Optical Non-invasive Blood Pressure: PPG Waveform-based Estimation and Verification

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Optical Non-invasive Blood Pressure: PPG Waveform-based Estimation and Verification

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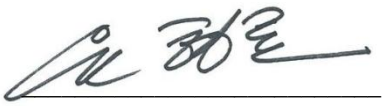
This certifies that the dissertation
of Incheol Jeong is approved.



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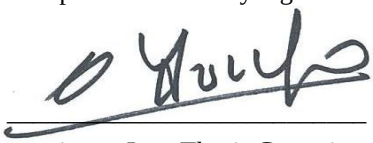

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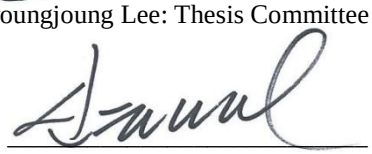

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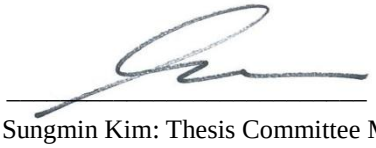

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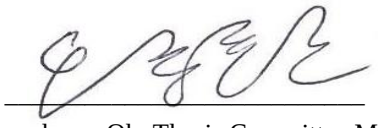

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Thank God for leading me better.

Never seem more learned than the people you are with. Wear your learning like a pocket watch and keep it hidden. Do not pull it out to count the hours, but give the time when you are asked. (Lord Chesterfield)

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from Incheol Jeong

Abbreviations

AC	Aalternating current
BP	Blood pressure
BV	Blood volume
CO	Cardiac output
CVDs	Cardiovascular diseases
CF	Contact force
DBP	Diastolic blood pressure
DC	Direct current
ECG	Electrocardiogram
Finger BP	Finometer blood pressure
HR	Heart rate
IBP	Invasive blood pressure
NIBP	Non-invasive blood pressure
Central BP	Oscillometric blood pressure
PPG	Photoplethysmograph
PTT	Pulse transit time
SST	Skin surface temperature
SBP	Systolic blood pressure
TPR	Total peripheral resistance
VR	Vascular resistance

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Abstract

Optical Non-invasive Blood Pressure: PPG Waveform-based Estimation and Verification

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Photoplethysmograph (PPG) is an optical measurement technique that can be used to detect blood volume (BV) changes in the micro vascular bed of tissue. It has widespread clinical application, with the technology utilized in commercially available medical devices. PPG waveform is believed to have significant information regarding the patient's cardiovascular condition which has not been fully utilized in the current clinical practice.

The objective of the current study is to assess the feasibility of using multiple features derived from the finger PPG waveform as markers of BP. The specific objectives are; first, to study the change in PPG waveform during BP change from patients in emergency room and intensive care unit based on a blood flow model and to evaluate their potentials as non-invasive indicators of cardiovascular diseases (CVDs), second, to evaluate the potential use of the finger PPG waveform derived BP as a non-invasive indicator of BV and vascular resistance (VR) by investigating its association with progressive change in the central BV and the total peripheral resistance (TPR) induced by cardiac stimulants, third, to investigate the propriety of using normalized PPG derived the finger PPG waveform to track variations in contact force (CF) change at measurement area and

progressive changes in PPG waveform induced by forced gradual cooling and heating, forth, to develop an automated method of detecting BP from the finger PPG waveform and evaluate the reliability of the measurement by direct comparison with the BP measured from clinical non-invasive blood pressure (NIBP) equipment.

The results from current study clearly show the possibility of finger PPG waveform as a noninvasive determine tool for BP change. BP detection model were verified by the relationship study, which involved change of cardiovascular status from a group of healthy human subject that constituted blood pressure change and a group of healthy animal subject that induced via commonly used cardiac stimulants. The results from these studies have supported that morphological features derived from the finger PPG waveform could be very useful for detecting the change in central BP, and the trends of features might be possible to identify not only the local BV change but also the VR change in peripheral vasculature. The relationship between effects of environment and the finger PPG waveform was confirmed that CF and skin surface temperature (SST) changes in groups of healthy subjects produced the progressive PPG waveform change. The clinical study focused on long-term comparison and has shown that morphological features of the finger PPG waveform could be potential markers of BP change, which may help to patients who are interested in monitoring their daily BP.

In terms of clinical application, this approach is best way to identify BP change as easily as possible, because we can apply the long-term monitoring possibility of BP measurement system. In this perspective, the finger PPG waveform-based technique may prove to be extremely valuable detection technique of BP. The technique proposed in the current study may be applied in home and mobile healthcare phase, so that whenever and wherever the patient are, BP assessment can be more convenient with very simple monitoring procedures. When the simple, comfortable and totally noninvasive BP measurement is required, PPG waveform will be the ideal application for continuous BP monitoring of the patient.

Key words: Photoplethysmograph, Blood pressure, Blood volume, Vascular resistance, Contact force, Skin surface temperature, Non-invasive blood pressure, Cardiovascualr diseases

Chapter 1 Introduction

1.1 Research motivation

In modern time, uncontrolled blood pressure (BP) has been one of the major causes of death in human beings. Based on statistics, uncontrolled BP leading to cardiovascular diseases (CVDs) occurs to almost 20% of disorder to adults. Ignored control of BP has been recognized as a major contributor to preventable cardiovascular deaths.

Abnormal BP has close relation with the generation of main CVDs including the coronary heart diseases, the cardiac insufficiency, and the cerebrovascular disorders. The proper control of BP to prevent the frequent adult diseases is very meaningful not only for the personal health of patients but also for the public health care of the government [1-3]. The most basic method to control BP is to measure and monitor BP periodically. It is because, except some emergency cases, the long-term trend of the pressure change is more important than the temporary BP of the present [4-5]. Therefore, it is very important to measure BP periodically in the ordinary life [6].

BP measurement method developed up to now can be largely divided into the invasive and the non-invasive methods. The invasive method also called ‘the direct method’ is the way to insert the catheter directly into the blood vessel of the patient. The non-invasive method also called ‘the indirect method’ includes the auscultation, the facilitation, the oscillometric method, the Finapres method, the phase shift of tactile sensor and the pulse transit time (PTT) method. The typical ones among BP measuring methods are the direct method and the auscultation using the mercury (Hg) BP gauge. But the direct method is used only for the study or in the intensive care room because of the high cost and the risk. The mercury pressure gauge has been used for years in the hospital but its use is getting decreased in the USA and Europe due to the strengthened restriction of hazardous materials. Both of these methods require the additional help of medical person in their measurement [7].

Presently, the most general BP measuring methods are the auscultation and the

oscillometric method [8-10]. In both of these methods, the cuff is attached to the upper arm or the wrist of the attested and compressed with the higher pressure than the systolic blood pressure (SBP) to block the artery. BP is measured while the pressure is gradually diminished. But, this measurement method with the cuff is not appropriate for the continuous measurement because BP cannot be measured again until the blocked artery is restored [11]. Furthermore, the press by the cuff can make the patients uneasy and uncomfortable or inflict the damage on the measuring part [6, 12]. To solve this problem, the method using the pulse transit time was proposed [13-15]. In this method, BP is estimated with the relation of inverse proportion between BP and PTT by analyzing the photoplethysmograph (PPG) and the electrocardiogram (ECG) signal. If BP goes up, the elasticity of the vessel wall is decreased and thus PTT tends to increase [16-18]. But this method requires the additional acquisition of ECG signal. Therefore, in the previous studies, only the transit time of the reflective wave was acquired without ECG signal and BP was estimated just by the volume pulse [19]. But, even though it is simple and convenient, this method also requires additional studies because it estimates BP only through the elasticity of vessel wall and the resistant elements.

1.2 Research hypotheses

The main hypothesis of the current work was that multiple features derived from the finger PPG waveform based on pulse wave analysis could reflect blood volume (BV) and vascular resistance (VR) induced by cardiovascular condition and therefore was potentially useful for the detection of BP. In order to test the hypothesis that morphological features derived from the finger PPG waveform could reflect the central BP, we simultaneously measure BP and the finger PPG waveform.

We also hypothesized that the contact force (CF) and the skin surface temperature (SST)

in measurement area would lead to an unexpected change to the finger PPG waveform, even when the changes in BP and the heart rate (HR) were minimal. To test this hypothesis, graded CF change and SST change were used as models to simulate the cardiovascular response to mild environment effects.

1.3 Objectives of current study

The overall objective of the current study is to assess the feasibility of using multiple features derived from the finger PPG waveform as markers of BP. The specific objectives are:

1. To study the change in PPG waveform during BP change from patients in emergency room and intensive care unit based on a blood flow model and to evaluate their potentials as non-invasive indicators of CVDs.

2. To evaluate the potential use of the finger PPG waveform derived BP as a non-invasive indicator of BV and VR by investigating its association with progressive change in the central BV and the total peripheral resistance (TPR) induced by cardiac stimulants.

3. To investigate the propriety of using normalized PPG derived the finger PPG waveform to track variations in CF change at measurement area and progressive changes in PPG waveform induced by forced mild cooling and heating.

4. To develop an automated method of detecting BP from the finger PPG waveform and evaluate the reliability of the measurement by direct comparison with the BP measured from clinical non-invasive blood pressure (NIBP) equipment.

1.4 Outline of current study

The current study consists with 6 chapters. Chapter 1 (this chapter) has stated the main hypotheses and objectives of the current work and the motivations behind. Chapter 2 provides background information related with the current work, including cardiovascular response to BP change, models of blood flow, and potential applications of PPG waveform, including a brief description of the physiological meaning and information content of the finger PPG waveform. Chapter 3 presents the results obtained from the relationship study. It comprises two study modules: (1) Investigation of the change in the finger PPG waveform derived BV and VR during BP change from patients in thoracic surgery, emergency room, and intensive care unit; (2) Investigation of the change in the finger PPG waveform derived progressive change in central BV and TPR induced by cardiac stimulants. Chapter 4 presents the results obtained from compensation study. It comprises two study modules: (1) Investigation of the change in the finger PPG waveform derived normalized PPG waveform during CF change at measurement area induced progressive local vascular structure change; (2) Investigation of the change in the finger PPG waveform derived normalized PPG waveform during SST change at measurement area induced progressive vasoconstriction and vasodilatation. Chapter 5 presents the results obtained from the clinical long-term study, which assesses the correlation between clinical NIBP measurements and BP derived from finger PPG in a group of subjects. Chapter 6 briefly summarizes the overall body of work and presents suggestions for future research.

Chapter 2 Background

2.1 Overview

The potential applications of PPG waveform analysis are mentioned in section 2.2, including a brief description of the physiological meaning of PPG waveform and the possible features that can reflect cardiovascular conditions.

2.2 Potential applications of PPG waveform

PPG is an optical measurement technique that can be used to detect BV changes in the micro vascular bed of tissue [20]. It has widespread clinical application, with the technology utilized in commercially available medical devices [21]. PPG waveform is believed to have significant information regarding the patient's cardiovascular condition which has not been fully utilized in the current clinical practice [21-25]. This section reviews the physiological meaning of this signal and clinical applications, and mentions the potential benefits and limitations of using this signal as a diagnostic tool for BP change.

2.2.1 Physiological meaning of PPG waveform

PPG also called photoelectric plethysmogram. PPG signal can be acquired by a sensor probe consisting of a light source and a photodetector, which is usually a matched light

emitting diode (LED) and photodiode pair. The measuring site is illuminated with light, some of which is absorbed by the blood and tissue beneath the skin surface. The photodetector picks up either the transmitted light (in transmission mode) or the reflected light (in reflection mode). The basis of PPG measurement is the Beer-Lambert law, which relates the amount of light transmitted through the light absorbing substance with the amount of that substance, based on the following equation:

$$I = I_0 e^{-\varepsilon dc} \quad (1)$$

I_0 = Incident light intensity
I = Transmitted light intensity
c = Concentration of light absorbing substance
ε = Extinction coefficient of light absorbing substance
d = Path length or thickness of light absorbing substance

According to this equation, the log of detected light intensity would have a negative linear relationship with the concentration of the light absorbing substances. In peripheral PPG measurement, the light absorbing substances include the arterial blood, the venous blood and the tissue of the body site being monitored. As shown in Figure 2.1, the measured PPG signal typically consists of an alternating current (AC) component corresponding to systolic BV pulsation and a direct current (DC) component that represents predominantly fluctuation in the baseline arterial and venous BV [21, 23, 26]. The major cause of the observed variation in the PPG signal was believed to be the change in BV in the underlying tissue leading to the change in the absorption of light by the hemoglobin in the blood [26]. Other factors may also affect the amount of light detected, including the orientation effect of the erythrocytes, the movement of the vessel walls and the temperature-dependent optical characteristics of the tissue, but the effect of absorption usually dominates, such that arterial pulsation will produce a small reduction in the light detected, in synchrony with each heart beat [26, 27]. The complex manner in which light intensity is modulated by the underlying BV makes it difficult to quantify BV change using the PPG technique. [21]

As the AC component of PPG signal acquired by the photodetector represents the change of BV, it can be expressed as equation (2). The flow of BV is generated in the artery vessel, it can reflect the condition of the artery vessel. And the DC component (including DC offset and AC component) acquired by the photodetector can reflect the BV in the vein and the capillary vessels as well as the artery. Therefore, as shown in equation (3), the change of DC component is directly in inverse proportion to the BV [28].

$$\Delta\textbf{Blood Volume} = \textbf{AC component} \quad (2)$$

$$\textbf{Blood Volume} = \textbf{constant} - \textbf{DC component} \quad (3)$$

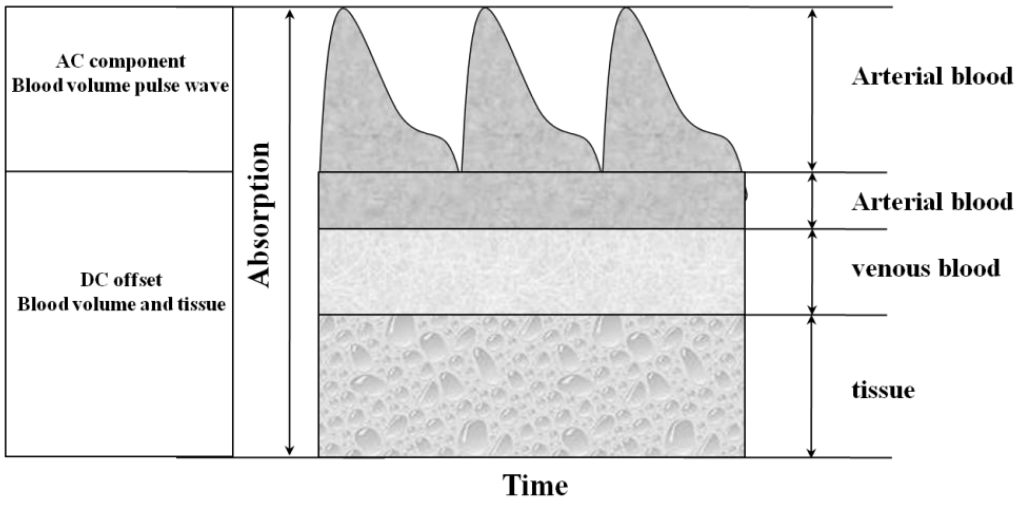


Figure 2.1. Composition of PPG waveform.

2.2.2 Clinical applications of PPG waveform

PPG has been applied in many different clinical settings including clinical physiological monitoring, vascular assessment, and autonomic function. Table 2.1 summarizes each measurable physiological parameters, measurement methods, and references. [21]

Table 2.1. Clinical applications I [21].

	Parameter	Method	Reference
Clinical physiological monitoring	Blood oxygen saturation	The differences in the light absorption of HbO_2 and Hb	[29]
	Heart rate	Pulse interval measurement	
	Blood pressure	Finapres^{TM}(for FINger Arterial PRESsure) technology	[30]
		PTT	[31, 32]
	Cardiac output	Pressure Recording Analytical Method	[33]
		ModelFlow^{TM} method	[34]
	Respiration	Respiratory induced intensity variations	[35, 36]
Vascular assessment	Arterial disease	Risetime, frequency characteristics, width/height ratio, amplitude and shape	[37-44]
	Arterial compliance and ageing	Pulse wave velocity	[45-47]
		Pulse shape characteristics	[48-51]
	Endothelial function	Shape-related information	[52]
	Venous assessment	Light reflection rheography	[53-55]
	Vasospastic conditions, e.g. Raynaud's phenomenon	The pulse amplitude and the slope of the rising edge	[56]
	Microvascular blood flow and tissue viability	Amplitude of the PPG pulse	[57]

Table 2.2. Clinical applications II [21].

	Parameter	Method	Reference
Autonomic function	Vasomotor function and thermoregulation.	PPG amplitude variations	[58-61]
	Blood pressure and heart rate variability	Finger-pressure cuff/PPG technology	[62, 63]
		PTT and RR interval	[64]
	Orthostasis	Changes in pulse with orthostatic stress	[65]
	Neurology	Trigemino-parasympathetic reflex The second derivative of the PPG pulse	[66, 67]

2.2.3 Benefits of using PPG waveform

There are various benefits associated with using PPG waveform for BP detection. The measurement of continuous arterial BP waveform requires an invasive catheterization or leads inconvenient compression of the measurement site; however PPG waveform can be continuously acquired for a long period of time in a totally non-invasive and comfortable manner. The measurement of PPG waveform is also remarkably easy to perform, simply by attaching a sensor probe on the skin without the need for much skill or expertise. The fact that PPG waveform measurement can be performed in a relatively operator independent manner and only requires the accessibility of a peripheral site, which is typically the fingertip, the ear, or the toe, has made it a very attractive option for BP monitoring.

Almost vital sign monitor would measure pulse oximetry, meaning that no extra equipment would need to be installed for measuring BP with PPG waveform-based technique. This is another important consideration for the feasibility of the BP monitoring technique. The time and cost associated with the installation of new equipment and the training of medical staff for proper operation of the equipment may deter wide deployment of these techniques in the critical care sector, the waiting room of the often overcrowded clinical center to assist pre-diagnosis and triage of BP disorder patients, given the budget constraint of the health care department.

The development of microelectronic technology has led the development of lightweight and miniature wearable PPG biosensors, such as the ring sensor designed by the MIT group [68]. These types of sensors are not only useful for early diagnosis and triage of patients during the pre-hospital phase, but also permit continuous remote cardiovascular monitoring, for example, in a home, mobile, sports healthcare setting. A typical feature of these wearable biosensors is the integration of data acquisition and wireless transmission facilities; such that the subject is free to perform daily activities while being continuously monitored. [69]

2.2.4 Limitations of using PPG waveform

Despite the advantages of PPG waveform, the various external and internal influences of PPG waveform may limit its application. These influences include motion artifact [70], vascular tone [70, 71] and contact force with the sensors [72, 73]. Motion artifact and peripheral vasoconstriction can degrade the quality of the PPG waveform signal and cause problems in reliable pulse detection [64]. Measurement of PPG waveform at alternative sites such as ear or forehead other than finger may help to reduce the problem [74]. An alternative approach is to perform an active warming procedure prior to finger to induce vasodilatation and improve signal quality [75], but this technique is only acceptable if one is not trying to measure the finger vascular tone.

Motion artifact in PPG waveform recording is almost unavoidable during continuous monitoring. The origin of motion artifacts in PPG waveform has been considered tissue movement, venous blood movement, and probably optics movement. Some researchers have proposed the use of multiple wavelength systems to eliminate these artifacts [76, 77]. However, it is likely that some artifacts cannot be eliminated, for example those associated with the distortion of arterial volume pulse at the vascular level, in which case robust automatic technique to differentiate between artifacts and true cardiac pulses will be much needed. Some pulse oximeters use the R-wave of ECG to synchronize PPG waveform and achieve significant improvement in the detection of noisy pulsatile signal [70]. In the design of wearable PPG devices for mobile monitoring, motion artifact minimization is one of most important consideration. The reduction of motion artifacts depends on elegant sensor design, including where and how the optical sensors are attached on the skin, what type of optical sensors are used, and whether an extra signal can be used as a noise reference [68]. With further advancement in sensor and signal processing technology, motion artifact may no longer be a big issue in future generations of PPG applications. [69]

Chapter 3 Relationship study

3.1 Overview

This chapter explores the utility of PPG waveform as a BP tool by using human and animal subjects. The relationship study was carried out in collaboration with the thoracic surgery, emergency room, the critical care medicine, and the animal experiment laboratory in Wonju Christian Hospital. Section 3.2 studies the change in finger PPG waveform derived by BV and VR during BP change from patients in thoracic surgery, emergency room, and intensive care unit. This section is built upon the results obtained from the human correlation coefficient study. In section 3.3, a study is taken by investigating of the change in PPG waveform derived progressive change in central BV and TPR induced by cardiac stimulants. The feasibility of using morphological analysis to characterize a hemodynamic response will be investigated.

3.2 A study of the estimation for blood pressure using the PPG waveform

3.2.1 Introduction

According to hemodynamics, increase of BP can explain with increase of BV and/or increase of TPR. However, BP is generated by processes of complex internal factors in human and any factor is impossible to represent the whole incidence mechanism of BP [78]. So a new method that can analyze BV and VR without the analysis of whole factors is developed and selected to estimate arterial BP.

In the study of Takazawa et al., they showed not only PPG waveform is similar to BP waveform but also mechanism of vasoconstrictions and vasodilatation [79, 80]. From these backgrounds, a basis that presents BP is led by analyzing BV and VR using PPG waveform.

PPG waveform is measured by using a light source. When a light source radiates on the skin, it is absorbed into arterial blood, venous blood, tissue and etc. Therefore, the pulsed part is affected by the cardiac contraction and relaxation and the non-pulsed part presents the absorption for non-pulsed arterial blood, non-pulsed venous blood, tissue and etc. [81]. Specially, the value of non-pulsed arterial blood presents the residual blood during the cardiac relaxation [82]. The change of BV in finger is generated by vasoconstrictions and vasodilatations in affected tissue by sympathetic nervous system [83]. For instance, vasoconstrictions are results of tissue hypovolemia and the low flexibility (high resistance) of arteries. Therefore, the analysis of BV and VR becomes an item that can detect the relationship of BP [84−88].
The verification of hypothesis is confirmed with the existing vascular models and the evaluation of experimentations is performed with the physiological investigation in

animal tests and clinical tests.

3.2.2 Models

3.2.2.1 Blood pressure

BP means the pressure acting on the vessel during the flow of blood along the vessel while the heart is contracting and dilating. As shown in equation (4), BP is dependent on both blood flow (Q) and VR.

$$\mathbf{BP} \propto \mathbf{Q} \times \mathbf{VR} \tag{4}$$

This equation makes equation (5), BP is calculated with the times of cardiac output (CO) and TPR.

$$\mathbf{BP} = \mathbf{CO} \times \mathbf{TPR} \tag{5}$$

3.2.2.2 Vascular physiology

3.2.2.2.1 Basic cardiovascular system

The vascular model as Figure 3.1, is composed by heart, aorta, and peripheral vascular. This model explains variations and characteristics of aorta and peripheral vascular according to the blood flow change between systolic and diastolic heart conditions. As shown in equation (6), the sum of aorta BV and peripheral vascular BV is the BV that ejects from ventricular during systolic.

$$Q_i = Q_s + Q_p \tag{6}$$

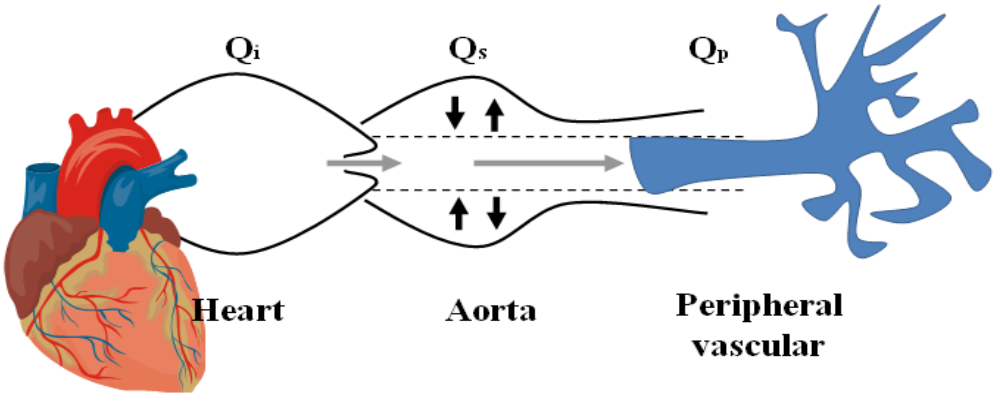


Figure 3.1. Basic cardiovascular system.

