Published in final edited form as:

Hypertens Pregnancy. 2017 May ; 36(2): 161–167. doi:10.1080/10641955.2017.1280048.

Myocardial performance index in hypertensive disorders of pregnancy: The relationship between blood pressures and angiogenic factors

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Abstract

Objective—To study the association between cardiac function measured by myocardial performance index (MPI), blood pressures and angiogenic factors measured at the time of echocardiography in patients with and without hypertensive disorders of pregnancy (HDP).

Methods—We prospectively studied 189 pregnant women and evaluated whether changes in cardiac function observed on echocardiography were correlated with higher blood pressures and whether higher blood pressures were associated with antiangiogenic proteins (soluble fms-like tyrosine kinase, sFlt1; soluble endoglin, sEng). Comprehensive echocardiograms, including measurement of MPI, were performed on all patients. sFlt1 and sEng levels were measured using enzyme-linked immunosorbent assay.

Results—Overall, 189 patients were divided into tertiles based on mean arterial pressure (MAP). The MPI was worst in tertile 3 (0.50 ± 0.15) compared to tertile 1 (0.42 ± 0.10), $p = 0.0004$. sFlt1 (pg/ml) and sEng (ng/ml) were highest in tertile 3 compared to tertile 1: 15055.37 vs. 1623.01 and 33.06 vs. 8.15, respectively, with p -value < 0.001 . In crude multivariate regression analysis, MAP was positively correlated with MPI ($r = 0.32$, $p < 0.001$), GLS ($r = 0.54$, $p < 0.001$), sFlt1 ($r = 0.60$, $p < 0.001$) and sEng ($r = 0.61$, $p < 0.001$). After adjustment for confounders, these

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relationships persisted between MAP and MPI ($r = 0.31$, $p = 0.0003$), GLS ($r = 0.46$, $p < 0.001$), sFlt1 ($r = 0.56$, $p < 0.001$) and sEng ($r = 0.58$, $p < 0.001$).

Conclusion—Mean arterial pressure correlates with worsening cardiac function as measured by MPI and serum levels of angiogenic factors. Further studies are needed to evaluate whether a reduction in blood pressure will reverse changes in MPI or reduce levels of angiogenic proteins seen among women with HDP.

Keywords

Mean arterial pressure; pregnancy; angiogenic factors; myocardial performance index; global longitudinal strain

Introduction

Hypertensive disorders of pregnancy (HDP), including gestational hypertension, chronic hypertension, preeclampsia, superimposed preeclampsia and eclampsia, affect ten percent of pregnant women (1). HDP are a leading cause of maternal mortality and comprise 16% of maternal deaths in developed countries (2). Pathophysiologically, preeclampsia represents a state of vascular endothelial dysfunction due primarily to an imbalance between circulating antiangiogenic factors (soluble fms-like tyrosine kinase, sFlt1; soluble endoglin, sEng) and pro-angiogenic factors (placental growth factor, PlGF). In animal models, antiangiogenic proteins have induced a preeclamptic state (3,4). Recent studies have identified elevated sFlt1 and sEng levels weeks before the onset of preeclampsia and suggested that these factor levels have a prognostic value for detecting adverse maternal and fetal outcomes (5–7).

The direct relationship between preeclampsia and endothelial dysfunction has led to studies of the relationship between HDP, cardiovascular morbidity and cardiac dysfunction at the time of onset of disease (8–11). Despite their frequent use, standard assessments of cardiac function have several limitations. Ejection fraction and left ventricular volume, two common indices of myocardial function, can be inaccurate due to variations in heart shape (12,13). Transmitral flow is also dependent on different risk factors (14). Inaccuracies can be magnified in parturients given that the physiological changes of pregnancy can alter cardiac volumes and chamber dimensions (15). However, more sophisticated measures to assess cardiac function such as myocardial performance index (MPI) and global longitudinal strain assessment have begun to emerge that may overcome the inherent limitations associated with other assessment methods. MPI is calculated by adding the isovolumic contraction time (IVCT) to the isovolumic relaxation time (IVRT) and dividing that sum by the ejection time (ET). MPI evaluates both systolic and diastolic function, correlates with New York Heart Association (NYHA) class, ejection fraction and ventricular volumes, and serves as a prognostic measure (16). In addition, MPI is independent of ventricular geometry, preload and heart rate (17,18). Global longitudinal strain (GLS) assessment is a recently developed technique which measures the final length of the cardiac segment relative to its initial length. In contrast to EF which measures global cardiac function, GLS measurement assesses both regional and global cardiac function. Among women with HDP, abnormal GLS is observed despite a preserved ejection fraction (11).

