The (Pulsed-Wave) Doppler Fetal Myocardial Performance Index: Technical Challenges, Clinical Applications and Future Research

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Key Words

Pulsed-wave Doppler · Fetal echocardiography · Fetal myocardial performance index · Myocardial performance index · Tissue Doppler Imaging

Abstract

Functional cardiovascular assessment is becoming an increasingly important tool in the study of fetal pathology. The myocardial performance index (MPI) is a parameter measuring global myocardial function. Since its introduction, several studies have proposed methods to improve its reproducibility and have constructed normative reference ranges. Fetal heart evaluation using the MPI is technically challenging, requiring specific training and expertise, and a consensus has yet to be reached on the method of delineating the time periods used to calculate the index. Despite these limitations, it has been shown to be a useful and highly sensitive parameter of dysfunction in a number of fetal pathologies. Further research is warranted into the effect of pathology on MPI, parameters of unilateral cardiac strain that utilise MPI, and automation of the MPI to encourage incorporation of the MPI as a useful tool in clinical practice.

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Introduction

Fetal surveillance increasingly includes functional ultrasonographic assessment [1, 2], with multiple cardiac parameters under evaluation for prenatal detection and monitoring of cardiac pathology [3]. As the heart's primary function is ejection of blood to deliver adequate tissue perfusion, Doppler ultrasound is commonly used to evaluate cardiac function through either assessing blood flow or cardiac time periods [4]. One quantitative measurement is the myocardial performance index (MPI), a pulsed-wave Doppler-derived index reflecting global myocardial function [5] which has been shown to be a highly sensitive measure of dysfunction [6, 7]. It utilises cardiac time intervals to assess right or left ventricular myocardial performance [5, 8] and is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET)

$$\text{MPI} = (\text{ICT} + \text{IRT}) / \text{ET}$$

The MPI is generally accepted as a reliable early marker of fetal cardiac dysfunction and may indicate the initial stages of cardiac adaptation to various perinatal insults

Fig. 1. Measurement of the left Mod-MPI. Above: location of the sample volume on schematic (left) and 2D echocardiograph (right). Below: reference points for time period estimations are based on echoes from mitral and aortic valve movements [40].

[4]. Ventricular dysfunction is associated with higher MPI values [9], frequently due to a prolongation of the IRT. Reduced calcium reuptake of cardiac cells occurs with a deterioration in cardiac function [4], leading to an increase in the time required to properly relax the myocardium [10]. This results in the IRT being the main MPI parameter that becomes abnormal in the very early stages of dysfunction. Prolonged IRT may therefore be an early marker of cardiac dysfunction common to several pathologies, with the common link between these being an increase in preload with consequent diastolic dysfunction [e.g. intrauterine growth restriction (IUGR) and recipient twin-twin transfusion syndrome (TTTS)]. An increased IRT is generally accompanied by a reduced ET, with the ICT the most stable MPI parameter [4]. The MPI has been used to demonstrate fetal cardiac dysfunction in a number of pathologies including maternal diabetes [11–16], TTTS [7, 17–22], congenital heart malformations [23–28], pre-eclampsia [29], IUGR [11, 30–34], and other fetal conditions [35–38]. Several studies have proposed methods to improve the repeatability of fetal MPI by defining fixed machine settings [39] and using the clicks of the aortic and mitral valves as landmarks to delineate the constituent time intervals [9, 40, 41].

In this review, we provide an overview of the development of the MPI in fetal echocardiography. We also discuss techniques, technical challenges, existing data and future research strategies.

Development of the MPI in Fetal Echocardiography

Originally described in adults by Tei [5], MPI correlated well with other invasive and non-invasive measurements of global left ventricular performance [8, 42–46] so was extrapolated to the paediatric and neonatal settings [47–53]. Tsutsumi et al. [11] first applied the MPI to assess fetal left and right myocardial function. When other authors subsequently evaluated the MPI in normal [35, 54–56] and sick fetuses [26, 57], wide variability was observed in values between studies [9, 11, 54, 55, 58], potentially due to technical variations in measurement of time intervals. Friedman et al. [9] first proposed acquisition of the left ventricular MPI in a single Doppler waveform. The small size of the fetal cardiac chambers and the close proximity of mitral inflow and aortic outflow allows both isovolumetric periods and ET to be recorded simultaneously on the spectral Doppler within the same cardiac cycle (fig. 1), reducing the effect of fetal heart variation on MPI values and enabling ICT and IRT to be determined individually [9]. Hernandez-Andrade et al. [40] then introduced the modified MPI (Mod-MPI) in the left ventricle, using the beginning of opening and closing Doppler echoes (or clicks) of the mitral and aortic valves to better define the three time periods for the calculation of MPI, thus improving repeatability. More recently, tissue Doppler imaging has also been proposed to measure left and right MPI [28, 32].

