CHAPTER V

5. DISCUSSION

In this study there were about 25% of unexpected accidental data loss from hard drive failure. Despite this catastrophe, the violation of random sampling was not severely affected. The number of subjects in each age groups and each sex (Table 4.2) were not very different. The total number of subjects (172) was about half of the calculated sample size (270). However, the width of confidence intervals of the means (Table 4.5) of the HRT parameters that used to calculate the sample size (0.11 for disc area, 0.09 for cup area and rim area, 0.04 for rim volume) were much less than the desired width of confidence interval proposed in Table 3.1 (0.20 for disc area and cup area, 0.15 for rim area, 0.10 for rim volume). This showed that the number of subjects in our study was adequate with very good precision of the measured HRT parameters. This was due partly to the very good reproducibility of the HRT instrument (20-40 microns).

From a geographical point of view (see map of Ubolrat District in Appendix F), subjects who lived far from Ubolrat hospital (that situated at tambon Kuean) like tambon Na-kham and Sri-suk were not very willing to participate in the study. From Table 4.3 the subjects from these 2 tambons are less than from others. Subjects from tambon Kuean which have no problem of traveling because it is so close to Ubolrat hospital also have small numbers. The reason is that most of them are not farmers and they have their own business to take care of. The number of subjects from tambons that are moderate distance from Ubolrat hospital (tambon Khok-sung, Thung-pong, Ban-dong) are large. This difference in numbers of subjects from each tambon had been taken into account appropriately in the regression analysis.

There were 38 subjects (66 eyes) excluded due to exclusion criteria (Table 4.1). Poor visual acuity and severe pterygia were the major reasons for exclusion. There were 3 subjects that we have difficulty of obtaining the HRT images due to corneal opacity and uncontrolled eye movement had been excluded. Seven subjects were suspect to have glaucoma; 5 subjects had nerve fiber layer defects and 2 subjects had visual field defects. These subjects were informed of their conditions and referred to have further investigations in the regular eye clinic. This showed that there are still many people that are otherwise healthy with unidentified glaucoma.

The eye is a fundamental unit of evaluation in an ophthalmologic research. In our study both eyes of each subject were measured and some eyes may be excluded there is a problem of what is the appropriate unit of analysis; eyes or subjects. For subjects that have data of only one eye (one-eyed subjects) there is no problem. We will use only that eye for analysis and that eye will be the representative of that subject. For subjects that have data of both eyes (two-eyed subjects) there is a problem of using eyes or subjects as unit of analysis. Five possible approaches for this problem are: analysis of all eyes; analysis of only right eye; analysis of only left eye; analysis of one eye chosen at random; and analysis by averaging the responses of the two eyes. All of these approaches have limitations.[59] Analysis using all eyes falsely increase the sample size and distort the purpose of the analysis from a subject-specific to an eye-specific basis. Unless pairs of eyes in a subject are perfectly correlated, choosing to use only one eye for analysis and discarding some data is inefficient. Separate analyses of right and left eyes will be problematic if the results are discordant. Averaging the responses between the two eyes will tend to dilute the value of the more impaired eyes For normal subjects study such as this study, since both eyes of the subjects are normal, this dilution effects may not be significant and this "averaging approach" may be appropriate.

Another distinct approach is to analyze the data on an eye-specific basis (using all eyes in all subjects), but to use a regression technique that formally accounts for the correlation between eyes. This approach offers the advantages over others as it efficiently uses all available data in a single model. The technique of *generalized estimating equations (GEE)* proposed by Liang and Zeger[60] for parameter estimation has been described. This technique will provide a greater precision and narrower confidence interval compared with other approaches.[59] However, this approach can not be used in our data because there was stratification into three age groups. The most appropriate approach then is to use the average of two eyes in the case of two-eyed subjects as the unit of analysis.

