Discrimination Ability and Reproducibility of a New Index Reflecting Autonomic Nervous Function Based on Pulsatile Amplitude of Photoplethysmography

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***Abstract*—A new physiological index (μ_{PA}) is proposed to represent the autonomic nervous system (ANS) function. The index μ_{PA} is defined as the natural logarithm of the ratio between two different frequency components of the pulsatile amplitude of the photoplethysmogram (PPG) signal. The discrimination ability and the reproducibility of μ_{PA} have been compared with other traditional ANS indices. In the experiment, the electrocardiogram, the PPG and continuous blood pressure were measured in 59 healthy young subjects (age 25.7 ± 6.3) and 86 healthy elderly subjects (age 70.2 ± 4.1) at rest. The discrimination ability and the reproducibility were evaluated by Cohen's d between young and elderly groups and by the interclass correlation coefficient, respectively. The results showed that the elderly subjects were significantly ($p<0.001$) lower than young subjects in μ_{PA} and a few traditional indices introduced to be compared with μ_{PA}. Therefore, it suggests that μ_{PA} is associated with the decrease in the ANS function accompanied by aging. Moreover, it showed that the discrimination ability and the reproducibility of the proposed index are comparable or larger than those of traditional indices. The proposed index based on the PPG signal will be applied to tele-healthcare systems for monitoring people's health in daily life in combination with the ratio of the standard deviation of the R-R intervals to their average value (CVRR).**

I. Introduction

Tele-healthcare systems for monitoring people's health in daily life using smartphones or wearable devices have been developed and recently begun to be applied worldwide [1]. In this trend, physiological indices related to the autonomic nervous system (ANS) are frequently used for inexpensive health monitoring because quantitative evaluation of the ANS function may be important for prevention and early detection of life style related diseases.

The electrocardiogram (ECG) and the photoplethysmogram (PPG) are typical biological information which can be measured noninvasively in daily life. The ECG and the PPG can yield many kinds of indices related to the ANS function. Because of simplicity in measurement and calculation, the indices based on heart rate variability such as CVRR, pNN50, LF/HF, which will be defined in detail in the next section, have been used most frequently [2-5]. It has been reported that CVRR and pNN50 are related to the parasympathetic nervous system and LF/HF corresponds to the balance between the sympathetic and parasympathetic nervous activity.

In general, indices used for health monitoring should have the discrimination ability to discriminate the performance of the ANS function and the reproducibility which is the capability that similar measurements can be reproduced at a different time in a short period of time when the ANS function may not change. It has frequently been said that the LF/HF index reflects sympathetic nervous activity related to the vasomotion. However, it has also been reported that the LF/HF ratio does not accurately measure the cardiac sympatho-vagal balance [6].

On the other hand, a PPG signal directly represents the arterial volume change caused by the vasomotor response, and thus the signal may reflect the sympathetic nervous function.

In the present study, we have proposed a new ANS index which is defined as the natural logarithm of the ratio between two frequency components of the pulsatile amplitude of the PPG signal. In this paper, the discrimination ability and the reproducibility of the proposed index calculated from experimental data will be compared with other ANS indices and the adequacy of the index will be discussed.

II. Methods

A. Proposed Index μ_{PA} Based on Photoplethysmogram

To estimate the ANS function, we focused on the PPG which is measured as quantity of light transmitting through or reflected by peripheral blood vessels at a finger or an ear. The PPG signal is affected by venous blood volume and skin tissue as well as arterial blood volume. To extract only information on the change in arterial blood volume from the signal as much

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as possible, we used the pulsatile amplitude (PA) at each heart beat defined by

$$PA = I_{\max} - I_{\min} \tag{1}$$

where $I_{\max}$ and $I_{\min}$ are, as shown in Fig.1, the maximum and the minimum value of the PPG signal over each beat, respectively.

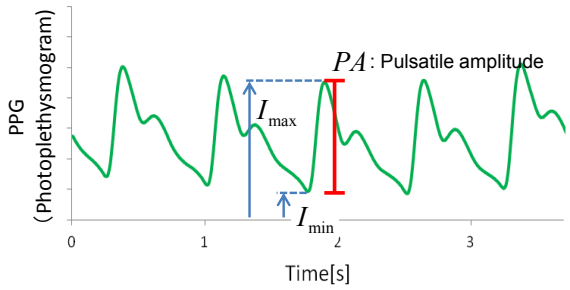

Fig.1 Pulsatile amplitude (PA) extracted from a photo-plethysmogram (PPG) signal.

