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**PROJECT TITLE:** The role of tissue Doppler imaging using transesophageal echocardiography in the non-invasive assessment of left ventricular filling pressures during cardiac surgery

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**SUMMARY:**

**Background:** Cardiac surgical patients often require invasive pulmonary artery catheters (PAC) to determine left ventricular filling pressures (LVFP) in order to guide fluid management. Tissue Doppler imaging (TDI) as derived by transthoracic echocardiography (TTE), non-invasively assesses pulmonary capillary wedge pressure (PCWP), which is a surrogate for LVFP. With the use of TDI as derived by TTE, the ratio of transmitral inflow to mitral annular velocity during early diastole ( $E/E'$ ) correlates with PCWP. However, little is known on the role of TDI using intra-operative transesophageal echocardiography (TEE) in the assessment of LVFP during cardiac surgery.

**Objective:** To determine if TDI indices obtained by intra-operative TEE during cardiac surgery accurately estimates PCWP using PAC as the gold standard.

**Methods:** Patients undergoing cardiac surgery were prospectively enrolled at a single tertiary care centre. Conventional and novel echocardiographic parameters were evaluated using intra-operative TEE with concurrent invasive PAC monitoring before and after cardiopulmonary bypass (CPB).

**Results:** The study population included 34 patients (26 males, mean age  $64 \pm 9$  years). The correlation between  $E/E'$  using TEE and PCWP was poor to modest at best. Pre-CPB, the correlation ratio between mean  $E/E'$  and PCWP was  $r=0.23$ . Post-CPB, the correlation ratio between mean  $E/E'$  and PCWP was  $r=0.42$ .

**Conclusion:** Intra-operative TEE was unable to accurately assess LVFP in patients undergoing cardiac surgery. The PAC continues to be the gold standard in the assessment of LVFP for this patient population.

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## ***INTRODUCTION***

In Canada, the number of patients undergoing coronary artery bypass surgery (CABG) has been stable during the past 15 years in part due to the emergence of percutaneous coronary intervention (PCI).<sup>1</sup> Despite this, cardiac surgical patients are at high risk of increased morbidity and mortality due to increasing trends in advanced age, co-morbidities, poor left ventricular (LV) function, and multi-vessel coronary artery disease (CAD).<sup>2-4</sup> Consequently, management of these high-risk patients often requires accurate assessment of LV filling pressures (LVFP) in order to guide fluid management intra-operatively.

The pulmonary artery catheter (PAC) allows for the invasive assessment of filling pressures in cardiac patients. It is a dual-lumen catheter with a balloon tip that is percutaneously advanced through a large-calibre vein such as the femoral vein or the right internal jugular vein in the setting of cardiac surgery. With continuous pressure monitoring at the distal lumen, characteristic pressure waveforms are used to guide its placement, ultimately “wedging” in the pulmonary artery. Properly placed, the PAC measures the pulmonary capillary wedge pressure (PCWP). This is done by transiently inflating the balloon, thus occluding antegrade flow and creating an uninterrupted column of blood between the catheter tip and the left atrium (LA). Thus, PCWP reflects the LA pressure, and in the absence of mitral valvular disease, it reflects LVFP. Monitoring LVFP allows for intra-operative fluid management by restoring intravascular volume and improving systemic oxygenation through the augmentation of cardiac output.<sup>5</sup> Therefore, serial measurements of PCWP as a surrogate of LVFP using PAC allow for the invasive assessment of hemodynamic responses to therapeutic interventions.

