

Application of a MEMS Blood Flowmeter for Power Spectrum Analysis of Heart Rate Variability

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Abstract: We investigated the possibility of applying a MEMS blood flowmeter to heart rate variability (HRV) analysis. We conducted simultaneous measurements of HRV by electrocardiogram and MEMS blood flowmeter. TPP for the MEMS blood flowmeter was defined as the interval between peaks, which were designated as where the first-order differential of the signal changes from negative to positive. TRR (i.e., the R-R interval of the electrocardiogram) and TPP were compared by regression analysis. Autonomic indices transformed by power spectrum analysis were also compared by regression analysis. Fast Fourier transform (FFT) and maximum entropy method (MEM) were employed in the frequency analysis. By FFT analysis, the coefficient of determination for the regression between LF%, HF%, and LF/HF derived by TRR versus TPP was 0.8781, 0.8781, and 0.8946, respectively. By MEM analysis, the coefficient of determination for the regression between LF%, HF%, and LF/HF derived by TRR versus TPP was 0.9649, 0.8026, and 0.9181, respectively. These high correlations suggest that the TPP of the MEMS blood flowmeter is a reliable metric that can be utilized in applications of HRV analysis.

1 INTRODUCTION

The autonomic nervous system plays key roles throughout the body, including the control of involuntary activities such as blood circulation, respiration, digestion, regulation of body temperature through perspiration, endocrine function, generative function, and metabolism. One noteworthy example is the pumping of the heart, which is caused by periodic excitement of the sinoatrial node, a rhythm that typically fluctuates. Fluctuation of heartbeat rhythm is known as heart rate variability (HRV), and it reflects the health of the cardiovascular autonomic nervous system. Research into HRV began in dogs in 1981 using quantitative spectral analysis with the FFT, and it has since been studied in humans (Akselrod et al., 1981, Pomeranz et al., 1985). The prospect that HRV might be measurable more easily without the need for large equipment attracted much attention within the information engineering and biomedical engineering fields in the 1990s, with advances in wireless networks and miniaturization of biological sensors at that time informing attitudes that considered the prospect feasible. As the autonomic

nervous system innervates many organs, symptoms of its dysfunction are observed in various diseases, and recordings of parameters it controls may be useful for studying the occurrence, pathogenesis, response to treatment, and prognosis of a multitude of diseases. While many clinical applications of HRV analysis have been reported, it has been most accurately used as a clinical marker of diabetic neuropathy, as well as a predictive factor for the risk of sudden cardiac death and the occurrence of arrhythmias after acute myocardial infarction (Stys et al., 1998). Moreover, it has been employed to identify neurological diseases and to confirm the effects of therapy and medicine targeting them.

Because of the wide range of disease factors (pathology, prognosis, etc.) that are related to autonomic nervous system function and dysfunction, it is a highly regarded health metric in many fields. However, symptoms of its dysfunction are more difficult to capture via short-term measurements compared with other health indices; indeed, in cases where its function fluctuates based on circadian changes (e.g., temperature regulation, where body temperature is cooler during the nighttime), accurate evaluation becomes difficult because of the need to

collect data through continuous monitoring throughout a subject's daily activities. Autonomic nervous system function reacts to situation and environment in real-time to maintain homeostasis. Early detection of symptoms of its dysfunction may be possible by analyzing reactions to return the body to homeostasis. For example, in the case of diabetes, the body would be slow to release insulin in response to high blood sugar; pancreatic neurological dysfunction could be reflected in HRV. If these data were accessible by medical institutions that provide health and medical services, better and more-effective service could likely be provided.

