Cardiovascular assessment after treatment for retinopathy of prematurity: a comparative study between anti-VEGF agent (aflibercept) and laser
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Abstract

Objective: The aim of this study was to compare the cardiac effects and aortic arterial indices following intravitreal aflibercept treatment or diode laser photocoagulation for the treatment of retinopathy of prematurity (ROP) in infants.

Methods: This single-centre, retrospective study was conducted in infants who were administered laser photocoagulation (LPC) or intravitreal aflibercept (IVA) treatment as initial treatment and had completed at least one year of corrected age. The patients were evaluated in terms of aortic elastic parameters, right and left ventricular systolic and diastolic function using conventional, pulsed Doppler and tissue Doppler imaging (TDI) echocardiographic parameters.

Results: Fifteen infants were in the LPC group, 16 in the IVA group, and 20 in the control group. Although there were some statistically significant differences in terms of pulsed and TDI echocardiographic parameters between the treatment and control groups, these values could not clearly be adopted as a diastolic dysfunction and myocardial performance indices were not influenced. The aortic elastic parameters were impaired in both LPC and IVA groups compared to the control group. Consequently, we observed only minor differences between the treatment groups, which may suggest subtle changes due to the anti-angiogenic treatment.

Conclusion: Although favourable and promising outcomes were obtained with intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents to treat ROP, concerns have been raised about potential systemic side effects, including potential cardiovascular side effects caused by these agents. The small reduction in right ventricular Doppler velocities could probably be explained by the use of anti-angiogenic or laser treatment in infants.

Keywords: Doppler, echocardiography, retinopathy of prematurity, vascular stiffness, ultrasonography,
circulation. As a consequence, a decline in plasma VEGF levels has been demonstrated.14 Because the role of VEGF has been proven in the normal developmental stages of the human brain, lung, heart and kidney, possible adverse effects of VEGF-dependent development should be closely monitored. Previous studies attributed the mechanisms of anti-VEGF-induced hypertension to such action as stimulating arterial vascular remodelling.10,11 Therefore, the aim of our study was to compare changes in aortic elastic parameters, using tissue Doppler and conventional echocardiographic measurements for both right and left ventricular systolic and diastolic function after LPC and IVA therapy in infants with ROP.

Methods

This single-centre, retrospective study was performed by evaluating the medical records of infants who were treated for ROP in a tertiary centre for screening and treatment of ROP. The study was carried out between October 2016 and February 2017. The institutional review board at Adana Numune Training and Research Hospital approved the study. Informed written consent was obtained from all parents or guardians. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

During this period, premature infants who completed the corrected age of one year were evaluated using echocardiography for routine cardiac control. Decision about the treatment option for ROP was made as reported by the indications in the Early Treatment for ROP (ETROP) study.1 The study was carried out between October 2016 and February 2017. According to the study, infants with type 1 pre-threshold ROP, threshold ROP or aggressive posterior ROP were selected. If infants had treatment-requiring ROP in the posterior zone (zone I and/or zone II), anti-VEGF treatment was recommended for them because laser treatment has low efficacy in posterior disease, along with decreased visual field and high refractive outcomes.

All parents were informed about the treatment effects and systemic concerns of the IVA. They were also informed about LPC treatment regarding its lower efficacy in posterior ROP, and possible side effects such as preventing peripheral retinal vascularisation. The parents were then left with the decision of whether to treat with LPC or IVA. Patients who received laser or aflibercept treatment as monotherapy and primary treatment were included in the study.

Patients who were treated at a different centre, who were administered another treatment option (cryotherapy, surgery and other anti-VEGF agents) or combined therapy (infants who received additional treatment after primary treatment) for ROP and who could not be followed regularly were excluded from the study. Infants with stage 4 and 5 ROP or infants who underwent vitreoretinal surgery were also excluded, as were those who had systemic or ocular disease such as congenital cataract, glaucoma or other ocular anomalies. Further exclusions were infants with congenital heart, lung or other systemic disease and dysrhythmia.

Twenty age- and gender-matched patients were selected from among the patients who were referred for evaluation of an ROP screening and who did not receive any treatment. They were found to have normal intra-cardiac structural anatomy and function.

In this period, 67 medical records were reviewed. Among them, four patients were treated with combined therapy, six received other anti-VEGF agents, two were treated at a different centre, three had ocular or systemic anomaly, and one patient had stage 4 ROP. These 16 patients were excluded from the study (Fig. 1).

