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A novel parameter derived from photoplethysmographic pulse wave to distinguish preeclampsia from non-preeclampsia

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ABSTRACT

Objective: To describe the comparative hierarchical area ratio (CHAR), a novel parameter derived from the photoplethysmographic (PPG) pulse wave and differences in CHAR values in parturients with and without preeclampsia (PE).

Methods: A total of 59 parturients (37 without and 22 with PE) was conducted at the Women's Hospital, Zhejiang University, School of Medicine in Hangzhou, China. We calculated the CHAR values derived from the PPG pulse wave and compared them in parturients with and without PE.

Result: The values of CHAR derived from the parturients with PE were lower compared to those without PE ($p < 0.01$). The ROC analysis indicated that the best threshold for the mean value of CHAR was 7.92 to predict PE with a sensitivity of 86.4% and a specificity of 87.1%, while the threshold for the standard deviation of CHAR was 0.76 with a sensitivity of 77.3% and a specificity of 77.4%. The area under the curve (AUC) was 0.91 for mean value of CHAR while 0.78 for standard deviation of CHAR. Meanwhile, a contrast of AUC between CHAR and the former parameter we proposed showed CHAR had better performance in distinguishing PE (0.908 over 0.615, $p < 0.01$).

Conclusion: The novel parameter, CHAR, derived from PPG pulse wave differs in parturients with and without PE with high sensitivity and specificity, suggesting that the CHAR might be an effective tool in differentiating the presence of PE.

1. Introduction

Preeclampsia (PE) is a disorder affecting 6–8% of pregnancies worldwide characterized by new onset hypertension and proteinuria after 20 weeks of pregnancy [1–5]. While the etiology of the disease has not been fully elucidated yet, several factors are associated with PE, including maternal age, parity, prior PE, multiple gestation, and obesity [1,2]. PE could can result in maternal cerebrovascular, cardiac, hepatic, hematologic, and renal complications, as well as prematurity, growth restriction and neonatal mortality [6–8]. Given the morbidity and mortality associated with PE, accurate identification and diagnosis of parturients with PE is critical to provide the best care possible [9,10].

While blood pressure and proteinuria are both widely used as criteria to diagnose PE, proteinuria is not necessarily always present thus making blood pressure the more important factor to diagnose the disease [11]. Other physiologic markers, including the pulse waveform, have been recently investigated as potential noninvasive methods of diagnosing PE [12–15]. One of the major advantages of the pulse waveform is that it can be monitored continuously at the digits, providing detailed information about the peripheral vascular bed. Recently, the augmentation index (AIX) has been used in pulse waveform analysis for clinical purposes [9,14–16]. However, AIX is derived from invasive blood pressure pulse data so its real time clinical guidance is limited. Therefore, use of the photoplethysmographic (PPG) pulse wave may be the optimal approach for continuously obtaining noninvasive measurements [12,13].

Prior studies have described the diversity in PPG waveform shapes and have proposed several parameters to describe those shapes,

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including the ratio of mean-to-peak wave amplitude and the area difference ratio (ADR) [17,18]. While use of the ADR to differentiate parturients with PE from those without PE has been previously described, the ADR does not offer a complete understanding of PE and thus more analyses of the PPG waveforms is necessary.

In this study, we described a novel parameter, the comparative hierarchical area ratio (CHAR), which may be useful to help diagnose hypertensive disorders of pregnancies.

2. Methods

2.1. Study subjects

Study subjects were recruited from the Department of Gynaecology and Obstetrics at the Women's Hospital, Zhejiang University, School of Medicine from June 2017 to April 2018. The study was approved by the Research Ethics Committee (No. 20140047) and written informed consent was obtained from all participants. A total of 37 normotensive parturients were enrolled to study the basic elements of the CHAR. In addition, 22 parturients with PE were enrolled to describe differences, if any, in the CHAR between parturients with PE and those without. For the purposes of this study, PE was defined as a pregnancy after 20 weeks of gestation complicated by new onset hypertension (blood pressure ≥140/90 mm Hg on two separate readings, 2 h to 2 weeks apart) and proteinuria (urine dipstick with ≥2+ protein at presentation, or 24-hour urine protein ≥300 mg/d) [11,19].

Parturients were excluded from enrollment if they had a history of cardiovascular, renal, or other hypertension-associated disease, were taking antihypertensive drugs, had pregestational diabetes, or had a history of alcohol or illicit drug abuse. Parturients were also excluded if they had multiple gestation, congenital fetal abnormalities, fetal chromosomal disorders, or were conceived by in vitro fertilisation.

