Pediatric Dermatology Vol. 32 No. 4 468–475, 2015

Color Doppler Ultrasound Follow-Up of Infantile Hemangiomas and Peripheral Vascularity in Patients Treated with Propranolol

Ana M. Kutz, M.D.,* Ligia Aranibar, M.D.,* Nelson Lobos, M.D.,* and Ximena Wortsman, M.D.†

**Department of Dermatology, Hospital Clinico U. Chile, Faculty of Medicine, University of Chile, Santiago, Chile,*
†*Department of Radiology and Department of Dermatology, Institute for Diagnostic Imaging and Research of the Skin and Soft Tissues, Clinica Servet, Faculty of Medicine, University of Chile, Santiago, Chile*

Abstract

Background: Infantile hemangiomas (IHs) are the most common vascular tumors in childhood. Diagnosis of IHs is usually clinical, however, to determine the actual dimensions of the lesion or the anatomic changes that occur during its evolution and treatment, a color Doppler ultrasound (CDU) examination can be performed. To date, there are few publications that assess the sonographic response to propranolol in IHs, and to our knowledge, none that consider simultaneous evaluation of both intralesional and normal peripheral blood vessels in these cases.
Objective: Evaluation of the anatomic effect of propranolol in IHs and peripheral blood vessels using CDU.
Methods: A cohort study was performed in 10 pediatric patients with a diagnosis of IH in whom systemic therapy with propranolol was indicated. The patients underwent a baseline and 3-month follow-up CDUs of the tumor and the main peripheral vessels of the right upper extremity.
Results: The group was composed of 7 (70%) girls and 3 (30%) boys. The average CDU decrease in size of the longitudinal axis was 11%; of the transverse axis, 24%; tumor thickness, 30%; and intralesional vessel thickness, 46%. Hemangioma volume measured by CDU decreased an average of 51%. The thickness of the peripheral vessels did not change significantly between the baseline and 3-month follow-up CDUs.
Conclusion: CDU permits noninvasive quantification of the changes in IHs and peripheral vessels in patients receiving propranolol therapy. In our cohort of cases there was a significant reduction in tumor volume; however, peripheral vascularity was not significantly affected.

Address correspondence to Ximena Wortsman, M.D., Department of Radiology and Department of Dermatology, Institute for Diagnostic Imaging and Research of the Skin and Soft Tissues, Clinica Servet, Faculty of Medicine, University of Chile, Lo Fontecilla 201, of 734, Las Condes, Santiago, Chile, or e-mail: xworts@yahoo.com.

DOI: 10.1111/pde.12596

Infantile hemangiomas (IHs) are benign proliferations of endothelial cells and the most common vascular tumors in childhood (1–6). They can be clinically classified as superficial, deep, and mixed according to the location of the vascular proliferation in the dermis, hypodermis, or both (1,7–10). Although the volume and depth of IHs can be estimated on clinical examination, imaging can confirm and augment the clinical impression, especially with regard to depth.

IH evolve in three sequential phases: proliferaton, stabilization, and involution. Although changes in the superficial component may be readily apparent to clinicians, the extent of the deep component cannot be accurately appreciated using inspection and palpation.

The extent of the deep component may be of importance in mixed or deep hemangiomas, in which the involvement of critical structures such as the orbit, glands, cartilage, or muscle may increase the risk of complications or poor cosmetic outcome. Therefore color Doppler ultrasound (CDU) can be performed to assess the extent of the lesion or the anatomic changes that occur during its evolution and treatment (11). This technique is usually considered the gold standard for evaluating most vascular anomalies noninvasively (11–20).

CDU is a widely available imaging method that allows evaluation of the skin and deeper structures as well as vascular perfusion patterns (12,15). It also allows us to distinguish between hemangiomas, vascular malformations, and other vascular tumors. This differentiation is critical for adequate management and correct assessment (12,14–17). There are reports on the use of ultrasound in hemangiomas for diagnosis and to assess changes in tumors during their natural evolution or treatment (14,15,19,20).