We found very weak relationships of age to 5 HRT parameters; hvcoutou, rimvol, cupshape, meanrnfl and rnflarea (Table 4.4). The coefficients of determination (R^2) for these parameters were less than 0.12; less than 12% of the variance of these parameters could be accounted for by age. With these minimal relationships, they were not clinically relevant. Again, this does not mean that such a relationship does not exist, but that it could barely be demonstrated in this study. The weak correlation of age and retinal nerve fiber thickness agreed with reports from other investigators.[39-42] Three population-based study, on the contrary, did not find such a correlation.[34, 43, 44] These studies, however, did not use the HRT for measuring optic disc but used less reproducible methods such as planimetry. This may partially explained why they could not find the correlation. Nonetheless, the study of Saruhan et al[58] which used HRT to describe the optic disc topography also found very weak correlation of age and retinal nerve fiber thickness ($r = -0.14$, $R^2 = 0.02$). The very weak, not clinical relevant, relationships of the HRT parameters that we found did not warrant the categorization of the values of HRT parameters into age groups. As a result, we had described the estimates of the HRT parameters for all age groups.

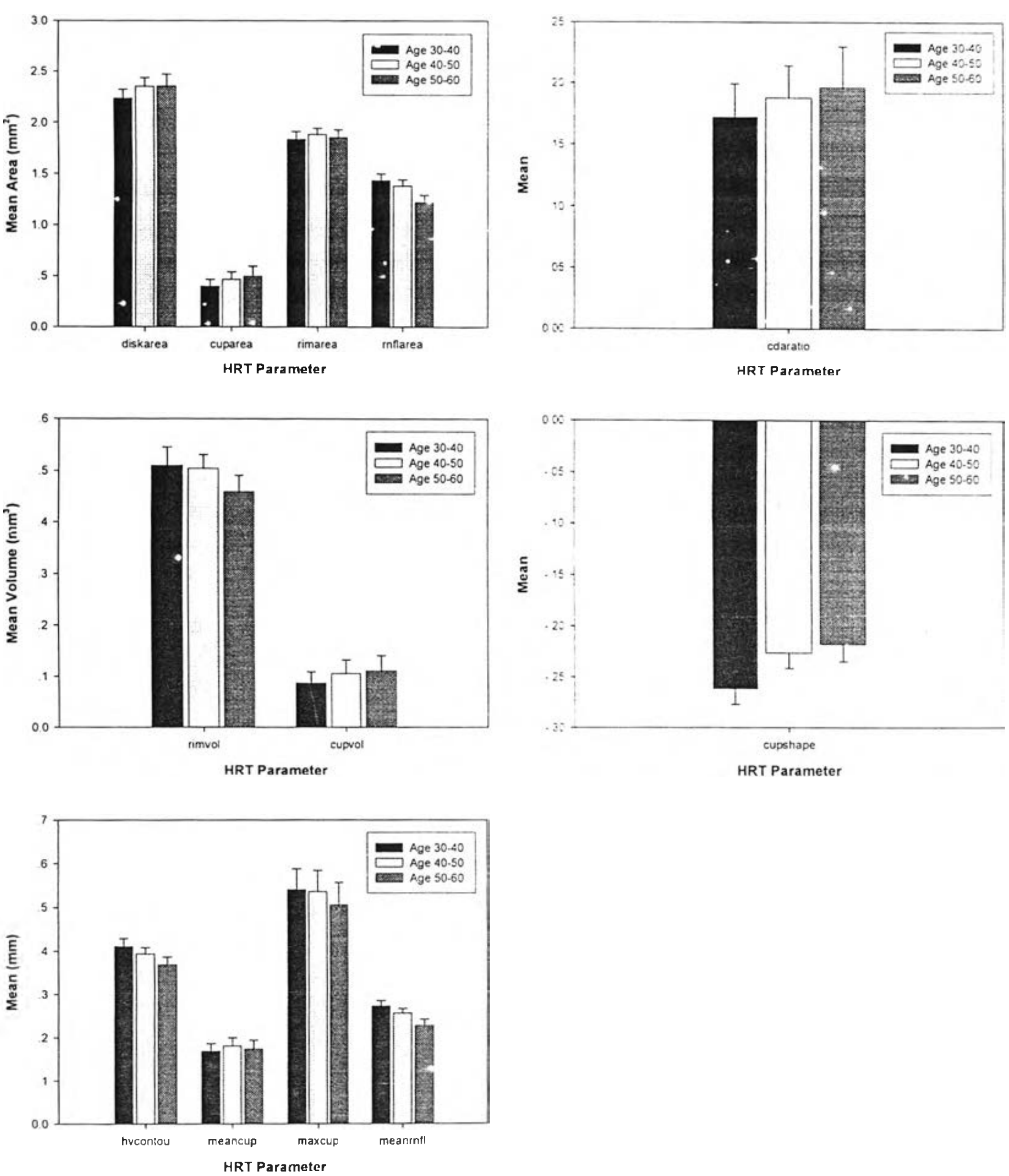
To demonstrate the minimal differences of the values of the HRT parameters between each age group, the bar graphs of means and 95%CI of the 12 HRT parameters were shown in figure 5.1. It is obvious from figure 5.1 that the means of the 12 HRT parameters between the 3 age groups are very similar and their confidence intervals overlap. So it is reasonable to describe the values of the HRT parameters as independent of age groups.