To this end, we have recently developed a perhaps more widely applicable solution: a micro-integrated laser Doppler blood flowmeter (micro-electromechanical system (MEMS) blood flow sensor), which is $1/300^{\text{th}}$ the volume of a conventional laser Doppler blood flowmeter (Higurashi et al., 2003, Kimura et al., 2010). The weight of this sensor is approximately $1/30^{\text{th}}$ of a conventional instrument, and its power consumption is only $1/20^{\text{th}}$. The instrument also makes blood flow measurements possible while subjects are moving by omitting the optical fiber that is the source of significant noise in conventional instruments. This makes MEMS blood flowmetry ideal for the continuous measurement of blood flow volume over time. Moreover, since the blood flow data obtained by MEMS blood flowmetry are a result of analyzing the skin sympathetic nerves, blood pressure, and body temperature, MEMS blood flowmetry is capable of performing multivariate analysis of many indices, a significant advantage over single-index methods in the efforts to understand the complex systems of the living body.

The R-wave of the electrocardiogram is one candidate parameter often used in HRV analysis to assess autonomic function. Several commercial products on the market today allow ECG measurements during training/movement with an acceptable accuracy. However, we believe that a MEMS blood flowmeter is advantageous for evaluation of the autonomic nervous system for two reasons. One reason is that a MEMS blood flowmeter is a small and simple system and, unlike the ECG, does not require operator skill to affix it in order to obtain pulse. Another reason is its ready applicability to multivariable analysis for the evaluation of autonomic nervous function. If autonomic nervous system-based changes in pulse obtained from the pulse waveform of blood flow volume can be accurately determined, both simple measurement and further detailed evaluation of

biological state would be possible, which would be a boon to applications in healthcare and medical treatments.

At present, R-wave (obtained from electrocardiography) and pulse (obtained from acceleration plethysmography) data are typically used in HRV analysis (Takada et al., 2008). To confirm whether HRV analysis is possible from the pulse data obtained from the blood flow volume waveform of MEMS blood flowmetry, we performed simultaneous measurement of the R-R interval (TRR) obtained from an electrocardiogram and the pulse wave interval (TPP) obtained from a MEMS blood flowmeter for 100 beats, and then investigated the relationship between TRR and TPP by regression analysis (Fig. 1). Furthermore, we compared the accuracy of the frequency analysis of the fast Fourier transform (FFT) versus the maximum entropy method (MEM) for the HRV signal over 100 beats.

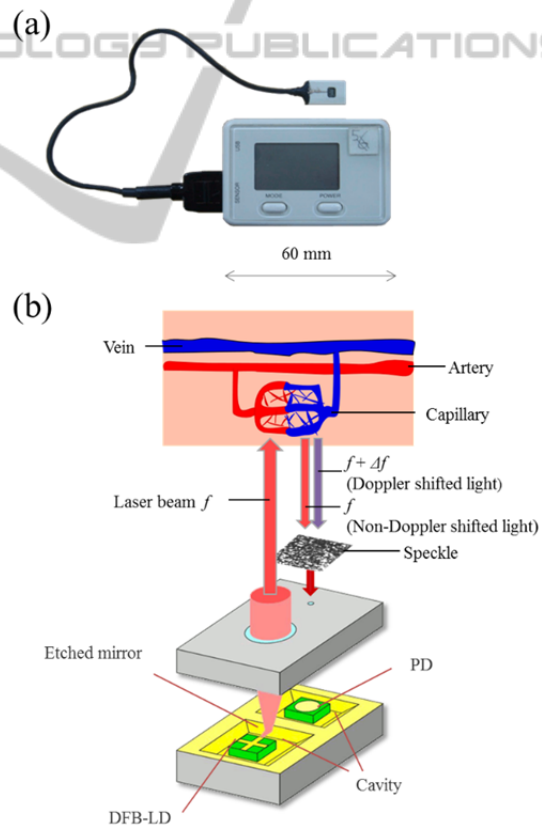


Figure 1: (a) Photograph of the MEMS blood flowmeter; (b) Measurement principle and schematics of its optical MEMS chip.

PD: photodiode, DFB-LD: distributed feedback-laser diode.

2 MATERIALS AND METHODS

In this section, we provide information on the study subjects, MEMS blood flowmeter, data analysis, and experimental method.

2.1 Subjects

The investigation complied with the ethical standards of the committee responsible for human experimentation of Kyushu University and with the Helsinki Declaration of 1964 as revised in 2008. A total of 6 healthy volunteers (6 males, age range: 21–26 years) participated in this study.

