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Physiological indices for the categorization of Mibyeong severity

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ABSTRACT

Background: Individuals with Mibyeong are difficult to identify. Although extensive research has attempted to introduce an easy and clear method for Mibyeong diagnosis, the indices used to categorize Mibyeong severity are unclear. We hypothesized that individuals with severe Mibyeong have reduced physiological function, thus activating homeostatic regulatory functions and inducing alterations in vascular resistance and capacitance.
Methods: Novel indices used to categorize Mibyeong severity based on the cardiovascular system model are described. We analyzed resistance and capacitance values using a simple cardiovascular system model optimally satisfying the measured systolic and diastolic pressures, heart rate, and age.
Results: Clinical data from 509 individuals were examined to test our hypothesis. A statistical analysis revealed that the vascular resistance was lower in individuals with severe Mibyeong symptoms and decreased with increasing Mibyeong severity, whereas the vascular capacitance showed an opposite trend.
Conclusion: We derived indices to categorize Mibyeong severity and tested 509 individuals. An epidemiological analysis revealed that the vascular resistance decreased while the capacitance increased with increasing Mibyeong severity, indicating the validity of the values as Mibyeong indices.

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1. Introduction

Mibyeong (China: *Weibing*, Japan: *Mibyou*) indicates a gray zone between disease and a normal state. There are diverse definitions for Mibyeong: abnormal examination findings or subjective symptoms without a specific disease,[1] a state intermediate between health and disease,[2] and an unbalanced state in which one is able to maintain one's own self.[3] Lee et al[4] used the Delphi process to reach a consensus among researchers in the field.

According to an epidemiological investigation, approximately 47% of adults in Korea complain of several symptoms but are not diagnosed with any disease.[4] However, due to the ambiguity of the definition, it is not easy to categorize those with Mibyeong. Several previous studies have attempted to diagnose Mibyeong. As reviewed by Lee et al,[4] many methods have been proposed to diagnose Mibyeong (e.g., a tongue analyzer and questionnaire). A feeling of pain or fatigue is considered to be critical in Mibyeong; however, no clear and objective method for making a diagnosis has been proposed. Additionally, the severity of the disorder in people with Mibyeong varies, further complicating the diagnostic process. In this aspect, it is crucial to find indices for the categorization of Mibyeong, including whether the patient is in the Mibyeong state or not, and how to identify the severity of Mibyeong. Although heart rate variability was considered a plausible candidate index for Mibyeong, there is no evidence to support its use.

In this study, we hypothesized that cardiovascular hemodynamics may be closely related with a Mibyeong state with the variations of the hemodynamic variables, such as peripheral resistance (R) or overall vascular compliance (C), in people with Mibyeong. To validate this, epidemiological data were analyzed to obtain R and C values for each individual. The R and C values of Mibyeong individuals were then compared to those of normal individuals.

2. Methods

2.1. *Hemodynamic compensatory hypothesis*

The hemodynamic properties of the cardiovascular system (e.g., R and C) are controlled by feedback mechanisms to maintain homeostasis. Thus, we hypothesized that if the body's physiological state is not normal (i.e., the Mibyeong state), the feedback mechanism tries to increase blood flow to peripheral tissue, leading to a decrease in R and an increase in C. From this, it was also hypothesized that people in the Mibyeong state will have a relatively lower R value and a higher C value. Here, R and C values were normalized to body weight.

2.2. *Hemodynamic variable estimation*

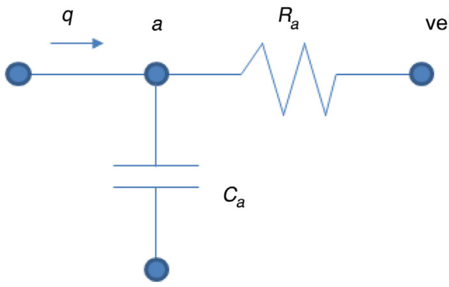

Fig. 1 – An electric circuit representing the hemodynamics of the cardiovascular system from the aorta to veins. Here, q, R, and C indicate the flow rate from the left ventricle, resistance, and capacitance, respectively. The subscript '*a*' indicates the artery compartment.

