Accuracy of Passive Leg Raising Test in Prediction of Fluid Responsiveness in Children

Ahmed A El-Nawawy[1], Passant M Farghaly[2], Hadir M Hassouna[3]

Abstract

Aim: To assess the accuracy of the passive leg raising (PLR) test to anticipate fluid responsiveness in critically ill children under age of 5 years.

Materials and methods: A prospective observational study was conducted, in a university hospital pediatric intensive care unit from June 1, 2017, to January 30, 2018. Hemodynamic parameters including stroke volume using bedside transthoracic echocardiography were assessed at baseline I (45° semi-recumbent position), after PLR, at baseline II, and following fluid challenge. Changes in the stroke volume (delta SV) and in the cardiac index (CI) were recorded after PLR and fluid challenge.

Findings: Delta SV of 10% after PLR was an excellent discriminator of the fluid responsiveness with an area under ROC (AUC) of 0.81 (95% CI 0.68–0.9) with a sensitivity of 65.38% and a specificity of 100%. The change in CI of 8.7% after PLR was a significant discriminator of fluid responsiveness with an AUC of 0.7 (95% CI 0.56–0.81) with 57.78% sensitivity and 91.67% specificity.

Conclusion: Passive leg raising can identify nonresponders among seriously ill children under the age of 5 years but it cannot identify all responders with certainty.

Clinical significance: Passive leg raising is reliable test in under 5 year-old-children if performed appropriately using bedside echocardiography for the measurement of its transient effect.

Keywords: Critically ill children, Fluid overload, Fluid responsiveness, Hemodynamic monitoring, Passive leg raising.

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Introduction

Intravenous fluid administration is the keystone of resuscitation in seriously ill patients. Moreover, all patients admitted to pediatric intensive care units (PICUs) would receive intravenous fluid for one reason or another.[1] Fluid replacement is often necessary to optimize the cardiovascular function by maintaining adequate cardiac preload and output providing enough tissue oxygen delivery, which is essential in the management of critically ill patients.[2] Optimal fluid management is crucial to avoid the deleterious effect of over, under, or inappropriate resuscitation.[2,3] The aim of volume management is to maintain the adequate circulating volume to improve oxygen delivery to tissues while avoiding interstitial edema. Nonoptimized fluid administration, cardiovascular derangements, as well as aggressive uncontrolled infection are the main causes of multiple organ dysfunction syndrome (MODS), which is a significant cause of mortality in the intensive care units worldwide.[4–6] Fluid overload impedes organ oxygenation and causes peripheral and pulmonary edema with prolonged hospital stay and higher mortality.[6]

The heart in the early phase of the Frank-Starling curve still has a preload reserve. Increasing the heart preload will lead to expansion of stroke volume (SV). The patient responds positively to fluid administration during this phase. On the other hand, if the heart is functioning near the flat part of the Frank-Starling curve, with exhausted preload reserve, SV will not expand significantly in spite of fluid administration.[7,8]

The fluid challenge is the gold standard method for evaluating fluid responsiveness to direct fluid therapy in seriously ill patients.[7,9] Fluid responsiveness is generally defined as an increase in SV or cardiac output (CO) of 10–15% in response to a crystalloid fluid bolus.[7] The main disadvantage of a fluid challenge is the unavoidable fluid volume given that when it is repeated in a short time may cause fluid overload.[10] The idea of "mini-fluid challenge" has come out to conduct a fluid challenge with a fluid volume less than the "conventional" challenge. The reduced volumes of fluid cause little increase in cardiac preload and only minimal changes in CO. Therefore, it is doubtful that the mini-fluid challenge is valid.[11]

Lately, the passive leg raising (PLR) test has been proposed as a simple bedside method to assess fluid responsiveness, which is similar to an "auto-fluid challenge" without external fluid. The effects of PLR must be evaluated with a real-time measurement of CO.[7,10,12] The smaller lower body size in children makes this reservoir less functioning as compared to adults.[1,9] Thus, PLR evaluation in children is more challenging. The rationale of the current study was to assess the ability of PLR to anticipate fluid responsiveness in critically ill, under age of 5 years, when compared with the standard fluid challenge.

Materials and Methods

This prospective observational study was conducted in the PICU of a tertiary university hospital from June 1, 2017 to January 30, 2018. This study was registered in the Cochrane Library under registration number PACTR201707002408136.

