Regulation of sensory nerve conduction velocity (SCV) of human bodies responding to annual temperature variations in natural environments

Article

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Title Page

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Running head

temperature and SCV

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Abstract

The extensive research interests in environmental temperature can be linked to human productivity/performance as well as comfort and health; while the mechanisms of physiological indices responding to temperature variations remain incompletely understood. This study adopted a physiological sensory nerve conduction velocity (SCV) as a temperature-sensitive biomarker to explore the thermoregulatory mechanisms of human responding to annual temperatures. The measurements of subjects' SCV (over 600 samples) were conducted in a naturally ventilated environment over all four seasons. The results showed a positive correlation between SCV and annual temperatures and a Boltzmann model was adopted to depict the S-shaped trend of SCV with operative temperatures from 5 °C to 40 °C. The SCV increased linearly with operative temperatures from 14.28 °C to 20.5 °C and responded sensitively for 10.19 °C - 24.59 °C, while tended to be stable beyond that. The subjects' thermal sensations were linearly related to SCV, elaborating the relation between human physiological regulations and subjective thermal perception variations. The findings reveal the body SCV regulatory characteristics in different operative temperature intervals, thereby giving a deeper insight into human autonomic thermoregulation and benefiting for built environment designs, meantime minimizing the temperature-invoked risks to human health and well-being.

Keywords

Natural environment; Temperature variation; Sensory nerve conduction velocity (SCV); S-Shaped characteristics; Thermoregulatory zone; Thermal sensation;

Practical implications:

- The regulatory characteristics of human physiological indices responding to temperature variations annually remain incompletely understood due to the limited and discrete temperature conditions in current chamber experiments.
- This study adopts the sensory nerve conduction velocity (SCV) and reveals the S-shaped trend in healthy populations under natural environments based on a large number of measurements around years.
- The findings quantify the temperature zones of body SCV variations and provide in-depth knowledge of human physiological regulation, which is beneficial for thermal environment building and risk evaluation, with the aim of securing human comfort and health.

1. INTRODUCTION

The relations between temperature and human comfort and health have long been investigated by specialists worldwide; the interest has increased with increasing concentration on global climate changes [1, 2] and built environment improvements [3, 4]. A number of population-based epidemiological studies have verified the U- or V-shaped relationships between environmental temperatures and the corresponding outcomes on population mortality and morbidity [5, 6]. However, these outcomes reported the temperature impacts but the mechanisms underlying human physiological regulation have been less examined due to the limitations of population-based investigations [7]. Therefore, to fill in this gap, a method that allows for an objective human physiological index should be given attention, in order to better understand the body's physiological interactions with environments, and evaluate comfort and health.

Humans are homeotherms and maintain relatively constant body temperatures and homeostasis. There is a thermo-neutral zone of ambient temperatures for body thermoregulation. Within this temperature range, the body's metabolic rate would be at the basal level and the responses of body to temperature changes can be accomplished only by the control of sensible heat loss (convective and radiative) via skin by vasoconstriction and vasodilatation. Beyond the lower critical temperature, the metabolic heat production increases by shivering, or nonshivering. Above the upper limit, the loss of body heat is promoted by increased sweat production [8]. Among a series of body physiological regulations, the body's peripheral nervous system is remarkably temperature-sensitive [9]. There are a number of thermoreceptors broadly distributed under the skin surface, sensing temperature changes (e.g. from below 8°C to above 52°C [10]), transforming the temperature signals into bioelectrical signals; then the body identifies the electrical signals and conducts the signals to the central nervous system through afferent nerves, demonstrating by nerve conduction velocity. Nelson, *et al.*[11] conducted experiments on skin surface temperatures and nerve characteristics in nonimpaired individuals and addressed the significant effect of temperature on nerve conduction. Among the effects of warm-up-attributed temperature-related mechanisms, there was a significant increment of the nerve conduction velocity [12]. The study by Halar, *et al.* [13, 14] showed a significant correlation between skin surface temperature and nerve conduction velocity that the nerve conduction velocity increased by 1.5-2m/s in per 1 °C increase in skin surface temperature. Conversely, the cold temperatures were found to slow down the nerve conduction velocity, prolong the distal latency, and increase the amplitude and duration of recorded potentials [15]. Overall, these researchers have found that the temperature stimuli have significant effects on skin surface temperatures and on the electrophysiologically conductive velocity along the afferent nerves [16].

As mentioned, both skin temperature and nerve conduction velocity play roles in human thermoregulatory signal pathways. To date, there are a number of studies focusing on the human skin temperatures, the thermoreceptors at skin surface, their responses to thermal stimuli, and their relations with human thermal perceptions[17-19]. The outcomes showed that the skin temperature and the change rates of skin temperatures were significantly affected by temperature stimuli, reflecting human thermal comfort [20-22]. This mechanism was explained by the thermoreceptors sensing the temperature stimulus and inducing impulse to send signals at a high frequency [23, 24]. In physiology, the receptors are confirmed as acting transducers, which can convert the thermal signals to bioelectrical signals and conducted along the afferent nerve fibers to thermoregulatory center[25]. Therefore, it is reasonably inferred that the nerve conduction may bridge the pathways between thermoreceptors sensing temperature signals and central nerve receiving electric signals. However, a limited body of research had focused on the nerve conduction regulation, especially in the built environment field, and the characteristics of conductive velocity of nerve during thermoregulation is still underexploring. What is the following outcome of sending impulse signals? What are the regulatory laws of nerve conduction velocity? What is the consequent effect on human subjective sensation? These remain unclear but it is of importance to promote our knowledge to thermal regulation of human and thermal building environment.

In electrophysiological studies, the temperature is a significant physical stimulus influencing the velocity of the nerve conduction[26]; consequently the changes of nerve conduction velocity involved in human thermoregulation significantly affect the body's thermal responses, where the relative degree of temperature stimuli on nerves determines a person's perception and intensity of thermal sensation [27]. However, due to the different discipline contexts, the majority of nerve conduction velocity studies have been conducted in electrophysiology: one aspect of them focus on index measurement, including the standard measuring methods of nerve conduction velocity [11, 9], the normal ranges in healthy people [28], the correction caused by temperature effect [15, 29]. Another aspect of these studies apply the measurement of nerve conduction velocity to disease diagnosis like diabetes [30, 31], carpal tunnel syndrome [32], etc., where the patients had peripheral neuropathy, leading to abnormal variation. However, few attentions have been paid to the real regulation of nerve conduction in the human body under annually natural environments. Since the skin temperatures and thermoreceptors have been paid much attentions, familiarity with the skin regulation related index-nerve conduction velocity and the effects of environmental temperature on the nerve conduction velocity under natural conditions is a necessity. This is expected to provide a better understanding on the physiological mechanisms underlying the function of body thermoregulation, which would be beneficial for built environment designs.

