

### **Original Article.**

Effect of **Phototherapy** on Cardiac **Functions** in **Neonates** with Hyperbilirubinemia. A Prospective Cross-Sectional Study Amar Taksande<sup>1\*</sup>, Jayant Vagha<sup>2</sup> and Yash Dalal<sup>3</sup> DOI: 10.21608/ANJ.2021.76113.1027 \*Correspondence: Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra: 442004 Email: amar.taksande@gmail.com Full list of author information is available at the end of the article.

### Abstract

**Background:** Phototherapy has been reported to alter cardiovascular function by causing increased peripheral blood flow, diminished cardiac output and increased sympathetic activity that may be of concern, particularly in neonates with hyperbilirubinemia. Aim of work: To assess the myocardial function in neonates with hyperbilirubinemia by using echocardiography, especially tissue Doppler imaging (TDI). Patients and Methods: It was a prospective, cross- sectional study. All participants in this study were full-terms and appropriate for gestational age newborns with hyperbilirubinemia who received phototherapy for jaundice (bilirubin level greater than 15 mg/dl). Myocardial functions were assessed using conventional echocardiography and tissue Doppler imaging techniques. Results: The study population consisted of 110 neonates with hyperbilirubinemia; their mean gestational age was 38.8  $\pm$  1.7 weeks and mean birth weight 2785  $\pm$  652 g. After phototherapy, respiratory rate and heart rate were faster whereas oxygen saturation and systolic blood pressure were lower (p < 0.000). There was no significant difference in the left ventricular interventricular septum in diastole (LVIVSd), left ventricular interventricular septum in systole (LVIVSs), left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs), left ventricular posterior wall in diastole (LVPWd), left ventricular posterior wall in systole (LVPWs), ejection fraction (EF) and fraction shortening (FS) before and after phototherapy (p > 0.05). Pulsed wave Doppler parameters showed no significant difference in the mitral E velocity, mitral A velocity, and E/A ratio (p > 0.05).

**Conclusion:** Phototherapy had no adverse effects on either systolic or diastolic function of the left ventricle in term neonates with indirect hyperbilirubinemia.

Key words: Cardiac function; hyperbilirubinemia; neonate; tissue Doppler imaging.

# Introduction

In the newborn nursery, neonatal jaundice is widespread, and phototherapy is regarded the standard of care when treatment is necessary. Although various adverse effects have been reported, phototherapy is both safe and effective [1]. These include deoxyribonucleic acid (DNA) damage in lymphocytes, as well as physiologic and behavioral impacts on the newborn infant's organ systems [2]. Hyperbilirubinemia has no effect on DNA damage, whereas both intensive conventional and phototherapies are associated with DNA damage in hyperbilirubinemia-affected term infants [3]. Short-term adverse effects of phototherapy include disruption of the mother-infant relationship, alteration of the thermal environment with water loss, electrolyte imbalance, bronze baby syndrome, and circadian rhythm abnormalities. Furthermore, phototherapy may cause long-term negative effects such as melanocytic nevi and skin cancer.

allergic disorders, patent ductus arteriosus. and retinal injury[4-5].However, phototherapy has been shown to modify cardiovascular function by increasing peripheral blood flow, decreasing cardiac output, and increasing sympathetic activity, which may be concerning in unwell or preterm neonates [5]. It seems that although phototherapy does affect cardiac function; several issues still require verification. The purpose of this study determine the effects to of was phototherapy on systolic and diastolic function in cardiac neonates with hyperbilirubinemia.

# **Methods**

Study setting: Between January 2018 and December 2019, this study was carried out at a newborn care unit linked to the department of paediatrics at Jawaharlal Nehru Medical College & AVBR Hospital in Sawangi, Wardha, Central India.

Studydesign:Aprospective,observational, cross- sectional study.

