Int J Clin Exp Med 2018;11(5):5087-5094
www.ijcem.com /ISSN:1940-5901/IJCEM0072924

Original Article

Analysis on hemodynamic change and related risk factors to heart failure in cesarean section for pregnant women with heart disease and pulmonary hypertension

Peirong Lin, Zhen Fan, Yuxi Hou, Liyun Zhao

Department of Anesthesiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Disease, Beijing City, China

Received January 17, 2018; Accepted February 27, 2018; Epub May 15, 2018; Published May 30, 2018

Abstract: Objective: To observe hemodynamic change in cesarean section for pregnant women with heart disease and pulmonary hypertension and analyze related risk factors to heart failure during and after the surgery. Methods: Prospective observational study on clinical data of 140 cases of pregnant women with cardio disease and pulmonary hypertension in cesarean section in obstetrics and gynecology was conducted in Beijing Anzhen Hospital from October 2012 and October 2017 to analyze hemodynamic change in peri-operative period. These enrolled patients were p erformed spinal anesthesia elective cardiac capacity monitoring. In addition, single factor analysis and logistic regression analysis of multi factors were adopted to analyze dangerous factors to heart failure during and after the surgery. Results: Firstly, compared with the basic blood pressure upon entering the room, blood oxygen (P=0.031) and blood pressure (systolic pressure (SBP), P=0.012; diastolic pressure (DBP), P=0.018) before anesthesia for the patient were reduced. Blood pressure (SBP, P=0.000; DBP, P=0.026) and systemic vascular resistance were reduced (P=0.015) three minutes after narcotized medication compared with that before anesthesia. Blood pressure (SBP, P=0.000; DBP, P=0.000), blood oxygen (P=0.015) and systemic vascular resistance (P=0.000) were all reduced three minutes after narcotized medication compared with that before delivery of the baby, but cardiac output (P=0.041) and heart rate (P=0.000) were increased. Blood pressure (P=0.036, P=0.039), systemic vascular resistance (P=0.029) and blood oxygen (P=0.039) of the patient were all increased and other indexes gradually and slowly recovered to the level before delivery of the baby. But heart rate of the patient was still relatively fast (P=0.046). Secondly, 15 cases were subject to heart failure among 140 cases in the data and the ratio was 10.7%. Analysis of single factors and multi factors showed hypoproteinemia (P=0.008, OR=2.015), increase of blood plasma brain natriuretic peptide (BNP) (P=0.024, OR=2.485), anemia (P=0.002, OR=2.484), reduction ejection fraction (P=0.019, OR=1.752), heart structure change (P=0.005, OR=5.012), cardiac function above III grade (P=0.000, OR=261.174), moderate-severe pulmonary hypertension (P=0.003, OR=4.912), rheumatic heart disease (P=0.039, OR=3.156) and systolic time interval (P=0.018, OR=20.228) are independent dangerous factors of heart failure. Conclusion: Hemodynamic change for pregnant women in peri-operative period is obvious and closely monitoring is needed. Moreover, heart failure risk of pregnant women with heart disease and pulmonary hypertension is related to hypoproteinemia, increase of blood plasma BNP, anemia, reduction of ejection fraction, heart structure change, cardiac function above III grade, moderate-severe pulmonary hypertension, rheumatic heart disease and systolic time interval.

Keywords: Pulmonary hypertension, gestation, hemodynamics, heart failure, dangerous factors

Introduction

Pulmonary hypertension (PH) is a malignant pulmonary vascular disease due to the increase of pulmonary arterial pressure with or without smaller pulmonary arterial disorders [1]. Heart failure can be easily caused by pulmonary arterial hypertension in gestational patients, which may threaten the life of fetus or babies. For the pregnant women with PH, the cardiac output will be increased by 30%-50% than that before gestation and the blood volume will also be increased by about 40%-50% in middle gestational period (32-34 weeks); the oxygen consumption of the whole body will be also increased by 20%, but the vascular resistance

of the whole body will be reduced [2]. Hence, there is basically no change of mean pulmonary arterial pressure in normal gestational period compared with that in pro-gestational period [2]. But the pulmonary artery cannot adapt to the change upon increase of cardiac output and blood volume for patients of pulmonary arterial hypertension due to pulmonary contraction and remolding and mean pulmonary arterial pressure is obviously increased compared with that before gestation, so that back load of the right ventricle was increased and finally lead to right heart failure [3]. Therefore, cesarean section is generally adopted for such patients to terminate gestation. It is the premise of maintaining stable circulation to understand hemodynamic change rule in the surgery [4].

