

Study Protocol

Official title:

**The Precise Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension:
Pulmonary Endarterectomy Guided by Three-dimensional Pulmonary Angiography**

Brief title

**Pulmonary Endarterectomy Guided by CT Scanning for Patients With Chronic
Thromboembolic Pulmonary Hypertension----PEACT**

Acronym:PEACT

Sponsor:Fuwai Hospital,Chinese Academy of Medical Sciences,Peking Union Medical College

Study types: interventional,Randomized single-blind controlled study

Document Date: 12/19/2018

Abbreviation and acronyms

CTEPH=chronic thromboembolic pulmonary hypertension;PEA=pulmonary endarterectomy;PAP=pulmonary artery pressure;PVR=pulmonary vascular resistance;PTG=precise therapy group;UCG=ultrasonic cardiogram;CPET=cardiac pulmonary exercise test;CT=computed tomography;RHC=right sided heart catheterization;WHO=World Health Organization;NT-pro BNP=N-terminal pro B-type natriuretic peptide.INR=international normalized ratio;6MWD=6 minutes walking distance; mmHg=millimeter mercury column;CF=coagulation factor;UCSD=University of California,San Diego;NOAC=new oral anticoagulant;3-D=Three-dimensional;

Brief Introduction of this study

This study is a randomized single-blinded controlled study to investigate the efficiency of 3-D pulmonary imagings,including 3-D pulmonary angiography and 3-D enhanced computed tomography,patients received PEA surgeries in our center was randomized into 2 groups,the PTG group(group 1) and traditional PEA therapy group(group 2),the peri-operative hemodynamic improvement and peri-operative prognosis such as peri-operative mortality and other severe complications were documented for both groups,and the follow-up result of UCG,CPET and RHC are compared for these 2 groups so as to investigate their long-term result after PEA surgeries.A total of more than 72 cases of patients with CTEPH are expected to included into this study,with informed consent form signed,a longest 48 months follow-up result will be recorded,and the whole designed study is expected to end at the year 2022.

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1 Background

CTEPH is an acquired pulmonary hypertension disease with poor prognosis, 5-year mortality rate of the patients without any intervention can be as high as 90%[1]. It is generally believed that pulmonary thrombosis in these patients can be attributed to residual unresolved thrombus in acute pulmonary embolism patients or to the deep vein thrombus in lower extremities[2, 3]. 12000 to 15000 new cases of CTEPH was found every year in the United States[4], for these patients, PEA surgeries was reported as a golden standard therapy with a significantly better survival prognosis and life quality achieved compared with pure medicine therapy or pulmonary balloon angioplasty by many centers[5-7]. However, even in the United States, only 300 cases can received PEA therapies each year, the reasons for this low population received PEA surgeries are as below: 1). PEA is a extremely skill-demanding operation for the cardiac surgeons, it is reported that 1/2 to 1/3 of CTEPH patients are considered inoperable by surgeons in Europe[7]. Half of the reasons considered inoperable was the embolism location considered difficult to be found and removed during the operation[7]; Therefore, accurate positioning and complete removal of the embolism for patients with CTEPH are the key to successful operation. The latest 3-D imaging technology can accurately assess the obstructive severity of each pulmonary segments, Rotating 3-D pulmonary angiography can analyze the location and direction of each pulmonary artery, which can help the surgeons to determine the surgical difficulty of each pulmonary segment for each patient. In summary, PEA surgeries guided with high-definition 3-D imaging techniques might lead to a better hemodynamic result better survival result in the long-term period after surgeries, and might provide a solution to position the embolism before surgeries, so as to more conveniently remove the pulmonary embolism during the surgeries.

