Fluid Responsiveness to Passive Leg Raising in Patients with and without Coronary Artery Disease: A Prospective Observational Study

Abstract

Introduction: Hemodynamic stability and fluid responsiveness (FR) assume importance in perioperative management of patients undergoing major surgery. Passive leg raising (PLR) is validated as assessing FR in intensive care unit patients. Major few studies have examined FR to PLR in intraoperative scenario. We prospectively studied FR to PLR using transesophageal echocardiography (TEE), in patients with no coronary artery disease (CAD) undergoing major neurosurgery and those with CAD undergoing coronary artery bypass grafting (CABG). Methods: We enrolled 29 adult consenting patients undergoing major neurosurgery with TEE monitoring and 25 patients undergoing CABG. After induction of anesthesia, baseline hemodynamic parameters were obtained which was followed by PLR using automated adjustment of the operating table. Clinical and TEE-derived hemodynamic parameters were recorded at 1 and 10 min after PLR following which patients were returned to supine position. Results: A total of 162 TEE and clinical examinations were done across baseline, 1 and 10 min after PLR; and paired comparison was done at data intervals of baseline versus 1 min PLR, baseline versus 10 min PLR, and 1 min versus 10 min PLR. There was no significant change in hemodynamic variables at any of the paired comparison intervals in patients undergoing neurosurgery. CABG cases had significant hemodynamic improvement 1 min after PLR, partially sustained at 10 min. Conclusion: Patients undergoing CABG had significant hemodynamic response to PLR, whereas non-CAD patients undergoing neurosurgery did not. A blood pressure–left ventricular end-diastolic volume combination represented strong correlation in response prediction (Pearson’s coefficient 0.641; P < 0.01).

Keywords: Coronary artery disease, fluid responsiveness, passive leg raising, transesophageal echocardiography

Introduction

Hemodynamic stability assumes importance in perioperative management among patients undergoing major surgical procedures. Anesthesiologists often target optimizing intravascular volume to achieve hemodynamic stability but its determination can be arduous during major surgery. The concept of fluid responsiveness (FR) attains relevance in maintaining optimal homeostasis, in the context that fluid loading is the first step in the resuscitation of hemodynamically unstable patients.[1] Hypovolemia is a common complication encountered perioperatively in patients who undergo major surgery. Inadequate volume replenishment leads to hypoperfusion of tissues, whereas fluid overloading impedes oxygen delivery thereby compromising patient outcome. Early goal-directed therapy-driven protocols which optimize the preload and with the resultant cardiac output (CO) improvement significantly reduced postoperative morbidity and duration of hospital stay in both noncardiac and cardiac surgeries.[2-3] FR is the ability of stroke volume (SV) and thereby CO to augment in response to a fluid load, either extraneous or intrinsic. Dynamic hemodynamic parameters far excel static counterparts in precisely appraising FR.[4-6] Passive leg raising (PLR) amounts to a reversible intrinsic fluid load, which transfers approximately 150–300 mL of blood from the lower limbs to the central circulation.[7] Apart from treatment of hypovolemia, this method serves as a test to determine FR without administering a single drop of extraneous fluid.[8-14] Transesophageal echocardiography (TEE), a standard of practice in cardiac surgery, has gained wider acclaim in noncardiac procedures.
surgery, especially neurosurgery to monitor for venous air embolism, and in the intensive care unit (ICU). Both static and dynamic hemodynamic parameters may be assessed to build a picture of circulatory state using TEE.

The present evidence on PLR assessed FR is predominantly limited to the ICU setting where multitude of comorbid conditions such as sepsis, acute kidney injury, cardiac dysfunction, and ionotropic therapy can confound fluid dynamics. Moreover, the use of TEE as a method to assess FR is not widespread. In this background, we proposed this study with the aim to compare FR, 1 and 10 min after PLR, in the intraoperative scenario using clinical and TEE-derived parameters in patients without and with coronary artery disease (CAD), undergoing neurosurgery and coronary artery bypass grafting (CABG), respectively.

