ART-VENA: Retinal Vascular Caliber Measurement

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Abstract. The size of retinal vascular caliber in eye fundus images is a fundamental diagnosis parameter in the study of systemic vascular pathologies, like arterial hypertension or arteriosclerosis. ART-VENA is a semiautomatic system to measure the retinal vascular caliber. From the medical point of view, its repeatability (coefficients of variation under 1.5%) turns it into a reliable tool to objectify vascular changes which previously depended on the observer's subjectivity.

1 Introduction

The automatic computerized analysis of blood vessels from medical images has played, in the last years, an important role in many clinical and research studies on a large number of diseases. The presence of noise, the variability of the anatomical fundus and the low and changing contrast of vessels in many image modalities make the reliable vessel detection a difficult task. Therefore, automatic detection becomes a key starting point. Particularly, retinal vascular caliber is a fundamental parameter in the study of systemic vascular pathologies, like arterial hypertension or arteriosclerosis. Vessels present in the eye are the first to manifest the symptoms of the arterial hypertension [1]. The abnormalities in the retinal vascularization can reflect the degree of damage provoked by these diseases, an aspect that decisively influences the development of brain and cardiovascular complications.

Before the analysis of the alterations in the retinal vascular caliber due to these systemic diseases, it is necessary to study the variations caused by age in normal patients. This is a controversial topic in the medical field. Several classic authors have observed that old age is directly related to arteriolar caliber alterations in normal patients, though there is not an agreement on the causes of this relation [2, 3, 4]. On the

contrary, other authors do not find retinal vascular caliber changes in old patients [5, 6, 7]. It has to be taken into account that these descriptions are highly subjective.

It would be very useful, therefore, to develop an effective and reproducible method to objectively evaluate the retinal vascular caliber. This objective measure could definitively determine whether observed alterations are related to age in normal patients, and, in case that this relation exists, it could distinguish between these changes and those originated by general diseases, like arterial hypertension or arteriosclerosis.

1.1 Retinal Vascular Caliber Measurement

Retinal vascular caliber measurement has been a widely studied subject in the area of Ophthalmology. In the middle of the 20th century many works begin to be carried out with the aim of predicting, from these measures, the state and prognosis of diseases like arterial hypertension or arteriosclerosis.

In a first stage, from the 50's to the 80's, vascular width measurement from eye fundus photographs was manually made by means of retinal image projections [8, 9, 10, 11, 12, 13]. Several works prove that these measures can be performed with an error inferior to 3μm at the retina level [11, 14]. Obtained results turned out to be contradictory in many cases, probably as a result of the high subjectivity of the analysis and the lack of statistical studies on the acquired data. Brinchmann-Hansen and col. realized the first studies statistically analyzed [15]. They found the caliber of three arteries and three veins, achieving a coefficient of variation of 3.6 %. Posterior studies reach a decrease in the coefficient of variation down to 2.3% [16, 17].

At the end of the 80's decade, computerized vessel measurement techniques appeared. In the main, these techniques use the computer just to visualize and store the data. The spotting of blood vessel boundary points is made manually by the specialist. Some works reached coefficients of variation between 0.6% and 4.0%, with mean value around 2.2% [18, 19, 20]. Especially important are the works of Polak and col. on the reproducibility and sensitivity of the Zeiss' analyzer of retinal vessels (Zeiss RVA) [21]. In size measurements of arteries and veins they obtained coefficients of variation values of 1.3% and 2.6% respectively. These data place the Zeiss' vessel analyzer among the reference commercial instruments in this area.

1.2 Vessel Detection

Automatic detection of vessels has involved much research in the field of digital image processing during the last years. Many works in the literature address the problem of automatic detection of blood vessels in various domains.

Tracking of vessels has been one of the more studied techniques in recent years [22, 23]. In general, given a starting vessel contour point and one search direction, vessel tracking involves exploring the image to find other contour points. The criterion to define boundary points is based on the analysis of the pixel gray level values on a section that is orthogonal to the tracking direction. More sophisticated versions of this idea transform the problem of vessel contour detection in that of graph optimal

path search [24]. Other artificial intelligence or computer vision methods have been also proposed to obtain a complete automation of the detection procedure, exploiting in a more exhaustive way the available anatomical knowledge [25, 26].