2 Objectives(Focus of the study)

- 1) To investigate the importance of the appliance of the 3-D imaging technique for PEA surgeries,especially for patients with peripheral UCSD levels;
- 2) To establish a standard assessing method with high-definition enhanced CT scanning and pulmonary angiography;establish a quantitative scoring method using CT scanning and pulmonary angiography to assess the severity of CTEPH and surgical indications;
- 3) To compare the result between group 1 and group 2,so as to find out the possible benefits in the precise therapy group(group 1);
- 4) To promote the appliance of 3-D imaging techniques for patients with CTEPH,and establish a standard precise PEA strategy guided by enhanced CT scanning and pulmonary angiography,in order to further improve the surgical result for patients with CTEPH,especially for patients with peripheral changes.

3 Design and Method

1) General design

This is a randomized single-blinded controlled study, 72 cases of patients are expected to be enrolled into this study, and randomized into 2 groups. The endpoint of these 2 groups will be compared to determine the efficiency of the appliance of 3-D imaging techniques for PEA procedures.

2) Clinical data collection process:

Pre-operative period: From admission to the moment before surgeries. Basic clinical information including the patients' age, gender, symptoms, clinical diagnosis, WHO classes, disease history et al. Blood test such as the thrombus forming tendency test, blood coagulation function test, coagulation factor activity test and N-terminal B-type natriuretic peptide (NT-proBNP) et al were collected. Other examinations included CT scanning, MRI, CPET, RHC and pulmonary angio-graphy, pulmonary nuclide perfusion imaging, respiratory function test and UCG et al. The major parameters of these examinations are collected.

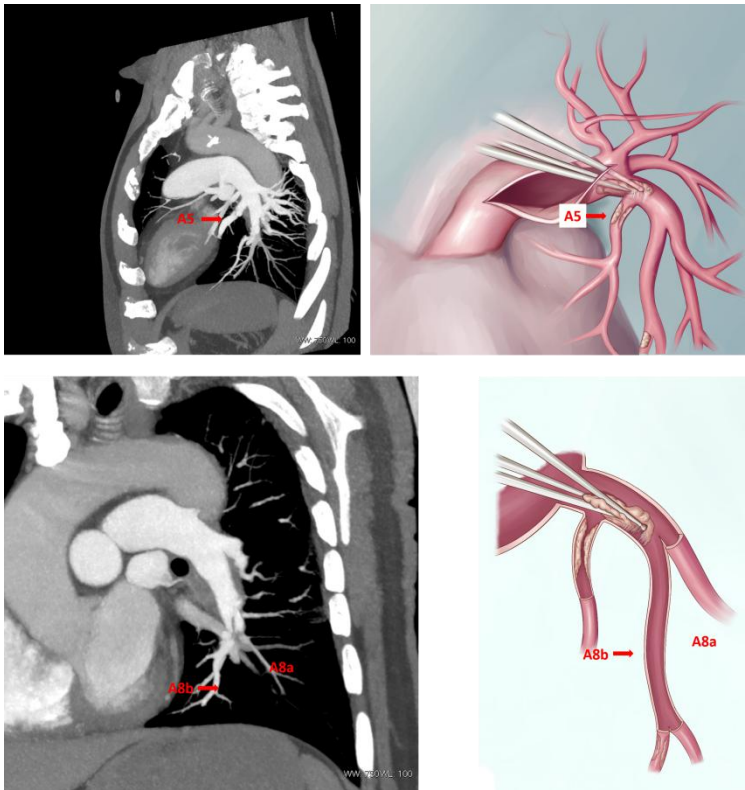
Operation period: The RHC result immediately before and after PEA surgeries are documented, the anesthesia record and CPB record, surgical specimen pathological record, intra-operative cerebral oxygen saturation data will be collected;

Post-operative period before discharge: Pulmonary nuclide perfusion imaging, CT scanning and UCG should be done in this period.

Follow-up period: A routine 3-, 6-, 12-, 24 months follow-up will be done, the follow-up contents include the measuring of NT-pro BNP, UCG, CPET, CT scanning, RHC, pulmonary angiography, pulmonary perfusion imaging, MRI and RHC. Among which the CPET, MRI, RHC and pulmonary angiography should be done after 6 months after surgeries. All the redo examinations could be done in any follow-up period, but at least of 1 time of these examinations should be done in the whole follow-up period, and the follow-up time should be recorded.