[1–3]Pediatric Department (PICU), Faculty of Medicine, Alexandria University, Egypt

Corresponding Author: Hadir M Hassouna, Pediatric Department (PICU), Faculty of Medicine, Alexandria University, Egypt, Phone: +2 0100 3568008, e-mail: hadirelrouby@yahoo.com

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Sample Size

A sample size of 55 was the minimum required to detect an area under the ROC curve (AUC) of 0.65, relative to a null value of 0.5, as statistically significant with 80% power and at a significance of 0.05. The sample size was calculated using the Medcalc Program version 12.2.[13]

Inclusion Criteria

Children from 1 month to 5 years were included for whom fluid was decided to be given based on the existence of at least one sign of poor tissue perfusion: (a) tachycardia defined as a mean heart rate >2 SD above normal for age, (b) decrease in blood pressure <5th percentile or systolic blood pressure <2 SD below normal for age, (c) urine output <0.5 mL/kg/hour, and (d) prolonged capillary refill: >5 seconds.

Exclusion Criteria

Patients having a shock that required immediate resuscitation with rapid changing hemodynamic conditions or patients who needed prompt change in inotropic or vasoactive drug infusion were excluded during the resuscitation phase. They were then included after the resuscitation phase when further fluid was needed. Patients having irregular dysrhythmia or increased intra-abdominal/intracranial pressure were also excluded. Contraindications to fluid bolus or leg elevation were considered exclusion criteria.

The main aim was to assess fluid responsiveness when a patient apparently required fluid administration. Sonosite Doppler echocardiography (WK2LN3, USA) was used with the standard transthoracic probe (S8-3). Echocardiography was performed by a 5-year experienced operator who received adequate training course in functional echocardiography for an intensivist. All results were reviewed instantaneously by a pediatric cardiologist who was blinded to the clinical condition of the studied patients and the purpose of the study. All readings were repeated in three consecutive cycles and results were averaged. A pilot study including 15 patients showed an excellent degree of intraobserver reliability in three baseline measurements of SV. The average measure intraclass correlation (ICC) was 0.93 [95% confidence interval (CI) = 0.91–0.95, $p < 0.001$].

In the left parasternal view, the diameter of the aortic annulus was measured. The left ventricular outflow tract (LVOT) area was calculated by the device using the following equation: [LVOT area = 0.785 × (diameter of the aortic annulus)^2].[14] Velocity time integral (VTI) of aortic blood flow is equivalent to the product of the mean velocity (obtained by tracing the spectrum of LVOT flow) and ejection time.[15] The pulsed wave Doppler signal from the five chambers apical view is directed parallel to flow through the LVOT below the aortic valve and the velocity was recorded (cm/systole). When the velocity signal was integrated with respect to time, the distance blood moves with each systole was calculated in cm/systole.[16] The device calculated SV [SV = VTI × LVOT area] and CO [CO = SV × heart rate]. The CO was expressed in the form of a cardiac index (CI) [CI = CO/body surface area].[16]

Study Design

Measurements were taken in a semi-recumbent position (baseline I). Then, the patient's lower limbs were elevated 45° from the horizontal passively by the automatic raising of the bed's leg while simultaneously lowering the bed's head to the horizontal position (PLR). After 1 minute, all hemodynamic parameters were remeasured. The change in SV (delta SV) and the change in CI were calculated after PLR compared to baseline I. Next, the patient was replaced in the initial position (baseline II) and all hemodynamic parameters were remeasured after 1 minute. Finally, all hemodynamic parameters were remeasured immediately following a bolus of 10 mL/kg of isotonic saline infused intravenously over 10 minutes (fluid challenge). Delta SV and change in CI were recalculated after fluid challenge compared to baseline II. Ventilator settings (in ventilated patients), as well as infusion rates of inotropic/vasopressor agents and sedation/analgesia, were held constant during fluid bolus administration. According to previous studies, fluid responsiveness was considered positive when delta SV was more than 10% after fluid challenge.[1,17]

Statistical Analysis

Collected data were revised, coded, and fed into the statistical software SPSS-IBM version 21.[18] The Kolmogorov-Smirnov test of normality revealed significance in the distribution of the variables, so the nonparametric statistical tests were adopted.[19] Comparisons were carried out among related samples by the Friedman's test "alternative to the one-way ANOVA with repeated measures."[20] Pairwise comparison when the Friedman's test was significant was carried out using the Dunn-Sidak method by the mean rank of the median.[21] The area under the ROC curve (AUC) was carried using the MedCalc Software version 14. The best cut-off value was determined using the Youden index.[22] The statistical significance level of ≤0.05 was accepted.