On sonography, IHs can vary in echogenicity and vascularization depending on their phase of evolution (14–18). During the proliferation phase, they are seen as hypoechoic, ill-defined, hypervascular solid masses. They usually have arterial and venous flow and sometimes arteriovenous shunts (14,15). During involution, their echogenicity is heterogeneous, showing mixed hypoechoic-hypervascular areas and hyperechoic-hypovascular areas. Totally involuted hemangiomas appear as hyperechoic masses, due to adipose and fibrous tissue infiltration, with hypovascularity (14,15,18). CDU has a reported diagnostic sensitivity of 84% and a specificity of 98% for the evaluation of vascular lesions (14,16,17).

Propranolol is considered to be first-line systemic treatment for IHs (21–28). Multiple studies have evaluated its clinical effectiveness and found adequate safety with excellent results (21–28). It seems to stabilize growth and accelerate involution of IHs, shortening the natural history, and acts during proliferation and involution (21,23,27).

Few reports have assessed the sonographic response of propranolol in IHs (19,27,28) and, to our knowledge, none have considered simultaneous evaluation of intralesional changes and changes in normal peripheral blood vessels. The objectives of this investigation were to evaluate the anatomic effect of propranolol in IHs and peripheral vessels through follow-up with CDU, to assess the correlation between the ultrasound and clinical findings, and to investigate the value of CDU as a tool in the follow-up of patients with IHs treated with propranolol.

MATERIAL AND METHODS

We performed a prospective cohort study of 10 sequentially selected patients younger than 4 years old with IHs who underwent baseline (T0) and 3-month follow-up (T1) CDUs of their lesions. In patients with multiple hemangiomas, the most representative, largest lesion was evaluated.

Inclusion and exclusion criteria for the study are described in Table 1. All patients received 2 mg/kg/day of propranolol divided into two doses. Patients were clinically evaluated at days 7 and 15 and then monthly. The clinical parameters included measurement of the hemangiomas in longitudinal and transverse axes, assessment of signs of involution, and secondary effects of propranolol. Longitudinal and transverse axes were measured using a flexible plastic ruler. The ethics committee at the institution where the children were clinically evaluated and where the ultrasound tests were performed approved the study.

TABLE 1. *Inclusion and Exclusion Criteria*

Inclusion criteria
Children with a diagnosis of infantile hemangioma (IH) confirmed by a dermatologist
IH with an indication for systemic treatment
Cardiologist consent to start treatment with propranolol
Signed informed consent by the guardian of the patient before entering the study protocol and color Doppler ultrasound examination
Exclusion criteria
Contraindications to the use of propranolol
Inability to follow the study protocol
Use of corticosteroids or other systemic treatments before propranolol
Previous use of a β-blocker (topical or systemic)

The CDU examination was performed using the same protocol described for studying localized lesions of the skin (12), although this evaluation included the hemangioma and peripheral vessels of the right upper extremity. Thus the right brachial artery and vein and right radial artery were studied. CDU was performed before initiation of treatment (T0) and at 3 months of treatment (T1). The sonographer obtained two sets of measurements in the hemangioma, one in the longitudinal and one in the transverse view (perpendicular axes), and recorded the measurements of the thicker vessels that resulted from three different locations and included the higher value (mm) for the study (Fig. 1). Thickness was considered as the distance between the two opposite outer layers of the vessel. We also measured the maximum thickness of the right brachial vessels (artery and vein) and the right radial artery in the longitudinal axis at the anterior aspect of the elbow and wrist, respectively. The maximum thickness of intralesional vessels in hemangiomas was measured on color Doppler and the maximum arterial peak systolic velocity was obtained from color Doppler spectral curve analysis. Because peripheral vessels are more easily detectable, their maximum thickness was measured on a gray scale and their maximum arterial peak systolic velocity was obtained from color Doppler spectral curve analysis (Fig. 2).