Therefore, this study was aimed to better identify the mechanisms of human physiological responses to temperature variations under natural conditions, taking the sensory nerve conduction velocity (SCV) as the target. Moreover, differing from the majority of the studies which are performed in an artificial climate chamber, this study conducted a large-sale experimental measurements of SCV in a naturally ventilated room. To identify the annual response characteristic of SCV, the experiments were continuously conducted in different annual seasons. This aimed to elucidate a valuable insight into how the environmental temperature affects the SCV regulation of human body and what the differences of SCV responses for different temperature ranges. The findings are expected to provide a review of the relation between environmental temperatures and body thermoregulatory mechanisms, and reveal the abilities and limitations of human thermoregulation. The work would be beneficial for indoor thermal environment designs, understanding the temperature range for which the human automatic thermoregulation exists and for which the assisted operation of a heating/cooling system is necessary to ensure human comfort and health.

2. METHODS

2.1 Measurement of the sensory nerve conduction velocity (SCV)

The nervous system of the human body consists of the central nerves, the cranial nerves, and the peripheral nerves, distinguished by the sensory and motor nervous systems. Temperature variations would affect the skin temperature and hypodermis, and the time and process of cellular depolarization, dominating the bioelectrical signal conduction along the afferent nerves. To evaluate the effect of temperatures on human thermoregulation, in our previous study Liu [33] explored a series of physiological indices through experiments under natural conditions, and figured out six out of these indices being significantly related to temperature changes, including sensory nerve conduction velocity(SCV), motor nerve conduction velocity(MCV), skin temperature, body temperature, skin resistance and heart rates. Although the skin temperature is well acknowledged as an index to reflect human thermal regulation, it may be unable to reflect the real conditions of body thermal strain in hot environments, where the skin temperatures tend to be stable, even conversely reduced by the sweat regulation and perspiration evaporation. Considering that both skin temperature and SCV pertain to sensory nervous system of human body and respond to temperature variations in the thermoregulatory pathway, this study adopted a electrophysiological index-SCV-to examine the real thermal responses of human body and further explore the regulatory characteristic of sensory nerve system. The SCV is defined by Equation (1):

$$SCV=L/T \qquad (1)$$

Where L is the length of the measured nerve segment between the stimulating point and recording point (Figure 1(a)) on the skin surface along the nerve bundle, mm. T is the measured time from the beginning of the stimulus artifact to the onset of the sensory nerve action potential (e.g., the time detecting the voltage signal on the instrument), namely, the initial latency, ms.

Generally, there are two ways to measure the SCV: median nerve orthodromic and antidromic conduction [34]. Given that studying nerve excitability was better suited to the antidromic than to the orthodromic technique [34], the antidromic conduction was used in the experiments. The measurement was performed on the subject’s median nerve sensing fiber, mainly distributed in the palm side of the right hand and outside the hand skin, using the myoelectricity-evoked potential apparatus (MEB-9140K, 4 channels, voltage resolution: 0.01μ, Japan). The instrument was set up for a 50mA current, a 1kHz sampling frequency. During the test, the distance (L in Equation (1)) from the stimulating electrode point to the recording electrode point, was measured using a soft leather ruler. The stimulus duration was set 0.1ms, starting with a 1mA stimulus, and increasing by 1mA per stimulation until a maximal response (voltage signal) was monitored by the instrument. All the measured parameters were read and recorded by the instrument automatically. The measuring points, sketch, and interface can be seen from Figure 1.

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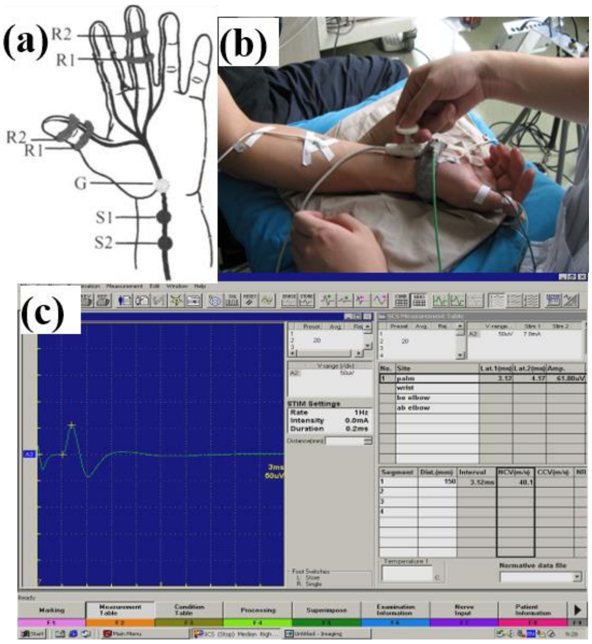

STIM Settings
Rate 1Hz
Intensity 0.0mA
Duration 0.2ms

No.	Site	Lat.1(ms)	Lat.2(ms)	Amp.
1	palm	3.12	4.17	61.80uV
	wrist			
	be elbow			
	ab elbow			

Segment	Dist.(mm)	Interval	NCV(m/s)	CCV(m/s)	NR
1	150	3.12ms	48.1		
2					
3					
4					

Figure 1: The measurement sketch map of SCV

Note:

1) S1, S2: Stimulating electrode point at the wrist; R1, R2: Recording electrode; S2, R2: Reference electrode; G: Earth line;
2) L in Equation (1) is the distance between S1 and R1.

2.2 Subjects

Subjects were recruited randomly. All of them were college students, aged between 20 and 30 in good health, to minimize the individual differences such as age, body components, etc., and to ensure no signs or symptoms of neurological impairments that may affect SCV measurements.

The study complied with the guidelines in the latest version of the Declaration of Helsinki [35] and was approved by the Ethics Review Committee for Life Science Study of Central China Normal University (approval ID: CCNU-IRB-2009-003). The procedures had been approved by the Chongqing local ethics committee. Before the experiments, written informed consents were obtained from the participants. Care was taken to exclude the subjects for any underlying neurological problem after a physical examination. The participants were asked to withdraw from the test at any point in time if they were not comfortable with the test.