The use of PAC has been controversial since its introduction into clinical practice.<sup>6</sup> The ability of PAC to measure hemodynamic parameters including cardiac output and PCWP has been suggested to improve patient outcomes, thus justifying its use. However, the potential for non-fatal complications associated with the insertion of PAC<sup>7-9</sup> raises concerns with its routine use in the critically ill population. Previous retrospective studies have suggested that there is an increased rate of mortality associated with PAC use.<sup>10,11</sup> However, a more recent randomized controlled trial (RCT) by Harvey et al. involving medical and surgical patients in the intensive care unit (ICU) found no increased risk of mortality.<sup>12</sup> They concluded no clear evidence of benefit or harm with the use of PAC in the management of critically ill patients.<sup>12</sup> Among high-risk surgical patients, a recent, large randomized controlled trial demonstrated that morbidity and mortality rates were similar between individuals who received PAC as compared to those individuals who did not.<sup>13</sup> No formal studies in the form of RCT have been performed that assesses the efficacy and safety of PAC among the cardiac surgical population. Despite this, the PAC remains vital in the management of cardiac surgical patients with severe LV dysfunction, pulmonary hypertension and on-going ischemia. It was felt by many cardiac anesthetists that the added invasive physiologic data obtained by PAC contributed significantly to intra-operative decisions.<sup>14-16</sup> As such, the American Society of Anesthesiologists<sup>17</sup> recommends the continued use of PAC in these high-risk cardiac surgical patients.

Conventional Doppler echocardiography measures the velocity of blood flow by detecting high-frequency, low-amplitude signals from red blood cells. Using conventional Doppler, the velocity of blood flow across the mitral valve during early diastole (E) has been

**STUDENT NAME:** *Roman G. Nepomuceno*

shown to correlate poorly with PAC-derived LVFP as it is sensitive to physiologic changes in loading conditions (Figure 1).<sup>18</sup> Alternatively, tissue Doppler imaging (TDI) using echocardiography measures the higher-amplitude, lower-velocity signals of myocardial tissue.<sup>19</sup> Early diastolic mitral annular velocity ( $E'$ ) as measured by TDI has been to be independent of loading conditions (Figure 1). Using simultaneous transthoracic echocardiography (TTE) and right-heart catheterization, it has been shown that the ratio of E wave (obtained by conventional Doppler) and  $E'$  (obtained by TDI) provides an accurate estimate of PCWP.

The ratio of  $E/E'$  by TTE provides a non-invasive estimate of LVFP using echocardiography.<sup>18</sup> ***Using TTE, it has been shown that  $E/E' < 8$  is predictive of normal LVFP (PCWP < 15 mmHg) while  $E/E' > 15$  is predictive of elevated LVFP (PCWP  $\geq$  15 mmHg).***<sup>20</sup> An  $E/E'$  ratio between 8 and 15, however, is non-diagnostic.<sup>20</sup> The positive relationship between  $E/E'$  and PCWP has been widely validated in healthy individuals as well as in cardiac patients in the non-surgical setting. This includes those with structural heart disease, chronic hypertension, atrial fibrillation, sinus tachycardia, aortic stenosis, and heart failure.<sup>18,20-35</sup> The ratio of  $E/E'$  as a non-invasive surrogate for LVFP has also been evaluated in non-cardiac patients with sepsis and acute lung injury.<sup>36</sup> To our knowledge, only one study has previously evaluated the use of  $E/E'$  for the non-invasive assessment of LVFP in cardiac surgical patients. Hadano et al. used TTE to derive Doppler indices before and after CABG or aortic valve replacement (n=52), concluding that  $E/E'$  correlated well with PCWP (r=0.79) before and after surgery.<sup>37</sup> Little is known, however, on whether the relationship between  $E/E'$  and PCWP is valid during the intra-operative period of cardiac surgery, during which time, critical shifts in fluid pressures tend to occur.

Intra-operative transesophageal echocardiography (TEE) is commonly used in the cardiac surgical setting because it provides the cardiac anesthetist and surgeon valuable information on cardiac anatomy and function.<sup>38</sup> While sternotomy precludes the use of TTE, TEE is attainable and has become standard practice in many cardiac surgical centres. The estimation of LVFP using echocardiography has been validated extensively using TTE,<sup>18,20-36</sup> as described above, but only two studies have used TEE. Both of these studies demonstrated promising results involving ICU patients.<sup>39,40</sup> The validity of intra-operative TEE for the determination of LVFP during cardiac surgery remains unresolved. Hence, the objective of our study is to determine if TDI indices obtained by intra-operative TEE during cardiac surgery accurately estimates PCWP using the PAC as the gold standard.