The absolute value of the PA is also affected strongly by the intensity of the light source and the setting state of the photo sensor. Therefore, it is necessary to normalize the PA in some way to reduce these artifacts and an effect of the vascular extensibility caused by arteriosclerosis. Thus, we introduced the following new index named μ_{PA}:

$$\mu_{PA} = \ln\left(\frac{MF_{PA}}{HF_{PA}}\right) \tag{2}$$

where MF_{PA} and HF_{PA} are the middle frequency spectral component (0.08Hz-0.15Hz) and the high frequency spectral component (0.15Hz-0.40Hz) of the variability of the PA, respectively. That is to say, the index μ_{PA} is defined as the natural logarithm of the ratio between the above two frequency components of the PA.

The reason why the middle frequency component, MF_{PA} was adopted instead of the low frequency component, LF_{PA} (0.04Hz-0.15Hz) is that the MF band is believed to represent sympathetic modulation of vascular tone under the influence of the baroreflex while the LF band may represent sympathetic-related vascular activities including both neural and non-neural modulations [7-9]. The natural logarithm was employed to make the distribution of the values as closer to the Gaussian distribution as possible.

The PA variability (PAV) was obtained as follows:

1) A transmission type photoelectric sensor (PPG100C; Biopac Systems Inc.) was used to measure the PPG signal and the signal was sampled at 100Hz.

2) A four order Butterworth high pass digital filter with a cutoff frequency of 1.59Hz was used to remove low frequency component from the signal.

3) The PAV was obtained beat by beat on the basis of I_d and I_s according to (1).

4) The PAV was resampled at 0.5Hz after an interpolation with the third order spline function.

5) The Welch method with the FFT was used to calculate power spectrum of the PAV to get MF_{PA}, HF_{PA} and μ_{PA} defined by (2).

B. *Traditional Indices for Control*

To evaluate the adequacy of the proposed index μ_{PA}, comparing with traditional indices representing the ANS activity or function, the following four kinds of parameters were calculated.

1) LF/HF

The index LF/HF is one of the most frequently used parameters which is defined as the ratio of the LF (0.04-0.15Hz) spectral component to the HF (0.15-0.40Hz) spectral component of heart rate or RR-interval (RRI) variability. As known well, it has been shown that the LF component reflects both sympathetic and parasympathetic nervous activities corresponding to the so-called 10-second rhythm or the Mayer wave while the HF component corresponding to the respiratory sinus arrhythmia reflects parasympathetic nervous activity [10]. The index is normalized to be the ratio between the two variables and then expected to reduce the individual difference. The RRI variability was obtained from interpolated signal based on the ECG signal sampled at 1kHz.

2) CVRR

The index CVRR (coefficients of variance of RR intervals) is defined as the standard deviation of the heart rate or the RRI variability divided by its mean value over 100 beats. The heart rate or RRI variability fluctuates with respiration, and then the index is regarded as parasympathetic nervous activity [3].

3) pNN50

The index pNN50 [4] is defined as the ratio of an RRI whose difference from its adjacent interval is larger than 50ms to all the observed RRIs. The index is also considered to represent parasympathetic nervous activity.

4) α_{LF}

The index α_{LF} is defined as

$$\alpha_{LF} = \sqrt{\frac{S_{RRI}}{S_{SBP}}} \tag{3}$$

where S_{RRI} and S_{SBP} are the LF spectral components of the RRI and systolic blood pressure (SBP), respectively. The index represents the baroreflex sensitivity which is related to the ANS function to regulate blood pressure through heart rate [5]. A continuous pressure sensor (Portapres;

TNO-TPD Biomedical Instrumentation) was used to measure SBP. The beat-to-beat SBP was transformed to the resampled SBP at equal sampling period of 0.5Hz.