Aorta has the compliance by blood flow and pressure. This compliance regards as the capacitor that controls blood flow increases and decreases in the cardiovascular system [89]. Figure 3.2 shows the idealized segments of artery.

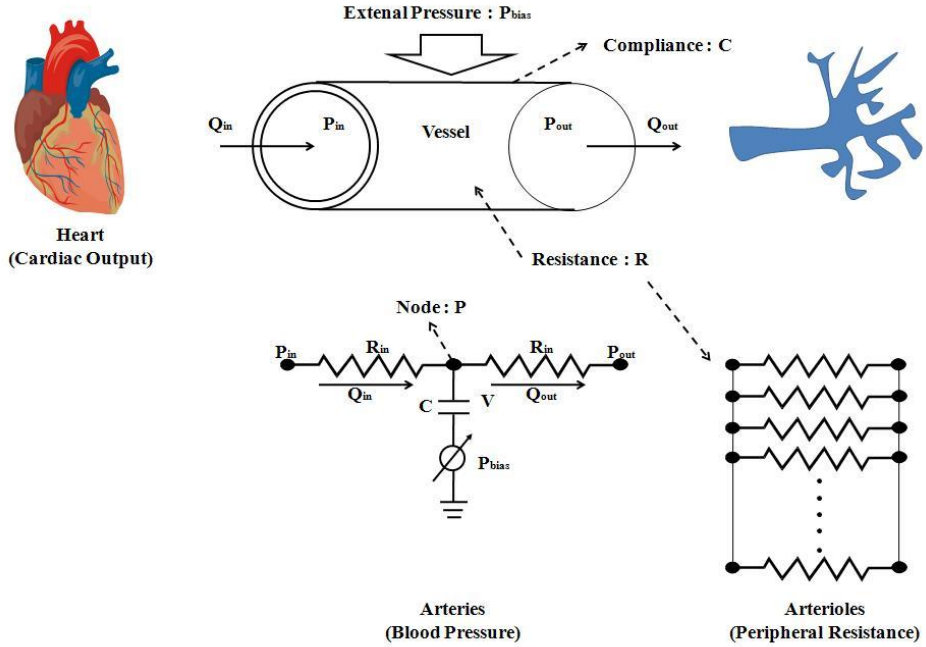


Figure 3.2. Idealized segments of artery.

3.2.2.2.2 Windkessel models

Two-element windkessel model is composed by resistance and capacitor. The electrical equivalent circuit show as Figure 3.3. Capacitor represents BV changes for the blood flow increases and decreases in aorta, and resistance represents BV decrease by the blood pressure decreases in peripheral vascular. Equation (7), (8), (9) and (10) explain this windkessel model.

$$Q_s = C\frac{dP}{dt} \tag{7}$$

$$Q_p = \frac{P}{R_p} \tag{8}$$

$$Q_i(t) = C\frac{dP}{dt} + \frac{P}{R_P} \tag{9}$$

$$P(t) = P_0 \exp(-\frac{t}{R_P C}) \tag{10}$$

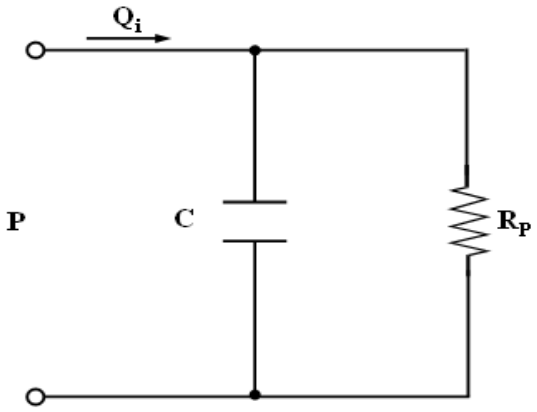


Figure 3.3. Electrical equivalent circuit of two-element windkessel model.

Two-element windkessel model is effective on low frequency condition. The developed vascular model, three-element windkessel, consider high frequency condition for the impedance characteristic of aorta, so this model adds the resistance of arterial

characteristic, as shown in Figure 3.4. [90-92] Relationships between BP and the blood flow indicate in equation (11) and (12).

$$Q_i(t) = C\frac{dP_{C(P)}(t)}{dt} + \frac{P_{C(P)}(t)}{R_P} \tag{11}$$

$$P(t) + RC\frac{dP(t)}{dt} = (R + Z_0)Q_i(t) + Z_0RC\frac{dQ_i(t)}{dt} \tag{12}$$

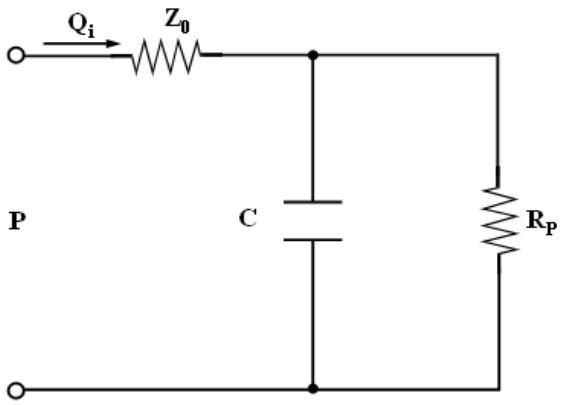


Figure 3.4. Electrical equivalent circuit of three-element windkessel model.

Four-element windkessel model includes the inertia of aorta blood flow as shown Figure 3.5. [93] Equation (13), (14), and (15) represent the total inertia of arteries, BP, and BV.

$$L_i = \int_0^{ls} c_u \frac{\rho}{A(x)} dx \tag{13}$$

$$\frac{dP_{C(P)}(t)}{dt} = -\frac{1}{RC}P_{C(P)}(t) + \frac{1}{C}Q_i(t) \tag{14}$$

$$\frac{dQ_L(t)}{dt} = -\frac{Z_0}{L}Q_L(t) + \frac{Z_0}{L}Q_i(t) \tag{15}$$

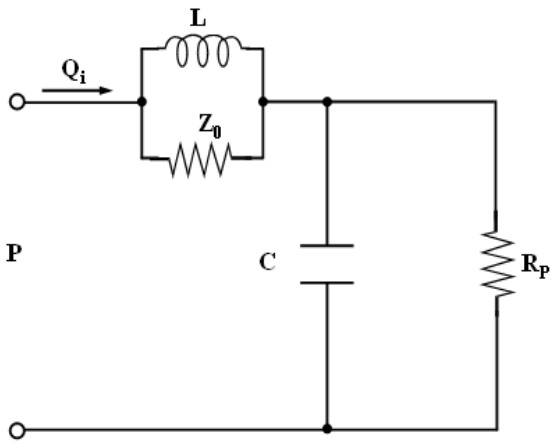


Figure 3.5. Electrical equivalent circuit of four-element windkessel model.

Equation (4) represents that BP is dependent on both blood flow (Q) and VR. Therefore, if we find components that reflect blood flow and VR, we could estimate BP. For this hypothesis, we would like to find these components from these models, so we assumed that the PPG waveform had these components.

3.2.3 Methods

These tests were progressed at the thoracic surgery, and the critical care medicine in Wonju Christian Hospital. First of all we checked the relationship between BP and the finger PPG waveform.

3.2.3.1 Subjects and experimental protocol

The clinical test was processed with 6 patients who were 9 to 83 years and were using an invasive blood pressure (IBP) instrument in Wonju Christian Hospital. In the test we used non-invasive sensors however we measured data with specialists' supervision and help.

The patients were selected by a significant situation that we could observe changes of IBP with patients' stability.

Figure 3.6 shows the acquisition site of sensors that are ECG, PPG, and IBP. We used the BP transducer and set additionally on the BP catheter in a patient monitor. ECG electrodes used in a normal way and the PPG sensor was set on the index fingertip. During the tests we never artificially changed patients' BP.

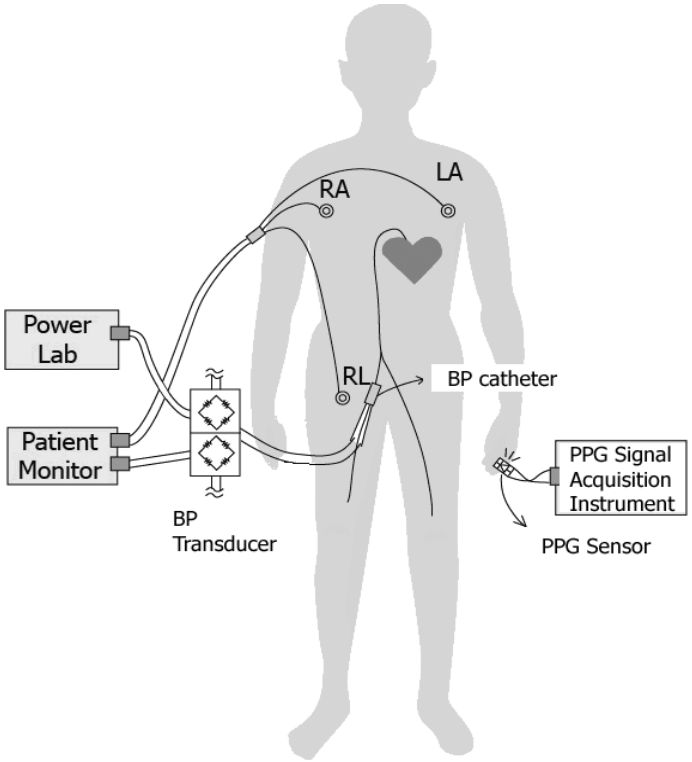


Figure 3.6. Acquisition sites of sensors for clinical tests.

3.2.3.2 Sensor

In this study, sensor devices were classified into two classes. One was for the relationship between the finger PPG waveform and BP, the other was for the relation between the finger PPG waveform and physiological conditions. Figure 3.7 shows cross sections of

sensor. Sensor was designed for acquiring data at index finger in the measured region. Optical sensors were made of LEDs which could radiate 640 nm and 940 nm wavelengths and a photodetector which had the center frequency response on 900 nm.

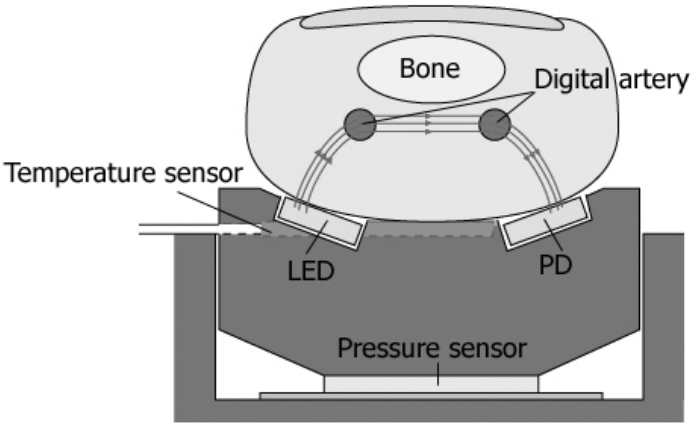


Figure 3.7. Cross sections of sensor. Illustration showing the cross section of the finger.

3.2.3.3 Data acquisition and analyzing

To acquire data, we used a Power Lab (AD Instrument Co.) and acquired IBP, ECG, reflected red BV data, reflected red VR, reflected infra-red BV, reflected infra-red VR. Figure 3.8 shows an acquisition program that is the Chart4 for the window. The sampling rate was 200 Hz. The data acquisition was for comparing and analyzing data. The data processing was operated off-line. We used software which is LabVIEW for Windows XP.

We used multi-regression methods for analysis of correlation between the finger PPG waveform and BP with a program, which is SPSS 12.0 for Windows XP. In the analysis we set a dependent variable IBP waveform and independent variables BV and VR.

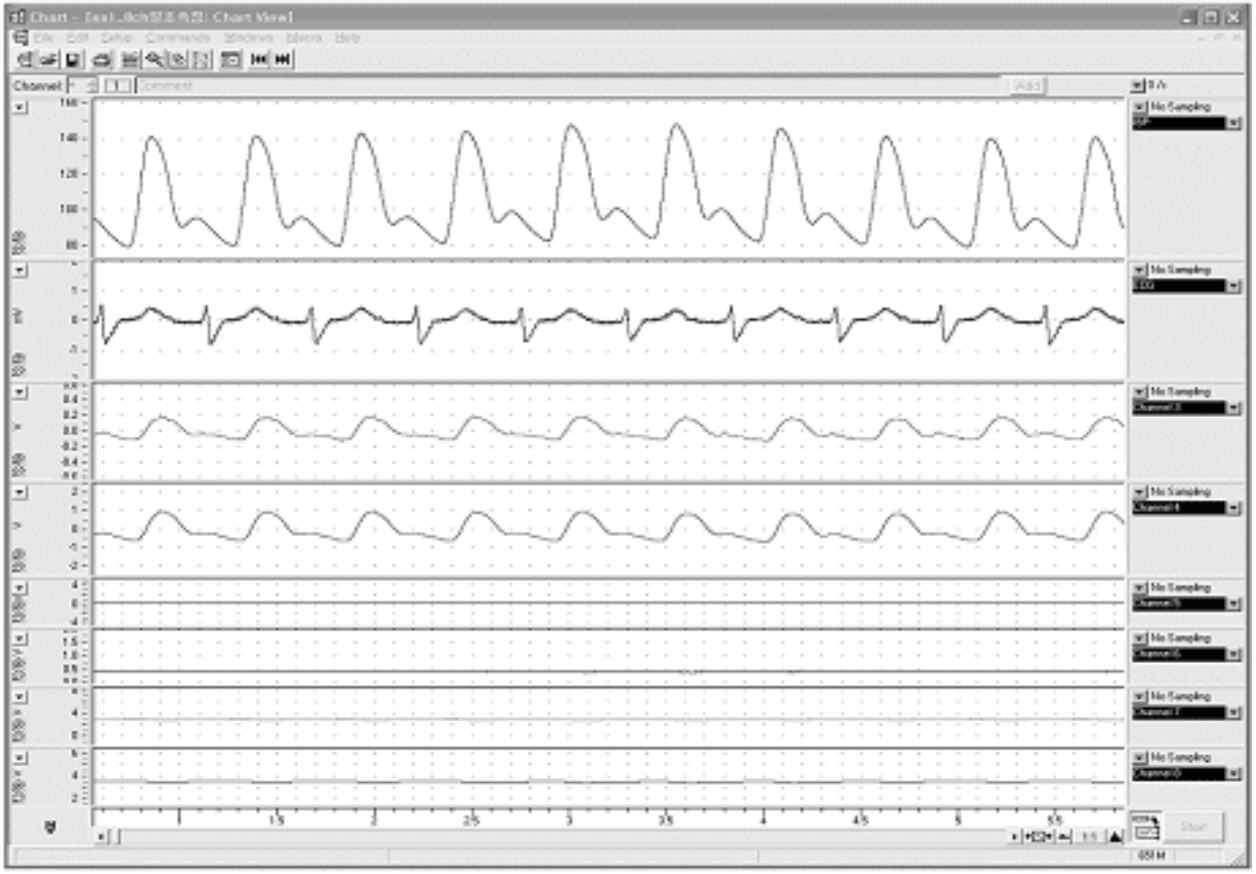


Figure 3.8. Power LAB data acquisition window.

3.2.3 Results

In multi-regression analysis, correlation coefficients were 0.722 ± 0.090 for SBP and 0.831 ± 0.113 for diastolic blood pressure (DBP) ($p < 0.01$). Standard errors of the estimate were 1.938 ± 2.280 mmHg for SBP and 1.647 ± 2.390 mmHg for DBP. Results refer to the propriety for using dependent and independent variables in these tests. (Table 3.1, 3.2)

Table 3.1. Model summary.

Model	R	R^2	Adjusted R^2	Estimated Standard Error	Significance Probability	Independent Variables	Dependent Variable
1	0.601	0.361	0.360	0.89916	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.794	0.630	0.630	0.65121	$P < 0.01$	(const.), Is, IRdia	IBP_DIA
2	0.747	0.558	0.555	0.86577	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.915	0.837	0.836	0.46205	$P < 0.01$	(const.), Is, IRdia	IBP_DIA
3	0.736	0.542	0.538	0.81766	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.952	0.906	0.905	0.33244	$P < 0.01$	(const.), Is, IRdia	IBP_DIA
4	0.648	0.421	0.418	1.04260	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.839	0.704	0.703	0.69652	$P < 0.01$	(const.), Is, IRdia	IBP_DIA
5	0.859	0.738	0.735	6.57014	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.855	0.732	0.729	6.48257	$P < 0.01$	(const.), Is, IRdia	IBP_DIA
6	0.743	0.551	0.547	1.43243	$P < 0.01$	(const.), Is, IRsys	IBP_SYS
	0.630	0.397	0.391	1.25764	$P < 0.01$	(const.), Is, IRdia	IBP_DIA

IBP_SYS = Invasive systolic blood pressure, IBP_DIA = Invasive diastolic blood pressure

Table 3.2. Coefficient.

Model		Unstandardized B	Coefficients Standard Error	t	Significance Probability	Dependent Variable
1	const,	110.623	2.841	38.943	0.000	IBP_SYS
	IRsys	–23.436.	1.193	–19.651	0.000	
	Is	–1.236	0.380	–3.251	0.001	
	const,	79.874	1.942	41.134	0.000	IBP_DIA
	IRdia	–14.756	0.810	–18.216	0.000	
	Is	–5.372	0.322	–16.668	0.000	
2	const,	168.483	5.481	30.739	0.000	IBP_SYS
	IRsys	–47.204	2.276	–20.743	0.000	
	Is	–1.906	0.484	–3.942	0.000	
	const,	129.182	2.638	48.971	0.000	IBP_DIA
	IRdia	–35.755	1.087	–32.902	0.000	
	Is	–1.956	0.309	–6.327	0.000	
3	const,	166.850	9.153	18.229	0.000	IBP_SYS
	IRsys	–43.582	3.620	–12.039	0.000	
	Is	–7.570	0.549	–13.796	0.000	
	const,	139.276	3.295	42.274	0.000	IBP_DIA
	IRdia	–38.679	1.299	–29.784	0.000	
	Is	–4.145	0.216	–19.232	0.000	
4	const,	109.123	3.384	32.244	0.000	IBP_SYS
	IRsys	–20.482	1.186	–17.268	0.000	
	Is	–6.756	0.453	–14.913	0.000	
	const,	100.576	2.176	46.227	0.000	IBP_DIA
	IRdia	–23.549	0.759	–31.016	0.000	
	Is	–5.213	0.235	–22.157	0.000	
5	const,	3886.661	168.078	23.124	0.000	IBP_SYS
	IRsys	–473.364	21.364	–22.157	0.000	
	Is	–0.327	0.243	–1.349	0.179	
	const,	3730.533	164.810	22.635	0.000	IBP_DIA
	IRdia	–456.255	20.941	–21.788	0.000	
	Is	–0.353	0.239	–1.475	0.142	
6	const,	703.017	47.942	14.664	0.000	IBP_SYS
	IRsys	–124.619	10.860	–11.475	0.000	
	Is	–7.229	30.467	–0.237	0.813	
	const,	486.380	44.439	10.945	0.000	IBP_DIA
	IRdia	–86.767	10.051	–8.633	0.000	
	Is	–20.229	27.288	–0.741	0.459	

IBP_SYS = Invasive systolic blood pressure, IBP_DIA = Invasive diastolic blood pressure

3.2.3.1 Blood pressure estimation

According to clinical test, we are able to lead followed equations.

$$IBP_{SYS} = a_{SYS} IR_{SYS} + b_{SYS} I_S + c_{SYS} \quad (16)$$

$$IBP_{DIA} = a_{DIA} IR_{DIA} + b_{DIA} I_S + c_{DIA} \quad (17)$$

where IBP_{SYS} indicates SBP, IBP_{DIA} indicates DBP, IR_{SYS} indicates systolic BV, IR_{DIA} indicates diastolic BV, Is indicates VR.

.

The reason why we establish individual multi-regression equations, PPG waveform is dependent on each model when we estimate BP. This condition comes from physical differences of patients. Therefore we concentrate on signs of correlation coefficients as Table 3.3.

Table 3.3. Correlation coefficient and sign.

CORRELATION COEFFICIENT	SIGN
a	Negative
b	Negative
c	Positive

3.2.4 Discussion

SBP and DBP are proportioned to BV and inverse-proportioned to VR without constant terms. Therefore PPG waveform from the artery is proposed a basis to detect BP. We are also able to get transitions BV and VR when PPG waveform is acquired during long term. These processes can predict the change of BP. From the experimental result, we discovered the possibility that we can develop the system which complements the weak points of existent cuff BP measurement by offering both accuracy and convenience.

3.2.5 Summary of findings

Preceding studies have shown PPG waveform resembles BP waveform and varies. Some investigators also have studied this relationship to explain complex hemodynamic characterization. The purpose of this study is to make a trial of finding arterial BP using PPG waveform. This new attempt is based on the theory that BP consists of the change of BV and the resistance of vessels. This study proposes a method to estimate BP from PPG waveform and points to be considered when we use this method. From the experimental results, we suggest the relationship of the estimation of BP from PPG waveform. When PPG waveform is normalized by CF and SST, this PPG waveform offers more accurate estimation of BP. However, these effects ignores with limits in this test, so we could regard as we use normalized PPG waveform. This study could be able to provide a new BP measurement system that has not only convenience but also accuracy.

3.3 Non-invasive estimation of systolic blood pressure and diastolic blood pressure using PPG components

3.3.1 Introduction

BP is an important parameter in the evaluation of cardiovascular function and status. It has generally been accepted that BP control is significantly affected by the resistance in the peripheral vessels and CO that correspond to BP control during systole and diastole, respectively. The cardiovascular system is a closed loop comprising the heart and blood vessels; its internal pressure is continuously changing due to changes in BV and vascular capacity. On the basis of this physiological foundation, change in blood flow and vessel status can be evaluated by monitoring the change in BP [94-96].

According to these previous studies, it is possible that the DC component reflects change in BV, and the AC component reflects vascular compliance and resistance. Moreover, a PPG waveform can provide useful physiological information for evaluating the cardiovascular system along with BP. Previous studies have researched these relationships with NIBP, general BP range or only one PPG component.

In this study, forced hemodynamic changes were induced via commonly used cardiac stimulants in an animal experiment, and the PPG components recorded by a noninvasive method at the peripheral blood vessels were compared with IBP findings. In addition, the cause of a BP change induced by the infusion of dopamine and epinephrine was evaluated via a pharmacological approach. Thus, the possibility of evaluating the cardiovascular system by using the PPG components was investigated.

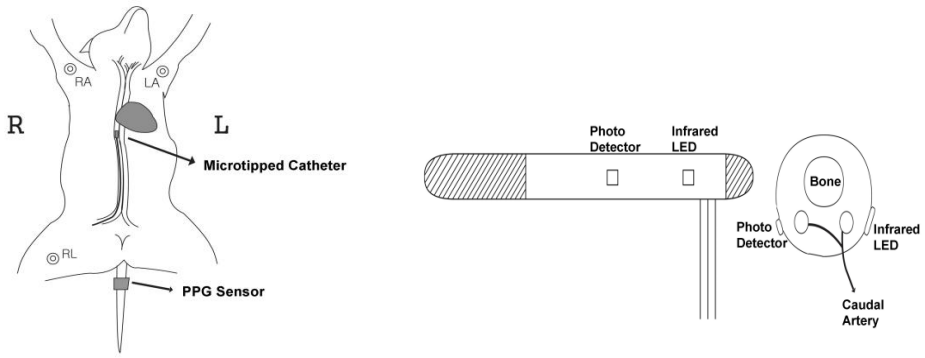
3.3.2 Methods

The experimental protocol was reviewed and approved by the Animal Research Committee of the Wonju College of Medicine, Yonsei University.