## ***MATERIALS AND METHODS***

### ***Study Population***

A total of 34 consecutive patients undergoing cardiac surgery at a single tertiary care centre were prospectively enrolled from 2009-2011 inclusive. Study participants who were in normal sinus rhythm were included. Elective and urgent cases were considered. Cardiac surgery indications included 32 (94%) CABG, 1 (3%) aortic valve repair, and 1 (3%) ascending aortic repair. Exclusion criteria included emergent and salvage cases, atrial fibrillation, conduction abnormalities, paced rhythm, relative contraindications to PAC insertion, and in those in which TEE was unobtainable. The study protocol was approved by the local institutional review board and individual patient consent was obtained.

**STUDENT NAME:** *Roman G. Nepomuceno*

### ***Intra-operative Protocol***

Transesophageal echocardiographic and hemodynamic measurements were obtained at two intra-operative time points: (1) pre- and (2) post-cardiopulmonary bypass (CPB). Pre-CPB measurements were obtained after anaesthetic induction, prior to sternotomy. Post-CPB measurements were obtained once the patient had been safely weaned off CPB, following sternal closure (Figure 2).

### ***Echocardiography Studies***

Routine TEE (Phillips 7500, Andover, MA) studies included peri-operative assessment of chamber dimensions and LV ejection fraction (LVEF) as per the American Society of Echocardiography guidelines.<sup>41</sup> Conventional Doppler parameters were measured in the mid-esophageal four-chamber view, including the peak early (E) and late (A) diastolic transmitral inflow velocities, deceleration time (DT), and isovolumetric relaxation time (IVRT). Tissue Doppler imaging (TDI) was performed including systolic (S'), early diastolic (E') and late diastolic (A') mitral annular velocities. This was achieved by placing a 5-mm sample at the lateral and septal aspects of the mitral annulus in the mid-esophageal four-chamber view. Measurements were obtained by level III-trained cardiac anesthetists experienced in TEE. The E/E' ratios for lateral and septal mitral annular measurements were then calculated. Mean E/E' is the arithmetic average of lateral and septal E/E'.

### ***Hemodynamic Measurements***

Routine central venous access and arterial lines were established in all patients. A PAC was advanced on a supine patient via the right internal jugular vein and characteristic pressure waveforms were used to guide the balloon-tip into the pulmonary artery. Hemodynamic measurements including central venous pressure (CVP), pulmonary artery pressure (PAP), and mean arterial pressure (MAP) were obtained. Cardiac output was measured using the thermodilution method in triplicate and the mean value was reported. Heart rate was evaluated by standard ECG.

### ***Statistical Analysis***

Data was presented as mean values with standard deviations. Paired *t*-tests were used to compare differences between the pre- and post-CPB where  $p < 0.05$  was considered significant. Linear regression analysis was used to ascertain correlation between echocardiographic and hemodynamic parameters. Diagnostic accuracy was assessed using standard formulas for sensitivity, specificity as well as positive predictive and negative predictive values. All analyses were performed using Excel (Version 2007, Microsoft, USA).

## ***RESULTS***

### ***Study Population***

The total study population included 34 patients (26 males, mean age  $64 \pm 9$  years). Baseline characteristics are summarized in Table 1. A cardiac history of recent myocardial infarction was present in 7 (21%) patients, and 5 (15%) had a history of congestive heart failure (CHF). All patients had cardiac risk factors, including current or former smokers (56%), diabetes (65%), family history of CAD (26%), dyslipidemia (74%), and hypertension (76%). The pre-

**STUDENT NAME:** *Roman G. Nepomuceno*

operative LVEF was  $\geq 60\%$  in 16 patients, 40-60% in 11 patients, and  $< 40\%$  in the remaining 7 patients.

### ***Comparison between Pre- and Post-CPB***

Hemodynamic and echocardiographic measurements taken before and after CPB are summarized in Table 2.