In our study, hemodynamic change in peri-operative period for hospitalized pregnant women with heart disease complicated with pulmonary hypertension during cesarean section was observed and related dangerous factors for heart failure during and after the surgery were explored; it is now reported as follows.

Materials and methods

General data

The study was approved by the Ethics Committee of Beijing Anzhen Hospital and informed consent was signed by all included patients. A total of 150 gestational patients with heart disease complicated with pulmonary arterial hypertension subject to cesarean section at Beijing Anzhen Hospital during October in 2012 and October in 2017 were recuited; two cases with uncompleted data and eight premature delivery cases were excluded, so 140 cases were included.

Inclusion criteria

Patients meet the diagnosis of heart disease and pulmonary arterial hypertension; gestational patients in middle and later periods; patients selected cesarean section; there is no diagnosis manifestation in early and clinical stage before the surgery.

Exclusion criteria

Patients not meeting the diagnosis of pulmonary arterial hypertension; patients with symptom of heart failure in the early or clinical stage before the surgery; patients of premature delivery; patients with mental disorders who cannot cooperate.

Collection of general data

Including age, gestational times, pregnant weeks, past heart disease type, heart surgery record before gestation; a detailed physical examination, eye-ground examination, electrocardiogram, dynamic electro-cardiogram for 24 hours, cardiac color ultrasound inspection and related clinical blood inspection should be conducted once a month until six months after delivery and related data to the patient should be recorded in details.

Hemodynamic monitoring

General monitoring indexes include central venous pressure (CVP), systolic pressure (SBP), diastolic pressure (DBP), oxygen saturation (SpO_2) and heart rate (HR); monitoring indexes of cardiac output monitoring method with arterial pressure waveform (APCO) are cardiac output (CO), heart index (CI), stroke volume index (SVI) and systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) [5-7]; seven observation time points are: after entering the operating room (T1), before anesthesia, three minutes after anesthesia (T2), before delivery of the fetus (T3), three minutes after applying oxytocin (T4), five minutes after applying oxytocin (T5), before leaving the operating room (T7).

Diagnostic standard

It was diagnosed according to results of medical record, physical examination, electro-cardiogram, ultrasonic cardiogram. Diagnosis of pulmonary arterial hypertension: it was divided into three grades of minor, middle and serious grades, namely (30-50, ≥50-80, ≥80) mmHg according to determination of systolic pressure of pulmonary arterial hypertension through applying altrasonic diagnostics of tricuspid regurgitation [8]. Diagnosis of heart failure and cardiac function: Diagnosis was conducted in early and clinical periods of heart failure during and after the surgery in reference to the heart failure standard issued by International Cardiopulmonary Institute [9, 10]; cardiac functions were graded in reference to the standard

Table 1. General hemodynamic change in the operation (n=140, $\bar{x} \pm sd$)

Items	T1	T2	T3	T4	T5	T6	T7
CVP (mmHg)	6.6±2.7	6.8±2.8	6.7±2.9	6.7±2.7	6.8±2.9	6.9±2.8	7.2±2.9
SBP (mmHg)	142.8±24.5	137.4±21.9[a]	121.6±19.2[d]	141.6±26.7[b,c]	118.3±19.1[c,e]	118.8±20.6[b,c,f]	124.9±17.1
DBP (mmHg)	80.3±11.6	77.1±10.2[a]	74.5±10.5[c]	73.6±8.3[c]	68.9±10.2[c]	68.1±12.8[b,c]	74.1±9.8[h]
SpO_2 (%)	92.5±8.3	96.4±5.7[a]	96.7±5.8	96.8±6.0	94.7±7.9[d]	95.7±7.7[c]	95.4±7.8
HR (time/min)	90.9±14.9	90.1±13.7	89.8±14.8	89.7±14.0	97.6±13.7[d,f]	94.6±13.2[a]	94.9±16.9[a,g]

