Noninvasive Assessment of Right Ventricle function and Pulmonary Artery Pressure Using Transthoracic Echocardiography in Women with Pre-eclampsia. An Exploratory Study

Ahmed Zaky[1], Michael Froelich[1], Jacob Meers[2], Adam Sturdivant[1], Ryan Densmore[1], Akila Subramaniam[3], Tekuila Carter[1], Alan Tita[1], Sadis Matalon[1], and Tamas Jilling[1]

[1]Affiliation not available
[2]The University of Alabama at Birmingham School of Medicine
[3]University of Alabama at Birmingham

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Abstract

Objectives: Much less attention has been given to the right heart and pulmonary circulation compared to the left heart and systemic circulation in patients with pre-eclampsia (PEC). We used transthoracic echocardiography (TTE) to estimate pulmonary artery pressure and right ventricular function in women with PEC. Methods: A case-control study at a tertiary care academic center. Ten early PEC (<34 week gestation) and nine late PEC ([?]34 weeks gestation) patients with eleven early and ten late gestational age-matched controls. Two dimensional TTE was performed on all patients. The estimated mean PA pressure (eMPAP) was calculated based on pulmonary artery acceleration time (PAAT). Pulmonary vascular resistance (ePVR) was estimated from eMPAP and right ventricular (RV) cardiac output. RV myocardial performance index (RV MPI), tricuspid annular plane systolic excursion (TAPSE), tissue tricuspid annular displacement (TTAD) and lateral tricuspid annular tissue peak systolic velocity (S') were measured. Results Compared to early controls, in early PEC the eMPAP and ePVR were elevated, PAAT was reduced, RV MPI was increased, TTAD was reduced and TAPSE and TV S' were unchanged. Compared to late controls, in late PEC, estimated MPAP and estimated PVR were elevated, PAAT was reduced and RVMPI was increased, while TAPSE, TTAD and TV S' were unchanged. Conclusions: Early PEC is associated with increased eMPAP and ePVR. A subclinical decrement of RV function is noticed. TTE is a useful screening tool for early detection of PH and RV dysfunction in PEC.

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Ahmed Zaky M.D.[1], M.P.H.[1], Michael A. Fröelich M.D.[1], Brad J. Meers M.D.[1], Adam B. Sturdivant, M.P.H.[1], Ryan Densmore M.D.[1], Akila Subramaniam M.D.[2,4], Tekuila Carter M.D.[1], Alan T. N. Tita M.D.[2,4], Sadis Matalon Ph.D.[1*] and Tamas Jilling M.D.[3*]

Departments of: (1) Anesthesiology and Perioperative Medicine, (2) Obstetrics and Gynecology, (3) Pediatrics and (4) Center for Women's Reproductive Health

University of Alabama at Birmingham School of Medicine

Birmingham, Al, 35233, USA

*S. Matalon and T. Jilling contributed equally to this work.

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A.Z. This author designed the study with T.J. and S.M., performed all TTE recordings, performed analysis of TTE recordings, analyzed data and drafted manuscript.

M.A.F. This author contributed to study design, data analysis and red/commented on the manuscript.

B.A.M. This author performed analysis of TTE recordings, contributed to data analysis and red/commented on the manuscript.

A.B.S. This author oversaw patient recruitment and consenting, collected/organized clinical data, contributed to data analysis and red/commented on the manuscript.

R.D. This author collected/organized clinical data, contributed to data analysis and red/commented on the manuscript.

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A.T.N.T. This author contributed to study design, data analysis and red/commented on the manuscript.

S.M. This author designed/directed the study with A.Z. and T.J., edited/finalized the manuscript.

T.J. This author designed/directed the study with A.Z. and S.M., analyzed data, edited/finalized the manuscript.

Corresponding author:

Ahmed Zaky, MD, MSc., MPH, FCCM

Associate Professor of Anesthesiology and Perioperative Medicine University of Alabama At Birmingham 950 Jefferson Tower 625 19th Street South Birmingham AL 35249-6810 Phone: 205 975 0189 Fax: 205 975 1948

Email: azaky@uabmc.edu (AZ)

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Abstract

Objectives: Much less attention has been given to the right heart and pulmonary circulation compared to the left heart and systemic circulation in patients with pre-eclampsia (PEC). We used transthoracic echocardiography (TTE) to estimate pulmonary artery pressure and right ventricular function in women with PEC.

Methods: A case-control study at a tertiary care academic center. Ten early PEC (<34 week gestation) and nine late PEC ([?]34 weeks gestation) patients with eleven early and ten late gestational age-matched controls. Two dimensional TTE was performed on all patients. The estimated mean PA pressure (eMPAP) was calculated based on pulmonary artery acceleration time (PAAT). Pulmonary vascular resistance (ePVR) was estimated from eMPAP and right ventricular (RV) cardiac output. RV myocardial performance index (RV MPI), tricuspid annular plane systolic excursion (TAPSE), tissue tricuspid annular displacement (TTAD) and lateral tricuspid annular tissue peak systolic velocity (S') were measured.

Results

Compared to early controls, in early PEC the eMPAP and ePVR were elevated, PAAT was reduced, RV MPI was increased, TTAD was reduced and TAPSE and TV S' were unchanged. Compared to late controls,

in late PEC, estimated MPAP and estimated PVR were elevated, PAAT was reduced and RVMPI was increased, while TAPSE, TTAD and TV S' were unchanged.

Conclusions: Early PEC is associated with increased eMPAP and ePVR. A subclinical decrement of RV function is noticed. TTE is a useful screening tool for early detection of PH and RV dysfunction in PEC.