3.3.2.1 Subjects and experimental protocol

The study subjects included 6 dogs (20-25 kg), regardless of the gender. After an intramuscular injection of 25 mg/kg ketamine sulfate, endotracheal intubation was performed and anesthesia was maintained with 2% enflurane. Each anesthetized dog was fixed on a stand, and its respiration was maintained using an artificial ventilator. Figure 3.9(a) shows the positions of the direct BP sensor for IBP, ECG electrodes, and PPG sensors. IBP was monitored by inserting a microtipped catheter into the right femoral artery, and PPG waveform was measured at the dog's tail because the tail is one of easiest areas to set a PPG sensor and one of best areas to acquire precious vascular information. The overall experimental procedure is shown in Figure 3.9(c). The experimental animals were stabilized for 15 min after the experimental preparation was completed. To induce a hemodynamic change, 16 mg/mL of diluted dopamine was injected into a vein for 2 min at the rate of 20 μg/kg · min-1 by using an infusion pump. Thereafter, the infusion pump was ceased, and 1 mg of epinephrine was intravenously injected in order to induce a stronger hemodynamic change.

(a) (b)



(c)

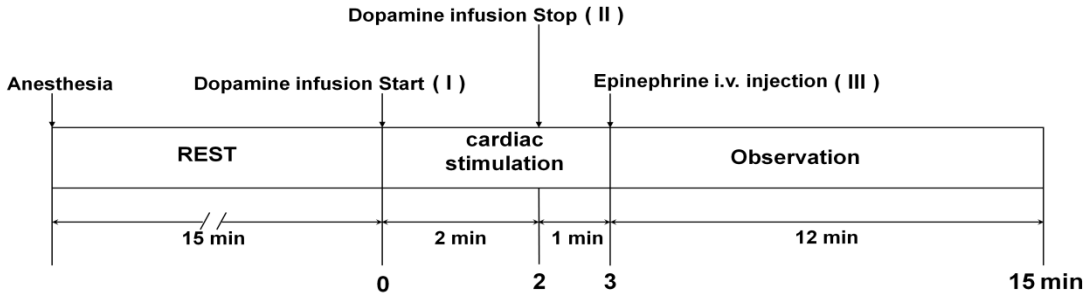


Figure 3.9. (a) Sensor positions in the animal experiment; (b) External view and cross section of contact pressure-fixed type sensor; (c) Flow diagram showing the course of experiment in this study.

3.3.2.2 Expected hemodynamic changes

Considering the pharmacological properties of dopamine and epinephrine, these two drugs are established as important frequently used cardiac stimulants [97-99]. Dopamine (3, 4- dihydroxyphenylethylamine) is a precursor of norepinephrine and is produced by the decarboxylation of dihydroxyphenylalanine (dopa) during the biosynthesis of catecholamines [100]. It is metabolized by monoamine oxidase (MAO) and catechol O-methyl transferase (COMT), and it becomes inactive after destruction in the digestive

tract. During dopamine medication, depending on the concentration, it exhibits different hemodynamic effects on dopaminergic, β1-adrenergic, and α1-adrenergic receptors. In most cases, 160 mg dopamine is diluted in 100 mL of glucose solution to obtain a concentration of 16 mg/mL for i.v. administration. Different hemodynamic effects are exhibited depending on the dose [101, 102]. At a low dose (0.5-3.0 μg/kg ˙ min-1), it mainly activates the dopaminergic receptor. At an intermediate dose (3.0-7.0 μg/kg ˙min-1), dopamine activates the β1-adrenergic receptors to increase HR and CO. At a high dose (> 10 μg/kg˙min-1), it mostly activates the α1-adrenergic receptors in the vessels, and vascular constriction raises BP [101, 103, 104].

Epinephrine is a hormone secreted from the adrenal medulla and is also known as adrenaline. Epinephrine is accepted as a stimulation transmitter in the sympathetic nerve, and epinephrine injection excites the β1-adrenergic receptors in the heart to enhance myocardial contraction via positive inotropic effects. Epinephrine increases HR via positive chronotropic action and enhances the irritability of the cardiac muscle via positive bathmotropic action. Its positive dromotropic action reduces stimulus conduction [105, 106]. Thus, CO increases; however, cardiac efficiency is reduced because of the remarkable increase in oxygen consumption in the cardiac muscle [99]. A significant reduction in systole than in diastole is observed in the heart activated by epinephrine. Conclusively, the total number of diastoles per minute increases with CO [98, 104]. However, if HR is increased beyond the physiological range, sufficient relaxation will not occur; therefore, CO will be reduced. Epinephrine in the vessels simultaneously activates the α-receptor and β-receptors, but the activation of the α-receptors is dominant and manifested as vasoconstriction. Epinephrine is the strongest agent for increasing BP, and an abrupt increase in BP is noticed depending on the i.v. injection dose [105]. This rise in BP results from increased CO due to enhanced myocardial contraction and HR. Moreover, SBP increases abruptly to a value more than DBP, i.e., pulse pressure increases [97, 99, 106].

3.3.2.3 Data collection and analysis

PPG waveform is influenced by external factors such as the distance between the light source and the photodetector, CF, and temperature [107]. In our experiment, a band type PPG sensor (MAX-N, Nellcor, Pleasanton, CA, USA) was used to monitor the change in the waveforms obtained from the cardiovascular system and minimize the effect of CF [72]. To minimize the effect of temperature [108], ambient temperature was maintained at 24 ± 0.7℃. To measure PPG waveform, an infrared light-emitting diode (LED) with a center wavelength of 890 nm and a photodetector with a center wavelength of 900 nm were used. The signal was measured in the transmission mode. The DC component of PPG waveform was detected by the photodetector, using an analog low-pass filter with a cutoff frequency of 20 Hz. Then the AC component of PPG waveform was extracted using a high-pass filter with a cut-off frequency of 0.15 Hz. Power Lab (ML880, ADInstruments, Bella Vista, NSW, Australia) with a 12-bit A/D converter was used to acquire signals at a sampling rate of 200 Hz per channel and digitize them. A constant current source circuit was used to drive the LED, and the amplification ratio was kept constant.

A pressure transducer (SPC-350, Millar Instruments,Houston, TX, USA) was used to measure IBP, and the signals were acquired at a sampling rate of 200 Hz using Power Lab. The acquired data was additionally analyzed with LabVIEW 8.2 (National Instruments). HR was detected from the ECG signal using a set of automatic programming routines involving the zero-crossing-Based QRS detection algorithm [109]. SBP, DBP, and PPG components were detected using a set of automatic programming routines involving low-pass filtering, zero-phase filtering, differentiation, and threshold peak/foot detection algorithm.

Figure 3.10 shows that the PPG signal has the following components: transmission current (I_T), absorption current (I_A), pulsation current (I_S), and cycle (R), which are related to the total current (I_0). I_T is inversely related to tissue blood volume, while I_S is proportional to increase in blood volume during contraction periods. R is the actual cardiac cycle. Transmission and pulsation currents (I_T and I_S) usually fluctuate in a low-

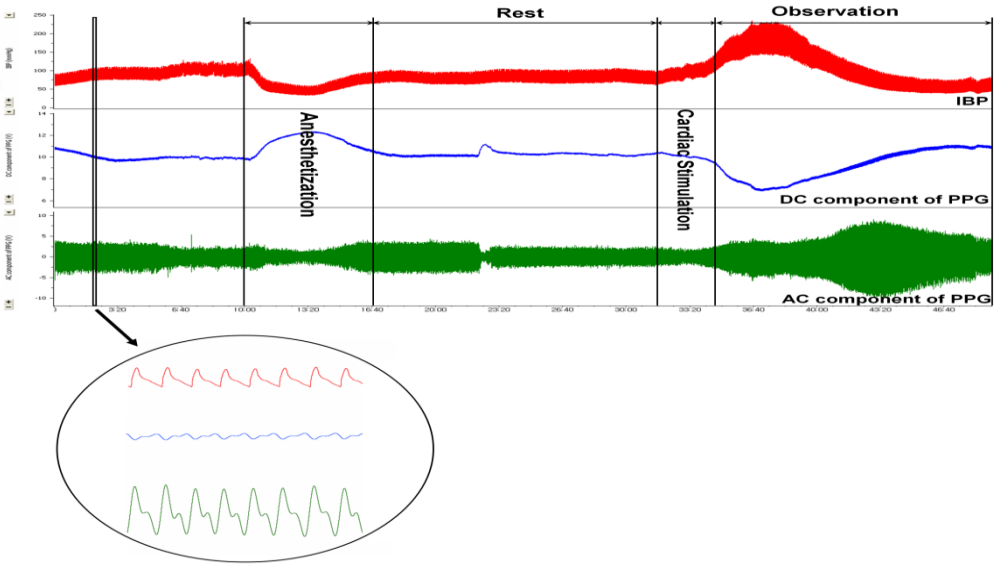
frequency range such as the respiration rate. Low-frequency fluctuation in the cardiac cycle is mainly controlled by the sympathetic nerve [110]. Variation in blood flow (I_A and I_S) is generated due to vasoconstriction and vasodilation, both of which are significantly affected by the sympathetic nervous system [111]. Therefore, PPG waveform specifically provides information regarding blood volume as well as that on blood pumping and its transportation status [21]. The I_T component is used in studies that measure BV, while the I_S component validates the existence of resistance in studies on the vascular compliance with the cardiovascular system, such as hypertension [112].

Low-frequency fluctuation of I_T and I_S originates from automatic variations in the sympathetic nerve activity. Activation of the sympathetic nerve leads to vasoconstriction. This is the result of low compliance (high resistance) in the arterial system and reduction in blood flow in tissue, which results in the increase of I_T and reduction of I_S [28, 113-115].

To monitor the hemodynamic change induced after the drug injection, HR, SBP, and DBP were measured every 30 sec for 15 min. For normalization, these parameters were also measured for 30 sec before the drug injection.

The absolute values for the DC and AC waveforms in PPG waveform were in different ranges because of the anatomical differences in the measured area for each subject. To compare the results of all the subjects under the same conditions, the average value for 30 sec before the injection was set at 1 and the average value for every 30 sec was normalized to analyze the 15-min data. These were used for comparing the changes in the PPG signal components with IBP changes. With regard to the values of the PPG components, transmission current during systole (I_{Tsys}) and transmission current during diastole (I_{Tdia}) were detected from the foot and peak of the DC signal, respectively. Pulsation current (I_S) was analyzed by the amplitude of the AC signal.

(a)



(b)

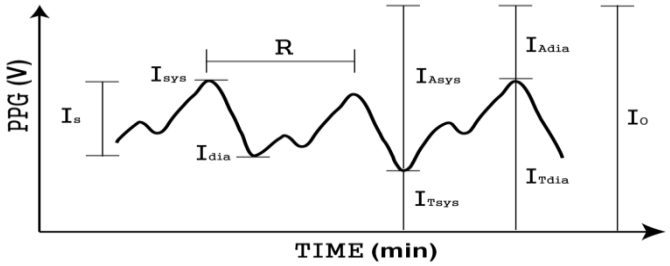


Figure 3.10. (a) IBP and PPG waveform from animal experimentation; (b) PPG components for analyzing. Just before 23:20, dog's tail moved so it caused a temporary fluctuation in PPG components. However, our data analysis focused from cardiac stimulation. (IBP): invasive blood pressure.

3.3.2.4 Statistical analysis

The statistical program used in this study was SPSS 12.0 (SPSS Inc, Chicago, IL, USA) for Windows. Statistical analyses were performed to evaluate the difference in response of data between two points of drug administration time for IBP, HR and PPG components

by the Student t-test. The changes in the IBP, HR, and PPG components were expressed as means with standard deviations. Pearson's correlation coefficients were evaluated via the correlation analyses of the PPG components and IBP. For all statistical analyses, $p < 0.05$ was considered significant.

3.3.3 Results

3.3.3.1 Variation in invasive blood pressure and heart rate

During the first 2 min of dopamine injection at the rate of 20 μg/kg ˙min-1, SBP increased from 92.3 ± 12.69 mmHg to 108.7 ± 20.23 mmHg, while DBP increased from 66.1 ± 10.75 mmHg to 81.8 ± 18.22 mmHg. After cessation of dopamine administration, BP slightly reduced. After the intravenous (i.v.) injection of epinephrine, SBP, and DBP significantly increased from 102.6 ± 18.44 mmHg to 214.5 ± 23.82 mmHg and from 76.7 ± 18.28 mmHg to 153.0 ± 15.17 mmHg, respectively. BP was observed to be a maximum 2-3 min after the injection of epinephrine. In addition, the pulse pressure, i.e., the difference between SBP and DBP, also increased.

HR before drug injection was 91.4 ± 12.69 bit/min, and the maximum HR was 122.9 ± 13.75 bit/min at 4 min after drug injection. During the injection of dopamine, HR tended to show a consistent elevation. After the i.v. injection of epinephrine, HR increased for 1 min and then reduced slightly (Figure 3.11).

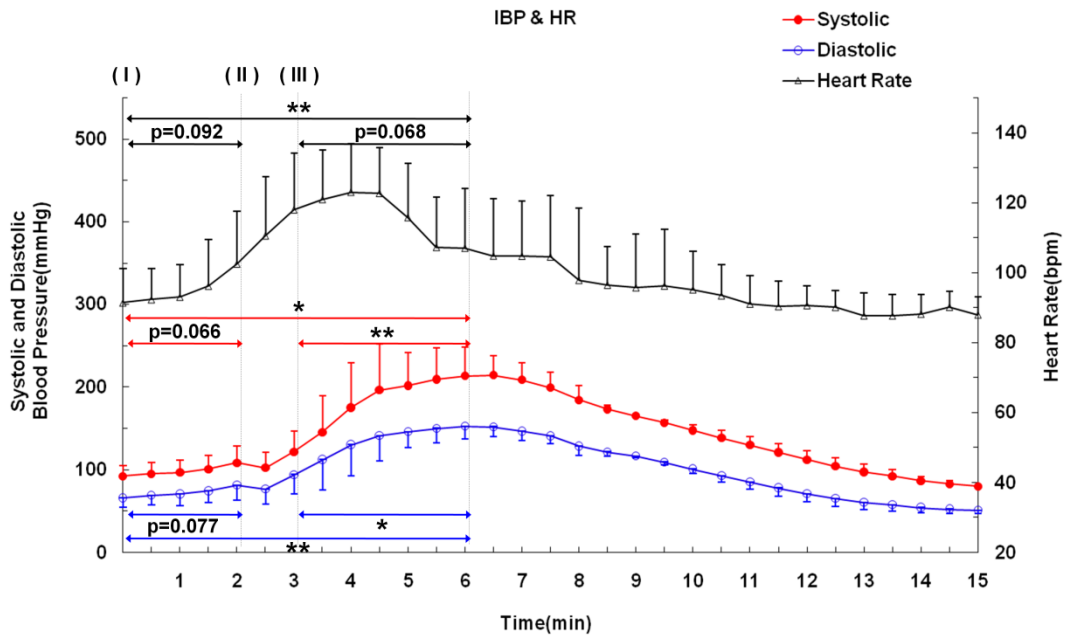


Figure 3.11. Response of blood pressure and heart rate to intravenous infusion and injection of cardiac stimulants. Systolic blood pressure (Systolic) and diastolic blood pressure (Diastolic) were monitored continuously by an invasive method. Heart rate was calculated from ECG. Points represent average values over a 30 sec period. Data shown as mean and SD. * $p<0.05$, ** $p<0.01$: significant increase / decrease.

3.3.3.2 Variation in the PPG Components

Before injection, the average values for 30 sec of DC and AC components of PPG waveform were set at 1. After the injection, the average values for every 30 sec were normalized. After the drug injection, the changes in I_{Tsys} (foot of the DC component of PPG waveform) and I_{Tdia} (peak of the DC component of PPG waveform), which reflect changes in BV, were minimal with values of 0.70 ± 0.035 and 0.71 ± 0.035, respectively, at 5-6 min. The variations in I_S (amplitude of the AC component of PPG waveform), which reflect changes in vascular compliance and resistance, were maximized with the value of 1.024 ± 0.273 at 11-13 min (Figure 3.12).

In regards to the variation in I_T (the DC component of PPG waveform) according to change in IBP in all the subjects, an increase in IBP indicated a significant reduction in I_{Tsys} and I_{Tdia}. In addition, the correlation coefficient between I_{Tsys} and SBP as shown in Table 3.4 was 0.939 ($p < 0.01$). It was 0.942 ($p < 0.01$) for DBP and I_{Tdia}. From these findings, a high correlation could be determined between IBP change and variation in the DC component of PPG waveform (Figure 3.13, Table 3.4).

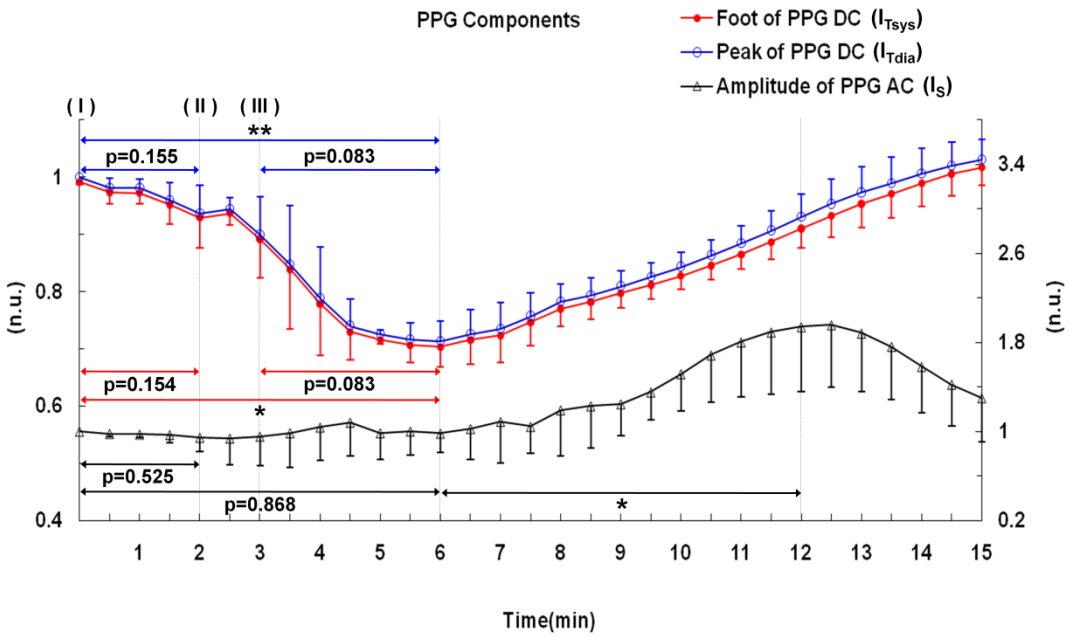


Figure 3.12. Response of PPG components (I_T: foot and peak of the DC component of PPG, I_S: amplitude of the AC component of PPG) to intravenous infusion and injection of cardiac stimulants. PPG were continuously measured by a non-invasive method, and normalized in order to compare the results of all the subjects under the same conditions. Points represent average values over a 30 sec period. Data shown as mean and SD. * $p<0.05$, ** $p<0.01$: significant increase / decrease.

(a) (b)

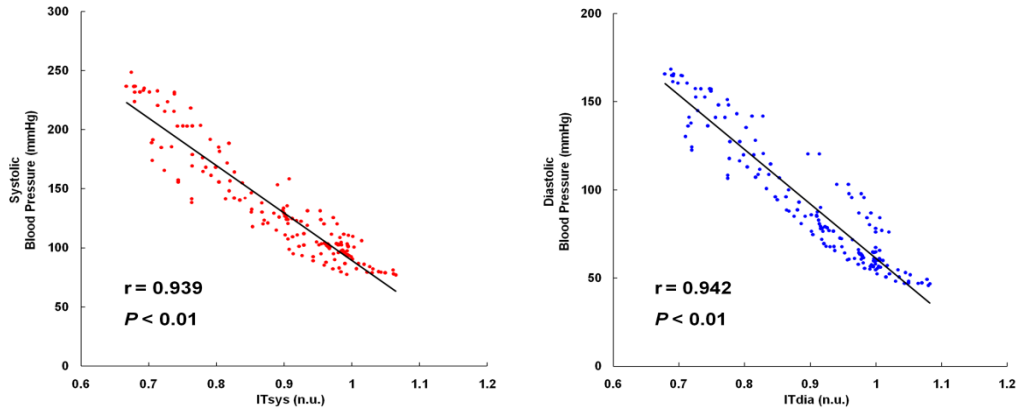


Figure 3.13. Relationship between invasive blood pressure (IBP) and the DC component of PPG (I_T). (a) Systolic blood pressure vs. foot of the DC component of PPG (I_{Tsys}); (b) Diastolic blood pressure vs. peak of the DC component of PPG (I_{Tsys}).

Table 3.4. Correlation and significant coefficients between invasive blood pressure and PPG component.

N = 180

		Heart Rate	Systolic	Diastolic	I_{Tsys}	I_{Tdia}
Systolic	Pearson Correlation	0.487**	1.000			
	Sig. (2-tailed)	0.000				
Diastolic	Pearson Correlation	0.586**	0.982**	1.000		
	Sig. (2-tailed)	0.000	0.000			
I_{Tsys}	Pearson Correlation	-0.426**	-0.939**	-0.936**	1.000	
	Sig. (2-tailed)	0.000	0.000	0.000		
I_{Tdia}	Pearson Correlation	-0.434**	-0.938**	-0.942**	0.998**	1.000
	Sig. (2-tailed)	0.000	0.000	0.000	0.000	
I_S	Pearson Correlation	0.061	-0.103	-0.144	0.061	0.097
	Sig. (2-tailed)	0.414	0.170	0.053	0.415	0.193

** Correlation is significant at the 0.01 level (2-tailed). Foot of the DC component of PPG (I_{Tsys}), peak of the DC component of PPG (I_{Tsys}), amplitude of the AC component of PPG (I_S).

3.3.4 Discussion

This study aims to investigate the relationship between IBP and the PPG components. The major purpose of this study was to investigate the possibility of monitoring the status of the cardiovascular system by using a noninvasive and inexpensive optical device, and provide information regarding the same. The change in the cardiovascular system due to cardiac stimulants, such as a change in IBP and the PPG components, was detected and analyzed by the presented animal experiments. The results indicate that the PPG components have a clinical potential to monitor BV, VR, and BP. Therefore, a noninvasive and easy monitoring method for the evaluation of cardiovascular function was proposed.

At a high dose, dopamine enhances myocardial contractility and CO through increased HR, resulting in an increase in SBP. In addition, DBP increases due to enhanced vasoconstriction [101, 105]. For the first 2 min of dopamine infusion, SBP and DBP showed an identical increase with HR. This indicated a distinctive reaction of dopamine.

After the epinephrine injection, we confirmed that the increase in SBP was more than that in DBP. Thus, pulse pressure increased. Hence, dopamine and epinephrine, the experimental cardiac stimulants, were confirmed to increase HR. Among the hemodynamic reactions, the change in HR was faster than that in BP (Figure 3.11).

The measured signals in our animal experiment were IBP and PPG waveform. PPG waveform measures the transmission of light through tissue as a function of time. Due to the increment in BV in the tissue during systole, PPG waveform shows low transmission. In addition, light transmission is pulsating along with the cardiac cycle (Figure 3.10) [113].