The majority of the developed methods adopt boundary detection as the basic tool for vessel detection. Since vessel contours are usually smooth and fuzzy and the fundus is noisy, a number of authors have applied, as an initial strategy, the maximization of vessel enhancement. Some approaches are based on rotation invariant operators or linear morphological operators of suitable size and orientation, which are applied to the image to minimize noise [25, 27]. Alternative approaches involve image convolution with multiple filters per model, each of them designed to detect vessels of given size and orientation [28]. The main drawback to these methods is their high computational cost, which renders them practically unusable for on-line diagnosis assistance systems or systems requiring relatively short response times. Zana and Klein developed a vessel bifurcation detection method as a previous step to image registration [29]. Quek and Kirbas carried out a method for vessel extraction from angiographies based on wave propagation [30].

2 Retinal Vascular Caliber Measurement

The measurement method developed in this work is nearly completely automatic. The operator is initially required just to mark the optic nerve, though high accuracy is not necessary. Once this initial reference is set, the automatic sequence of detection and measurement of the vessels on the image starts. The method output is a list of the structures identified as vessels and their widths, ready to be analyzed by the expert.

As the fundus vascular structures are inherently radial, the width measurement of retinal vessels will be performed over various circumferences centered on the optic nerve, at distances that are multiple of the optic disk radius, depicted by the operator (a common procedure in Ophthalmology). Using a polar coordinate space, a linear representation of the gray level profiles is obtained for each of the analyzed circumferences, as shown in left side of Fig. 1. The gray level profile along each circumference is characterized by the presence of valleys, which are potential vessels. They are placed over the noise of the anatomical fundus that is nearly uniformly distributed. Before its detection, a preprocessing stage is needed to minimize noise effects.

The employed filter for noise reduction must not modify the location of the profile transition regions, which determine vessel widths in the measurement phase. To minimize noise, a median filter has been chosen. It permits to remove gray level values that differ too much from the surrounding values. This filtering reduces the detection of valleys caused by noise perturbations induced by the anatomical fundus. The median filter used in this work has a window size of 11 pixels centered in the pixel under analysis. One important property of this filter is that it does not alter the magnitude of the gray level gradient and, therefore, respects the position of transitions. The right side of Fig. 1 shows the profile obtained after the filtering process.

Although the median filter eliminates many noise valleys, some of them, produced by illumination variations and the presence of fundus anatomical structures other than

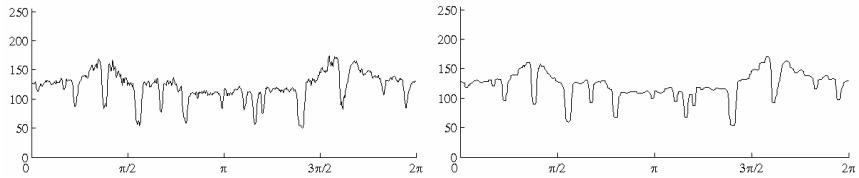

Fig. 1. Left: Gray level profile along one circumference centered at the optic nerve. Right: Gray level profile after median filter application.

vessels, still remain, together with the blood vessel valleys. For that reason, the simple detection of filtered sequence minima does not warranty correct identification of vessels. The definitive detection of blood vessels valleys is established as a function of their 1D and 2D morphology. In this work the hypothesis that the traversal vessel profiles are deep is assumed (1D model), i.e., their gray levels are much smaller than the surrounding fundus ones. Consequently, the intensity differences between vessel valleys and fundus are greater than those of noise valleys. Moreover, the vessel valley structure is stable in the radial direction regarding the optic disk (2D model).