C. Discrimination Ability and Reproducibility

In this study, discrimination ability and reproducibility were evaluated as follows:

1) Discrimination ability

In general, ordinary significant difference tests depend on the sample size. That is, with a sufficiently large sample, a statistical test will almost always demonstrate a significant difference. To eliminate the effect of the sample size, we adopted Cohen's d [11], i.e., a kind of the effect size, defined as

$$d = \frac{|\bar{x}_1 - \bar{x}_2|}{s} \tag{4}$$

where $\bar{x}_1$ and $\bar{x}_2$ are the mean values of two groups, s is the pooled standard deviation defined as

$$s = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}} \tag{5}$$

where s_1^2 and s_2^2 are the standard deviations of these groups with sample size n_1 and n_2, respectively. It can be expected that the larger Cohen's d is, the stronger the discrimination ability is.

2) Reproducibility

If an environment surrounding a person changes to some extent, his or her ANS activity will, of course, change as much. However, his or her intrinsic function or performance of the ANS will not change so much even if the environment changes. This means that an index representing the ANS function should have reproducibility.

In this study, a model $ICC(1,1)$ in the intra-class correlation coefficient (ICC) [11] was employed to represent the reproducibility, given by

$$ICC(1,1) = \frac{BMS - WMS}{BMS + (k-1)WMS} \tag{6}$$

where BMS and WMS are, respectively, the between mean square and the within mean square obtained from the one-way ANOVA applied for k samples for each subject. The $ICC(1,1)$ may be interpreted as the proportion of total variance in observed scores that can be accounted for by the subject-to-subject variability in the true, but unobserved scores. For simplicity, let $ICC(1,1)$ be abbreviated as ICC hereafter. The ICC is rated from $-1/(k-1)$ to 1 and it means that the larger the value is, the stronger reproducibility is.

C. Experiment

1) Subjects and protocols

In the experiment, total 145 healthy subjects shown in Table I participated. They were recruited from students in Tohoku University or a temporary work agency for aged people (The Sendai Silver Staff Center). All participants provided informed consent to participate in this study, which was approved by the Research Ethics Committee Involving Living Human Participants, the Graduate School of Engineering, Tohoku University. They were divided into a younger group with 59 subjects younger than 60 and an elderly group with 86 subjects older than 60.

The ECG, PPG and BP of each subject seated at a chair were measured over 3min at rest. Each subject performed 2 or 4 trials for measuring these signals but the number of subjects who performed 4 trials was 48 subjects as shown in Table II. In this case, the latter 2 trials were performed one week after the former ones. The reason why we used only 48 subjects out of 145 subjects is because it was not easy to collect subjects who could participate the experiment twice over two weeks. The subjects' data in Table I were used for calculating Cohen's d given by (4) for the mean value of each parameter such as μ_{PA}, LF/HF, CVRR, pNN50 or α_{LF} over 2 or 4 trials. The subjects' data consisting of 4 times of measurement of each parameter in Table II were used for calculating ICC given by (6) for letting $k = 4$.

TABLE I TOTAL SUBJECTS

	Number of subjects	Mean age	Male : Female
Young	59	25.7 ± 6.3	48:11
Elderly	86	70.2 ± 4.1	83:3
Total	145	52.1 ± 22.5	131:14

TABLE II SUBJECTS WITH 4 TIMES OF MEASUREMENT FOR CALCULATING THE INTRA-CLASS CORRELATION COEFFICIENT, ICC

	Number of subjects	Mean age	Male : Female
Young	36	24.1 ± 4.33	31:5
Elderly	12	70.1 ± 4.34	10:2
Total	48	35.6 ± 20.6	41:7

2) Measurement and analysis

The ECG signals were measured with an amplifier (ECG100C; BIOPAC System Inc.) and bipolar standard extremity lead. The same sensors described above were used to measure the PPG and BP. These signals were recorded with a 16-bit A/D converter at the sampling frequency of 1kHz.

The one-way ANOVA was applied to the mean values of the above mentioned 5 kinds of parameters for the subjects shown in Table I and Student's two-tailed t-test and

Mann-Whitney U test were used to check the statistical difference.

III. Results

Figure 2 shows typical examples of the PAV obtained from a) a young subject (age 22) and b) an elderly subject (age 74). This figure reveals that more complicated structure can be seen in the young subject's wave form than the old subject while the elderly subject's wave form is simpler and the amplitude of the respiratory arrhythmia around 0.3Hz is more dominant.