Increased BP due to dopamine and epinephrine can be analyzed by the increase in CO based on pharmacological basis [104, 116]. Therefore, reduction in I_{Tsys} and I_{Tdia} by the injection of dopamine and epinephrine can be explained by the increase in CO. I_S, which

corresponds to vascular compliance, did not reveal any significant change after the dopamine and epinephrine injection. Even though after the injection of epinephrine the pulse pressure increased, a constant I_S can be explained by vasoconstriction. In addition, the maximum variation in I_S was found at 11-13 min, and it can be elucidated by the physiological relaxation of the peripheral vessels to reduce increased BP (Figure 3.12). On the basis of this result, we confirmed the possibility that a change in the cardiovascular system can be detected by measuring the PPG components noninvasively.

Hemodynamic variations induced by dopamine and epinephrine could be confirmed by the increase in HR and BP, as shown in previous studies. Direct changes in BP due to dopamine and epinephrine and indirect changes in the vascular condition due to the hemodynamic variations were compared and analyzed through the animal experiment.

Previous studies on the effects of medical agents on the cardiovascular system have reported that a rise in BP is induced by increased static volume of blood in the vessels of the measurement area [97-99]. Our results are in close agreement with those of previous studies. Variation in the DC component of PPG waveform, which was noninvasively measured at the periphery, could be confirmed to have significant relationships with IBP (I_{Tsys} vs. systolic: $r = -0.939$, $p < 0.01$; I_{Tdia} vs. diastolic: $r = -0.942$, $p < 0.01$) (Table 3.4). Together with the DC component, the AC component of PPG waveform, which reflects vascular compliance and resistance, can show the physiological change in the cardiovascular system. Therefore, the AC component can predict increase and reduction in VR.

The undeniable advantage of PPG lies in its non-invasiveness and minimal restriction to patients [72]. In addition, PPG in conjunction with pulse oximetry, which is usually used for patient monitoring, can predict the change as well as the pattern of change in the cardiovascular status [21]. Moreover, PPG can be obtained from various locations in the human body, is rather inexpensive, and is a small-sized portable optical device [71, 117].

Thus, it fulfills the developmental conditions for a personal health monitoring and mobile physiological monitoring device. Although absolute accuracy in evaluating the

cardiovascular system may not be achieved, PPG components may be useful for indirect monitoring of the cardiovascular function and status. Analysis results of PPG components along with physiological changes induced by medical agents will provide useful clinical information to a doctor.

3.3.5 Summary of findings

PPG waveform is a noninvasive optical technology that detects changes in BV in the vascular system. This study aimed to investigate the possibilities of monitoring the cardiovascular system status by using PPG waveform. Forced hemodynamic changes were induced using cardiac stimulants; dopamine and epinephrine, and the PPG components were recorded by a noninvasive method at the peripheral blood vessels. The results were compared among 6 dogs. Endotracheal intubation was performed after an intramuscular injection of 25 mg/kg ketamine sulfate, and anesthesia was maintained with 2% enflurane. After stabilizing the animals for 15 min, 16 mg/mL diluted dopamine was injected into a vein for 2 min at 20 μg/kg· min-1 by using an infusion pump. Thereafter, the infusion pump was stopped, and 1 mg epinephrine was injected intravenously. Fluid administration was controlled to minimize preload change in BP. After stimulant administration, SBP and DBP increased. The DC component, which reflects changes in blood volume, decreased while the AC component, which reflects changes in vascular compliance and resistance, increased. The correlation coefficient between SBP and the foot of the DC component was 0.939 ($p < 0.01$), while it was 0.942 ($p < 0.01$) for DBP and the peak of the DC component. The AC component could predict the increase in VR from a stable pulse BV, even with increased pulse pressure. These results support the possibility that PPG components may be used for easy and non-invasive measurement of hemodynamic changes in the cardiovascular system.

3.4 Conclusions of relationship study

In this chapter, humans and animals were used to examine the utility of finger PPG waveform as a BP monitoring tool. PPG waveform change involves actual change of cardiovascular status from the subject, which depicts a more realistic representation of BP change. Two relationship studies for comparing BP and normalized PPG waveform have been investigated, both showing encouraging results: first was human relationship analysis in section 3.2, which involved the validation of the findings from BP change; second was animal relationship analysis in section 3.3, which involved computation of morphology measures from BP change with cardiac stimulants. In the former case, it was shown that shortening of PPG waveform change could induce BP change. More interestingly, progressive BP change is characterized by increase or decrease trend in PPG waveform that reflects BV and VR change, which are accompanied by effect or cardiac stimulants at a later stage. These results are in agreement with those obtained from blood flow model, and provide further evidence that monitoring trends in PPG waveform features can possibly be a non-invasive and convenient way of identification of BP change. Therefore, the originality of relationship study is that PPG waveform only use to estimate BP and established components represent the components of cardiovascular status that can summarize changes in BP.

The two major limitations of using relationship study are the inability to control the rate of BP change in human and the presence of physiological stress associated with cardiac stimulants in animal. Real life PPG waveform is often associated with various physiological or psychological condition changes, so these conditions have to consider for BP detection.

Chapter 4 Compensation study

4.1 Overview

This chapter presents that graded CF change and SST change were used as models to simulate the cardiovascular response to mild environment effects. The first model is the effect of CF and the second model is the effect of SST. Although graded CF and SST do not involve an actual change in BP, these can give the effect of progressive change in central BP similar to that which occurs during local vasoconstriction and vasodilatation. The experiments of compensation investigate the usefulness of the normalized finger PPG waveform features for identification of BP change. Section 4.2 starts with the investigation of effect of CF from measurement area. Section 4.3 then explores the change in the finger PPG waveform derived normalized PPG waveform during SST change at measurement area induced progressive vasoconstriction and vasodilatation.

4.2 The effect of contact force on PPG signal

4.2.1 Introduction

X F Teng and Y T Zhang well researched about the effect of contacting force on PPG signals. The followed information is the summary of their study.

The PPG signal is affected by CF between the PPG sensor and the measurement area as the shape of artery can be deformed by compression. The AC amplitude of reflective PPG signal may be influenced by the pressure applied on the skin by the transducer [118] and the amplitude increased when the pressure applied [119]. With the increase in the CF at the fingertip, the DC component of the reflective PPG signal measured at the finger nail had a corresponding changing trend [120]. Previous studies also investigated the influence of different applied brachial recording forces on arterial pulse waveform measured in brachio-radial arterial segment [121, 122]. Only a few studies have given an analysis of the effect of CF on PPG signal waveform. Therefore, in this study, a series of CF were exerted on the reflective finger PPG sensor and the characteristic changes of the signals were examined, including the AC and DC components of PPG waveform. With the increase in CF, which might significantly reduce vessel diameter, the signal waveform was expected to change due to local distortion and change in light path. [72]

4.2.2 Methods

4.2.2.1 Data collection

This experiment was carried out for 58 subjects (male: 42, female: 16, age: 28.9 ± 7.23) from 20 to 53 years old. All the subjects had no cardiovascular diseases except hypertension or hypotension and were under no treatment with the medicine. Before the experiment, all the subjects were educated about the experiment and wrote down the consent to participate in the study. The experimental protocol was reviewed and approved by the Clinical trial Research Committee of the Wonju College of Medicine, Yonsei University.

The compensation test of PPG waveform for CF was carried out by changing CF gradually(0.030 ~ 0.100 Kgf/㎠) while maintaining the SST of the subjects hand measured by the temperature sensor constant (higher than 32℃) within the range of the transmural pressure to prevent the signal distortion due to the damage by external pressure [18, 123].

In the experiment, the subjects were made to take the rest till their SST was stabilized and the measurement range of the pressure sensor was divided into stages where the patients did not feel uncomfortable. At this time, while CF is maintained at each stage, PPG waveform responding to the stepwise contact pressure was obtained. The measurement was made for about 10 sec at each stage, and the stages were divided into 8~16. A visual display was used to monitor and maintain the applied contact force to the subjects for the real-time feedback and the test was repeated 3 times.

4.2.2.2 Data analysis

PPG signal includes the elements like the reflection current (I_R), the absorption current (I_A), the pulsation component current (I_S) and the period (R) related with the whole supplied current (I_0). I_R is inversely proportional to the blood volume of the organ, I_S is proportional to the increase of the blood volume in the organ during the contracting period, and R is the actual period of the cardiac circulation.

PPG signal was analyzed offline using LabVIEW. For each pulse, DC amplitudes, AC amplitude, and period were calculated. The difference in PPG signals between two levels of CF was analyzed by the Student t-test. $p < 0.05$ was considered statistically significant. All results are presented as mean ± SD.

4.2.3 Results

The change of PPG waveform according to the change of CF was investigated by Mascare and Asada [120] and X F Teng and Y T Zhang [72]. In their experiments, it was confirmed that the DC and AC components according to the increase of CF tend to increase linearly only in the specific range by the personal physiological differences. Figure 4.1 is the result of the experiment when CF was increased stepwise for each person.

An example of the four traces of an original recording is shown in Figure 4.1. It includes PPG AC signal, PPG DC signal, temperature and CF.

Table 4.1 gives the correlation between PPG waveform and contact pressure in the form of mean ± SD. During the experiment, there were significant changes in PPG AC and DC signal ($p < 0.001$).

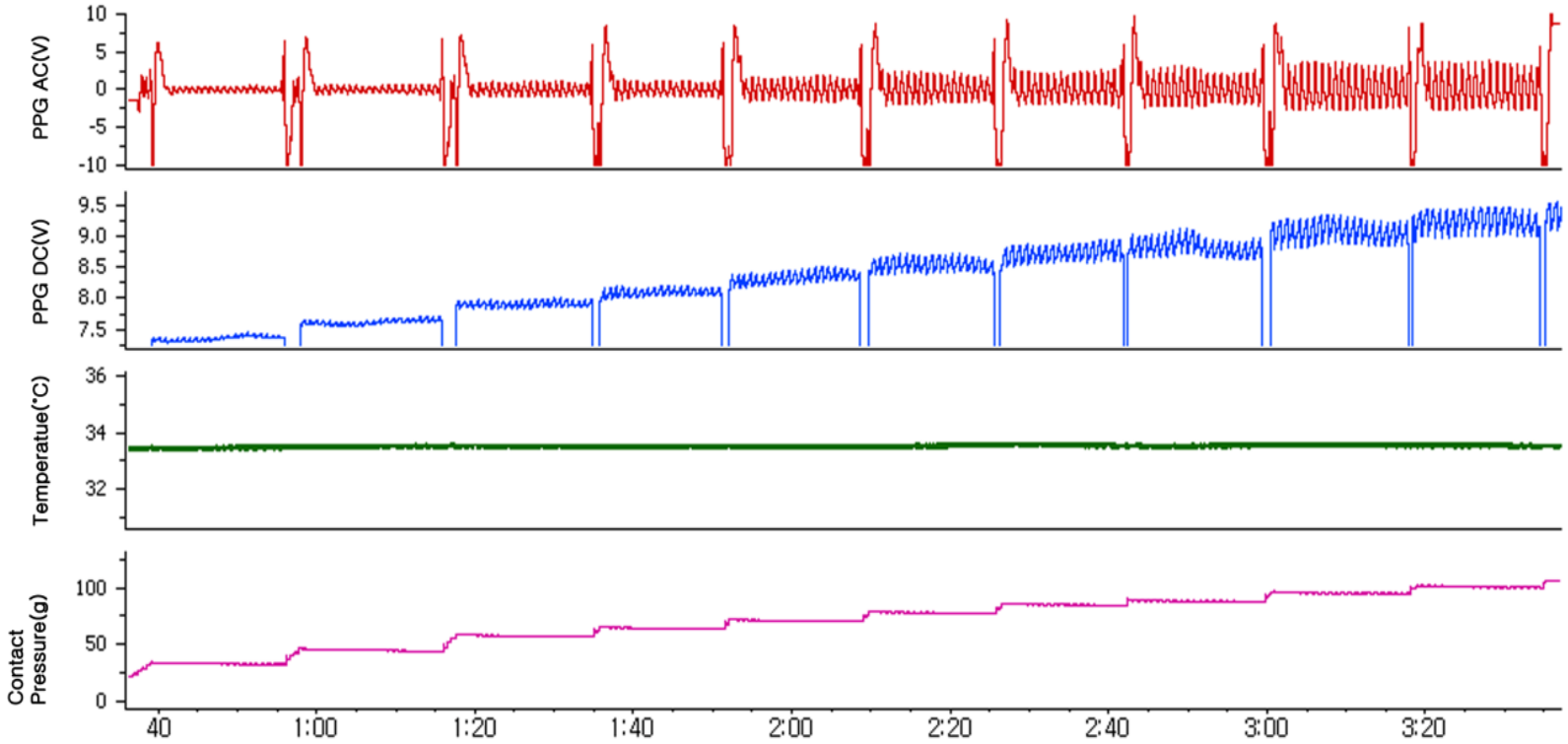


Figure 4.1. Change of PPG waveform according to change of contact force measured by compensation experiment of this study.

Table 4.1. Analysis of the correlation between PPG signal and contact pressure.

Independent Variable	Dependent Variable	R	Adjusted R^2	T	Sig.
Contact force	IRsys	0.92±0.054	0.85±0.100	25.21±14.216	0.000
	IRdia	0.93±0.051	0.86±0.094	26.63±14.427	
	Is	0.87±0.042	0.75±0.075	15.18±3.918	

4.2.4 Discussion

4.2.4.1 Amplitude related changes with contact force

At X F Teng and Y T Zhang study, the coefficients were about 10%. These results are consistent with a previous report that the coefficient of variability of pulse amplitude is 11% when signals are obtained from the fingers of healthy subjects [124].

When CF applied on the PPG sensor is increased, the arterial wall begins to flatten, as the result of compression, and the external pressure caused by CF approaches the intra-arterial pressure. The difference between the intra-arterial pressure and external pressure is defined as transmural pressure [72].

From the viewpoint of the arterial wall properties, the AC amplitude increases as CF increases up to a certain point where the transmural pressure goes to zero [125, 126]. After that peak point, the AC amplitude decreases since the artery begins to be occluded. Eventually, the artery is pushed against bone and the distal arterial wall will eventually flatten completely and the pulsation will disappear [72].

In X F Teng and Y T Zhang experiment, it was found that the DC amplitude of reflective PPG signals significantly increased when CF changed. Gradual increases of CF derive progressive decreases in the vessel diameter. This results in pooling of arterial blood in the capillaries underneath the fingernail. With the increase in the CF, blood vessel diameter decreases and blood is squeezed out of the vessel into the palm side of the finger. The decreasing BV tends to absorb less light, so more light is reflected and the DC output of the photodetector increases. The DC output approaches an asymptotic value when the veins are completely collapsed. Their finding is consistent with previous findings [120], where reflective PPG signals were recorded at the fingernail. [72]

In our study, with increasing contacting force, the DC and AC amplitudes increased until the transmural pressure. So this result supports X F Teng and Y T Zhang’s research.

4.2.5 Summary of findings

The waveform of the PPG signal may be affected by CF between the sensor and the measurement area. The aim of this study is to confirm X F Teng and Y T Zhang's study. Signals were recorded from the fingers of 58 healthy subjects. With increasing CF, the DC and AC amplitudes increased ($p < 0.001$) until the transmural pressure. The results suggest that the effects of CF should be carefully examined in the design of PPG-based health care devices.

4.3 Effects of local skin surface temperature during gradual cooling and heating on the photoplethysmography

4.3.1 Introduction

PPG signal is affected by external factors, such as the method for attaching the probes to tissue, the pressure between the probe and contact area, the subject's alertness and environment adaptation, and temperature, because these factors can affect the light absorption from the photodetector [21].

The purpose of this study is to propose temperature control or compensation when components of the PPG signal are used to evaluate vascular compliance, BP, and blood flow. To compare diverse changes in PPG signal in relation to the changes in SST from the measurement area, the air temperature in the chamber was controlled. After that, physiological changes of the subjects were induced using changes in the SST of the exposed areas. Evaluation was made by direct comparison of temperatures, PPG signal components, and cardiovascular status induced by temperature control.

4.3.2 Methods

The experiment was conducted on 16 subjects (15 male) and all subjects were healthy individuals who were not undergoing any drug treatment and did not have Raynaud`s phenomenon (Table 4.2). Before the experiment, all subjects underwent a training program and signed the research participation agreement.

All of the subjects were instructed to avoid smoking, alcohol consumption, and extreme exercise for 12 h and to prohibit caffeine intake for 4 h before the experiment in order to minimize factors such as exercise, nicotine, and caffeine, which can affect blood flow and blood vessel conditions, and to obtain more reliable data in accordance with the changes in SST [127].

4.3.2.1 Temperature Chamber Design

A polypropylene chamber that can heat and cool the skin of the hand and that was isolated from the outside temperature was created. Silicon was used for the front hole at the site of hand insertion. To enable observation of the fingers while performing the experiment, monitoring windows were installed in the front and rear using acrylic. Four cylinders were placed within the chamber, and a fan was installed in each cylinder to enable the smooth supply of air. Small holes on the cylinder were created so that the temperature within the chamber changes consistently as a whole and the fingers are prevented from being directly heated or cooled. On the sides of the chamber, opening and closing air passages were provided for air circulation within the chamber. (Figure 4.2(a).)

4.3.2.2 Measurement of temperature

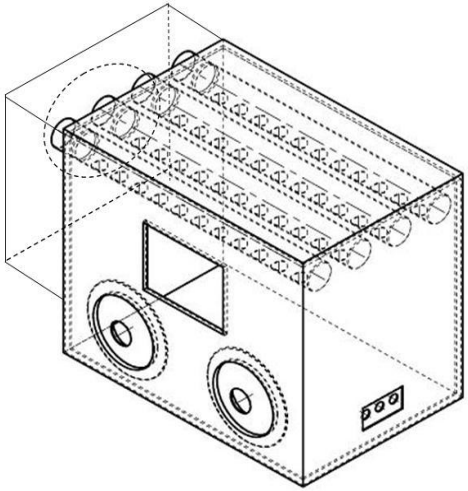
The changes in finger SST in accordance with the changes in air temperature within the chamber were obtained at the fourth finger through a contact temperature sensor (LNTG473FW, Lattron, Korea). To measure continuous SST, a PowerLab (ML880, AD Instrumentation, Australia) with a 12-bit A/D convertor was used at a sampling rate of 200 Hz. An infrared camera (TH5104, NEC, Japan) was used to show the finger SST distribution for both hands at 5-min measured intervals (0, 5, 10, 15, 20, 25 min). The SST distribution was acquired in order to observe that changing SST of five fingers per hand in the identical way.

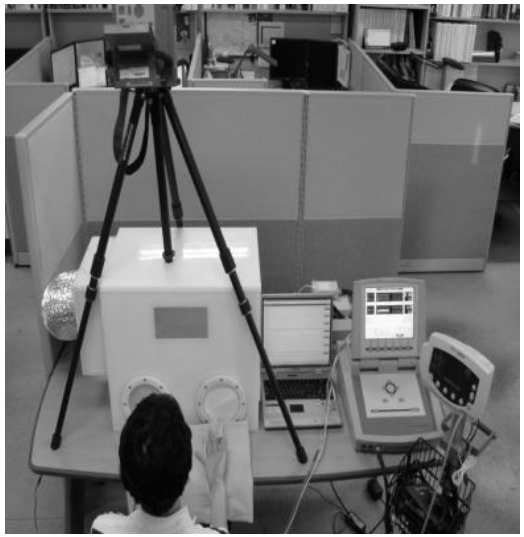
Table 4.2. Physical characteristics of subjects (n=16).

Variables	Min	Max	Mean±SD
Age (years)	23	30	26.4 ± 2.1
Height (cm)	167	184	174.1 ± 4.1
Weight (kg)	60	85	72.4 ± 6.5
BMI (kg/m2)	20.1	26	23.8 ± 4.8
Resting HR (beats/min)	57.7	82.5	73.8 ± 8.8
Resting SBP/DBP (mmHg)	102/59	135/94	120.4 ± 10.2 / 77.1 ± 11.5

BMI = body mass index, HR = Heart rate, SBP/ DBP = Systolic/Diastolic blood pressure.

(a) (b) (c)





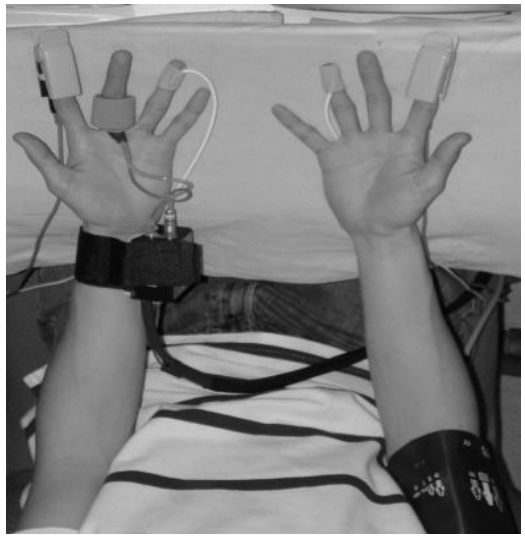


Figure 4.2. Temperature Chamber & the experiment Environment. (a) Model diagram of the temperature chamber (b) Experiment equipment & environment (c) Sensors & measurement points Architecture of the Whole System Architecture.

4.3.2.3 Measurement of PPG signal

Clip type probes (DS-100A, Nellcor, Japan) were used to minimize signal changes due to external factors, such as CF and the distance between the light-emitting diode (LED) and the photodetector, and to measure only the changes of PPG signal in accordance with changes in finger SST. An infrared LED with a center wavelength of 890 nm and a photodetector with a center wavelength of 900 nm were used; the signal was measured in the transmission mode.

The DC and AC components of each PPG signal detected on the index fingers of both hands from the photodetector were extracted using an analog non-inverting low-pass filter with a cut-off frequency of 20 Hz and an inverting high-pass filter with a cut-off frequency of 0.15 Hz, respectively. A PowerLab with a 12-bit A/D converter was used to acquire signals at a sampling rate of 200 Hz per channel and to digitize data. The current supplied to the LED drive and the amplification ratio was kept constant.

4.3.2.4 Measurement of cardiovascular parameters

For measurement of the middle finger of the left hand, the Finometer was used, which non-invasively measures finger artery BP and using the Oscillometric sphygmo-manometer (Model-53000, Welchallyn, USA) on the upper right arm, BP was measured at 0 min and in 5-min intervals (2.5, 7.5, 12.5, 17.5, 22.5, 27.5 min).

4.3.2.5 Experiment procedure

In order to measure the changes in the PPG signal in accordance with the local finger SST changes, a chamber enabling air temperature changes, with cooling and heating devices and a device to measure PPG signal changes was produced. To measure cardiovascular parameters and BP, the Finometer and Oscillometric sphygmomanometer were used.

Temperature changes were induced (cooling: ~13.6 ± 0.6℃, heating: ~48.6 ± 0.4℃) by supplying warm and cool air using the heating and cooling devices; in the chamber, the cooled and heated area of the subject was separated from the outside. During the experiment, the laboratory temperature was maintained at 24.9 ± 0.9℃.

One cooling experiment and one heating experiment were conducted for all subjects, and throughout the experiment, the subjects were seated in a comfortable chair and their hands were placed at heart level on the table, to help keep the finger steady. After body positioning, the left hand was put in the chamber up to the elbow and the right hand was positioned outside the chamber. For the initial 10 min of the cooling experiment and the heating experiment, PPG signals, cardiovascular parameters, and BP were obtained in an environment identical to the temperature in the laboratory. Next, the same data were continuously obtained for 20 min while the temperature was changing inside the chamber.

4.3.2.6 Statistical Analysis

Statistical analysis was performed to evaluation the changes in the PPG signals and cardiovascular characteristics with changes in local SST. The changes in the PPG components and cardiovascular characteristics were expressed as means with standard deviations over time. Person`s correlation coefficients were evaluated via the correlation analyses of the PPG components and SST. The statistical program used in this study was SPSS 12.0 for Windows.