2.2. Data acquisition

The PPG pulse wave was recorded using the CARESCAPE B650 Patient Monitor, our standard medical monitoring device (General Electric Company, Boston, USA) with a sample rate of 100 Hz. After the study subject had at least 5 min of rest, the oxygen sensor (DS-100A Durasensor, OxiMax, Nellcor Puritan Bennett Inc, USA) was placed on the index finger of the non-dominant hand. The PPG signals were processed by the device in arbitrary units and exported to a PC as comma-separated values for further analysis.

2.3. Morphologic characteristics of the PPG pulse wave

The morphologic characteristics of the PPG pulse wave were studied and compared between groups of the health parturients and those with PE. The characteristic PPG pulse waveforms from parturients with and without PE are shown in Fig. 1. The amplitude and duration of the waveform were higher, and the notch of the pulse was obscured in parturients with PE. However, our pre-research suggested that these parameters were limited in distinguishing PE.

2.4. Comparative hierarchical area ratio

We proposed the hierarchical area ratio (HAR) as a novel parameter to better understand vessel elasticity and blood viscosity from the PPG pulse wave morphology. To calculate the HAR, the peak amplitude of the PPG pulse wave is divided into 10 equal segments as shown in Fig. 2. And the descending domain of PPG (the part from point P to U_2) was segmented into 10 area pieces. Then, the ratio of each individual piece (S_i) to the total area of all the descending domain (S) is calculated as the HAR in the formula 1: $HAR_i = S_i / S$. To simplify understanding of the HAR, the CHAR was calculated by dividing the sum of S_9 and S_{10} by the sum of S_1 and S_2, such that its formula can be simplified as in the

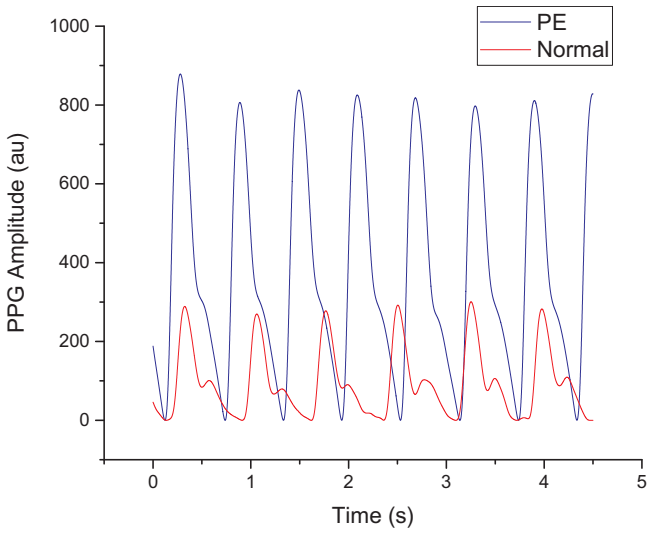

Fig. 1. Two typical pieces of PPG pulse wave data in the study. Signals from the parturients with/without PE were drawn in different colors. There were differences in the duration and amplitude of the pulses as well as the positions of notch points. PPG pulse wave signals were shown with magnitudes in arbitrary units (au).

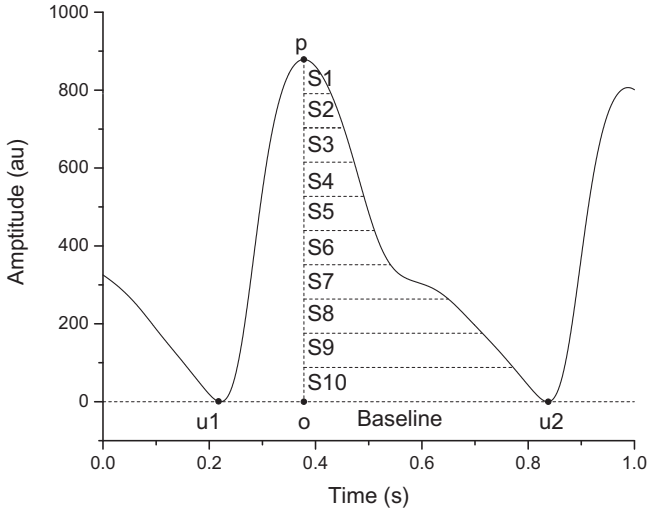

Fig. 2. The schematic of CHAR in a PPG pulse wave. Baseline was adjusted to 0. Point P and G were the peak and end position of the pulse respectively. Point O was the vertical projection of point P on the baseline. PPG pulse wave signal was shown with magnitude in arbitrary units (au).

formula 2: $CHAR = (S_9 + S_{10}) / (S_1 + S_2)$.