Thirty-one infants with a history of prematurity who underwent treatment for ROP were selected for the patient groups, and 20 infants diagnosed with ROP but who did not need any treatment were selected as the control group. Infants with similar demographic features (age, gender, gestational age, birth weight) were involved in this study.

A total of 31 premature infants with ROP and 20 premature infants without ROP were included in this study. They were divided into three groups: the LPC group included 15 infants (mean age: 17 ± 4.4 months) who received diode laser photocoagulation; and the IVA group included 16 infants (mean age: 14.4 ± 4.9 months) who received only a single dose of intravitreal injection of aflibercept (1 mg/0.025 ml) as the primary treatment for ROP; and 20 infants constituted the control group (mean age: 14.5 ± 2.8 months).

Height, weight, birth weight, gestational age and heart rate of the infants were recorded in both patient groups. Ten minutes after calming down in the room and while the infants were held in their parents’ laps, a validated oscillometric device (Omron HEM 907; Omron Healthcare, Kyoto, Japan) was used to measure systolic and diastolic blood pressure in the right arm with an appropriate cuff size covering two-thirds of the upper arm.

Fig. 1. Flow chart of the study population.
Laser ablations were performed with an 810-nm diode laser (IRIDEX; Oculeight SL, Mountain View, CA, USA) using a 28-day condensing lens. The laser settings were arranged to a power ranging between 150 and 250 mW with a duration of 200 ms and an interval of 200 s, so that a moderately white laser burn could be achieved. All patients received intravitreal aflibercept (Eylea®, Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA) 1 mg/0.025 ml in the operating room under sterile conditions with topical anaesthesia, using 0.5% proparacaine hydrochloride (Alcaine; SA Alcon-Couvreur NV, Puurs, Belgium) and ketamine sedation. All the treatments were performed by the same specialist (EAS).

Standard two-dimensional, M-mode, pulsed-Doppler and tissue Doppler echocardiographic examinations were performed with the S5® cardiac ultrasound system (GE Medical Systems; Horten, Norway) and a 6-MHz transducer. Simultaneous echocardiographic recordings were obtained. One echocardiographer (blinded to the patients’ clinical and laboratory data) interpreted each echocardiographic examination independently. All the patients were examined while at rest in the supine position and images were taken from the third or fourth intercostal space. The measurements were recorded according to the American Society of Echocardiography guidelines. Three values were recorded for each examination and the average of the values was used.

The examination consisted of two-dimensional, M-mode and pulsed- and continuous-wave Doppler velocities of the cardiac valves and tissue Doppler imaging (TDI) of the ventricles. Left ventricular (LV) dimensions, shortening fraction, ejection fraction, and mitral (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were measured using the standard M-mode technique. TAPSE and MAPSE were measured in an M-mode examination in the apical four-chamber view during systole, at the junction of the right and left ventricle with the tricuspid and mitral valve, and expressed in mm.

Pulsed Doppler measurements were performed with the transducer from the apical four-chamber view. The LV inflow pattern at the tips of the mitral valve provided peak early (E) and late (A) filling velocities and the E/A ratio was determined. LV and right ventricular (RV) tissue Doppler echocardiographic evaluations were performed from the apical four-chamber position by placing the pulsed-wave Doppler beam on the part of the mitral annulus that was closest to the LV lateral wall and inter-ventricular septum for the left ventricle, and on the part of the tricuspid annulus that was closest to the RV lateral wall for the right ventricle.

Peak systolic (S), early diastolic (E') and late diastolic (A') myocardial velocities at the basal segments of the lateral mitral annulus, septal mitral annulus and tricuspid annulus were determined using TDI. The isovolumetric contraction time (interval from the end of the A’ wave to the beginning of the S’ wave) and the isovolumetric relaxation time (interval from the end of the S’ wave to the beginning of the E’ wave) were measured on TDI for the lateral mitral annulus, septal mitral annulus and tricuspid annulus.

The following formula was used with a view to calculating the myocardial performance index (MPI):

$$\text{MPI} = \frac{\text{IVCT} + \text{IVRT}}{\text{ET}}$$

where IVCT = isovolumetric contraction time, IVRT = isovolumetric relaxation time and ET = ejection time (defined as the duration of the S’ wave). All values used for analysis represented the average of three consecutive cardiac cycles, with the exception of patients with dysrhythmia, in whom three-beat averages were obtained.

