QUANTITATIVE ANALYSIS OF THE RETINAL BLOOD FLOW USING DIGITAL FLUORESCEIN ANGIOGRAPHY

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Abstract: We have performed a quantitative and objective analysis of the blood flow in nonproliferative diabetic retinopathy (NPDR) using an automatic image registeration technique of fluorescein angiographic images (FAG). Twenty intermittent sequential images of FAG were acquired in NPDR by digital fundus camera and stored in JPEG format. Misalignment of the each image was corrected by the registration techniques using mutual information and affine transform. The signal intensity of the each pixel in sequential image was fitted into the gamma-variate function and the perfusion map was generated on the basis of the parameters of the gamma-variate function of each pixel. Ischemic area showed prolonged transit time compared to the normal area. Microaneurysm showed intermediate transit time and washout. However, transit time of the major retinal vessels of NPDR was similar to that of the normal control. Misalignments of the sequential images could be corrected by proposed methods. Image registration and perfusion mapping may be helpful in the localization and evaluation of the ischemic areas in NPDR.

Introduction

Fluorescein angiography (FAG) of the eyes are useful methods in detecting and characterizing the various pathologic changes of the retina in such diseases as diabetic retinopathy (DMR) and choroidal neovascularization (CNV), which are the major cause of the blindness over 65 years of age.

We have developed a systematic approach for automatic registration of FAG images using mutual information and a quantitative analysis of them. However, the images are not aligned precisely due to the eye movement during image acquisition and this makes the quantitative analysis of the blood flow on FAG difficult. In this poster, we present a method of registering the FAG images and measure the accuracy of the registration by root mean square error (RMSE) analysis.

We hypothesized that quantitative assessment of regional perfusion may be possible using FAG images. We also analyzed the blood flow quantitatively by gamma-variate curve fitting.

Materials and Methods

Intermittent sequential images of FAG was acquired by Canon CF-60Uvi fundus camera system with Canon D60 digital SLR camera. In general, from the point of the intravenous indocyanin green injection, 10 to 20 images were acquired for 10 minutes. Misalignment of the each image generated by the minute eye movement of the patients was corrected by the mutual information method because the distribution of the contrast media on image is changing throughout the time sequences. The mutual information method, well-known for one of typical multi-modality methods1 has been employed. In addition, there is need for pre-processing the images for more accurate registration.

A. Fundus angiographic images

To investigate the quantitative analysis of the blood flow on FAG, systematic approach for automatic registration of using mutual information and a quantitative analysis was developed.

FAG images of seven cases of nonproliferative diabetic retinopathy (NPDR) were recruited from the image database of the Seoul National University Hospital department of ophthalmology.

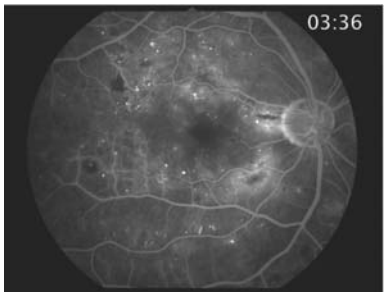

Figure 1: Original FAG image

B. Pre-processing

Recruited angiographic images were not optimized for this study and some additional artificial image information such as patient information, acquisition time, and round mask, etc were overlaid. So the pre-processing was needed for the accurate registration. For example, FAG images had the problem of circular outer boundary.

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There are several cases of aligning images not by vascular and internal structure, but by circular outer boundary and other artificial image information. To solve these problems, erasing artificial information (Figure 2) and filling the background as the average intensity (intensity: 37) of internal image (scale: 256 gray) were adopted.

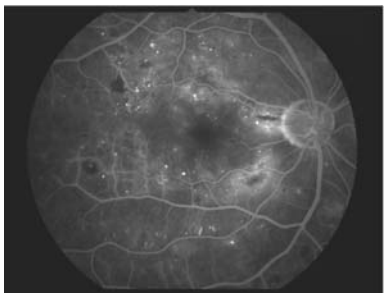

Figure 2: Pre-processing: erasing useless region, and filling the background for tuning

C. Exclusion criteria

1) The case of eye movement during acquisition of single image: this makes the partial deformation, especially vertical non-rigid distortion.

2) The case of the unreliable distance between the eye and fundus camera during angiography: this makes the magnification discrepancy between the sequential images.

3) The case of prolonged time interval between the images: this makes insignificant affinity between the consecutive images

D. Registration

Because of the changing distribution of the angiographic dye on image and movement of the eye, it is hard to register images using a simple registration method. We solved this problem by employing the mutual information method, well-known for one of typical multi-modality methods. The mutual information method calculates the entropy of joint histogram constructed by counting the number of times a combination of corresponding gray values occurs and register images for the direction of minimizing the entropy.

In this study, we adopted three kinds of transforms: Translation only, Translation & Rotation, and Affine Transform.

The affine transform shows the best performance of registration, which means that the registration results of affine transform have the least RMSE among them.