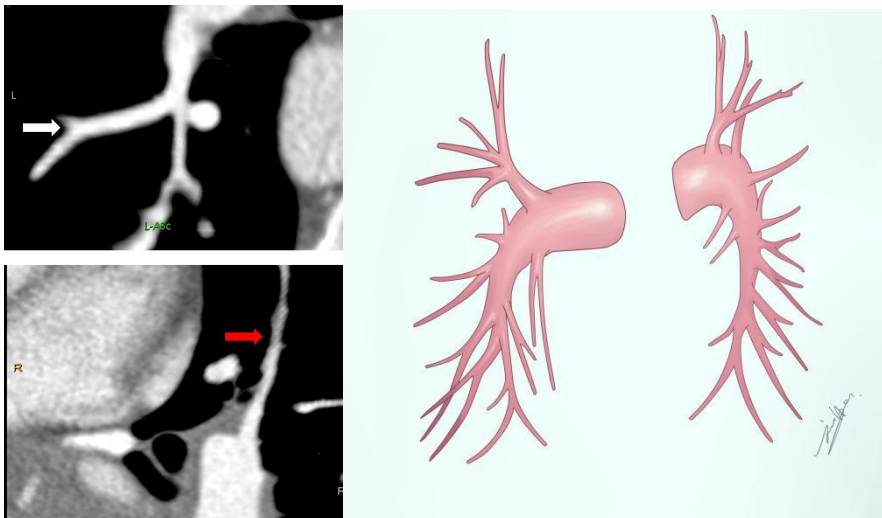
3) CT Imaging assessment:

① According to the imaging examinations before surgeries, the location of each occluded pulmonary segment and their shape were identified and the affected pulmonary segments were divided into 3 types: i) segments that is easy to reach; ii) segments that is hard to reach (seen in the picture below), and severely occluded; iii) segments that is hard to reach but slightly occluded;



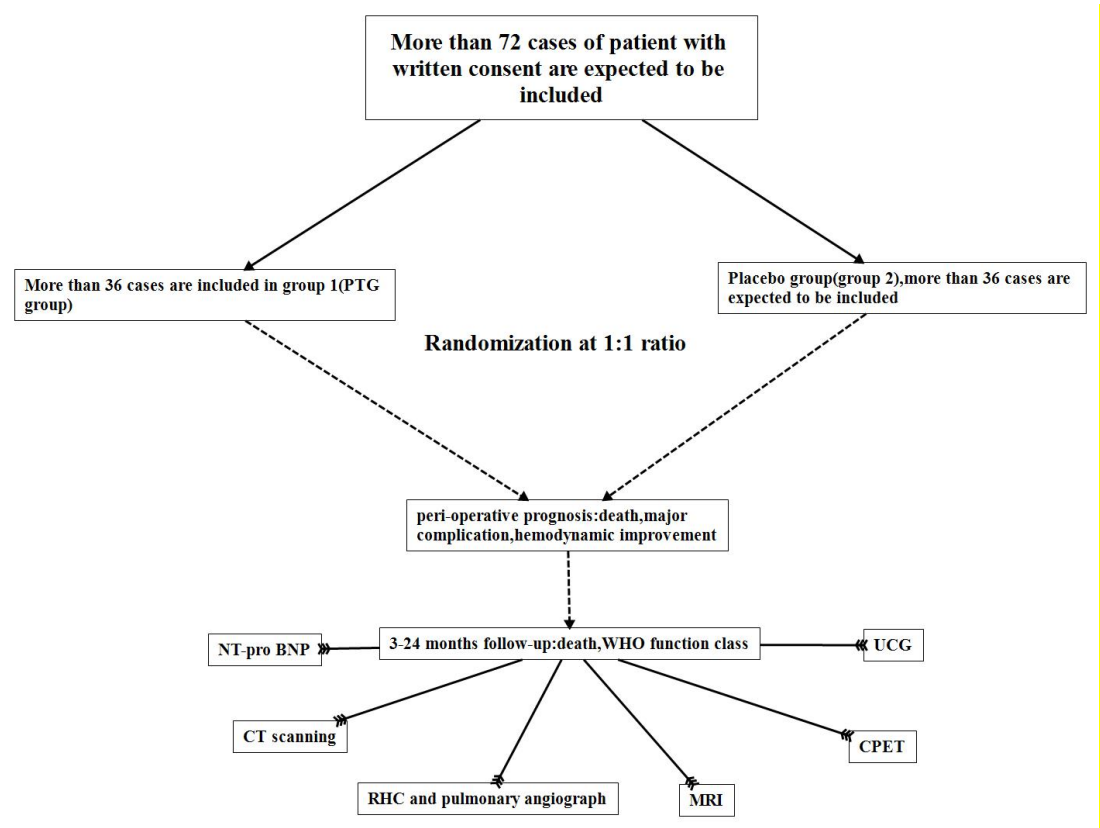
An example of segments hard to reach. As shown in the picture, the shape of LA5 of this patient is exactly perpendicular to the surgical direction, which leads to the fact that the embolism in this segment is very hard to strip. For the subsegment LA8a+b, it is too far away from the proximal artery, which is very hard to reach at surgeries.