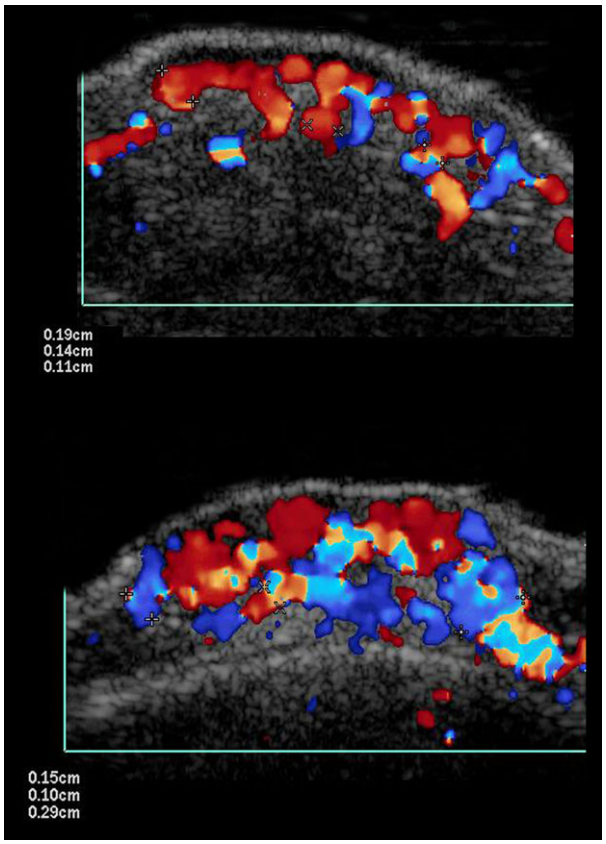

Figure 1. Examples of color Doppler ultrasound measurements of maximum thickness of the intralesional vessels in two cases with infantile hemangiomas (transverse axes). The measurements that have been selected for recording were 1.9 mm (top) and 2.9 mm (bottom).

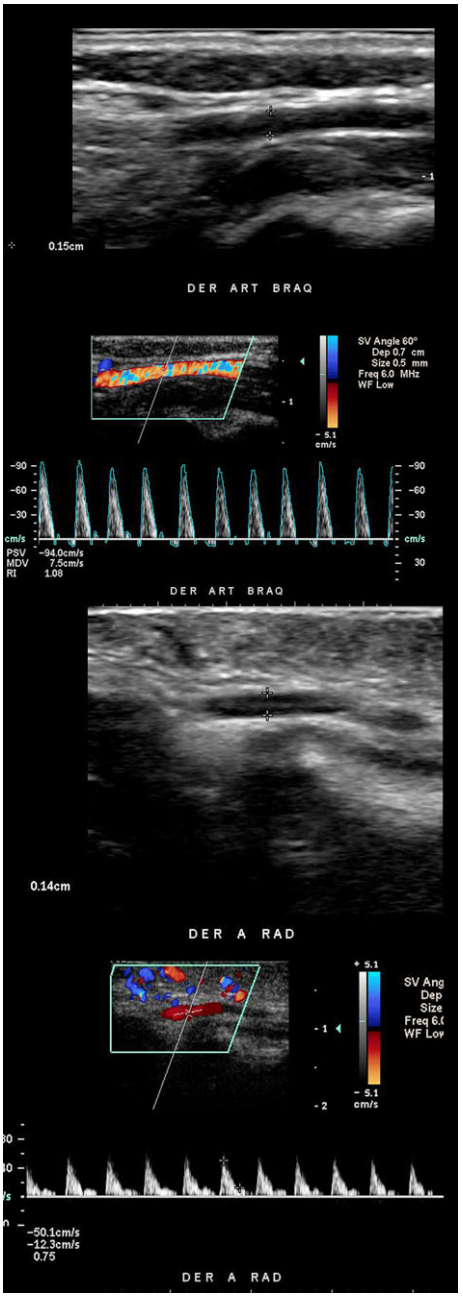

Figure 2. Sonographic measurements of maximum thickness and arterial peak systolic velocity of the brachial and radial arteries (gray scale and color Doppler ultrasound spectral curve analysis).

Ultrasound imaging was performed using an HDI 5000 (Philips Medical Systems, Bothell, WA) with a compact linear probe of variable frequency (7–15 MHz). The settings were as follows: musculoskeletal superficial, wall filter low, pulse repetition frequency (PRF) 1,000 Hz. Hemangioma volume was obtained using the following formula: longitudinal axis (cm) × transverse axis (cm) × thickness (cm) × $\pi/6$, with results expressed in cm^3.