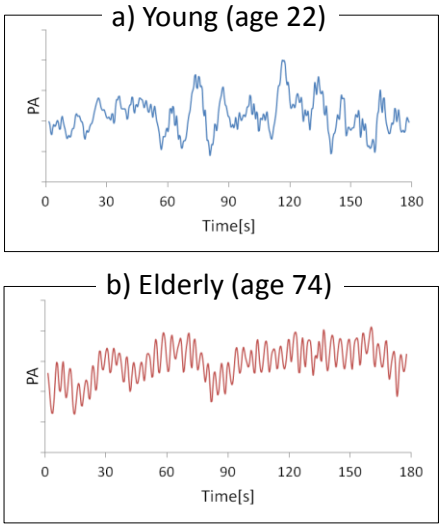

Fig.2 Examples of pulsatile amplitude variability (PAV).

Figures 3, 4, 5 and 6 show the changes in the proposed index μ_{PA}, the variance coefficient *CVRR*, the sensitivity index α_{LF} and the balance index of the ANS activity *LF/HF* with age, respectively. These figures indicate that μ_{PA}, *CVRR* and α_{LF} had a moderate correlation (r=0.592, 0.695 and 0.612, respectively) and decreased with age but *LF/HF* did not depend on age (r=0.076).

Three correlation diagrams between two kinds of indices out of three parameters, μ_{PA}, *CVRR* and α_{LF} are depicted in Figs. 7, 8 and 9. As shown in Fig.7, *CVRR* and α_{LF} had a high correlation (r=0.803) between each other, and thus it suggests that they are similar information. On the other hand, as shown in Fig.8, the correlation between μ_{PA} and *CVRR* was low (r=0.404). In the same way, the correlation between μ_{PA} and α_{LF} was also low (r=0.374), as shown in Fig.9. These facts suggest that the proposed index μ_{PA} has different information from *CVRR* and α_{LF}.

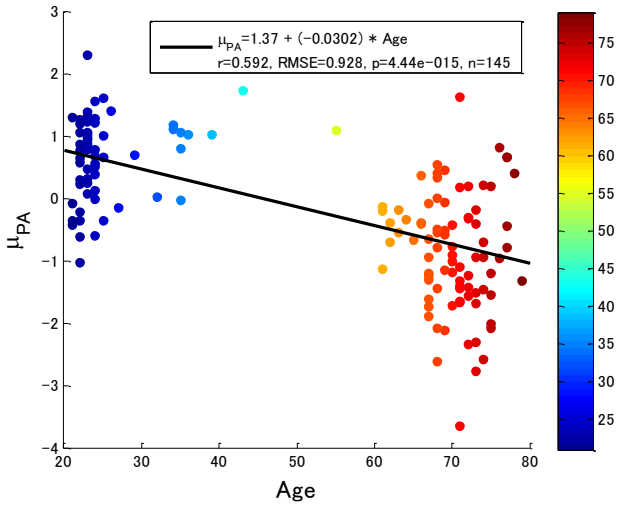

Fig.3 Change in the proposed index μ_{PA} with age.

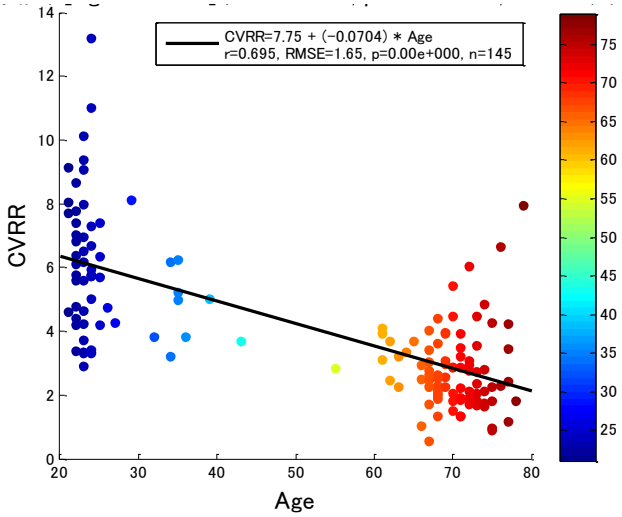

Fig.4 Change in *CVRR* with age.