Table 1 presents the subjects' physical information. The sample in Table 1 reflects the sample capacity, namely, the number of tests being conducted during experiments. Since the experiments were conducted throughout the year, some of the subjects participated in the tests in different seasons more than one time. In addition, as the experiments were conducted in natural environments, subjects were not asked to wear the uniform clothes during tests and they were free to choose clothes according to the outdoor climates. However, before experiments, the clothing information was recorded by testers. Besides, to make sure it was convenient for testers to attach the instrument, they were suggested to wear loose clothes to make sure that the arms were uncompressed during the test.

Table 1: Basic physiological parameters of subjects (mean ± SD)

Sex	Sample	Age (year)	Height (cm)	Weight (kg)
Male	347	23.7 ± 3.87	172.9 ± 5.88	62.4 ± 8.71
Female	333	23.2 ± 3.17	160.2 ± 4.99	49.0 ± 6.83
Total	680	23.4 ± 3.52	166.5 ± 5.44	55.7 ± 7.77

2.3 Experimental process

The experiment was to figure out the real responses of subjects' SCV under natural conditions. Considering the measurement of body physiological parameters was difficult to conduct via on-site survey, we conducted the tests in a naturally ventilated room. To cover the annual temperature variations, we took the indoor temperature interval of 1 °C as scale to conduct the experiments from summer in 2005 to winter in 2011. To ensure a sufficient testing sample capacity of SCV for reliability, more than 20 subjects were involved in tests for each 1 °C interval. However, since the maximum sample size at each temperature interval was not set, the sample size in each temperature interval was not constant and for some temperature intervals this might be higher than 20.

As the experimental periods spanned a long-time, before the experiments were conducted in each season, the instruments were calibrated and maintained in accordance with good medical practice to ensure proper measurement conditions. The local hospital collaborated with the tests to provide the technical support and tester training.

One subject was asked to participate in a test each time. He/she was forbidden to embark on strenuous exercises during the previous day. At the testing day, he/she was asked to arrive at the room 30min in advance and report their clothing conditions in questionnaires. Then, the subject's skin at the measuring positions were cleaned using alcohol prep pad and dried before wearing the electrodes, to minimize the perspiration effect. A conductive gel was used to reduce the skin resistance and to ensure a good contact between the skin and surface electrodes. After the preparation, he/she was asked to wear the SCV equipment and briefed on the experimental process.

Each test lasted 120min. During the test, the SCV measurement was performed in accordance with the recommendations in standard texts and the required settings of the measuring equipment. The measured arm of the subject was in a relaxed state and the ring electrodes were attached at the measuring points (see Figure 1(b)). The distance was first measured by ruler between the stimulating point (S1, Figure 1(a)) and the recording point (R1, Figure 1(a). The stimulus duration at each test was kept short to minimize discomfort. Latency was measured by the time from conducting the current stimulus to identifying the onset of the first negative voltage peak. The amplitude of nerve excitability was measured from onset to the first maximal negative peak after the current was conducted and expressed in microvolts. During the whole process, the instrument was attached to the subjects and the test was repeated every 10min during the 120min at the same place of subjects' hand and wrist. To note, between the period of conducting two tests, there was 10min allowance for the subjects to rest and move their arms slightly. Since the recovery time was much longer than the duration of stimulus current (0.1ms), this provided time for recovery of the measured nerve.

Besides, subjects' thermal perceptions were investigated during the experiments. Their thermal sensation, which was referred to the ASHRAE 55[36] 7-point scale (-3 cold, -2 cool, -1 slightly cool, 0 neutral, +1 slight warm, +2 warm, +3 hot), was measured by identical questionnaires every 10min. Throughout the whole experiments, subjects were not permitted to adjust their clothes. They were only allowed to be sedentary, doing light activities like reading or rest, to keep their metabolic rate stable.

Meantime, the indoor environmental parameters were measured by the Thermal Comfort Monitoring Station (LSI, Italy) complying with the required standards [36]. The physical parameters included air temperature (range: -25°C -150 °C, accuracy: ±0.1 °C), relative humidity (15%-40%, ±2%; 40%-70%, ±1%; 70%-90%, ±0.5%), air velocity (0-50m/s, ±0.04m/s) and black-bulb temperature (-10 °C-100 °C, ±0.15 °C). Sensors were positioned at a height of 0.6m and 0.5m away from subjects. The operative temperature was calculated by the average values of air temperature and radiant temperature and was used in the statistical analysis.

2.4 Statistical analysis

The preliminary tests of data validity and reliability were carried out first and the outliers and deviation values were pooled to ensure data quality. The raw data were checked for normal distribution with the Shapiro-Wilk test. ANOVA was used to test the differences of SCV and of the related indices for different seasons. A p-value<0.05 was considered statistically significant.

The measured temperatures in experiments were distributed over a large range under natural conditions, pertaining to continuous variables. This made it difficult to observe the relation between the temperatures and the measured SCV of subjects so that dispersing the temperature values into limited temperature intervals was need. Thus, after the data screening, the BIN method was employed for data discretization. To determine the appropriate temperature interval and number of intervals in the BIN method, we adopted the minimum information entropy method [37]. This method, based on the entropy characteristics of continuous variables, takes advantage of balancing the entropy loss and the appropriate intervals and fully reflects the relation between independent variables and dependent variables (e.g., the temperature and SCV in this study). In this study, the operative temperature was used, as the mean values of measured indoor air temperatures and radiant temperature. Using the SPSS22.0 software, the operative temperatures from the experimental data ranged from 7.6 °C to 36.9 °C, and the calculated optimal number of intervals was 39 and the optimal temperature interval was 0.75 °C. In the following analysis, the measured SCV of subjects were thus averaged in each temperature interval of 0.75 °C. In a similar vein, the method was conducted when correlating SCV and TSV.

Linear and nonlinear regressions were conducted to analyze the relations between operative temperature and SCV, the TSV and SCV, etc. The Matlab 2014b tool (The MathWorks, Inc., MA, 2014) was employed to calculate the variables in the original function, the derived function, and the inverse function.