2.2 MEMS Blood Flowmeter

The MEMS blood flowmeter employed in the study is a blood flowmeter that is integrated with MEMS technology. Its features of ultra-compactness, lightweight, low power consumption, and wireless function make it possible to always be attached to the body. In addition, since its design omits the optical fiber that causes significant noise in conventional blood flowmeters, peripheral blood flow is measurable while the subject is in motion.

2.2.1 Structure

Figure 1 shows a schematic of the MEMS blood flowmeter. The MEMS blood flowmeter consists of the main body and the probe. The main body has a digital signal processor (DSP), a Bluetooth wireless link, a display, and a battery. The probe has a sensor chip and an amplifier circuit. The sensor chip consists of two crystal silicon substrates, a DFB-LD (distributed feedback-laser diode) and a PD (photodiode). One of the silicon substrates contains two cavities that hold the bonded LD and PD, while the other contains a microlens and a hole. Gold etched into the cavity leads the laser beam from the LD into the microlens. The antireflection-coated microlens optimizes the laser beam from the LD. Another silicon substrate is used to seal the cavity.

2.2.2 Principle

The design of the MEMS laser Doppler blood flowmeter is based on the principle of a laser Doppler flowmeter (Bonner et al., 1981). The measurement object is irradiated with a laser beam. Incident light is scattered multiply by static tissue, such as a skin and blood vessels, and moving tissue, such as red blood cells. All light scattered back

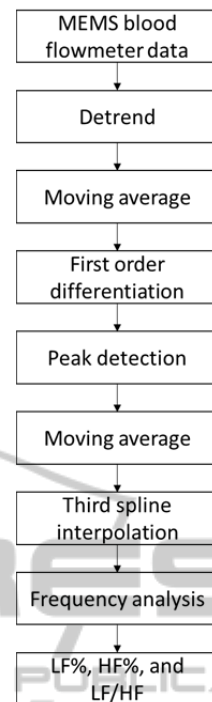


Figure 2: Data analysis process.

toward the PD interferes on the PD to form a speckle pattern. Statistical analysis of the output signal of the PD with respect to the speckle pattern gives a relative blood flow.

2.3 Data Analysis

Figure 2 is a flowchart of the data analysis process. The signal obtained by the MEMS blood flowmeter is detrended, and smoothing is performed by the moving average and first-order differential. We obtain the pulse by detecting the peak of the signal. The pulse is smoothed by the moving average and

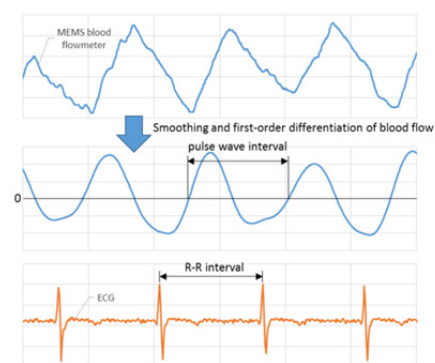


Figure 3: Waveforms of the electrocardiogram and the MEMS blood flowmeter.

third-order spline interpolation. Frequency analysis by the FFT or MEM is performed to obtain the power spectrum of HRV. Finally, we derive autonomic indices from the HRV spectrum (details of index calculations below).

2.3.1 Peak Detection

The signal of the laser Doppler flowmeter is influenced by peripheral blood flow, which is in turn influenced by many factors such as blood vessel conditions, body temperature, vasoconstriction, and vasodilation by skin sympathetic nerves, vascular endothelial cell metabolism, respiration, and blood pressure. In addition, changes in peripheral blood flow due to heartbeat are smaller than arterial blood flow. Therefore, we anticipated that the detection of the signal peak would be difficult compared with analyses of the clear waveforms in electrocardiograms and plethysmographs. Methods of detecting the peak of the pulse waveform may define the peak as the minimum, maximum, or point of 10% of the minimum within the waveform. There are also peak detection methods that instead emphasize change in the signal in terms of the first order-differential and second-order differential. When the latter strategy is applied to peripheral blood flow, the first-order differential and the second-order differential may indeed be suitable for functioning as a high-pass filter for detecting changes in the signal trend. However, we assumed that peaks could not be detected more stably with reference to other, higher-frequency signals in peripheral blood flow more reliably than simply with reference to the zero order peak. Therefore, we consider that the optimum pre-filtering strategy is to remove only high-frequency fluctuations before the first-order differential and the second-order differential. By the above logic, in this study we decided to perform a first-order differential after smoothing by the moving average, and detected peaks as when the signal changed from negative to positive (Figure 3).