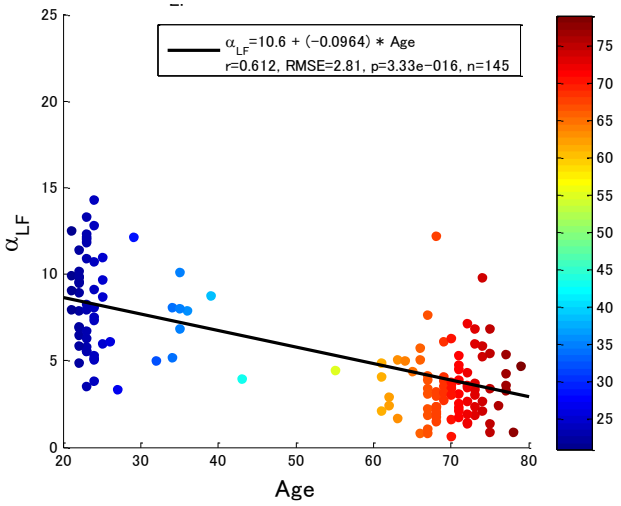

Fig.5 Change in α_{LF} with age.

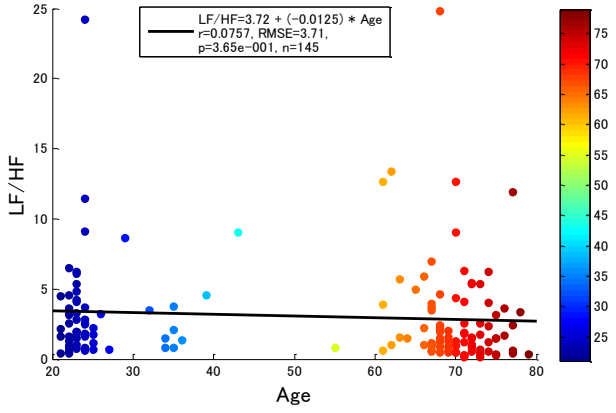

Fig.6 Change in *LF/HF* with age.

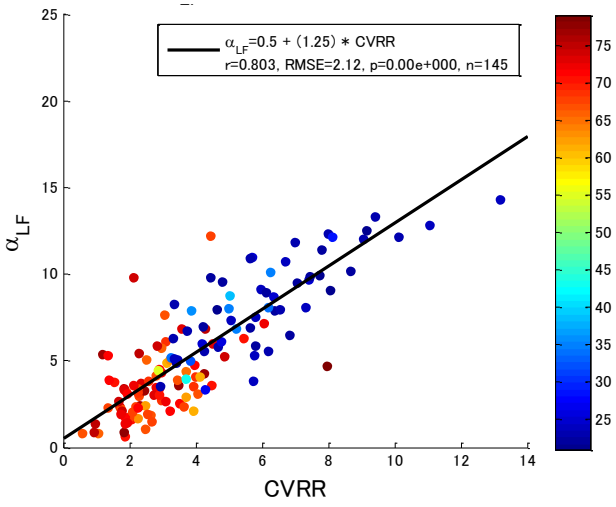

Fig.7 Correlation between *CVRR* and α_{LF}.

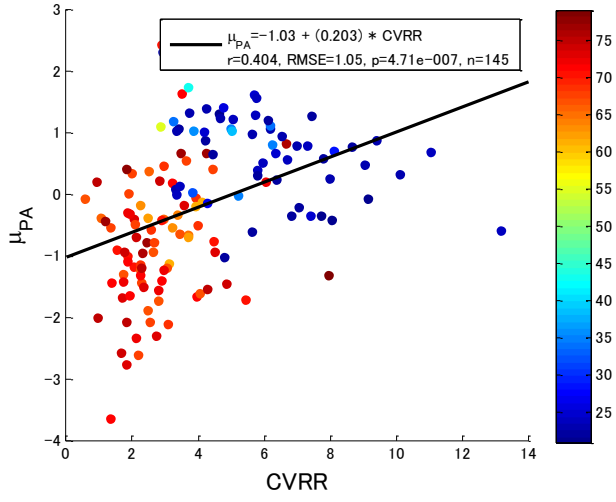

Fig.8 Correlation between *CVRR* and μ_{PA}.