Note: [a]P<0.05 and [b]P<0.01 compared with those after entering the operation room (T1); [c]P<0.05 and [d]P<0.01 compared with the last time point; [e]P<0.05 compared with that before anesthesia (T2) and [f]P<0.05 compared with that three minutes (T3) after anesthesia medication; [g]P<0.05 compared with that before delivery of the baby (T4) and [h]P<0.05 compared with that three minutes after applying oxytocin (T5). Central venous pressure (CVP), systolic pressure (SBP), diastolic pressure (DBP), oxygen saturation (SpO_2) and heart rate (HR).

Table 2. Hemodynamic index change determined through APCO (n=140, $\bar{x} \pm sd$)

Items	T1	T2	T3	T4	T5	T6	T7
CO (L/min)	6.9±1.7	7.0±1.4	6.8±1.7	6.6±1.6	7.2±2.0[c]	7.1±1.7	7.1±2.1[g]
CI ($L \cdot min \cdot m^2$)	4.4±1.1	4.3±1.0	4.1±0.9	4.0±1.0	4.6±1.1[c,e]	4.2±1.1	4.3±1.1
SVI ($mL/beat \cdot cm^2$)	47.6±10.4	47.8±11.3	45.7±11.4	45.6±10.2	46.1±10.5	45.8±9.6	45.3±10.1
SVR ($dynes/sec \cdot cm^5$)		884.4±80.1	835.7±98.1[c]	887.6±105.6[a]	789.5±97.2[b,d]	832.9±102.4[c]	920.4±109.4[a,f,g]
SVRI/($dynes/sec \cdot cm^5 \cdot m^2$)		539.9±60.8	513.9±69.1[c]	541.9±73.5[c]	485.7±71.6[b,d]	510.9±70.6[c]	559.4±76.8[h]

Note: [a]P<0.05 and [b]P<0.01 compared with those after entering the operation room (T1) on indexes of SVR and SVRI; [c]P<0.05 and [d]P<0.01 compared with the last time point; [e]P<0.05 compared with that before anesthesia (T2) and [f]P<0.05 compared with that three minutes (T3) after anesthesia medication; [g]P<0.05 compared with that before delivery of the baby (T4) and [h]P<0.05 compared with that three minutes after applying oxytocin (T5). Cardiac output (CO), heart index (CI), stroke volume index (SVI) and systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI). APCO, arterial pressure waveform.

of American New York Association of Heart Disease [11].

Observational indexes

Hemodynamic index changes and related dangerous factors to heart failure during and after the surgery of the patient were observed.

Statistical analysis

SPSS17.0 statistical software was adopted for data analysis in the research. Mean ± standard deviation ($\bar{x} \pm sd$) was adopted to express measurement data such as ages and pregnant weeks, etc. and single-factor variance analysis was adopted for significance testing; repeated measured variance was adopted to analyze the repeated measured data in multi time points; enumeration data was expressed as frequency (percentage) and Fisher's exact test or X^2 test was adopted for the inspection.

Single factor analysis was firstly adopted to initially explore the relation between heart failure and various factors; then the variables with P<0.10 in single factor analysis were included for regression analysis model; the final variables were selected through condition forwardness method ($\alpha_{Inclusion}$=0.05, $\alpha_{Exclusion}$=0.10). There was statistical difference if P<0.05.