The hemodynamics of vessels from the aorta to veins can be roughly expressed as a series of equivalent elements, including resistance and capacitance, in an electric circuit, as shown in Fig. 1. In the figure, *q* represents the flow rate from the left ventricle (LV). The application of Kirchhoff's law to the arterial node '*a*' in the hemodynamic model leads to the following equation[5]:

$$C_a {}^{dP_a}\!/\!_{dt} = q_{inflow} - q_{outflow} \tag{1}$$

Here, t, P, q_{inflow}, and $q_{outflow}$ represent the time, blood pressure, flow rate coming into node '*a*', and flow rate going out from arterial node '*a*', respectively. The term q_{inflow} indicates the flow rate from the LV. We assumed a parabolic profile of flow according to time from the LV, as shown in Fig. 2. This profile is similar to one that was observed clinically.[6] Here, T is the cardiac cycle and q_{max} is the maximum flow rate. The systolic time duration was assumed to be one-third of the cardiac cycle. Thus, we assumed the following relationships for q_{inflow} and $q_{outflow}$:

$$q_{inflow} = q = \begin{cases} -k \times \left(t - 0.5 \times T_{sys}\right)^2 + q_{max} & 0 \le t \le T_{sys} \\ 0 & T_{sys} < t \le T \end{cases} \tag{2}$$

$$q_{outflow} = {}^{(P_a - P_{vein})}\!/\!_{R_a}\ (P_{vein} = 5.8mmHg) \tag{3}$$

In Eqs. (2) and (3), 'sys' and '*vein*' indicate systole and vein, respectively. The constant, k, in Eq. (2) is represented in the

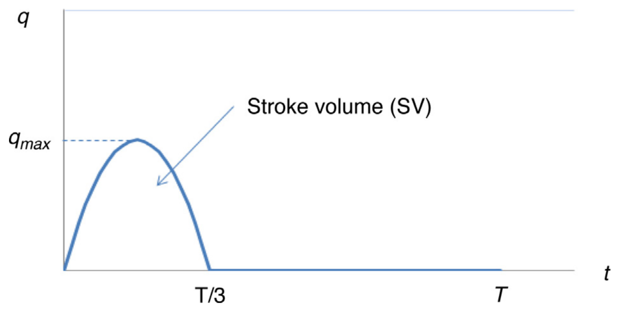

Fig. 2 – Flow rate from the left ventricle to the artery compartment according to time. Here, *T* represents the cardiac cycle and q_{max} is the maximum flow rate. The duration of systole was assumed to be one-third of the cardiac cycle.

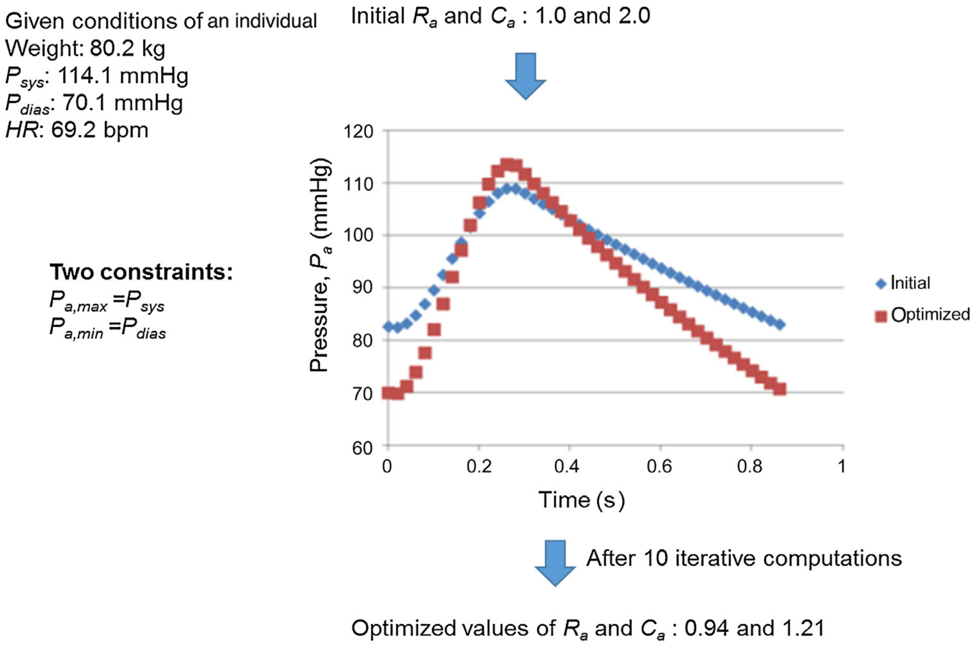

Fig. 3 – An example of how hemodynamic variables such as R_a and C_a were estimated.