After signed informed consent was obtained, chloral hydrate 50 mg/kg was orally administered for sedation 30 minutes before the CDU examination. Patients were monitored in the Department of Radiology using the modified Aldrete score (evaluation of activity, respiration, circulation [blood pressure], consciousness, and oxygen saturation) and discharged when the score was ≥9 (12). This low dosage of sedation was used to minimize artifacts derived from movement or crying. The same pediatric dermatologist performed all clinical evaluations and the same radiologist with experience in dermatologic ultrasound performed all CDU examinations.

Statistical Analysis

Data were analyzed using descriptive statistics. STATA 11.2 (StataCorp, College Station, TX) was used for general description and analysis. The values of the studied variables were compared between T0 and T1 using the Wilcoxon–Mann–Whitney test. A p-value <0.05 was considered to be statistically significant.

RESULTS

Ten patients entered the study protocol (7 [70%] girls, 3 [30%] boys). The clinical characteristics of the patients are described in Table 2. On CDU, all cases involved the dermis and hypodermis, and one case also included spreading of the hemangioma to the left parotid gland. A positive clinical response to treatment was observed in all patients, which included flattening, softening, and lightening of all lesions between T0 and T1 (Figs. 3–5).

Clinically, the mean dimensions of the longitudinal and transverse axes decreased by 25% and 26%, respectively, between T0 and T1. On CDU there was a mean decrease of 11% and 24% in the longitudinal and transverse axes, respectively. We did not observe adverse effects from sedation or propranolol in any of the patients.

Using CDU, a positive response to treatment was observed in all patients. Thus all hemangiomas showed a reduction in the studied parameters between T0 and T1. The sonographic volume of the hemangioma had a mean reduction of 51% and the thickness of the vessels within the hemangioma decreased by 46% between T0 and T1. Thus the mean thickness of IH vessels significantly decreased between T0 and T1 ($p < 0.001$). Changes observed in the peripheral vasculature regarding thickness and peak systolic velocity between T0 and T1 were statistically insignificant in each vessel.

When clinical and ultrasound responses were compared, a statistically significant difference was observed between clinical and ultrasound assessments of the longitudinal axis ($p = 0.01$), with a greater decrease in the clinical evaluations. No significant difference was observed between transverse axis measurements ($p = 0.25$). The mean percentage of clinical and CDU variations in parameters (T0–T1) are summarized in Table 3.

TABLE 2. *Clinical Characteristics of Infantile Hemangiomas (IHs)*

Characteristic	*n* (%)
Sex	
Female	7 (70)
Male	3 (30)
Gestational age	
Full term	9 (90)
Premature	1 (10
Birthweight	
Normal	9 (90)
Low	1 (10)
Age at initiation of treatment, mos	
1–12	8 (80)
13–24	1 (10)
≥25	1 (10)
Type of IH	
Superficial	–
Deep	1 (10)
Mixed	9 (90)
Number of IHs	
Single	8 (80)
Multiple	2 (20)
Location of single IH	
Head and neck	9 (43)
Trunk	1 (5)
Arms	3 (14)
Legs	6 (28)
Genitalia	2 (10)

DISCUSSION

To our knowledge, this study represents the first in the PubMed literature to evaluate and describe in depth the anatomic changes in a cohort of patients receiving propranolol at the lesional site of IHs and in peripheral blood vessels. This study showed that CDU is a