Results

Basic data of included patients

The average age of the 140 gestational patients with heart disease complicated with pulmonary arterial hypertension was 29.2±4.3 years old and gestational weeks were 34.1±2.9. Before the surgery, there were 104 primiparas and 36 multiparas with average systolic pressure (SBP) 142.8±24.5 and average diastolic pressure (DBP) 80.3±11.6 and mean pulmonary arterial pressure 58.4±12.9. There were 5 (3.57%) cases of I grade of cardiac functions, 4 (2.86%) cases of II grade, 19 (13.57%) cases of III grade and 119 (85.00%) cases of IV grade. As for heart disease type, there were 44 cases (31.4%) of atrial septal defect, 30 cases (21.4%) of ventricular septal defect, 3 cases (2.2%) in combination with atrial septal defect and ventricular septal defect, 16 cases (11.4%) of patent ductus arteriosus, 10 cases (7.1%) of Fallot's tetrad, 9 cases (6.4%) of eisenmenger, 5 cases (3.6%) of aortic stenosis, 3 cases (2.2%) of pulmonary stenosis, 2 cases (1.4%) of

Table 3. Comparison between the group with heart failure and the group without heart failure

Danger factors	Group of heart failure (n=15)	Group of no heart failure (n=125)	P
Age (years)	29.4±3.1	29.1±3.8	0.574
Multipara	4 (26.7)	32 (25.6)	0.584
Number of antenatal care			0.651
<6	3 (20)	26 (20.8)	
≥6	12 (80)	99 (79.2)	
Operation history			0.758
Have	4 (26.7)	30 (24)	
Not have	11 (73.3)	95 (76)	
Heart structure change			0.001
Have	11 (73.3)	35 (28)	
Not have	4 (26.7)	90 (72)	
Abnormal rate of electrocardiogram			0.007
Have	12 (80)	40 (32)	
Not have	3 (20)	85 (68)	
Cardiac murmur			
Have	9 (60)	48 (38.4)	0.016
Not have	6 (40)	77 (61.6)	
Cardiac function III grade (case)	9 (60)	12 (9.6)	0.001
Cardiac function above III Grade (case)	6 (40)	113 (90.4)	
Hypoproteinemia (g/L)	30.63±5.44	35.24±4.98	0.014
Increase of blood plasma BNP	841.25±215.32	125.14±264.86	0.003
Anemia (g/L)	108.42±15.63	120.45±16.64	0.007
Decrease of EF	46.52±3.93	55.64±4.23	0.026
PAH			0.001
Mild	6 (40)	88 (70.4)	
Moderate	4 (26.7)	30 (24)	
Severe	5 (33.3)	7 (5.6)	
CHD	4 (26.7)	111 (88.8)	0.001
STI	4 (26.7)	1 (0.8)	0.002
RHD	5 (33.3)	5 (4)	0.001

Note: CHD, congenital heart disease; STI, Systolic time interval; RHD, rheumatic heart disease; PAH, pulmonary arterial hypertension; EF, ejection fraction; BNP: brain natriuretic peptide.

dilated cardiomyopathy, 3 cases (2.2%) of transposition of the great arteries, 1 case (0.8%) of mitral stenosis, 9 cases (6.4%) of arrethmia, 5 cases (3.6%) of hypertensive heart disease; 34 cases (24.2%) with surgical treatment and 106 cases (75.8%) without surgical treatment.

Hemodynamic change during the surgery

Index change of central venous pressure (CVP), systolic pressure (SBP), diastolic pressure (DBP), oxygen saturation (SpO_2) and heart rate (HR); cardiac output (CO), heart index (CI), stroke volume index (SVI) and systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) can be found in **Tables 1** and **2**.

There was statistical difference in reduction of blood pressure (SBP and DBP) and SpO_2 at T2 compared with that at T1 (all $P< 0.05$), but there was no obvious difference in HR and CO at these two time points. There was statistical difference in reduction of blood pressure (including SBP and DBP) and systemic vascular resistance at T3 compared with that at T2 ($P<0.05$), but there was no obvious difference in HR, SpO_2 and CVP. Blood pressure (including SBP and DBP), SpO_2 and SVR were reduced and CO and HR wee increased at T4 compared with that at T5 ($P< 0.05$). Blood pressure, blood oxygen and systemic vascular resistance were all increased at T6 compared with that at T5. And at T6, the cardiac output were gradually and slowly recovered to the level at T4, while the HR of patients at T6 was still higher than that at T4.