Introduction

Pre-eclampsia (PEC) is a leading cause of maternal and perinatal morbidity and mortality worldwide affecting 1%-7% of all pregnancies[1]. PEC is defined, based on the most recent statement by the American College of Obstetricians and Gynecologists, as a systolic blood pressure [?]140mmHg or diastolic blood pressure [?]90 mmHg measured on two occasions at least 4 h apart and proteinuria, or in the absence of proteinuria, any signs of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms, all starting after 20 weeks of gestation[2]. The incidence of PEC has been increasing steadily in the US during the last thirty years[3] with about 50-60,000 related deaths per year worldwide[4].

Left ventricular function and the systemic circulation has been studied extensively in PEC[5, 6]. Much less attention has been paid to the pulmonary circulation and to RV function. The potential for increased pulmonary vascular resistance, elevated PA pressure and an effect on the RV in PEC is substantiated by the well-documented presence of circulating anti-angiogenic factors which are known to act on both the systemic and pulmonary vasculature [7, 8].

In this exploratory study, we hypothesize that PEC is associated with an altered echocardiographically-estimated surrogate of pulmonary artery pressure and pulmonary vascular resistance namely; pulmonary artery acceleration time. Furthermore, we hypothesize that PEC is associated with a decrement in RV function as assessed by quantifying RV MPI, RV FAC, indexed RV SV, indexed RV CO, TAPSE, TTAD and TV S' by transthoracic echocardiography.

Materials and Methods

Study design: A prospective cross-sectional study carried out at the University of Alabama At Birmingham from June 2016 to December 2016 and approved by the Institutional Review Board of the University of Alabama At Birmingham (RB-170119002) and written informed consent was obtained from all subjects.

Study population: Patients were enrolled sequentially as they met study inclusion criteria identified by the Obstetric Anesthesiology fellow at the time of daily patient board check out. A total of 46 patients with singleton pregnancies were enrolled into four groups: early and late PEC with early and late gestational age-matched normotensive pregnant controls. The incidence of PEC was defined and classified according to the American College of Obstetricians and Gynecologists (ACOG) (2013) revised criteria[2]. Early PEC was defined as PEC diagnosed at or before 34 weeks of gestation and late PEC was defined as PEC [?] 34 weeks of gestation. Blood pressure at the time of enrollment was measured manually according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in pregnancy. All of the measurements were performed in the left arm, in the sitting position, with the arm at the level of the heart. Patients underwent physical exams to rule out signs of severe PEC in the form of visual disturbances, headaches or right upper quadrant abdominal pain. Patients with severe preeclampsia, with history of heart failure or ejection fraction (EF) <40%, valvular heart disease, chronic hypertension, PA stenosis, congenital heart disease, and those who were in eclampsia, were excluded from the study. None of the patients had chronic kidney disease.

Echocardiography: TTE was performed on all participants upon the diagnosis of PEC and admission to the ward before delivery. All TTE exams were performed by a board-certified single provider (AZ) with a 10-year experience in echocardiography and ultrasonography, using the same device (SPARQ (Philips Vingmed Ultrasound, Horten, Norway) and transducer (S5-1, MHz phased-array). A second board certified observer (BJM) who was blinded to the patients' group designation and who had not attended the initial

examination analyzed the echocardiographic exams post hoc. The values entered by the initial examiner were concealed prior to the examinations entered by the second observer. Electrocardiography was recorded continuously during echocardiographic studies. Two-dimensional, M-mode, and tissue Doppler TTE imaging were performed according to American Society of Echocardiography guidelines[9].

A conventional, focused, and modified apical four-chamber view (mA4CW), parasternal long axis (PLAX), parasternal short axis (PSAX), left parasternal RV outflow, and the left parasternal RV inflow (RV) views were obtained. RV basal diameter (RV-Bd) was measured from mA4CW, focusing on RV at end-diastole. The right atrium (RA) long and short axis diameters (RAd-lax/RAd-sax) and right atrial area (RAA) were measured from mA4CW at end-systole. The RVOT outflow tract (RVOT) diameter was measured from left PSAX at end-diastole. RV free wall thickness (RV-FWT) was measured from left PLAX at end-diastole using M-mode. Pulsed wave Doppler was performed at the mitral, tricuspid, pulmonary, and aortic valves. RV systolic function was evaluated using the fractional area of change (FAC), tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler imaging of the peak systolic velocity of the lateral tricuspid annulus. TAPSE was measured using M mode from the apical 4 chamber view. RV diastolic function was estimated using early and late diastolic waves across the tricuspid valve and across the tricuspid annulus. RV myocardial performance index (RV MPI), a representation of the global systolic and diastolic function of the RV was calculated as described before using pulsed wave Doppler velocity and the formula RV MPI = (RV isovolumic contraction time (IVCT)) + RV isovolumic relaxation time (IVRT)/ RV ejection time (ET) [10]. RV ejection time was measured from the pulsed wave Doppler across the right ventricular outflow tract in the left parasternal RV outflow view. RV MPI reference range RV MPI < 0.4. RV cardiac output and stroke volume were calculated in accordance of guidelines[9]..

Apical 4 chamber views were specifically optimized to visualize the RV to obtain echocardiographic cine loops by recording 3 consecutive heart cycles with a frame rate > 60 frames/sec. Offline analyses were performed using a dedicated software (Qlab 10.3, Philips Healthcare). To assess tissue-tracking tricuspid annular displacement (TTAD) user defined 3 points were selected in RV focused view as follows: at the point of insertion of the lateral (TTAD L), and septal (TTAD S) leaflets and at midpoint (TTAD MP) of the tricuspid valve to the tricuspid annulus and the RV apex. The software automatically tracked tissue-tracking tricuspid annular displacement (TTAD) and calculated the TTAD at the RV free wall, the TTAD at the interventricular septal wall and the TTAD at the midpoint of TV annulus, as well as the percent displacement of midpoint (TTAD MP%). In some patients (n=1 in Early C, n=2 in early PEC, n=3 in late C and n=2 in late PEC) the image quality was inadequate to reliably assess TTAD and in the case of one patient there was no agreement between the two observers, resulting in exclusion from the analysis. The resulting number for TTAD measurements are listed in Table 3. The apical 4 chamber and the parasternal SAX views were used to measure left ventricular (LV) EF by the area-length technique[9]. LV endocardial fractional shortening measured by M mode, fractional area of change, and lateral mitral annular peak tissue velocity measured by tissue Doppler imaging, were all measured from the parasternal long axis, parasternal SAX, and apical 4 chamber views, respectively, according to guidelines[9].

