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Maternal cardiac function at 19–23 weeks' gestation in the prediction of gestational diabetes mellitus

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Short title: Maternal cardiac function and gestational diabetes

Keywords: maternal cardiac function; gestational diabetes; second trimester; screening; ultrasound; echocardiography

What are the novel findings of this work

At 20 weeks' gestation women at risk for GDM, compared to those who will not develop GDM, have lower left ventricular function and increased peripheral vascular resistance. The performance of screening for GDM by maternal demographic characteristics and medical history is not improved by the addition of maternal cardiovascular indices.

What are the clinical implications of this work

Women with GDM have subtle functional and hemodynamic cardiac changes prior to the development of GDM which relates mostly to their demographic characteristics and medical history. Maternal cardiac assessment at 20 weeks' gestation is not useful in identifying women at risk for GDM.

ABSTRACT

Objectives: To examine differences in maternal cardiovascular indices at 19-23 weeks' gestation between pregnancies that develop gestational diabetes mellitus (GDM) and those without GDM and determine whether such cardiovascular changes are the consequence of maternal demographic characteristics and medical history or the GDM per se.

Methods: This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 23^{+3} weeks' gestation. This visit included recording of maternal demographic characteristics and medical history and maternal echocardiography for assessment of E/A, E/e', myocardial performance index, global longitudinal systolic strain, left ventricular ejection fraction, peripheral vascular resistance, left ventricular cardiac output and left ventricular mass indexed for body surface area. The measurements of the maternal cardiac indices were standardized to remove the effects of maternal characteristics and elements from the medical history and the adjusted values in the GDM group were compared to those in the non-GDM group. Likelihood ratios were derived for those indices that were significantly altered in GDM and these were used to modify the prior risk derived from maternal demographic characteristics and medical history. The area under the receiver operating characteristic (ROC) curve (AUC) and detection rate (DR) of GDM, at 10%, 20% and 40% false positive rate (FPR), in screening by a combination of maternal factors with cardiovascular indices were determined.

Results: The study population of 2,853 pregnancies contained 199 (7.0%) that developed GDM. The main findings of the study were: first, in pregnancies that developed GDM there were significant differences from the non-GDM group in E/A, E/e', myocardial performance index and global longitudinal systolic strain; second, after adjustment for maternal demographic characteristics and medical history known to affect cardiac indices the only cardiovascular indices that were significantly different between the GDM and non-GDM groups were peripheral vascular resistance and myocardial performance index and they were both marginally increased; and third, the performance of screening for GDM by maternal demographic characteristics and medical history was not improved by the addition of cardiovascular indices.

<u>Conclusion:</u> Women with GDM have subtle functional and hemodynamic cardiac changes prior to the development of GDM. These cardiac changes are mostly related to the adverse risk factor profile of these women. Maternal cardiac assessment at 20 weeks does not offer additional predictive information for GDM development in pregnancy to that calculated based on demographic characteristics and medical history.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a risk factor for future cardiovascular disease including atherosclerosis, hypertension, stroke, coronary artery disease, and heart failure; women with GDM, compared with those who did not have GDM, had a two-fold higher risk of future cardiovascular events.[1,2] However, it is uncertain whether this increased risk is due to cardiovascular changes occurring during pregnancy and persisting thereafter or to an adverse underlying cardiovascular risk factor profile. Echocardiographic studies during pregnancy have reported that in women with GDM, compared to those without GDM, there is reduced systolic and diastolic left ventricular function.[3-6]

In a previous study of 75161 singleton pregnancies, including 1827 (2.4%) that developed GDM, we used logistic regression to develop a predictive model for GDM based on maternal demographic characteristics and medical history.[7] In the model there is a 50-fold increase in risk for women that had developed GDM in a previous pregnancy and 1.5 to 3-fold increase in risk for women of Black, South Asian or East Asian racial origin, those with first- or second-degree family history of diabetes mellitus, and in cases where conception is by use of ovulation induction drugs.[7] Additionally, the risk increases with increasing age, weight and birth weight z-score of a baby from a previous pregnancy and decreases with increasing maternal height.[7]

The objective of this study in an unselected population undergoing detailed cardiovascular assessment at 19-23 weeks' gestation is to examine differences in maternal cardiovascular indices between pregnancies that develop GDM and those without GDM and determine whether such cardiovascular changes are the consequence of maternal demographic characteristics and medical history or the GDM per se.