University ethical committee approval and informed consent from the patients' parents/legal guardians were obtained.

Results

Eighty-two patients were admitted during the study. Twenty-five patients were excluded per exclusion criteria. Fifty-seven patients were included in which 91% (52/57) were fluid responders (delta SV was more than 10% after fluid challenge) (Flowchart 1).

Baseline characteristics and initial assessment are presented in Table 1. The comparisons of hemodynamic parameters between responders and nonresponders are shown in Table 2. Table 3 shows that there was insignificant difference in heart rate by the repeated measure analysis between all four situations ($X^2 = 0.67$, $p = 0.88$). However, SV, CO, and CI differed significantly among different situations ($X^2 = 83.31$, $X^2 = 69.64$, $X^2 = 86.47$, respectively;

Flowchart 1: Flow diagram of the study

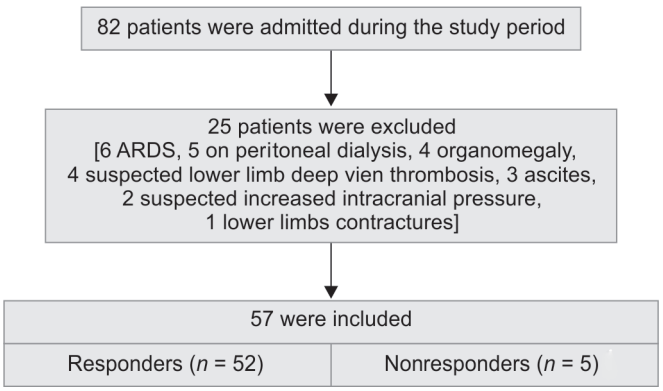

Table 1: Baseline characteristics and initial assessment

	Nonresponder	*Responder*	*p value*
Age (month)[1]	5 (2–9)	5.5 (2–13.5)	$p_{(MW)} = 0.67$
Sex *n* (%)			
Males	4 (80%)	27 (51.92%)	$p_{(\chi 2)} = 0.463$
Females	1 (20%)	25 (48.08%)	
Provisional diagnosis *n* (%)			
Sepsis and septic shock	4 (80%)	27 (51.92%)	$p_{(MC)} = 1.00$
Hypovolemic shock	1 (20%)	11 (21.15%)	
Encephalitis	0	3 (5.77%)	
Inborn error of metabolism	0	2 (3.85%)	
Pneumonia	0	6 (11.54%)	
Hepatic encephalopathy	0	1 (1.92%)	
Bronchiolitis	0	2 (3.85%)	
Mortality	3 (60%)	8 (15.38%)	$p_{(\chi 2)} = 0.069$
PELOD day 1[1]	24.6 (21.4–38.2)	22.4 (13.8–26.5)	$p_{(MW)} = 0.072$
PIM 2[1]	33.7 (20–33.7)	16.7 (13.4–37.4)	$p_{(MW)} = 0.270$
Mechanical ventilation *n* (%)	3 (60%)	32 (61.54%)	$p_{(\chi 2)} = 1.00$
Days of ventilation[1]	3 (2–7)	3.5 (2–5)	$p_{(MW)} = 0.904$
Use of vasopressors/inotropes *n* (%)	4 (80%)	21 (40.38%)	$p_{(\chi 2)} = 0.217$
VIS (before PLR test)[1]	50 (35–75)	50 (20–80)	$p_{(MW)} = 0.677$
Urine output (day 1)[1]	1.10 (1.10–1.20)	2.50 (2.15–3.15)	$p_{(MW)} = 0.001$*
Lactate[1]	3.40 (3.00–3.60)	1.35 (1.10–2.00)	$p_{(MW)} = 0.001$*