2.3.2 Heart Rate Variability Analysis

Heart rate is controlled by the electrical impulses of the sinoatrial node, which are in turn controlled by the central nervous system through the sympathetic and parasympathetic branches of the autonomic nervous system. Sympathetic nerves increase heart rate by accelerating the electrical impulses of the sinoatrial node, while parasympathetic nerves decrease heart rate by suppressing them. The central nervous system also controls various functions based

on the information sent from the sensory organs. Therefore, fluctuations that are generated by the body modulate heart rate through the autonomic nervous system via the central nervous system. Of particular relevance to our study is that fluctuations in blood pressure—i.e., the Mayer wave, over a 10-second period—and respiration cycle are transmitted by this route to modulate heart rate. An important fact that can be leveraged for analysis is that the frequency responses of sympathetic nerves and parasympathetic nerves are different: about 0.15 and 1 Hz, respectively. As a consequence, although sympathetic and parasympathetic nerves work antagonistically in general, heart rate is modulated by fluctuations in blood pressure (i.e., the 10-s Mayer wave) when it receives input from the former, but by fluctuations in both blood pressure and respiration when it receives input from the latter (Penaz, 1978). Therefore, it is possible to evaluate the relative strength of sympathetic and parasympathetic function on heart rate by frequency analysis of heart rate fluctuation. These two indices are defined as follows from each interval:

- Low-frequency component (LF) : 0.04-0.15 Hz of power spectral density
- High-frequency component (HF) : 0.15-0.40 Hz of power spectral density

Thus, it is possible to evaluate the relative sympathetic function by calculating LF/HF. In addition, the HF estimates the parasympathetic function. However, since the HF is a relative value, it must be normalized by the total power to be of analytical use.

2.4 Experimental Method

In order to compare the TPP obtained by MEMS blood flow sensor and TRR obtained by electrocardiogram, simultaneous measurement with conventional electrocardiogram and MEMS blood flowmeter was conducted on six healthy volunteers (6 males). The experimental protocol is based on the method of measuring blood flow as follows: after attaching the conventional electrocardiogram and MEMS blood flowmeter to the subject's body, we provided a break-time of 10 minutes, after which heart rate was continuously measured for 100 beats. We conducted experimental measurements in the sitting position throughout the experiment. The MEMS blood flowmeter was attached to the right index finger. The right hand was fixed at the vertical level of the heart to prevent it from moving. Measurements of peripheral blood flow are deformed by changing the measurement site because

