# Comparison of Micro-bubble Hang-out Time and Cardiac Catheterization in Determining Reversal of Pulmonary Vascular Resistance by Oxygen Challenge Test Among Patients with Shunt Anomalies: The BUBBLE Study

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**OBJECTIVES** To determine the utility of micro-bubble hang-out time (MHT) in determining reversal of pulmonary vascular resistance (PVR) by oxygen challenge test among patients with shunt anomalies.

**METHODS** This is a cross-sectional study involving 16 in-patients aged older than 14 years, with an isolated shunt anomaly, a pulmonary artery pressure of greater than 60 mmHg who underwent a hemodynamic study (HS). Agitated saline was injected intravenously before and after an oxygen challenge. MHT in the right sided chambers was measured in seconds using the apical 4-chamber view. Patient then had a HS within 24 hours, determining PVR and reversibility. Non-invasive and invasive parameters were then correlated.

**RESULTS** Thirteen patients were found to have reversible PVR as determined by HS (pre-oxygen MHT of 76.36 s ± 25.35 and post-oxygen MHT of 37.18 s ± 15.04; p=0.001), and three patients had irreversible PVR (pre-oxygen MHT of 158.37 s ± 120.41 and post-oxygen MHT of 108.82 ± 80.17; p=0.167). A 60-s cut-off for post-oxygen MHT in determining reversibility had a 100% sensitivity, specificity, and positive and negative predictive values (Kappa=1.000).

**CONCLUSION** A post-oxygen MHT cut-off of 60 s, independent of the pre-oxygen MHT, can be used as an alternative to an HS in labeling patients with isolated shunt anomalies and moderate to severe pulmonary hypertension, into those with reversible (≤ 60 s) and irreversible (> 60 s) PVR.

**KEYWORDS** *Contrast, bubble study, hang-out time, pulmonary vascular resistance, pulmonary hypertension, congenital heart disease, shunts.*

The pulmonary circulation is characterized by high flow, low pressure and low resistance. The normal pulmonary vascular bed offers less than 10% of the resistance flow offered by the systemic bed. The effect of oxygen on the pulmonary vasculature is the most distinctive characteristic by which it differs from the systemic vasculature. The hypoxic pulmonary vasoconstrictor response is an important adaptive mechanism so blood flow will be shunted away from hypoxic regions toward better ventilated areas of the lung, improving the ventilation-perfusion matching in the lung. Although the acute effects of this response are beneficial, chronic hypoxemia can result in sustained elevation of pulmonary artery pressure, vascular remodeling, and development of pulmonary arterial hypertension (PAH). The response of the smooth muscle cells in the pulmonary arteries to hypoxia begins within seconds. Whereas acute hypoxia causes reversible changes in vascular tone, chronic hypoxia induces structural remodeling and is mediated by a number of growth factors.[1]

PAH refers to any elevation in the pulmonary arterial pressure above normal, and is defined as such when the pulmonary artery pressure (PAP) increases to more than 25 mmHg at rest or 30 mmHg with exercise.[2] PAH can develop from any congenital heart defect that increases pulmonary blood flow.

Cardiac catheterization is the gold standard in the evaluation of pulmonary vascular resistance (PVR). Reversible causes of significant PAH and elevated PVR like in patients with shunt anomalies can be evaluated at the cardiac catheterization laboratory. Oxygen and vasodilators can be used to lower the PVR.

In the ideal situation, when clinicians are faced with patients with shunt anomalies and severe PAH, oximetry can be used to determine if the pulmonary status is amenable to intervention or not. If the result is not ideal for surgery, an oxygen challenge test that uses 100% oxygen via a Douglas mask to note for improvement of oxygen saturation may be used. Finally, cardiac catheterization can be used to confirm the reversibility of PVR. Reversibility can then indicate suitability for surgical repair of shunt anomalies.

It is very important to have a non-invasive means of assessing PVR especially in the Philippine setting because of the high cost, discomfort, and risks of cardiac catheterization.

Non-invasive means of determining the reversibility of PVR has been shown in a study by Gonzales-Velasquez et al.[3], concluding that assessment of PVR by two-dimensional echocardiography is similar to findings measured via cardiac catheterization. However, in patients with a non-reactive pulmonary bed, cardiac catheterization would still be needed.