***Hemodynamic.*** Heart rate increased significantly from  $55 \pm 10$  to  $70 \pm 7$  bpm, mean arterial pressure decreased from  $76 \pm 14$  to  $71 \pm 9$  mmHg, and cardiac output increased from  $3.6 \pm 0.9$  to  $4.5 \pm 1.2$  L/min, when comparing pre- and post-CPB, respectively. All other hemodynamic parameters showed no statistically significant changes.

***Echocardiography.*** There was no statistical difference in TEE parameters pre-CPB and post-CPB (Table 2). The conventional Doppler parameter E, was  $0.76 \pm 0.22$  m/s pre-CPB and  $0.79 \pm 0.22$  m/s post-CPB. TDI parameters of E' measured at the lateral and septal mitral annuli also showed no statistically significant changes. Pre-CPB, E/E' ratios were  $7 \pm 6$ ,  $10 \pm 5$  and  $9 \pm 5$  for lateral, septal and mean E/E', respectively. Post-CPB, E/E' ratios were  $13 \pm 6$ ,  $15 \pm 5$  and  $14 \pm 5$  for lateral, septal and mean E/E', respectively.

### ***Correlation between PCWP and E/E'***

The regression analyses between PCWP (using PAC) and E/E' (using TEE) obtained before and after CPB are summarized in Figures 3 and 4, respectively. Pre-CPB, the correlation coefficients for lateral, septal, and mean E/E' were  $r=0.18$ ,  $r=0.27$ , and  $r=0.23$ , respectively. Post-CPB the correlations were  $r=0.34$ ,  $r=0.38$ , and  $r=0.42$  for lateral, septal, and mean E/E', respectively. The overall correlation between E/E' obtained by TEE and PCWP by PAC was weak.

### ***Optimal E/E' Cutoff Values and Diagnostic Accuracy***

The optimal cutoff values for detecting normal (PCWP  $< 15$  mmHg) and elevated (PCWP  $\geq 15$  mmHg) LVFP were determined by analyzing diagnostic accuracy at incremental cutoff values for E/E' ranging from 6 to 20. Cutoff values at which diagnostic accuracy was highest were reported.

The optimal lower cutoff values were lateral E/E'  $< 11$  (64-65% sensitive, 55-67% specific), septal E/E'  $< 13$  (64-65% sensitive, 64-67% specific), and mean E/E'  $< 12$  (52-61% sensitive, 55-67% specific) for predicting *normal* LVFP. The optimal upper cutoff values were lateral E/E'  $\geq 11$  (60-67% sensitive, 64-67% specific), septal E/E'  $\geq 13$  (67-70% sensitive, 64-67% specific), and mean E/E'  $\geq 12$  (60-67% sensitive, 52-63% specific) for predicting *elevated* LVFP.

## ***DISCUSSION***

Our study characterized the relationship between intra-operative E/E' obtained by TEE and PCWP obtained by PAC during cardiac surgery. We demonstrated that in the cardiac surgical population, intra-operative TEE does not accurately predict LVFP using the PAC as the gold standard. Specifically: (1) the correlation between intra-operative E/E' and PCWP was poor during cardiac surgery; and (2) diagnostic accuracy was modest at best. Our findings were in

**STUDENT NAME:** *Roman G. Nepomuceno*

contrast to previous studies involving Doppler indices derived outside the intra-operative setting using either TTE or TEE.

It has been shown using TTE that  $E/E' < 8$  predicts *normal* LVFP (PCWP < 15 mmHg) while  $E/E' > 15$  predicts *elevated* LVFP (PCWP  $\geq 15$  mmHg).<sup>20</sup>  $E/E'$  between 8 and 15 was a “grey zone” and could not predict LVFP.<sup>20</sup> The correlation between  $E/E'$  and PCWP has been validated extensively in the non-surgical setting for patients with cardiovascular<sup>18,20-35</sup> and non-cardiovascular conditions.<sup>36</sup> Only one study has been performed to date involving cardiac surgical patients. Using TTE before and after surgery, Hadano et al. concluded that  $E/E'$  correlated well with PCWP ( $r=0.79$ ) in patients undergoing CABG or aortic valve replacement ( $n=52$ ).<sup>37</sup> In their study, the pre-operative measurements were obtained at an unspecified time prior to surgery while the post-operative measurements were taken on average of  $30 \pm 15$  days after surgery.<sup>37</sup> Due to open sternotomy during cardiac surgery, measurements during surgery would not have been possible using TTE. On the other hand, TEE would have been attainable during cardiac surgery.