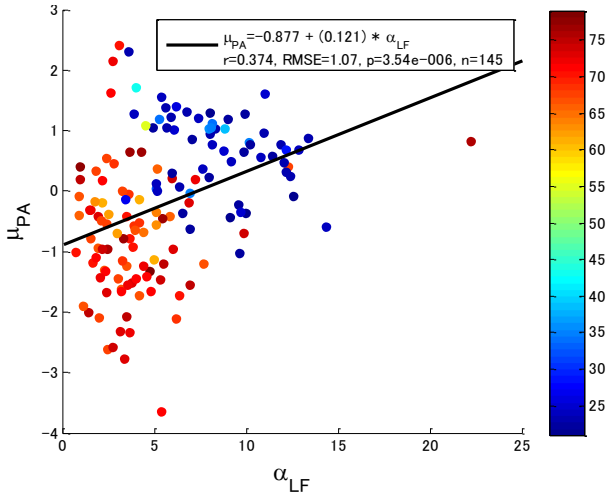

Fig.9 Correlation between α_{LF} and μ_{PA}.

The indices μ_{PA} and *CVRR*, which are moderately independent of each other, can be used to estimate subjects' age as shown in Fig.10. The regression plane estimating age (*Age*) is drawn as the green plane in Fig.10 and represented by

$$Age = 72.6 - 5.37 \cdot CVRR - 7.29 \cdot \mu_{PA} \qquad (7)$$

Its correlation coefficient was higher (r=0.774) than the case (r=0.695) of Fig.4 where only *CVRR* was used, and the root mean square value of the estimation error with respect to age using (7) was 14.4.

Figure 11 shows the results of Student's t-tests and Mann–Whitney U tests for mean values of five physiological parameters: μ_{PA}, LF/HF, CVRR, pNN50 and α_{LF} between young and elderly groups shown in Table I. This figure indicates that there were significant differences ($p<0.001$) recognized by both two tests in these parameters except LF/HF. This fact suggests that these parameters except LF/HF reflect the decrease in the ANS function accompanied by aging [13].

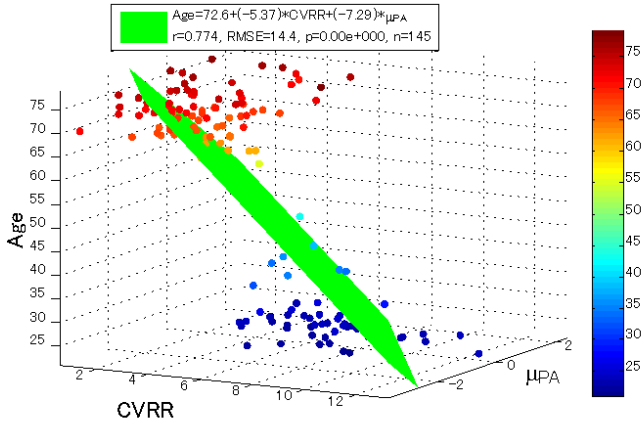

Fig.10 Linear regression from *CVRR* and μ_{PA} to age.

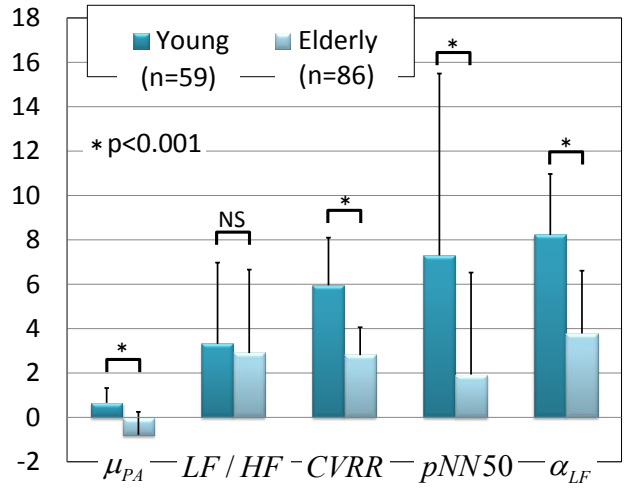

Fig.11 Results of Student's t-tests and Mann-Whitney U tests ($p<0.001$) for mean values of five physiological parameters between young and elderly groups shown in Table I. "NS" means non-significant difference ($p>0.05$).