This present study was designed to study the association between MPI and mean arterial pressure at the time of diagnoses, among this previously published cohort of patients. Our primary analysis assessed the correlation between mean arterial pressure and MPI. Secondary analyses assessed the association between antiangiogenic factors and both mean arterial pressures and MPI.

Methods

Human subjects

Data were collected prospectively at Beth Israel Deaconess Medical Center (Boston, MA) from July 2013 through November 2014. All patients provided written informed consent, and the study was approved by the institutional review board.

Patients with a singleton pregnancy at less than 41 weeks gestation and with a diagnosis of PE, without any hypertensive disorder of pregnancy, or gestational or chronic hypertension were eligible for enrollment. Women with preexisting pulmonary disease, ischemic or valvular heart disease, diabetes mellitus or patients presenting in active labor were excluded. Patients were recruited at routine prenatal visits or upon admission to the labor and delivery and antepartum wards. All clinical and demographic information was passively collected from the patients' medical records. In addition, blood pressures were recorded at the time of the echocardiogram.

The diagnoses of preeclampsia, gestational hypertension and chronic hypertension were based on modified American College of Obstetricians and Gynecologists criteria (19). An obstetrician (S.R.) unaware of the study results confirmed the clinical diagnosis for all patients. Further details about diagnosis and patient cohort were previously published (11).

Echocardiography

Transthoracic echocardiograms were performed at the time of diagnosis using the Philips CX-50 (Andover, MA) machine by a research sonographer who was blinded to the subject's diagnosis and angiogenic factor levels. The American Society of Echocardiography guidelines (20) were used to report the results. Patients were in the supine or left lateral decubitus position during the procedure. Storage of images was done in a cine-loop format of three cardiac cycles of noncompressed data with their electrocardiography information. Complete two-dimensional and color-flow Doppler valvular assessment and indices of diastolic dysfunction were included. Isovolumic contraction time was defined and measured as the time between the end of the annular A' wave and the beginning of the annular S' wave. Ejection time was measured as the time between the start and end of the S' wave. Isovolumic relaxation time was measured as the time between the termination of the S' wave and the beginning of the E' wave. The Simpson's biplane disc method was used to calculate the ejection fraction and left atrial volume. The area length method was used to calculate left ventricular mass index (LVMI). TomTec software (AutoStrain, TomTec Image Arena 1.2, Unterschleissheim, Germany), a vendor independent software that uses a computer learning algorithm to facilitate endocardial border detection, was used to measure global longitudinal strain (GLS) as described previously (11).

Measurement of antepartum circulating angiogenic proteins

Blood samples were collected within 24 hours of imaging, centrifuged at 1449 g for 8 minutes at -4°C , aliquoted and labeled with a study ID to be stored at -70°C . ELISA for sFlt1 and sEng was done in duplicates using commercially available kits (R&D Systems Inc., Minneapolis, MN) in one batch after one thaw by a technician (D.Z.) who was blinded to the patients' diagnosis and echocardiographic findings. These angiogenic factor measurements have been previously reported (11).