② All the occlusion severity of each segment and narrow severity of each segment is assessed with CT scanning;



An example of constructed CT imaging of the pulmonary segment: A demonstration of the anatomic structure of pulmonary segments. White arrow: not severely narrow segment of RA9; Red arrow: severely narrow segment of LA4.

4) Research process:seen in the picture below.



4 Eligibility/intervention information/Arm information

Eligibility:

Patients were **eligible** if they had met all the following conditions:

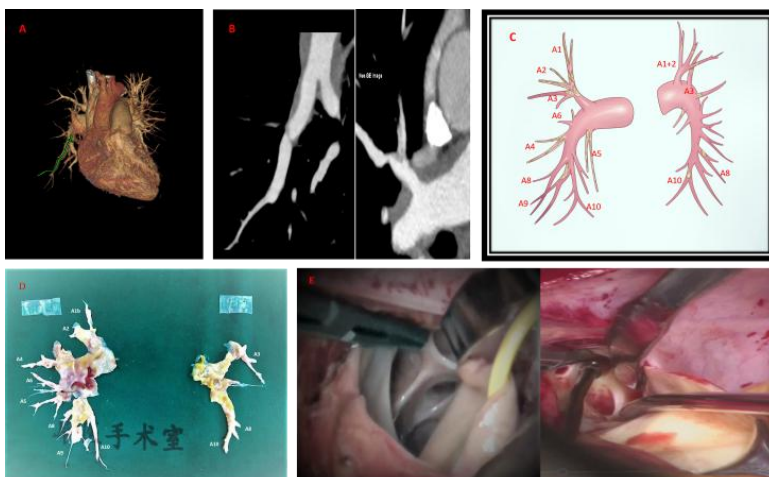
- 1) Diagnosed with CTEPH by pulmonary angiography and RHC examinations;
- 2) The location of the embolism can be reached in surgery;
- 3) Whether or not combined with auto-immune diseases;

Patients were **not eligible** if they had met any one of the following conditions:

- 1) history of other severe diseases and surgical therapy is contraindicated;
- 2) Unwillingness to participate or without informed consent;
- 3) acute pulmonary embolism;
- 4) pulmonary sarcoma;
- 5) Patients with mitral valve diseases, or other conditions that may lead to cardiogenic pulmonary hypertension;
- 6) Pulmonary hypertension caused by pulmonary arteritis.