equation below. The systolic time duration, T_{sys}, is assumed to be one-third of the cardiac cycle T.[5]

$$k = 4.0 \times {}^{q_{max}}\!/_{T_{sys}^2} \tag{4}$$

To solve Eq. (1) according to time, we used a numerical method and applied a forward Euler method to the time derivative in Eq. (1). The following equation was then used to obtain the arterial blood pressure, P_a, for a cardiac cycle:

$$P_a^{n+1} = P_a^n + \Delta t \times {}^{\left(q_{inflow} - q_{outflow}\right)^n}\!/_{C_a} \tag{5}$$

Here, 'n' and '$n+1$' indicate time step indices, Δt indicates the time step size, and q_{inflow} and $q_{outflow}$ are substituted by Eq. (2) and Eq. (3). If the initial conditions of P_a, the cardiac cycle, T, and q_{max} are given, the transient values of P_a for a cardiac cycle are obtained by solving Eq. (5) in a time-marching manner. The cardiac cycle, T, is computed from the heart rate of the individual. To calculate q_{max}, we assumed the following empirical equation of stroke volume (SV) proposed by Webb.[7] Thus, SV was computed from the systolic and diastolic pressures and the individual's age:

$$SV\,(mL) = 93 + 0.62 \times \left(P_{sys} - P_{dias}\right) - 0.45 \times P_{dias} - 0.61 \times age \tag{6}$$

In the above equation, '*dias*' indicates diastole and the units of pressure and age are mmHg and year, respectively. In Fig. 2, the area under the curve during systole indicates the SV. Considering that the time integration of q_{inflow} in Eq. 2 during systole is equal to the SV, we can calculate q_{max} as follows:

$$q_{max} = SV \times {}^{1.5}\!/_{T_{sys}} \tag{7}$$

To estimate hemodynamic variables such as R_a and C_a, we used the following procedure: (1) For given values of P_{sys}, P_{dias}, heart rate, and age, we first calculated SV, T, T_{sys}, and q_{max}; (2) then, we computed the time-varying values of P_a. However, there are two unknown variables in Eq. (5) – R_a and C_a. Here, the computed P_a values should satisfy two constraint conditions: the maximum and minimum values of P_a represent the systolic and diastolic pressures, respectively. Therefore, if we assume the values of R_a and C_a, then P_a can be obtained; (3) thus, determining R_a and C_a is an optimization problem that can be solved by a simplex method.[8] That is, we can iteratively calculate R_a and C_a values that satisfy the two constraints; (4) the computed R_a and C_a values were normalized to body weight. For this purpose, we divided R_a by weight, whereas C_a was multiplied by body weight; and (5) these values were then divided by the average value for normalization purposes.

2.3. *Analysis of epidemiological data*

We analyzed epidemiological data to show the validity of the hemodynamic index for Mibyeong diagnosis. Epidemiological data were collected from 509 nondiseased volunteers between the age of 20 years and 40 years at Daejeon University (Daejeon, Republic of Korea) and Gachon University (Incheon, Republic of Korea) between 2014 and 2015. This study was approved by the Institutional Review Board of the institutes and informed consent was obtained from all participants.

To classify the severity of Mibyeong, we used the Mibyeong score developed by the Korea Institute of Oriental Medicine. The score uses a multinomial logistic regression analysis based on integrated data [pain feeling and questionnaire responses (i.e., physiological symptoms)] to classify the severity of Mibyeong. More detailed explanation for the method to classify Mibyeong group is represented in our previous paper.[9]

Table 1 – Classification of Mibyeong severity.

	Mibyeong Group 1	Mibyeong Group 2	Mibyeong Group 3
Males	77 (34.1)	65 (29.4)	53 (27.5)
Females	67 (32.1)	111 (31.3)	136 (43.4)
Total	144 (33.2)	176 (30.3)	189 (37.3)

Data are presented as *n* (%).