M mode of the ascending aorta was obtained above 2–3 cm from the aortic valve to calculate arterial wall stiffness indices, and systole (AoS) and diastole (AoD) measurements were averaged from five consecutive heartbeats. Aortic strain (AS), aortic distensibility index (DI) and aortic stiffness index (SI) were calculated from the following formulae:15

$$\text{AS} (%) = \frac{(\text{AoDS} - \text{AoDD})}{\text{AoDD}} \times 100$$

$$\text{SI} = \frac{\ln(SBP/DBP)}{(\text{AoDS} - \text{AoDD})/\text{AoDD}}$$

$$\text{DI (cm²/dynes} \times 10^4) = \frac{\text{AoDS} - \text{AoDD}}{(\text{AoDD}/(\text{SBP} - \text{DBP})) \times 2}$$

where SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg), AoDS = aortic diameter in systole (mm), AoDD = aortic diameter in diastole (mm), ln = natural logarithm.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (version 24.0, SPSS, Inc). Normally distributed data are presented as mean and standard deviation (SD), and non-parametric data are presented as median and ranges. Data obtained by echocardiography were compared between the three groups using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests, depending on the distribution of data. An overall p-value of less than 0.05 was considered to show a statistically significant result.

Results

The demographic data of the studied population are presented in Table 1. No significant differences were found between the groups in terms of age at enrollment, gender, gestational age, birth weight and weight at enrollment. There were no statistically significant differences between the patient groups and the control group in terms of systolic or diastolic blood pressure and heart rate.

The mean for gestational age (GA) of the patients was found to be 29.8 ± 2.7 weeks (range 24–35) in the LPC group, 29.3 ± 2.9 weeks (24–34) in the IVA group, and 29.5 ± 2.8 weeks (25–36) in the control group. The mean for birth weight (BW) of the patients was found to be 1,464 ± 451 g (730–2,500) in the LPC group, 1,279 ± 320 g (720–1,950) in the IVA group, and 1,352 ± 394 g (770–2,450) in the control group. The mean age was 17 ± 4.4 months for the patients in the LPC group, 14.4 ± 4.9 months for the patients in the IVA group, and 14.5 ± 2.8 months for the patients in the control group (Table 1). The mean echocardiographic evaluation time was 12.9 ± 2.3 months following the injection of aflibercept, and 13.2 ± 2.8 months after LPC treatment.

All infants in the groups had favourable anatomical outcomes after treatment for ROP.

There were no statistically significant differences between the groups in LV M-mode diameters and function (ejection fraction and fractional shortening). M-mode measurements are shown in...
Table 2. From the Doppler parameters, tricuspid E-wave values were increased significantly in the treatment groups rather than in the control group ($p = 0.037$), and in comparison between the treatment groups, tricuspid E-wave values were increased significantly in the IVA group ($p = 0.001$). Comparison of the other standard trans-mitral and tricuspid Doppler parameters yielded similar E wave, A wave and E/A ratio for the three groups. TAPSE measurements were also similar between the patient and control groups. MAPSE values were reduced in the treatment groups but not in the control group ($p = 0.002$); in addition, there were no significant differences between the treatment groups ($p = 0.175$).

Comparison of TDI parameters measured from the lateral mitral annulus (m) demonstrated similar S’, E’ and A’ velocities; E/E’ ratios; ejection time and isovolumetric contraction time; isovolumetric relaxation time; and myocardial performance index among the three groups (Table 3). The treatment groups

Table 3. Conventional and tissue Doppler echocardiographic parameters of the study groups