Only two prior studies have evaluated the use of TEE to estimate LVFP. Combes et al. used TEE to estimate LVFP in patients with various medical conditions such as shock and multi-organ failure in the intensive care unit (ICU).<sup>39</sup> Both TTE and TEE were used in their study. TTE was used primarily ( $n=14$ ) but TEE was used as an alternative whenever TTE was unable to provide adequate information ( $n=23$ ).<sup>39</sup> Both TTE ( $r=0.73$  for lateral,  $r=0.61$  for septal) and TEE ( $r=0.91$  for lateral,  $r=0.86$  for septal) demonstrated good correlation.<sup>39</sup> They further demonstrated that lateral  $E/E' \geq 7.5$  (86% sensitive, 81% specific) and septal  $E/E' \geq 9$  (76% sensitive, 80% specific) estimated PCWP  $\geq 15$  mmHg.<sup>39</sup> Similarly, Vignon et al. examined ICU patients with similar medical conditions as Combes et al.<sup>39</sup> and they concluded that lateral  $E/E' \leq 8$  (83% sensitive, 100% specific) predicted PCWP  $\leq 18$  mmHg.<sup>40</sup>

While the use of TEE to predict LVFP has been validated in the ICU setting<sup>39</sup> with concordant data using TTE with non-surgical patients,<sup>18, 20-22, 24-35,42</sup> the relationship between  $E/E'$  and PCWP during cardiac surgery warranted further investigation. Cardiac surgical patients are unique because they have high-risk, multi-vessel CAD that is often compounded by myocardial ischemia, LV systolic dysfunction, and other co-morbidities that may influence the ability of blood flow and myocardial velocities to accurately reflect LVFP. In the present study, we demonstrated that intra-operative  $E/E'$  was unable to accurately predict PCWP in cardiac surgical patients, questioning the feasibility of using TEE to guide fluid management in this patient population. Although TEE remains vital for the assessment of cardiac structure and function in cardiac surgery, its potential role for assessing diastolic filling pressures is limited as demonstrated by our study.

There are three main reasons why  $E/E'$  did not accurately predict LVFP in our cardiac surgical population. First, regional wall motion abnormalities (RWMA) alter the relationship between  $E/E'$  and PCWP as motion along the mitral annular plane may not be uniform in patients with multi-vessel CAD.<sup>39,43</sup> A reduction in *regional*  $E'$  parameter<sup>43,44</sup> with a subsequent increase in the  $E/E'$  ratio<sup>45</sup> has been shown in ischemic regions of the myocardium in patients with CAD. Cardiac surgical patients often have multiple areas of infarct with extensive RWMA. Our present study demonstrated that mean  $E/E'$ , which is the average of lateral and septal  $E/E'$ ,

**STUDENT NAME:** *Roman G. Nepomuceno*

showed better correlation to PCWP than either lateral or septal E/E' alone during the post-CPB time period. This suggests, as shown in a previous study,<sup>44</sup> that incorporating indices from multiple sites may provide a more global assessment of LV function when CAD is present. Second, as diastolic myocardial excursion results from the summation of movement in all three axes (radially, circumferentially and longitudinally),<sup>46</sup> indices measured only at the mitral annulus may not fully reflect alterations in myocardial velocities that occur longitudinally in the LV. This discrepancy exists during the period before and after cardiac surgery as seen using speckle Doppler tracking in CABG patients<sup>47</sup> and needs to be investigated as it relates to LVFP intra-operatively. Finally, superimposed catecholamines/inotropes have been shown to affect Doppler indices in patients with CAD.<sup>45,48</sup> Catecholamines/inotropes resulting from the physiologic insult of surgery, as well as those used for hemodynamic control, may influence the ability of Doppler indices to accurately reflect LVFP.