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3. RESULTS

3.1 Thermal environment variation and its effect on SCV regulation

Figure 2 shows the relationship between the outdoor air and indoor operative temperatures during the experiments. Here, tests in different seasons were distinguished with different colors (Winter: Dec, Jan, Feb; Spring: Mar, Apr, May; Summer: Jun, Jul, Aug; Autumn: Sep, Oct, Nov) based on the climatic characteristics in Chongqing. From Figure 2, during the experiments the indoor operative temperature was linearly related to the outdoor air temperature ($R^2=0.98$), fluctuating from 5 °C to 40 °C. The close relationship between indoor operative temperatures and outdoor temperatures, i.e. the slope was nearly 0.9, indicated that the occupants would be significantly affected by the outdoor climate in naturally ventilated buildings.

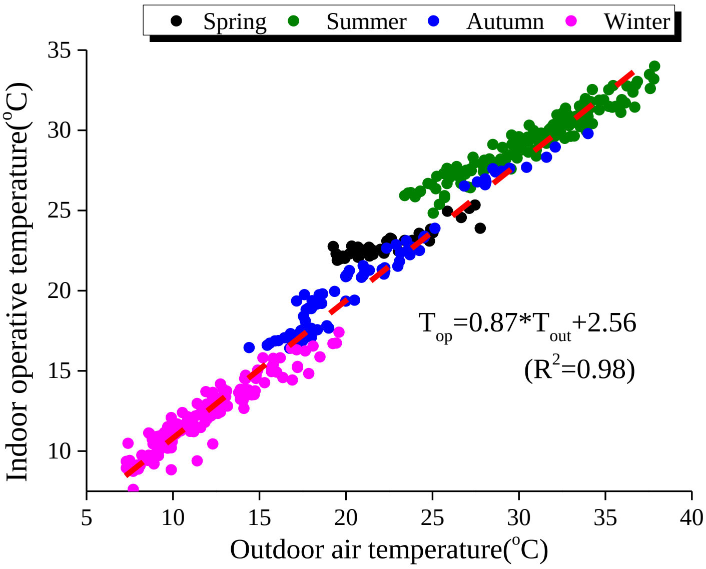

Figure 2: The relation between indoor operative temperatures and outdoor temperatures

The measured electrophysiological changes of the SCV-related events of subjects at steady state were averaged according to seasons, including the stimulus current, latency, amplitude, and the calculated conduction velocity, as shown in Table 2. Compared to other seasons, Table 2 shows that in summer, the stimulus current required to initiate nerve excitability was the smallest (4.55±1.93mA), coupled with the shortened latency (2.00±0.44ms) and reduced amplitude (37.64±11.85μV). As a result, the mean value of subjects' SCV was highest in summer (about 54.00m/s) compared to other seasons. In wintertime, the opposite situation was found: as the temperature decreased (see Figure 2), the required stimulus current increased (4.84±2.03mA), the latency extended (3.07±0.53ms), and the amplitude increased (57.39±21.45μV). This was accompanied by a decreased conduction velocity (36.15±5.72m/s). By contrast, the moderate temperature in transitional seasons contributed to all these electrophysiological results fluctuating in the range of that between summer and winter. The statistical results showed significant differences between the seasons on latency, amplitude voltage, and SCV, except for the stimulus current (ANOVA, $p<0.05$), indicating that temperature changes would significantly affect the human body's nerve system regulation.

Table 2: The SCV responses under different thermal conditions (Mean ± SD)

Season	Parameters				
	Distance (mm)	Stimulus Current (mA)	Latency (ms)	Amplitude Voltage (μV)	SCV (m/s)
Spring	107.26±8.76	4.68±2.35	2.36±0.53	50.24±13.14	47.63±9.34
Summer	110.09±10.70	4.55±1.93	2.00±0.44	37.64±11.85	54.00±4.98
Autumn	112.08±8.53	4.67±1.37	2.49±0.47	48.18±13.44	46.09±6.77
Winter	107.52±9.32	4.84±2.03	3.07±0.53	57.39±21.45	36.15±5.72
Sig.	/	0.246	0.000**	0.000**	0.000 **

(Note: ** $p < 0.05$)

3.2 The responses of subjects' SCV to annual temperature variations

The significant effect of temperature on SCV responses has been verified from Table 2. To understand further the thermoregulatory characteristics of the body SCV responding to temperature stimuli, Figure 3 shows the measured raw values of subjects' SCV with annual operative temperatures in natural conditions. When the temperature changed in the range of approx. 15 °C to 25 °C, the regulation of SCV was relatively remarkable, and the values were from 40m/s to 60m/s approximately. However, when the temperature was higher (i.e. above 25 °C), the SCV increased slightly regardless of temperature change. When the temperature decreased under 15 ^{o}C, the measured SCV fluctuated. This indicated that the responses of SCV may be different for different operative temperature ranges. However, due to the scatter in the SCV data, a clear trend was not observed and this should be further explored.