Study participants: All patients in this trial were full-term and appropriate for gestational age (AGA) neonates with hyperbilirubinemia (bilirubin level more than 15 mg/dl) who were treated with phototherapy in accordance with AAP guidelines [6-7]. The following were the inclusion criteria for study participation: (1) full-term newborns who are healthy (gestational age: 37–42 weeks), (2) have a birth weight of 2500–3500 g, (3) have an Apgar score of 8–10 at delivery, and (4) are undergoing phototherapy for hyperbilirubinemia. Exclusion criteria included dehydration, electrolyte imbalance, acid-base disorders, neonatal sepsis, small for gestational age babies, intrauterine growth restriction, perinatal congenital anomalies. asphyxia, congenital heart defects and neonates who suspected to have were chromosomal abnormalities. The study authorized by our Institute's was institutional review board, and informed permissions were acquired from the parents of the neonates.

hyperbilirubinemia (study cases) had their demographic information gathered, including their age, gender, gestational age, and birth weight. All patients had a perinatal relevant history (including maternal sickness, manner of birth, Apgar score, history of cyanosis or convulsions) and clinical examination (with specific attention on vital signs, anthropometric measurements. the of presence cephalhematoma and neurological examination) was done for Laboratory all cases. investigations included complete blood count. peripheral smear, blood group and Rh typing of the neonate and mother. Total and direct serum bilirubin concentration measured by using the was spectrophotometric method with the Selectra-2 auto-analyzer at the initiation of phototherapy and every 6 hourly by transcutaneous bilirubin-meter. The phototherapy was stopped when the level of total serum bilirubin dropped to less than 12 mg/dl by lab. Serum Calcium

Assessments: All term neonates with

Echocardiography:

and cardiac troponin levels were measured before starting phototherapy and 24 hours after termination of phototherapy treatment.

Phototherapy: In general, healthy fullterm infants were discharged at 3 days of age. If newborn jaundice was discovered and phototherapy was available in the NICU. they treated there. were Fluorescent tubes are often used to give phototherapy at a distance of 45-60 cm efficient from the An neonate. device emits specified phototherapy blue-light wavelengths (peak emission: 450  $\pm$  20 nm), preferably in a narrow bandwidth encompassing approximately 80% of the baby's body surface area [8]. The baby was covered with minimal clothing should be naked except the eyes and genitalia to increase the exposed skin surface area to the therapy light. However, the neonate's eyes and genitalia were covered to prevent damage. Phototherapy was stopped when the level of bilirubin decreased to less than 12 mg/dL.

was performed using a GE Vivid-e echocardiography machine, United States in accordance with the guidelines of the American Society of Echocardiography [9]. (ASE) Α single paediatric performed cardiologist the echocardiographic measurements. Using M-mode echocardiography by parasternal long axis The interventricular septum thickness in (IVSd), the interventricular diastole septum thickness in systole (IVSs), the left ventricular internal dimension in diastole (LVIDd), the left ventricular internal dimension in systole (LVIDs), the LV posterior wall thickness in diastole (LVPWd) and the LV posterior wall thickness in systole (LVPWs) were measured. The fractional shortening (FS) of the left ventricle was calculated using the left ventricular dimensions. FS is calculated as follows: LVIDd-

Echocardiography

FS is calculated as follows: LVIDd-LVIDs/LVIDd  $\times 100\%$ . The biplane modified Simpson's method was used to calculate left ventricular end-diastolic and end-systolic volumes, as well as left ventricular ejection fraction (EF). The apical four-chamber view was also used to record LV inflow velocities, with the peak flow velocities of the LV inflow measured in early diastole (E) and late diastole with atrial contraction (A), and the E/A ratio calculated.

Tissue Doppler Imaging (TDI): We employed TDI to assess the LV's systolic and diastolic function. At the apical fourchamber abutment, a 2-mm pulse-wave (PW) sample volume was inserted on the left ventricular septal mitral annulus. Systolic velocity (S'), early diastolic velocity (E'), late diastolic velocity (A'), and time intervals: isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and ejection time (ET) were measured at each site. The IVRT was measured from the end of the S'wave to the beginning of the E'wave, while the IVCT was measured from the beginning of the A'wave to the beginning of the S'wave. The Tei index was

calculated [10] using the following formula: (IVCT + IVRT / ET).

Sample size calculation:Prior to the research, the sample size was estimated. The predicted minimum detectable difference in heart rate before and after phototherapy in means = 4, standard deviation difference = 4, effect size = 0.307, both sidedness; power = 90%, and alpha error = 5%. The study required a minimum sample size of 110 people.

# **Ethical consideration**

The study was approved by the Committee of Ethics of Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra. Written consents were taken by the fathers of all neonates enrolled in the study.