[1]Median (IQR)
ELOD2, pediatrics logistic organ dysfunction 2; PIM2, pediatric index of mortality 2; VIS, vasopressor-inotropic score
$p_{(MW)} = p$ value of Mann–Whitney U test, $p_{(\chi 2)} = p$ value of Chi-square test, $p_{(MC)} = p$ value of the Monte Carlo's exact probability test
*Statistically significant ($p < 0.05$)

Table 2: Hemodynamic parameters among responders and non-responders

	Baseline I	*PLR*	*Baseline II*	*FC*
Heart rate (bpm)				
Responders	142 (129–157)	145 (131–158)	143 (131.5–157)	145 (126–157)
Nonresponders	165 (154–167)	170 (162–174)	165 (155167)	176 (156–176)
p value	$p_{(MW)} = 0.06$	$p_{(MW)} = 0.006$*	$p_{(MW)} = 0.057$	$p_{(MW)} = 0.016$
CO(L/minute)				
Responders	1.2 (0.7–1.6)	1.3 (0.8–1.75)	1.2 (0.7–1.6)	1.4 (1–1.9)
Nonresponders	0.9 (0.62–1.2)	0.9 (0.63–1)	0.9 (0.7–1.2)	0.7 (0.6–1.3)
p value	$p_{(MW)} = 0.420$	$p_{(MW)} = 0.154$	$p_{(MW)} = 0.488$	$p_{(MW)} = 0.041$*
SV (mL)				
Responders	7.75 (4.88–11)	8.49 (5.24–13.5)	7.75 (4.88–11)	10.2 (6.47–13.2)
Nonresponders	5.74 (3.78–7.23)	5.74 (3.69–7.36)	5.74 (3.78–7.23)	4.48 (3.87–7.42)
p value	$p_{(MW)} = 0.259$	$p_{(MW)} = 0.121$	$p_{(MW)} = 0.259$	$p_{(MW)} = 0.019$*
CI (L/minute/m^2)				
Responders	2.93 (2.29–3.91)	3.47(2.83–4.17)	2.83 (2.25–3.83)	4.15 (3.26–4.93)
Nonresponders	2.72 (2.69–3.63)	2.72 (2.6–3)	2.72 (2.69–3.63)	2.72 (2.70–3.93)
p value	$p_{(MW)} = 0.888$	$p_{(MW)} = 0.146$	$p_{(MW)} = 0.724$	$p_{(MW)} = 0.055$
Mean arterial pressure (mmHg)				
Responders	51 (48–60)	57 (51–66)	51 (48–60)	56 (53–66)
Nonresponders	59 (52–62)	54 (48–57)	62 (56–61)	58 (54–67)
p value	$p_{(MW)} = 0.053$	$p_{(MW)} = 0.153$	$p_{(MW)} = 0.053$	$p_{(MW)} = 0.723$

Data presented in median (IQR); PLR, passive leg raising; FC, fluid challenge
$p_{(MW)} = p$ value of Mann–Whitney *U* test, *Statistically significant ($p < 0.05$)

Table 3: Hemodynamic parameters measured by echocardiography

	Heart rate (bpm)	*SV (mL)*	*CO (L/minute)*	*CI (L/minute/m²)*
Baseline I	148 (132–158)	7.45[a,c] (4.81–11)	1.20[a,c] (0.70–1.5)	2.90[a,c] (2.36–3.88)
PLR	146 (135–160)	7.81[b] (5.24–11.9)	1.20[b,c] (0.80–1.7)	3.40[b] (2.72–4.21)
Baseline II	146 (132–159)	7.45[a,c] (4.81–11)	1.20[a,b,c] (0.7–1.5)	2.81[a,c] (2.29–3.82)
Fluid challenge	146(130–159)	8.96[d] (6.09–12.2)	1.40[d] (1–1.8)	4.00[d] (3.4–4.86)
Repeated measure analysis	$X^2_{(Fr)(df=3)} = 0.67$, $p = 0.880$	$X^2_{(Fr)(df=3)} = 83.31$, $p \leq 0.0001$*	$X^2_{(Fr)(df=3)} = 69.64$, $p \leq 0.0001$*	$X^2_{(Fr)(df=3)} = 86.47$, $p \leq 0.0001$*

Data presented in median (IQR), *n*: number of patients
Fr, Friedman test; df, degree of freedom
Different superscript letters indicate significant pairwise comparison using the Dunn-Sidek method of adjustment; a: baseline I, b: PLR, c: baseline II, d: fluid challenge
*Statistically significant ($p \leq 0.05$)