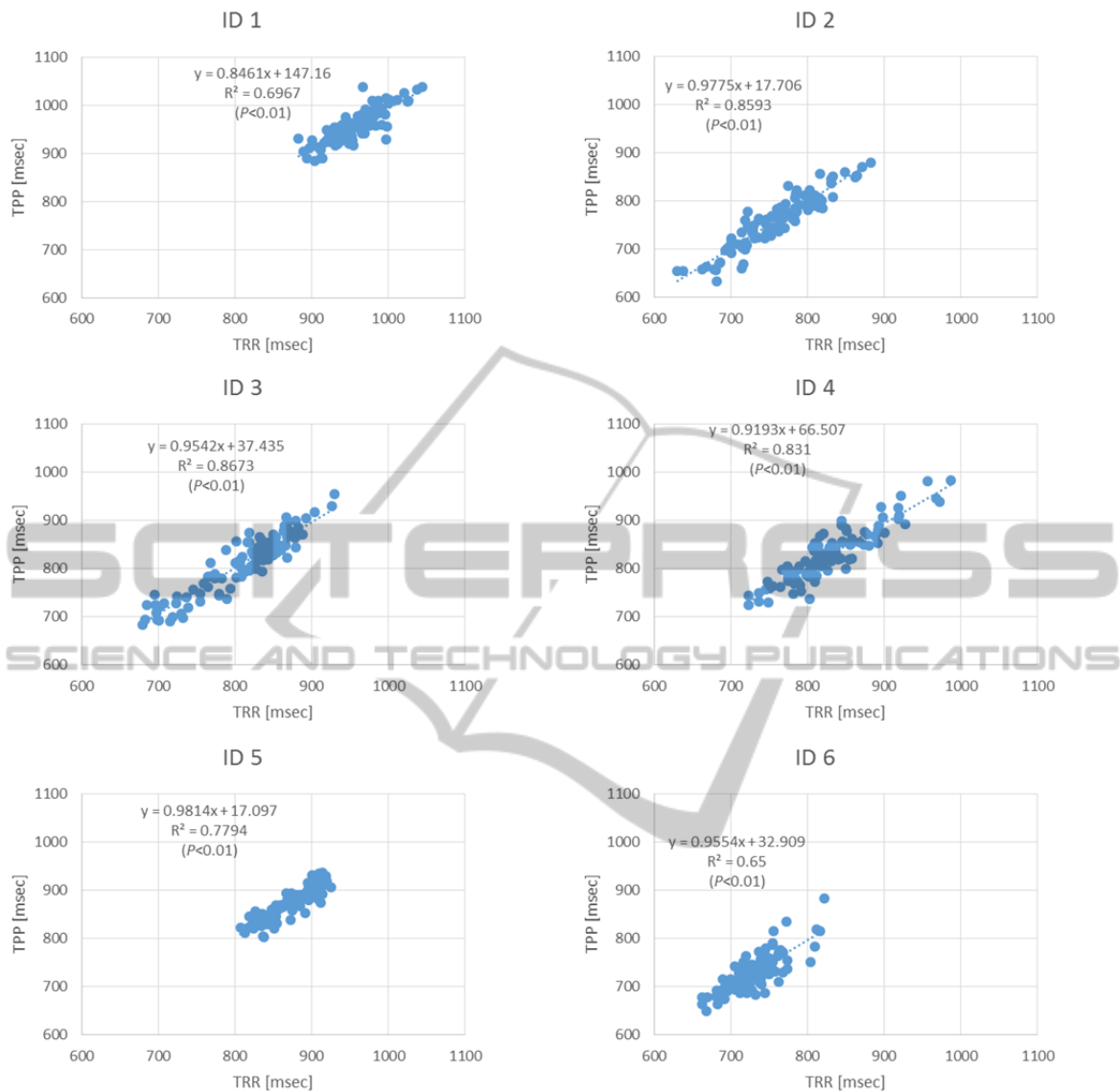


Figure 4: Relationship between the TRR of the electrocardiogram and the TPP of the MEMS blood flowmeter by regression analysis.

TRR: R-R interval obtained from electrocardiogram, TPP: pulse wave interval obtained from MEMS blood flowmeter.

the density and shape of blood vessels differ across measurement sites. Therefore, the experiment was conducted with the flowmeter attached to the same site throughout. In addition, since contact pressure by the flowmeter compresses blood vessels and thus changes peripheral blood flow, the MEMS blood flowmeter was lightly fixed with double-sided tape. Furthermore, since peripheral blood flow is altered by skin temperature, room temperature was held at constant 25 °C throughout the experiment. The LF and HF components of the TRR and TPP spectra were defined as 0.04–0.15 Hz and 0.15–0.40 Hz of power spectral density, respectively. From the power

spectral density obtained from TRR and TPP, LF% and HF% (normalized to total power) in addition to LF/HF were calculated.