Estimation of PA pressure by echocardiography: We first attempted to estimate PA systolic pressure using the Bernoulli equation (PAP = 4 x $TRvel^2$) from the tricuspid regurgitation jet velocity, in case a tricuspid regurgitant jet was discerned[11]. Since we only had three patients with reliably detectable tricuspid regurgitation jet, these data are not reported.

Since in most cases the tricuspid regurgitant jet was not discerned, the mean pulmonary artery pressure (MPAP) was estimated from the PAAT measured across the pulmonary valve using pulsed Doppler waveform. We were unable to use the most commonly used formulas that rely on linear equations to estimate MPAP (if PAAT is [?] 120ms, estimated MPAP = 79 - (0.45x PAAT), if PAAT is $<$ 120 ms, estimated MPAP = 90 - (0.62xPAAT), because several (5/11) control pregnant patients had PPAT beyond the cut-off limit of these equations (170 ms). Instead we used a logarithmic equation according to the formula validated by Kitabatake et al[12] and Yared et al [13], which is not limited by the extremes:

estimated $MPAP=10^{-0.0068*(PAAT)+2.1}$

PAAT-based analysis was also analyzed by categorical assessment using cutoff value of PAAT =100 ms. It was shown that in non-pregnant individuals, PAAT<100ms predicts PAH and increased pulmonary vascular resistance with a sensitivity of 84% and specificity of 90% [14].

Pulmonary vascular resistance was estimated from estimated MPAP and RV cardiac output (RV CO) using the following formula[15]:

'Estimated PVR=estimated MPAP/RV CO'

Estimation of left atrial pressure by echocardiography: We utilized a noninvasive method to assess the filling pressure for the left ventricle, which is based in measuring the E and A waves of mitral valve flow velocity and by measuring the velocity of the mitral annulus (e'). Mitral E/A >2 and E/e' >14 show good correlation with elevated LV filling pressures [16].

Statistical analyses: Statistical analyses were performed using Prism (GraphPad Software, La Jolla, CA), unless noted otherwise. The primary variables for assessing differences was estimated mean pulmonary artery pressure and PAAT. Since estimated pulmonary artery pressure is directly calculated from PAAT, we considered these as a single primary variable. All other variables reported are secondary variables. Continuous variables were presented as mean +- standard deviation. Normality test was calculated by four different methods automatically by Prism: Anderson-Darling (A2*) (AD), D'Agostino-Pearson omnibus (K2) (DP), Shapiro-Wilk (W) (SW) and Kolmogorov-Smirnov (distance) (KS). PAAT, RVMPI, maternal age, GA at admission, diastolic BP, Heart rate, RV FAC, RV COi and TAPSE passed normality tests by all four methods, estimated pulmonary artery pressure, RV SVi, Systolic BP passed three, BMI, estimated PVR, TTAD S and TTAD MP % passed two, MV E/e', TTAD L and TTAD MP only passed DP, MV E/A only passed KS, mean BP and GA at delivery did not pass any. For variables that failed at least two normality tests we used Kruskal-Wallis test with Dunn's post-hoc analysis. Variables that tested at least three normality tests were considered to be continuous variables and ANOVA was used with Bonferroni's post-hoc analysis. Categorical variables were analyzed using first by Fisher's exact test for 2x4 tables (VassarStats free online calculator developed by Richard Lowry, PhD;*http://vassarstats.net/fisher2x4.html*) followed by pairwise Fisher's exact test with Bonferroni's correction. A P value <0.05, after applying correction for multiple comparisons, was considered to be statistically significant. Inter-observer reliability was determined using Bland– Altman methodology and expressed as bias (mean difference) and 95% limits of agreement (2 X SD mean difference). The correlation between estimated MPAP and mean AP was analyzed using linear regression analysis. Since this is an exploratory study with the main purpose to determine whether a larger study is warranted, the sample sizes were not based on power calculation.

Results

A total of 46 women were enrolled. Six patients were excluded due to: Delivery at another institution (2), withdrawn consent (2), technical difficulties with echo (1) non-reassuring fetal heart tones (1), leaving 40 patients for final analysis. The 40 women studied were distributed into the 4 groups as follows: early PEC (N=10) matched early controls (N=11), late PEC (N=9) and matched late controls (N=10). Women with multiple gestations were excluded from the study. Demographic and clinical characteristics of the study groups are presented in Table 1. Mean maternal age and the incidence of smoking were not different across the four groups. The incidences of diabetes in the late PEC group and was significantly higher (P=0.011) than in the late control group. BMI was not significantly different between the groups, but all groups had high BMI and the number of obese patients was >50% in all groups. The mean gestational age in the early groups was significantly different from the late groups, as expected, and there was no difference between the mean gestational age of control and PEC cohorts within the early and late groups.

Systolic arterial pressures were significantly higher in the early and late PEC groups as compared to the corresponding control groups (Table 1). The diastolic arterial pressure was significantly higher only between

the early PEC and control groups (Table 1). Heart rates were not significantly different across groups (Table 1).