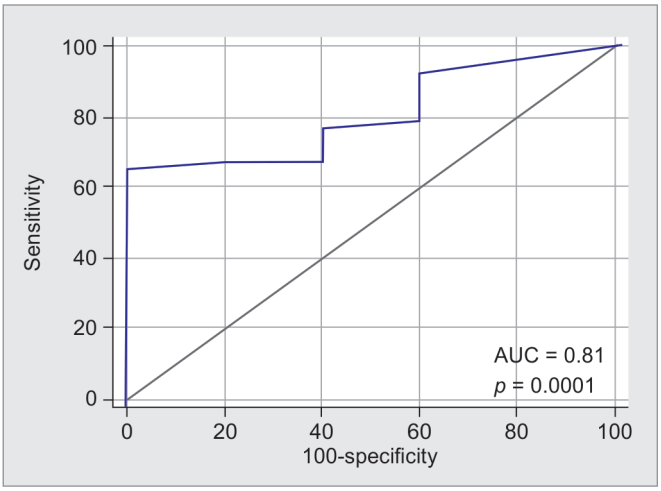

Fig. 1: Receiver's operating characteristic curve of delta stroke volume after passive leg raising test as a predictor of fluid responsiveness

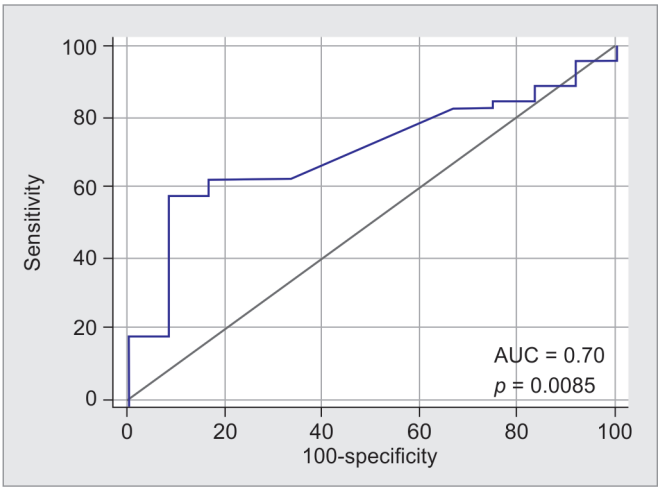

Fig. 2: Receiver's operating characteristic curve of the change in cardiac index as a predictor of fluid responsiveness

$p \leq 0.001$). The pairwise comparison revealed that SV, CO, and CI after PLR significantly increased compared with baseline I ($p \leq 0.001$, <0.001, 0.028, respectively). The SV, CO, and CI after fluid challenge significantly increased compared with baseline II ($p \leq 0.001$ for all).

Delta SV of ≥10% after PLR was an excellent discriminator of fluid responsiveness with AUC of 0.81 (95% CI = 0.68–0.9) with a sensitivity of 65.38% and a specificity of 100% (Fig. 1). Change in CI of ≥8.7 % after PLR was a significant discriminator of fluid responsiveness with AUC = 0.7 (95% CI 0.56–0.81) with a sensitivity of 57.78% and a specificity of 91.67 % (Fig. 2).

Discussion

In the current study, delta SV of ≥10% after PLR was an excellent discriminator of fluid responsiveness with a sensitivity of 65.4%. In other words, 65.4% of fluid responders were correctly identified by having delta SV of ≥10% after PLR, i.e., 35.5% false-negative. Passive leg raising is inconvenient in profound hypovolemia as the blood volume mobilized by leg raising, which is dependent on total blood volume, could be minimal and can show slight or no increase in SV and CO even in fluid responsive patients.[23] Most of the patients were diagnosed as septic or hypovolemic shock, which explains underdiagnosis of some responders by the PLR test. With a specificity of 100%, all fluid nonresponders were correctly identified by having delta SV of <10%, which is crucial to avoid administration of unnecessary fluids to prevent fluid overload. This could not be estimated by clinical examination alone, which is the method used to detect a fluid need in critically ill children.[24] Using a fluid challenge in these patients would be deleterious.