Single factor analysis on factors related to heart failure

Heart failure of 15 cases (10.7%) in 140 cases occurred and they were diagnosed according to their physical signs, auxiliary examination and

Table 4. Logistic regression analysis result of multi factors for heart failure

Danger factors	Adjusted OR value	CI (95%)	P
Hypoproteinemia (g/L)	2.015	0.872-2.456	0.008
Increase of blood plasma BNP	2.485	2.269-2.841	0.024
Anemia (g/L)	2.484	2.158-2.874	0.002
Decrease of EF	1.752	1.654-2.741	0.019
Heart structure change	5.012	1.612-15.611	0.005
Cardiac function above III grade (case)	261.147	33.114-2,066.548	0.000
Moderate-severe PAH	4.912	1.714-13.945	0.003
STI	20.228	1.594-259.149	0.018
RHD	3.156	1.041-8.314	0.039

Note: STI, Systolic time interval; RHD, rheumatic heart disease; PAH, pulmonary arterial hypertension; EF, ejection fraction; OR, odds ratio; CI, confidence interval; BNP, brain natriuretic peptide.

symptoms including palpitation, chest tightness and wheezing, edema of both lower limbs, weak and oliguria. There were 21 cases of III grade of cardiac functions and 119 cases of IV grade of cardiac functions; it was predominant in congenital heart disease, rheumatic heart disease and hypertensive heart disease. The single-factor analysis showed that heart structure change rate (P=0.001), abnormal rate of electrocardiogram (P=0.007), cardiac murmur rate (P=0.016), the rate of cardiac functions above Grade III (P=0.001), hypoproteinemia rate (P=0.014), increase rate of blood plasma Brain natriuretic peptide (BNP) (P=0.003), anemia rate (P=0.007), reduction rate of ejection fraction (P=0.026), moderate-severe pulmonary hypertensive rate (P=0.001), rheumatic heart disease rate (P=0.001), rate of systolic time interval (P=0.002) in the group of heart failure were all higher than those indexes in the group without heart failure. There was no statistical difference in other indexes including age (P=0.574), primipara (P=0.584), rate of production inspection times (P=0.651) and operation record (P=0.758) in the two groups. See **Table 3**.

Logistic regression analysis of multi factors for heart failure

Observational indexes for which P<0.10 in single factor analysis were set as independent variables and whether heart failure occurred was set as the dependent variable. Logistic regression analysis was conducted on quantized and assigned multi factors such as hypoproteinemia (with=1, without=0), increase of blood plasma BNP (with=1, without=0), anemia (with=1, without=0), reduction of ejection fraction (<50%=1, ≥50%=0), heart structure change (with=1, without=0), cardiac functions above grade III (with=1, without=0), moderate-severe pulmonary hypertension (≥50 mmHg=1, <50 mmHg=0), rheumatic heart disease (with=1, without=0), systolic time interval (with=1, without=0).

The results indicated that OR value of hypoproteinemia, increase of blood plasma BNP, anemia, reduction of ejection fraction, heart structure change, cardiac functions above grade III, moderate-severe pulmonary hypertension, rheumatic heart disease and systolic time interval was over 1 and *P* value was less than 0.05, so they were considered as dangerous factors of heart failure, as shown in **Table 4**.

Discussion

Our study found that the three most important reasons for the primary affection for pulmonary arterial hypertensive patients are: atrial septal defect, ventricular septal defect and patent ductus arteriosus, which is consistent with reports abroad [12]. Peri-operative period of cesarean section is the risk period when pulmonary arterial hypertensive crisis and respiratory circulatory failure occur for gestational pregnant women in combination with pulmonary arterial hypertension. Hemodynamics is a branch of hydromechanics with very wide application scope and there is important meaning of the monitored indexes to change of various diseases and pathological and physiological change [13, 14]. It is generally considered that cyclical fluctuation in effect initiating phase of anesthesia and before and after delivery of the baby is relatively obvious and the research on hemodynamic change in the operation for such patients reported in current literatures is only limited to common vital signs (CVP) such as SBP, DBP, SpO_2, HR [15, 16]. In our study, continuous and accurate peripheral arterial pres-