Fig. 2. Measurement of the right Mod-MPI. Doppler waveforms showing 'a' and 'b' intervals.

Technical Aspects of MPI Measurement

Acquisition

Hernandez-Andrade et al. [40] describe placement of the Doppler sample volume in an apical four-chamber view on the lateral wall of the ascending aorta, below the aortic valve and just above the mitral valve, with the transducer slightly cranially displaced to visualise the mitral and aortic valves [59] (fig. 1). Fast Doppler sweep velocity (15 cm/s) and low angle of insonation ($<30^\circ$) are used. Clear valve clicks must be observed to ensure correct placement of the time cursors, and estimation of time intervals should be performed at least three times [59].

The ICT represents the time when there is increasing pressure applied by myocardial contraction but this is insufficient to open the semilunar valves [4] and for the left MPI is measured from the mitral valve closure click to the aortic valve opening click (fig. 1) [40]. The IRT represents the time after systole when the semilunar valves are closed, pressure reduces, and calcium reuptake in cardiac myocytes begins (fig. 1) [60]. It is measured from the aortic valve closure click to the mitral valve aperture click [40]. The ET represents the ejection phase of ventricular systole, measured from the aortic valve aperture click to aortic valve closure click (fig. 1) [40].

In the right side of the heart, the anatomical separation of the tricuspid and pulmonary valves after 20 weeks' gestation means that the right Mod-MPI is generally calculated from two different anatomical planes in two different cardiac cycles (fig. 2) [28] as

$$(a-b)/b$$

The 'a' interval is measured from the closure click to the aperture click of the tricuspid valve using an apical four-chamber view. The 'b' interval (right ventricular ET) is

measured from the aperture click to closure click of the pulmonary valve (fig. 2), in either the short axis view or sagittal plane. Machine settings must be kept constant while obtaining both recordings [4]. Despite requiring two different imaging planes in two cardiac cycles, the right Mod-MPI demonstrates comparable reproducibility to the left Mod-MPI, although standard deviation of reference interval means are wider [61].

Valve Click Measurement

As valve leaflets open and close, they create 'original' Doppler clicks in the same direction as flow (for opening clicks) and opposite direction to flow (for closing clicks). Smaller Doppler echoes may be detected in the opposite direction ('reflected' clicks). The original and reflected clicks share a single peak time-point [41] (fig. 3). It is thought that a thinner click (e.g. reflected click) allows more precise measurement of time intervals [62].

MPI Measurement by Tissue Doppler Imaging

Tissue Doppler can be also used to obtain systolic (S'), early diastolic (E') and late diastolic or atrial (A') myocardial velocity waveforms in the same timeline, and measure left, right and septal MPI' (fig. 4). Pulsed-wave mode with a sample volume size between 2 and 4 mm is applied in the basal part of the right free ventricular wall (tricuspid annulus), interventricular septum or left free ventricular wall (mitral annulus) in an apical or basal four-chamber view. The insonation of the ultrasound beam should be kept at an angle of $<30^\circ$ to the orientation of the ventricular wall or the interventricular septum with no angle correction. The velocity of myocardial movement toward the Doppler cursor is displayed as a

Fig. 3. Schematic representation of valve clicks and time intervals for (a) left Mod-MPI Doppler waveform and (b) right Mod-MPI Doppler waveforms.

spectrum and a minimum of three myocardial velocity waveforms should be obtained. In order to calculate MPI by tissue Doppler (MPI'), the following periods must be calculated from the same cardiac cycle: ICT' defined from the end of A' to the beginning of S'; ET' from the beginning to the end of S', and IRT' from the end of S' to

the beginning of E' as shown in figure 4. Left, right, and septal MPI' can be calculated as $(ICT' + IRT')/ET'$. Most studies have used online spectral tissue Doppler to evaluate MPI'; however, off-line colour tissue Doppler can be also used [63].