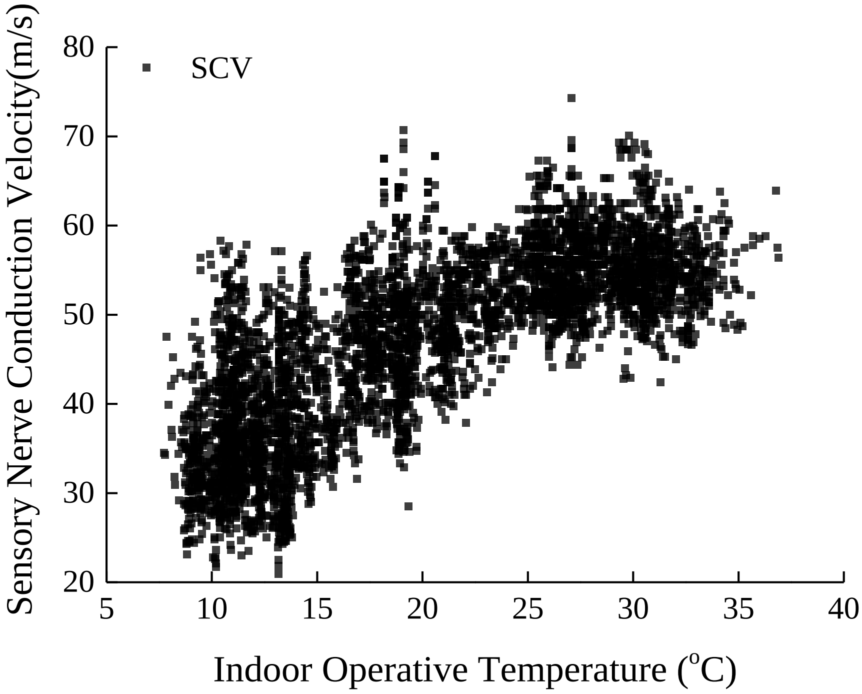

Figure 3: The SCV distribution with annual operative temperature changes

Figure 4 further depicts the characteristics change of subjects' SCV for different operative temperature intervals, where the values were averaged according to the temperature interval (Δt =0.75 °C), as mentioned in Section 2.4. The maximum, minimum, mean, and quantile (25% and 75%) values are also presented in Figure 4. Compared to Figure 3, Figure 4 shows clearly a positive correlation between SCV and temperature. The SCV was sensitive to temperature and increased gradually before the temperature reached 30 °C. This was because as the temperature increased, the heat stimulus inhibited the blood vasoconstriction innervated by sympathetic nerves, which promoted the blood vasodilatation and enhanced the blood circulation and increase in skin temperatures, thus leading to the increases in SCV. When the temperature continued to increase, the SCV fluctuated slightly and stabilized at around 55m/s. For electrophysiological studies, the normal SCV measurement for healthy people are usually conducted under neutral environments [15, 29]. We inferred that the skin temperature reached its peak in hot environments due to body thermal regulation. In that case, the effect of environmental temperatures on SCV was also attenuated. However, when the temperature decreased continuously below the middle temperature range (e.g., 15 °C-25 °C in the figure) where the SCV decreased linearly with temperature decrease, the SCV slightly decreased and even had a slight up trend under 10 °C. During our tests, subjects were observed to have much higher clothing insulation in cold environments under 10 °C and reported their shivering sensations in the questionnaires during the investigated periods. Therefore, we inferred that the slight fluctuation of subjects' SCV may be partly due to the coupled effect of environmental temperature, body shivering, and regulation by subjects' clothing. However, due to the temperature limits for the cold seasons in Chongqing, we were unable to collect data for much lower temperature ranges. It is therefore recommended that changes in SCV below 10 ^{o}C should be further explored.

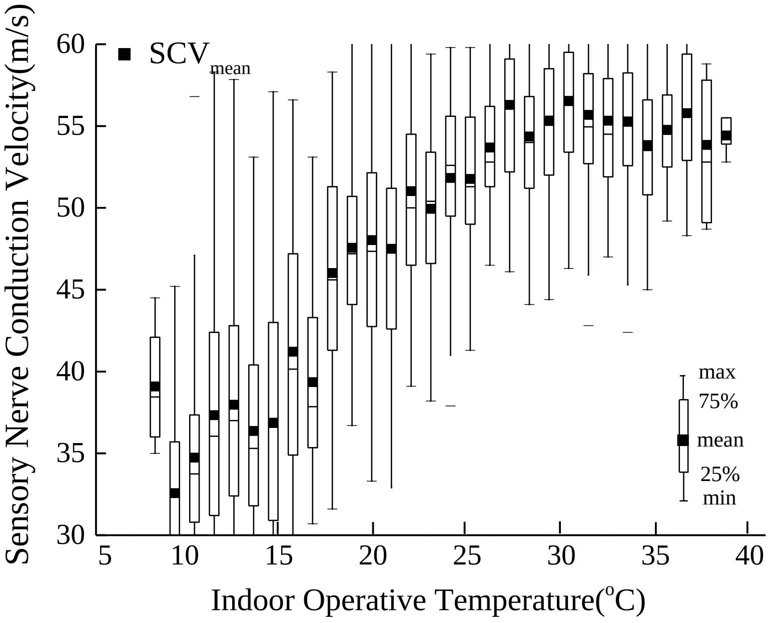

Figure 4: The SCV changes with indoor operative temperatures

3.3 The regulatory laws of the body SCV over a large temperature range

While there are many linear relationships in neurophysiology, interestingly, there are also many nonlinear ones [38]. In Figure 4, the SCV shows a linear relation with temperature over moderate temperature ranges but the trends are broken in hot and cold conditions, indicating an S-shape variation with temperature. In electrophysiological studies, the Boltzmann's function is widely used to reflect the characteristics of human physiological regulation, such as that shown in Equation (2), which is also adopted in the following analysis.

$$y=(A_1-A_2)/(1+\exp((x-x_0)/dx))+A_2 \qquad (2)$$

where A_1 is the initial value of y and A_2 is the final value; x_0 is the value where the function reaches the maximum gradients, dx is the interval from x_0.

Based on Equation (2) and Figure 4, the relation between the SCV and operative temperatures is as shown in Figure 5.

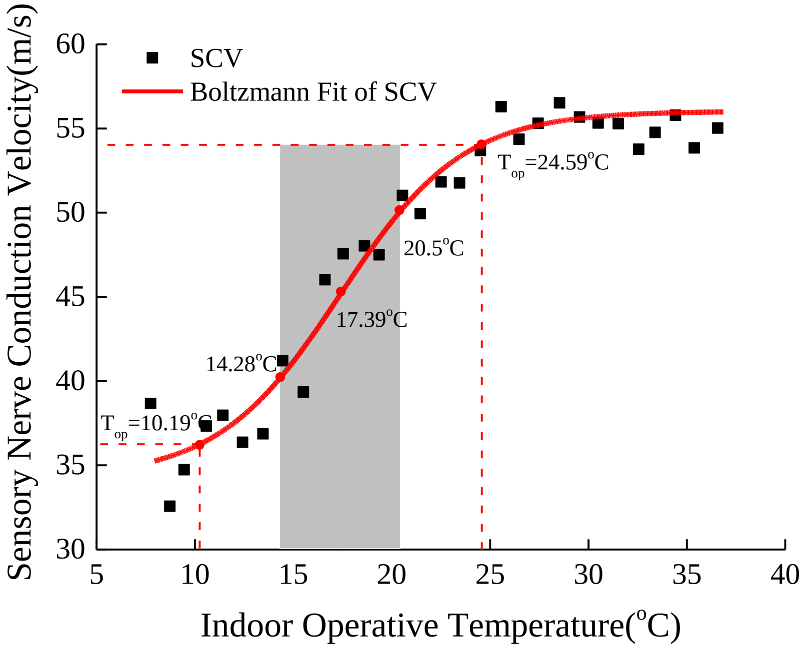

Figure 5: The change of SCV with operative temperature

The fit between the SCV and the operative temperature is shown in Equation (3).

$$SCV=55.99-21.76/(1+\exp((T_{op}-17.39)/3.11)) \qquad (R^2=0.94) \qquad (3)$$

In Equation (2), when x is equal to x_0, y is the average of A_1 and A_2 and the y has the most significant sensitivity to x in the range (x_0-dx, x_0+dx). In this case, according to Equation (3), the SCV changes in the range of 34.33m/s to 55.99m/s. In particular, the SCV increases by nearly 1.73m/s per 1°C operative temperature increase between 14.28 °C to 20.5 °C and has the maximum slope (r=1.75) when the temperature is 17.39 °C (see Figure 5). In addition, from Equation (3), it can be concluded that the SCV changes significantly when the operative temperature fluctuates between 14.28 °C to 20.5 °C. Correspondingly, the SCV increases sensitively from 40.08m/s to 50.14m/s, as marked by the grey shading in Figure 5.