4.3.3 Results

4.3.3.1 Finger SST and blood pressure response to local cooling and heating

In both the cooling and heating experiments, the temperature within the chamber was not

altered for the initial 10 min; in the subsequent 20 min, the temperature was raised and lowered. The results of the changes in SST of both fingers obtained from the contact temperature sensors, the periodic temperature image data (I, II) using an infrared camera, and BP, are shown as the mean and standard deviation (Figure 4.3 and 4.4).

The continuous digital BP was measured using a Finometer, and the periodic central BP was measured using Model-53000 (Figure 4.4). The values of the changed SST and BP before and after the experiment are shown in Table 4.3.

4.3.3.2 Variation of PPG signals during finger SST change

The components of the PPG signal obtained in the rest condition for the initial 10 min in each case were averaged as 1; the values of the changed the components of the PPG signal by a change in finger SST during the subsequent 20 min were normalized by the initial values (Figure 4.5).

As seen in Table 4.4, the N is different for all subjects, which indicates the range of changed temperature according to each subject. Correlations in relation to changes in each component of the PPG signals as detected by changes of finger SST are also shown. The components of the PPG signal of the right hand are similar to those of the left hand which was directly affected by temperature changes.

Although the DC foot of the left finger (DCFL), DC peak of the left finger (DCPL), DC foot of the right finger (DCFR) and DC peak of the right finger (DCPR) all had differences in individual correlations in temperature increase, negative correlations were found: –0.86 ± 0.110, –0.85 ± 0.120, –0.88 ± 0.195, and –0.87 ± 0.188, respectively. The AC gap of the left finger (ACGL) and AC gap of the right finger (ACGR) showed positive correlations, 0.68 ± 0.269 and 0.66 ± 0.477, respectively.

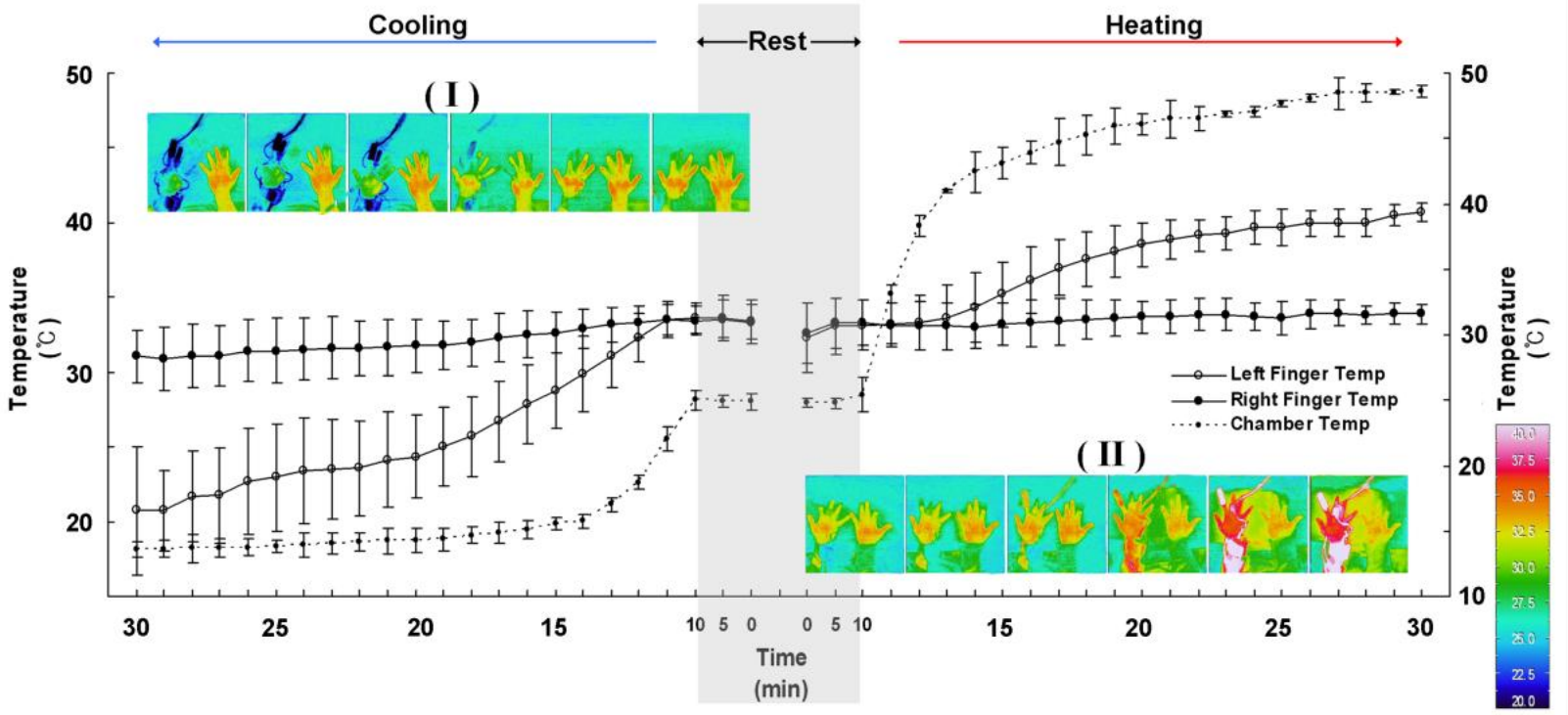


Figure 4.3. The temperature variation of left and right finger during cooling and heating in the chamber. Data are shown as the mean and SD. (Temp): Temperature.

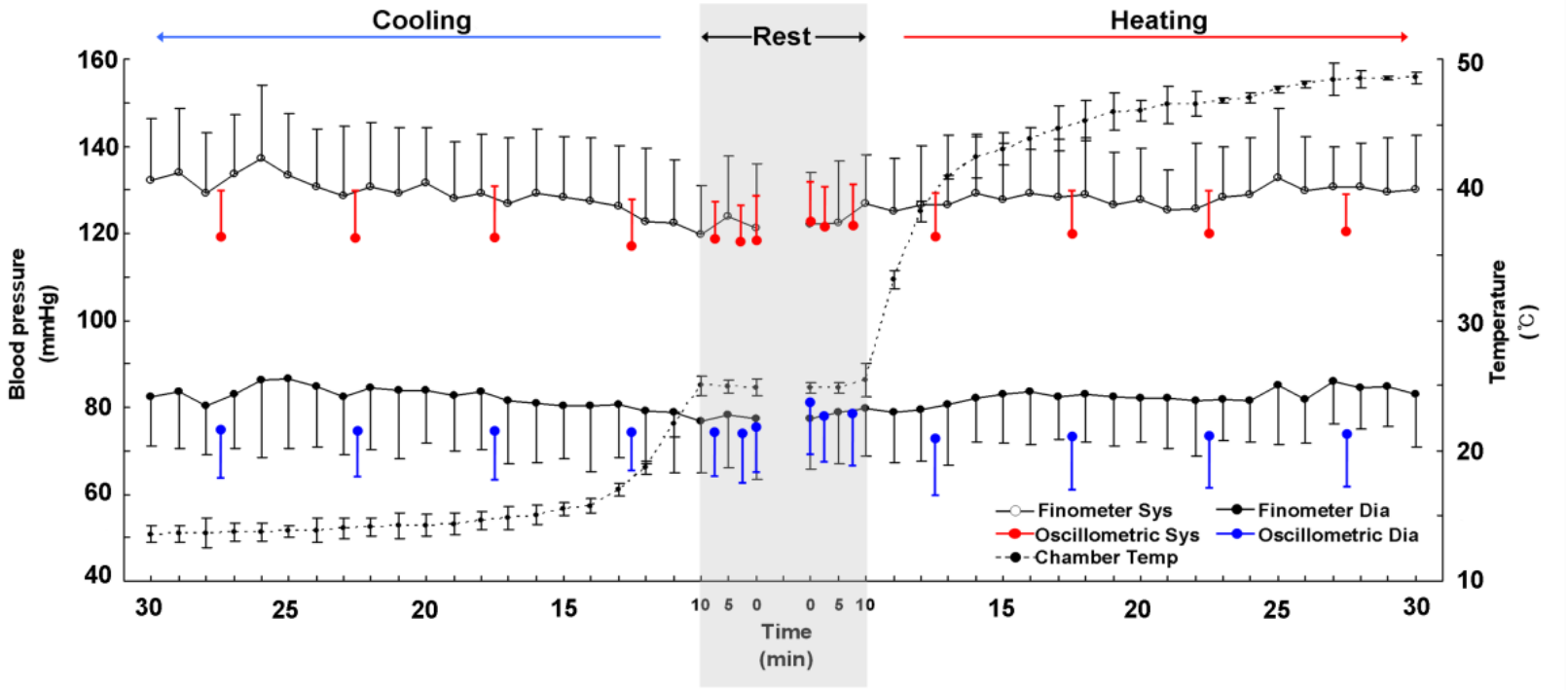
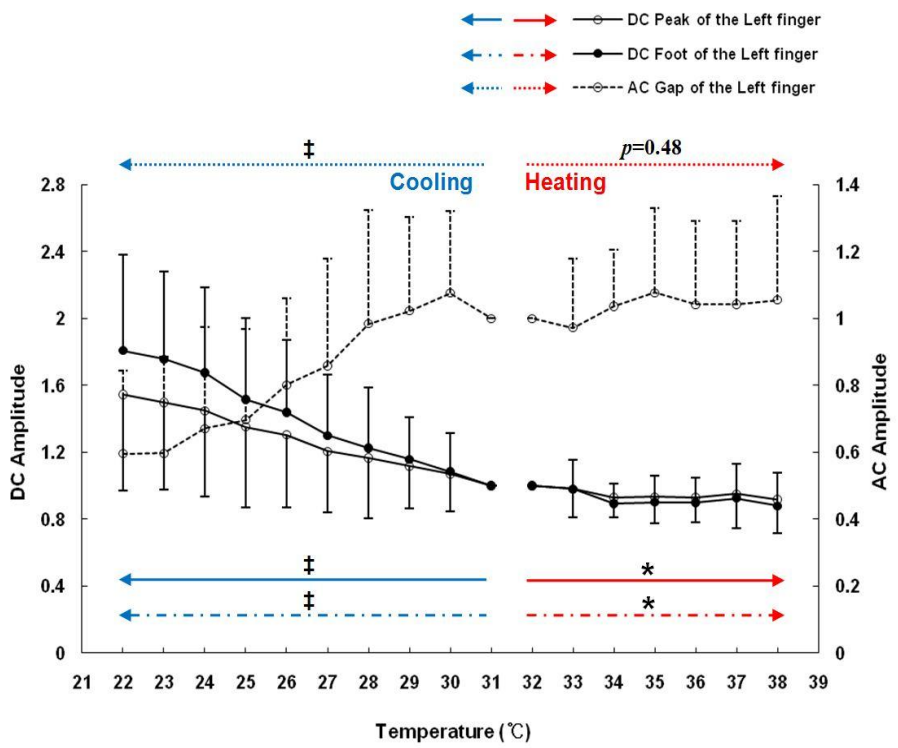


Figure 4.4. Blood pressure was measured using the Finometer and Oscillometric sphygmomanometer during cooling and heating in the chamber. Data are shown as the mean and SD. (Sys): Systolic, (Dia): Diastolic, (Temp): Temperature.

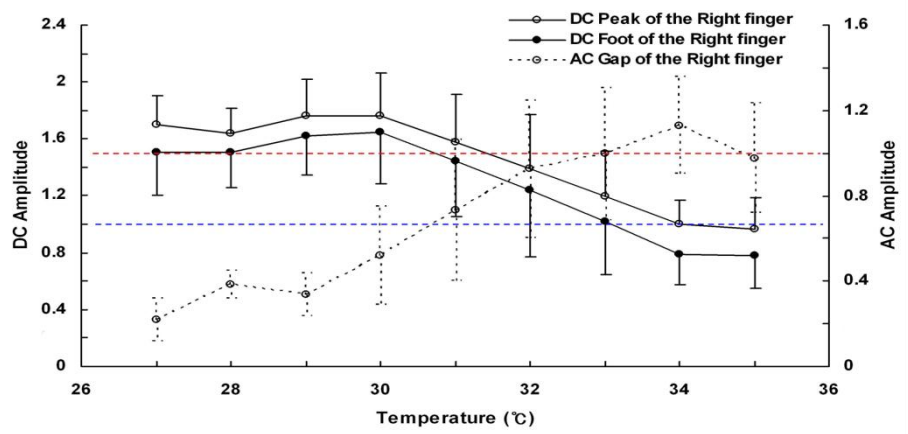
Table 4.3. Systolic and diastolic pressure, left hand surface temperature, right hand surface temperature, and the average temperature values & standard deviation within the chamber pre & post cooling and heating experiments.

Variables		Cooling			Heating		
		Before	After	Difference (After– Before)	Before	After	Difference (After– Before)
Finometer	Systolic (mmHg)	122±13	132±14	13±9‡	124±12	130±12	4±11†
	Diastolic (mmHg)	77±13	82±11	8±8‡	79±12	83±12	5±8†
Oscillometric	Systolic (mmHg)	118±11	119±11	2±7	123±10	120±9	–1±5
	Diastolic (mmHg)	75±11	74±11	–2±11	81±12	73±12	–3±8*
Temperature	LeftTemp (℃)	34±1	21±4	–13±3‡	33±2	41±1	8±3‡
	RightTemp (℃)	34±1	31±2	–3±2‡	33±2	34±1	1±2*
	ChamberTemp (℃)	25±1	14±1	–11±1	25±1	49±1	24±1

** $p < 0.05$, †$p < 0.01$, ‡$p < 0.001$*



(a)



(b)

Figure 4.5. Changes in Photoplethysmography components in accordance with changes in finger skin surface temperature. Data are shown as the mean and SD. (a) Left finger, (b) Right finger.

Table 4.4. The correlation between normalized components of photoplethysmography signal and temperatures obtained from both fingers in each individual.

	DCFL		DCPL		ACGL		DCFR		DCPR		ACGR	
	Correlation	*P*-value	Correlation	*P*-value	Correlation	*P*-value	Correlation	*P*-value	Correlation	*P*-value	Correlation	*P*-value
Min	–0.63	0.00	–0.59	0.00	0.94	0.00	–0.23	0. 77	–0.26	0.74	–0.20	0.80
Max	–0.98	0.00	–0.98	0.00	0.11	0.62	–1.00	0.00	–1.00	0.00	0.99	0.00
Mean±SD	–0.86±0.110	0.00±0.000	–0.85±0.120	0.00±0.001	0.68±0.269	0.07±0.169	–0.87±0.196	0.09±0.193	–0.87±0.188	0.10±0.190	0.66±0.478	0.13±0.286

N = The range of changed temperature, DCF = DC foot, DCP = DC peak, ACG = AC gap, L = Left, R = Right.

4.3.4 Discussion

4.3.4.1 Finger SST and blood pressure response to local cooling and heating

The results of the initial 10 min of the test in rest conditions before heating and cooling did not indicate any significant changes or effects. Although individual vasoconstrictions and vasodilatations of the subjects appeared, this occurrence results from the natural process of temperature control, so there was no occurrence of factors that affected the data trend. The method employed in this study was the application of temperature stimulation in air; this stimulation was relatively low. Changes in the finger SST of the subjects for each 20 min experiment period decreased in the cooling process and increased in the heating process along with temperature changes of the chamber.

The SST data from the fourth finger was compared with the SST data from the free finger from sensors using an infrared camera; this comparison was performed under the assumption that all fingers have similar SST distributions, because healthy subjects without cardiovascular disease were tested.

During the experiment, the left hand was placed inside the chamber while the right hand was placed outside, so the SST of the left hand, which was directly affected, showed more rapid changes in accordance with the temperature changes within the chamber than the right hand (Figure 4.6 left hand 16℃~41℃, right hand 27℃~35℃). The results of the SST changes using the infrared camera can be seen to be identical to those of the contact temperature sensor (Figure 4.3). After the SST reached 24℃ in the chamber during the cooling experiment, the temperature change was very slight; after the SST reached 37℃ in the heating experiment, the temperature change was also very slight.

There are slight differences in the temperature change between individuals, but with surface temperatures from 23℃ to 39℃, SST changes in all subjects could be observed. (Figure 4.6) The finger SST varied due to the physiologically proposed thermo-natural process of the limbs and gradually changed after a sudden initial change. However, the

reduction among subjects was not identical, due to individual physiological differences.

As seen in the experiment by Stroud [107], the data of the non-cooled right hand when compared to the data of the left hand did not show a considerable change, but did show a similar reduction trend; a continuous increasing trend was also seen in the heating process. Although local cooling did not affect the other side, the finger of non-experimental hand was affected by the mechanism of temperature control within the subjects, so correlated results were produced. Physiological differences amongst subjects could be witnessed here also.

In both the cooling and heating experiments, similar values of BP were obtained in both the central and finger region for the initial 10 min, when the temperature stimulation was not applied. However, the values were significantly different for the subsequent 20 min, when the temperature within the chamber was raised and lowered. BP measured with the oscillometric method was not affected by temperature; measurement with a Finometer, which employs a PPG signal to measure BP, was affected by temperature (Figure 4.4).

By placing the finger at the same height as the chest, the effects of hydrostatic pressure were eliminated. The changes in SBP and DBP in the experiment showed a rising trend, different than the central BP, for which there was no change or an insignificant change. The differences in the pre- and post-experiment values were very clear, which is thought to be the result of the physiological change of the left hand induced by the heating and cooling; this physiological condition is produced by the temperature adaptation mechanism resulting from the changes in blood flow and blood vessels.

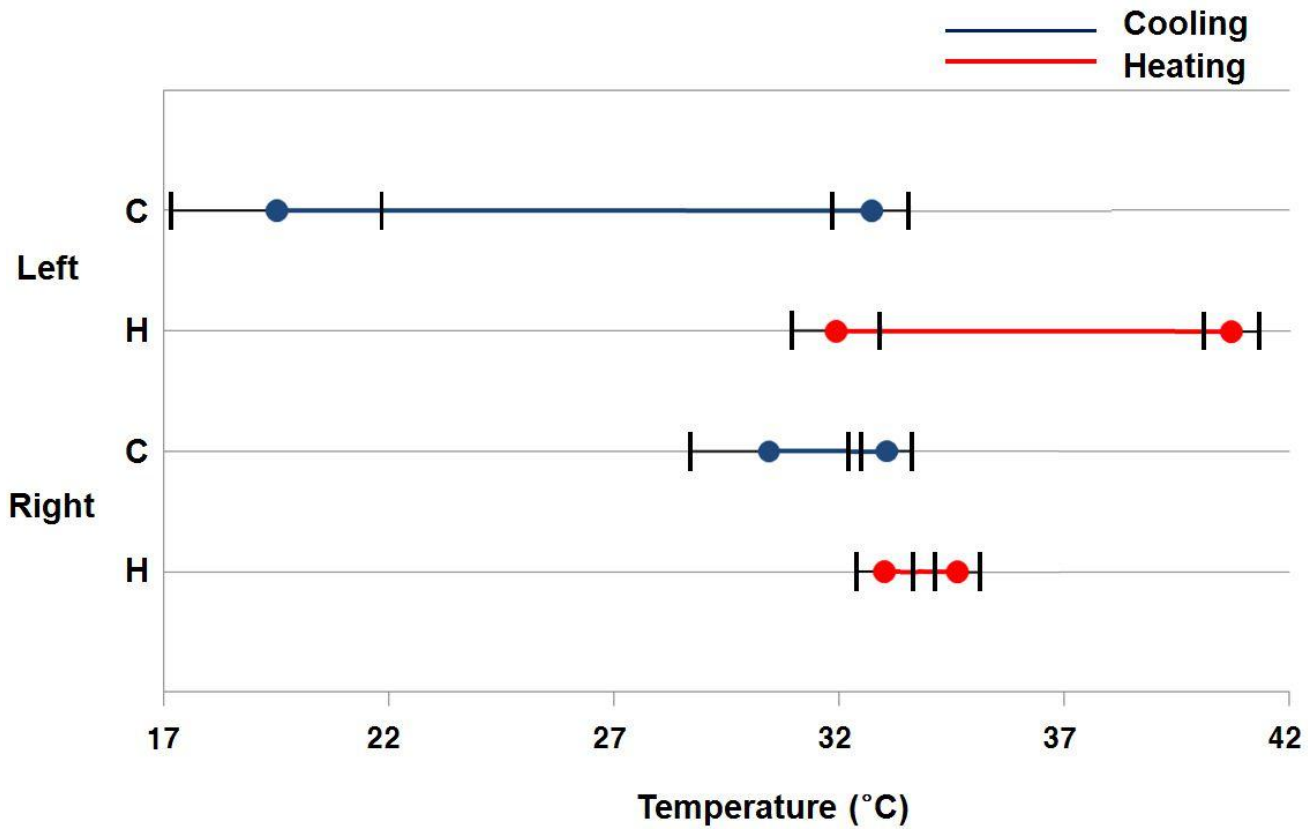


Figure 4.6. The range of variation in skin surface temperature of both fingers between subjects in the cooling and heating experiment.

4.3.4.2 Variation of PPG signals during finger SST change

The left side of Figure 4.7 shows a 30 min recording of the data from both hands in the cooling experiment (Temperature, PPG DC, and PPG AC components for both hands), and the right side shows 5 s of measured data from the left hand. It also shows the components of the PPG signal used in this study.

The PPG signal is derived as a voltage signal generated by a photodetector for light, which detects changes in BV; the light passes through the skin, arterial blood, venous blood, and tissue [128]. The signal consists of DC and AC components. The DC component represents static BV in the artery, vein, and tissue [129] and the AC component indicates pulsed blood flow in the artery, which is influenced by the contraction and relaxation of the heart [130]. Accordingly, the DC component reflects change in BV, and the AC component reflects vascular status. The compositions determined from PPG indicate the changes in BV, and when the resulting voltage value outputted from the values of the DC components rises, BV decreases; when it falls, the BV increases. This occurrence reflects the increase in blood flow per heart beat when the voltage value outputted from the AC component rises, and the decrease in blood flow when it falls [28]. The analysis is shown separately for the left and right fingers (Figure 4.5). In the results of the raised temperature in the confidence range of 22℃ to 38℃ of the left finger, a decrease in the DC components of the PPG signal and an increase in the AC component can be seen. The same results are shown for the right finger, although the scope of variation is much smaller. These results are consistent with the physiological phenomenon where vasoconstrictions are caused by the cooling process and vasodilatations are caused by the heating process; this process is due to the effects on the vessels of a heating and cooling reaction in a local area, based on the fact that the blood vessels in the hand actively contract and expand to control heat [131, 132]. That is, the cooling of the blood vessel walls causes the loss of contractive capacity, while heating increases this capacity. However, as seen in the data, the above explanation was accurate for the cooling process, but weaker results were produced for the heating process. This phenomenon backs up the concept of stronger protection against cold than heat [132] in that the cooling is observed to be more decisive than the heating in terms of the human

body reaction.

The results demonstrate that the components of PPG signal changes are linked to body temperature changes and support the theory that control of body temperature is achieved mainly through blood flow control; that is, the body temperature in the environment is controlled by the contraction and expansion of the blood vessels and the blood distribution is controlled for the increase and decrease of heat loss [131].

This pilot study was performed on a small number of subjects and gender was not taken into consideration. However, the definition of physiological changes based on clinical phenomena has been explained by changes in cardiovascular status according to changes in time, the chamber temperature, and the SST of both hands measured by the designed hardware and clinical equipment through air cooling and heating methods that closely match the real environment. Moreover, comparisons were made with the results of previous studies that were performed through cold water [128]. Through these comparisons, our proposal is clear with the use of clinical equipment using PPG signals to explain the changes in cardiovascular characteristics and the changes in peripheral vessels. The point is that temperature must absolutely be taken into account to evaluate the status and functioning of the cardiovascular system through PPG signals. Temperature will be a priority issue for a more accurate evaluation of the cardiovascular system.