Gas-containing microbubbles are intense ultrasound reflectors and reflect ultrasound at a level several orders of magnitude greater than non-gas-containing structures. The simplest ultrasound contrast agent consists of saline microbubbles, which can be used to improve echocardiographic assessment.[4-6]

Micro-bubble disappearance or hang-out time can be an alternative test to a hemodynamic study and improve assessment of tricuspid regurgitation velocity (TRV) and right ventricular outflow tract (RVOT) velocity time integral (VTI)-derived PVR because it is not affected by primary diseases of the tricuspid valve and the severity of the tricuspid regurgitation. In addition, the technique is non-invasive, less expensive and with less risk than cardiac catheterization.

Applying the micro-bubble hang-out time (MHT) principle in patients with shunt anomalies and moderate to severe PAH and elevated PVR, it is assumed that there will be a significant delay in the time of disappearance of the microbubbles in the right sided chambers (right atrium and right ventricle) in patients with elevated PVR, which will improve after oxygen challenge, thus shortening MHT after oxygen administration if PVR is still reversible.

It is the objective of this study to use MHT, using 2D transthoracic echocardiography, and compare this technique with the gold standard of cardiac catheterization in determining reversibility of PVR after an oxygen challenge.

## METHODS

This is a cross-sectional study conducted at the Philippine Heart Center from May 2012 to March 2013. The study included patients with isolated shunt anomalies; either atrial septal defect (ASD), ventricular septal defect (VSD) or patent ductus arteriousus (PDA) admitted at the Philippine Heart Center, and who were scheduled to undergo hemodynamic studies. Patients had to be age 15 years and above and had moderate to severe PAH (PAP greater than 60 mmHg) determined by 2D transthoracic echocardiography using the Philips iE33 at the cardiac graphics section of the Philippine Heart Center. Patients with complex congenital anomalies; poor echocardiographic window; pneumonia; pleural effusion; and other medical illnesses such as hepatic failure, renal failure and vascular diseases that could alter the hemodynamic parameters; pregnant patients; and those without consent were all excluded from the study.

The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. Prior to study initiation, the study protocol and ammendments were reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board.

*Study Maneuver*

Maneuvers were performed at the hospital's cardiac graphics division. Complete echocardiographic assessment was performed before catheterization, using Philips iE33 ultrasound system equipped with an S5 transducer. Measurements included PAP using tricuspid regurgitation jet; right ventricular acceleration time (RVAT) and Qp:Qs (pulmonic to systemic flow ratios) at room air. The sonographer was blinded to the results of cardiac catheterization.

Determination of PVR was done using Fick's principle to calculate the pulmonary blood flow and oxygen consumption using the formula: PVR=TRV/RVOT-VTI x 10 + 0.16. The RVOT-VTI was obtained by placing a 1 to 2 mm pulsed wave Doppler sample volume in the proximal RVOT just within the pulmonary valve when imaged from the parasternal short-axis view. The sample volume was placed so that the closing but not the opening of the pulmonary valve was visualized. This measurement was carried out thrice in each case and the mean of these three values was used.

TRV was obtained using continuous wave Doppler from the apical 4-chamber, parasternal and subcostal views; and

the highest peak value was retained.

The TRV/RVOT-VTI ratio was calculated.

Left ventricular ejection fraction was assessed from an apical 4-chamber view using the monoplane modified Simpson's rule.

Saline bubble contrast was then done using an apical 4-chamber view to determine the baseline MHT within the the right atrium and right ventricle. Intravenous access was established using a Terumo intravenous catheter gauge 22 inserted via a left or right antecubital vein. Micro-bubble test was performed by mixing thoroughly 9.5 ml of saline and 0.5 ml of air in a solution using two (2) 10 ml-syringes and injecting it intravenously. MHT was measured in seconds (within two decimal places) measured from the time of opacification of the right sided chambers up to the time when less than 5 micro-bubbles were seen in the right-sided chambers. The subject's heart rate was noted in the data collection form.

Patients then underwent fifteen minutes of oxygen challenge at 10 liters per minute via a Douglas valve. Oxygen saturation and oxygen partial pressure were measured using standard spectroscopic methods. Patients then underwent re-determination of the Doppler variables mentioned above (PAP, RVAT, Qp:Qs, PVR and MHT).