All analyses were conducted using SAS 9.3 (SAS institute, Cary, NC) with p-values < 0.05 considered statistically significant. Data were presented as mean $\pm$ standard deviation, median (quartile 1, quartile 3) or number (percentage) depending on the variable type and distribution. Differences between groups were assessed using a t-test, Wilcoxon–Mann–Whitney test or chi-square test as appropriate. The Shapiro–Wilk test for normality was used in order to assess the distribution of the data. Angiogenic factors that did not meet normality assumptions were transformed using a logarithm function in order to allow for the use of parametric testing. In order to assess the association between mean arterial blood pressures, angiogenic factors and myocardial function (MPI and GLS), Pearson's correlation coefficients were employed. We then fit univariate and multivariate linear regression models, adjusted for age, parity, gravidity, body mass index and gestational age at the time of echocardiogram.

Results

We enrolled 215 patients and included 189 in our analysis. Three participants withdrew from the study, 3 had twins, 2 patients had gestational diabetes mellitus, and 18 patients had an echocardiogram of poor image quality and MPI could not be calculated. Since our primary objective was to define the relationship between blood pressure and MPI, we divided our patient cohort into tertiles based on mean arterial pressures (MAP) at the time of echocardiogram. Tertile 1 had a MAP of 71.69 ± 3.96 , tertile 2 MAP of 85.49 ± 5.33 and tertile 3 MAP of 103.94 ± 6.80 . A total of 30 (48.39%) patients in tertile 3 were taking any antihypertensive medications, followed by 9 (14.29%) and 4 (6.35%) patients in tertiles 2 and 1, respectively.

Patient demographics

Patient demographics are shown in Table 1. Compared to tertile 1, patients in tertile 3 were older and had lower gravidity and parity and higher rates of cesarean section. These patients also had a higher likelihood of chronic hypertension and higher gestational age (GA) at the time of echocardiogram. As expected, tertile 3 also had a higher proportion of patients with a HDP diagnosis. The tertiles did not differ with respect to BMI, race, smoking, birth weight and GA at delivery.

Angiogenic profile among different categories of MAP

We found that patients in the highest tertile of MAP had the highest serum levels of sFlt1 and sEng, comparing tertile 3 to tertile 1, sFlt1 (pg/ml) 15055.37 vs. 1623.01 and sEng

(ng/ml) 33.06 vs. 8.15, respectively, with p -value <0.001 . Angiogenic profiles of patients in the three MAP tertiles are shown in Table 1.

Echocardiography parameters

The MPI (mean $\pm$ standard deviation) was highest (representing worse myocardial function) among patients in MAP tertile 3 (0.50 ± 0.15) and tertile 2 (0.46 ± 0.12) compared to tertile 1 (0.42 ± 0.10), with p -values 0.0004 and 0.02, respectively. Similarly, GLS was lowest (worst) in tertile 3 (-19.16 ± 3.52) and tertile 2 (-22.06 ± 3.30) compared to tertile 1 (-23.64 ± 2.58), p values <0.001 and 0.003, respectively. Other parameters such as left ventricular mass index (LVMI), mitral inflow (E/A ratio) and indices of mitral annular motion (septal E', lateral E', septal E/E' and lateral E/E') were significantly worse among patients in tertile 3 than tertile 1 (all $p < 0.05$). Left ventricular ejection fraction (LVEF) did not differ between the three groups. These findings are shown in Table 2.

In crude multivariate regression analysis, MAP was positively correlated with MPI ($r = 0.32$, $p < 0.001$), GLS ($r = 0.54$, $p < 0.001$), sFlt1 ($r = 0.60$, $p < 0.001$) and soluble endoglin ($r = 0.61$, $p < 0.001$) (Figs. 1 and 2). After adjustment for maternal age, parity, gravidity, body mass index and gestational age at the time of the echocardiogram, relationships between MAP and MPI ($r = 0.31$, $p = 0.0003$), GLS ($r = 0.46$, $p < 0.001$), sFlt1 ($r = 0.56$, $p < 0.001$) and sEng ($r = 0.58$, $p < 0.001$) persisted, Table 3.