METHODS

Study design and participants

This was a prospective observational study in women attending for a routine hospital visit at 19^{+1} - 23^{+3} weeks' gestation at King's College Hospital, London, UK between August 2019 and April 2020. This visit included recording of maternal demographic characteristics and medical history and maternal echocardiography for assessment of cardiovascular function. Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[8,9] The women gave written informed consent to participate in the Advanced Cardiovascular Imaging Study (REC No 18/NI/0013, IRAS ID:237936) which was approved by the NHS Research Ethics Committee.

Patient characteristics included maternal age, weight, height (which were measured at the time of screening) racial origin (White, Black, South Asian, East Asian and mixed), method of conception (natural or assisted conception requiring *in vitro* fertilization or the use of ovulation drugs), history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of GDM (first and second degree relative) and obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥24 weeks), previous pregnancy with GDM, gestational age at delivery and birth weight of the neonate in the last pregnancy.

The inclusion criteria for this study were singleton pregnancies delivering a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Maternal cardiovascular assessment

All participants were studied by 2-dimensional and Doppler transthoracic echocardiography at rest in the left lateral decubitus position and data were acquired during unforced expiration. The protocol included standard parasternal and apical views acquired with a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) as per American Society of Echocardiography (EAE/ASE) guidelines.[10,11] Echocardiography was performed by seven Fetal Medicine Fellows who were trained in acquisition and analysis of echocardiograms. In a previous study we reported excellent interobserver reproducibility of various cardiac indices.[12]

Cardiac output was calculated from stroke volume (derived from the left ventricular outflow tract velocity-time integral) multiplied by heart rate. Left atrial area was calculated in end-systole from the four-chamber view. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis. The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E/A ratio was calculated. Pulsed tissue Doppler recordings were obtained at the septal and lateral aspects of basal left ventricle at the junction with the mitral valve annulus in the apical four-chamber view. The E/e' ratio was calculated using the mean value between septal and lateral peak e' waves. Speckle tracking was employed to assess global longitudinal systolic strain of the left ventricle.

Screening diagnosis and management of gestational diabetes mellitus

The diagnosis of GDM in our hospital is based on the results of the oral glucose tolerance test (OGTT) with administration of 75 g glucose; the diagnosis is made if the fasting plasma glucose level is ≥5.6 mmol/L and/or the 2-hour plasma glucose level is ≥7.8 mmol/L.[13] The OGTT is carried out in three groups of women. First, women with any one risk factor (body mass index >30 kg/m^2, previous birth of macrosomic baby weighing >4.5 kg, previous GDM, first degree relative with diabetes or persistent glucosuria) are offered measurement of HbA1c at booking and if the value is ≥ 5.7% then they have an OGTT, usually at 12 weeks' gestation. Second, in all women at 26-28 weeks' gestation a plasma glucose level is measured 1-2 hours after eating ≥50 g carbohydrate and if the concentration is ≥6.7 mmol/L then OGTT is carried out. Third, after 28 weeks' gestation OGTT is performed if there is polyhydramnios or the fetus becomes macrosomic.

Women with the diagnosis of GDM are given dietary and exercise advice and are encouraged to test capillary blood glucose before and 1 h after each meal. If during a period of 1-2 weeks the pre-meal or 1-hour post-meal blood glucose level is ≥5.5 and >7 mmol/L, respectively, the women are treated with metformin or insulin.

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Students t-test and χ2-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively.

The following eight cardiovascular indices were examined: E/A, E/e', myocardial performance index, global longitudinal systolic strain, left ventricular ejection fraction, peripheral vascular resistance, left ventricular cardiac output and left ventricular mass indexed for body surface area. The measured values of cardiovascular indices were converted to multiple of the median (MoM) or difference from the median (Delta) values, where appropriate, to remove the effects of maternal demographic characteristics and elements from the medical and obstetric history as previously described; these factors included gestational age, maternal age, weight, height, racial origin, heart rate, method of conception, history of chronic hypertension or antiphospholipid syndrome .[14] We found no significant contribution from family history of diabetes mellitus or history of GDM in a previous pregnancy.