The estimated MPAP was within the normal reference range (8-20 mmHg) in the early control group (12.8+-6.0 mmHg, mean+-S.D. 95% C.I 8.8 – 16.8), whereas estimated MPAP in the early PEC group was above the normal reference range (31.4+-6.7 mmHg, mean+-S.D., 95% C.I. 26.6-36.2) and it was significantly higher than the early control group (12.8+-6.0 mmHg, mean+-S.D., 95% C.I. 9.8-18.0; Fig. 1 A; P<0.0001). Similarly, estimated MPAP was within the normal reference range in the late control group (13.9+-5.7 mmHg, mean+-S.D., 95% C.I. 9.8-18.0). The estimated MPAP in the late PEC group was slightly above the normal range (22.2+-4.9 mmHg, mean+-S.D., 95% C.I. 18.5-26.0), and it was significantly different from the late control group (P=0.024, 95% C.I. 18.5-26.0) (Fig. 1 A). At a PAAT cut off of 100 ms, there were significantly more patients with early PEC that had a PAAT < 100 ms compared with early controls (Table 2). There was no significant difference in the number of patients with PAAT<100 between late PEC and late controls (Table 2).

RV MPI was significantly increased in early PEC (0.32+-0.11 mmHg, mean+-S.D., 95% C.I. 0.25-0.40) and late PEC (0.36+-0.07 mmHg, mean+-S.D., 95% C.I. 0.30-0.41) compared to respective controls(Early control: 0.22+-0.06 mmHg, mean+-S.D., 95% C.I. 0.18-0.26) and (Late control: 0.25+-0.08 mmHg, mean+-S.D., 95% C.I. 0.19-0.31) (Figure 1, D). RV FAC, indexed RV SV, indexed RV CO, MV E/A, MV E/e', TAPSE and TV S' were not significantly different across any of the groups (Table 3). TTAD L was not significantly different across groups, but TTAD MP, TTAD S and TTAD MP % were all significantly decreased in early PEC vs early controls (Table 3) and Figure 2.

The Bland Altman assessment of PAAT between both observers showed a bias close to 0 (0.455) and the SD of bias was 8.61, revealing that there was no systematic bias between the two observers (Figure 3). Data shown in figure1 and supplemental figures 1 and 2 are by the first observer. Performing the analysis with the data obtained by the second observer resulted in identical statistical conclusions as performing the analysis with the data obtained by the first observer (data not shown).

Patients with a history of heart failure or those with EF < 40% were excluded from the study and none of the actual enrolled subjects had EF <55%. In all of the enrolled patients, LVEF measured by the area length methodology, LV endocardial fractional shortening, FAC and lateral mitral annular peak S' wave velocity were within normal limits and there were no statistically significant differences in these parameters of LV function across the groups (data not shown). Additionally, we assessed whether there are signs of elevated LA pressure based on recently validated criteria of E/A>2 or E/e'>14[16]. None of our patients had an E/A>2 or E/e'>14 that would indicate elevated left atrial pressure. Additionally, we plotted correlation between systemic mean arterial pressure (AP) and estimated MPAP (Figure 4). There was no positive correlation between mean AP and estimated MPAP, indicating that PAP was not simply "tracking" elevation of systemic pressure.

Discussion

In this exploratory study we demonstrate an echocardiographic evidence that suggests a subclinical increase in estimated mean PAP and estimated PVR, and a modest decrement in RV function in patients with an established diagnosis of early and late PEC compared with age- and gestationally- matched pregnant controls. Pulmonary artery acceleration time at cut off value of 100 ms differentiated patients with early PEC compared with controls, substantiating the likelihood of increased PA pressure. Likewise, validated equations that estimate mean PAP based on PAAT revealed an increase in estimated MPAP in PEC compared with controls. Estimated PVR was significantly elevated in both early and late PEC compared to controls. We detected significantly increased RV MPI and reduced mid-point TTAD in early PEC, but the change in RVMPI did not reach the threshold that is considered to be clinically significant (RVMPI>5), and other parameters of RV function, such as RV FAC, indexed RV SV, indexed RV CO, TAPSE, and TV S' were

unchanged. In the absence of clinical or echocardiographic evidence of valvular, or systolic, or diastolic LV dysfunction, we speculate that the increased estimated MPAP, decreased PAAT and increased estimated PVR are due to a pulmonary vascular phenomenon rather than a left heart disease etiology. Our study highlights the value of echocardiography as a safe and non-invasive tool in the assessment of cardiac structure and function in PEC patients.

Non-invasive assessment of the pulmonary circulation and RV function and structure in PEC is an evolving area of investigation. We are aware of only two studies assessing PA flow dynamics non-invasively in PEC, and both studies corroborate our findings in general, although by using slightly different methodology, without distinguishing between early and late onset PEC and without excluding patients with severe PEC[17, 18]. Importantly, although the gold standard for diagnosing PAH is right heart catherization, it is invasive and increases the risk of maternal and fetal radiation exposure. Echocardiographic estimation of PAP provides an invaluable non-invasive and safe screening tool for increased PA pressure that warrants further follow up and investigation. Similarly, echocardiography is a more feasible, bedside option of measuring RV function and structure compared to the gold standard, cardiac magnetic resonance imaging[19].

A recent meta-analysis of 21 published studies indicate that estimation of mean PAP using PAAT shows very good correlation with values obtained using catheterization, that a cutoff value of PAAT<100 ms has 84% sensitivity and 90% specificity in the diagnosis of pulmonary hypertension and that PAAT can be reliably measured in >90% of patients[14]. In our study we used both the method of using the PAAT<100ms cutoff value and also the estimation of MPAP to test whether there is evidence for increased PAP in PEC.

In our early PEC cohort, we found estimated mean PAP to be above the maximum of normal range. Both Caglar et al.[17] and Vaught et al.[18] found significantly increased estimated PA pressures in preeclamptic patients, but their reported values were below or at the limit of maximum normal pressure (20mmHg). The difference could be methodological, since they used TV regurgitant jet velocity for their estimate and we based our estimate on PAAT. Alternatively, the difference may be in the patient cohort analyzed as our findings suggest a greater effect in early PEC, and Caglar et al[17]. and Vaught et al. [18] did not analyze early PEC separately.