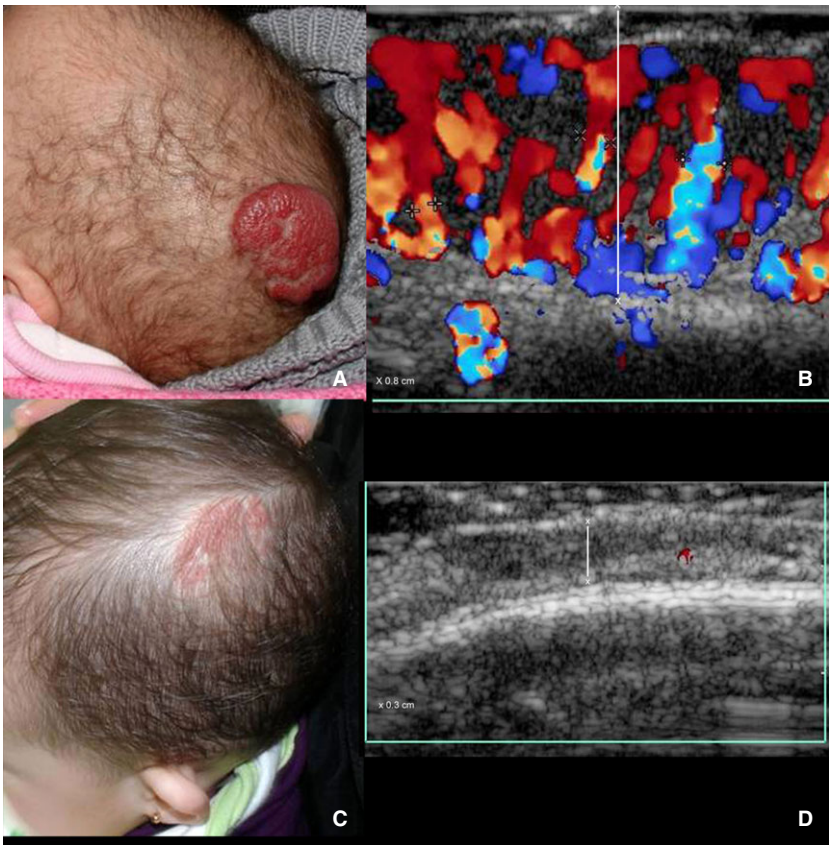

Figure 3. Hemangioma on the scalp. (**A**) Clinical evaluation before treatment. (**B**) Color Doppler ultrasound (CDU) evaluation before treatment shows hypervascularity within the lesion that involves the dermis and hypodermis. (**C**) Clinical follow-up at 3 months. (**D**) CDU follow-up at 3 months shows flattening and hypovascularity of the same lesion. Thickness (x) measurements are described in **B** and **D** (CDU longitudinal axes).

helpful tool that allows documentation of profound anatomic changes that occur during propranolol administration. All hemangiomas demonstrated a reduction of their volume, and this observation was positively correlated with the clinical outcome.

In 80% of patients, treatment was started before the first year of life, during the hemangioma's proliferative phase. In the other two cases, propranolol was started after the first year of life. A similar positive response was observed in both groups. On CDU, the greatest change was observed in tumor thickness (↓30%), thickness of blood vessels inside the hemangiomas (↓46%), and in hemangioma volume (↓51%), which noninvasively confirms the positive effect of propranolol on these dimensions of IHs that cannot be accurately measured on clinical examination.

The main mechanisms of propranolol action include vasoconstriction, inhibition of angiogenesis, and inducing apoptosis of endothelial cells (22,24). Being a β-blocker, propranolol inhibits the vasodilatation induced by catecholamines, generating vasoconstriction. In IHs, vasoconstriction of capillaries and intratumoral vessels induces a decrease in blood flow inside the lesion. These phenomena could explain the change in color observed clinically and the decrease in the thickness of blood vessels inside the tumor associated with a minimal increase in their arterial peak systolic velocity (↑1%) observed on CDU. These findings are similar to those obtained in the study of Talaat et al (28), in which a decrease in IH thickness (↓50%, $p < 0.01$), associated with an increase in the resistance index of intratumoral vessels (↑50%, $p < 0.01$), was observed through CDU. In the study of Bingham et al (27), a significant reduction of blood vessel density inside the hemangioma ($p < 0.01$) was observed in patients treated with propranolol.

In turn, β-receptor blockade induces apoptosis of endothelial cells through alteration of apoptosis inhibition. This could explain the softening, thinning, and decrease in volume of lesions seen clinically and on ultrasound in this and previously published studies