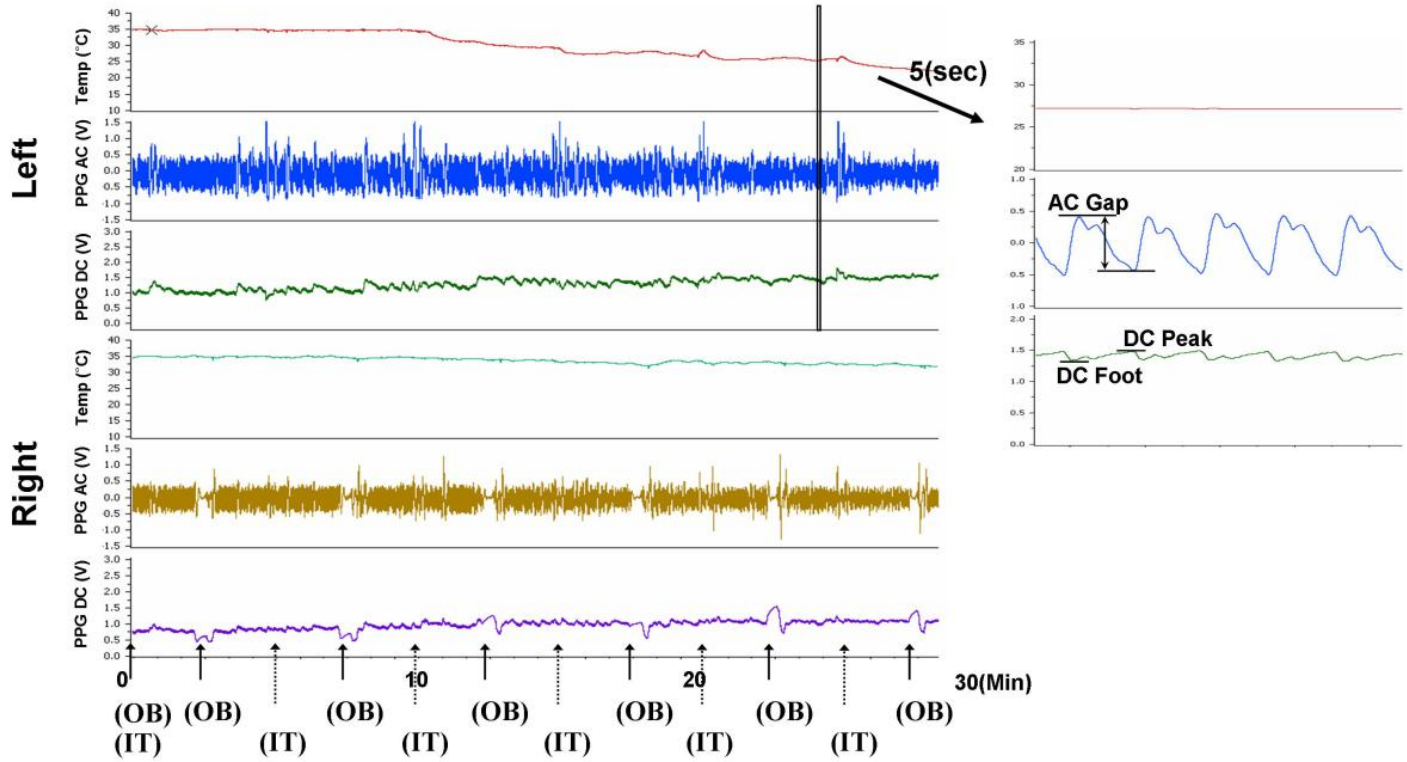


Figure 4.7. Skin surface temperature and Photoplethysmography signals during the cooling experiment. (OB): Oscillometric measurement of blood pressure; (IT): Infrared camera measurement of temperature.

4.3.5 Summary of findings

The purpose of this pilot study is to propose temperature control or compensation when components of PPG signal are used to evaluate vascular compliance, BP, and blood flow. Under laboratory conditions, each gradual air cooling and heating experiment (initial ambient: 25 ± 0.9℃, cooling: ~14 ± 0.6℃, heating: ~49 ± 0.4℃; Mean ± SD chamber temperature) were conducted on 16 healthy subjects (15 males, 26 ± 2.1; Mean ± SD age) who were not undergoing any drug treatment. Throughout the experiment, the subjects were seated in a comfortable chair and their hands were placed at heart level on the table, to help keep the finger steady. The left hand was put in the chamber and the right hand was positioned outside the chamber. For the initial 10 min, PPG signals, cardiovascular parameters, and BP were obtained in an environment identical to the temperature in the laboratory, and the same signals were continuously monitored for 20 min under different temperatures within the temperature chamber. The experimental results showed that local temperature changes affected PPG signal and the Finometer blood pressure (Finger BP), but not the oscillometric blood pressure (Central BP) (DC foot: –0.86 ± 0.110, DC peak: –0.85 ± 0.120, AC gap: 0.68 ± 0.269; Mean ± SD correlation coefficient, Systolic Finger BP: 13 ± 8.9 mmHg, Diastolic Finger BP: 8 ± 8.0 mmHg, Systolic Central BP: 2 ± 7.2 mmHg, Diastolic Central BP: -2 ± 10.9 mmHg; Mean ± SD BP in the cooling experiment). These results suggest that temperatures must be carefully controlled or compensated for in the measurement of PPG signal in order to reduce for the errors in the values when evaluating cardiovascular status through PPG signal in a local heating and cooling treatments or in temperature variation environments.

4.4 Conclusions of compensation study

In this chapter, the hemodynamic effect of gradual environment condition change has also been presented. The CF and SST change has been associated with increase and decrease of PPG waveform features. These increase and decrease of PPG waveform response identified by joint interpretation of changing trends in local vascular condition may be very helpful for characterizing the extent of BP change. For CF change, we followed X. F. Teng and Y. T. Zhang [72] study that is one of golden standard. The difference is we consider CF effect until transmural pressure because of our application of test method. For the SST change, previous studies have applied sudden temperature change method, such as cool water, air compressor, and so on. However, the SST of both hands measured by the designed hardware and clinical equipment through air cooling and heating methods that match the real environment.

These compensation studies have the two major limitations. First, the physiological mechanisms are not exactly equal to the actual living environment. Second, the morphological features were extracted from finger PPG waveform, which were measured the controlled condition that other conditions are stable without focused condition. It remains to be investigated that PPG waveform could be reliably detected under various condition factors change.

Chapter 5 Clinical study

5.1 Overview

The normalized finger PPG waveform to estimate BP has been studied in Chapter 3. Because the change in morphological features of finger PPG waveform is able to indicate a hemodynamic response to BP change, a single measurement of morphological features can also be a practical indicator of cardiovascular condition change. In section 5.2, the correlation between long-term BP change and morphological features change derived from the finger PPG waveform will be evaluated. The purpose of the clinical study is to establish a new method estimating BP in non-invasive way.

5.2 A new approach for non-invasive measurement of blood pressure using the normalized components of PPG waveform

5.2.1 Introduction

This study has the purpose to suggest the possibility for the design of BP measuring system with easy accessibility while promoting the maximized comfort of the patient. And the development of the health care system with the generated physiological information is another purpose. Therefore, to induce the comfort and the accessibility of the patients, the minimum restriction in the design of sensor used for the PPG measurement was presupposed and the development of the method to measure BP only through PPG waveform was aimed. For this, the normalized PPG waveforms of the same condition were induced to restrict the change of PPG waveform by CF and SST of

specific part among the external factors. The proposed method is BP measurement method of a new finger print type which can maximize the accessibility of the patient and the feasibility of the measurement.

5.2.2 Models

5.2.2.1 PPG waveform measured in reflection mode

As shown in Figure 5.1, the light amount, I_0, from the light source can be represented as equation (18) according to the kubelka-Munk theory.

$$\mathbf{I_0 = \frac{dI}{dx} - \frac{dJ}{dx} + J_0 + I_D} \tag{18}$$

Therefore, the light amount, J_0 detected by the photo detector can be arranged as equation (19).

$$\mathbf{J_0 = I_0 - \frac{dI}{dx} + \frac{dJ}{dx} - I_D} \tag{19}$$

As the thickness of the finger is constant, the light amount, I_D, penetrating the finger is constant, too. The change of the light amount detected by the photodetector can be explained with the scattering and the absorption by the finger organs and the blood. It can be expressed as equation (20).

$$\mathbf{J_0 = I_0 - \frac{dI}{dx} + \frac{dJ}{dx}} \tag{20}$$

The equation (19) can be re-expressed with equation (21) by differentiating it with the back scattering (s) and the absorption (k) coefficients.

$$\mathbf{J_0 = I_0 - sI - kI + sJ - sJ - kJ + sI} \tag{21}$$

And equation (21) can be, in turn, arranged as equation (22).

$$\mathbf{J_0 = I_0 - kI - kJ} \tag{22}$$

If the light amount, I_0, from the light source is constant, the changed light amount detected by the photodetector can be expressed as equation (23).

$$\mathbf{\Delta J_0 = \Delta(kI + kJ)} \tag{23}$$

Based on equation (22) and (23), we can see that the light absorption of the blood is measurable with the reflection mode. Therefore the change of blood can be indirectly measured with PPG waveform.

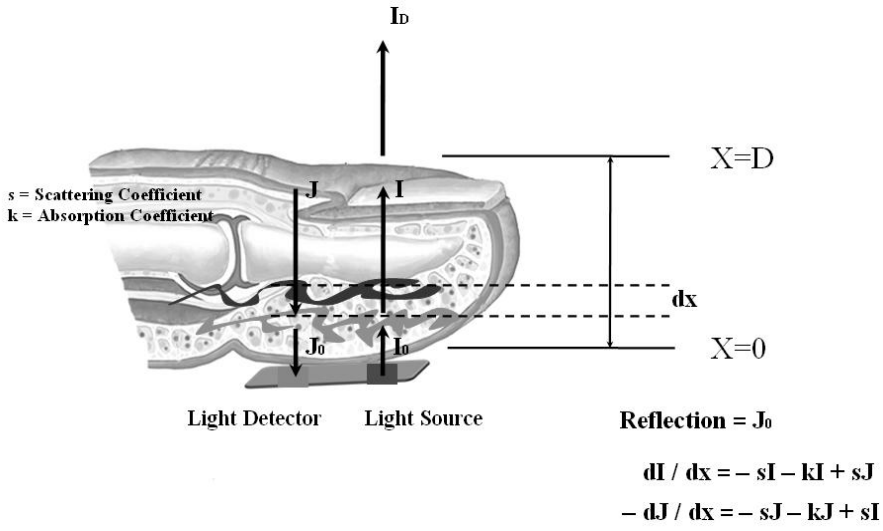


Figure 5.1. The reflection mode based on the kubelka-Munk model.

5.2.2.2 Microcirculation model

A microcirculation model is required to evaluate cardiovascular system using PPG waveform. PPG waveform can indirectly measure blood flow at measurement area. Above-mentioned models concluded that peripheral blood vessels were the resistance; however the blood vessels had various components characteristics. Therefore, a correct model is required to more reliable evaluation of cardiovascular system.

Figure 5.2 shows the microcirculation model. Relationships between BP and blood flow indicate in equation (24). [133]

$$\frac{d^2Q_P(t)}{dt}+\frac{1}{RC}\frac{dQ_P(t)}{dt}+\frac{1}{LC}Q_p(t)=\frac{1}{RLC}P_A \tag{24}$$

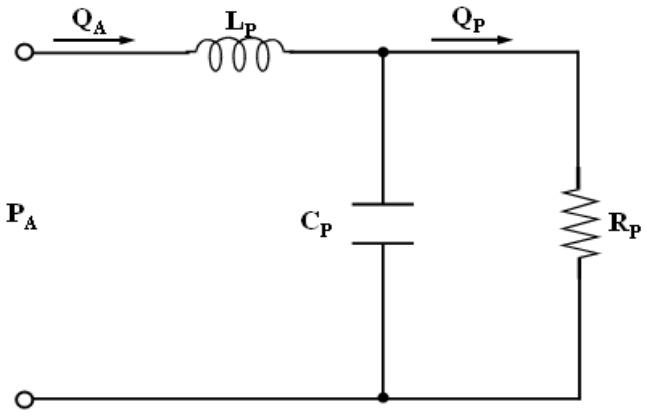


Figure 5.2. Electrical equivalent circuit of microcirculation model.

5.2.2.3 Artery and capillary model

Figure 5.3 shows the artery and capillary model. Relationships between BP and blood flow at each node indicate in equation (25), (26), (27), (28), and (29).

$$Q_i(t) = Q_A(t) = C_A \frac{dP_A(t)}{dt} + \frac{P_A(t)}{Z_A} \tag{25}$$

$$Q_p(t) = C_p \frac{dP_p(t) - P_{bias}}{dt} + \frac{P_p(t)}{R_p} \tag{26}$$

$$Q_{out}(t) = \frac{P_p(t)}{R_p} \tag{27}$$

$$L_P \frac{dQ_A(t)}{dt} + R_A Q_A(t) + P_P(t) = P_A(t) \tag{28}$$

$$\frac{d^2 P_P(t)}{dt^2} + \left(\frac{1}{R_P C_P} + \frac{R_A}{L_P}\right)\frac{dP_P(t)}{dt} + \frac{R_A + R_P}{R_P L_P C_P} P_P(t) = P_A(t) \tag{29}$$

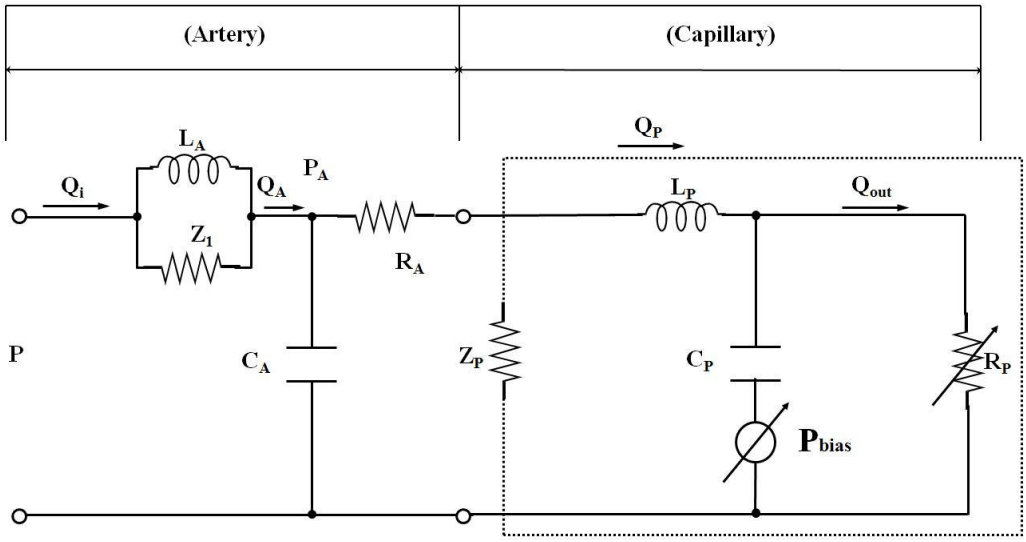


Figure 5.3. Electrical equivalent circuit of artery and capillary model.

5.2.2.4 Peripheral vascular model

In chapter 4, the compensation was used as normalized models of PPG waveform to evaluate the potential application of BV change and VR change extracted from finger PPG waveform in detection of central BP change. This model has external effects and explain how effects blood flow and BP. Because we use PPG waveform at the peripheral vascular area to estimate BP, we have to consider these effects and use normalized PPG waveform.

Figure 5.4 shows the peripheral vascular model and Figure 5.5 shows BP waveform in the peripheral vascular model. Relationships between BP and blood flow indicate in equation (30). Equation (31) and (32) represents PPG DC component and PPG AC component, respectively.

$$Q_p(t) = C_p \frac{dP_p(t) - P_{bias}}{dt} + \frac{P_p(t)}{R_p} \tag{30}$$

$$PPG_{DC}(t) = \alpha - Q_{out}(t) = \alpha - \frac{P_P(t)}{R_P} \tag{31}$$

$$PPG_{AC}(t) = \beta Q_{P\,\mathrm{gap}}(t) = \beta Q_{P\,\max} \frac{T_1}{C_P + R_P} \tag{32}$$

$$\mathrm{Blood\ Volume} = \mathrm{Const.} - \mathrm{DC component}$$
$$\Delta\mathrm{Blood\ Volume} = \mathrm{AC component}$$
$$\alpha = \mathrm{constant}, \beta = \mathrm{constant}$$

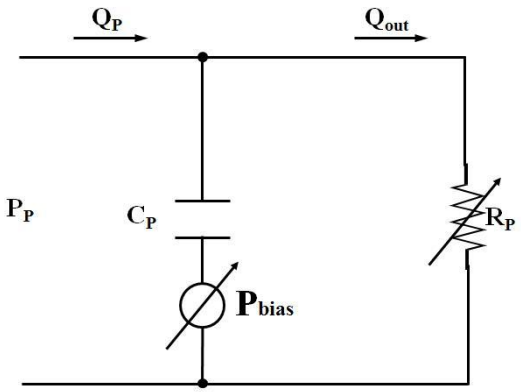


Figure 5.4. Electrical equivalent circuit of peripheral vascular model.

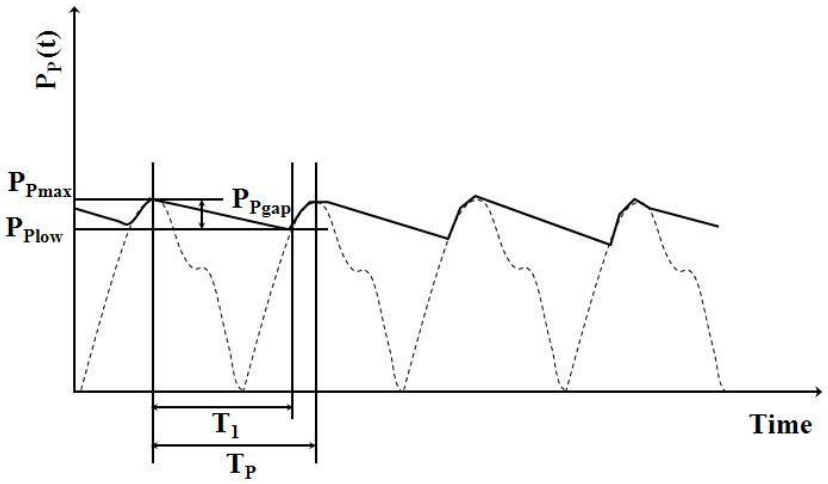


Figure 5.5. Blood pressure waveform in the peripheral vascular model.

5.2.3 Methods

5.2.3.1 System

In this study, the reflection mode PPG waveform measuring system of the finger print type was developed to measure BP only through PPG signal. We designed the sensor to compensate the signal while minimizing the external factors due to CF and SST of the finger.

As shown in Figure 5.6, the whole system can be largely divided into the sensor unit to measure CF and SST along with the PPG waveform, the data acquisition unit to deal with the measured signal and the analysis unit to obtain BP by using the measured data.

It was designed in reference to Webster`s pulse oximeter system [29] to measure the PPG signal. For the PPG sensor, the infrared LED (SEP 8705, Honeywell, American) with 880nm wavelength and the photo detector (SEP 8105, Honeywell, American) with the central response frequency of 900nm were used. Each PPG signal detected by the photodetector was cut off with the frequency of 20Hz for the low-pass filtering and with 0.15Hz for the high-pass filtering to draw out the DC and AC components. The current supplied to LED drive was controlled to be constant at all times, and so was the amplification rate.

The sensor which was newly designed in this study to compensate the change of PPG waveform due to CF and SST is shown in Figure 5.7. The flexiforce pressure sensor (ps-01 American) to measure CF and the contact temperature sensor (LNTG473FW, Lattron, Korea) was used to measure SST. For the signal of CF and SST, constant amplification rates were supplied. Each signal was acquired by Power LAB (ML880, AD Instrumentation) with 12bit A/D converter and 200Hz sampling frequency.

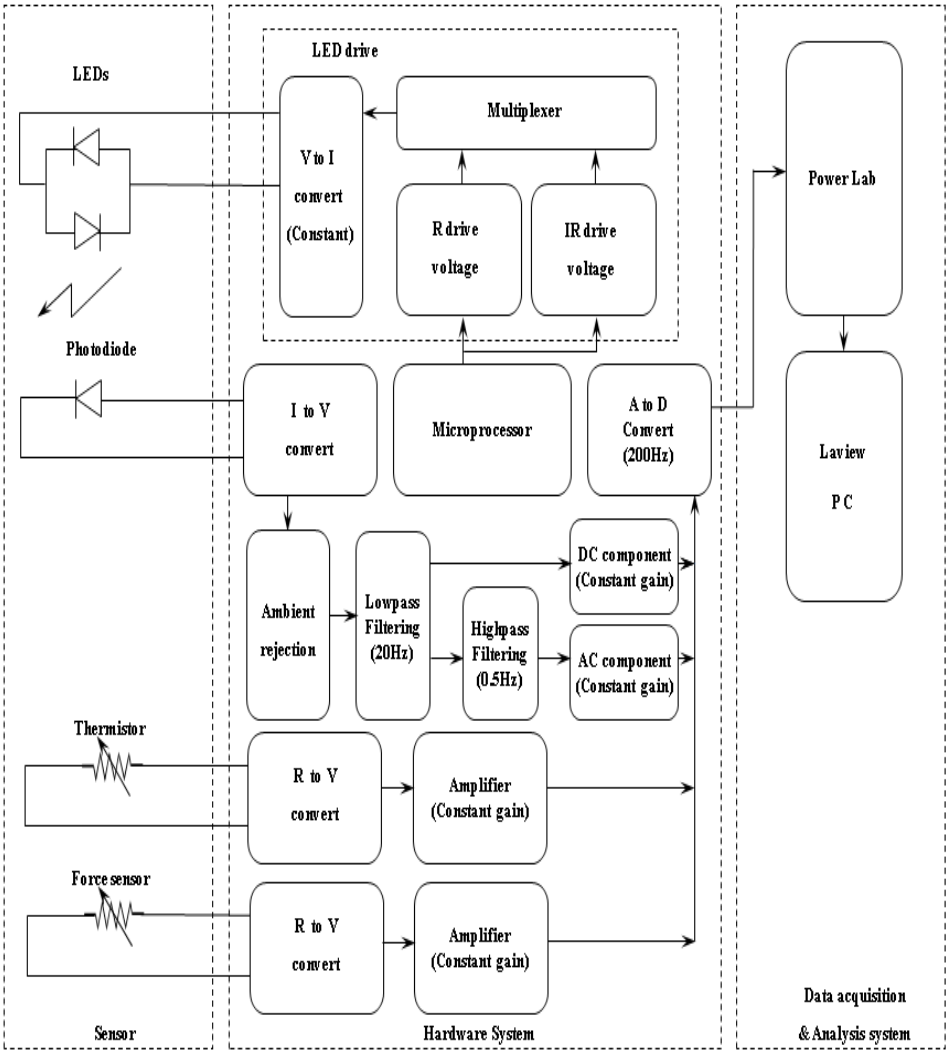


Figure 5.6. Configuration Diagram of Whole System.

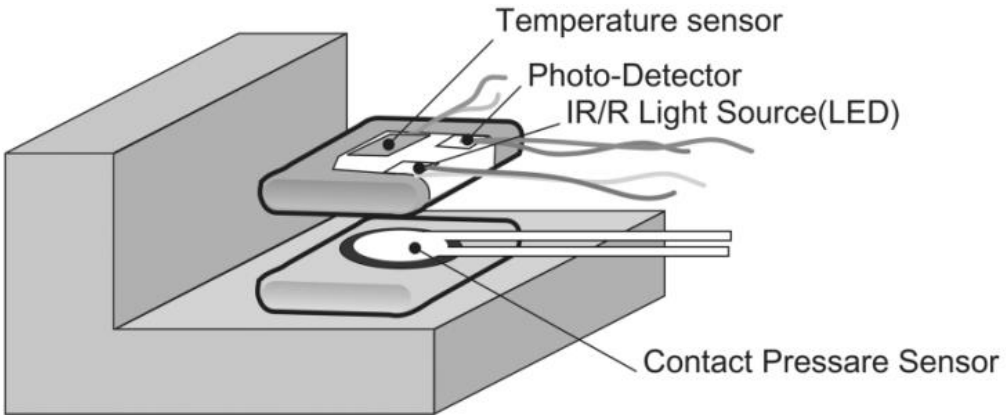


Figure 5.7. Structure of PPG sensor newly designed in this study; for the compensation of PPG waveform due to contact force and skin surface temperature. Contact force and skin surface temperature were measured along with the PPG signal.