Table 2 – Statistical analysis of the computed resistance and capacitance values for the three Mibyeong groups.

			N	Average	SD	*p*	*Post hoc* analysis
Gachon/Daejeon University Hospital data	R_a	Group 1	144	1.111	0.380	0.000	Group 1 > Group 2, Group 3
		Group 2	176	0.986	0.342		
		Group 3	189	0.929	0.347		
	C_a	Group 1	144	0.916	0.353	0.000	Group 3 > Group 1, Group 2
		Group 2	176	0.985	0.324		
		Group 3	189	1.078	0.349		

SD, standard deviation.

3. Results

An example of how to estimate hemodynamic variables such as R_a and C_a is presented in Fig. 3. The initial values of R_a and C_a are given and an iterative simplex algorithm is run to search for values that satisfy the constraints.

Table 1 shows the analysis of epidemiological data from 509 individuals. The severity of Mibyeong was divided into three groups. Mibyeong Group 1 was defined as healthy individuals with no clear symptoms of Mibyeong, whereas Mibyeong Group 3 represented individuals with severe symptoms of Mibyeong. Individuals with mild symptoms were classified as Mibyeong Group 2. Based on the data, the numbers of individuals in Mibyeong Group 1, Group 2, and Group 3 were 144, 176, and 189, respectively. The method to classify Mibyeong groups and their averaged Mibyeong scores are described in our previous paper.[9]

The R_a and C_a values were computed for 509 individuals as described in the Methods section. The computed values are shown in Table 2. Here, the data were analyzed using an analysis of variance. According to the analysis, the value of R_a was highest in Mibyeong Group 1 (healthy) and lowest in Mibyeong Group 3 (severe Mibyeong). Inversely, C_a was the highest in Mibyeong Group 3 and the lowest in Mibyeong Group 1. A *post hoc* analysis (Scheffe's test) was used to evaluate the statistical difference between R_a and C_a according to Mibyeong severity (Table 2). The values for Mibyeong Group 1 were markedly higher than those for the other groups.

4. Discussion

Mibyeong exists in a gray zone between healthy state and diseased one. Until now, a clear definition and the clinical boundaries of Mibyeong have not been established. Although there have been several studies, the diagnostic indices used to classify Mibyeong are unclear.

In this study, novel physiological indices were proposed to categorize Mibyeong severity. For this purpose, we assumed a physiological hypothesis in which the homeostatic regulation of hemodynamic variables (e.g., vascular resistance and compliance) is activated when body function is slightly out of the normal state due to Mibyeong. Therefore, it was assumed that vascular resistance and compliance may be dependent on Mibyeong severity.

To validate the efficacy of the indices, we first analyzed epidemiological data. For the analysis, 509 individuals were classified into three groups: normal (Group 1), mild Mibyeong (Group 2), and severe Mibyeong (Group 3). Vascular resistance and capacitance values were then calculated. To compute the vascular resistance and capacitance values, we used the cardiovascular system model and parameter optimization algorithm of the simplex method. We also compared the average vascular resistance and capacitance values among the three groups.

The current study produced two major findings. First, the group-averaged R_a and C_a values showed clear differences between groups, indicating that vascular resistance and capacitance may be used as indices to classify Mibyeong. Vascular resistance, R_a, decreased according to the increase in Mibyeong severity; conversely, C_a showed an opposite trend. Secondly, in the present study, we proposed a physiological hypothesis in which homeostatic function can alter hemodynamic variables such as vascular resistance and compliance due to the Mibyeong state. This was proven by the vascular resistance and capacitance values, which were dependent on Mibyeong severity.

Although our data clearly explain the efficacy of the indices with respect to Mibyeong severity, our study has several limitations from a cardiovascular hemodynamic viewpoint. First, we used the empirical relation of SV, which is a rough estimation and can introduce some errors into the estimation process. Second, our sample size of 509 individuals was relatively small; a large-scale study is needed to validate the proposed indices for Mibyeong diagnosis. Third, the present study did not analyze the epidemiological data with gender or age due to the limited number of study population. However, these limitations do not detract from our results, which support the use of hemodynamic variables to determine Mibyeong severity.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgments

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