Methods

We designed a prospective observational study to find the diagnostic accuracy of clinical and TEE-assessed parameters in predicting FR to PLR in two groups of patients – group 1: patients (without CAD) undergoing elective neurosurgical procedures under general anesthesia (GA) and group 2: patients with CAD undergoing CABG procedure under GA. The study was conducted at the neurosurgery and cardiothoracic surgery operating rooms of our hospital. Institutional ethics committee clearance was obtained prior to initiating the study and the study was registered with the Clinical Trial Registry of India. Written informed consent was obtained from all participants. The study was conducted between January 2017 and December 2017. Ethics committee approval has been obtained "Reference number: SCT/IEC/980/ DECEMBER-2016 dated 06.01.2017".

Patients in group 1 required routine intraoperative TEE monitoring on account of their surgical/disease factors/risk for venous air embolism (e.g., intracranial space-occupying lesions with major venous sinus involvement, head-up surgical position enhancing risk of entrapment of air into dural venous sinuses) irrespective of the study requirement. All patients undergoing CABG (group 2) are monitored with TEE intraoperatively in our institution. The following cases were excluded from the study – on patient refusal: age <18 years or >65 years; patients with left ventricular (LV) dysfunction (ejection fraction <55%); presence of cardiac arrhythmias; valvular heart disease, intracardiac shunts; peripheral vascular disease; pregnant or nursing woman; presence of esophageal or cervical spine disease contraindicating TEE probe placement; and/or hip/knee arthritis restricting conduct of PLR.

During preanesthetic visit, patients were explained about the study protocol. American Society of Anesthesiologists (ASA) standard monitors were used intraoperatively. GA with endotracheal intubation was induced in both the groups using our hospital protocol, that is, preoxygenation with oxygen, intravenous induction with propofol 1–2 mg/kg, fentanyl 4 µg/kg, vecuronium 0.1–0.2 mg/kg, and maintained with air: oxygen mixture = 1:1 and sevoflurane with minimum alveolar concentration of 0.8–1.0, following which TEE probe was inserted (GE Vivid 7 0-10.0 MHz multi-plane TEE probe; GE Healthcare, Wauwatosa, WI, USA, for neurosurgical cases; and iE33, RT3D TEE ultrasound machine; Philips Ultrasound, USA, with matrix array TEE transducer X7-2t for cardiac surgical cases). All patients were mechanically ventilated using volume-controlled ventilation (Datex‑Ohmeda, GE Healthcare, Illinois) with a square wave constant inspiratory flow, an inspiratory/expiratory ratio of 1:2, a respiratory rate of 12/min, a tidal volume of 8 mL/kg, and a PEEP of 0 cmH₂O. The study intervention was started after 10 min of inducing GA so as to achieve a hemodynamically steady state and to ensure that patient remained essentially unstimulated for the study period.

Baseline TEE variables were obtained using mid-esophageal four-chamber view, mid-esophageal bicaval view, and deep transgastric long-axis view. In the mid-esophageal four-chamber view, short loops were saved, and end-systolic and end-diastolic frames were identified. LV volume was calculated using the modified Simpsons method. The left ventricular outflow tract (LVOT) diameter was measured using the mid-esophageal aortic valve long-axis view. Anatomical M-mode was used with the mid-esophageal bicaval view to measure the diameters of the superior vena cava (SVC) and further superior vana caval collapsibility index (SVCCI) was calculated.

Furthermore, the TEE probe was pushed into the deep transgastric position and the tip of the probe was anteflexed. The pulse wave Doppler cursor was placed 5 mm above the level of aortic valve inside the LVOT. The SV, CO, and stroke volume variability (SVV) were calculated from the tracing of Doppler waves at high and low peaks using the software provided in the TEE machine. Subsequently, using electronic adjustments of the operating theater table, patients were made semi-recumbent initially, following which PLR was performed by elevating the patient’s legs and by simultaneously transferring the trunk from the semi-recumbent position to a horizontal position as per standard protocol.