### ***Study Limitations***

Our study is limited by the small study population, affecting the statistical power of our findings. PCWP can vary with ventilation because intrathoracic pressures transmit to the pulmonary vasculature. While done concurrently within 5 min of each other, we did not time TEE measurements according to ventilation and thus they may not coincide exactly with appropriate PCWP measurements. TDI is angle-dependent and variations in the transducer position may affect one measurement in relation to another. Finally, other parameters of diastolic filling including LA volume and propagation velocity were not evaluated in the current study, which may influence the relationship between Doppler indices and LVFP.

### ***Conclusion***

During cardiac surgery, intra-operative TEE was unable to accurately assess LVFP, questioning its role in guiding fluid management. Although TEE remains vital for the assessment of cardiac structure and function during cardiac surgery for the time being, its potential role for assessing diastolic filling pressures is limited, as demonstrated by our study. For cardiac surgical patients at high risk for sudden changes in fluid pressures, such as those with low cardiac output and severe LV dysfunction, the use of the invasive PAC still remains the gold standard for assessing LVFP. An alternative non-invasive estimate of LVFP during cardiac surgery has yet to be validated.

**STUDENT NAME:** *Roman G. Nepomuceno*

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**STUDENT NAME:** *Roman G. Nepomuceno*

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**STUDENT NAME:** *Roman G. Nepomuceno*

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**STUDENT NAME:** *Roman G. Nepomuceno*

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**STUDENT NAME:** *Roman G. Nepomuceno*

**TABLES & FIGURES**

**TABLE 1:** Baseline demographic and clinical characteristics of study population with corresponding p-value as determined by *t*-test.

<b>Characteristics</b>	
Age, mean±SD (yrs)	64±9
Female gender, n (%)	8 (24%)
Smoking history/current, n (%)	19 (56%)
Diabetes, n (%)	22 (65%)
Family history of CAD, n (%)	9 (26%)
Dyslipidemia, n (%)	25 (74%)
Hypertension, n (%)	26 (76%)
Chronic renal insufficiency, n (%)	7 (21%)
Previous CVA/TIA, n (%)	4 (12%)
COPD, n (%)	1 (3%)
PVD, n (%)	5 (15%)
Atrial fibrillation, n (%)	1 (3%)
CCS Classification, mean±SD	3.03±0.63
Recent MI (<21 days), n (%)	7 (21%)
CHF history, n (%)	5 (15%)

**TABLE 2:** Intra-operative hemodynamic and echocardiographic measurements obtained pre- and post-CPB with corresponding p-value as determined by *t*-test.

<b>Measurements</b>	<b>Pre-CPB</b>	<b>Post-CPB</b>	<b>p-value</b>
<b><i>Hemodynamic</i></b>			
Heart rate, mean±SD (bpm)	55±10	70±7	<0.05
Mean arterial pressure, mean±SD (mmHg)	76±14	71±9	<0.05
Central venous pressure, mean±SD (mmHg)	11±5	11±5	0.65
Cardiac output, mean±SD (L/min)	3.6±0.9	4.5±1.2	<0.05
PCWP <sup>1</sup> , mean±SD (mmHg)	13±5	12±4	0.21
<b><i>Echocardiographic</i></b>			
E, mean±SD (m/s)	0.76±0.22	0.79±0.22	0.69
Lateral E', mean±SD (m/s)	0.10±0.02	0.07±0.02	0.29
Lateral E/E', mean SD (m/s)	7±6	13±6	0.41
Septal E', mean SD (m/s)	0.06±0.01	0.06±0.02	0.98
Septal E/E', mean SD (m/s)	10±5	15±5	0.47
Mean E/E', mean SD (m/s)	9±5	14±5	0.40

<sup>1</sup> PCWP=pulmonary capillary wedge pressure, <sup>2</sup>CPB=cardiopulmonary bypass, <sup>3</sup>SD=standard deviation