Our study is the first to assess TTAD in preeclamptic patients. TTAD detects the systolic displacement of the TV annulus, relative to the apex, at three points. As such, TTAD serves as a surrogate of the longitudinal deformation of the tricuspid valve annulus. The lateral point of TTAD (TTAD L) shows close correlation with TAPSE and mid-point TTAD (TTAD MP) has been shown to be more predictive of RV dysfunction in patients with PAH compared with TAPSE[20] and to better correlate with cardiac magnetic resonance imaging-measured RV EF[21]. As such, TTAD L did not show a difference between controls and PEC, whereas TTAD MP was significantly decreased in early PEC vs early controls.

Reduced RV function in PEC was shown by previous studies, yet with the use of different indices of assessment[17, 22]. The study by Melchiorre et al. [22] demonstrated biventricular increased wall thickness, and diastolic dysfunction, as well as reduced LV EF and cardiac output. Comparatively, we did not find a change in cardiac output or a biventricular diastolic dysfunction. These differences may be related to the study population. Our study did not include women with the diagnosis of severe PEC, and we excluded patients with low EF, whereas the study by Melchiorre et al [22] did not use these exclusions. Additionally, the latter study used TDI to assess strain and strain rate, a technique that suffers from some limitations[23]. The study by Vaught et al .[18] was consistent with our finding of increased RV MPI in PEC patients compared with controls, yet it demonstrated biventricular hypertrophy. This difference may be related to the study population. Vaught et al[18] studied parturients with early PEC and severe findings and we excluded patients with the diagnosis of severe preeclampsia. Collectively, our study aligns with the literature in terms of the presence of subclinical decrement in RV function and increased PA pressure in patients with early PEC. Notably, the mild changes in RV function can be considered to be subclinical. Whether the mildly reduced RV function is a consequence of increased afterload or whether it develops independently due to circulating mediators is yet to be determined. Intriguingly, a recent study found persistent abnormalities in RV function in women who formerly had early onset PEC for up to three years post-delivery[24].

Preexisting pulmonary arterial hypertension (PAH) portends an increased mortality in pregnancy and current recommendation for patients with preexisting pulmonary hypertension is to avoid becoming pregnant, due to a 15-40% incidence of mortality among women who become pregnant with preexisting PAH[25]. There is evidence that PEC and PAH share common mechanisms in their etiology [7, 26-29]. Therefore, we reason that changes in the pulmonary circulation and right ventricle function in PEC warrant further investigation.

Our study is limited by its small sample size and needs to be validated using a larger cohort that will also allow correlating echocardiographic estimates of MPAP and PVR with indices of disease severity. The small sample size precludes appropriate adjustment for comorbidities, which should be addressed in subsequent larger studies. Seven of the nineteen PEC patients in this study received anti-hypertensive therapy during the echo exam, which may have altered the echocardiographic findings compared with controls. However, none of the three drugs, labetalol, hydralazine or nifedipine are likely to cause an increase in PA pressure as we observed in this study in the PEC group. Instead, all three drugs have been proposed in the past to be used to treat PAH, although they were not shown to be effective. Given the cross-sectional design of our study, our echo exams were conducted very close to delivery. Hence the findings may represent a mixed pattern of pregnancy and labor rather than a single pattern. This can be remedied by studying serial exams in future studies. While PEC and control patients were matched by gestational age, there may be likely other systematic differences between the groups that could confound the results. Furthermore, due to the lack of 3-D capability of our echocardiography instrumentation at the time of the study, we were unable to measure 3-D volumetric LV EF, known to be more accurate echocardiographic modality of measurement of LV EF[30]. Furthermore, due to the lack of suitable apical LV 2 chamber views, we were unable to measure 2-D LVEF using the biplane modified Simpson methodology. The area-length method of LVEF estimation suffers from the limitations of geometric assumption of LV shape as well as sensitivity to foreshortening and wall distortions[9]. Yet, none of our patients had diseases that would lead to LV wall motion abnormalities known to affect the accuracy of this methodology. Rather, we used the area-length methodology to estimate LV EF as recommended by the American Society for Echocardiography and European Society of Cardiovascular Imaging. A normal LV FAC and the absence of clinical history or symptomatology of heart failure make us deduct that the elevated estimated MPAP is not due to a left heart pathology.

It is to be emphasized that echocardiographic indices of PAH are only estimations and they are used to raise the probability of PAH rather than to establish a conclusive PAH diagnosis.

In conclusion, non-invasive assessment of PA hemodynamics and RV function may have utility in assessing the cardiovascular status of PEC patients. Our findings suggest that there is an increase in estimated MPAP and estimated PVR in PEC, particularly in case of early onset. There is some evidence of a parallel mild deterioration of RV function, the significance of which is yet to be determined in future longitudinal studies. An adequately powered longitudinal study would also assess whether there is a correlation between echocardiographic findings of pulmonary hemodynamics and maternal and fetal outcomes and to assess responsiveness to antihypertensive therapy.

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Figure legends

Figure 1. *Elevated estimated PA pressure and pulmonary vascular resistance in PEC. Flow characteristics in the RV outflow tract (RVOT) were examined using TTE as described in methods. Data shown are scatter plots of individual measurements overlaid with Mean+-95% C.I. of: (A) Estimated mean pulmonary arterial pressure. Reference range is indicated by dashed lines. (B) RVOT Doppler waveform PAAT; inversely correlated with PA pressure and pulmonary vascular resistance). A 100ms cutoff (reference value) is indicated with dashed line. PAAT<100ms detects PAH with sensitivity=0.84 and specificity=0.9 (C) PVR estimated as PVR=(estimated MPAP)/RV CO, (D) RVMPI. estimated MPAP, estimated PVR and RVMPI increased and PAAT decreased in early PEC as compared to early and in late PEC vs late controls. Statistics by ANOVA with Bonferroni's post hoc analysis, * = P<0.05, ** = P<0.01, ***=P<0.01, **** = P<0.0001. PVR: pulmonary vascular resistance, estimated MPAP: estimated mean pulmonary arterial pressure; RVOT: right ventricular outflow tract; PAAT: pulmonary artery acceleration time; RV: right ventricle; MPI: myocardial performance index; PA: pulmonary artery; PEC: pre-eclampsia*