Real-time assessment of hemodynamic parameters was done at 1 and 10 min after PLR. The clinical and TEE-derived hemodynamic parameters studied include the following: heart rate, systolic blood pressure (BP), diastolic BP, pulse pressure (PP), systolic pressure variability (SPV), pulse pressure variability (PPV), LV end diastolic volume, SV, SVV, velocity time integral (VTI)-aortic, diameter of SVC, SVCCI, CO, and cardiac index (CI). The average of three readings for each measurement at – baseline, 1 min after PLR, and 10 min after PLR – was taken for all the hemodynamic recordings (clinical and TEE-derived).
The TEE image acquisition and measurements were performed by experienced investigators with advanced training in echocardiographic imaging. The same study investigators performed the TEE measurements in either of the groups. Patients were watched for any adverse events following PLR. In case of any adverse event in the form of hemodynamic instability or compromise in mechanical ventilation, patients were returned to supine position and excluded from study. Patients were returned to supine position after recording the observations after 10 min of PLR, following which surgical procedure was continued as planned by the surgical team.

Sample size calculation

Assuming an equivalence margin of 2% and standard deviation of 2.6% for FR measured by TEE, to achieve 80% power with alpha error of 5%, the minimum sample size required in each of the two groups was estimated to be 21. We recruited 29 patients to group 1 and 25 patients to group 2, to compensate for the outliers and confounders.

Analysis of data

Data collected during the study were compiled using Microsoft Office Excel. Variates were presented as mean ± standard deviation for continuous variates with normal distribution. Repeated measure analysis of variance was used for paired comparison of hemodynamic data in both groups at three intervals – baseline versus hemodynamic response at 1 min after PLR, baseline versus 10 min after PLR, and 1 min versus 10 min PLR response. A P value <0.05 was considered as statistically significant. Karl Pearson’s coefficients and receiver operating characteristic (ROC) curves were generated at significant paired comparison interval of hemodynamic data (clinical and TEE-derived). All statistical analyses were carried out with IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., USA).

Results

A total of 29 patients undergoing elective neurosurgery (group 1) and 25 patients undergoing elective CABG (group 2) were recruited into the study. Patients in group 1 underwent surgery for the following medical conditions: 11 cases (37.93%) for intracranial glioma, 11 cases (37.93%) for meningioma, and 1 case each (3.44%) for ependymoma, epidermoid tumor, cerebral metastasis, choroid plexus papilloma, middle cerebral artery aneurysm, trigeminal neuralgia, and colloid cyst. The demographic and baseline preoperative echocardiography characteristics of the observed cases were comparable between both the groups of cases. There was no incidence of hemodynamic instability during the conduct of the study.

A total of 162 TEE examinations and measurements were obtained across both the groups. Study variables were classified as clinical and echocardiographic and analyzed. Measurements were recorded as baseline, 1 min after PLR, and 10 min after PLR. Paired comparison was done for clinical and echocardiographic parameters at baseline versus hemodynamic response at 1 min after PLR, baseline versus 10 min after PLR, and 1 min versus 10 min PLR response. The percentage of change in each parameter at 1 and 10 min after PLR, from baseline, and also change at 10 min with regard to 1 min values was also calculated. A 9%–10% or more change in paired comparison of any clinical/echocardiographic variable was considered as hemodynamic response based on results from previous studies.[18-20] For SVCCI, a change of 35% or more was considered of hemodynamic relevance.[21]