Patients then underwent standard cardiac catheterization on the same day or with an interval of not more than 24 hours from echocardiography, performed through femoral access using Cournand or Goodale catheters to measure the following parameters: right atrial pressure (RAP), right ventricular pressure (RVP), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), mean pulmonary artery pressure (MPAP), right pulmonary capillary wedge pressure (PCWP), cardiac output (CO), Qp:Qs, Rp:Rs (pulmonary to systemic resistance ratio) and PVR, before and after an oxygen challenge.

PVR via cardiac catheterization was derived using the formula: PVR= (mean PAP – mean left atrial pressure)/ pulmonary blood floow x 80. Pulmonary artery wedge pressure was used to measure left atrial pressure if values were not available. Pulmonary blood flow in liters/minute was calculated by using the Fick's equation. The oxygen consumption (VO2) was assumed. An assumed value of oxygen consumption (in mL/min per square meter) was obtained from the Lafarge et al's standard nomogram (based on age, gender, and heart rate).[7]

The mean MHT pre- and post-oxygen challenge were then correlated with cardiac catheterization in determining the reversibility of PVR after an oxygen challenge (Rp:Rs). Reversibility was defined by a Rp:Ps of less than or equal to 1.0 after an oxygen challenge, or lower than the previous Rp:Ps value before oxygen was administered; or a drop of the mean PAP by at least 10 mmHg after oxygen administration or simulation of the effect of shunt repair (e.g. inflating a balloon in the shunt of a PDA patient), to an absolute level of <40 mmHg without a decrease in cardiac output.

*Statistical analysis*

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as frequencies and percentages. Pearson correlation analysis was used to find the correlation between MHT and cardiac catheterization derived Rp:Rs. The change in MHT pre-

**Table 1.** Mean baseline characteristics (n=16).

| | |
|---|---|
| **Age** (years ± SD) | 33 ± 9.96 |
| **Gender** (n, %) | |
| Male | 5 (31) |
| Female | 11 (69) |
| **Diagnosis** (n, %) | |
| Atrial septal defect | 11 (69) |
| Ventricular septal defect | 2 (12) |
| Patent ductus arteriosus | 3 (19) |
| **WHO functional class** (n, %) | |
| I | 3 (19) |
| II | 11 (69) |
| III | 2 (12) |
| IV | 0 |
| **Rest rhythm** (n, %) | |
| Atrial fibrillation | 2 (12.5) |
| Sinus rhythm | 14 (87.5) |
| **Heart rate** (beats per minute ± SD) | 83 ± 12 |
| **Pulmonary vascular resistance*** (Wood units ± SD) | 2.5 ± 1.7 |
| **Right atrial pressure*** (mmHg ± SD) | 4 ± 2 |
| **Pulmonary artery systolic pressure*** (mmHg) ± SD) | 88 ± 21 |
| **Right ventricular fractional area change*** (% ± SD) | 36 ± 11 |
| **Pulmonary regurgitation area*** (cm2 ± SD) | 2.6 ± 2.3 |
| **Tricuspid Annular Plane Systolic Excursion*** (cm ± SD) | 1.2 + 0.7 |
| **Pulmonary artery systolic pressure**** (mmHg ± SD) | 85 ± 31 |
| **Pulmonary artery diastolic pressure**** (mmHg ± SD) | 39 ± 24 |
| **Mean pulmonary artery pressure**** (mmHg ± SD) | 57 ± 26 |
| **Pulmonary capillary wedge pressure**** (mmHg ± SD) | 11 ± 6.4 |
| **Right atrial pressure**** (mmHg ± SD) | 10.6 ± 7.0 |
| **Pulmonary vascular resistance**** (Wood units ± SD) | 12.4 ± 15.5 |
| **Cardiac output**** (L/min ± SD) | 3.4 ± 1.0 |