2.5. Statistical analysis

Raw data filtering, pulse wave detection and calculation of the study parameters were performed using MATLAB (R2010b, MathWorks, Inc.). All PPG pulse wave data acquired were analyzed based on the CHAR calculation algorithm we developed. CHAR values were calculated and individually evaluated to avoid unexpected errors prior to statistical testing. Statistical analysis was performed using SPSS Statistics (version 25.0, IBM, Inc.). Student's *t* test and the Mann-Whitney *U* test were used for categorical variables. The receiver operator curve (ROC) and area under the curve (AUC) were also calculated. All figures were generated using Origin Pro (version b9.2.272, Northampton, MA, USA).

Table 1
Demographic information of study participants.

	Healthy parturients (n = 37)	Preeclamptic parturients (n = 22)	*p* value
Age (years)	32.0 ± 3.7	33.8 ± 5.2	0.226
Height (cm)	160.4 ± 3.7	158.4 ± 4.9	0.155
Weight (kg)	67.3 ± 8.1	72.1 ± 11.6	0.159
BMI (kg/m^2)	26.1 ± 3.2	28.7 ± 4.2	0.008*
Gestational weeks at sampling (weeks)	34.6 ± 4.2	33.4 ± 4.3	0.421
Heart Rate (beats per minute)	83.7 ± 13.8	85.7 ± 10.4	0.414
SBP (mm Hg)	110.8 ± 9.6	158.6 ± 19.5	< 0.001*
DBP (mm Hg)	66.4 ± 10.1	93.7 ± 13.8	< 0.001*

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; *Statistically significant.

3. Results

3.1. Demographics

Twenty-two parturients with PE and thirty-seven parturients without PE were enrolled in the study. Demographic information of the participants was summarized in Table 1. There were no clinically significant baseline differences in age, height, weight, BMI, heart rate, and gestational age at sampling between healthy parturients and those with PE. As expected, the Preeclamptic parturients had significantly higher systolic and diastolic blood pressures compared to the healthy parturients.

3.2. Comparative hierarchical area ratio

The raw CHAR values of parturients with and without PE for every PPG pulse wave are shown in Fig. 3. Parturients with PE had smaller variation ranges and smaller mean values of CHAR. Statistics showed that the mean value of CHAR was 6.87 (range 5.27–9.02) for PE parturients and 10.45 (range 4.73–18.68) for healthy parturients. To better understand how the CHAR value may predict PE, CHAR was validated using ROC with the mean and standard deviation value of CHAR as check variables (see Fig. 4). The AUC was 0.91 when using the mean value of CHAR to indicate PE and AUC was 0.78 when using the standard deviation of CHAR. The optimal threshold given by ROC analysis for mean value of CHAR was 7.92: a mean value of CHAR ≦7.92 predicted PE with a sensitivity of 86.4% and a specificity of 87.1%. The corresponding threshold value was 0.76 for standard deviation of CHAR (sensitivity 77.3%, specificity 77.4%). Further mean was plotted against standard deviation value of CHAR in Fig. 5. In 9 of 59 subjects, mean value indicated PE that was not indicated by the standard deviation. In 3 of the 9, patients were without PE. In 8 of 59 subjects, the standard deviation indicated PE that was not indicated by mean value. In 6 of the 8, patients were without PE.

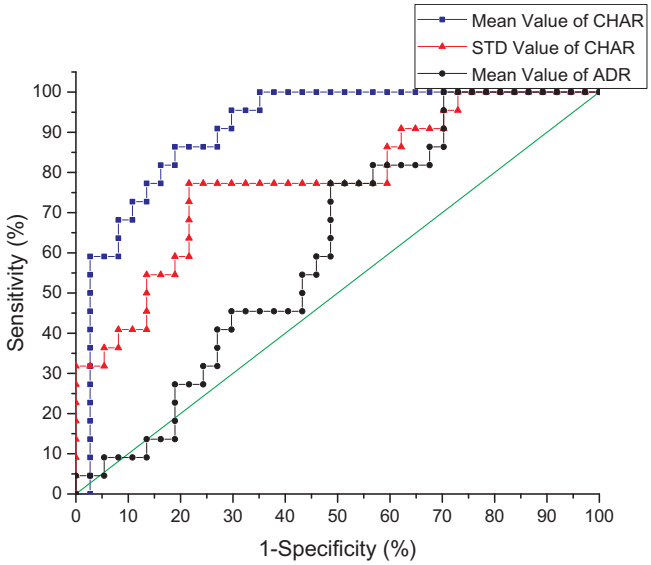

Fig. 4. ROC plot of the parameters indicating PE. Mean value of CHAR was drawn with blue line, standard deviation of CHAR was drawn with red line and mean value of ADR with black line. The AUC were 0.91, 0.78 and 0.62 respectively. Line of identity was also drawn in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