The median MoM or Delta value in the GDM and non-GDM groups were compared and those found to be significantly different were investigated further for predictive performance for GDM. The *a priori* risk for GDM was estimated from our previously reported model based on maternal characteristics and medical history.[7] Bayes theorem was then applied to combine the *a priori* risk of GDM with MoM or delta values of cardiovascular indices. To assess the performance of the markers in the prediction of GDM, detection rates (DR) for various false positive rates (FPR) were calculated, receiver operating characteristic (ROC) curves were produced and area under the curves (AUROC) calculated.

The statistical software package R was used for all data analyses.[15]

RESULTS

Study participants

The study population of 2,853 pregnancies contained 199 (7.0%) that developed GDM; the GDM was diagnosed at <20 weeks (median 12 weeks) in 39 (19.6%) cases, at 20-30 weeks (median 29 weeks) in 133 (66.8%) cases and at ≥31 weeks (median 33 weeks) in 27 (17.6%) cases. The same population was used for our previous study investigating the value of ophthalmic artery Doppler in the prediction of PE[16] and maternal cardiovascular indices in the prediction of PE.[14] Maternal and pregnancy characteristics of the study population are summarized in Table 1. In the GDM group, compared to the unaffected pregnancies, there was a higher median maternal weight and body mass index, and higher incidence of women of Black, South Asian and East Asian racial origin, family history of first and second degree relative with diabetes mellitus, and previous pregnancy complicated by GDM.

Cardiovascular indices and GDM

Preliminary analysis of cardiovascular indices unadjusted for maternal characteristics and medical history demonstrated that in the pregnancies that subsequently developed GDM, compared to the non-GDM group, there was a higher median E/e', myocardial performance index and global longitudinal systolic strain and lower E/A; there were no significant differences in left ventricular ejection fraction, peripheral vascular resistance, left ventricular cardiac output or left ventricular mass indexed for body surface area (Figure 1).

The distributions of MoM or Delta values of the cardiovascular indices in pregnancies that developed GDM are shown in Figure 2 and Table 2; the only indices with significantly different median value between GDM and no-GDM pregnancies were peripheral vascular resistance and myocardial performance index. Peripheral vascular resistance and myocardial performance index MoMs were marginally higher in those women with GDM that were treated with insulin than those that were not. There was no evidence of significant effects of GDM treatment or of gestational age at diagnosis of GDM on peripheral vascular resistance or myocardial performance index MoMs.

Performance of screening

The detection rates, at 10%, 20% and 40% FPR, of GDM in screening by maternal demographic characteristics and medical history were not improved by the addition of peripheral vascular resistance or myocardial performance index (Table 3).

DISCUSSION

Principal findings of this study

In this prospective screening study of an unselected population at 19-23 weeks' gestation we used standard echocardiographic techniques but also employed more advanced imaging modalities, such as speckle tracking, which allowed us to detect subtle cardiac functional changes. The data demonstrated that first, in pregnancies that subsequently developed GDM there was evidence of impaired myocardial function; second, after adjustment for maternal demographic characteristics and medical history only peripheral vascular resistance and myocardial performance index were marginally altered in GDM; and third, the performance of screening for GDM by maternal demographic characteristics and medical history was not improved by the addition of maternal cardiovascular indices.

Comparison with findings of previous studies

Maternal cardiovascular indices in GDM were previously examined in four case control studies. Two studies in 13 and 18 women with GDM, respectively, reported a mild degree of diastolic abnormality both during pregnancy and postpartum;[3,4] the diastolic changes were subtle and did not fulfill the criteria for adult clinical diastolic dysfunction as per European or American Guidelines.[10,17] Similarly, in a previous study by our group involving 161 women with GDM and 483 women with uncomplicated pregnancies at 35-37 weeks' gestation, we found that women with GDM had lower left ventricular diastolic and systolic functional indices with no significant differences in cardiac output, peripheral vascular resistance, left ventricular global longitudinal functional changes or left ventricular mass after adjustment for maternal characteristics.[6] In contrast, another study in 40 women with GDM reported increased left ventricular wall thickness and decrease in left ventricular global strain, but in that study no adjustments were made for maternal characteristics despite the fact that in the GDM group the body mass index and blood pressure were higher than in the controls.[5]