**Measured by echocardiography; **Measured by cardiac catheterization.*

**Table 2.** Congenital shunt anomaly and pre- and post-oxygen challenge MHT among included patients.

| Patient | Shunt | Pre-oxygen challenge | Post-oxygen challenge |
|---|---|---|---|
| 1 | VSD | 75.39 | 21.05 |
| 2 | ASD | 109.4 | 42.08 |
| 3 | ASD | 67.38 | 44.03 |
| 4 | ASD | 34.69 | 33.03 |
| **5*** | **ASD** | **85.39** | **62.04** |
| 6 | ASD | 58.39 | 17.41 |
| 7 | ASD | 43.04 | 43.02 |
| 8 | ASD | 104.39 | 15.39 |
| 9 | ASD | 92.71 | 51.38 |
| 10 | ASD | 80.4 | 47.73 |
| 11 | PDA | 48.37 | 47.72 |
| **12*** | **ASD** | **297.34** | **201.39** |
| 13 | VSD | 113.4 | 15.07 |
| 14 | ASD | 88.36 | 46.7 |
| 15 | PDA | 76.72 | 58.73 |
| **16*** | **PDA** | **92.37** | **63.02** |

**Irreversible by cardiac catheterization*
*MHT=micro-bubble hang-out time; VSD=ventricular septad defect; ASD=atrial septal defect; PDA=patent ductus arteriosus.*

to post- oxygenation was analyzed using paired t-test. Comparison between reversible and irreversible PVR was determined using independent T-test. A p value of ≤ 0.050 was considered significant. The validity of MHT at cut-off points of 60 seconds in indicating reversibility was evaluated for sensitivity, specificity, positive predictive value and negative predictive value. Kappa test was used to determine the degree of agreement.

The study sample size was computed to be 19, based on a 95% confidence level, 80% power and assumed correlation coefficient of 0.635 between TRV/RVOT-TVI and PVR determined by catheterization, as found in the study of Dheeraj Deo Bhatt D.M. et al.[6]

## RESULTS

Sixteen patients were enrolled in the study. All of them underwent baseline 2D echocardiography and MHT determination before and after an oxygen challenge test. Mean age was 33 years ± 9.96 years (Table 1). Sixty-nine percent of patients were female. All patients had isolated shunts, most commonly an ASD (69%). Majority of the patients (87.5%) were in sinus rhythm. Table 1 also shows baseline 2D transthoracic echocardiographic parameters.

Of the 16 patients enrolled in the study, 13 patients had reversible pulmonary vascular disease (Tables 2 and 3). Among the 13 patients with reversible PVR, the mean MHT was 76.36 s ± 25.35 before oxygen challenge and 37.18 s ± 15.04 after (p=0.001). The mean MHT patients with irreversible PVR was 158.37 s ± 120.41 before oxygen challenge and 108.82 s ± 80.17 after (p=0.167).

There was no significant correlation between pre-oxygen challenge MHT and pre-oxygen challenge Rp:Rs; as well as between post-oxygen challenge MHT and post-oxygen challenge (Table 4).

Table 5 shows a significant agreement between MHT of at most 60 s vs over 60 s and reversibility as determined by cardiac catheterization. All 13 patients who were determined to be reversible by the gold standard cardiac catheterization were found to have an MHT of less than or equal to 60 seconds, and all three patients with irreversible PVR had a MHT of over 60 s (100% sensitivity, 100% specificity, 100% positive and negative predictive values).

## DISCUSSION

Echocardiography is the most readily accessible tool for evaluation of cardiac function. Besides its availability, it is also a cost-effective, accurate, and non-invasive way of checking the overall status of the heart, anatomically and physiologically.

Cardiac catheterization on the other hand, has been used as the gold standard for many years to evaluate on anatomical and hemodynamic condition of the heart, as well as to assess the reversibility of PVR in shunt anomalies. However, it is relatively costly and risky compared to echocardiogram. Echocardiographic contrast studies using agitated saline and other contrast agents are used primarily for detection of right-to-left shunt and improved left ventricular endocardial border definition in cases where image quality is suboptimal.

Using agitated saline MHT and correlating it with the reversibility of PVR in patients with shunt anomalies has not been studied yet. This study is novel to this field and might open possibilities of the great utility of this echocardiographic modality in the discipline of congenital heart disease.

This study showed that in patients with reversible PVR as determined by cardiac catheterization, MHT before and after administration of 10 liters of oxygen via a Douglas valve differed significantly. On the other hand, in patients with irreversible PVR, the MHT did not differ significantly pre- and post-oxygen challenge, as expected.