<table>
<thead>
<tr>
<th>M-mode measurements</th>
<th>Group 1 (LPC: n = 15)</th>
<th>Group 2 (IVA: n = 16)</th>
<th>Controls (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSd (mm)</td>
<td>0.54 ± 0.09</td>
<td>0.51 ± 0.06</td>
<td>0.52 ± 0.04</td>
<td>0.656</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>0.56 ± 0.09</td>
<td>0.6 ± 0.08</td>
<td>0.54 ± 0.04</td>
<td>0.192</td>
</tr>
<tr>
<td>LVMI (mm)</td>
<td>2.58 ± 0.25</td>
<td>2.5 ± 0.36</td>
<td>2.57 ± 0.23</td>
<td>0.150</td>
</tr>
<tr>
<td>LVMI (mm)</td>
<td>1.59 ± 0.19</td>
<td>1.5 ± 0.19</td>
<td>1.51 ± 0.13</td>
<td>0.249</td>
</tr>
<tr>
<td>LVPWd (mm)</td>
<td>0.43 ± 0.04</td>
<td>0.45 ± 0.06</td>
<td>0.43 ± 0.04</td>
<td>0.584</td>
</tr>
<tr>
<td>EF (%)</td>
<td>70.9 ± 3.6</td>
<td>71.9 ± 4.2</td>
<td>72.8 ± 3.96</td>
<td>0.466</td>
</tr>
<tr>
<td>FS (%)</td>
<td>38.5 ± 3.1</td>
<td>39.6 ± 3.8</td>
<td>40.3 ± 4.1</td>
<td>0.535</td>
</tr>
<tr>
<td>MAPSE (cm)</td>
<td>10.2 ± 0.56</td>
<td>10.3 ± 0.99</td>
<td>11.1 ± 1.3</td>
<td>0.020*</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>17.1 ± 1.21</td>
<td>16.3 ± 2.2</td>
<td>16.4 ± 1.58</td>
<td>0.661</td>
</tr>
</tbody>
</table>

Data are presented as the mean values ± SD.

One-way analysis of variance (ANOVA) or Kruskal-Wallis tests: *p < 0.05 considered statistically significant.

Table 4. Comparison of aortic elasticity parameters of the study groups

<table>
<thead>
<tr>
<th>Aortic elasticity parameters</th>
<th>LPC group (n = 15)</th>
<th>IVA group (n = 16)</th>
<th>Controls (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elasticity parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic strain</td>
<td>16.2 ± 4.4</td>
<td>16.7 ± 3.9</td>
<td>22.6 ± 4.5</td>
<td>0.013*</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>3.4 ± 0.7</td>
<td>3.6 ± 0.6</td>
<td>2.2 ± 0.3</td>
<td>0.036*</td>
</tr>
<tr>
<td>Distensibility index</td>
<td>8.2 ± 1.6</td>
<td>8.0 ± 1.8</td>
<td>11.6 ± 2.4</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

Data are presented as the mean values ± SD.

One-way analysis of variance (ANOVA) or Kruskal-Wallis tests: *p < 0.05 considered statistically significant.

(IVA and LPC) had significantly higher ejection time and isovolumetric relaxation time, and lower E’ velocity, measured at the septal part of the mitral annulus, than the control group ($p < 0.001$), whereas S’ and A’ velocity, isovolumetric contraction time and MPI were similar. In addition, A’ velocity derived from the lateral tricuspid annulus was significantly higher in the treatment groups than in the control group ($p = 0.007$), whereas S’ and E’ velocity, ejection time, isovolumetric contraction time, isovolumetric relaxation time and MPI were similar. On the other hand, A’ velocity measured from the lateral tricuspid

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>LPC group (n = 15)</th>
<th>IVA group (n = 16)</th>
<th>Control (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>17.4 ± 4.8</td>
<td>14.4 ± 4.9</td>
<td>14.5 ± 2.8</td>
<td>0.257</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (26.7)</td>
<td>9 (56.3)</td>
<td>8 (40)</td>
<td>0.245</td>
</tr>
<tr>
<td>Female</td>
<td>11 (73.3)</td>
<td>7 (43.8)</td>
<td>12 (60)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.1 ± 1.4</td>
<td>9.6 ± 2.1</td>
<td>9.86 ± 0.3</td>
<td>0.743</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>78.2 ± 6.1</td>
<td>78.1 ± 10.2</td>
<td>78.3 ± 0.57</td>
<td>0.999</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>29.8 ± 2.7</td>
<td>29.3 ± 2.9</td>
<td>29.5 ± 2.8</td>
<td>0.641</td>
</tr>
<tr>
<td>BW (g)</td>
<td>1464 ± 451</td>
<td>1279 ± 320</td>
<td>1332 ± 394</td>
<td>0.196</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>127.5 ± 14.9</td>
<td>137.7 ± 20.8</td>
<td>139.8 ± 11.9</td>
<td>0.208</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>84 ± 9.7</td>
<td>90 ± 6.7</td>
<td>86 ± 9.0</td>
<td>0.971</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>(70–102)</td>
<td>(80–105)</td>
<td>(72–102)</td>
<td></td>
</tr>
<tr>
<td>PMA at treatment (weeks)</td>
<td>33.5 ± 1.66</td>
<td>35.5 ± 1.64</td>
<td>36.5 ± 1.64</td>
<td>0.972</td>
</tr>
<tr>
<td>Time of echo (months)</td>
<td>13.2 ± 2.8</td>
<td>12.9 ± 2.3</td>
<td>13.2 ± 2.8</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Data are presented as the mean values ± SD.