The goal of our study was to establish the 95% reference intervals (95%RI) or normal range for the topographic optic nerve parameters (HRT parameters). The two methods of calculations yielded slightly different results as shown in Table 4.6 and 4.7. The distribution of the HRT parameters had some effects on the calculation of 95%RI. From our data all parameters showed a unimodal distribution. There were 5 HRT parameters that were not normally distributed; cuparea, cdaratio, cupvol, meancup and maxcup. These parameters also showed asymmetry and skewness in which cupvol had the largest value of skewness followed by cuparea and cdaratio (results not shown). These results are not in concordant with previous report from

Whites population.[58] The reasons may be because of racial difference and/or different sampling technique.

For those HRT parameters that were distributed normally and not very skew the values from the two methods were not very different. For those HRT parameters that were not distributed normally and very skew i.e., cuparea, cdaratio and cupvol the differences from the two methods were more obvious. In addition, the minus values of the lower limits of 95%RI of cuparea, cdaratio and cupvol calculated from the method that assumed normality have no clinical meaning. To solve this problem, normal transformation could be used. In our case, normal transformation of the 5 HRT parameters that were not distributed normally was not successful (results not shown). We concluded that the calculation of 95%RI based on normal distribution was appropriate for those HRT parameters that were distributed normally but for those that were not distributed normally, the percentile method was more appropriate as shown in Table 4.8.

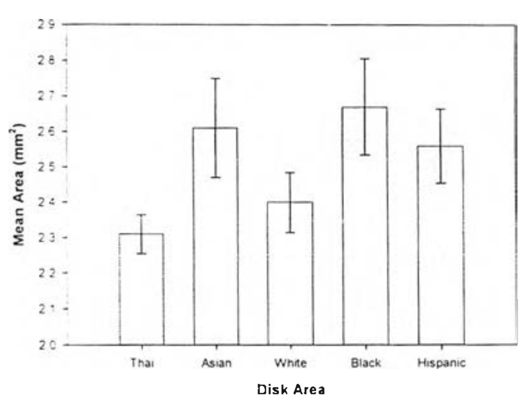
Figure 5.1 Bar graphs of means and 95%CI of 12 HRT parameters categorized by age groups. The vertical bars above the columns are 95%CI.