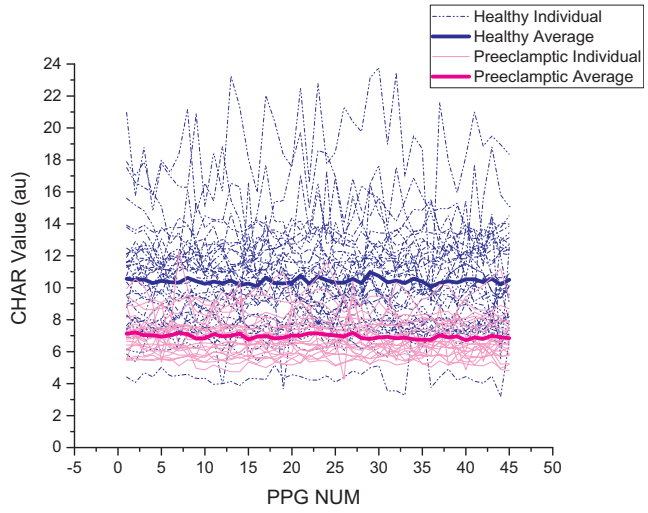

Fig. 3. The CHAR Trends for parturients with PE (solid line in light magenta) and without PE (dash dot line in bule). Individual and average response of CHAR were marked with different line widths for parturients as well (thin for individual and thick for average). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

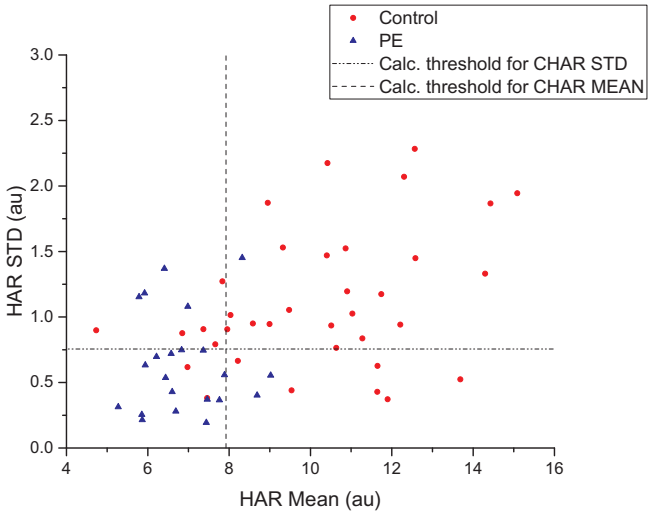

Fig. 5. Plot of mean value against standard deviation. Mean values of CHAR were plotted against the corresponding standard deviation values of CHAR, n = 59. Stars indicated preeclamptic parturients and circles indicated healthy parturients, lines indicated threshold values calculated by ROC analysis for PE (7.92 and 0.76 respectively).

3.3. Contrast between comparative hierarchical area ratio and area difference ratio

Both ADR and CHAR were proposed by our research group as parameters that may distinguish parturients with and without PE. The ADR proposed by our group has showed the ability to distinguish the presence of PE with limited sensitivity and specificity [18]. We compared ADR and CHAR to determine if either have any advantages. When the range of the two parameters differed even for same pulse (values < 1 for ADR while > 8 normally for CHAR), ROC analysis was used for the comparison. As demonstrated in Fig. 4, the AUC was 0.62 for ADR and 0.91 for CHAR which suggests that CHAR had an advantage over ADR in distinguishing PE.

4. Discussion

In this study, we describe the CHAR, a novel morphologic parameter of the PPG pulse wave. We observed that CHAR values were lower and had smaller variation ranges in parturients with PE compared to those without. We also found that CHAR had a high sensitivity and specificity in distinguishing PE.