We observed that there was no significant variation in heart rates after PLR [Table 1], across both the groups at any of the paired comparison intervals. A 2.8% decrease in heart rate in group 1 cases after PLR though statistically significant (P = 0.027) was not of hemodynamic relevance. There was significant change in clinical parameters in patients undergoing CABG (group 2) after PLR. Systolic BP increased by 17.4% (18.88 ± 1.639) and 13.3% (14.48 ± 1.835) and diastolic BP increased by 21.1% (13.12 ± 1.087) and 17.2% (10.68 ± 1.215) at paired comparison intervals of baseline versus 1 min after PLR and baseline versus 10 min after PLR, respectively. PP also increased at similar intervals in this group by 12.4% and 9.9%, respectively. There was significant decrease in BP (systolic/diastolic) at 1 min versus 10 min after PLR; however, this response was not of hemodynamic relevance. Among the other clinical parameters, SPV decreased significantly at intervals of baseline versus 10 min after PLR and 1 min versus 10 min after PLR at rates of 41.9% and 31.7%, respectively (P = 0.002 and 0.004, respectively) [Table 1]. A 15.1% decrease in SPV at paired comparison interval of baseline versus 1 min after PLR in this group was not significant. PPV decreased significantly at intervals of baseline versus 10 min after PLR and 1 min versus 10 min after PLR at rates of 44.8% and 41.9%, respectively (P = 0.017 and 0.003, respectively) [Table 1]. For echocardiographic parameters in this group, there was significant increase in SV, aortic VTI, CO, and CI at interval of baseline versus 1 min after PLR. Left ventricular end diastolic volume (LVEDV) increased significantly at both baseline versus 1 min after PLR and baseline versus 10 min after PLR with an 8.4% and 5.6% change, respectively. SVV decreased at baseline versus 10 min after PLR and 1 min versus 10 min after PLR at 14.2% and 15.5%, respectively; however, this was not significant (P = 0.365 and 0.268, respectively). The SVCCI decreased at rates of 21.2% and 23.1%, respectively, at baseline versus 10 min after PLR and 1 min versus 10 min after PLR (P = 0.145 and 0.084, respectively) [Table 2].

In patients undergoing neurosurgical procedures (group 1), the changes in BP were neither significant hemodynamically nor statistically. The changes in SPV in this group of cases...
occurred at baseline versus 1 min after PLR and 1 min versus 10 min after PLR at -14.1% and 24.1% rates, respectively \((P = 0.229\) and 0.068). PPV changed during all paired comparison intervals at \(-19.4\%\), \(16\%\), and \(43.8\%\), respectively \((P = 0.384, 0.568, \) and \(0.139\) \([\text{T}able \ 1]\). Echocardiographic variables of aortic VTI variability and SVCCI changed at paired intervals of baseline versus 1 min after PLR, and both baseline versus 10 min after PLR and 1 min versus 10 min after PLR, respectively, at rates of \(11.1\%\) \((P = 0.405)\), \(-15.6\%\) \((P = 0.086)\), and \(-11.5\%\) \((P = 0.212)\) \([\text{T}able \ 2]\). None of the clinical and echocardiographic responses in noncardiac disease cases was statistically significant. The average VTI and LVEDV changed significantly in this group at baseline versus 1 min after PLR; however, this could not be designated as significant hemodynamic response to PLR as these variables changed at only \(5\%\) and \(3.7\%\), respectively \([\text{T}ables \ 1 \ and \ 2]\).

Karl Pearson’s correlation coefficients calculated across significant clinical and echocardiographic variables in group 2 cases to forecast the best combination of either in predicting the response to PLR are as depicted in Table 3. A combination of SBP with LVEDV, DBP with LVEDV, and SBP with aortic VTI represented strong linear correlation in detecting a response to PLR in patients with CAD (Pearson’s coefficient \(0.641, 0.596, \) and \(0.521\), respectively, at \(P < 0.01)\). Combinations of SBP with SV, pulse pressure with LVEDV; and PP with aortic VTI represented moderate linear correlation to predict response to PLR (Pearson’s coefficient \(0.398, 0.408, \) and \(0.415\), respectively, at \(P < 0.05)\).

ROC curves generated for significant clinical and echocardiographic variables in group 2 cases varying the discriminating threshold for each parameter and area under curves (AUCs) calculated are depicted in Table 4 and Figure 1a and b. Among the clinical parameters, DBP after 1 min of PLR \([\text{AUC} \ 0.839, 95\% \text{confidence interval (CI)} \ 0.697–0.932]\) followed by SBP after 1 min of PLR \((\text{AUC} \ 0.810, 95\% \text{CI} \ 0.663–0.912)\), PP after 1 min of PLR \((\text{AUC} \ 0.704, 95\% \text{CI} \ 0.547–0.832)\), SPV after 10 min of PLR \((\text{AUC} \ 0.636, 95\% \text{CI} \ 0.478–0.776)\), and PPV after 10 min of PLR \((\text{AUC} \ 0.524, 95\% \text{CI} \ 0.368–0.676)\) were found to be predictive of clinical response to leg raising in that order \([\text{T}able \ 4 \ and \ Figure \ 1a]\). Among the TEE variables, LVEDV after 1 min of PLR \((\text{AUC} \ 0.635, 95\% \text{CI} \ 0.491–0.763)\) followed by aortic VTI after 1 min of PLR \((\text{AUC} \ 0.608, 95\% \text{CI} \ 0.464–0.739)\), CO after 1 min of PLR \((\text{AUC} \ 0.583, 95\% \text{CI} \ 0.439–0.717)\), and SV after 1 min of PLR \((\text{AUC} \ 0.581, 95\% \text{CI} \ 0.437–0.715)\) were found to be predictive of clinical response to leg raising in that order. CO and CI predicted response in PLR in CAD cases with similar accuracy \([\text{T}able \ 4 \ and \ Figure \ 1b]\).