Intervention information:

Precised analyzed CT scanning and pulmonary angiography will be done for the patients in the precise therapy group, and the patients in Group 1 will receive PEA procedure with the guide of precise 3-D imaging techniques (seen in the picture below)



An example of precise therapy process.A,3-D CT constructed images,which can provide the detailed information of each pulmonary segmental shape and their distribution;B,enhanced CT imaging of pulmonary segment,to assess the occluded severity of each pulmonary segment;C:Diagrammatic sketch of pulmonary artery embolism's location,red marked font refer to pulmonary segments with occupying changes;as shown in the picture,the RA4,RA2,RA5 is completely occluded,other affected segment is partially occluded.D.Surgical specimen;the occupying lesions in each pulmonary segment is stripped according to the embolism location identified by high-resolution CT scanning(seen in picture C);E,clearly opened pulmonary segment entrance after precise stripping therapy.

Arm information:All the patients included into this study met the requirements above and randomized into 2 groups:

group 1:precise PEA therapy with the guide of 3-D imaging techniques;

group 2:traditional PEA therapy solely by surgical probe and traditional CT scanning/pulmonary angiography method.

100 cases of randomized group were generated,which consisted of 50 cases of group 1 and 50 cases of group 2,and 100 cases of randomized number was generated paralleled with the randomized group.According to the date of admission of each patients,they are included into the randomized group one by one,any patient met the criteria of the **not eligible** described above will be excluded from this experiment,and all the patients consent to participate in this study will not know their specific group,the chief surgeon can only know the random grouping situation after the patients been admitted into hospital.

5 Outcome measures and time frame

The primary endpoint for assessment of the efficacy was the peri-operative hemodynamic improvement,peri-operative mortality,major complications after surgery,and deaths in the follow-up period.

Secondary endpoint were the measuring values of NT-pro BNP,parameters of MRI,UCG and CPET in the follow-up period,the CT scoring changes from baseline to follow-up period,and WHO function classes in the follow-up period,as well as disease directly associated cost(average cost) in the follow-up period.

6 Statistical Analysis Plan

This is a prospective randomized single-blinded controlled study, the major endpoint is the hemodynamic improvement after the surgeries.

1) Sample Size:

Sample size estimation was based on a hypothesis that the mean PAP of patients of PTG can be decreased by 8 mmHg more than that of the traditional group. Given the standard deviation of 12 mmHg was expected in the measurement of mean PAP, with a power of 80% and a significance statistically level of 5% on both side, a sample size of 36 of the PTG group was required.

2) Statistical Analysis:

The analysis was based on the principle of “Intention to Treat” (ITT). All randomized patients (regardless of whether they violate the protocol) will be included in the final analysis.

Continuous variables are presented as mean \pm standard deviation, unless otherwise specified. Significant differences were determined with the Mann-Whitney test or independent t-test according to their distribution, Wilcoxon matched pairs signed rank test or paired t-test for the paired variables. Categorical variables were compared between the 2 groups using the chi-square test or Fisher exact test. Kaplan-Meier method was used to estimate survival, log-rank test was used to evaluate the survival difference between different groups.

The pulmonary occluded severity will be scored using CT scanning and pulmonary angiography for each patient, the scoring result will be compared with the hemodynamic result to investigate their possible correlations using Spearman Correlation Analysis.

All the statistical analysis were performed using SPSS version 22.0. P value less than 0.05 was considered statistically significant.

7 Quality Control

1) Data accuracy:

All the participants in this study are responsible for the data collection process, all the original medical document should be pictured or scanned as the evidence of recorded data; for parameters with possible subjective error, the original imaging or assessment profile should be saved, the parameters estimated by

2) Group coordination

Fuwai hospital was the largest cardiac surgery center in China and also one of the largest center in the world. Up to now, we had established a coordination team of CTEPH in our center, which consist of cardiac surgery department, pulmonary disease center, radiology department, intensive-care unit and ultra-sonic department, nuclear medicine department in our center.

All the imaging data had been evaluated by at least 2 professional staffs in that field, and the CT constructed imaging, pulmonary angiography imaging had been saved for re-assessment in case of possible subjective bias.

3) Patient coordination

We had established a routine and standard follow-up process in our center, these complex re-examination item could be done within 5 days in our center, with a mature coordination team of CTEPH being established.