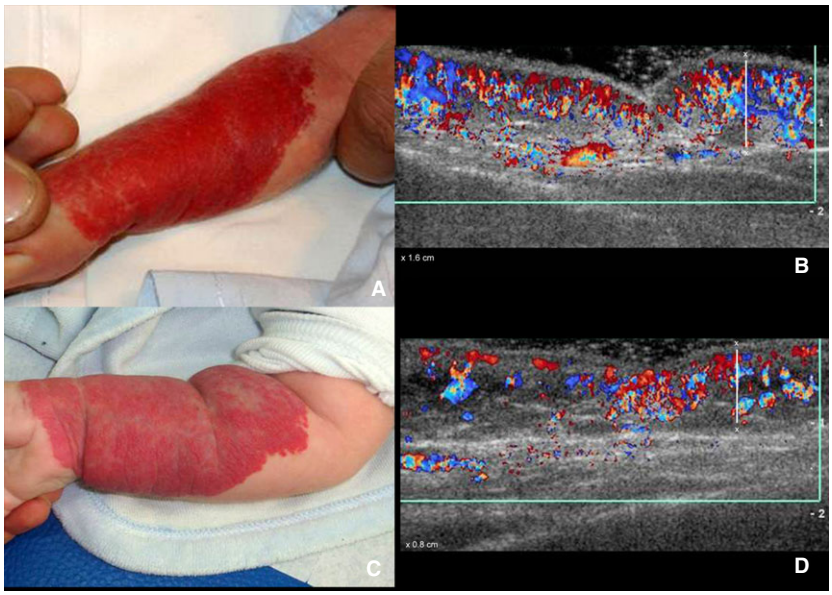

Figure 4. Hemangioma on the forearm. (**A**) Clinical evaluation before treatment. (**B**) Color Doppler ultrasound (CDU) evaluation before treatment shows diffuse hypervascularity within the lesion that affects the dermis and hypodermis. (**C**) Clinical follow-up at 3 months. (**D**) CDU follow-up at 3 months demonstrates isolated areas of hypervascularity within the same lesion. Thickness (x) measurements are shown in **B** and **D** (CDU longitudinal axes).

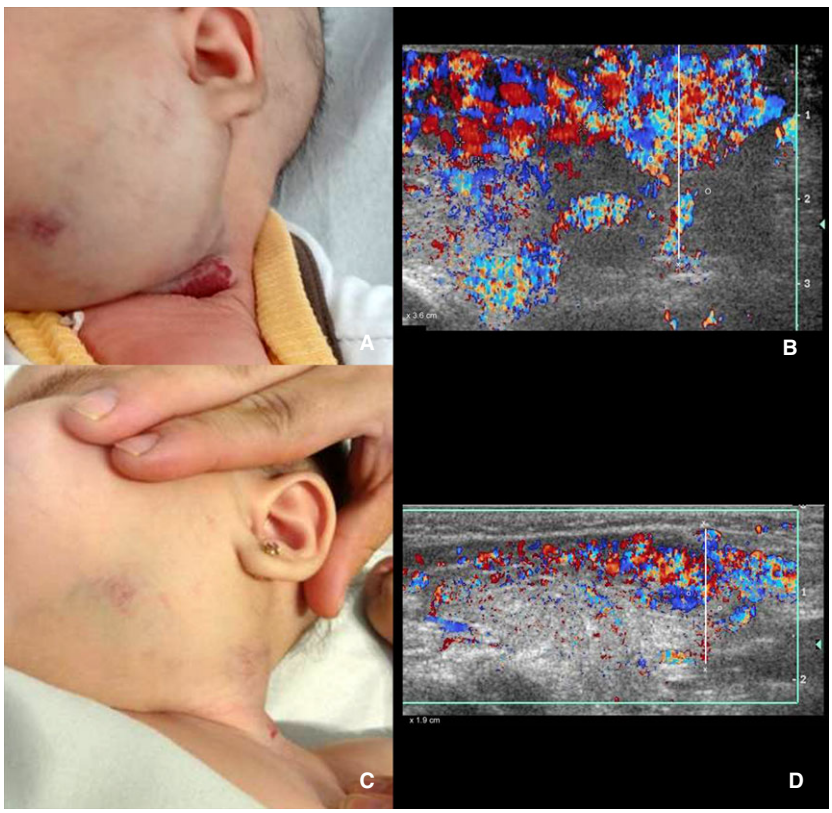

Figure 5. Hemangioma on the face and neck. (**A**) Clinical evaluation before treatment. (**B**) Color Doppler ultrasound (CDU) evaluation before treatment demonstrates diffuse lesional hypervascularity and involvement of the left parotid gland. (**C**) Clinical follow-up at 3 months. (**D**) CDU follow-up at 3 months shows decreased hypervascularity. Thickness (x) measurements and the parotid gland (o) are shown in **B** and **D** (CDU transverse axes).