However, when the temperature continues to increase or decrease, the SCV tends to be stable rather than continuing to increase or decrease. From Figure 5, the slope of the curve would decrease gradually from the maximum (1.75) to 0 when the operative temperature deviates from 17.39 °C. It is therefore hypothesized that there would be turning point temperatures where the SCV changes begin to be less sensitive to temperature changes. To identify the temperature turning points, we introduced the curvature function (Equation (4)) to depict the curving degrees in Figure 5 and determine the turning point temperatures.

$$K=|y''|/(1+y'^{2})^{\frac{3}{2}} \qquad (4)$$

where K is the curvature function, y’ is the first-order derivative of y, y’’ is the second derivative of y.

Equation (4) can be redefined as the function of SCV through introducing Equation (3), as shown in Equation (5).

$$K_{scv}=|F''_{SCV}(T_{OP})|/(1+F'_{SCV}(T_{OP}))^{\frac{3}{2}} \qquad (5)$$

where $F_{scv}(T_{op})$ is the function of SCV with indoor operative temperature, $F'_{scv}(T_{op})$ and $F''_{scv}(T_{op})$ were the first and second derivatives respectively.

Here the Matlab tool (Matlab 2014b) was used to calculate the derived function of F_{SCV} and to obtain the function K_{scv}. From that, the derived function - K_{scv} - is obtained and defaulted as 0 to obtain the maximum curvature and the corresponding temperature values. As there are two temperature points meeting the maximum curvature in Figure 5, the whole operative temperature range is thus divided into two subsections ((5 °C, 17.39 °C), (17.39 °C, 40 °C)) using the baseline of 17.39 °C. Taken together, the corresponding operative temperatures, T_{op}, in the two temperature subsections are finally obtained, i.e. 10.19 °C and 24.59 °C.

The operative temperature ranges that interpret the subjects’ SCV regulatory characteristics are summarized in Table 3, where the SCV is sensitive to the operative temperature range of 10.19 °C to 24.59 °C and stabilize beyond. This is inferred by the mechanism of SCV responses itself and the limitations of human thermoregulation with respect to certain temperature ranges. We will return to the SCV regulatory mechanism in the Discussion.

Table 3: Regulatory characteristics of SCV in response to annual operative temperature variation*

T_{op}/ Ranges (°C)	SCV/ Ranges (m/s)	Regulation Characteristics
< 10.19	< 36.19	SCV tends to be stable with temperature decreasing further in cold environments due to body thermoregulation limitations and the protection mechanism itself.
(10.19 - 14.28)	(36.19- 40.08)	SCV decreases gradually and becomes less sensitive to temperature decrease, indicating that cold environments slow down the SCV responses.
(14.28- 20.15)	(40.08- 50.14)	SCV shows a linear increase in temperature variation, reflecting the most significant thermoregulatory abilities within the moderate temperature range.
17.39	45.11	SCV has the maximum regulatory ability to temperature stimulus.
(20.15-24.59)	(50.14 - 54.03)	The increment of SCV caused by temperature is reduced gradually,

		suggesting the sensitivity of SCV is attenuated with temperature increases.
> 24.59	> 54.03	SCV reach its regulatory peak in a hot environment, meaning the body thermoregulatory abilities are restrained when the temperature exceeds the temperature limits of body regulation.

(Note: * the operative temperature ranges are conserved to 5 °C to 40 °C based on experimental measurements)

3.4 Changes of subjects' thermal sensation responding to SCV

It is reasonably believed that except for the direct feelings of occupants to environmental temperatures, the physiological regulation is one of the driving factors to offset human thermal comfort when exposing to temperature stimuli. To evaluate the relation between human physiological regulation and thermal comfort, we used the thermal sensation as a subjective index and related it to the changes of subjects' SCV. Figure 6 shows the changes of subjects' mean thermal sensation (TSV) with SCV, where the same BIN method is used to average subjects' thermal sensation votes in each interval of SCV (interval: 1.58m/s, number: 25).

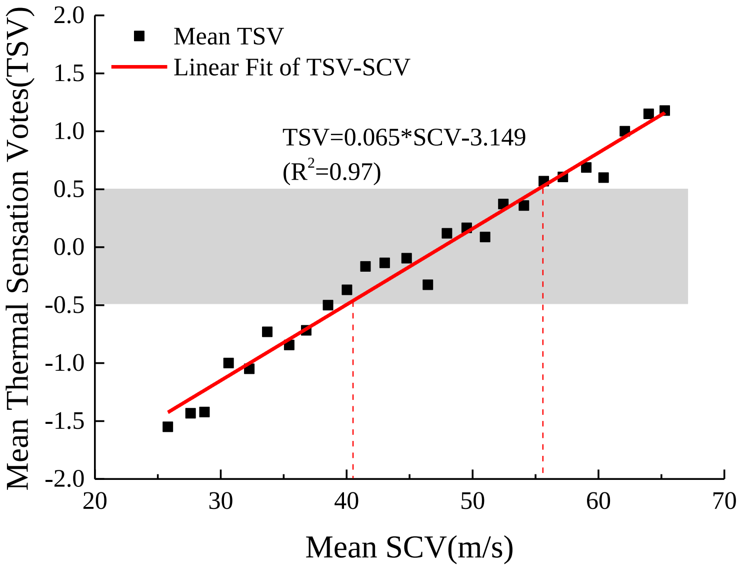

Figure 6: The relationship between TSV and SCV

The relation between TSV and SCV is regressed in Equation (6).

$$TSV=0.065\times SCV-3.15 \qquad (R^2=0.97) \qquad (6)$$

From Figure 6 and Equation (6), it can be observed that the subjects' TSV varies linearly with SCV and increases with increasing SCV. When the SCV increases from 25.8m/s to 65.3m/s then the subject's TSV increases from -1.5 to +1.5. According to ASHRAE 55 [39], thermal sensations in the range of -0.5 to +0.5 are acceptable for human comfort, during which the corresponding SCV is expected to vary between 40.75m/s to 56.14m/s (marked by grey shades in Figure 6), which is within the normal range for healthy people [28]. This demonstrates that the thermoregulation of SCV is consistent with the thermal sensations resulting from temperature changes, which reveals the underlying relations between human physiological regulation and subjective thermal perceptions.