Fig. 4. Systolic (S') and diastolic (E' and A') myocardial velocities at lateral mitral annulus obtained by spectral tissue Doppler in order to calculate myocardial performance index measuring ejection (ET') and isovolumetric contraction (ICT') and relaxation (IRT') times.

Reliability and Reproducibility of MPI

The reliability of left and right MPI' as measured by tissue Doppler has been evaluated by recent studies [28, 32] reporting intraclass correlation (ICC) values ranging between 0.70 and 0.94, similar to the reproducibility of left MPI by conventional Doppler with a reported ICC of 0.87 [61]. ICC is generally used to provide an assessment of the repeatability of a measurement in relation to the variation anticipated within the sample or group. The issue of optimal repeatability of Doppler measurements is currently under debate, as there is likely to be a compromise between perfect repeatability and inherent physiological variation [64, 65]. While both conventional and tissue Doppler techniques demonstrate good reproducibility, further refinements and standardisation of the technique is required to make the transition from research to clinical tool more precise. A recent paper has addressed the influence of equipment and settings on repeatability with the potential for ICC >0.9 [66].

Clinical Application of MPI

For MPI to translate from a research tool to clinical practice, several conditions must be met: (1) It must be possible for MPI to be routinely acquired and accurately calculated, using equipment readily available in obstetric ultrasound/maternal-fetal medicine units, sonographers who require only modest additional training to become proficient in MPI use, and with minimal variation in measurement and calculation between units. (2) There must be sufficient differences between MPI values in normal and pathological pregnancies to be clinically predictive. (3) To justify the extra time and training for clinical use of MPI, it needs to have a predictive value that current measures in routine clinical practice do not.

Regarding the first point, normal gestational age-adjusted reference values of second- and third-trimester singleton fetuses for the left Mod-MPI [59, 62, 67, 68], right Mod-MPI [69, 70], and uncomplicated monochorionic twin pregnancies have been published [7]. MPI has also been evaluated in first-trimester normal and complicated pregnancies [16, 69, 71–79], and compared with normal infants and children [11, 54]. Reported Mod-MPI values for normal singleton fetuses range from 0.35 to 0.60 [9, 11, 54, 55, 62, 67, 68, 79–81]. Some studies describe almost constant measurements throughout pregnancy [9, 54, 68, 79, 80], while others report gradual reductions [11, 81] or increases [39, 58, 67] with gestational age (fig. 5). MPI' values obtained by tissue Doppler are generally higher than those obtained by standard pulsed Doppler [28] and increase slightly with gestational age [82] (fig. 5). Reference ranges for the right MPI' and left MPI' have been constructed by Comas et al. [82]. The differences between studies in normal values and effect of gestational age on MPI limits the application of MPI in assessing complicated pregnancies such as IUGR and TTTS.

Notwithstanding the inconsistency of normal ranges between research groups, several studies have now applied Mod-MPI in second- and third-trimester complicated pregnancies. The results of these studies must be interpreted with caution as abnormal MPI values have not yet been defined against a universal reference range, though within many groups the pathological difference outweighs the physiological variation.

Intrauterine Growth Retardation

MPI in IUGR fetuses has been evaluated in a number of different studies by conventional and tissue Doppler [6, 11, 30–34, 83–88]. In fetuses followed longitudinally, MPI

Fig. 5. Gestational age-adjusted mean values for fetal left MPI in studies published from 1999–2012. Adapted from Cruz-Martinez et al. [67].

was identified as one of the earliest Doppler parameters affected and remained elevated throughout the different stages of deterioration with a steeper curve of deterioration compared with other Doppler indices (aortic isthmus and ductus venosus pulsatility indices) [34, 87]. The MPI is already affected when the umbilical artery waveform still has end-diastolic blood flow, reflecting an early adaptive process of the fetal heart to perinatal complications [31]. These findings may help optimise delivery timing and define the deterioration process of IUGR fetuses [4].