In contrast to previous studies, which were case control involving women with GDM,[3-6] our current study involved screening of an unselected population at mid gestation at the time of the routine anomaly scan. In our cohort, only few women had developed GDM at the time of cardiac assessment, whereas, in 80% of cases of GDM the diagnosis was made later in pregnancy. This provided us with the unique opportunity to differentiate the independent contribution of risk factor profile from that of hyperglycemia. GDM women had increased body mass index, were more of Black racial origin and had higher incidence of history of GDM. Such a phenotype, however, not only increases the risk for GDM development but also increases the risk for metabolic syndrome, type 2 diabetes and cardiovascular disease.[18,19] Consistent with this, we showed that most of the cardiac changes noted between women with and without GDM were attenuated or lost after accounting for the risk factor profile of the woman.

Previous studies have assessed maternal cardiac function after the development of GDM and few showed that cardiac changes persist in postnatal life.[20] From these studies, one of the questions which was raised was whether maternal cardiovascular assessment earlier in pregnancy would assist in identifying those at risk for GDM and potentially at increased later cardiovascular risk. Our data, however, would not support such an approach as cardiac indices did not improve the predictive performance of GDM by demographic characteristics and medical history and did not identify women with difficult to control diabetes that will require insulin treatment.

Strengths and limitations

The main strengths of the study are first, prospective examination of a large unselected population of pregnant women attending for a routine ultrasound examination at mid-gestation, second, use of a standardized technique for maternal cardiovascular assessment by appropriately trained research fellows, third, adjustment of the cardiovascular indices for maternal characteristics and elements from the medical history, and fourth, application of Bayes theorem to estimate patient-specific risks and determine the potential additive value of cardiovascular indices in the prediction of GDM achieved by maternal demographic characteristics and medical history alone.

The diagnosis of GDM was made before the cardiac assessment in 20% of our cases and there was no significant association between gestational age at diagnosis of GDM and cardiovascular indices. Our study was confined to the 19 - 23 weeks gestational window and we cannot provide information on potential deterioration of cardiac function with advancing gestational age.

Conclusions

Our study shows that women with GDM have a distinct risk factor profile which increases both the risk for GDM development but also contributes to an adverse cardiac functional profile. Cardiac assessment at mid gestation would not improve the performance of screening for GDM by demographic characteristics and medical history. However, GDM development might help in identifying women who will benefit from cardiovascular monitoring and risk factor modification.

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FIGURE LEGENDS

Figure 1. Box and whisker plots of cardiovascular indices unadjusted for maternal characteristics and medical history in pregnancies that developed GDM (grey boxes), compared to those that did not (white boxes). In the GDM group there was a significantly lower median E/A, and higher E/e', myocardial performance index and global longitudinal systolic strain.

Figure 2. Median (95% confidence interval) of MoM or delta values of cardiovascular indices in pregnancies that developed GDM plotted in standard deviation untits with vertical lines at +/- 0.1 and 0.2 standard deviations.

Table 1. Maternal and pregnancy characteristics of the study population.

Characteristic	Unaffected (n=2654)	Gestational diabetes (n=199)	p-value
Maternal age (years)	33.3 (30.3, 36.5)	34.3 (30.35, 37.7)	0.07
Maternal weight (kg)	70.7 (63.4, 79.1)	75.2 (66.0, 87.0)	<0.0001
Maternal height (cm)	167 (162, 171)	164 (161, 168)	0.0002
Body mass index (kg/m2)	25.4 (23.0, 28.5)	27.6 (24.5, 32.2)	<0.0001
Gestational age (weeks)	21.4 (21.0, 21.6)	21.3 (20.9, 21.6)	0.242
Racial origin			<0.0001
White	1997 (75.2)	108 (54.3)	
Black	363 (13.7)	37 (18.6)	
South Asian	133 (5.0)	28 (14.1)	
East Asian	63 (2.4)	19 (9.6)	
Mixed	98 (3.7)	7 (3.5)	
Medical history			
Chronic hypertension	42 (1.6)	4 (2.0)	0.865
Diabetes mellitus	40 (1.5)	0 (0.0)	0.219
SLE/APS	7 (0.3)	0 (0.0)	1
Smoker	36 (1.4)	2 (1.0)	0.923
Family history of diabetes			0.024
1st degree	264 (10.0)	29 (14.6)	
2nd degree	176 (6.6)	19 (9.6)	
Method of conception			0.351
Natural	2468 (93.0)	183 (92.0)	
In vitro fertilization	169 (6.4)	16 (8.0)	
Ovulation drugs	17 (0.6)	16 (8.0)	
Parity			<0.0001
Nulliparous	1458 (54.9)	91 (45.7)	
Parous with previous GDM	28 (1.1)	23 (11.6)	
Parous without previous GDM	1168 (44.0)	85 (42.7)	
Birth weight of last neonate (g)	3377 (3009, 3700)	3405 (3085, 3802)	0.263