TABLE 3. *Mean Percentage of Clinical and Sonographic Variation of Parameters Between T0 and T1*

Measurement	Clinical %	CDU %
Longitudinal axis, IH	↓25	↓11
Transverse axis, IH	↓26	↓24
Thickness, IH	n/a	↓35
Vessel thickness, IH	n/a	↓46
Arterial peak systolic velocity, IH	n/a	↑1
Thickness, brachial artery	n/a	↑5
Arterial peak systolic velocity, brachial artery	n/a	↓11
Thickness, radial artery	n/a	↓2
Arterial peak systolic velocity, radial artery	n/a	↑9
Thickness, brachial vein	n/a	↑13
Volume	n/a	↓51

IH, infantile hemangioma; n/a, not applicable.

(19,27,28). In the study of Bingham et al (27), a 41% mean volume reduction was observed, a figure similar to that observed in our study (51%).

The percentage variation in the mean thickness of the peripheral blood vessels was less than 15%. We presume that this variation is part of the physiologic compliance of normal peripheral blood vessels in response to endogenous and environmental stimuli. Nevertheless, this study shows that there was no significant effect on peripheral vascularity in patients using propranolol.

When clinical and CDU longitudinal axis assessments were compared, a statistically significant difference was observed ($p = 0.01$). This significant variation can possibly be explained as observer error in the clinical measurements, because the elevation of the lesion does not affect the longitudinal axis measurements on the images, which can be obtained more precisely and reproducibly. Similar results were obtained in the study of Bingham et al (27), with clinical measurements showing a greater change than ultrasound.

Because most IH growth can occur before 5 months of age (29), and maximum size can be reached at 8 months (30), this cohort may not be representative of the typical age of patients that clinicians treat. Indeed, further research should be performed to prove the clinical usefulness of CDU in the management of IHs at all ages, but CDU has the capability of measuring anatomic parameters at any age.

In the case of deep and mixed IHs, it may be difficult to measure the response objectively because the deep component cannot be visualized completely. In contrast, as seen in our group of patients, hypodermal or deep structure involvement and changes over time can be easily detected on sonography. Moreover, variations in the surface of the skin may not always translate into how the deepest component of the lesion is responding to treatment (27,28). Therefore CDU can be a useful tool to evaluate the full extent of the lesion, deep layer involvement, intralesional vascularity, and response to treatment, giving objective measurements of the changes that occur inside the lesion and potentially aiding in therapeutic decisions.

The main limitations of this study include the small number of subjects, the inability to have control lesions not exposed to propranolol because treatment is systemic, and the short period of time between evaluations, only 3 months. Nevertheless, despite the short period of time, significant anatomic changes were detected on CDU. Another limitation is that spontaneous involution of IHs cannot be separated from the effect of treatment, especially in patients older than 1 year, although the mean volume reduction of 51% within 3 months, especially in the younger cohort, strongly suggests a therapeutic effect.

Hemangiomas are generally diagnosed and followed by clinical examination, supplemented by digital photography, but these methods are not always suited for evaluating the extent of the deep component of hemangiomas or the underlying tissues affected. This could have been clinically significant in some of our cases, all of whom had subcutaneous involvement and one of whom had parotid involvement. Although the clinical utility of CDU in a broader range of IHs remains to be determined, our results suggest that this noninvasive technique may be a useful tool in clinical practice, particularly in cases with deep involvement or complicated IHs, and can have applicability in clinical trials and research.

CONCLUSION

CDU permits noninvasive quantification of changes in IHs and peripheral vessels in patients receiving propranolol therapy. In our cohort of cases there was a significant reduction in tumor volume, although peripheral vascularity was not significantly affected. In deep or complicated IHs, ultrasound can provide additional data that could influence clinical management.