Why CHAR values appear to be different in parturients with PE compared to those without remains to be further studied. One possible explanation is that CHAR might be a reflection of changes that occur within the vascular bed with PE, such as an increase in peripheral vascular resistance and stiffness, mean arterial pressure, and a decrease in small artery compliance, systemic blood flow and cardiac output [20–22]. Given that hemodynamic changes associated with PE occur throughout the vascular system, it is not surprising that the PPG pulse wave would be affected as the digits contain numerous arterioles, venules and capillaries. CHAR demonstrates the changes of the vascular bed indirectly as the descending domain of the pulse is quantitated through the CHAR calculation. The increase in the area of S_1 and S_2 and decrease in area of S_9 and S_{10} might be expected when vascular stiffness and resistance rise during PE (see Fig. 2 and Formula 2).

There are several features on pulse waveform analysis which are observed in parturients with PE, of which the AIX is most commonly used [9,14,15]. However, because AIX is calculated from the central aortic pulse derived from radial artery tonometry, its clinical use is limited. One of the major advantages of calculating the CHAR is that it can be obtained noninvasively to distinguish parturients with and without PE. Given that the AUC of mean CHAR value is greater than that of mean ADR (see Fig. 5), CHAR is superior to ADR in distinguishing parturients with and without PE.

This study has several important limitations. First, we have observed that in parturients who have already been diagnosed with PE by traditional criteria during the late part of gestation, the CHAR value differs compared to those without PE. However, this does not necessarily mean that CHAR could be used as a predictive tool prior to the traditional diagnosis of PE. Second, because we had a relatively small sample size in our study, results obtained could potentially different with larger sample sizes. Third, because we specifically studied parturients with PE, it is unclear if there would be a difference in parturients with PE compared to those with simply gestational hypertension or hypertension of any other non-PE related reasons.

Our study suggests a novel parameter to describe the morphology of the PPG pulse wave of parturients with PE. The parameter might be useful to distinguish parturients with and without PE. However, further studies are needed to better understand how CHAR might be useful in the clinical setting. Of particular interest would be to determine if CHAR could be used in the earlier stages of pregnancy, perhaps even before the traditional diagnosis of PE. Future studies should be performed to determine if CHAR may be useful as an early diagnostic tool.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.01.005.

References

[1] X.L. Li, P.L. Guo, Y. Xue, W.L. Gou, M. Tong, Q. Chen, An analysis of the differences between early and late preeclampsia with severe hypertension, Pregnancy Hypertension: Int. J. Women's Cardiovascular Health 6 (2015) 47–52, https://doi.org/10.1016/j.preghy.2015.12.003.
[2] K. Duckitt, D. Harrington, Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies, BMJ. 330 (2005) 565–567, https://doi.org/10.1136/bmj.38380.674340.E0.
[3] N. Varnier, M.A. Brown, M. Reynolds, F. Pettit, G. Davis, G. Mangos, A. Henry, Indications for delivery in pre-eclampsia, Pregnancy Hypertension: Int. J. of Women's Cardiovascular Health 11 (2018) 12–17, https://doi.org/10.1016/j.preghy.2017.11.004.
[4] M.A. Brown, Pre-eclampsia: a lifelong disorder, Med. J. Aust. 179 (2003) 182–184.
[5] C.M. Koopmans, D. Bijlenga, H. Groen, S.M. Vijgen, J.G. Aarnoudse, D.J. Bekedam, P.D.B. Van, K.B. De, J.M. Burggraaff, K.W. Bloemenkamp, Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial, Lancet 374 (2009) 979–988, https://doi.org/10.1016/S0140-6736(09)60736-4.
[6] L. Cui, C. Shu, Z. Liu, W. Tong, M. Cui, C. Wei, J.J. Tang, X. Liu, H. Hai, J. Jiang, J. He, D.Y. Zhang, F. Ye, Y. Li, Serum protein marker panel for predicting pre-eclampsia, Pregnancy Hypertension (2018), https://doi.org/10.1016/j.preghy.2018.01.009.
[7] N. Al-Jameil, K.F. Aziz, K.M. Fareed, H. Tabassum, A brief overview of pre-eclampsia, J. Clin. Med. Res. 6 (2014) 1, https://doi.org/10.4021/jocmr1682w.
[8] S. Rana, C.E. Powe, S. Salahuddin, S. Verlohren, F.H. Perschel, R.J. Levine, K.H. Lim, J.B. Wenger, R. Thadhani, S.A. Karumanchi, Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia, Circulation 125 (2012) 911–919, https://doi.org/10.1161/CIRCULATIONAHA.111.054361.
[9] G. Fullerton, M.A. Crilly, S. Bhattacharya, P.J. Danielian, Measurement of aortic augmentation index in pregnant women with raised blood pressure and subsequent outcomes: a preliminary prospective cohort study, Hypertension Pregnancy 33 (2014) 476–487, https://doi.org/10.3109/10641955.2014.946612.
[10] J.S. Cnossen, K.C. Vollebregt, N.D. Vrieze, G.T. Riet, B.W.J. Mol, A. Franx, K.S. Khan, Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis, BMJ 336 (2008) 1117–1120, https://doi.org/10.1136/bmj.39540.522049.BE.
[11] The American College of Obstetricians and Gynecologists, Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, Obstetrics Gynecol. 122 (2013) 1122–1131, https://doi.org/10.1097/01.AOG.0000437382.03963.88.
[12] F. Su, Z. Li, X. Sun, N. Han, L. Wang, X. Luo, The pulse wave analysis of normal pregnancy: Investigating the gestational effects on photoplethysmographic signals, Bio-Med. Mater. Eng. 24 (2014) 209–219, https://doi.org/10.3233/BME-130801.
[13] N. Han, X. Luo, F. Su, A quantitative investigation of hemodynamic adaptation to pregnancy using uterine artery Doppler ultrasonography and finger photoplethysmography, Hypertension Pregnancy 33 (2014) 498–507, https://doi.org/10.3109/10641955.2014.946615.
[14] B. Schiessl, A. Neubauer, M. Burgmann, H. Zeisler, M. Franz, Augmentation Index (AIX) and Pulse Wave Velocity (PWV) in Preeclampsia. Philadelphia: Taylor & Francis Inc.
[15] D.M. Carty, U. Neisius, L.K. Rooney, A.F. Dominiczak, C. Delles, Pulse wave analysis for the prediction of preeclampsia, J. Hum. Hypertens. 28 (2014) 98–104, https://doi.org/10.1038/jhh.2013.64.
[16] M. Spasojevic, S.A. Smith, J.M. Morris, and Gallery EDMPeripheral arterial pulse