# **Statistical analysis**

Stata software version 10 was used to conduct statistical analysis. Continuous variables are provided as means  $\pm$  standard deviations, whereas categorical data are provided as frequencies with percentages. To compare continuous variables, the paired student's t-test was utilized. Statistical significance was defined as a p-value less than 0.05.

# Results

The study population consisted of 110 neonates with hyperbilirubinemia; their mean gestational age was  $38.8 \pm 1.7$ weeks and mean birth weight  $2785 \pm 652$ g. In the study, 56 (50.90%) babies had hyperbilirubinemia at < 48 hours of life, 30 (27.27%)babies had hyperbilirubinemia at 48-72 hours, 13 (11.81%) babies had hyperbilirubinemia at 72-96 hours and 11 (10%) babies had hyperbilirubinemia after 96 hours of life. Out of 110 neonates admitted in NICU with hyperbilirubinemia, 61(55.45%) were males and 49 (44.55%) were females. Male to female ratio was 1.15:1. After phototherapy, respiratory rate (P <0.000) and heart rate (P <0.000) were faster whereas oxygen saturation ( P <0.000) and systolic blood pressure ( P <0.000)were lower which was statistically significant [Table 1].

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In terms of left ventricular systolic function. there were no significant differences in the LVIVSd, LVIVSs, LVIDd, LVIDs, LVPWd, LVPWs, EF and FS before or after phototherapy (P >significant 0.05). There were no differences in the measurement of left atrium and aortic sizes before and after phototherapy (Table 2 & Figure 4). Among pulsed wave Doppler parameters, study cases showed no significant difference in the mitral E velocity, mitral A velocity and E/A ratio (p > 0.05)(Table 3 & Figure 5). Similarly, among tissue Doppler parameters, cases showed no significant difference in the E' wave, A' wave, S'wave, IVRT, IVCT and ET, before and after the phototherapy [Table 4 and Figure 6]. Among tissue dopplerbased Tei index parameters, there were no significant differences noted before and after phototherapy (Table 4).

# Discussion

Phototherapy is the use of visible light to cure severe jaundice in the early stages of life. Conventional phototherapy uses

fluorescent bulbs, halogen lamps, or light-emitting diodes (LED), all of which are equally efficient in lowering serum bilirubin levels [7-8]. When super (highintensity) LED equipment are employed, hyperthermia and skin rashes are more common. The effects of light penetrating the heart in newborn newborns due to the thin chest wall are unclear. Non-ocular light exposure and melatonin suppression may have an effect on autonomic and behavioral abnormalities[4-5].However, phototherapy has been shown to modify cardiovascular function by increasing heart rate, decreasing mean arterial blood pressure, increasing peripheral blood flow, decreasing cardiac output, and increasing sympathetic activity, which may be of concern in ill or preterm neonates [11-13].

In newborns with our study. hyperbilirubinemia substantially had higher heart rates, respiration rates, and systolic blood following pressure phototherapy. This outcome is consistent certain earlier study with findings

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[11].However, Weissman A et al. 2009 [12] discovered a considerable decrease in heart rate variability (HRV) during phototherapy, a condition thought to be centrally mediated. According to the findings of Bader D et al 2006 [13] study, there was a substantial drop in respiratory rate, an increase in heart rate, and a decrease in respiratory effort in response to apnea during active sleep. These effects were not observed during peaceful sleep. Previous research has shown that [14] myocardial contractility was decreased in an in vitro investigation on hyperbilirubinemia, however in an in vivo investigation with rats, the left ventricular contractile parameters and (fractional ejection shortening and ejection fraction) were the same as in the control group. In addition, Gao XY et al. 2012 [15] found insufficient evidence to support the idea that neonatal jaundice causes cardiac injury in term infants of normal birth weight. Borenstein-Levin L et al 2016 [16] discovered that there is no clinically meaningful change in coronary

artery flow following phototherapy in healthy term newborns. The authors of this study hypothesized that measurements of cardiac output did not differ considerably. In another research, Walther FJ et al 1985 [17] discovered that decreased stroke volume during phototherapy lowered cardiac output by 6%. The decrease in stroke volume during phototherapy may be due to the newborn's reduced activity during phototherapy. Furthermore, Benders MJ et al 1999 [18] found that left ventricular dropped output (LVO) soon after phototherapy began. However, LVO rebounded to pre-phototherapy levels within 12 hours. After 12 hours of exposure, there was a considerable increase in mean left pulmonary artery blood flow (LPA).