**Discussion**

In this study, we examined the clinical and TEE response to a physiologic fluid load induced by PLR in patients without and with CAD undergoing elective neurosurgery or CABG.
Table 2: Paired comparison of TEE parameters across various intervals in groups 1 and 2 and the percent of change at each interval

| TEE parameter | Mean±SD | Paired comparison interval | Group 1 | Group 2 |
|---------------|---------|---------------------------|---------|---------|
|               | Group 1 | Group 2                   | Mean±SE | P       | Mean±SE | P       |
| LVEDV         |         |                           |         |         |
| Baseline      | 91.40±20.66 | 76.26±16.01               | 3.397±1.608 | 3.7 | 0.044 | 6.44±1.639 | 8.4 | 0.001 |
| 1 min PLR     | 94.79±18.49 | 82.70±15.51               | 0.672±1.381 | 0.7 | 0.63 | 4.28±1.623 | 5.6 | 0.014 |
| 10 min PLR    | 92.07±20.25 | 80.54±13.81               | -2.724±1.702 | -2.9 | 0.121 | -2.16±1.351 | -2.6 | 0.123 |
| SV            |         |                           |         |         |
| Baseline      | 64.8±23.9 | 54.9±17.1                 | 2.276±1.401 | 3.5 | 0.116 | 6.14±1.875 | 11.2 | 0.003 |
| 1 min PLR     | 67.1±20.1 | 61.0±18.1                 | 1.064±1.821 | 1.6 | 0.564 | 3.04±2.055 | 5.5 | 0.152 |
| 10 min PLR    | 65.9±21.2 | 57.9±19.4                 | -1.211±1.173 | -1.8 | 0.311 | -3.1±1.762 | -5.1 | 0.091 |
| SVV           |         |                           |         |         |
| Baseline      | 17.5±9.1 | 14.9±10.4                 | 1.109±2.146 | 6.3 | 0.609 | 0.222±1.695 | 1.5 | 0.897 |
| 1 min PLR     | 18.6±12.0 | 15.1±10.2                 | 1.323±2.571 | 7.6 | 0.611 | -2.114±2.291 | -14.2 | 0.365 |
| 10 min PLR    | 18.9±10.8 | 12.8±9.5                  | 0.213±2.365 | 1.1 | 0.929 | -2.336±2.058 | -15.5 | 0.268 |
| Aortic VTI    |         |                           |         |         |
| Baseline      | 21.7±5.4 | 17.6±4.8                  | 1.093±0.49 | 5.0 | 0.034 | 1.787±0.536 | 10.2 | 0.003 |
| 1 min PLR     | 22.8±4.5 | 19.4±4.3                  | 0.622±0.594 | 2.9 | 0.303 | 1.076±0.592 | 6.1 | 0.082 |
| 10 min PLR    | 22.3±5.0 | 18.7±5.0                  | -0.471±0.39 | -2.1 | 0.237 | -0.711±0.467 | -3.7 | 0.141 |
| dSVC          |         |                           |         |         |
| Baseline      | 1.44±0.27 | 1.45±0.31                 | 0.048±0.027 | 3.3 | 0.08 | 0.056±0.045 | 3.9 | 0.225 |
| 1 min PLR     | 1.49±0.27 | 1.50±0.23                 | -0.003±0.03 | -0.2 | 0.909 | 0.089±0.042 | 6.1 | 0.043 |
| 10 min PLR    | 1.43±0.23 | 1.54±0.26                 | -0.052±0.027 | -3.5 | 0.061 | -0.033±0.033 | -2.2 | 0.334 |
| SVCCI         |         |                           |         |         |
| Baseline      | 9.54±3.60 | 10.54±6.02                | -0.44±0.036 | -4.6 | 0.674 | 0.254±1.756 | 2.4 | 0.886 |
| 1 min PLR     | 9.10±4.65 | 10.80±8.72                | -1.486±0.834 | -15.6 | 0.086 | -2.237±1.485 | -21.2 | 0.145 |
| 10 min PLR    | 8.06±4.70 | 8.31±5.74                 | -1.046±0.819 | -11.5 | 0.212 | -2.491±1.381 | -23.1 | 0.084 |
| CO            |         |                           |         |         |
| Baseline      | 4.37±1.70 | 3.28±0.97                 | 0.1±0.113 | 2.3 | 0.386 | 0.303±0.128 | 9.2 | 0.027 |
| 1 min PLR     | 4.47±1.51 | 3.58±0.97                 | -0.019±0.142 | -0.4 | 0.893 | 0.146±0.145 | 4.5 | 0.325 |
| 10 min PLR    | 4.35±1.57 | 3.43±1.19                 | -0.119±0.088 | -2.7 | 0.186 | -0.158±0.11 | -4.4 | 0.163 |
| CI            |         |                           |         |         |
| Baseline      | 2.62±1.00 | 1.87±0.50                 | 0.068±0.071 | 2.6 | 0.344 | 0.171±0.074 | 9.1 | 0.029 |
| 1 min PLR     | 2.69±0.93 | 2.04±0.48                 | -0.009±0.087 | -0.3 | 0.914 | 0.076±0.087 | 4.1 | 0.389 |
| 10 min PLR    | 2.61±0.94 | 1.95±0.62                 | -0.078±0.055 | -2.9 | 0.171 | 0.095±0.064 | 4.7 | 0.155 |