Figure 3 shows overlay images between unregistered images, registered images using only translate transform and registered images using affine transform. You can recognize the slight misaligned in the lower two images of Figure 3, because there is rotational difference of the original images. This rotational difference can be fixed by affine transform.

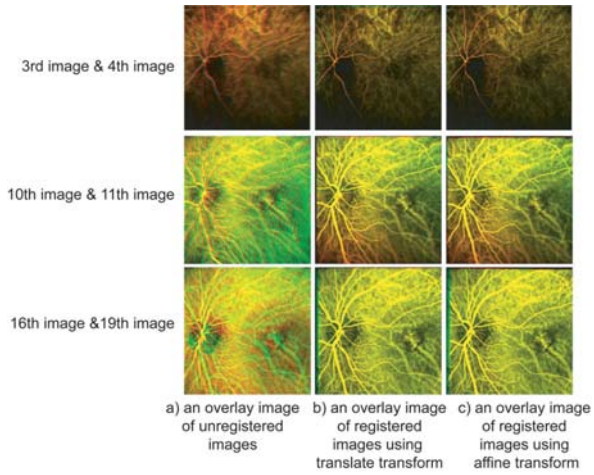

Figure 3: Comparison between unregistered images, registered images using translate transform and affine transform

Because of time dependency of images, longer time difference between images, more misaligned. After the 1st and the 2nd unaligned image are selected and calculated, the 1st registered image are created by the 2nd unaligned image. And then the 1st register image and the 3rd unregistered image are performed. In this way, incremental registration was used.

Signal intensity (SI) time curves after intravenous dye injection were generated by measuring the signal intensity in ROI defined in sixteen human studies. Several region of interest (ROI) were selected by the examiner and the intensities of the selected region were plotted according to the time sequences.

Three ROI is selected in Figure 4. In Figure 5, each graph presents average variation and standard deviation of intensity of ROIs. The uniform standard deviations mean the correctness of registration.

Figure 4. Selected ROI for comparison of the intensity

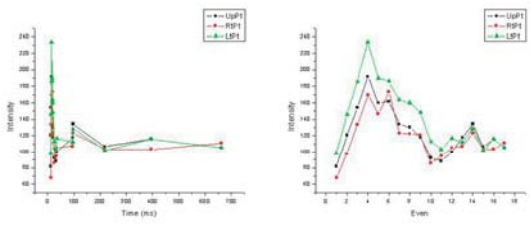

Figure 5. Graph showing average variation and standard deviation of intensity of ROIsE. Perfusion & RMSE

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$$[1]\ C_{tissue}(t) = K(t-T_0)^{\alpha} e^{-(t-T_0)/\beta} + SI_{base}$$

$$[2]\ t_p = \alpha\beta$$

$$[3]\ \tau_{app} = \beta(\alpha+1)$$

$$[4]\ V = \Sigma\, C_{tissue}(t) / \Sigma\, C_{arterial}(t)$$

$$[5]\ f = p / \tau$$

$$[6]\ f = p / \tau = V / \tau_{app}$$

$$[7]\ r = y_{responeded} - y_{predicted}$$

$$[8]\ RMSE = root\ \{ (\Sigma\, r^2) / N \}$$

In order to extract quantitative indices, the SI time curves were fitted to a gamma variate function described by the equation [1], where t is the time.

$C_{tissue}(t)$ is the measured signal intensity as a function of time which is related to the concentration of the dye (Figure 6).

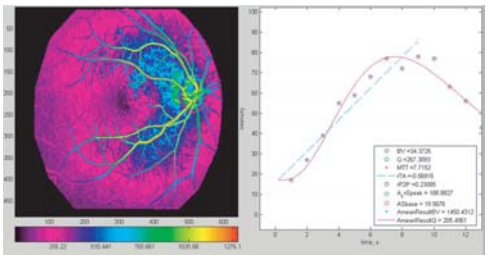

Figure 6: ROI selected gamma-variate curve fitting at blood flow map of perfusion

K is a constant scale factor. α,β are parameters that define the shape of the curve. SI_{base} is base signal and T_0 is time of arrival.

From the fitted values for α,β one could deduce perfusion indices such as the time to reach peak concentration (t_p) and an apparent mean transit time (τ_{app}) as [2] and [3].

Additionally, from measurements of the tissue and arterial concentration curves [$C_{tissue}(t)$ and $C_{arterial}(t)$], the volume of distribution of the agent was calculated directly as [4].

The central volume principle relates the terms perfusion (f), blood tissue partition coefficient (p) and the mean transit time (τ): This principle applies to any agent, whether it is extracted from the blood or not. We assumed that contrast agents behave as an intravascular agent during the first pass. Therefore, the mean transit time τ_{app} equals and the partition coefficient can be determined as distribution volume (V).

Therefore, we compared $V\tau_{app}$ with the absolute perfusion obtained with the colored microsphere technique. In addition, V and $1/\tau_{app}$ were also correlated with the absolute values of perfusion.

After fitting data with one or more models, the goodness of fit should be evaluated.