5.2.3.2 Subject

This experiment was carried out for 58 subjects (male: 42, female: 16, age: 28.9 ± 7.23) from 20 to 53 years old. All the subjects had no cardiovascular diseases except hypertension or hypotension and were under no treatment with the medicine. Before the experiment, all the subjects were educated about the experiment and wrote down the consent to participate in the study. The experimental protocol was reviewed and approved by the Clinical trial Research Committee of the Wonju College of Medicine, Yonsei University.

5.2.3.3 Experimental protocol

As shown in Figure 5.8, the experiment was carried out in three stages. In the first stage, each participant was tested to get the normalized PPG components from CF and SST. In the second stage, BP increased through the exercise and the normalized PPG components were compared and analyzed to find out their correlation. The experiment was carried out to obtain BP estimation equation through the multi-regression analysis. In the third stage, BP estimation equation obtained from each subject was compared with the measured BP through the oscillometric sphygmomanometer (Model-53000, Welchallyn, USA) and

analyzed for about 2 months.

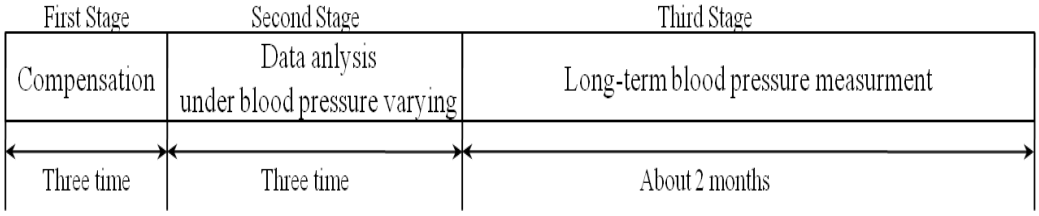


Figure 5.8. Experimental Procedure.

5.2.3.3.1 Acquisition of Compensated PPG signal from contact force and skin surface temperature (First stage)

The compensation experiment of PPG waveform for CF explained at chapter 4.2.

The compensation experiment of PPG waveform for SST of the measured part was carried out by changing the skin temperature of the peripheral hand part from 28 ~ 34℃ while maintaining CF constant (fixed pressure: 0.080 Kgf/㎠) to make each subject comfortable within the range of the transmural pressure. SST was changed in the air supply cooling/heating method (Figure 4.2(a)).

In the experiment, PPG waveform was measured after the 15 min rest to adapt the body of the subject to the experimental environment. Then, the temperature of the hand was decreased fast and the measurement was carried out while the temperature is restored naturally. Once the temperature of the hand was restored to normal, it was slowly increased in turn. This process was repeated 3 times during the experiment.

The data acquired by the compensation experiment for each subject were analyzed by stages of CF at the same SST, and by stages of SST at the same CF. In each stage, the linear regression analysis was carried out with the average values of the data to obtain the normalized PPG waveform.

5.2.3.3.2 Acquisition of blood pressure estimation equation under blood pressure varying (Second stage)

In the first stage experiment, normalized PPG waveforms for each person were derived from CF and SST. By using the normalized PPG components as the independent variables, we tried to derive BP estimation equation according to the change of BP through the multi-regression analysis. For this, BP of all the subjects was increased through the exercises such as stepping up the stairs and running and the data were obtained. All the exercises were made indoors. Through the repetitive experiments, BP equation was obtained for each person by using the multi-regression analysis between the normalized PPG components and BP.

5.2.3.3.3 Long-term blood pressure measurement (Third stage)

The results from the personal BP estimation equation obtained by the second stage experiment were compared with the long-term BP measurement in the oscillometric method. The measurement was made for all the participants 1~3 times a day for about 2 months.

5.2.3.4 Data collection and analysis

5.2.3.4.3 Blood pressure measurement using components of PPG signal

Let the total light amount from the light source be I_0. Then, the DC component of PPG signal detected by the photodetector is changed according to BV, as shown in Figure 5.9. I_S of the DC component reflects the flowing BV by the artery, which shows to be proportional to the AC component. In this study, I_S reflects the state of the blood vessel and is analyzed with the amplitude (Peak to Peak) of the AC component. In the DC components which reflect the total BV including the artery, the vein and the capillary vessels of specific part, I_{Rsys} was measured and analyzed with BV at the contracting point of the heart and I_{Rdia} with that at the dilating point of the heart.

The changing factors of the BP in the cardiovascular system are BV and the resistance (or compliance) of the vascular system. The physiological change in the cardiovascular system can be estimated from the PPG signal components, which are influenced by the external factors (Figure 5.10). To make the identical condition through the compensation of CF and SST, the normalized PPG components were drawn out and BP was estimated from the components.

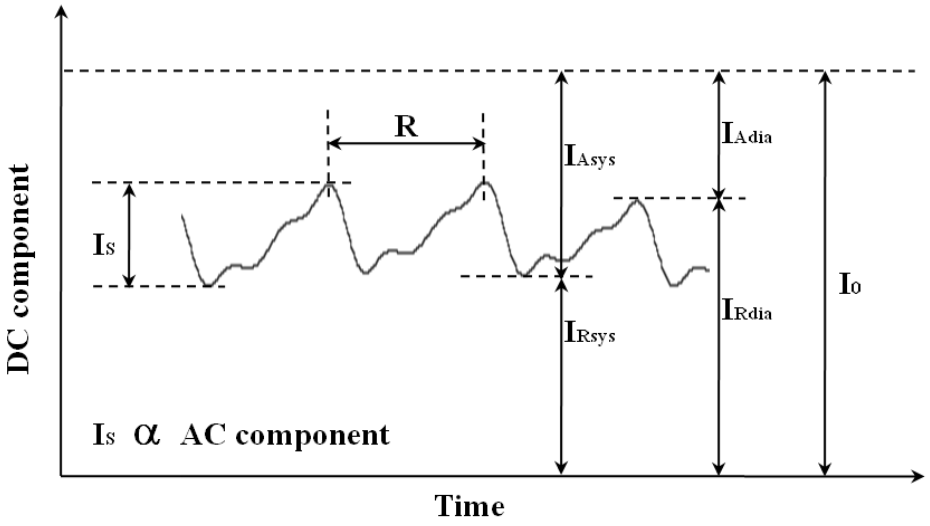


Figure 5.9. Change in components of PPG waveform acquired from photodetector.

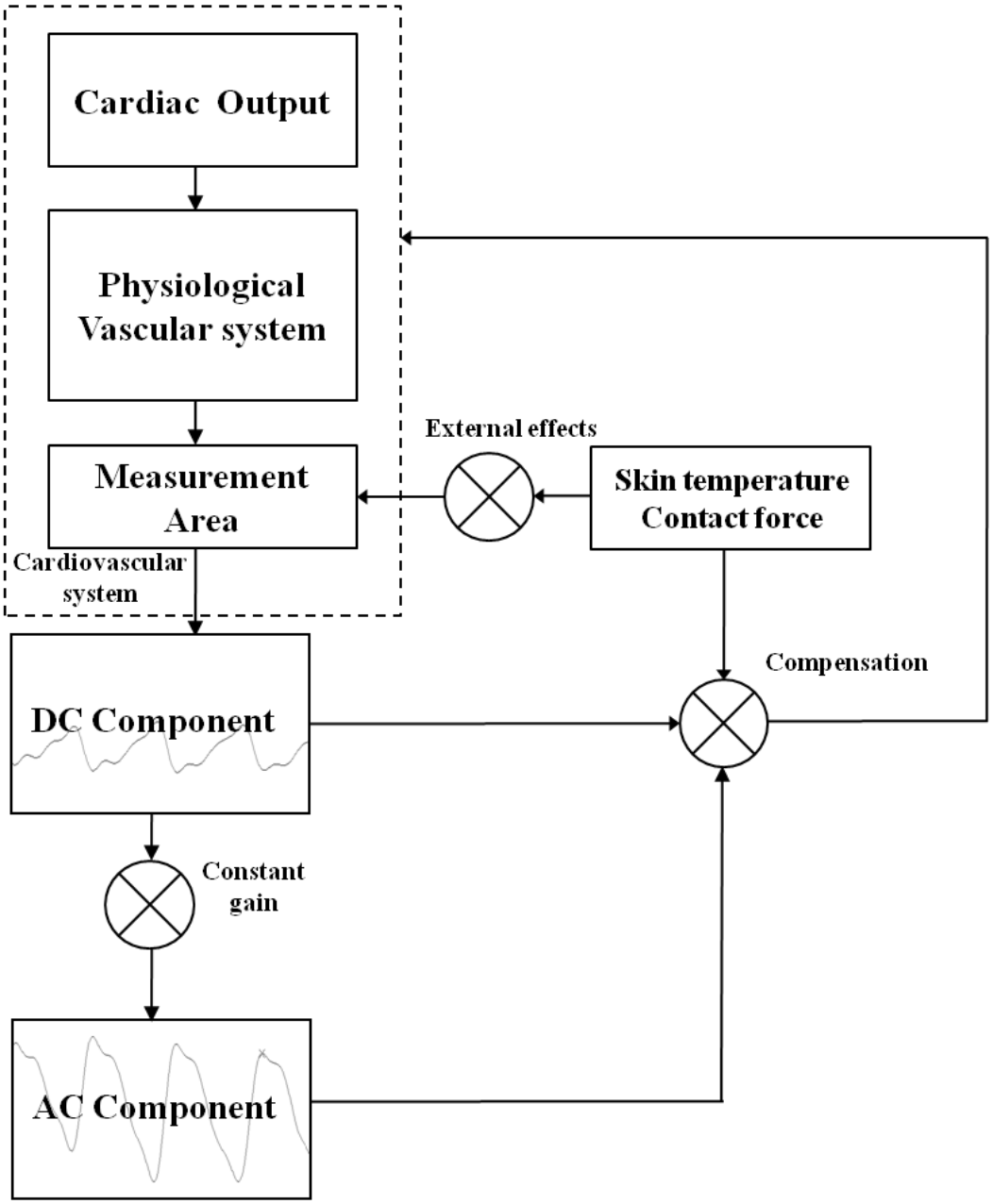


Figure 5.10. Schematic block diagram of the blood pressure measurement using components of PPG signal.

5.2.4 Results

5.2.4.1 Acquisition of Compensated PPG signal from contact force and skin surface temperature (First stage)

The change in PPG waveform according to CF and SST comes from the external factors rather than the change of the cardiovascular condition. It may give impact on the partial vascular system of the measuring part, but it can hardly be seen as the change of the whole cardiovascular system. Based on this ground, the compensation equations were derived from the PPG signal components, CF and SST measured in the first stage experiment. And the normalized PPG components were drawn out with the compensation equations to apply CF and SST of the same condition to PPG waveform.

The normalized PPG components were derived with the following equations to compare the component values of PPG signal and BP in the identical conditions of CF and SST.

When the number of total measurements is N, the equations are as follows:

$$\mathbf{F_I} = \frac{\mathbf{1}}{\mathbf{N}} \sum_{\mathbf{t=0}}^{\boldsymbol{N-1}} \mathbf{F(t)} \tag{33}$$

$$\mathbf{T_I} = \frac{\mathbf{1}}{\mathbf{N}} \sum_{\mathbf{t=0}}^{\boldsymbol{N-1}} \mathbf{T(t)} \tag{34}$$

Identical conditions for skin surface temperature(T_I) and contact force(F_I)

$_{Force}I_S(t)$ which is influenced by CF can be arranged like equation (35), (36), and (37).

$$_{\mathbf{Force}}\mathbf{I_S(t)} = \boldsymbol{\alpha}\mathbf{F(t)} + \boldsymbol{\beta} \tag{35}$$

$$_{\mathbf{Force}}\mathbf{I_{SI}} = \boldsymbol{\alpha}\mathbf{F_I} + \boldsymbol{\beta} \tag{36}$$

$$\frac{\mathbf{dI_S}}{\mathbf{dF}} = {}_{\mathbf{Force}}(\mathbf{I_{SI}} - \mathbf{I_S(t)}) = (\boldsymbol{\alpha}\mathbf{F_I} + \boldsymbol{\delta}) - (\boldsymbol{\alpha}\mathbf{F(t)} + \boldsymbol{\delta}) = \boldsymbol{\alpha}(\mathbf{F_I} - \mathbf{F(t)}) \tag{37}$$

α : contact force correlation coefficient, β : constant

$_{Temp}I_S(t)$ which is influenced by SST can be arranged like equation (38), (39), and (40).

$$_{\mathbf{Temp}}\mathbf{I_S(t)} = \boldsymbol{\gamma}\mathbf{T(t)} + \boldsymbol{\delta} \tag{38}$$

$$_{\mathbf{Temp}}\mathbf{I_{SI}} = \boldsymbol{\gamma}\mathbf{T_I} + \boldsymbol{\delta} \tag{39}$$

$$\frac{\mathbf{dI_S}}{\mathbf{dT}} = {}_{\mathbf{Temp}}(\mathbf{I_{SI}} - \mathbf{I_S(t)}) = (\boldsymbol{\gamma}\mathbf{T_I} + \boldsymbol{\beta}) - (\boldsymbol{\gamma}\mathbf{T(t)} + \boldsymbol{\beta}) = \boldsymbol{\gamma}(\mathbf{T_I} - \mathbf{T(t)}) \tag{40}$$

γ : skin surface temperature correlation coefficient, δ : constant

Based on the identical conditions for CF and SST, the compensation is made for the changed temperature and the pressure. The compensation equation for the normalized PPG components can be arranged like equation (41), (42), and (43).

$$_{\mathbf{Normalized}}\mathbf{I_S(t)} = \mathbf{I_S(t)} + \boldsymbol{\alpha}\big(\mathbf{F_I} - \mathbf{F(t)}\big) + \boldsymbol{\gamma}(\mathbf{T_I} - \mathbf{T(t)}) \tag{41}$$

$$_{\mathbf{Normalized}}\mathbf{I_{Rsys}(t)} = \mathbf{I_{Rsys}(t)} + \boldsymbol{\zeta}\big(\mathbf{F_I} - \mathbf{F(t)}\big) + \boldsymbol{\eta}(\mathbf{T_I} - \mathbf{T(t)}) \tag{42}$$

$$_{\mathbf{Normalized}}\mathbf{I_{Rdia}(t)} = \mathbf{I_{Rdia}(t)} + \boldsymbol{\varepsilon}\big(\mathbf{F_I} - \mathbf{F(t)}\big) + \boldsymbol{\epsilon}(\mathbf{T_I} - \mathbf{T(t)}) \tag{43}$$

$\alpha, \varepsilon, \zeta$: contact force correlation coefficient, γ, ϵ, η : skin surface temperature correlation coefficient

The compensation experiment result of PPG waveform for CF explained at chapter 4.2.

The change in SST can be interpreted as the result of natural temperature control process by the vasoconstriction and the vasodilatation. Even though the PPG signal measured at the finger tips reflects the change of whole vascular system and includes a lot of physiological information [133, 134] the signal can be distorted by the local vascular condition or the organic change of the measured part.

Mendelson and Ochs attached the reflectance sensor on the wrist and increased the temperature to check the correlation between PPG signal and the skin temperature [21]. Stround team found out the correlation between blood flow and the finger temperature. They also measured the change of PPG signal according to the temperature and BP in his experiment. Their studies reported that the AC component of PPG signal did not showed the rapid change and increased almost linearly at the increase of temperature, even if there were some personal differences. The change of temperature has the influence on other organs than the blood vessels, too [107]. Figure 5.11 tells that, as the temperature goes up, the AC components tend to increase and the DC components to decrease.

Table 5.1 gives the correlation between PPG waveform and SST in the form of mean ± SD. During the experiment, there were significant changes in PPG AC and DC signal ($p < 0.001$).

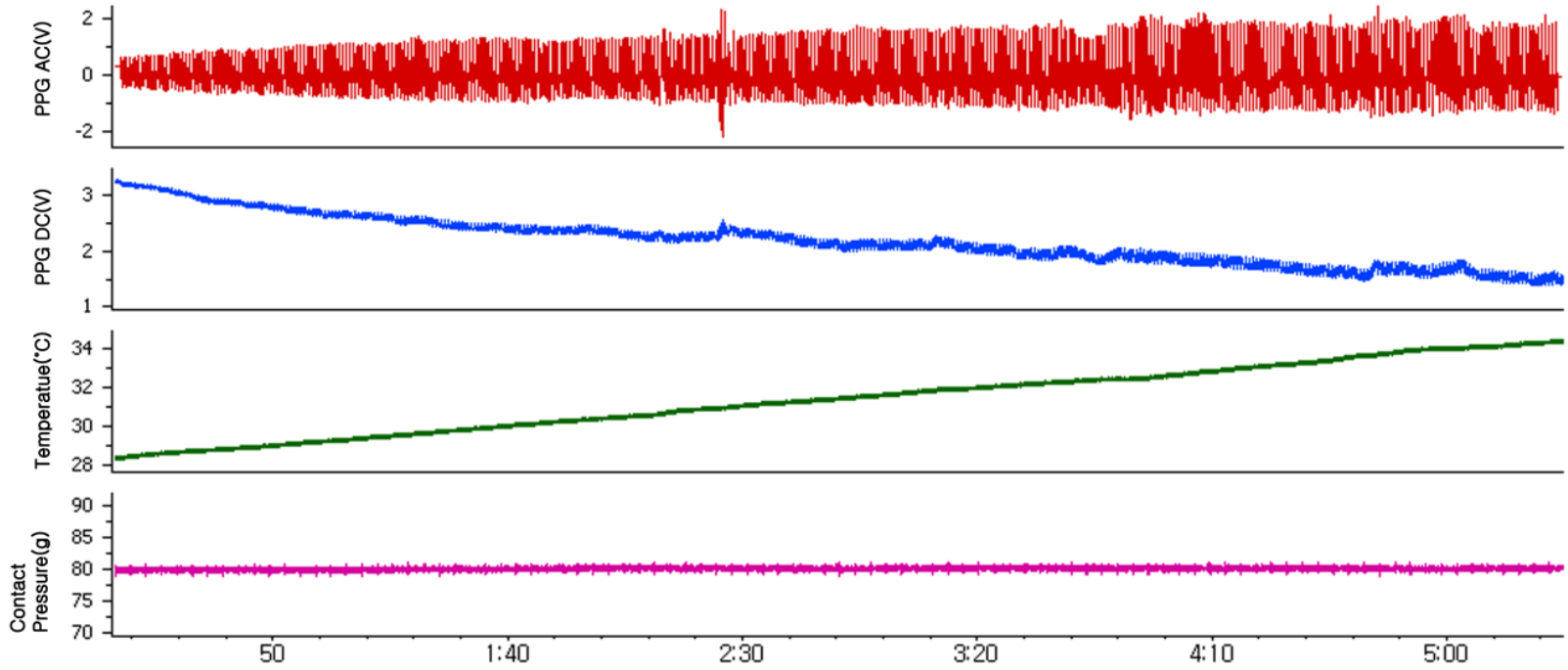


Figure 5.11. Change of PPG waveform according to skin surface temperature measured by compensation experience of this study.

Table 5.1. Analysis of the correlation between PPG signal and skin surface temperature.

Independent Variable	Dependent Variable	R	Adjusted R^2	T	Sig.
Skin Surface Temperature	IRsys	0.91±0.092	0.83±0.167	-25.99±18.580	0.000
	IRdia	0.90±0.103	0.82±0.183	-26.39±21.539	
	Is	0.75±0.058	0.55±0.089	7.51±1.072	

5.2.4.2 Acquisition of blood pressure estimation equation under blood pressure varying (Second stage)

To compensate the influences by CF and SST at the measuring point, the normalized PPG signals of the identical conditions were derived. With the components of the normalized PPG signal, the change of PPG signal according to BP was measured and, through the multi-regression analysis of the measurement results, BP estimation equation for each subject was obtained like equation (44) and (45). Table 5.2 is the result obtained through the multi-regression analysis

$$\mathbf{BP_{sys}(t) = m\ {}_{Normalized}I_S(t) + n\ {}_{Normalized}I_{Rsys}(t) + l} \quad (44)$$

$$\mathbf{BP_{dia}(t) = v\ {}_{Normalized}I_S(t) + w\ {}_{Normalized}I_{Rdia}(t) + u} \quad (45)$$

$BP_{sys}(t)$: systolic blood presuure

$BP_{dia}(t)$: diastolic blood pressure

m, n, v, w : $_{Normalized}$ PPG components correlation coefficient

l, u : constant

Table 5.2. Analysis of the correlation between blood pressure and normalized PPG waveform.

Independent Variable	Dependent Variable	R	Adjusted R^2	$_{Normalized}IR$ T	$_{Normalized}Is$ T	Sig.
Systolic Blood Pressure	$_{Normalized}IRsys$ $_{Normalized}Is$	0.76±0.112	0.59±0.170	-26.65±33.658	-9.10±9.083	0.013±0.023
Diatolic Blood Pressure	$_{Normalized}IRdia$ $_{Normalized}Is$	0.81±0.120	0.66±0.196	-31.37±46.245	-10.95±11.100	0.011±0.018

5.2.4.3 Long-term blood pressure measurement (Third stage)

With the personal BP estimation equations acquired in the second stage of the experiment, the long-term change of BP was measured. Figure 5.12 is the data of a person measured for 2 months. When the result of the oscillometric method and the result of measurement in Figure 5.12 with BP estimation equation derived in this study were compared with each other, we can check the long-term monitoring possibility of BP measurement system through the normalized PPG signal components.

The test results for all the data of 58 subjects for 2 months are shown in Figure 5.13 and 5.14. In Figure 5.13, it can be seen that BP during systolic and diastolic lies within the permissible error range in most measured cases. And, as shown in Figure 5.14, they have high correlation (SBP: R^2=0.8007, DBP: R^2=0.7657).