Fig.2*. Tissue-tracking tricuspid annular displacement (TTAD). TTAD was assessed at user-defined three points in RV focused view as follows: at the point of insertion of the lateral (TTAD L), and septal (TTAD S) leaflets and at midpoint (TTAD MP) of the tricuspid valve to the tricuspid annulus and the RV apex. Data shown are individual data points and mean+-S.D for each group for TTAD L (A), TTAD MP (B), TTAD S (C) and TTAD MP% (D). In TTAD MP, TTAD S and TTAD MP%, early PEC was significantly decreased as compared to early controls. Statistics by Kruskal-Wallis, exact P values are shown.*

Fig. 3. *Bland-Altman plot to illustrate inter-observer differences in assessing PAAT. The plot was generated by analyzing all measurements of PAAT performed by the first and second observers. Dashed lines indicate 95% limits of agreement. PAAT: pulmonary artery acceleration time*

Fig. 4*. Correlation between systemic mean arterial pressure (AP) and estimated MPAP. Mean AP and estimated MPAP were determined as described in methods and then plotted as shown. Data shown are: (A) correlation of estimated MPAP and mean AP in all control subjects and (B) correlation of estimated MPAP and mean AP in all PEC subjects. Linear regression is depicted in each graph by solid line. The slopes were not significantly different from 0 in either plots by linear regression. estimated MPAP: estimated mean pulmonary arterial pressure; PEC: pre-eclampsia*

Table 1 Maternal demographic information

	Statistics	**Early Control n=11**	**Early PEC n=10**	**Late Control n=10**	**Late PEC n=9**
Maternal Age (years) (Mean±S.D.)	ANOVA Overall P=0.14	28.4±4.9	29.7±7.4	27.38±4.8	29.2±5.8

Gestational Age At Admission (weeks) (Mean±S.D.)	ANOVA Overall P<0.0001	28.8±3.3	29.55±3.0	36.7±1.9 Vs early C P=0.0002	34.52±1.3 Vs early PEC P=0.010
Gestational Age At Delivery (weeks) (Mean±S.D.	K-W/Dunn Overall P=0.001	28.8±3.3	33.5±3.3	37.8±1.7 Vs early C P=0.002	36.7±1.1
Diabetes Yes (percent)	Fisher's Exact Overall P=0.019	3 (27)	1 (10)	0 (0)	5 (56) Vs. Late C P=0.02
BMI	K-W/Dunn Overall P=0.756	38.2±18.8	33.7±12.0	40.0±11.8	34.6±8.3
Smoker Yes (percent)	Fisher's Exact Overall P=0.48	3 (27)	0 (0) # (2)	1 (11) # (1)	1 (11)
Systolic Arterial Pressure (mmHg) (Mean±S.D.)	ANOVA Overall P<0.0001	116.3±10.6	142.6±14.5 Vs. Early C P=0.0008 -	135.8±16.4	157.0±16.5 Vs. Late C P=0.017
Diastolic Arterial Pressure (mmHg) (Mean±S.D.)	ANOVA Overall P=0.002	72.5±11.0	86.5±10.0 Vs. Early C P=0.002	74.9±12.5	81.3±9.2
Mean Arterial Pressure (mmHg) (Mean±S.D.)	K-W/Dunn Overall P=0.0006	87.1±9.8	105.2±10.4 Vs. Early C P=0.009	85.7±32.6	106.6±6.0
Heart Rate BPM (Mean±S.D.)	ANOVA Overall P=0.1643	81.6±8.6	93.5±16.2	89.0±11.5	84.4±12.6

Table 2. Distribution of observations based on accepted diagnostic criteria of PAH (PAAT<100 ms). Data were analyzed using Fisher's exact test, followed by pairwise analysis with Bonferroni's correction.

Overall P=0.00037	**Early Control n=11**	**Early PEC n=10**	**Late Control n=10**	**Late PEC n=9**
PAAT < 100ms (Diagnostic of MPAP>25mmHg and sPAP>38mmHg)	0 (0%)	6 (60%) Vs Early C P=0.008	0 (0%)	1 (11%)