Student’s t-test, Kruskal-Wallis test: p < 0.05 considered statistically significant.

annulus was not significantly different between the IVA and LPC groups.

DI and strain values were significantly lower in the treatment groups (LPC and IVA) than in the control group \((p < 0.05)\) (Table 4, Fig. 2). SI values were significantly higher in comparison with the control group \((p < 0.05)\) (Table 4). There was no statistically significant difference in aortic elastic parameters between the LPC and IVA groups.

Intra-observer reproducibility of aortic measurements was calculated after the re-evaluation of randomly selected images of 31 patients and 20 controls, and the results were 2.2 and 2.6%, respectively, for AoD, 3.1 and 3.4%, respectively, for AoS, 2.2 and 2.6%, respectively, for DI, and 3.4 and 3.1%, respectively, for SI.

Discussion

To the best of our knowledge, this is the first study that evaluates cardiac function detected by TDI echocardiography in premature children after ROP treatment with either anti-VEGF or LPC.

There has been great concern about these new agents due to their toxic side effects. There are reports of associated systemic side effects from systemic anti-VEGF agents used in cancer therapy, such as systemic hypertension, thromboembolism and LV dysfunction. They are also reported to have several side effects secondary to intravitreal anti-VEGF therapy, including systemic hypertension, congestive heart failure, proteinuria, arterial thromboembolic events, and systemic haemorrhage, which are linked to cardiovascular toxicities.16,17 On the other hand, Scott et al. published a commentary about anti-VEGF agents and the data suggested no difference in the risk of arteriothrombotic effect or death between anti-VEGF agents.18

A recent meta-analysis showed 23.6% incidence of all grades and a 7.9% incidence of high-grade hypertension after systemic bevacizumab treatment.19

In the present study, systolic and diastolic blood pressure and heart rate values in infants were found to be similar to those in the control group. Development of the blood vessels, vascular growth and organogenesis are extremely VEGF-dependent, as was demonstrated with early embryonic lethality caused by a deletion of the VEGF gene in the signalling pathway.20 VEGF also has a role in pathological blood vessel growth (macular degeneration), tumoural vasculature growth and normal physiological vasculature growth (menstrual cycle).21 The endothelium is an active endocrine organ secreting many cytokines and growth factors and interacting with cells that affect the function of many organs such as the heart, kidneys, liver and brain.

After the introduction of intravitreal VEGF treatment, these agents now have a key role in the treatment of ROP. Compared to conventional laser therapy, anti-VEGF agents have some advantages. Although conventional laser therapy led to a persistent destruction of the peripheral retina, it was shown that the development of peripheral retinal vessels continued after the treatment with intravitreal anti-VEGF agents. Due to their ease of use, these agents are preferred above other treatment options. Studies demonstrate that by allowing vasculature to develop further anteriorly and rapidly, intravitreal anti-VEGF treatment causes less visual loss and fewer refractive errors.22 In contrast to the requirement for general anaesthesia in laser therapy, these agents can be introduced only under topical anaesthesia.23 They allow the development of the posterior retina and foveal avascular zone and support the more immediate regression of ROP than laser treatment.24,25

Belcik et al. reported a significant increase in LV wall thickness and mass, a decrease in end-diastolic diameter in accordance with concentric hypertrophy, and they showed a reduction in thickening fraction and stroke volume over the five-week anti-VGEF treatment.26 In our study, we did not observe any statistically significant differences in LV M-mode measurements, ejection fraction or fractional shortening between the groups.