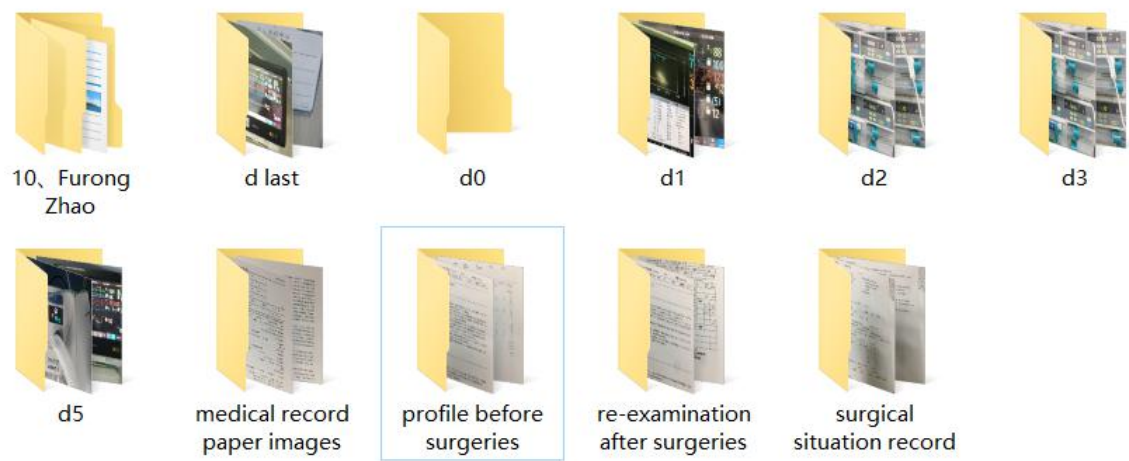
8 Reference

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9 Appendix

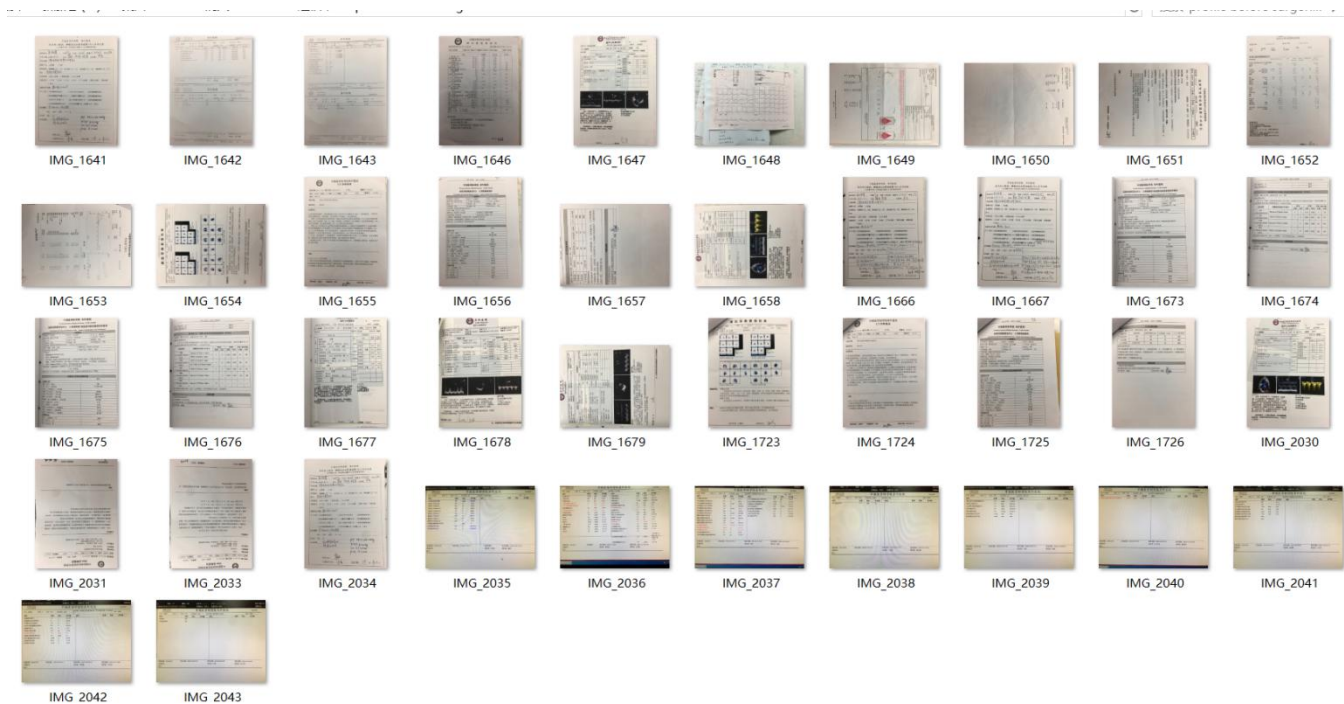
Sample of original medical record(1 patient)