Twin-Twin Transfusion Syndrome

A number of publications have evaluated the Mod-MPI in TTTS [18–21, 38, 57, 68, 89]. From early in the evolution of TTTS, both right and left Mod-MPIs of the recipient twin are systematically higher than those of the donor, which often remain within the normal range [7, 19, 21, 22, 38, 57, 68, 89–94]. Stirnemann et al. [18] and Quintero et al. [95] found significant myocardial dysfunction in the recipient twins in up to 55 and 44% of stage 1 cases respectively. This increase in MPI has been found to be primarily due to an increase in IRT, suggestive of de-

creased diastolic compliance [96, 97]. Other publications have demonstrated the absence of inter-twin difference in cardiac structure or function in uncomplicated MCDA twin pregnancies [98]. Papanna et al. [20] reported a significant increment in the recipient MPI during laser surgery which remained elevated and only normalised 48 h after the procedure. This may assist in determining the prognosis of the fetus prior to laser surgery [4].

Fetuses of Diabetic Mothers

Despite the recognition of fetal hypertrophic cardiomyopathy in fetuses with diabetic mothers, the effect of diabetes on global cardiac function is still in question [12, 15]. Fetuses of pre-gestational and poorly controlled diabetic mothers demonstrate increased right and left ventricular MPI compared to non-diabetic controls as early as the first trimester [16, 99, 100] and also in late gestation [11, 101, 102]. Abnormal fetal left Mod-MPI in gestational diabetes compared with normal fetuses has also been reported [13, 100]. However, other studies report no difference in fetal MPI between diabetic and control pregnancies [12, 15, 102].

Pre-Eclampsia

While Chen et al. [103] found a significant difference in the right and left MPIs between the control group and pregnancy-induced hypertension syndrome group, there is no consistent data currently available on pregnancies complicated with pre-eclampsia [29].

Other Fetal Conditions

The effect of several other fetal pathologies on MPI have also been evaluated [35–38, 104–113]. Romero et al. [113] demonstrated abnormal cardiac function in fetuses with pre-term rupture of membranes and positive microbial cultures in the amniotic fluid. Additionally, increased MPI values have been shown in fetuses with signs of fetal inflammatory response syndrome [36].

Technical Considerations and Limitations

Despite improvements in the repeatability of MPI, there are still several technical challenges relating to maternal and fetal factors that may influence image acquisition and MPI values.

Fetal Heart Size

The smallness of the fetal heart is advantageous in the calculation of the left MPI as both mitral inflow and aortic outflow can be captured within a single Doppler sample gate [9] of about 3–4 mm [59], though this may need to be increased to achieve satisfactory recordings [67]. This approach can only be applied to the right ventricle before 20 weeks of gestation because the increased distance between the tricuspid and pulmonary valves precludes the use of a single sample gate to capture both valve flows in later gestations [4]. An advantage of tissue Doppler is that it permits left, right and septal MPI' calculations to be obtained as myocardial peak velocities which are always displayed in the same time line for each location. However, tissue Doppler was initially designed and validated for the adult heart, with myocardial velocities usually >15 cm/s (versus fetal myocardial peak velocities usually <10 cm/s). Therefore, the relatively low resolution of some ultrasound equipment may limit the sharpness of myocardial velocity waveforms and accuracy of MPI' calculation. Despite these limitations, several recent studies have demonstrated that spectral tissue Doppler is feasible and reproducible in most fetuses even from early on in the second trimester of pregnancy [82, 114, 115].

Fetal Heart Rate

The fetal heart rate is both higher and shows greater beat-to-beat variability than that of adults [10]. Most studies have indicated that left MPI values are independent of heart rate [9, 59], although Meriki and Welsh [62] found MPI increased 7–8% as the heart rate increased from 130 to 160 beats/min. When calculating MPI in the right ventricle, fetal heart rates between the two recordings should differ by no more than 10 beats/min [4]. Due to this high fetal heart rate in fetuses, 2 ms must be the smallest measureable time increment to ensure the sensitivity and accuracy of measured time intervals [4].

Fetal Position and Movement

Factors such as maternal adiposity, oligohydramnios or an anterior placenta may interfere with image acquisition and quality [10]. If the fetal spine is persistently in an anterior position, optimal viewing can be impossible [10]. Both spectral and tissue Doppler are very sensitive to the angle of acquisition, which should be as close as possible to 0°. Ideally, MPI images should be obtained in the absence of fetal corporeal or respiratory movements, which may be difficult to achieve in clinical practice [10].