wave analysis in women with pre-eclampsia and gestational hypertension, BJOG: Int. J. Obstetrics Gynaecol. 112 (2005) 1475–1478, https://doi.org/10.1111/j.1471-0528.2005.00701.x.
[17] X. Wang, X.Z. Chen, S.M. Ye, Y. Feng, C. Huang, L.X. Hou, J. Liu, H. Chen, Changes in the photoplethysmogram with tracheal intubation and remifentanil concentration, Anaesthesia. 67 (2012) 1332–1336, https://doi.org/10.1111/anae.12001.
[18] Y. Feng, D. Drzymalski, B.H. Zhao, X. Wang, X.Z. Chen, Measurement of area difference ratio of Photoplethysmographic pulse wave in patients with pre-eclampsia, BMC Pregnancy Childbirth 18 (2018) 280, https://doi.org/10.1186/s12884-018-1914-y.
[19] K. Van der Tuuk, C.M. Koopmans, H. Groen, B.W. Mol, M.G. van Pampus, Impact of the HYPITAT trial on doctors' behaviour and prevalence of eclampsia in the Netherlands: Impact HYPITAT trial on doctor and patient, BJOG: Int. J. Obstetrics Gynaecology. 118 (2011) 1658–1660, https://doi.org/10.1111/j.1471-0528.2011.03138.x.
[20] C. Kaihura, M.D. Savvidou, J.M. Anderson, C.M. McEniery, K.H. Nicolaides, Maternal arterial stiffness in pregnancies affected by preeclampsia, Am. J. Physiol. – Heart Circulatory Physiol. 297 (2009) 759–764, https://doi.org/10.1152/ajpheart.01106.2008.
[21] L. Szczepaniak-Chicheł, W. Markwitz, A. Tykarski, Difference between central and peripheral blood pressure in healthy and hypertension-complicated pregnancy, Blood Pressure Monitoring. 21 (2016) 103–110, https://doi.org/10.1097/MBP.0000000000000170.
[22] J. Torrado, I. Farro, Y. Zócalo Farro, C. Sosa, S. Scasso, J. Alonso, D. Bia, Preeclampsia is associated with increased central aortic pressure, elastic arteries stiffness and wave reflections, and resting and recruitable endothelial dysfunction, Int. J. Hypertension 2015 (2015) 1–12, https://doi.org/10.1155/2015/720683.