A patient original medical record profile is documented,the shot imaging and scanning documents of different medical profiles of each patient is saved for further analysis.



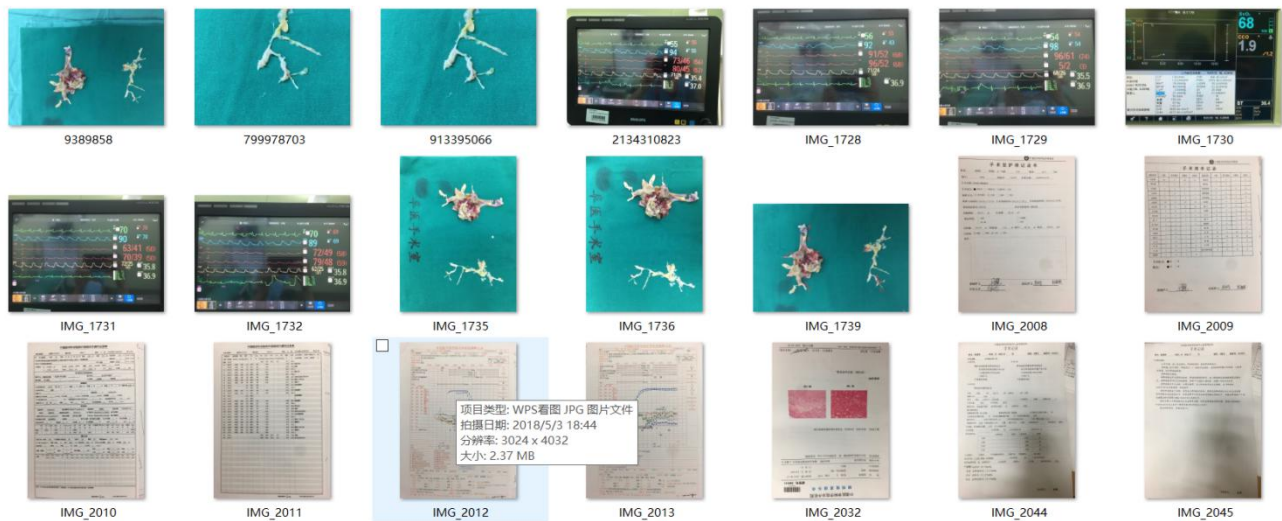
The original medical record is shotted so as to know the patient basic clinical profile,such as their genders,ages,disease history,medical complications before surgeries,and the post-operative prognosis,et al.



Main examinations images before surgeries, the result report paper of all the main examinations before surgeries, such as ultrasonic cardiogram, computed tomography, magnetic resonance imaging, right-sided heart catheterization, cardiac-pulmonary exercise test, pulmonary perfusion nuclide imaging, and other main blood test are pictured and saved for each patient.