Specific Training Required

Whilst a non-experienced examiner requires on average 65 fetal MPI measurements to achieve competence and reliability [116], an experienced examiner can measure MPI in a mean acquisition time of 2–3 min with a low degree of variability [40, 68].

Standardised Technique and Machine Settings

Machine Settings

Hernandez-Andrade et al. [59] described optimal machine settings including: a sample volume of 3 mm; angle of insonation <30°; fastest sweep velocity (15 cm/s) with a minimum displacement of 2 ms to clarify and separate valve clicks by 'stretching' the Doppler waveform [39]; lowest Doppler gain to exclude noise and artefacts and clearly visualise echoes corresponding to valve clicks [4]; high-pass wall motion filter (WMF) to omit slow blood motion signals [40], and the placement of the time cursor at the beginning of valve clicks [59].

Meriki et al. [39] have since shown that further refinements may improve the reproducibility and accuracy of MPI: (1) angle of insonation <15° and as close to 0° as possible [10, 62] (ICCs reduce with increasing angle) [39]; (2) WMF fixed at 300 Hz (sharpens and clarifies valve clicks while retaining the mitral valve aperture

Table 1. Technique and machine settings specified in various studies

First author [ref.]	Angle of insonation, °	WMF, Hz	Sample volume, mm	Sweep velocity, cm/s	Doppler gain	Doppler aliasing	Placement of time cursor
Tei [5]	ND	ND	ND	10	ND	ND	beginning of mitral inflow and aortic outflow waveforms
Hernandez-Andrade [40]	<30	70	3	15	Min	ND	beginning of valve clicks
Van Mieghem [68]	<15	≥120	ND	10	ND	ND	end of closing clicks to beginning of opening clicks
Meriki [39]	<15	300	3	15	Min	Nil	peak of valve clicks

ND = Not defined; Min = minimum.

click) [39]; (3) avoid Doppler aliasing, and (4) measure the peak of valve clicks (increased reproducibility). When combined, these machine settings as shown in table 1 exhibited the best overall reproducibility of time interval measurements [39] compared with the original Mod-MPI technique proposed by Hernandez-Andrade et al. [40].

The effect of different machine settings on MPI' assessment by tissue Doppler has not been evaluated. However, it is postulated that the measurement can be affected by machine settings as it is known that myocardial velocities (peak measurements and waveforms) can vary depending on the ultrasound equipment used [117]. Consequently, the use of the same echocardiographic equipment during patient follow-up and the use of reference ranges are recommended.

Calliper Placement in Phase of Valve Clicks

While the first published normative fetal MPI values defined that the time calliper be positioned just before the echo of the valve click [40], the criteria for delineation of valve clicks are inconsistent between studies. Subsequent studies, for example, have placed the cursor within the echo of the valve clicks (at the beginning) [29], from the end to the beginning of the valve clicks (corresponding to physiological time intervals) [68], at the peak (a clearer landmark used to overcome the variation in width of valve clicks) [62], or the method has not been defined [14, 79, 80]. The peak method has shown good intra- and interobserver variability and high repeatability compared with the original method [61].

The morphological characteristics of valve movements influence the measurement of cardiac time intervals [41], with small alterations of milliseconds in the measurement of time intervals resulting in a significantly different MPI.

A lack of consensus on calliper placement has resulted in wide variation in the quoted 'normal' ranges for the MPI which has limited its translation into clinical practice [62, 67].

Future Research Directions

A consensus must be reached regarding calliper placement to ensure consistency between research groups. Subsequently, universal normal reference ranges should be established to accurately assess the effect on MPI values in complicated pregnancies.

Several single-centre studies have previously evaluated the MPI in complicated pregnancies; however, large multicentre studies using standardised machine settings and technique are still required to evaluate the effect of pathology on the fetal MPI values. Furthermore, MPI' by tissue Doppler requires further validation with use of different equipment and various pathologies.