Values given as median (interquartile range) or n (%)
PE = preeclampsia; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome.

Comparisons between outcome groups were by chi-square or Fisher exact test for categorical variables and Students t-test for continuous variables.

Table 2. Median MoM or Delta value with 95% confidence interval.

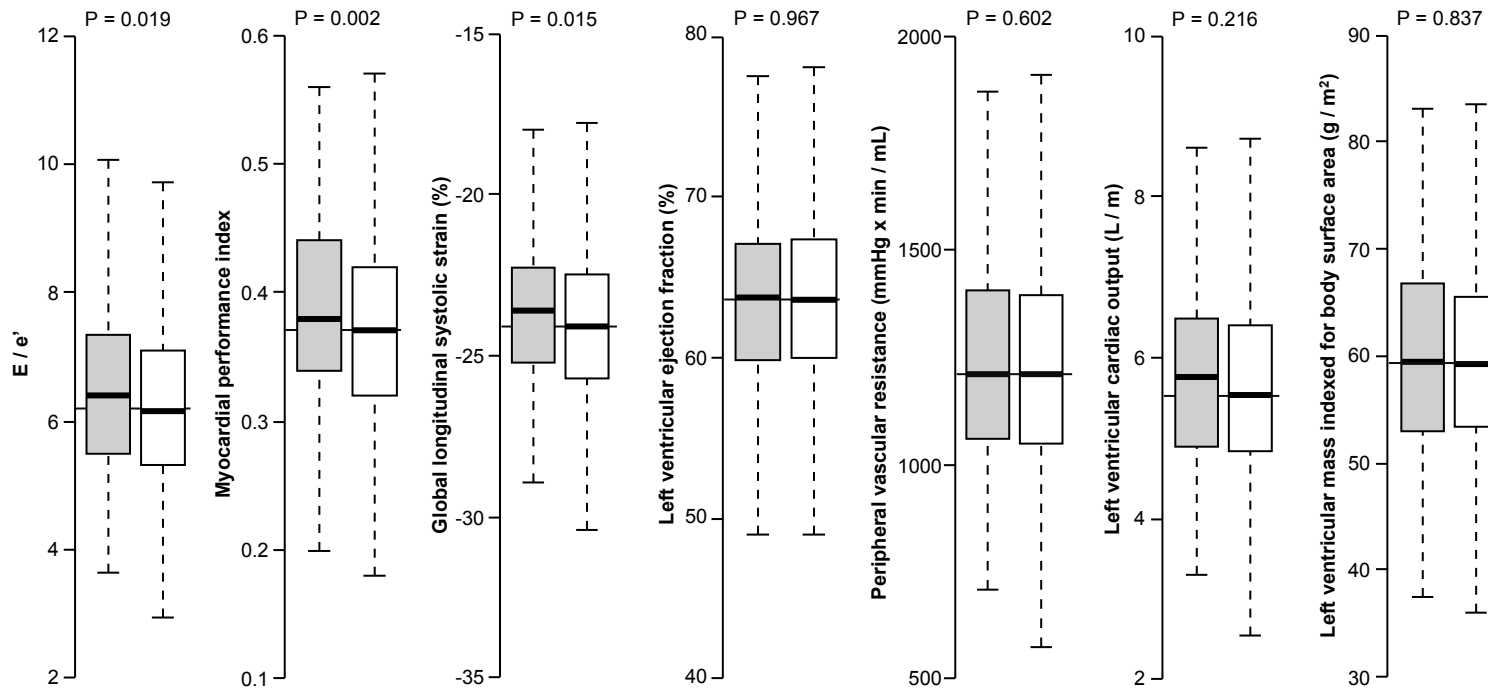| Cardiovascular index	Median MoM / Delta	p-value
E / A MoM	1.007 (0.962 - 1.055)	0.754
E / e' MoM	1.015 (0.984 - 1.048)	0.320
Myocardial performance index MoM	1.031 (1.003 - 1.060)	0.037
Global longitudinal systolic strain Delta	-0.014 (-0.328 - 0.299)	0.927
Left ventricular ejection fraction Delta	0.096 (-0.738 - 0.930)	0.815
Peripheral vascular resistance MoM	1.035 (1.007 - 1.064)	0.037
Left ventricular cardiac output MoM	0.988 (0.964 - 1.012)	0.299
Left ventricular mass* Delta	0.590 (-0.884 - 2.064)	0.414