LVEDV: Left ventricular end diastolic volume; SV: Stroke volume; SVV: Stroke volume variability; VTI: Velocity time integral; dSVC: Diameter of superior vena cava; SVCCI: Superior vena cava collapsibility index; CO: Cardiac output; CI: Cardiac index; PLR: Passive leg raising; SD: Standard deviation; SE: Standard error

Table 3: Correlation coefficient between clinical and echocardiographic parameters at significant paired comparison intervals for coronary artery disease cases (group 2)

| Pearson’s correlation of group 2 cases | LVEDV (baseline vs 1 min PLR) | Aortic VTI (baseline vs 1 min PLR) | SV (baseline vs 1 min PLR) | CO (baseline vs 1 min PLR) | CI (baseline vs 1 min PLR) |
|---------------------------------------|-------------------------------|-----------------------------------|---------------------------|---------------------------|---------------------------|
| SBP (baseline vs 1 min PLR)           | 0.641**                       | 0.521**                           | 0.398*                    | 0.340                     | 0.340                     |
| DBP (baseline vs 1 min PLR)           | 0.596**                       | 0.347                             | 0.242                     | 0.341                     | 0.341                     |
| PP (baseline vs 1 min PLR)            | 0.408*                        | 0.415*                            | 0.323                     | 0.200                     | 0.200                     |
| SPV (baseline vs 10 min PLR)          | -0.193                        | -0.001                            | 0.167                     | 0.077                     | 0.077                     |
| PPV (baseline vs 10 min PLR)          | -0.117                        | -0.126                            | -0.270                    | -0.330                    | -0.330                    |