In this paper, RMSE analysis was adopted for this purpose. The residuals from a fitted model are defined as the differences between the response data and the fit to the response data at each predictor value:

Figure 7 shows general example for calculating residuals (r) between estimated data and original data.

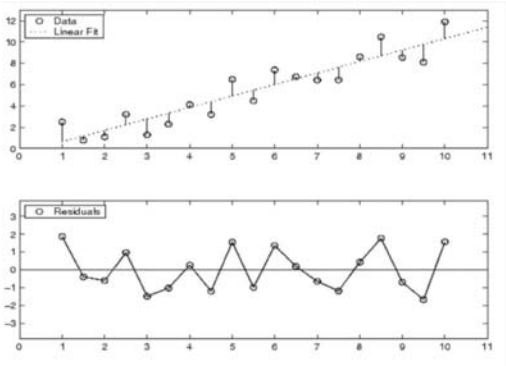

Figure 7: General example for residuals between fitted data and original data

Results

Ischemic area showed prolonged transit time compared to the normal area. Microaneurysm showed intermediate transit time and washout.

However, transit time of the major retinal vessels of NPDR was similar to that of the normal control (Figure 8 & 9).

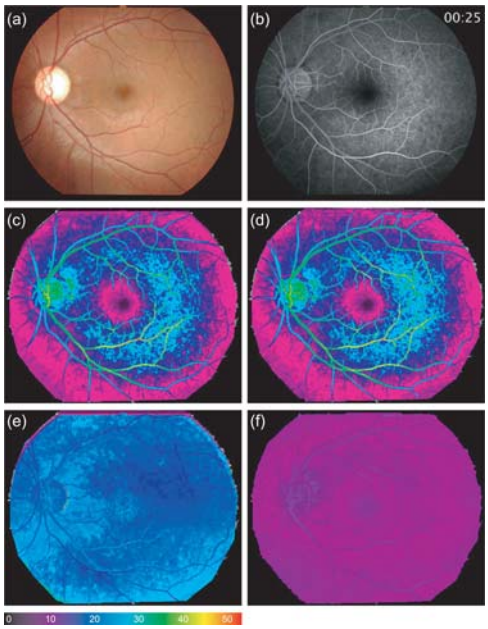

Figure 9. Blood flow analysis in the normal control. (a) fundus photograph of the patient, (b) fluorescein angiogram, (c) blood volume, (d) rate of blood flow, (e) mean transit time and (f) root mean square error map. Blood volume and flow rate is higher inside of the retinal vascular arcade compared to outside of the arcade. Mean transit time of the retina, retinal artery, retinal vein and retinal capillaries were almost equal.

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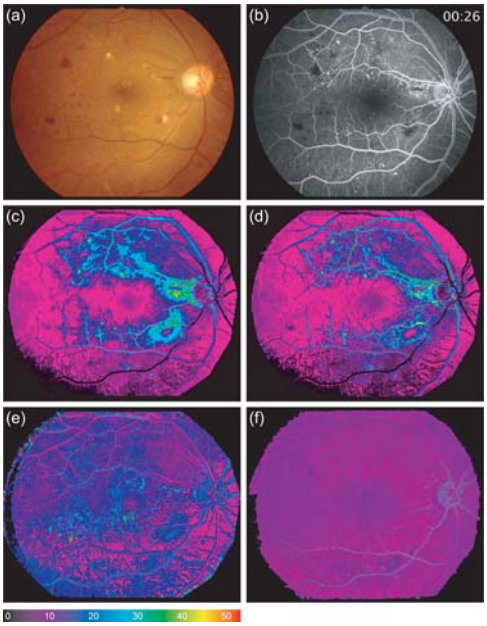

Figure 10: Blood flow analysis in the patients with nonproliferative diabetic retinopathy. (a) fundus photograph of the patient, (b) fluorescein angiogram, (c) blood volume flown during mean transit time, (d) rate of blood flow, (e) mean transit time and (f) root mean square error map. Note that mean transit time is prolonged at the inferotemporal part of the macula and the flow rate is decreased at ischemic area. Blood volume is increased at the area where the hard exudates and retinal hemorrhages coexist.

Table 1 presents the results of the unregistered case, registered case by translation transform and registered case by affine transform.

Table 1: paired t-test between unregistered and registered case

Cases	RMSE (average ± 1 S.D.)
Unregistered case	16.49 ± 4.37
Registered case (translation transform)	12.76 ± 4.01
Registered case (affine transform)	11.87 ± 3.86

At each case, the mean of every RMSE values from perfusion region was calculated.

Discussion

There are significant differences among RMSE of unregistered case, registered case by translation transform and registered case by affine transform (paired t-test, $p<0.01$). This shows that there is significant improvement by the registration and affine transform is more accurate than translation transform. The resulting registered images can be used not only for quantitative analysis, but also for perfusion analysis.

Conclusion

The resulting registered images can be used not only for quantitative analysis, but also for perfusion analysis. Various investigative approached using this method will be helpful in the characterisation of the lesion and follow-up of retinal and choroidal diseases.

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