* indexed for body surface area

Table 3. Performance of screening

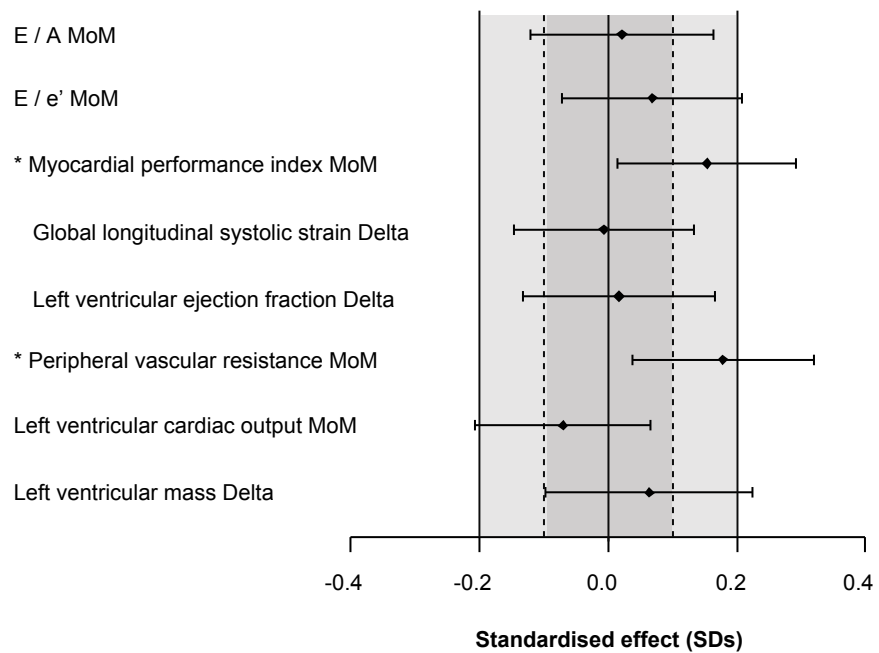| Method of screening	AUROC	Detection rate		
		10% FPR	**20% FPR**	**40% FPR**
Maternal factors	0.717 (0.679, 0.756)	30.7 (24.3, 37.6)	49.8 (42.6, 56.9)	72.9 (66.1, 78.9)
+ Myocardial performance index	0.720 (0.683, 0.758)	30.7 (24.3, 37.6)	52.3 (45.1, 59.4)	69.9 (63.0, 76.1)
+ Peripheral vascular resistance	0.722 (0.684, 0.760)	29.7 (23.4, 36.5)	53.3 (46.1, 60.4)	70.4 (63.5, 76.6)

Figure 1

E / A MoM

E / e' MoM

* Myocardial performance index MoM

Global longitudinal systolic strain Delta

Left ventricular ejection fraction Delta

* Peripheral vascular resistance MoM

Left ventricular cardiac output MoM

Left ventricular mass Delta

-0.4   -0.2   0.0   0.2   0.4

Standardised effect (SDs)

Figure 2