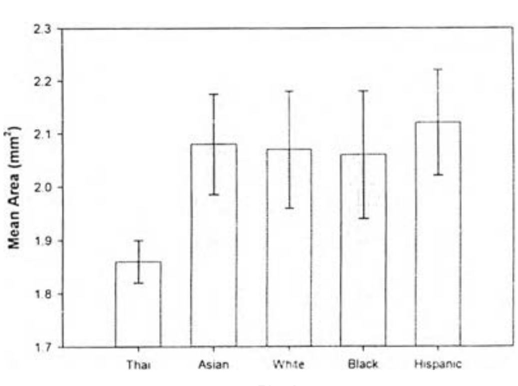


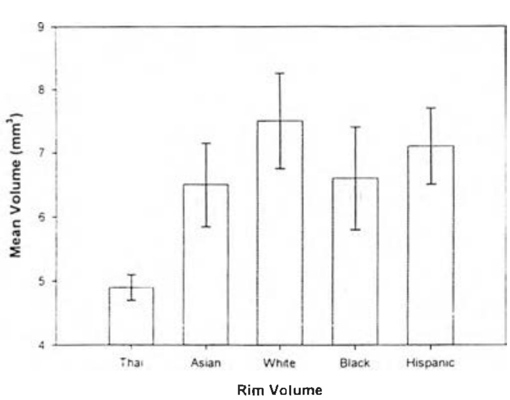
Because there were some data loss in our study, there would be the issue of adequate range of observations in the data set. In our data disc area ranged from 1.425 to 3.602 mm^2 (mean 2.296 mm^2). The reported disc area from Saruhan[58] and the Baltimore Eye Survey[34] were 0.948 to 3.569 mm^2 (mean 1.806 mm^2) and 1.15 to 4.94 mm^2 (mean 2.63 mm^2) respectively. These results were from Whites. There was only 1% of disc area reported by Saruhan to be more than 2.700 mm^2. In our study there were about 17% and 2% that had disc area over 2.700 mm^2 and 3.000 mm^2 respectively. For the upper limit, our data seemed to have adequate observations. On the lower limit there was about 5% of disc area reported by Saruhan to be less than 1.220 mm^2 and the lowest disc area reported by the Baltimore Eye Survey (Whites) was 1.15 mm^2. In our data there was no disc area that was less than 1.425 mm^2. It could be that our data had included too few small optic discs or that small optic discs were really rare in our population. Further study with larger number of subjects and cover more areas in other part of the country will answer this question. The differences in the range of observations could be explained partly by the different methods of sampling techniques or real racial difference in optic nerve topography.

Because previous reports had shown that there were differences of topographic optic nerve parameters between different ethnic groups, this issue was explored with one reported data that have adequate information for comparison. The data from our study was compared with the data from Tsai et al which used the same HRT instrument to evaluate topographic optic nerve measurements of several ethnic groups.[33] Since our study did not design to answer the ethnic differences of topographic optic nerve measurements and we did not have adequate data to weight the calculation, this comparison should be viewed as only exploratory and not inferential. Figure 5.2 showed bar graphs of means and 95%CI of disc area, rim area and rim volume of 5 different ethnic groups; Thai (from our data), Asians, Whites, Blacks and Hispanics.

Figure 5.2 Bar graphs of means and 95%CI of disc area, rim area and rim volume categorized by ethnic groups. The vertical bars above the columns are 95%CI.







From figure 5.2, compared to other ethnic groups, Thai subjects have the smallest disc size, rim area and rim volume. When compared with Asians, Thai also had smaller disc area, rim area and rim volume. This finding suggests that among Asian population there may be several distinct subgroups that have significant difference optic disc topography. A specific normative data for each of these subgroups need to be established to have more accurate classification of the optic disc. Normal data of topographic optic nerve parameters needs to be specific for the ethnic group that planned to be used. The normal data for Asians can not be generalized to Thai population. Clinically, a mismatched ethnic data may result in misclassification of subjects and wrong diagnosis. This hypothesis can only be proved by comparing sensitivity and specificity in glaucoma diagnosis after incorporating different ethnic-specific normative database into the HRT instrument.