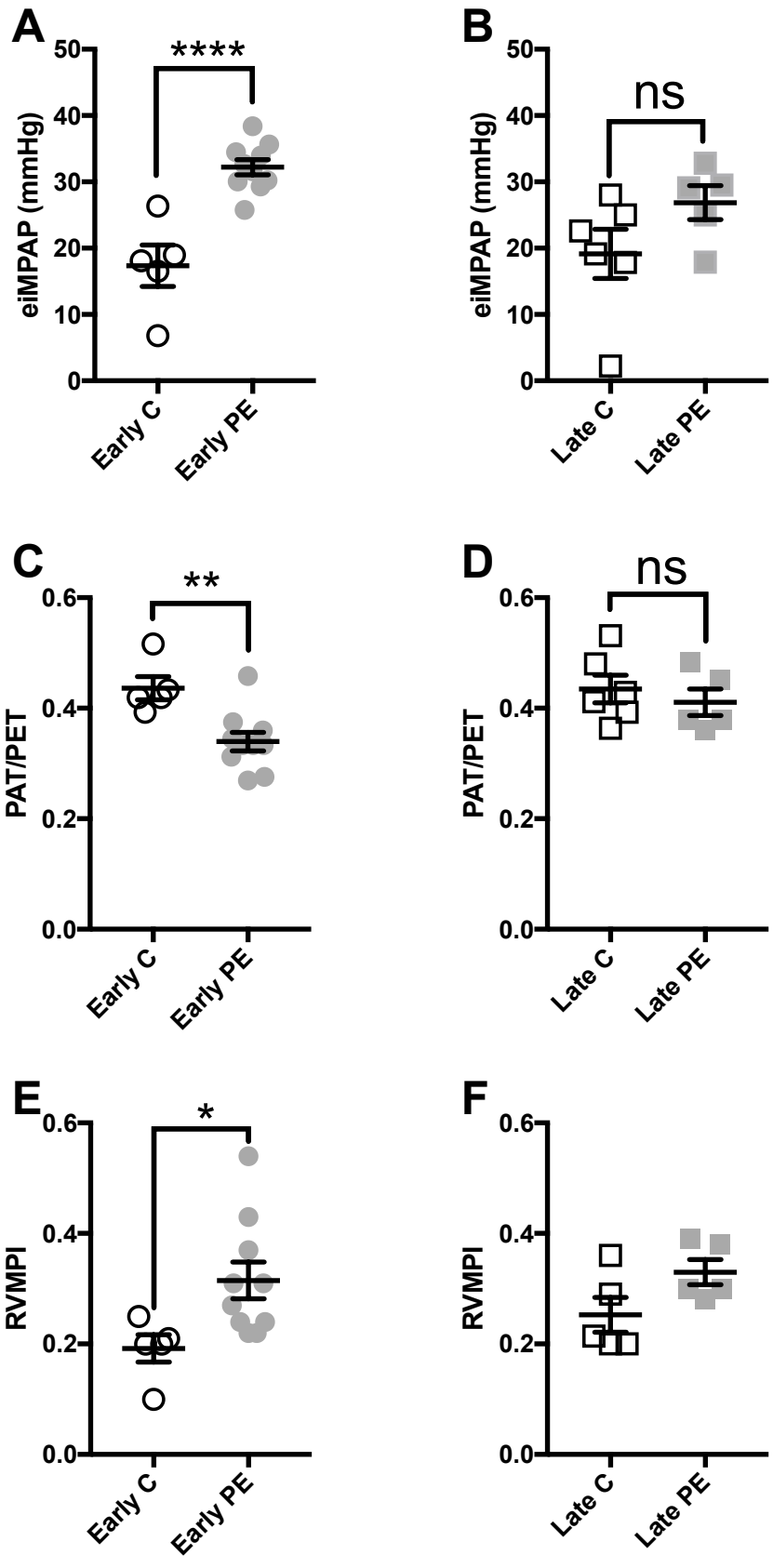
PAAT: pulmonary artery acceleration time; sPAP: systolic pulmonary artery pressure; MPAP: mean pulmonary arterial pressure; PEC: pre-eclampsia

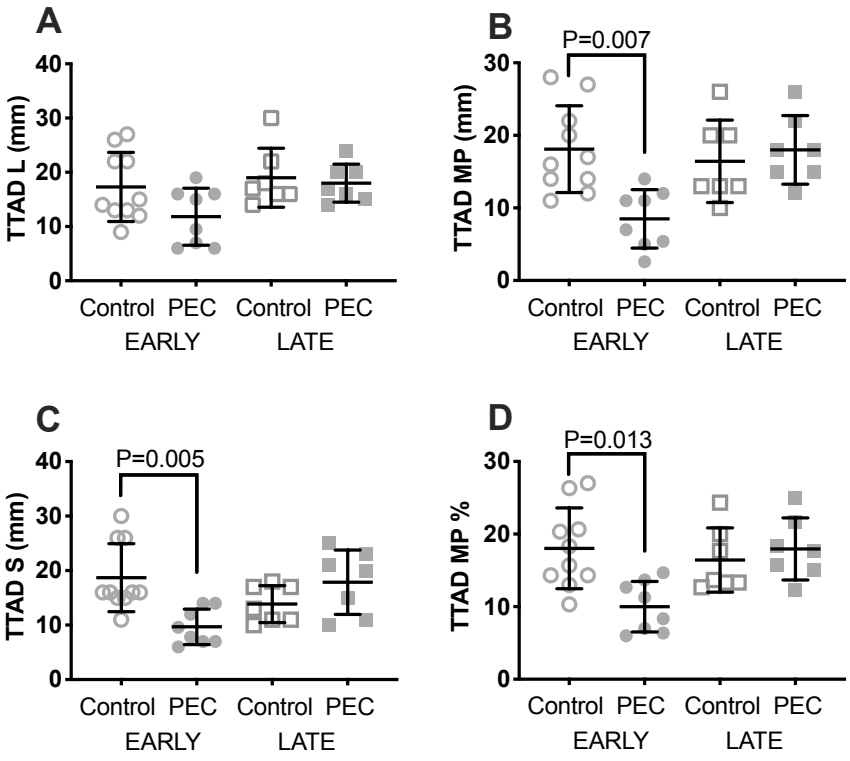
Table 3. Parameters of RV function. Statistics not labeled with * were analyzed by ANOVA with Bonfer-

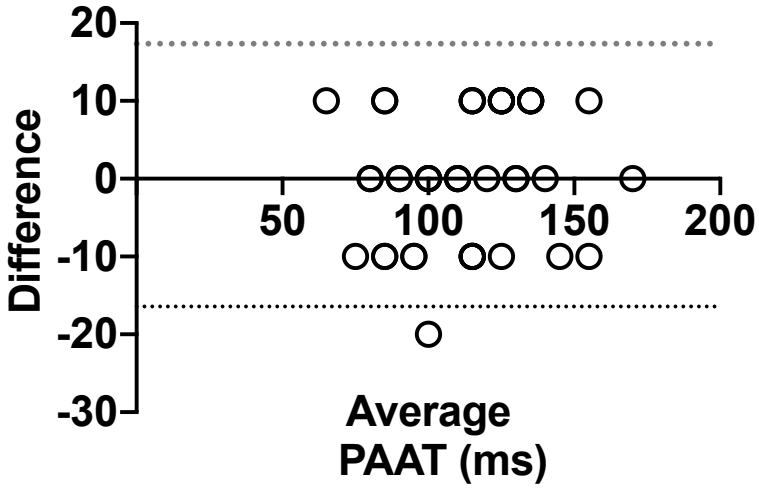
roni's post-hoc analysis and the ones labeled with * were analyzed by Kruskal-Wallis with Dunn's post-hoc analysis.