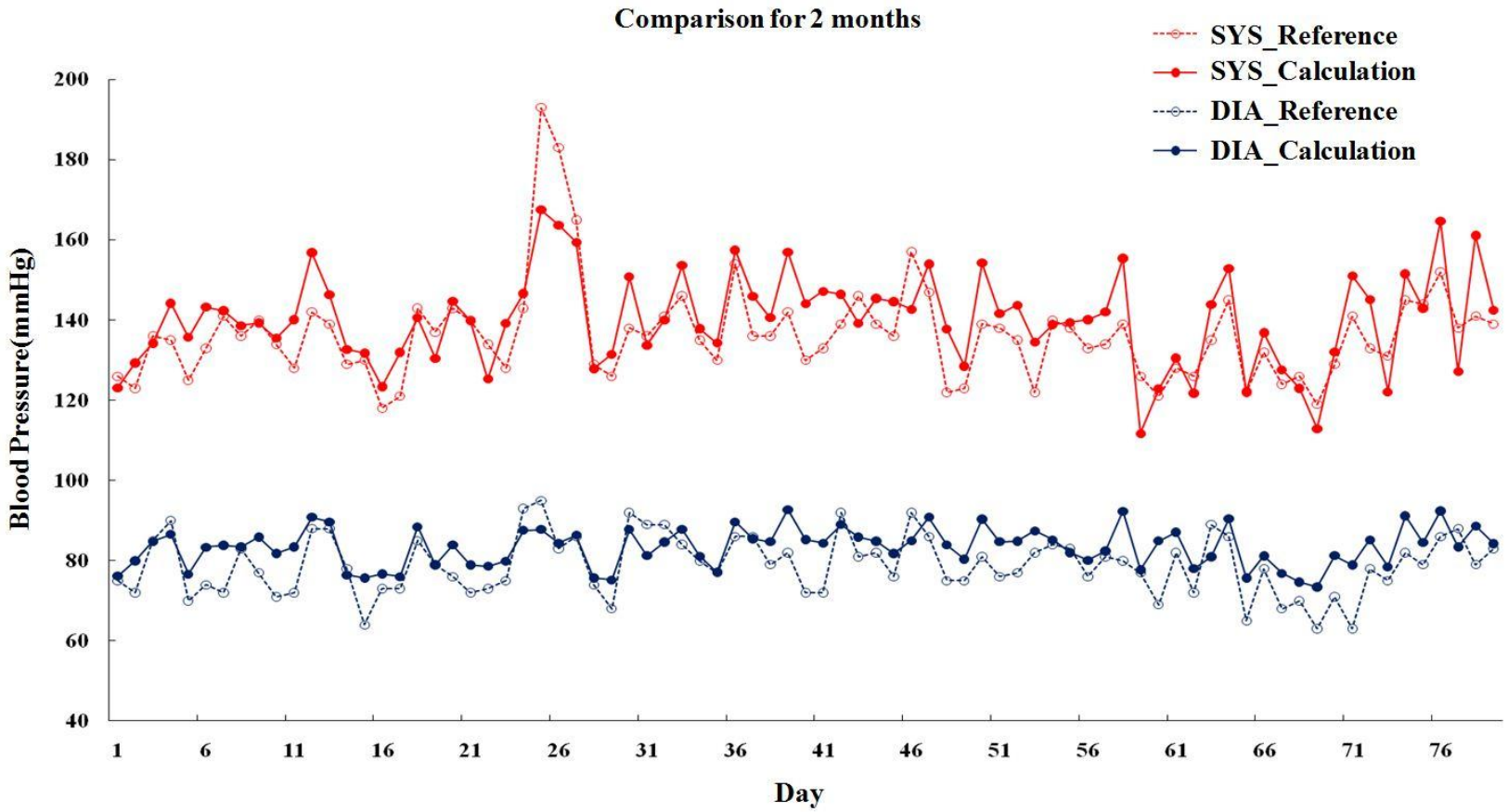


Figure 5.12. Data of a subject measured for 2 months.

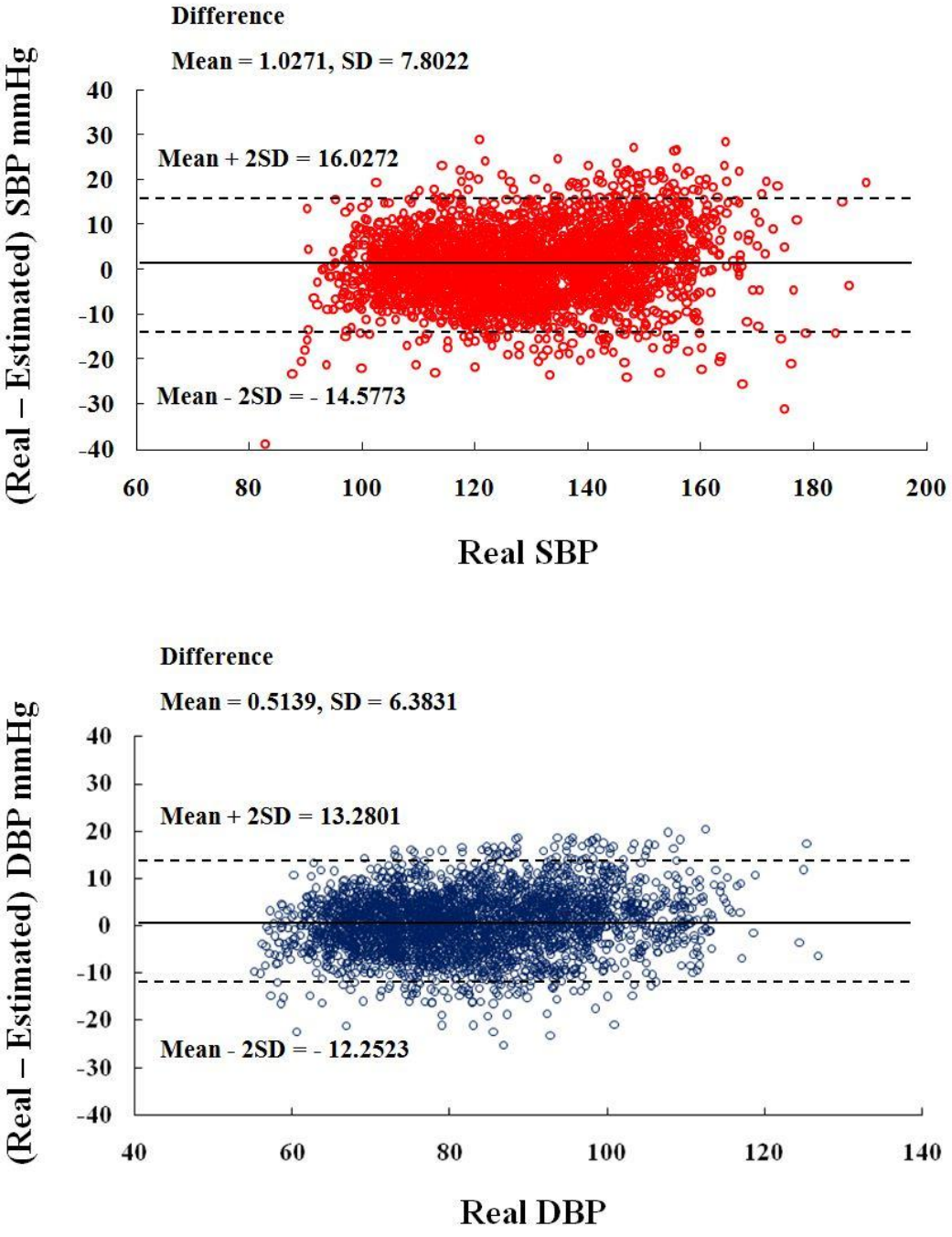


Figure 5.13. Blood pressure errors: difference between blood pressure and estimated blood pressure.

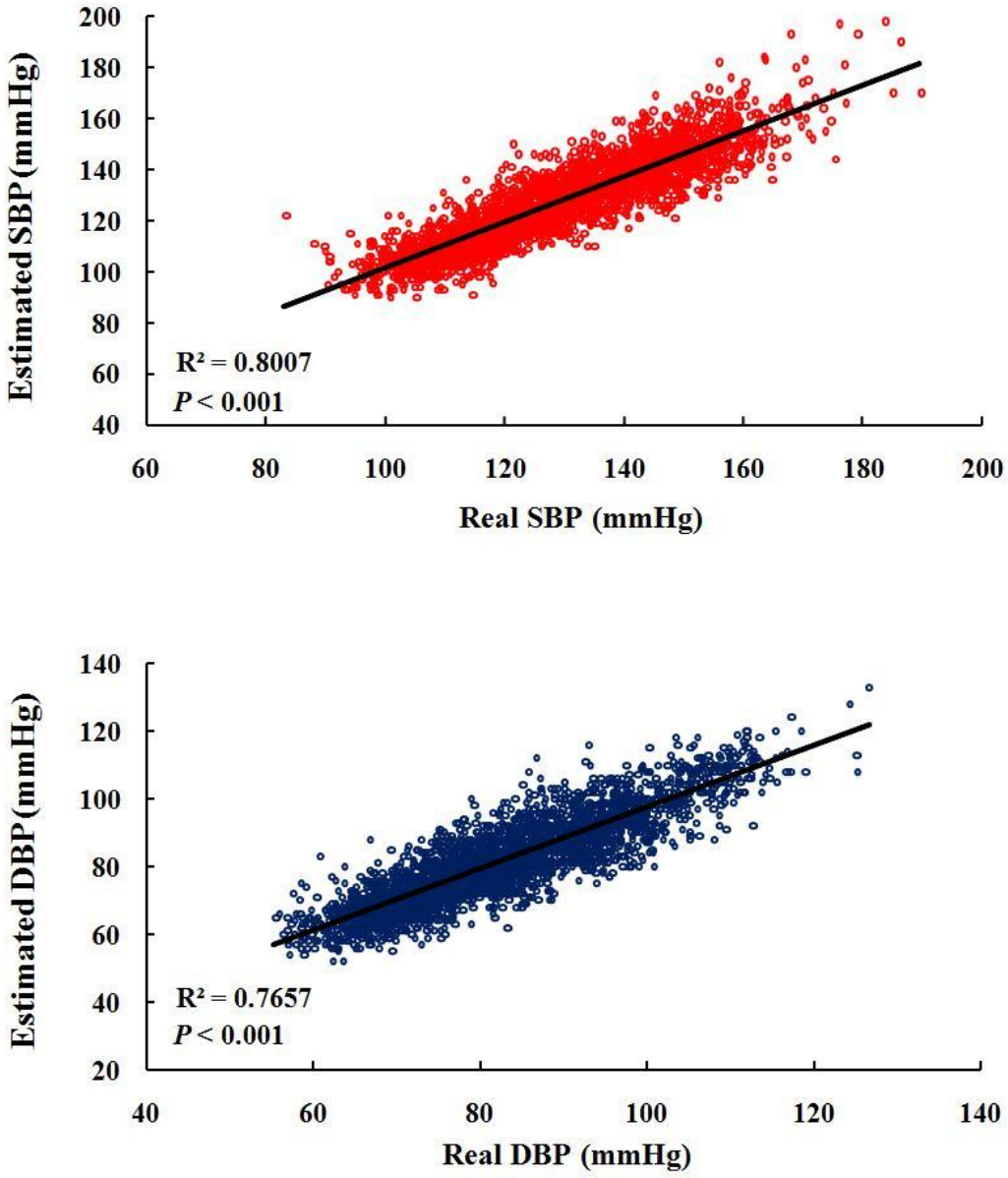


Figure 5.14. Correlation between blood pressure and estimated blood pressure.

5.2.5 Discussion

In this study, the AC component of PPG signal is BV pulse wave by the heart beating and gives us diverse pathological information on the cardiovascular system and the capillary vessels [133]. It is determined by the arterial compliance and resistance [28], and the increase of AC component magnitude can be interpreted as the dilatation of vessel wall [135]. And the DC component (including the AC component and DC offset) represents the total BV of the measuring part. The normalized PPG components were calculated with the compensation equations for the influence of CF and SST. To estimate BP with them, BP estimation equation was derived as equation (43) and (44) through the second stage experiment. The result of this BP estimation equation for each person was compared with that of the long-term measurement through the oscillometric sphygmomanometer (Model-53000, Welchallyn, USA). Figure 5.13 and 5.14 show the analysis results of the comparison, which have the permissible error (Table 5.3) ranges along with the high correlation.

Table 5.3. Bias (95% Confidence Interval [CI]), precision and limits of agreement between estimated blood pressure and real blood pressure.

	Systolic Blood Pressure	Diastolic Blood Pressure
Bias (95% CI)	1.03 (0.98 to 1.08)	0.51 (0.48 to 0.54)
Precision	7.802	6.383
Upper limit of agreement	16.03	13.28
Lower limit of agreement	-14.58	-12.25

Figure 5.12 is BP change trend of a test group for 2 months. The result of its comparative analysis turns out to be significant and the error was in the permissible range. Even though BP estimation with the normalized PPG signal is applicable just to the subject for whom the individual regression equation has been defined, if the compensation experiment is carried out for each subject and BP estimation equation is derived, not only

the long-term personal BP monitoring but also the non-vascular continuous BP monitoring will be possible. This result suggests the possibility to detect and monitor the risky elements in the cardiovascular system along with the clinical diagnosis and prediction in the ordinary life.

The long-term monitoring of BP and its periodic measurement in the ordinary life are clearly important. This study has developed a new method to estimate BP in non-invasive way, and completed the verification of BP measurement method using the normalized PPG signal through the long-term experiment.

This BP monitoring system can be performed conveniently various application during our life with patient specific calibration.

5.2.5 Summary of findings

The change in PPG waveform has been linked with cardiovascular condition change. We hypothesized that the morphological features of finger PPG waveform would be closely related to BP change. Analysis was performed on normalized finger PPG waveforms together with systolic and diastolic arterial BP measurements collected from 58 patients. The experiment was carried out in three stages: compensation, estimation, and long-term comparison.

The morphology analysis was carried out on normalized finger PPG waveform represented by BV and VR. PPG features were compensated by CF and SST, and then normalized. Normalized PPG components were calculated for identical condition. Individual BP estimation equation was obtained by finding the multi-regression analysis between real BP and PPG components. With the personal BP estimation equations, the long-term change of BP was measured. The analysis results of the comparison, which have the permissible error ranges along with the high correlation.

5.3 Conclusions of clinical study

Many studies have been carried out in the past linking cardiovascular status with PPG waveform change. This is the novel study to demonstrate a possibility that only the finger PPG waveform can estimate real blood pressure. Although we are hard to establish a general BP estimation equation, this individual information may be useful for judging the degree of personal BP change in real-life.

Since this study was carried out on 58 patients who have hypertension, hypotension, and normotension, it may be desirable to validate the proposed method on wider subjects and for longer-term in future.

Chapter 6 Conclusions

6.1 Overview

This chapter concludes the entire paper. The major contributions of current study, which include the relationship study, the compensation study, and the clinical study, are summarized in section 6.2. The implications of the results obtained from the current study are discussed in section 6.3. Possible future study is described in section 6.4.

6.2 Major contributions of current study

The current study consists of three major studies: the relationship study in chapter 3, the compensation study in chapter 4, and the clinical study in chapter 5. The major contributions of these studies are summarized as followings:

6.2.1 Relationship study

- When PPG signal which is normalized by measured CF and SST is acquired, SBP and DBP are proportioned to BV and inverse-proportioned to VR without constant terms. Therefore PPG signal from the artery is proposed a basis to detect BP. We are also able to get transitions BV and VR when PPG signal is acquired during long term. These processes can predict the change of BP.

- The DC component of PPG waveform is inversely proportional to static BV in the vessels and tissues. In addition, the AC component of PPG waveform shows subtle changes in the arterial system due to cardiac contraction and relaxation and provides information regarding vascular compliance and resistance. Therefore, these results support the possibility that the PPG components may be used for easy and noninvasive measurement of hemodynamic changes in the cardiovascular system such as BP.

6.2.2 Compensation study

- The waveform of the PPG signal may be affected by CF between the sensor and the measurement area. The DC and AC amplitudes of the reflective PPG signal increase with increasing CF until the transmural pressure. The results suggest that the effects of CF should be carefully examined in the design of PPG-based health care devices.
- Local temperature changes affected the PPG signals and the Finometer BP(Finger BP), but not the oscillometric BP(Central BP). These results suggest that temperatures must be carefully controlled or compensated for in the measurement of PPG signals in order to reduce for the errors in the values when evaluating cardiovascular status through PPG signals in a local heating and cooling treatments or in temperature variation environments.

6.2.3 Clinical study

- From BP change trend of an arbitrary test group for 2 months, the result of its comparative analysis was turned out significant and the error was in the

permissible range. Even though BP estimation with the normalized PPG signal is applicable just to the subject for whom the individual regression equation has been defined, if the compensation experiment is carried out for each subject and BP estimation equation is derived, not only the long-term personal BP monitoring but also the non-vascular continuous BP monitoring will be possible. This result suggests the possibility to detect and monitor the risky elements in the cardiovascular system along with the clinical diagnosis and prediction in the ordinary life. This study has developed a new method to estimate BP in non-invasive way, and completed the verification of BP measurement method using the normalized PPG signal through the long-term experiment.

6.3 Implication of results from current study

The results from current study clearly show the possibility of finger PPG waveform as a noninvasive determine tool for BP change. BP detection model were verified by the relationship study, which involved change of cardiovascular status from a group of healthy human subject that constituted blood pressure change and a group of healthy animal subject that induced via commonly used cardiac stimulants. The results from these studies have supported that morphological features derived from the finger PPG waveform could be very useful for detecting the change in central BP, and the trends of features might be possible to identify not only the local BV change but also the VR change in peripheral vasculature. The relationship between effects of environment and the finger PPG waveform was confirmed that CF and SST changes in groups of healthy subjects produced the progressive PPG waveform change. The clinical study focused on long-term comparison and has shown that morphological features of the finger PPG waveform could be potential markers of BP change, which may help to patients who are interested in monitoring their daily BP.

In terms of clinical application, this approach is best way to identify BP change as easily as possible, because we can apply the long-term monitoring possibility of BP measurement system. In this perspective, the finger PPG waveform-based technique may prove to be extremely valuable detection technique of BP. The technique proposed in the current study may be applied in home and mobile healthcare phase, so that whenever and wherever the patient are, BP assessment can be more convenient with very simple monitoring procedures. When the simple, comfortable and totally noninvasive BP measurement is required, PPG waveform will be the ideal application for continuous BP monitoring of the patient.

6.4 Future study

From this study, the possibility that the proposed technique based on PPG waveform is potentially useful for identifying changes in patients' central BP due to ongoing changes in cardiovascular condition may still exist. However, the small samples of healthy subjects who were under no treatment with the medicine and have no cardiovascular diseases except hypertension or hypotension remain future study. Therefore, future studies should consider wider groups who suffer from various other cardiovascular diseases, elderly or newborn subjects, as well as subjects with various pharmacological interventions.

A challenge of the current study will be offering one general estimation equation that includes both individual compensation term and BP estimation equation. If it can be successful, the proposed techniques will be beneficial in improving the BP management of general population. Since motion artifacts and other problems associated with the recording of PPG waveform will have any significant impact on the usefulness of the proposed techniques, additional studies are necessary to consider eliminating these effects

from real-life patient data for offering an important BP diagnostic application for future medical devices.

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국 문 요 약

비관혈적 혈압측정:
PPG 파형기반의 추정 및 검증

PPG 는 조직미세혈관에서 혈액량 변화를 검출하는데 사용되는 광학적 측정 기술이다. 이 기술은 상업적으로 사용 가능한 임상 의료기기에서 널리 사용되어 왔다. PPG 파형은 현 임상 업무에 완전히 활용되지 않아온 환자의 심혈관 상태에 관한 중요한 정보를 가지고 있다고 믿어진다.

현 연구의 목적은 혈압의 지시자로 손가락 PPG 파형에서 나온 다양한 특징점을 사용하는 타당성에 대해 평가하는 것이다. 자세하게 첫째, 응급실과 집중치료실 환자의 혈압이 변하는 동안 PPG 파형의 변화에 대해 연구하고 심혈관 질병의 비관혈적 지표로서의 가능성을 평가한다. 둘째, 심장자극제를 통한 점진적인 중심 혈액량과 총 말초저항의 변화와 연관된 혈압을 나타내는 혈액량과 혈관저항의 비관혈적 지시자들의 사용 가능성을 평가한다. 셋째, 측정부위의 접촉 압력의 변화와 점진적인 냉각과 가열에 기인하는 손가락 PPG 파형의 표준화 적절성에 대해 조사한다. 마지막으로, PPG 파형으로부터 혈압을 검출하는 자동적 방법을 개발하고 비관혈적 임상 혈압 측정 장비와 PPG 파형으로부터 검출된 값을 비교한다.

현 연구의 결과는 혈압 변화를 비관혈적으로 측정하는 손가락 PPG 파형의 가능성을 명확히 보여준다. 혈압 검출 모델은 건강한 인체 실험군의 심혈관 상태 변화와 심장자극제에 영향을 받은 건강한 동물 실험군의 혈압 변화에

따른 PPG 파형의 변화에 대한 상관성 연구에 의해 검증된다. 이 연구의 결과는 손가락 PPG 파형의 특징점들이 중심 혈압의 변화를 검출하는데 유용하다는 것과 이 특징점의 추세가 아마도 지역적 혈액량과 말초혈관계의 저항값을 찾을 수 있다는 것을 보인다. 외부환경의 효과와 손가락 PPG 파형 사이의 상관관계는 점진적인 PPG 파형의 변화를 제공하는 건강한 실험군의 접촉 압력과 피부표면온도의 변화에 의해 확인된다. 임상연구는 장기적 데이터의 비교를 통해 이루어졌으며 손가락 PPG 파형의 특징점이 혈압 변화의 잠재적 지시자임을 밝힌다. 이를 통해 연구된 기술은 일상에서의 혈압 감시가 필요한 환자들에게 도움을 줄 수 있다.

임상적 적용에 있어 이 기술적 접근은 장기적인 혈압 감시의 가능성을 제공할 수 있기 때문에 가능한 쉽게 혈압을 확인할 수 있는 최상의 방법이 될 수 있다. 이러한 관점에서 손가락 PPG 파형에 근거한 기술은 혈압의 매우 가치 있는 검출 기술이 될 것 이다. 현 연구에서 제안된 기술은 재택과 이동형 건강관리에 적용될 수 있다. 따라서 환자가 언제 어디서든 매우 단순한 검출 과정을 통해 보다 편리하게 혈압을 평가할 수 있다. 단순하고, 편리하며, 완전히 비관혈적인 혈압 측정이 요구될 때 PPG 파형은 환자의 연속적인 혈압 감시를 위한 이상적인 응용이 될 수 있다.

Key words: PPG, 혈압, 혈액량, 혈관저항, 접촉압력, 피부표면온도, 비관혈적 혈압, 실혈관계 질병

감사의 글

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대학원 생활을 동고동락한 이현웅, 이광재, 김재영, 정진, 이진술, 배기수, 최유나, 이동희, 남기태, 고준섭, 박성준, 연구실을 이끌어가는 노연식, 심명헌, 연구실의 자랑이 될 정상오, 윤욱진, 황인섭, 정운모, 한영면, 정재훈, 윤찬솔, 윤자웅, 연구실의 일원이 될 정주홍의 무한한 발전을 기원합니다. 논문을 쓰고 마무리하는데 많은 힘을 준 고재일, 전석환, 김민용에게 진심을 담은 고마움을 전하며 실험에 참여한 모든 분 들께 감사 드립니다. 언제나 선생님인 한상돈, 함께 걱정해주는 김영대, 충고를 아끼지 않는 서광석, 힘이 되었던 이계형, 연락을 잊지 않는 최한윤, 박신우에게 고마운 마음을 전합니다. 자신의 길을 멋지게 걸어가고 있는 서경석과 언제나 웃음으로 대해준 모든 친구들 진심으로 고맙습니다. 그리고 많은 관심을 아끼지 않는 누가의료기의 조승현 회장님, 김홍제 사장님, 이종수 부사장님, 김병제 이사님께 감사 드립니다.

지금까지 제가 성장하는 것을 지켜봐 주시고 돌보아 주신 많은 친지 여러분께도 감사 드립니다. 특히 언제나 저를 최고로 생각해주시는 할머니와 몸은 편찮으시지만 마음속으로 저를 보실 외할머니께 진심으로 감사 드립니다. 언제나 형을 위해주는 동생에게 사랑을 전하며 행복을 기원합니다. 무엇보다 언제나 그리고 지금도 항상 말없이 못난 불효자를 지켜봐 주시고 믿어주시며 무한

한 사랑을 주시는 부모님께 언제나 부족할 수 밖에 없는 감사의 마음과 사랑을 드립니다. 부모님의 가르침과 사랑이 없었다면 지금의 저는 존재할 수 없을 것입니다. 사랑합니다. 아버지. 사랑합니다. 어머니. 마지막으로 항상 먼저 걱정하고 따뜻한 사랑과 격려로 곁에서 힘이 되어준 나의 반려자와 가족들에게 고맙고 사랑한다는 말을 전합니다.

많은 분들의 격려와 애정 어린 관심에 대한 고마움으로 미약하나마 이 논문을 통해 감사의 마음을 전하고 싶습니다.

끝으로 이 모든 것을 이루어 주신 주님께 감사 드립니다.

Never seem more learned than the people you are with. Wear your learning like a pocket watch and keep it hidden. Do not pull it out to count the hours, but give the time when you are asked. (Lord Chesterfield)

2010년 12월

정 인 철 올림