The right and left ventricles of the fetal heart differ in structure and function, with the right ventricle demonstrating physiological dominance [28]. In pathological conditions, the right ventricle is affected to a greater degree and may manifest dilatation, hypertrophy and dysfunction prior to the left [118]. A measure of unilateral cardiac strain therefore has potential in the detection and monitoring of pathological conditions that affect myocardial performance [119]. One such index, the 'Delta-MPI' [120] has been proposed, but has not been evaluated in complicated pregnancies. Therefore, studies evaluating Delta-MPI in various pathological conditions are required.

Alternative indices of fetal myocardial function which utilise tissue Doppler such as myocardial veloci-

ties [114, 115, 121], strain and strain rate [122], and colour tissue Doppler [123, 124] have been shown to be sensitive for cardiac dysfunction in the fetus. More recently, non-Doppler 2D speckle tracking has been proposed, an angle-independent method that permits the measurement of strain and strain rate and has the potential to record complex fetal myocardial function such as torsion or twist [125]. As with all fetal myocardial-derived indices, factors such as maternal-fetal movements, suboptimal imaging, and a low frame rate limit its clinical application [125]. To date, 2D speckle tracking has been investigated in terms of its feasibility and application to fetal echocardiography [126–134]; however, further studies evaluating its use in pathological conditions are warranted.

Measurement of a single parameter may overlook important information about myocardial performance. Therefore, it is important to comprehensively assess cardiac morphometry and function by several parameters and integrate the information obtained to better understand the underlying myocardial changes. However, complete fetal echocardiographic assessment is resource intensive in terms of time, equipment, and sonographic expertise. In the future, MPI may be useful for screening due to its high sensitivity and relative ease of use, with an abnormal MPI serving as an indication for a complete fetal echocardiographic assessment. The information provided by the MPI and its time-period components represents early stages of cardiac adaptation associated with: increased placental vascular resistance as in growth-restricted fetuses [135, 136], increased blood volume in the recipient fetus of TTTS [7, 20], poorly controlled diabetic pregnant women [99, 137], and altered hemodynamics in pre-eclamptic women [29]. Most IUGR fetuses show a progression of hemodynamic deterioration with an increased MPI and/or brain vasodilatation followed by changes in other fetal vascular territories [31]. Although the original expectation that MPI might be used as an individual parameter for selecting the optimal time of delivery in IUGR fetuses has not been achieved, the MPI has shown signs of fetal cardiac adaptation more consistently than the E/A waveforms, ventricular outflow tracts, and stroke volume. The evaluation of the individual time periods might also contribute to the study of the different phases of the cardiac cycle in IUGR fetuses [138]. Standardisation of the technique for estimating the three time periods can further improve its reproducibility and clinical applications [39, 61], and the study of the right MPI might complement the assessment of the global cardiac function [62].

While MPI can provide information on the cardiac adaptation of complicated fetuses, clinical utility is limited by the lack of options for management and treatment in conditions studied thus far. In growth-restricted fetuses presenting with early signs of cardiac adaptation and/or brain vasodilatation, the only change might be a closer surveillance, without affecting the natural history of the disease. However, in other perinatal complications where treatment is available, the MPI can identify early stages of disease when fetal treatment might be more successful. In TTTS the timing of laser coagulation of vascular anastomoses might be based on cardiac signs of volume overload in the recipient twin manifested as a prolonged MPI [18, 89], and in anaemic fetuses an abnormal MPI might reflect the necessity for blood transfusion.

Most available studies of fetal cardiac function have failed to show an individual marker reliable enough in providing information on sequential changes of the cardiac performance [139, 140]. Most of the volumetric evaluations are influenced by the heart rate, peripheral resistance and blood volume. Visualisation of the coronary circulation is technically difficult and observed at late stages of fetal deterioration [141]. The MPI is a reliable marker of early cardiac adaptation; the benefits of its integration into the routine fetal surveillance will depend on the available options for management or treatment of complicated pregnancies.

Conclusion

The MPI is a sensitive parameter of fetal cardiac dysfunction, and developments in the technique of image acquisition and definition of ultrasound settings have improved the reproducibility of measurements substantially since its proposal. However, until a consensus is reached on the method for the delimitation of time periods used in the calculation of MPI and machine settings are strictly defined, the clinical value of this tool is limited. There is a need to establish a universal normal reference range to which pathological conditions may be compared. This will allow validation of any previous or future MPI studies. Future directions for research into the MPI include the effect of pathology and differential cardiac strain on MPI and automation of the measurement process.

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