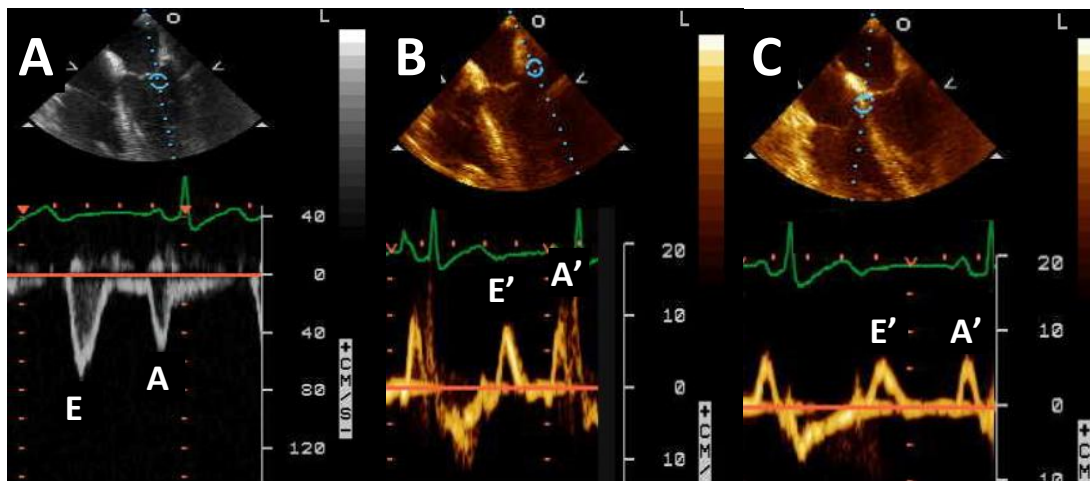
STUDENT NAME: *Roman G. Nepomuceno*

**TABLE 3:** Diagnostic accuracy of echocardiographic indices for predicting normal and elevated left ventricular filling pressures for lateral, septal and mean E/E'.

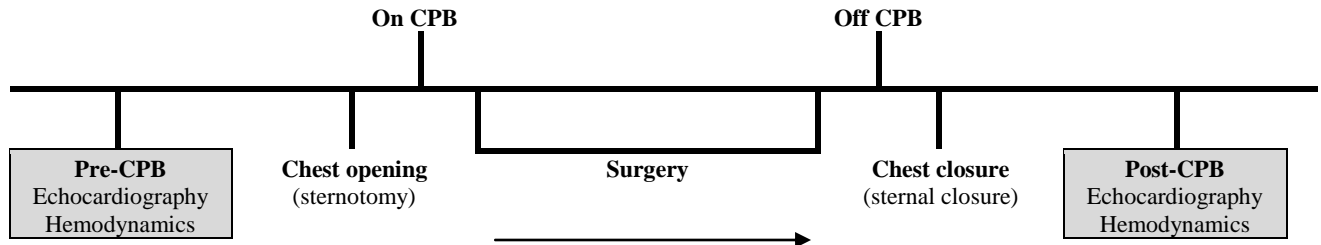
Index	Sensitivity	Specificity	PPV	NPV
<b>Normal LVFP (PCWP&lt;15 mmHg)</b>				
<b>Pre-CPB</b>				
Lateral E/E'<11	65%	55%	75%	43%
Septal E/E'<13	65%	64%	79%	47%
Mean E/E'<12	61%	55%	74%	40%
<b>Post-CPB</b>				
Lateral E/E'<11	64%	67%	84%	40%
Septal E/E'<13	64%	67%	84%	40%
Mean E/E'<12	52%	67%	81%	33%
<b>Elevated LVFP (PCWP≥15 mmHg)</b>				
<b>Pre-CPB</b>				
Lateral E/E'≥11	60%	67%	43%	80%
Septal E/E'≥13	70%	67%	47%	84%
Mean E/E'≥12	60%	63%	40%	79%
<b>Post-CPB</b>				
Lateral E/E'≥11	67%	64%	40%	84%
Septal E/E'≥13	67%	64%	40%	84%
Mean E/E'≥12	67%	52%	33%	81%