REFERENCES

1. Almaraz RL, Gutiérrez JC, Bieler CB et al. Infantile vascular tumors. An Pediatr (Barc) 2010;72:143.e1–143.e15.

2. Restrepo R, Palani R, Cervantes LF et al. Hemangiomas revisited: the useful, the unusual and the new. Part 1: overview and clinical and imaging characteristics. Pediatr Radiol 2011;41:895–904.
3. Haggstrom AN, Drolet BA, Baselga E et al. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr 2007;150:291–294.
4. Dickison P, Christou E, Wargon O. A prospective study of infantile hemangiomas with a focus on incidence and risk factors. Pediatr Dermatol 2011; 28:663–669.
5. Hochman M, Adams DM, Reeves TD. Current knowledge and management of vascular anomalies I Hemangiomas. Arch Facial Plast Surg 2011;13:145–151.
6. Boye E, Olsen BR. Signaling mechanisms in infantile hemangioma. Curr Opin Hematol 2009;16:202–208.
7. Schwartz RA, Sidor MI, Musumeci ML et al. Infantile haemangiomas: a challenge in paediatric dermatology. J Eur Acad Dermatol Venereol 2010;24:631–638.
8. Holland KE, Drolet BA. Infantile hemangioma. Pediatr Clin North Am 2010;57:1069–1083.
9. Bruckner AL, Frieden IJ. Infantile hemangiomas. J Am Acad Dermatol 2006;55:671–682.
10. Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003;48:477–493.
11. Rossler L, Rothoeft T, Teig N et al. Ultrasound and color Doppler in infantile subglottic haemangioma. Pediatr Radiol 2011;41:1421–1428.
12. Wortsman X, Wortsman J. Clinical usefulness of variable-frequency ultrasound in localized lesions of the skin. J Am Acad Dermatol 2010;62:247–256.
13. Resalkar DD, Chu WC, Cheng FW et al. An institutional review of pediatric haemangiomas: prevalence, imaging features, and outcomes. Hong Kong Med J 2010;16:334–340.
14. Paltiel HJ, Burrows PE, Kozakewich HP et al. Soft tissue vascular anomalies: utility of US for diagnosis. Radiology 2000;214:747–754.
15. Wortsman X. Common applications of dermatologic sonography. J Ultrasound Med 2012;31:97–111.
16. Dubois J, Patriquin HB, Garel L et al. Soft-tissue hemangiomas in infants and children: diagnosis using Doppler sonography. AJR Am J Roentgenol 1998; 171:247–252.
17. Dubois J, Alison M. Vascular anomalies: what a radiologist needs to know. Pediatr Radiol 2010;40:895–905.
18. Navarro OM. Imaging of benign pediatric soft tissue tumors. Semin Musculoskelet Radiol 2009;13:196–209.
19. Wester ST, Johnson TE. Echographic evidence of regression of a periocular infantile capillary hemangioma treated with systemic propranolol. Ophthalmic Surg Lasers Imaging 2011;42:18–21.
20. Navarro OM. Soft tissue masses in children. Radiol Clin North Am 2011;49:1235–1259.
21. Sans V, de la Roque ED, Berge J et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009;124:423–431.
22. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol 2010;163:269–274.
23. Sanchéz-Carpintero I, Ruiz-Rodriguez R, López-Gutiérrez JC. Propranolol in the treatment of infantile hemangioma: clinical effectiveness, risks and recommendations. Actas Dermosifiliogr 2011;102:766–779.
24. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics 2011;128:259–266.
25. Drolet BA, Frommelt PC, Chamlin SL et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131:128–140.
26. Schupp CJ, Kleber JB, Gunther P et al. Propranolol therapy in 55 infants with hemangioma: dosage, duration, adverse effects and outcome. Pediatr Dermatol 2011;28:640–644.
27. Bingham MM, Saltzman B, Vo NJ et al. Propranolol reduces infantile hemangioma volume and vessel density. Otolaryngol Head Neck Surg 2012;147:338–344.
28. Talaat AA, Elbasiouny MS, Elgendy DS et al. Propranolol treatment of infantile hemangioma: clinical and radiologic evaluations. J Pediatr Surg 2012;47:707–714.
29. Chang LC, Haggstrom AN, Drolet BA et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008;122:360–367.
30. Bauland CG, Lüning TH, Smit JM et al. Untreated hemangiomas: growth pattern and residual lesions. Plast Reconstr Surg 2011;127:1643–1648.