MAPSE is another useful evaluation parameter and reduced MAPSE implies impaired longitudinal function in patients with various cardiovascular diseases.27 Our study demonstrated lower MAPSE values in the IVA and LPC groups, and TAPSE values were similar. Advanced imaging techniques such as speckle-tracking methods are needed to prove that reduced MAPSE values show systolic dysfunction, because MAPSE provides only LV long-axis systolic performance, whereas other systolic parameters were in the normal range.

To assess ventricular diastolic function, Doppler data have an important role to depict distinct patterns of abnormality in ventricular filling, abnormal relaxation and restrictive filling. Abnormal relaxation is especially common in disorders producing myocardial hypertrophy. In such cases, atrioventricular early filling velocity is decreased and the atrial component of filling becomes potent.28

In our study, we observed statistically significant differences in only both ventricles ‘pulsed’ Doppler echocardiography parameters between the groups, except in E velocity derived from RV inflow. The IVA and LPC groups had significantly higher tricuspid E velocity than the control group. It is also known that during inspiration and apnoea, RV inflow velocities are significantly higher. Although the E wave represents the
early, rapid-filling period of diastole, higher E-velocity values of tricuspid inflow were more difficult to interpret than the impaired relaxation of the right ventricle alone without the E/A ratio change. 6

Due to such limitations on load conditions, heart rate and age, which may influence conventional Doppler parameters, TDI has a major potential in the diagnosis of diastolic ventricular dysfunction. 26 When diastolic ventricular relaxation is slowed, prolongation of the isovolumetric relaxation time and a slight increase in the systolic velocity can be observed.

The MPI is a more specific tissue Doppler parameter for diastolic dysfunction. In their animal experiment after the anti-VEGF therapy, using endocardial TDI, Belcik et al. reported a mild decrease in S′ and E′ velocities that were not statistically significant. 27 Various paediatric and adult studies have described subclinical impairment of systolic function with changes in MPI, isovolumetric contraction and relaxation time. 28 In our study, decreased E′ velocity and increased ejection time and isovolumetric relaxation time derived from the septal mitral annulus may indicate a subclinical systolic dysfunction of both ventricles.

Despite the significant differences in these parameters between the three groups, we demonstrated a statistically significant difference of only E velocity of RV inflow values in the comparison between the IVA and LPC groups. Therefore it is also possible that diastolic impairment may be due to retinopathy-related co-morbidities in the treatment groups, rather than to secondary treatment of retinopathy.

Arterial stiffness is an important predictor of cardiovascular events, and non-invasively calculated values showed a powerful correlation with invasive measurements. 29 In a recent study, the relationship with anti-angiogenic drugs and increased aortic stiffness was demonstrated in an adult population with cancer, independent of blood pressure changes. 30 We found that the aortic elastic indices in the treatment group were significantly different from the control group. Moreno et al. showed that an increase in arterial stiffness appeared after only two weeks and decreased in the patients whose treatment was ended. 30 On the other hand, there was no significant difference in aortic elastic indices between the LPC and IVA groups; however, higher vascular stiffness values would make it possible to determine whether an increase in this parameter was the direct result of aflibercept or due to hypertension and only indirectly caused by the drug.

Currently, little is known about the systemic effects of intraocular anti-VEGF injections. We have limited knowledge and experience, especially in intravitreal aflibercept in ROP treatment, and there are only a few reports with small series in the literature. In the present study, we evaluated both the cardiac effects of aflibercept and laser photocoagulation treatment in infants diagnosed with ROP in comparison to the untreated infant group. Using echocardiography, we demonstrated some differences that point to subtle diastolic dysfunction but we could not show any differences in aortic elastic parameters between IVA and LPC treatment compared with controls.

**Limitations**

The small sample size of each group and the retrospective, single-centre, cross-sectional design constitute the main limitations of our study. Another limitation is that the patients’ echocardiographic assessment should have been done before the treatment because it is important to obtain baseline strain measurements to observe subsequent changes after anti-VEGF treatment. Because the link between the agent and the cardiovascular outcomes could not be confirmed clearly, more observational studies are needed to confirm cardiovascular safety during long-term therapy.

**Conclusion**

This study assessing ventricular function using TDI demonstrated diminutive diastolic changes in the cardiac parameters measured by echocardiography. The ultimate future goal would be to identify these asymptomatic infants accurately with speckle-tracking echocardiography, using a more sensitive imaging method. Adequately powered, well-designed clinical trials are necessary to clearly define the cardiovascular effects of these anti-VEGF agents in infants.

**References**


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