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: Pulse pressure; SPV: Systolic pressure variability; PPV: Pulse pressure variability; LVEDV: Left ventricular end diastolic volume; VTI: Velocity time integral; SV: Stroke volume; CO: Cardiac output; CI: Cardiac index; PLR: Passive leg raising. **P<0.01, *P<0.05

respectively. Till date, few adequately powered studies have evaluated FR using TEE in two such different groups of cases in the intraoperative scenario. The use of TEE, though considered more invasive than FloTrac/Vigileo monitor,[22‑24] provides more data on structure and function of heart as well as more accurate estimates of static and dynamic hemodynamic variables. To our knowledge, very few studies have analyzed FR in patients with CAD undergoing CABG.[25‑27] The methodological strengths of our study need be emphasized. We had chosen PLR-induced physiologic autotransfusion instead of intravenous fluid infusions to assess FR. Administration of either colloids or crystalloids can lead to adverse events, many of which might be postoperatively and thus outside the study duration. None of our patients were hemodynamically unstable or hypovolemic preoperatively. Hence, none of our patients did lose the advantage of intravenous fluid therapy. This
further helped us in standardizing the patient population by avoiding a confounding factor of highest degree, that is, hypovolemia. Furthermore, choosing patients with CAD with good LV function undergoing CAGB standardized the definition of either. TEE was the primary monitoring modality to assess FR in our study. TEE is widely used in neurosurgery as a monitoring tool for VAE. Choosing such a patient population in group 1 aided in avoiding many of the systemic comorbidities that can confound FR and fluid dynamics.

Our study results showed that non-CAD patients undergoing neurosurgical procedures did not have hemodynamic response to PLR either immediately or after 10 min of PLR, whereas patients with CAD had significant hemodynamic response to PLR at 1 min after PLR which was partially sustained at 10 min [Table 1]. Lan et al.[28] found that LVEDV variations and SVV predict FR with significant sensitivity and specificity in ASA III–IV physical status patients undergoing craniotomy with goal-directed colloid therapy. However, the study was underpowered and only patients with hypovolemia were subject to colloid infusion. Hrish et al.[29] studied FR with TEE in 15 patients with subarachnoid hemorrhage (SAH) after infusion of colloid solutions and found 80% of the study population to be responders. It was found that an SVCCI >38% followed and delta aortic VTI >20% forecasts such a response. Inclusion of SAH cases, a condition with multisystemic derangement of physiologic milieu, precludes the extension of their results to all patients undergoing neurosurgery.

In our study, patients with CAD had significant increase in BP immediately after PLR [Table 1]. This increase in clinical variables was sustained until 10 min of maintaining PLR. Significant changes in SPV and PPV were not

Table 4: Comparison of area under receiver operating characteristic (AUROC) curves at significant paired comparison intervals of clinical and TEE variables, for coronary artery disease (Group 2) cases

| Parameter and paired comparison interval | AUC  | SE    | 95% CI       |
|----------------------------------------|------|-------|--------------|
| SBP Baseline to 1 min PLR              | 0.839| 0.0689| 0.697-0.932  |
| PP Baseline to 1 min PLR               | 0.810| 0.0745| 0.663-0.912  |
| PPV Baseline to 1 min PLR              | 0.704| 0.0849| 0.547-0.832  |
| PPV Baseline to 10 min PLR             | 0.636| 0.0854| 0.478-0.776  |
| LVEDV Baseline to 1 min PLR            | 0.635| 0.0794| 0.491-0.763  |
| VTI Baseline to 1 min PLR              | 0.608| 0.0793| 0.464-0.739  |
| CI Baseline to 1 min PLR               | 0.583| 0.0814| 0.439-0.717  |
| SV Baseline to 1 min PLR               | 0.583| 0.0814| 0.439-0.717  |
| dSVC Baseline to 1 min PLR             | 0.553| 0.0828| 0.410-0.690  |
| SVV Baseline to 1 min PLR              | 0.530| 0.0827| 0.388-0.669  |

DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; PP: Pulse Pressure; SPV: Systolic Pressure Variability; PPV: Pulse Pressure Variability; LVEDV: Left Ventricular End Diastolic Volume; VTI: Velocity Time Integral; CO: Cardiac Output; CI: Cardiac Index; SV: Stroke Volume; dSVC: Diameter of superior venacava; SVV: Stroke volume variability; PLR: Passive leg raising