sure signal of APCO was applied to monitor cardiac output, observe cardiac functions of the patients and monitor hemodynamic change in the operation based on common hemodynamics and our results indicated that blood pressure increase and fast heart rate might be related to tension, anxiety and pain in uterus constriction at T1, which was consist of the previous report [17]. Blood oxygen and blood pressure are obviously reduced, but there is no obvious change of heart rate and cardiac output at T2 compared with that at T1; blood pressure and systemic vascular resistance are both reduced, but thee is no obvious change of heart rate, blood oxygen and central venous pressure at T3 compared with that at T2; blood, blood oxygen and systemic vascular resistance are all reduced and cardiac output and heart rate are increased at T4 compared with that at T5, which may be related to "withdrawal phenomenon" of estrogen, etc. upon delivery [18]; blood pressure, systemic vascular resistance and blood oxygen of the patient are all increased at T6 and heart rate is still faster than that at T1. Cardiac agents such as dopamine, dobutamine, etc. can be pumped into vein of the patient for whom average arterial pressure reduces to 80 mmHg and SpO_2 is obviously reduced and blood oxygen cannot be maintained, so as to maintain the cardiac functions and complete the operation.

Rear load pressure of the right ventricle can be increased by long pulmonary arterial hypertension to cause right ventricular hypertrophy and to finally develop to right heart failure and even the whole heart failure. Patients in severe condition are more likely to suffer heart failure because heart load is too heavy for pregnant patients in late gestational period and delivery period [18]. Patients selection in our research was conducted according to heart failure diagnosis standard of International Cardiopulmonary Institute and heart failure of 15 cases (10.7%) among 140 cases occurred [10, 11].

Pathogenesis mechanism of heart failure is closely related to remolding of myocardium and ventricle to change heart structure [19]; for example, heart structure of pregnant women with rheumatic heart disease, systolic time interval and pulmonary hypertension is changed so as to conform to hemodynamic change. A research found that cardiac output was increased by 30%-50% in middle and late gestational periods compared with that before gestation, while the blood volume was also increased by 40%-50% along with it and oxygen consumption of the whole body was also increased by 20% with it; but the vascular resistance of the whole body would be reduced with it and cardiac reserve function on condition of anemia was reduced to induce heart failure [2]. Peripheral resistance is increased by increased blood pressure and heart failure is worsened due to insufficiency of blood volume. Heart failure can be rapidly diagnosed and cardiovascular event risk for heart disease patients can also be predicted by blood plasma BNP, which was widely applied in clinic [20]. It is also found in our research that hypoproteinemia, increase of blood plasma BNP, anemia, reduction of ejection fraction, heart structure change, cardiac function above III grade, severe pulmonary hypertension, rheumatic heart disease and systolic time interval, etc. are dangerous factors of heart failure during and after operation, which is consistent with above results.

There is certain limitation in our research due to relatively small sample quantity. Therefore, sample quantity should be increased and randomized controlled trial of large sample should be added for further research.

Comprehensively, hemodynamic change for pregnant women in peri-operative period is obvious and closely monitoring is needed and heart failure risk of pulmonary hypertensive pregnant women is related to hypoproteinemia, increase of blood plasma BNP, anemia and reduction of ejection fraction, heart structure change and cardiac function above III grade, severe pulmonary hypertension, rheumatic heart disease and systolic time interval.

Disclosure of conflict of interest

None.

Address correspondence to: Liyun Zhao, Department of Anesthesiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Disease, No.2 Anzhen Road, Chaoyang District, Beijing City 100029, China. Tel: +86-010-64456329; E-mail: zhaoliyun1007@163.com

References

[1] Obican SG and Cleary KL. Pulmonary arterial hypertension in pregnancy. Semin Perinatol 2014; 38: 289-294.