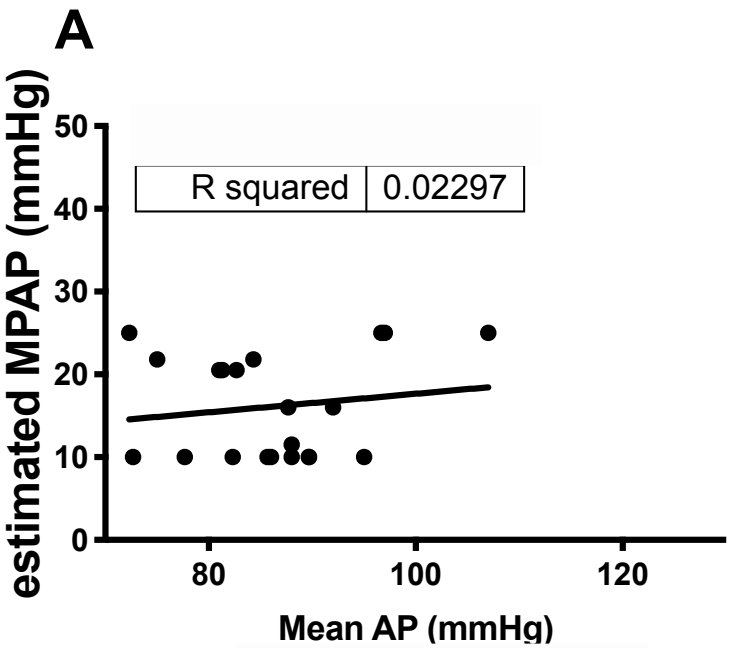
	Statistics	Early Control n=11	Early PEC n=10	Late Control n=10	Late PEC n=9
MV E/A	*P=0.12	1.46±0.33	1.25±0.16	1.54±0.61	1.22±0.29
MV E/e'	*P=0.24	7.70±2.14	8.52±3.08	7.75±2.54	6.53±2.84
RV FAC (%)	P=0.30	49.0±6.1	41.8±10.5	46.0±6.1	44.8±10.2
RV SV_i (mL/m^2)	P=0.69	23.6±7.8	26.8±10.2	26.0±6.3	28.0±7.2
RV CO_i ($L/min/m^2$)	P=0.33	4.1±1.2	4.6±0.8	5.2±1.5	4.4±1.6
TAPSE (cm)	P=0.74	2.77±0.4	2.71±0.1	3.00±0.5	2.79±0.6
TV S' (cm/s)	P=0.13	13.2±3.9	14.8±5.5	11.4±3.3	14.8±3.1
TTAD n		n=10	n=8	n=7	n=7
TTAD L (mm)	*P=0.11	17.3±6.4	11.8±1.9	19.0±5.4	18.0±3.5
TTAD MP (mm)	*P=0.004	18.1±6.0	8.5±4.0 P=0.008 vs Early Control	16.43±5.7	18.0±4.7
TTAD S (mm)	*P=0.005	18.7±6.2	9.7±3.3 P=0.005 vs Early Control	13.9±3.4	17.9±5.9
TTAD MP %	*P=0.007	18.0±5.6	10.0±3.5 P=0.013 vs Early Control	16.4±4.4	17.9±4.3

RV: right ventricle, TTAD: tissue tricuspid annular displacement, L: lateral; M: medial; MP: midpoint: MP%: midpoint percentage, SVi: stroke volume indexed to body surface area; COPi: cardiac output indexed to body surface area; TAPSE: tricuspid annular systolic excursion; FAC: fractional area of change; E/A: ratio of early to late peak diastolic velocity across the mitral valve; E/e': ratio of transmitral early diastolic peak velocity to early mitral annular peak diastolic velocity; PEC: pre-eclampsia









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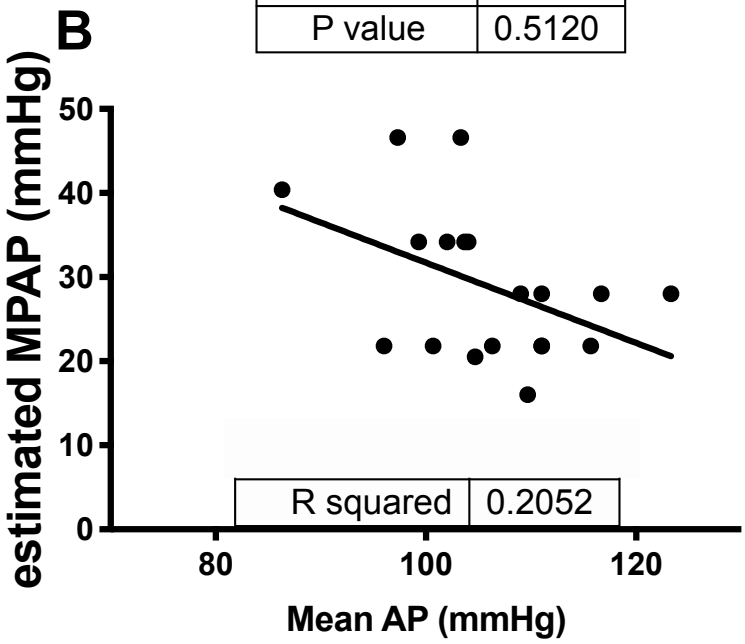
P value	0.5120



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