No significant association was observed between MPI and the angiogenic factors, as described in Table 4. Similarly, after stratifying by clinical diagnosis, MPI was not associated with angiogenic factors among patients in tertiles 2 and 3 (Supplementary Table 1).

Discussion

In this prospective cohort study of pregnant patients with varying diagnoses of HDP, we demonstrated that higher mean arterial pressure correlated with worsening cardiac function, as measured by MPI. Furthermore, rising MAP correlated with both worse metrics of cardiac function (MPI, LVMI, GLS) and higher serum levels of angiogenic factors (sFlt1 and sEng). These relationships remained significant after adjusting for confounders (age, gravidity, parity, body mass index and gestational age at time of echocardiogram). We found no correlations between angiogenic factors and MPI.

Our data are consistent with prior studies on cardiac function and hypertensive disorders (8,9,21) and show an association between MAP, MPI and angiogenic factors measured at the time of echocardiogram. We have previously observed a relationship between worsening myocardial strain and angiogenic factor abnormalities (11). This study expands those findings by incorporating MPI, a measure of cardiac performance that includes diastolic function, thereby demonstrating that diastolic function is also dysregulated among patients with HDP and angiogenic factor abnormalities. Though the changes we observe are small, they have previously demonstrated to be significant predictors of multiple adverse cardiac events. For example, in nonpregnant patients with myocardial infarction, a MPI 0.47

showed a 90% sensitivity for identifying patients with death, heart failure, arrhythmias or post-infarction angina (22).

Diastolic function is particularly important to consider in HDP; prior studies have noted that left ventricular diastolic dysfunction can occur in nonpregnant hypertensive patients before other manifestations of cardiac hypertrophy and can often persist despite remodeling antihypertensive medications (23,24). It has been hypothesized that the diastolic dysfunction seen in hypertensive patients is secondary to increased afterload and to fibrotic changes in the subendocardium, which can then lead to compensatory left ventricular hypertrophy (25,26). Therefore, based on our data, treatment of blood pressure may help decrease the magnitude of diastolic dysfunction observed in HDP. As previously demonstrated, increased levels of the angiogenic markers sFlt1 and sEng are associated with increasing blood pressures (27). Interestingly, treatment with beta blockers may have the additional effect of decreasing sFlt1 which is known to be pathogenic and directly correlated with adverse outcomes in pregnancy (28).

Our study has several limitations. Because our data focus on only a single point during pregnancy, the baseline cardiac function of our patients is unknown. Therefore, the time course of MPI, MAP or angiogenic factors cannot be described. Although the adjusted correlation coefficient was strong when correlating angiogenic factors with MAP (>0.5), it was only moderate when correlating MPI and GLS with MAP (0.31 and 0.46, respectively). Thirdly, our study focused solely on the antepartum period. Thus, we cannot postulate on whether cardiac function, MAP and biomarkers have the same relationship in the postpartum period. Furthermore, blood pressure measurements at a single point in time can be transient, and the MAP we recorded at the time of echocardiogram may have been elevated due diet, anxiety, pain or other factors.

In summary, we observed a direct correlation between elevated MAP and cardiac dysfunction (as measured by MPI) and between MAP and angiogenic factors in this cohort of pregnant patients. It is mechanistically plausible that angiogenic factor abnormalities lead to the development of pregnancy-associated hypertension and that either higher MAP or angiogenic factor imbalances worsen MPI and GLS. Further studies should focus on serial echocardiograms throughout pregnancy and evaluate whether reduction in blood pressures or reduction in levels of sFlt1 and sEng will lead to improvement in cardiac function. In addition, future studies should include postpartum monitoring to describe long-term changes in biomarkers and cardiac function in relation to cardiovascular morbidity and mortality related to hypertensive disorders of pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Correlation between mean arterial pressure (MAP) and cardiac indices. Blood pressures were taken at the time of echocardiogram and the relationship was assessed with (A) myocardial performance index (MPI) and (B) global longitudinal strain (GLS).

Figure 2.