Karabulut B et al 2019 [19] found no significant differences between the cases and controls in EF, FS, LVEDd, and LVEDs. They also discovered no statistically significant variations in mitral, tricuspid, septal E', A', and S'

across groups. Firouzi M et al 2020 [20] found that the mean stroke volume before and after phototherapy was 6.99  $\pm 2.17$  and  $6.55 \pm 1.85$  L/m2 (p = 0.011), respectively, and concluded that phototherapy can lower left ejection fraction in newborn babies with hyperbilirubinemia. In addition, Kapoor S et al 2020 [21] reported that chest shielding of preterm neonates during phototherapy had no influence on the incidence hemodynamically of significant patent ductus arteriosus. Furthermore, Negrine RJ et al 2012 [22] shown that the TDI is viable in newborns. with increased gestation resulting in larger cardiac velocities and lower E/E' ratios. Premature newborns' jaundice is with best treated phototherapy. However, phototherapy has been associated to ductus arteriosus closure failure in these newborns. This might be due to light entering the thin chest wall of extremely preterm neonates and relaxing the smooth muscle of the aorta via the nitric oxide-cyclic GMP

pathway and Ca2+ dependent K+ ion channels. As a result, neonatal phototherapy may have a relaxing effect on the smooth muscles of the ductus arteriosus in neonates, inhibiting the closure of the patent ductus arteriosus and perhaps causing the ductus arteriosus to reopen [23].

Phototherapy is not associated with the risk of hypocalcemia in healthy, full-term One previous neonates. study has suggested that [24] there is no need of prophylactic calcium for healthy, fullterm neonates who have undergone phototherapy. However, the study done by Shengyu Y et al 2011 [25] mentioned hyperbilirubinemia that causes а temporary myocardial injury. They also advised that cardiac troponin I and CK -MB can help monitor myocardial injury in jaundiced babies. Li Wei Zhong et al 2004 [26] in his study mentioned that the myocardial enzymes and isoenzymes activities especially CK and CK-MB elevated in with were neonates hyperbilirubinemia. unconjugated He

found also that pathological hyperbilirubinemia in a neonate may induce myocardial function impairment which can be correlated with the degree and duration of jaundice. Because other approaches, particularly invasive measurements are risky in newborns. Hence, echocardiography was the sole technique employed to assess cardiac function in our research. Echocardiography measurements of cardiac size and velocity before and after phototherapy were nearly identical.

### Conclusions

Phototherapy had no adverse effects on either systolic or diastolic functions of the left ventricle in term neonates with indirect hyperbilirubinemia.

# List of abbreviations

- TDI= Tissue doppler imaging
- LVIVSd= Left ventricular interventricular septum in diastole
- LVIVSs= left ventricular interventricular septum in systole
- LVIDd= left ventricular internal dimension in diastole
- LVIDs= left ventricular internal dimension in systole
- LVPWd= left ventricular posterior wall in diastole

- LVPWs=left ventricular posterior wall in systole
- EF= Ejection fraction
- FS= Fraction shortening
- DNA= Deoxyribonucleic acid
- E=Early diastolic velocity
- A=Late diastole with atrial contraction
- AGA= Appropriate for gestational age
- AAP = Americal Academy of Paediatrics
- S'=Systolic velocity
- E'=Early diastolic velocity
- A'=Late diastolic velocity
- IVCT= Isovolumetric contraction time
- IVRT=Isovolumetric relaxation time
- ET=Ejection time
- LED=Light-emitting diodes

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#### **Author's contributions**

All of authors shared equally in this work and have seen and agreed to the submitted version of the manuscript.

#### **Conflict of interest**

The authors have no conflict of interests to declare.

