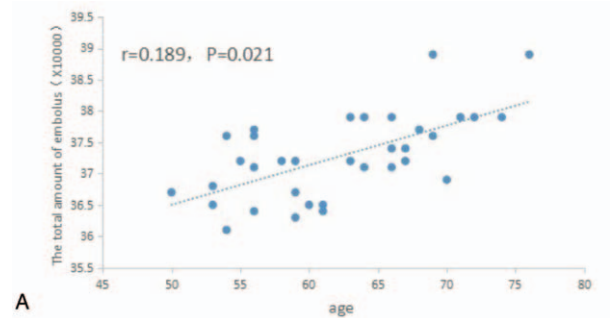


Figure 8. A correlation scatter diagram with the total amount of embolus and age, BMI and pulmonary arterial pressure ($n=40$). (A) Correlation scatter diagram with the total amount of embolus and age; (B) correlation scatter diagram with the total amount of embolus and BMI; (C) correlation scatter diagram with the total amount of embolus and pulmonary arterial pressure. Correlation coefficients and *P*-values are shown. BMI = body mass index.

Table 3
Logistic analysis of positive and negative embolus groups.

Variables	RC	SE	P-value	OR	95% CI
Age	0.321	0.403	.028	1.632	1.445–1.832
Gender	−47.341	5411	.962	1.016	0.907–1.058
BMI	0.245	0.392	.021	1.231	1.032–1.381
Fat content of the medullary cavity	0.241	0.442	.006	1.432	1.335–1.592

BMI = body mass index, CT = confidence interval, OR = odds ratio, RC = regression coefficient, SE = standard error.

emboli, and its underlying mechanism require further investigations through larger clinical studies and animal studies in the future.

The present study also demonstrated the positive correlation between the total amount of emboli and pulmonary arterial pressure. Therefore, we consider that more emboli at the right atrium would lead to a greater effect on lung function. Logistic regression results revealed that bone marrow fat content, age and BMI are significantly associated with risk of pulmonary hypertension. Therefore, orthopedic surgeons should be aware of the potential high risk of pulmonary fat embolism during TKA in patients who are older and obese, in which intervention may be initiated.^[16,25] We also found that the fat composition of the bone marrow was not correlated to the age or BMI of patients, which was also supported by other studies.^[30,31] Another potential reason may be that patients in the present study had a lower age range, which weakened the age effect on marrow fat, although it was acknowledged that red marrow becomes yellow, and that this would contain more adipose tissues due to ageing. In the present study, we did not find any correlation between female gender and the amount of embolus or risk of embolism, as shown by other studies.^[12] This may be due to the lower sample size of the present study.

4.4. The value of the use of tourniquets

Tourniquets have long been used in orthopedic surgery to effectively reduce bleeding, infusion volume, and operation time. However, these have no effect in reducing the total amount of blood loss. A previous study also revealed that tourniquets might be associated with prolonged hospital stay.^[32] In the present study, it is possible that the use of tourniquets may have had a negative effect on embolism due to mobilization, because it could increase the cumulative effect of fat embolism.

4.5. Study limitation

The sample size of the present study was relatively small. Hence, the results of the data analysis should be confined to the Chinese population, because the median BMI was smaller. We used the semiquantitative method for embolus quantification. The method used to measure medullary fat content in the present study was empirical. More accurate methods such as MRI^[33] can be used for future studies.

5. Conclusion

The present study demonstrated that bone marrow tissue debris, which is composed of adipose tissues, entered the venous circulation through the right atrium during TKA after tourniquet

release. The fat embolus peaked at 30 seconds after tourniquet release, followed by the increase in pulmonary arterial pressure. More importantly, older age, higher BMI and higher fat content of the bone marrow were significantly associated with higher risk of pulmonary hypertension. Orthopedic surgeons should be more vigilant on the possibility of fat embolism during TKA. Furthermore, preoperational interventions in older and obese patients may be warranted.

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