Change in CI ≥8.7% was also a significant discriminator of fluid responsiveness after PLR with AUC of 0.7 (95% CI 0.56–0.81) with a sensitivity of 57.8% and a specificity of 91.7%. This means that 57.8% of fluid responders and that almost all fluid nonresponders were correctly identified by having a change in CI of ≥8.7%. Change in CI had less sensitivity and specificity compared with delta SV to detect responders after PLR. In accordance with Lukito et al.[14] who stated that in shock, the fluid challenge that is applied to expand SV does not always achieve the required rise in CO and CI.

Lu et al.[25] demonstrated that the PLR test is an unreliable marker in children under 5 years of age due to wide range of variations in CI with PLR. Unlike the current study, Lu et al. used the bioreactance-based noninvasive cardiac output monitoring (NICOM) technique for measuring SV and CO rather than real-time echocardiography, which is the gold standard method. In the current study, starting from the semi-recumbent position followed by trunk lowering and leg raising led to the mobilization of venous blood from the splanchnic area besides that from the lower limbs. This technique was not mentioned by Lu et al. depending on the lower limbs reservoir only, which varies greatly among young children below 5 years. However, Lu et al. found that 10% increase in CI after the PLR test would predict fluid responsiveness with a higher sensitivity (100% vs 91%) and similar specificity (27% vs 25%) for those over 5 years as compared to under 5 years, respectively.[25]

The effects of PLR are rapidly reversed after the legs are put back in a horizontal position; therefore, PLR is a transient reversible challenge.[26,27] It can be repeated several times to reevaluate fluid responsiveness safely without development of fluid overload in potential nonresponders. Monnet et al.[10,12,26] demonstrated that CO must be assessed before, during, and after PLR to ensure that it comes back to its baseline. In the current study, there was insignificant difference between baseline I and II as regards to SV, CO, and CI before and after PLR denoting that CO variations during PLR did not result from inevitable changes related to the original illness of the unstable patients. This shows without doubt that PLR is reversible with a transient effect that avoids inevitable administration of fluids to nonresponders surpassing the standard fluid challenge. Hemodynamic parameters were measured 1 minute from the start of PLR, which is in accordance with Monnet et al.[12] who stated that the hemodynamic changes take place within seconds and are maximal just about 1 minute after initiating the maneuver.

Passive leg raising is a reliable test on condition that its effects are evaluated by a real-time fast response device used to measure transient changes in SV and CO.[26] In the present study, echocardiography was used to measure hemodynamic parameters in the different situations providing real-time assessments of SV and CO.

The method of applying PLR has a major significance because it affects greatly the hemodynamic effects and thus the test reliability.[12,28] In the present study, the test was started in the semi-recumbent position. Adding trunk lowering to leg raising resulted in the mobilization of additional venous blood from the splanchnic area, augmenting the effect of leg elevation on cardiac preload and thus maximizing the test's sensitivity.[12,29] Pain, cough, and discomfort could induce adrenergic stimulation, resulting in an inaccurate evaluation of CO changes after PLR.[12,14,26,29] When there is a marked increase of heart rate accompanying PLR, sympathetic stimulation should be suspected, which may be an indicator of an altered test result.[12,26] Several researchers noted that PLR did not produce changes in the heart rate, suggesting that catecholamine stimulation is not present.[12,26,30] In the present study, PLR was performed by adjusting the bed automatically to avoid pain and discomfort. Accordingly, there was insignificant difference in the heart rate between all four situations confirming the absence of sympathetic stimulation. Vasoactive medications may also alter the response to the PLR.[23,27] Accordingly, a constant vasoactive drip rate was maintained during PLR in the current study.

An important limitation of the current study is that 77% of patients were infants. The young age of the study cohort may affect external validity and generalizability of the results. However, few studies dealt with this age group. Also, the need of well-trained staff to perform echocardiography around the clock is another limitation. So, it is recommended that PICU staff should receive echocardiogram hands-on training courses.

Conclusion

Passive leg raising can identify nonresponders among critically ill children under the age of 5 years but it cannot identify all responders with certainty. So, a negative PLR means do not give fluids while a positive PLR means there is still uncertainty if the child is a responder.

Clinical Significance

Passive leg raising is a reliable test in children under the age of 5 years if performed appropriately using bedside echocardiography for the measurement of its transient effect.

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