Correlation between mean arterial pressure (MAP) and angiogenic factors. Plasma angiogenic factors were measured within 24 hours of echocardiogram and the relationship between the natural logarithm of (C) sFlt1 and (D) endoglin was assessed with MAP.

Table 1

Participant characteristics.

	MAP Tertiles			
	Tertile 1	Tertile 2	P-Value [†]	Tertile 3
MAP at assessment	71.69 ± 3.96	85.49 ± 5.33	<0.001 [*]	103.94 ± 6.80
Characteristic				
Age (years)	29.56 ± 6.58	31.40 ± 5.61	0.09	34.31 ± 4.94
Gravidity	2 (2, 4)	2 (1, 3)	0.24	2 (1, 3)
Parity	1 (0, 2)	0 (0, 1)	0.04 [*]	0 (0, 1)
Delivery Type			0.27	
Vaginal	25 (39.68)	29 (46.03)		21 (33.87)
Cesarean	23 (36.51)	26 (41.27)		39 (62.9)
Other	15 (23.81)	8 (12.7)		2 (3.23)
Pre-pregnancy BMI (kg/m ²)	25.72 ± 7.33	27.72 ± 7.59	0.16	28.04 ± 7.61
Race/Ethnicity (%)			0.18	
White/Caucasian	35 (54.69)	45 (71.43)		40 (64.52)
Black/African American	10 (15.63)	9 (14.29)		5 (8.06)
Asian	8 (12.5)	4 (6.35)		9 (14.52)
Other/Unknown	11 (17.19)	5 (7.94)		8 (12.9)
History of Chronic Hypertension (%)	1 (1.56)	10 (15.87)	0.004 [*]	21 (33.87)
Smoking (%)			0.61	
Never	41 (65.08)	46 (74.19)		46 (76.67)
Past/Quit Before Pregnancy	14 (22.22)	10 (16.13)		13 (21.67)
Quit Early Pregnancy	5 (7.94)	5 (8.06)		1 (1.67)
Current	3 (4.76)	1 (1.61)		0 (0.0)
GA at ECHO (weeks)	30.19 ± 4.84	32.51 ± 4.40	0.01 [*]	33.55 ± 3.97
BP at Time of ECHO				
Systolic BP at assessment (mmHg)	101.00 ± 8.42	117.13 ± 10.68	<0.001 [*]	141.73 ± 10.41
Diastolic BP at assessment (mmHg)	57.03 ± 4.69	69.67 ± 6.15	<0.001 [*]	85.05 ± 7.79

	MAP Tertiles			P-Value [†]	Tertile 3	P-Value [‡]
	Tertile 1	Tertile 2	Tertile 3			
Highest BP on Day of ECHO						
Systolic BP (mmHg)	109.25 ± 11.64	125.06 ± 16.413874	149.82 ± 11.04	<0.001 *		<0.001 *
Diastolic BP (mmHg)	63.67 ± 8.13	75.13 ± 8.78	90.56 ± 8.4127557	<0.001 *		<0.001 *
Birth Weight (grams)	2506.00 ± 935.06	2362.64 ± 733.18	2238.12 ± 1014.33	0.38		0.16
GA at Delivery (weeks)	35.18 ± 4.60	35.75 ± 3.06	34.53 ± 3.90	0.47		0.43
Type of Diagnosis				0.0001 *		<0.001 *
Normal	57 (89.06)	35 (55.56)	1 (1.61)			
Preeclampsia	2 (3.13)	11 (17.46)	47 (75.81)			
Gestational/Chronic HTN	5 (7.81)	17 (26.98)	14 (22.58)			
Angiogenic Factors at ECHO						
sFlt1 (pg/ml)	1623.01 (1190.63, 3771.42)	3227.26 (1459.16, 9871.16)	15055.37 (6042.89, 25295.11)	0.01 *		<0.001 *
Endoglin (ng/ml)	8.15 (5.72, 10.41)	9.83 (6.60, 23.86)	33.06 (17.01, 57.80)	0.002 *		<0.001 *

MAP = mean arterial pressure; BMI = body mass index; GA = gestational age; BP = blood pressure; ECHO = echocardiogram; sFlt1 = soluble fms-like tyrosine kinase-1
Data are presented as mean ± standard deviation, median (quartile 1, quartile 3) or number (percentage).