<sup>1</sup> CPB = cardiopulmonary bypass, <sup>2</sup>PPV = positive predictive value, <sup>3</sup>NPV = negative predictive value

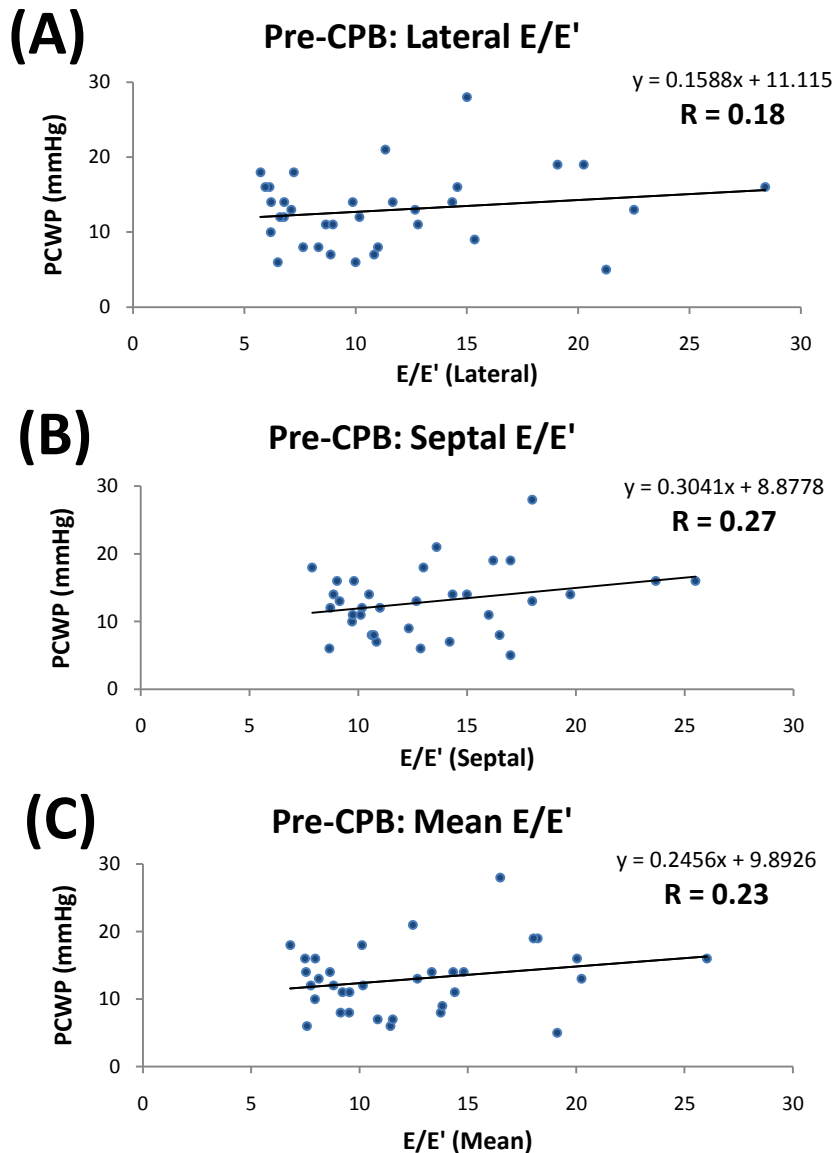
**FIGURE 1:** Sample tracings of (A) conventional Doppler showing E and A waves and tissue Doppler imaging showing E' and A' at the (B) lateral and (C) septal mitral annuli.



**FIGURE 2:** Timeline indicating when Doppler echocardiographic indices are measured using TEE concurrently with invasive hemodynamic parameters.



**FIGURE 3:** Linear regression analyses between PCWP and E/E' obtained at the (A) lateral, (B) septal mitral annuli and (C) mean E/E' during the pre-cardiopulmonary bypass period.



STUDENT NAME: *Roman G. Nepomuceno*

**FIGURE 4:** Linear regression analyses between PCWP and E/E' obtained at the (A) lateral, (B) septal mitral annuli and (C) mean E/E' during the post-cardiopulmonary bypass period.