Figure 1: (a) Comparison of area under receiver operating characteristic (AUROC) curves at significant paired comparison intervals of clinical variables, for coronary artery disease (group 2) cases. [SBP: Systolic BP; DBP max: Diastolic BP (maximum); PP: Pulse pressure; SPV: Systolic pressure variability; PPV: Pulse pressure variability; PLR: Passive leg raising]. (b) Comparison of area under receiver operating characteristic (AUROC) curves at significant paired comparison intervals of echocardiographic variables, for coronary artery disease (group 2) cases. [CI: Cardiac index; SV: Stroke volume; SVV: Stroke volume variability; VTI: Velocity time integral; LVEDV: Left ventricular end diastolic volume; SVC max: Diameter of superior vena cava (maximum); PLR: Passive leg raising]. Note: Cardiac output and cardiac index had the same AUROC
immediate as both decreased only at 10 min after PLR. We attribute this to the fact that SPV and PPV are affected by vessel wall plasticity. Vessel wall plasticity in patients with CAD can be reduced due to atheromatous changes in blood vessels, hence causing delayed reduction in SPV and PPV. The variations in TEE-derived hemodynamic data in patients with CAD were not sustained up to 10 min unlike clinical variables. We assume this to the reason that the increase in systemic vascular resistance after PLR must have sustained the increase in BP, whereas the effect on LV filling must have waned off at 10 min after PLR. However, central venous pressure monitoring and subsequent analysis of SVR were not part of our study protocol.

The much suboptimal increase in SVC diameter after leg raising in CAD cases can be attributed to the method of conducting PLR in our study. Among the multitude methods of inducing PLR, we chose the method in which the patient was made semi-recumbent first followed by leg raising, all with automated adjustments of the electronic operated operating theater table. This methodology must have induced a partial SVC emptying, hence contributing to the suboptimal increase in SVC diameter after PLR. We attribute same etiology to the suboptimal change in SVCCI.

Previous studies assessing FR in perioperative scenario in patients with CAD used intravenous fluids,[25-27] Although adverse events to this intraoperatively were not reported in any of these studies, postoperative complications to colloid infusions in those study populations cannot be excluded. Our study was more homeostatic in that we used a highly physiologic maneuver of fluid loading, that is, PLR. We reemphasize the need for dynamic indices for predicting FR. The assessed parameters were classified as clinical and TEE based for the clarity of description in this study. Both static and dynamic parameters were included in the clinical and TEE-derived parameters of our study. Such a classification is unique to our study. Use of TEE for FR evaluation had the unique benefit in our study as TEE monitoring is a standard of care for complex neurosurgical cases and all CABG procedures in our institution. In our study, there were no adverse events reported due to insertion and placement of TEE probe.

The limitations of our study are that echocardiographic measurements, though only semi-invasive, are operator-dependent and with high inter-rater variability. In our study, we standardized this by the same investigators performing the measurements across both the groups. Notwithstanding the elaborate and refined hemodynamic estimation it provides, we affirm that TEE is not the gold standard in CO measurement. PLR can decrease RV end-diastolic/systolic volume index in patients with depressed RV function;[30] however, we included only cases with good cardiac function across both the groups. Group 2 cases in our study were on one or more of afterload reductive home regimens with beta-blockers, anti-hypertensives, or diuretics for primary treatment of their cardiac condition. This must have contributed to the FR to PLR in this group, however; a stratified analysis across various medication use and its effect on FR were not part of our study protocol. We ensured maximum comparability between two groups by including only cases with good preoperative cardiac function in the study.

Conclusion

Our study results show that TEE is an efficient tool which provides dynamic parameters to evaluate FR. This can be consolidated with static and dynamic parameters evaluated clinically. ASA I/II patients undergoing neurosurgery did not significantly respond to fluid load induced by PLR. Patients undergoing CABG had significant hemodynamic improvement in both clinical and TEE parameters at 1 min after PLR; the effects were partially sustained at 10 min. An increment in DBP at 1 min after PLR proved to be the best clinical parameter to assess FR to PLR. An increment in CO or CI at 1 min after PLR proved to be the best TEE-derived parameter to assess FR to PLR. A paired combination of BP to LVEDV or aortic VTI, at interval of baseline versus 1 min after PLR, represents strong linear correlation to predict such response in patients with CAD undergoing CABG.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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