Fig. 2 shows the 1D vessel model. Points x_1, x_2 and x_3 correspond respectively to the sites of the previous maximum, the minimum and the posterior maximum on the valley structure. Parameters y_1, y_2 and y_3 are the profile heights (gray levels) measured at x_1, x_2 and x_3 respectively. Using the three height parameters, a valley quality measure reflecting relative depth is established. This measure is given by the expression

$$Q = 1 - \frac{2y_2}{y_1 + y_3}. \qquad \textbf{(1)}$$

Valleys with Q values greater than 0.06 are considered candidates to form blood vessels. This process is realized individually over 2n+1 circumferences, with n positive integer and with their radius differing in one pixel, being the innermost circumference radius selected by the specialist. The n value, which can be modified by the operator, is recommended to be set between 5 and 9. Smaller values do not warranty the straight vessel hypothesis which will be applied in the width measurement stage. These data are the input to the 2D modeling phase. For a region to be considered a true vessel, a valley must appear in 2/3 of the analyzed circumferences. In addition, the angular distance between valleys associated to consecutive circumferences must be lesser than 0.089 radians. In the top left hand side of Fig. 3, a sequence of 11 valleys (n=5) can be observed, which verifies the 1D and 2D imposed conditions, so that they determine the existence of a blood.

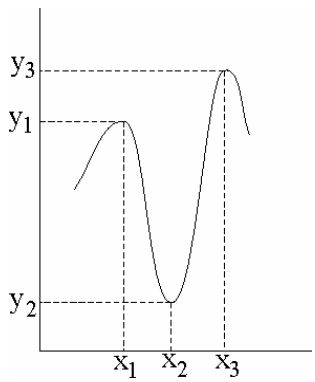

Fig. 2. Vessel model

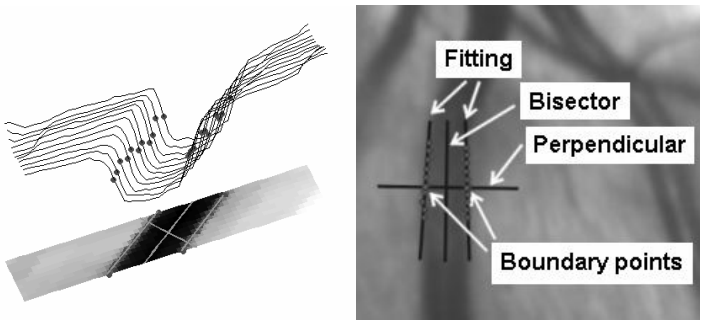

Fig. 3. Left: Sequence of profiles verifying 1D and 2D modeling conditions. Right: Geometric calculus of the straight line that is used to determine de the blood vessel width.

When the vessel positions are located, the next step is width measurement. This task is accomplished by locating the extremes of the gray level derivative along the angular direction, i.e., along the profiles. Hence, positions of vessel walls are set at the maximum transition points of the intensity profile. These extreme points are obtained by means of quadratic interpolation (fit to a parabola) of the derivative values, to obtain subpixel accuracy. In this way, potential image quantization ambiguities are avoided and results are better assessed. Assuming the hypothesis of the analyzed vessel segment is straight, the available points can be fitted to a straight line, as shown on the bottom left hand side and on the right hand side images in Fig. 3. Caliber is finally estimated over a line perpendicular to the bisector of the lines fitted to both vessel borders, as can be seen in Fig. 3.

3 Results

In order to validate the developed procedure, a reproducibility/reliability study has been designed in three stages. These phases are intended to evaluate the reproducibility/reliability of the method against diverse factors that can influence the study. These factors include variability on the measurements made by an observer, variability among different observers and variability due to the patient under study.