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|                                 | Before       | After        |         |  |
|---------------------------------|--------------|--------------|---------|--|
| Vital parameters (n=110)        | Phototherapy | Phototherapy | P value |  |
|                                 | Mean±SD      | Mean±SD      |         |  |
| Heart rate (Beats/min)          | 133.435±5.44 | 137.55±6.83  | 0.000** |  |
| Respiratory rate (cycles/min)   | 44.13±4.73   | 46.11±4.87   | 0.000** |  |
| SpO2 (%)                        | 98.67±0.84   | 97.29±0.94   | 0.000** |  |
| Systolic Blood pressure (mmHg)  | 66.71±3.82   | 64.92±4.82   | 0.000** |  |
| Diastolic Blood pressure (mmHg) | 38.30±3.32   | 38.42±4.49   | 0.548   |  |

Table (1): Distribution of vital parameters of the studied neonates before and after phototherapy

\*\* highly significant

| Systelia Darameter            |    | of           | of LV   | Before Phototherapy | After      |       |
|-------------------------------|----|--------------|---------|---------------------|------------|-------|
| Systolic Parameter of (n=110) | 01 | Phototherapy |         |                     | P value    |       |
|                               |    | Mean±SD      | Mean±SD |                     |            |       |
| LVIVSd                        |    |              |         | 4.69±0.78           | 4.74±0.64  | 0.488 |
| LVIVSs                        |    |              |         | 5.56±0.79           | 5.60±0.62  | 0.419 |
| LVIDd                         |    |              |         | 13.22±1.21          | 13.23±1.04 | 0.903 |
| LVIDs                         |    |              |         | 8.01±0.89           | 8.12±0.77  | 0.128 |
| LVPWd                         |    |              |         | 4.48±0.85           | 4.59±0.65  | 0.071 |
| LVPWs                         |    |              |         | 4.95±0.65           | 4.90±0.73  | 0.604 |
| EF                            |    |              |         | 65.95±4.43          | 66.06±6.6  | 0.629 |
| FS                            |    |              |         | 33.81±2.28          | 33.61±2.32 | 0.237 |
| Left Atriun                   | n  |              |         | 9.34±1.15           | 9.40±1.26  | 0.336 |
| Aorta                         |    |              |         | 7.85±0.96           | 7.92±0.88  | 0.459 |
| LA/Ao                         |    |              |         | 1.20±0.19           | 1.19±0.18  | 0.640 |

 Table (2): Assessment of the left ventricular systolic function by M-mode echocardiography before and after phototherapy

LVIVSd= Left ventricular interventricular septum in diastole; LVIVSs= left ventricular interventricular septum in systole; LVIDd= left ventricular internal dimension in diastole; LVIDs= left ventricular internal dimension in systole; LVPWd= left ventricular posterior wall in diastole; LVPWs= left ventricular posterior wall in systole; EF=ejection fraction; FS=fraction shortening; LA=Left atrium; Ao=Aorta

| Diastolic Parameter of LV (n=110) | Before<br>Phototherapy | After<br>Phototherapy | P value |
|-----------------------------------|------------------------|-----------------------|---------|
|                                   | Mean±SD                | Mean±SD               |         |
| E wave                            | 44.34±8.08             | 44.57±8.19            | 0.675   |
| A wave                            | 56.73±9.77             | 57.01±11.35           | 0.723   |
| E/A                               | 0.79±0.18              | 0.81±0.23             | 0.406   |

E=Early diastolic velocity; A=Late diastole with atrial contraction

| Tissue Doppler Imaging (TDI)<br>parameter of LV (n=110) | Before Phototherapy<br>Mean±SD | After        |         |
|---|--------------------------------|--------------|---------|
|   |                                | Phototherapy | P value |
|   |                                | Mean±SD      |         |
| E' wave   | 5.70±0.95                      | 5.78±0.95    | 0.238   |
| A' wave   | 7.45±1.30                      | 7.49±1.15    | 0.464   |
| S' wave   | 5.79±0.76                      | 5.71±0.99    | 0.215   |
| IVCT  | 26.31±5.89                     | 26.72±5.35   | 0.465   |
| IVRT  | 24.89±3.98                     | 24.45±4.07   | 0.367   |
| ET  | 219.91±34.85                   | 218.53±32.01 | 0.221   |
| Tei Index   | 0.23±0.04                      | 0.22±0.05    | 0.961   |

Table (4): Assessment of myocardial velocity and time interval at mitral valve by tissue Doppler imaging

E'=Early diastolic velocity; A'=Late diastolic velocity S'=Systolic velocity; IVCT= Isovolumetric contraction time; IVRT=Isovolumetric relaxation time; ET=Ejection time