血流动力学及血氧饱和度	
	基础
血流动力学	
HR (心率), bpm	68
BP (血压), mm Hg	123/79/100
SVC (上腔静脉压), mmHg	4
RAP (右心房压), mm Hg	6/4/4
RVP (右心室压), mm Hg	70/2/7
PAP (肺动脉压), mm Hg	69/31/44
PAWP (肺小动脉楔压), mm Hg	9/10/8
CO (心输出量), L/min	2.70
CI (心指数), L/min/m ²	1.64
CO (心输出量, Fick 法), L/min	2.05
CI (心指数, Fick 法), L/min/m ²	1.24
PVR (肺血管阻力), Wood U	13.33
TPR (全肺阻力), Wood U	16.30
SVR (体循环阻力), Wood U	35.56
血氧饱和度	
SVC (上腔静脉), %	51.6
RA (右心房), %	57.7
RV (右心室), %	57.5
PA (肺动脉), %	57.8
SaO ₂ (桡动脉), %	95.7

An example of the right-sided heart catheterization result before surgery, the original RHC report paper is pictured and saved for each patient.



An example of the surgical situation record. The pathological specimen pictures, the anesthesia record, the CPB record and monitor parameters immediately before and after surgeries is pictured and saved.



An example of the surgical specimen.



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The photos taken in the ICU, the main medical therapy method is seen in pic.427598833, and the parameters of right-sided heart catheterization were photographed, mainly including the pulmonary artery pressure, pulmonary vascular resistance, cardiac output et al.



A picture taken in the ICU, the parameters of right-sided heart catheterization is shown in this picture. The parameters shown in this monitor is a reflection of the post-operative hemodynamic result in the ICU period.



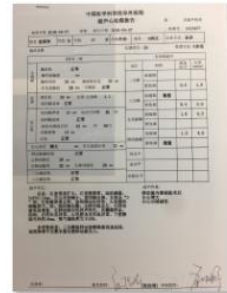
IMG_2003



IMG_2004



IMG_2019



IMG_2020

Re-examination after surgeries,including the UCG,CT scanning and pulmonary perfusion nuclide imaging et al.All the re-examinations result was pictured for each patient.

M型及二维				多普勒超声				
主动脉	瓣结构 正常			项目	时相		流速 (m/s)	压差 (mmHg)
	瓣开放幅度 mm			二尖瓣	收缩期			
	瓣环内径 22 mm 窦部前后径 32 mm				舒张期		0.5	1.0
左房	升主动脉径 28 mm 弓降部 正常			三尖瓣	收缩期	微量		
	前后径 30 mm 左房/主动脉 1.1				舒张期		0.4	0.6
左心室	房间隔延续 正常			主动脉瓣	收缩期		1.0	4.0
	室间隔厚度 10 mm 运动与后壁 反向				舒张期			
	室间隔延续 正常			肺动脉瓣	收缩期		1.0	4.0
	舒张末期前后径 42 mm EF 65 %				舒张期	微量		
后壁厚度 10 mm				房水平				
心包 正常					室水平			
右心房径 增大 mm 右心室前后径 31 mm				动脉水平				
肺动脉瓣结构 正常								
主肺动脉径 28 mm								
右肺动脉径 20 mm 左肺动脉径 20 mm								
二尖瓣结构 正常								
三尖瓣结构 正常								

超声所见:

右房、右室明显扩大,右室壁增厚,运动减弱,TAPSE:12mm。左心内径减小。室间隔左移,左室呈“D”形,左室壁厚度正常,室间隔运动异常,左室壁收缩幅度可。房、室间隔完整。主肺动脉及左、右肺动脉明显增宽,右肺动脉内低回声消失。各瓣膜形态、结构、启闭未见异常。心包腔未见明显异常。下腔静脉内径约18mm,吸气塌陷率大于50%。

多普勒检查:三尖瓣级肺动脉瓣微量高速返流,返流频谱不完整未能估测肺动脉压力。

超声印象:

肺动脉内膜剥脱术后
右心增大
右心功能减低

An example of the UCG result(written in Chinese) after surgeries.