4. DISCUSSION

4.1 Mechanism of human physiological regulations responding to temperature variation

As described earlier, the purpose of this study was to explore the mechanism of SCV in human thermoregulation. As the skin temperature has been well acknowledged as the most significant index in human thermoregulation[20, 17, 33], this study focused on the analysis of the changes in skin temperatures and SCV during the experiments (*to make this study more focused, the results of skin temperatures are provided as additional material; see the Supporting Information File for details*). Our results showed that the SCV and skin temperature shared similar trends with annual temperatures under natural conditions. Some explanations are given here to underlie of the link between SCV and skin temperature regulations. Physiologically speaking, there are a number of free nerve endings, namely thermoreceptors, distributed under skin surface[27]. These receptors have sensitive responses to temperature changes and act as transducers[24]: when the receptors receive the environmental temperature stimulus, they are activated and produce the receptor potential[25]. The potential transmits and induces an action potential at the first ranvier node[25]. During this process, the temperature signal is transformed into the bioelectrical signal and conducted along the afferent sensory nerve fibers. Therefore, the measured SCV in our study is indeed the conductive velocity of the bioelectrical signal on nerve fibers. When the central nerve system receives the signal and integrates the information, the body would activate the effectors, causing a series of responses, including vasoconstriction, vasodilatation, sweating, shivering, etc., to adapt to temperature changes [25, 24]. The outcomes of vasomotor are reflected by the changes in skin temperatures[27]. In this case, this study based on the SCV contributes to our understanding of the regulatory pathways of the efferent nerves in the body thermoregulatory system.

Further, the human thermoregulation is influenced by an inherent temperature-sensitive body structures, such as the voltage-gated ion channels [9] mediating during signal transduction. However, these specialized ion channels in the plasma membrane of primary afferents and the action potential propagation are significantly affected by temperature changes[40]. From the changes of SCV (Figure 5) and skin temperatures (Figure 3, *Supporting Information File*), these two physiological indices are linearly sensitive to operative temperature in the range of around 15 ^{o}C to 25 ^{o}C. This can be related to the cell depolarization regulation. A decrease in temperature would slow down both the opening and closing of the Na^+ channel of cell, and thus slow down the occurrence of action potential. As a result, the SCV decreases along the axon in the cold sides. While when the temperature increases, the cell depolarization is enhanced and the durations of both the opening and closing of the Na+ channels are shorten, the SCV thus increases [41, 15], indicating a quick response of body thermal regulation.

However, under normal conditions, humans maintain an inner core temperature within a narrow range, e.g., 36 ^{o}C to 38 ^{o}C, to maintain a series of normal body life activities[27] . This means that the human physiological regulations work in a moderate ambient temperature range, to maintain heat exchanges to and from the surrounding environments. Our results presented earlier have revealed the consistent regulation of SCV and skin temperature. With higher or lower temperature stimuli, the heat exchange via blood flow regulation in exercising limbs of the peripheral nervous system may be restrained, in order to avoid the deleterious consequences on human performance of either hyperthermia or hypothermia [42]. As a results, the SCV and skin temperature would not be increased, or decreased directly with temperatures in the extreme hot/cold environments. Jia and Pollock [43] found that after the sciatic nerve of rats was cooled through the gradient of 1-5 ^{o}C for 3h using the water, there were dramatic and irreversible reductions, down to approximately 25% of normal, in nerve blood flow within 50min. Early, experiments by Hodgkin and Katz [44] had found that warming the axon to 35 °C - 40 °C would prevent impulse propagation. They attributed that to the Na^+ channels opening and closing so rapidly that insufficient currents were being generated to excite the adjacent channels and thereby adversely reduced the ion influx. These findings partly explain in this study that the SCV stabilizes outside the operative temperature range of 10.19 °C to 24.19 °C.

4.2 Connections and differences of physiological indices of human body in previous studies and this study

To-date a number of physiological indices have involved human thermoregulation, such as the skin temperature[24, 19, 45], heart rate and blood flow[46], heart rate variability[47, 48], metabolic rates[49], electroencephalogram[50], etc. Among these indices, the skin temperature and the change rates of skin temperature are acknowledged as significant indices that influence human thermal comfort in a variety of steady-state and dynamic thermal environments[27, 23, 24]. Zhang *et al.* [21], through combining their experimental data and experimental data from others, also found a nearly S-curve relation between thermal sensation and mean skin temperatures, thermal sensation and skin temperature differences($T_{skin,t}$-$T_{skin,0}$). However, the subjective thermal sensation was referred to a seven-point scale (or nine-point scale) in ASHRAE 55 and subjects voted their thermal sensation from -4 to +4 (or, from -3 to +3) in a certain range. In such a case, even the subjects felt hot, they voted thermal sensation at the maximum scale +3 (+4), regardless of the skin temperature increasing. By contrast, we in the current study relate the SCV to temperature changes, both of which are continuous variables without limitations for certain ranges. Therefore, the analysis contribute towards identifying the response characteristics of the body's physiological SCV for a wide temperature range, which is different from Zhang's study[21]. More important, as aforementioned, the regulations of skin temperature and nerve conduction velocity are linked to different signal pathways in the sensory nerve system during body thermoregulations. Apart from the regulatory mechanisms of skin temperature and thermoreceptors, this study fills in a gap to understand the body regulation of nerve conduction in the afferent signal pathways and the effect of temperature, which differs from those studies of skin temperatures alone.