Once the goals of this experience were explained to the volunteers, chosen from the companion of the patients that came to the Servicio de Urgencias de Oftalmología of the Complejo Hospitalario Universitario de Santiago de Compostela (Spain) and after they had signed the informed consent to proceed with pupil dilation and an ophthalmologic exam, the volunteer pupil was dilated using an instillation of two drips of tropicamide and two drips of phenylephrine. After a period of 20 to 30 minutes, an eye fundus photograph was taken from both eyes of each subject at 50 degrees, with aneritra light (540 nanometers) and centered at the papilla. The camera used to take the fundus photographs was the Topcon TRC-50 IA connected to the IMAGEnet 1024 Digital Imaging Systems by Topcon Instruments, Paramus, NJ. All captured images

were directly stored in optical disks and displayed on a high resolution monitor (1280x1024 pixels) for their visualization and posterior analysis. The direct digitalization of the captured image was made by means of a digital camera connected to the aforementioned fundus camera. The elimination of the intermediate step, usually included in many other procedures, avoids the introduction of error factors [31].

To achieve the objectives of this work, a basic population sample was formed by 120 normotensive volunteers (240 fundus images), without any known vascular pathologies. A subject is classified as normotensive in the absence of a previous diagnosis of arterial hypertension and the presence of PAS/PAD quantities under 140/90, following the procedures of the American National Committee of HBP [32]. Subject ages ranged from 10 to 69 years, with a 1:1 ratio between sexes. Each age group (10-19; 20-29; 30-39; 40-49; 50-59; 60-69) is constituted by 20 individuals, 10 males and 10 females. In all cases the volunteers had transparent media in both eyes and a refractive defect inferior to 3 diopters of hypermetropia, myopia and astigmatism.

Table 1 shows the results obtained for the coefficient of variation over the individual measures and the Pearson's momentum correlation coefficient ($p<0.001$) over the global measures. The intraobserver reproducibility indicates agreement in measurements made by the same observer when repeating the measure over the same set of images. To analyze this factor, one single observer evaluated 40 images corresponding to 40 eyes of 20 individuals (20 left eyes and 20 right eyes) two times, separated from each other by an interval of 24 hours, without knowing nor the results neither the measurement points in the previous attempt. The interobserver reproducibility indicates agreement in measurements realized independently by two different observers. In this case, two observers evaluated, without information exchange, 30 images corresponding to 30 eyes of 15 individuals (15 left eyes and 15 right eyes). Intraindividual reproducibility indicates concordance in measurements, realized in a blind fashion, by the same observer over images of the same subject and same eye taken with a difference in some time interval. To analyze this factor, one single observer evaluated two images of the same eye, separated by a time period of one month, repeating the process for 30 eyes of 15 individuals (15 left eyes and 15 right eyes), without knowing nor the results neither the measurement points in the previous trial.

Table 1. Coefficient of variation (CV) and Pearson's momentum correlation coefficient (r) obtained in the various planted experiments.

	CV (r)			C
	Intraobserver	Interobserver	Intraindividual	Polak, 2000
Artery	1.10 % (0.96)	1.30 % (0.94)	1.08 % (0.93)	1.3 %
Vein	0.98 % (0.91)	1.47 % (0.86)	1.12 % (0.93)	2.6 %
Arteriovenous index	0.50 % (0.99)	0.99 % (0.95)	0.40 % (0.99)	

4 Discussion

Reproducibility of measurement methods is a crucial aspect in Medicine [31]. For this reason, the first planted goal in this work is to demonstrate that repeated vascular

caliber measurements over the same photograph without knowing the reference points bring the same results. As a second objective, it has been proposed to demonstrate that the same thing happens when one certain photograph is measured by two different observers. And, as a third objective, to demonstrate also that vascular caliber measurements from two photographs of the same individual with a time difference of one month do not present significant variations.

Intraobserver, interobserver and intraindividual variabilities are small in our method and the measurement reproducibility in the three groups presents a very high degree of concordance, with a Pearson's momentum correlation coefficient (equivalent to the intraclass correlation coefficient) over 0.86 and a coefficient of variation inferior to 1.47% in all cases, while Polak et col. obtained coefficient of variation values between 1.3% and 2.6% in their work with the Zeiss' retinal vessel analyzer (Zeiss RVA) [21]. In particular, this coefficient of variation superior bound is the best obtained by the whole of the previously commented methods. These results render the presented method a secure tool to objectify microvascular changes which previously depended on the observer's subjectivity.

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