3 RESULTS

Figure 4 shows the correlations between TRR and TPP for each subject. The regression equation and the coefficient of determination obtained by regression analysis are also shown. For subjects ID1–6, the slope was 0.8461, 0.9775, 0.9543, 0.9193, 0.9814, and 0.9554, and the intercept was

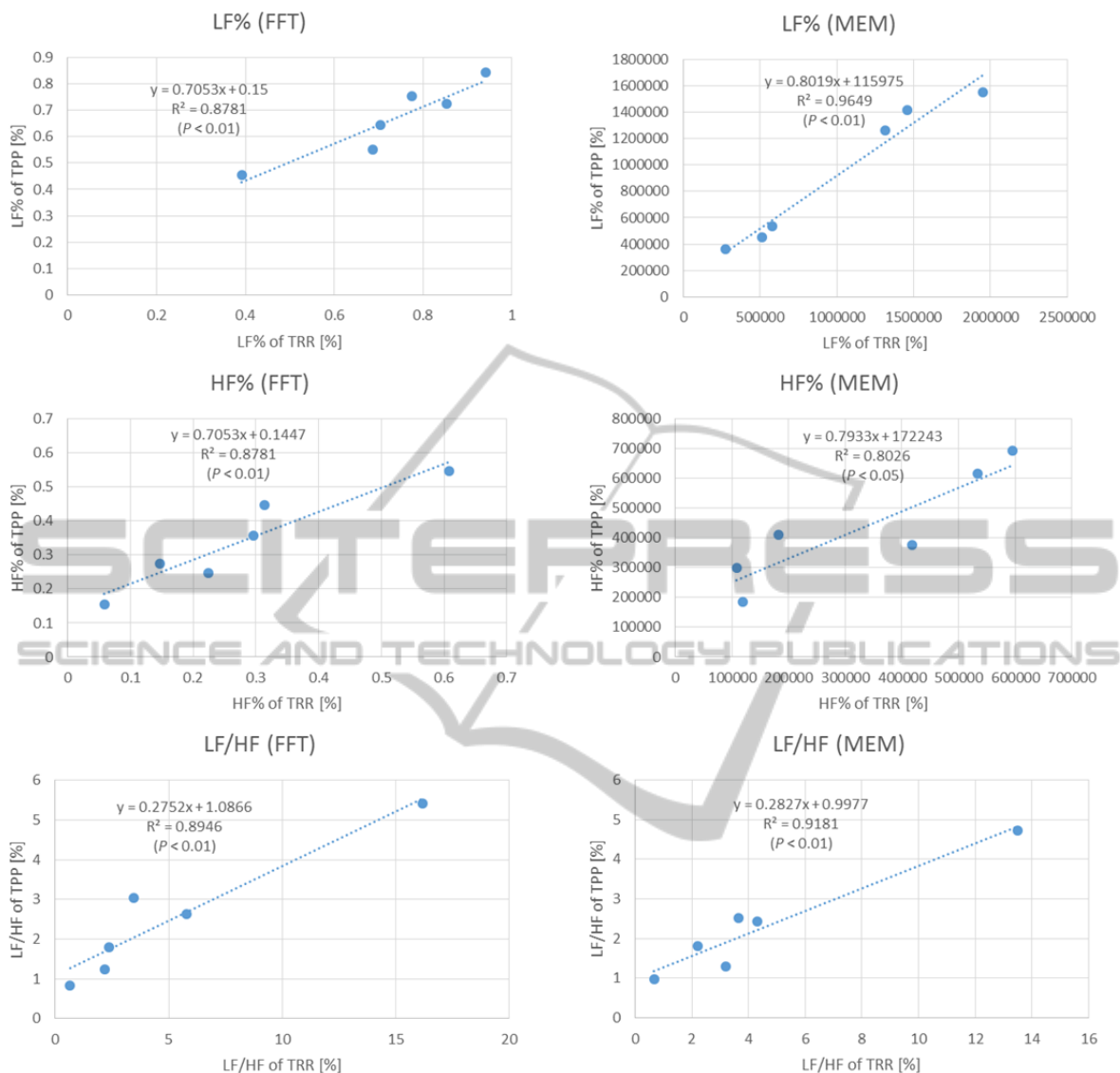


Figure 5: Relationships of LF%, HF%, and LF/HF as calculated by TRR (electrocardiogram) versus by TPP (MEMS blood flowmeter) by regression analysis. Each dot in the graphs represents a data point from one individual. A total of 6 healthy male volunteers (age range: 21–26 years) participated in this study. FFT frequency analysis was performed for TRR data (left side); MEM frequency analysis was performed for TPP data (right side).