In addition, to the authors' knowledge, the majority of experiments on human physiological indices were conducted in artificial environments of a climate chamber. For those experiments, due to the limited resources, the testing temperature conditions were limited and discrete. Only a small number of subjects were involved and the sample capacity was limited. This makes it insufficient to understand the whole regulatory system of human body to temperature variations. Moreover, the artificial environments intervene with the real regulatory responses of the human body, which may cause data deviation of the measured physiological indices. In our case, thanks to a wide range of temperature variation under natural conditions and involving a large number of samples, the study goes a step further in making up for the paucity of current laboratory investigations. Based on the tests, this study indicates the S-shaped law of SCV, as well as skin temperature (see the *Supporting Information File*), which broaden our understanding of human thermal regulations, especially outside the common regulatory zone.

On the negative side, however, compared to a skin temperature investigation, the instruments used for SCV are at present costly and complex and the measurement can be inconvenient. However, in hot conditions, for example, the skin temperature may be stabilized, owing to the weakening convective heat transfer via skin surface. More importantly, when the sweat regulation occurs, the perspiration may interfere the sensor accuracy and the perspiration evaporation even reduces the skin temperatures. In such a case, the skin temperature may be inappropriate to reflect the real thermal regulation of human body. As the regulation of SCV and skin temperature pertains to different stages during thermoregulation and the SCV is indeed determined by near-nerve temperature under skin tissue and less affected by skin sweating, the SCV can be an alternative index to verify the regulation of skin temperature and evaluate human thermal responses. With a reduction in the cost of wearable sensors and ubiquitous wireless connectivity in buildings, tracking people's physiological responses to thermal environments has become more accessible over the years [51-53]. In such cases, we are confident that our study on SCV represents a fundamental research from the engineering point of view and it is likely to become more possibly used in future.

4.3 The application potential of SCV method in thermal environment building

Based on our experiments, we have found that the SCV regulation of human body responding to different annual temperature intervals is applicable to people in natural environments. As described in Figure 5 and Table 3, between 14.28 °C to 20.5 °C, the SCV increases significantly from 40.04m/s to 50.14m/s, indicating a significant physiological response and a stronger regulatory ability of the human body in response to temperature stimuli. Outside this temperature range, the SCV begins to slow down and be less sensitive to operative temperature changes in the range 10.19 °C to 24.19 °C. The SCV tends to be stabilized when the operative temperatures are above 24.19 °C, or below 10.19 °C. This temperature range is slightly different from that of some other studies from the viewpoint of body thermoreceptors. Guyton and Hall [54] reported that the cold receptors began to be stimulated when the temperature rose to 10 °C to 15 °C, reaching peak stimulation at about 24 °C and fading out slightly above 40 °C at skin temperature; while the warmth receptors began to be stimulated above about 30 °C, having the peak impulse frequency over 40 °C and fading out at about 49 °C. However, they reported the static impulse frequency of these thermoreceptors at the corresponding skin temperatures, which is different from SCV regulation responding to ambient temperatures. Therefore, due to different disciplines, the study by Guyton and Hall[54] and the results in this study are not contradictory in terms of the temperature ranges.

Considering that the neurophysiological approach is favorable for understanding the human annual thermoregulation characteristics, due to being in line with the underlying physiological thermoregulation [55], we study the characteristics of SCV in healthy people when exposing to ambient temperatures, in spite of the slightly complex measurements. In spite of the improvement of indoor thermal environments by the popularization of heating/cooling, balancing the thermal comfort demands and building energy efficiency is still an undergoing research focus. In line with this thought, our study identifies the S-shaped regulatory characteristics of SCV and the linear relationship between the SCV regulation and subjects' thermal sensation, which provide an in-depth understanding of human thermoregulation. Moreover, the environmental temperature zones responding to SCV regulation (Table 3) are expected to contribute to our knowledge in the design of a building heating and cooling needs around the year. The study showed that people can be dependent on thermoregulations themselves in natural environments in the operative temperature range of 10.19 °C to 24.19 °C; but auxiliary heating/cooling devices should be applied beyond that temperature range. This approach relies on making the best use of human thermoregulation to alleviate the dependence on heating/cooling system and reduce the health risk of people to temperature changes as well as providing guidance for the application of the assisted heating/cooling systems.

4.4 Limitations and further research

A few limitations need to be taken into consideration with respect to the general interpretation of the results here. Since the near-nerve temperature differs from the environmental temperature, the temperature zones obtained with respect to SCV regulation are comparatively different from those in electrophysiological studies [56, 57]. In this regard, the outcome of this study is better suited for temperature exposure assessment in thermal comfort. In addition, as the experiments were conducted in naturally ventilated environments in Chongqing, China, the indoor operative temperatures changed in the range of 5 °C to 40 °C, and the extreme temperatures are not covered within this range. Therefore, the SCV showed a S-shaped trend and tended to be stable when temperatures were below 10.19 °C and above 24.19 °C. However, when the temperature continues to increase or decrease, or when the body is under heat/cold strains for a long time period, the stabilization of SCV under extreme conditions may no longer be maintained [9, 58]. Conversely, acute events may be triggered when the body exceeds its thermoregulatory threshold [59]. In such cases, temperature exposures are predictably doing harm to human physiological regulation, possibly causing physiologically irreversible damage[58]. Therefore, the thermoregulatory changes, body strain, and health risk caused by extreme temperatures should be further examined in-depth.

5. CONCLUSIONS

The study was based on over six-year long measurement of human sensory nerve conduction velocity in a healthy population under natural environmental conditions, and revealed the S-shaped regulatory law of SCV responding to temperature change, which offered a deeper understanding of human thermoregulation and environmental design requirements. Some conclusions are drawn as follows:

1) The SCV is positively related to temperature variations. A Boltzmann model is employed to depict the S-shaped characteristics of SCV over a large operative temperature range (5 °C - 40 °C), as given below:

$$SCV=55.99-21.76/(1+\exp((T_{op}-17.39)/3.11))$$

2) Based on this model, the SCV increases by nearly 1.73m/s for 1 °C operative temperature increment in the range 14.28 °C to 20.5 °C. The SCV regulation is sensitive within 10.19 °C to 24.59 °C, but tends to be stabilized beyond this range, manifesting the human autonomic thermoregulation.
3) Subjects' thermal sensation is linearly related to SCV regulation, which elaborates the mechanism underlying human physiological regulation and subjective changes in thermal perception.

The findings provide an in-depth knowledge of human physiological thermoregulation, which can be useful for selecting a suitable design temperature for the built environment to militate against adverse human discomfort and health consequences and improve the quality of life with consequential benefits to human wellbeing and performance.

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CONFLICT OF INTERESTS

No conflicts of interest, financial or otherwise, are declared by the authors.

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