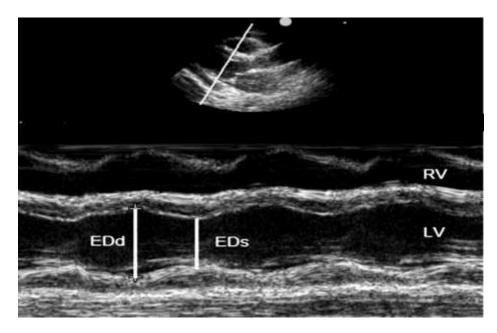


Figure (1): M-Mode echocardiography for the measurement of left ventricular dimensions in systolic and diastolic phase

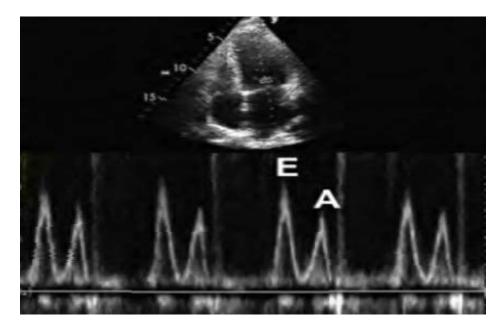


Figure (2): Pulse Doppler echocardiography across the mitral valve for the assessment of diastolic function

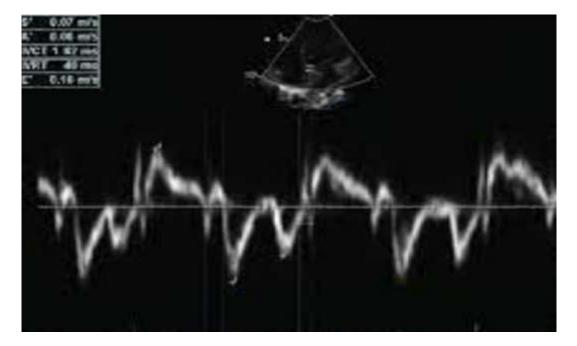


Figure (3): Tissue Doppler imaging for the assessment of systolic and diastolic function of the LV

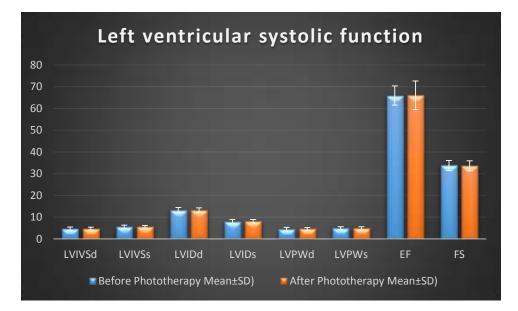
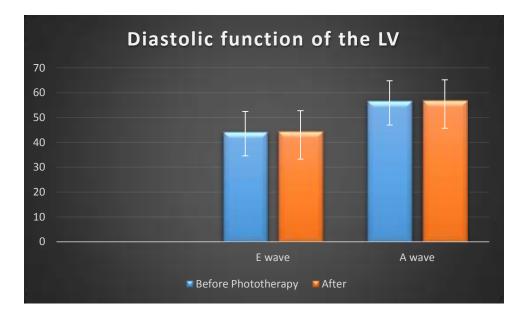
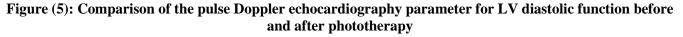


Figure (4): Comparison of the M-mode echocardiography parameter of LV systolic function before and after phototherapy





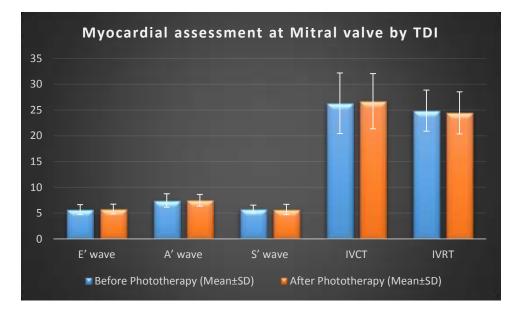


Figure (6): Comparison of the tissue Doppler imaging parameter, before and after phototherapy

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