LF%: proportion of power spectral density in the low-frequency domain of HRV, HF%: proportion of power spectral density in the high-frequency domain of HRV, LF/HF: ratio of LF and HF power spectral density, FFT: fast Fourier transform, MEM: maximum entropy method.

147.16, 17.706, 37.435, 66.507, 17.097, and 32.909, respectively, with the corresponding coefficients of determination being 0.6967, 0.8593, 0.8673, 0.831, 0.7794, and 0.65 ($p < 0.01$).

Figure 5 shows the relationships between LF%, HF%, and LF/HF, as determined by frequency analysis using FFT versus MEM to analyze TRR and TPP (respectively). The coefficients of determination and the regression equation obtained

by regression analysis are also shown.

According to FFT analysis, the slope between TRR and TPP for LF%, HF%, and LF/HF was 0.7053, 0.7053, and 0.2753, respectively; the coefficient of intercept was 0.15, 0.1447, and 1.0866. The coefficient of determination was 0.8781, 0.8781, and 0.8946, respectively.

According to MEM analysis, the slope between TRR and TPP for LF%, HF%, and LF/HF was

0.8019, 0.7933, and 0.2827, respectively; the coefficient of intercept was 115975, 172243, and 0.9977. The coefficient of determination was 0.9649, 0.8026, and 0.9181, respectively.

4 DISCUSSION

We conducted a comparison of the RR interval obtained by an electrocardiogram and the pulse interval obtained from the pulse signal of our MEMS blood flowmeter. Coefficients of determination showed a strong relationship between the two, and ranged from 0.65–0.87 in the regression analysis. In addition, autonomic indices obtained via the former metric showed a strong relationship with autonomic indices obtained via the latter, with coefficients of determination ranging from 0.80–0.96. The MEMS blood flowmeter measures the pulse signal transmitted from the heart to peripheral blood vessels. Many factors modulate this pulse signal. For example, blood vessel structure changes due to low-frequency fluctuation of skin sympathetic nerves and vascular endothelial cells. These skin sympathetic nerves also cause short-term expansion and contraction of blood vessels. Strong correlation of blood flow signal modulation with the electrocardiogram TRR metric was also observed in this experiment. These results suggest high promise for evaluating autonomic function and heart rate variability from the pulse interval of the pulse signal of MEMS blood flowmeter.

In the future, we will determine whether the MEMS blood flowmeter can measure relative changes in autonomic indices induced by physiological or psychological stressors.

5 CONCLUSIONS

The feasibility of using a MEMS blood flowmeter to evaluate autonomic function by heart rate variability was evidenced by comparable findings with electrocardiogram and pulse waveform data. Frequency analysis of each signal fluctuation of 100 consecutive heartbeats by the FFT and MEM was performed, followed by comparison of the resultant autonomic nervous indices by regression analysis. We confirmed a strong relationship between MEMS- and electrocardiogram-derived indices from a comparison of autonomic function indices and pulse. We also confirmed the strong relationship between the electrocardiogram and MEMS blood

flowmeter with power spectrum analysis by both FFT and MEM. Although MEM has a frequency resolution higher than the FFT, the FFT also has comparable ability to analyze data at least to the extent of the 100 consecutive heartbeats monitored in this study. The signal obtained by the MEMS blood flowmeter reflects many indicators such as skin sympathetic nerve activity (Söderström et al., 2003), body temperature, and blood pressure, and, to date, was successfully applied to the evaluation of hemodynamics during exercise and the detection of signs of dehydration (Nogami et al., 2011) and alcohol ingestion (Iwasaki et al., 2012). As autonomic function evaluation by the MEMS blood flowmeter becomes more and more feasible in the future, its applications are expected to grow in a wide range of fields.

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