However, when comparing patients with reversible and

**Table 3.** MHT pre- and post-oxygen challenge by PVR reversibility.

| | n | Pre-oxygen challenge (mean + SD) | Post-oxygen challenge (mean + SD) | P value | Difference (mean + SD) | % change (mean + SD) |
|---|---|---|---|---|---|---|
| **Reversible PVR by HS** | 13 | 76.36 s ± 25.35 | 37.18 s ± 15.04 | 0.001 | 39.18 s ± 31.86 | 44.03 s ± 30.48 |
| **Irreversible PVR by HS** | 3 | 158.37 s ± 120.41 | 108.82 s ± 80.17 | 0.167 | 49.55 s ± 40.3 | 30.33 s ± 2.89 |
| **P value** | | 0.359 | 0.261 | | 0.633 | 0.136 |

*MHT=micro-bubble hang-out time; PVR=pulmonary vascular resistance; HS=hemodynamic studies.*

irreversible PVR, MHT pre- and post-oxygen challenge testing, did not achieve statistical significance (Table 4). This may be due to some of the study's limitations: there may be some subjective component when doing the micro-bubble hang-out timing in the right-sided chambers; and there were only a few cases of isolated shunt anomalies who underwent cardiac catheterization. Twenty two patients were qualified by the inclusion criteria in this study, but six patients did not consent to the procedure. A total population of 16 may be slightly under-powered.

It was noted that patients proven by cardiac catheterization to have irreversible PVR have a post-oxygen challenge MHT of greater than 60 seconds. In contrast, those with reversible PVR have MHT of 60 seconds or less. Hence, a MHT cut-off of 60 seconds seems to be correlated with reversibility by cardiac catheterization (Kappa=1.000).

Two patients included in the study died. However, the reasons for death cannot be attributed to the study technique. The first patient was a 20-year old female with ASD and severe PAH and severe irreversible pulmonary vascular disease. She died 36 hours after the bubble study and 8 hours after cardiac catheterization due to sudden onset of dyspnea and subsequent cardiac arrest. It has been documented that high-risk patients should be monitored during and after 30 minutes of contrast administration.[8,9] Since the patient died 36 hours post-procedure, it is unlikely that the cause of death was related to the study procedures.

The second patient was a 23-year old female with ASD and moderate PAH and reversible PVR. Following a failed attempt to close the shunt percutaneously, she eventually underwent an open repair of the shunt. However, she later developed a malignant stroke and died subsequently.

Another patient, a 16-year old female with ASD and severe irreversible pulmonary vascular disease, suffered severe headache after two injections of 9.5 ml saline-0.5 ml gas mixture. She was monitored closely, and the headache eventually resolved. The rest of the patients did not have any subjective complaints during and after the study.

Based on the collected data, there is significant difference between MHT and reversibility of PVR among patients with shunt anomalies who were known to be reversible on cardiac catheterization, while there was no significant difference between MHT before and after an oxygen challenge test in patients known to be irreversible on cardiac catheterization.

A MHT cut-off of 60 seconds in the right-sided chambers may help determine patients with reversible (≤ 60 seconds) or irreversible (> 60 seconds) PVR.

These suggest that patients with isolated congenital cardiac shunt anomalies with moderate to severe PAH who are hesitant to undergo cardiac catheterization may alternatively do MHT in the right sided chambers after an oxygen challenge test to suggest reversibility.

It is suggested that similar future studies include more patients, have the MHT adjusted according to the patient's heart rate, and have a set constant 2D image gain and depth.

**Table 4.** Correlation of MHT pre- and post- oxygen challenge with Rp:Rs pre- and post- oxygen challenge.

| Variables | R | p value |
|---|---|---|
| Pre-O2 MHT versus Pre-O2 Rp:Rs | -0.060 | 0.826 |
| Post-O2 MHT versus Post-O2 Rp:Rs | 0.098 | 0.761 |

*MHT=micro-bubble hang-out time; Rp=pulmonary vascular resistance; Rs=systemic vascular resistance.*

**Table 4.** Agreement of MHT post-oxygen challenge test with reversibility by cardiac catheterization.

| | Cardiac catheterization | | |
|---|---|---|---|
| **MHT** | **Reversible** | **Irreversible** | **Total** |
| **≤60 s** | 13 | 0 | 13 |
| **>60 s** | 0 | 3 | 3 |
| **Total** | 13 | 3 | |

*MHT=micro-bubble hang-out time.*
*Sensitivity 100%* *Positive Predictive Value 100%*
*Specificity 100%* *Negative Predictive Value 100%*
*Kappa=1.000.*

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