Figure 12 shows the distribution of the effect size, Cohen's d representing discrimination ability and the intra-class correlation coefficient, *ICC* representing reproducibility for the five parameters of the subjects shown in Table II. This result indicates that the best index is the CVRR located at the most upper right, which means both the strongest discrimination ability and the highest reproducibility. The next best is either the proposed index, μ_{PA} or α_{LF}, and the worst one is LF/HF.

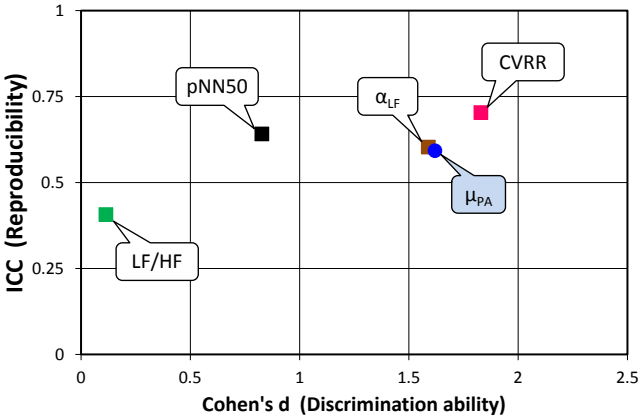

Fig.12 Distribution of the intra-class correlation coefficient (*ICC*) and an effect size (Cohen's d) for five physiological parameters for the subjects shown in Table II.

IV. Discussion

The definition of the proposed index μ_{PA} given by (2) is similar to *LF/HF* except the operation of logarithm. However, μ_{PA} correlated with age as good as *CVRR* or α_{LF} as shown in Figs. 3, 4 and 5, and its effect size, Cohen's d representing discrimination ability and the intra-class correlation coefficient, *ICC* representing reproducibility were much higher than *LF/HF* as shown in Fig.12. The reason for this difference may be because μ_{PA} reflecting vasomotion at the MF region is normalized by the HF components to reduce the effect of individual difference of thickness and light absorption rate of skin tissue and vessels.

It has been reported that the variance coefficient of fluctuation in cardiac cycle, the CVRR includes information on both the Mayer wave at low frequencies and the respiratory sinus arrhythmia at high frequencies, which are caused by the sympathetic and parasympathetic nervous functions, respectively [3]. On the other hand, as shown in Figs.8 and 9, the proposed index μ_{PA} which was rather independent of the CVRR and α_{LF} may include different information on a function to regulate blood pressure or blood infusion through vasomotion at peripheral vessels.

The sensitivity α_{LF} has been used as a good index for the ANS function [5]. As shown in Fig.7, however, it has been found that α_{LF} provided almost the same information as the CVRR in spite of cumbersome measurement of continuous BP.

Equation (7) suggests that the combination of the two indices, μ_{PA} and *CVRR*, which can be obtained from only measurement of the PPG signal, would estimate a subject's age. This fact suggests a possibility to quantify the decrease in the ANS function accompanied by aging if it is true that aging is almost equivalent to the decrease in any physiological function. Calculating the symbolic age from a more accurate prediction formula such as Equation (7), a person will be able to recognize superiority or inferiority of his or her autonomic nervous system as the deviation from the standard value expressed by the regression plane, which will be obtained from much more data including middle-aged ones.

V. Conclusion

A new index, μ_{PA} based on the photoplethysmogram (PPG) has been proposed to represent the autonomic nervous system (ANS) function and compared with other traditional indices. The experimental results showed that the elderly subjects were significantly lower than young subjects in μ_{PA} and traditional indices except LF/HF. Therefore, it suggests that μ_{PA} is associated with the decrease in the ANS function accompanied by aging. Moreover, it showed that the discrimination ability and the reproducibility of the proposed index are comparable or larger than those of traditional indices. It was also found that the index μ_{PA} could be used to estimate the ANS function in combination with the CVRR. This method will be applied to tele-healthcare systems for monitoring people's health in daily life because both indices can be calculated from only measurement of the PPG signal in some wearable tools connected with the Internet.

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