* Significant at P < 0.05;

[†] comparison is between women in MAP tertiles 1 and 2;

[‡] comparison is between women in MAP tertiles 1 and 3

Table 2

Cardiac systolic and diastolic function indices and cardiac morphology.

Indices	MAP Tertiles			
	Tertile 1	Tertile 2	P-Value [†]	Tertile 3
MPI	0.42 ± 0.10	0.46 ± 0.12	0.02 *	0.50 ± 0.15
GLS (%)	-23.64 ± 2.58	-22.06 ± 3.30	0.003 *	-19.16 ± 3.52
LVEF (%)	0.59 ± 0.06	0.56 ± 0.07	0.15	0.57 ± 0.06
LVMI (g/m ²)	68.17 ± 13.43	69.43 ± 11.29	0.57	72.83 ± 11.02
LAVI (ml/m ²)	24.71 ± 7.15	22.35 ± 5.61	0.04	25.55 ± 8.67
Mitral Inflow				
E/A ratio	1.38 ± 0.30	1.33 ± 0.29	0.42	1.23 ± 0.30
DT (msec)	186.09 ± 39.10	176.17 ± 36.97	0.15	170.82 ± 35.98
Mitral Annular Motion				
Septal E'	12.16 ± 2.86	10.17 ± 2.33	<0.001 *	9.04 ± 1.81
Lateral E'	16.99 ± 3.38	14.75 ± 3.38	0.0003 *	12.18 ± 2.31
E/E' (septal)	8.75 ± 1.87	9.48 ± 2.46	0.06	10.01 ± 2.65
E/E' (lateral)	6.24 ± 1.43	6.52 ± 1.64	0.31	7.45 ± 2.20
Cardiac Morphology				
Septal Wall Thickness	0.87 ± 0.14	0.96 ± 0.15	0.001 *	1.05 ± 0.16

MPI = myocardial performance index; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LAVI = left atrial volume index; DT = deceleration time; E = early filling; A = atrial contraction; septal E' = septal tissue Doppler velocity; lateral E' = lateral tissue Doppler velocity; E/E' = estimated filling pressures;

* significant at P < 0.05;

[†] comparison is between women in MAP tertiles 1 and 2;

[‡] comparison is between women in MAP tertiles 1 and 3

Table 3

Unadjusted and adjusted correlation coefficients.

	MPI		GLS		sFlt1 [‡]		Endoglin [‡]	
	r	P-value	r	P-value	r	P-value	r	P-value
Unadjusted								
MAP	0.32	<0.001 *	0.54	<0.001 *	0.60	<0.001 *	0.61	<0.001 *
Adjusted [‡]								
MAP	0.31	0.0003 *	0.46	<0.001 *	0.56	<0.001 *	0.58	<0.001 *

MAP: mean arterial blood pressure; MPI = myocardial performance index; GLS = global longitudinal strain; sFlt1 = soluble fms-like tyrosine kinase-1;

[‡] natural log transformed;

[‡] adjusted for maternal age, parity, gravidity, body mass index and gestational age at the time of the echocardiogram;

* significant at P < 0.05

Table 4

Unadjusted and adjusted correlation coefficients with MPI.

	sFlt1 [‡]		Endoglin [‡]	
	r	P-value	r	P-value
Unadjusted				
MPI	0.15	<0.05	0.16	<0.03 *
Adjusted [‡]				
MPI	0.05	0.57	0.09	0.31

MPI = myocardial performance index; sFlt1 = soluble fms-like tyrosine kinase-1;

[‡] Natural log transformed;[‡] Adjusted for maternal age, parity, gravidity, body mass index, and gestational age at the time of the echocardiogram;

* Significant at P < 0.05