[2] Roche-Kelly E and Nelson-Piercy C. Managing cardiovascular disease during pregnancy: best practice to optimize outcomes. Future Cardiol 2014; 10: 421-433.
[3] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H and Luis Zamorano J. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J 2016; 37: 67-119.
[4] Fernandes SM, Arendt KW, Landzberg MJ, Economy KE and Khairy P. Pregnant women with congenital heart disease: cardiac, anesthetic and obstetrical implications. Expert Rev Cardiovasc Ther 2010; 8: 439-448.
[5] Akiyoshi K, Kandabashi T, Kaji J, Yamaura K, Yoshimura H, Irita K. Accuracy of arterial pressure waveform analysis for cardiac output measurement in comparison with thermodilution methods in patients undergoing living donor liver transplantation. Journal of Anesthesia 2011; 25: 178-183.
[6] Pugsley J and Lerner AB. Cardiac output monitoring: is there a gold standard and how do the newer technologies compare? Semin Cardiothorac Vasc Anesth 2010; 14: 274-282.
[7] Terada T, Maemura Y, Toyoda D, Iwasaki R, Sato N and Ochtai R. Semi-invasive monitoring of cardiac output in renal transplantation by a new device using arterial pressure waveform analysis compare with intermittent pulmonary thermodilution. Masui 2010; 59: 897-901.
[8] Akiyoshi K, Kandabashi T, Kaji J, Yamaura K, Yoshimura H, Irita K and Hoka S. Accuracy of arterial pressure waveform analysis for cardiac output measurement in comparison with thermodilution methods in patients undergoing living donor liver transplantation. J Anesth 2011; 25: 178-183.
[9] Madden BP. Pulmonary hypertension and pregnancy. Int J Obstet Anesth 2009; 18: 156-164.
[10] Gao L, Li J, Kasserra C, Song Q, Arjomand A, Hesk D and Chowdhury SK. Precision and accuracy in the quantitative analysis of biological samples by accelerator mass spectrometry: application in microdose absolute bioavailability studies. Anal Chem 2011; 83: 5607-5616.
[11] Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M and Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension: the task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS), endorsed by the international society of heart and lung transplantation (ISHLT). Eur Heart J 2009; 30: 2493-2537.
[12] Landgraf K, Bollig F, Trowe MO, Besenbeck B, Ebert C, Kruspe D, Kispert A, Hanel F and Englert C. Sipl1 and Rbck1 are novel Eya1-binding proteins with a role in craniofacial development. Mol Cell Biol 2010; 30: 5764-5775.
[13] Yagi H, Sumino H, Aoki T, Tsunekawa K, Araki O, Kimura T, Nara M, Ogiwara T and Murakami M. Impaired blood rheology is associated with endothelial dysfunction in patients with coronary risk factors. Clin Hemorheol Microcirc 2016; 62: 139-150.
[14] Shadden SC and Arzani A. Lagrangian postprocessing of computational hemodynamics. Ann Biomed Eng 2015; 43: 41-58.
[15] Martinez MV and Rutherford JD. Pulmonary hypertension in pregnancy. Cardiol Rev 2013; 21: 167-173.
[16] Shim SM, Yun YU and Kim YS. Folic acid alone or multivitamin containing folic acid intake during pregnancy and the risk of gestational hypertension and preeclampsia through meta-analyses. Obstet Gynecol Sci 2016; 59: 110-115.
[17] Hamlyn EL, Douglass CA, Plaat F, Crowhurst JA and Stocks GM. Low-dose sequential combined spinal-epidural: an anaesthetic technique for caesarean section in patients with significant cardiac disease. Int J Obstet Anesth 2005; 14: 355-361.
[18] Hemnes AR, Kiely DG, Cockrill BA, Safdar Z, Wilson VJ, Al Hazmi M, Preston IR, MacLean MR and Lahm T. Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute. Pulm Circ 2015; 5: 435-465.
[19] Tuder RM, Archer SL, Dorfmuller P, Erzurum SC, Guignabert C, Michelakis E, Rabinovitch M, Schermuly R, Stenmark KR and Morrell NW. Relevant issues in the pathology and pathobiology of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D4-12.

[20] Kampman MA, Balci A, van Veldhuisen DJ, van Dijk AP, Roos-Hesselink JW, Sollie-Szarynska KM, Ludwig-Ruitenberg M, van Melle JP, Mulder BJ and Pieper PG. N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. Eur Heart J 2014; 35: 708-715.