

## RESEARCH ARTICLE


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SCIENCE**

# Impact of Cardiovascular Factors on Pulse Wave Velocity and Total Vascular Resistance in Different Age Group Patients with Cardiovascular Disorders



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**Abstract: Background:** Pulse Wave Velocity (PWV) is the propagation speed of the wave-induced along the aorta and arterial tree, each time the heart beats. PWV increases with increased arterial stiffness, thus establishing it as a reliable prognostic marker for cardiovascular morbidity and mortality. On the other hand, Total Vascular Resistance (TVR) is the overall resistance offered by systemic circulation and pulmonary circulation. This resistance needs to be overcome in order to create the flow of blood through the circulatory system. The goal of this study was to investigate the influence of different cardiovascular factors on arterial stiffness and vascular resistance in CVD patient from eastern India population.

**Methods:** Total of 782 patients with Cardiovascular Disease (CVD) like hypertension, Ischemic heart disease, Congestive cardiac failure and peripheral arterial disease were included to evaluate the cardiovascular hemodynamic and non-hemodynamic parameter by oscillometric method and investigated those factors on PWV and TVR in subjects of both sexes aged between 15 to 87 years.

**Results:** The old age (> 55 years) was found to have greatest impact on PWV as compared with younger age group. Systolic Blood Pressure (SBP), Heart Rate (HR), augmentation pressure and Body Surface Area (BSA) had a positive association with the PWV. Augmentation Index and Body Mass Index (BMI) had a negative impact on the PWV.

**Conclusion:** Despite the limitations, like unequal number of male and female participants, wide variation of the age of the subjects and analyzing association of many factors at a time, our large and community-based study show individual blood pressure and pulse pressure depending on complex interaction between large arteries and arterioles. This study sheds light on the relationship between proximal and distal part (PWV and TVR) of the arterial tree as well as their association with different hemodynamic and non-hemodynamic parameters.

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## 1. INTRODUCTION

Cardiovascular Disease (CVD) has been a leading cause of increased mortality rate in the west and is now fast approaching the east. In India reported cases of CVDs were 29 million in 2000 and the number is estimated to have reached 64 million by 2015 along with more than double the number of deaths [1]. To prevent the CVD epidemic and to assess other non-communicable diseases Indian government initiated the program “Integrated National Program for

Prevention and Control of Diabetes, Cardiovascular Diseases, and Strokes”.

As is known, the cardiovascular system is a closed system. During systole, the heart pumps the blood and blood flows down first through the elastic arteries (aorta and carotid artery) which buffer the pulsation, followed by muscular or distributing arteries (like femoral, brachial and radial artery) that actively alter the propagation velocity and then blood flows through the arterioles, which serve as major reflection sites. As the heart pumps blood, 40% of cardiac stroke volume enter into the peripheral arteries and rest 60% in capacitive arteries or large arteries [2]. As a result of the Wind Kessel, arterial wall is distended which recoils during the diastole and blood is propelled to the peripheral

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circulation. So, the pulsatility of the blood flow is generated by the heart and reduced by arterial system. This leads to a continuous blood flow at the level of the capillaries in the organ and tissue [3].

Contraction of the heart generates the pulse wave. Pulse wave travel through the wall of vessels and the speed of travel is referred to as Pulse Wave Velocity (PWV). PWV is related to arterial stiffness, which is inversely proportional to arterial compliance [4]. PWV is related to intrinsic elasticity of arterial wall. If arteries are stiffer then PWV is higher, reflected wave arrives earlier and augment central SBP. If arteries are relatively compliant, PWV is slow, as a result, reflected wave return to central aorta in diastole and augment DBP [5, 6]. Arterial stiffness and PWV increase with age [7]. Arterial stiffness increases at higher pressure. Cardiovascular risk factors like diabetes mellitus, hyperlipidemia, smoking and increased body mass index increase arterial stiffness and PWV [8-11]. Proximal vessels which can be considered as a proximal part, largely determine the arterial compliance characteristics of the entire arterial circulation [12]. On the other hand, the state of the arteriolar and capillary bed determines the peripheral resistance located in the distal part of the arterial tree [13]. Important cardiovascular parameters like SBP and PP in CVD patient are determined by the interaction between the proximal and distal part of the arterial tree [14].

To understand this interaction, it becomes vital to explore the association of hemodynamic and non-hemodynamic factors with arterial stiffness and vascular resistance in CVD patient. Aim of this study is to comprehensively investigate the influence of hemodynamic and non-hemodynamic factors on arterial stiffness and vascular resistance in CVD patient in eastern India population.

**2. MATERIALS AND METHODS**

A study on 782 patients with Cardiovascular disease like hypertension (HTN-460), Ischemic Heart Disease (IHD-152), Congestive cardiac failure (HD-155), Peripheral Arterial Disease (PAD-15) were conducted in Cardiovascular

outpatient clinic during the period August 2015 to December 2015. Patients were consecutively enrolled for this study. We have included only the young and adult patients aged more than 15 years. 28% population was young *i.e.* less than 40 years old, 38.10% of population were elder and aged between 40-55 years age group and remaining 33.90% were old having more than 55 years of age. We excluded the subject with mental illness, and patients unwilling to provide informed consent form. The participants were grouped into three groups young, elderly and old to study the effect of aging.

Initial evaluation included age lifestyle parameters, anthropometry including smoking habit; and medical history. The study was approved by the Institute Ethics Committee of AIIMS Bhubaneswar. Subject did not eat heavy meal or drink any caffeine-containing product, alcohol, and refrained from smoking for at least 2 hours prior to study.

The primary objective of this research work was to determine how the factors are affecting the TVR and PWV, and the multiple linear regression model is suitable for this analysis since the response variable was continuous and normally distributed (Fig. 3 histogram plot). Also, stepwise estimation approach was used to obtain the most significant predictor in the regression model.

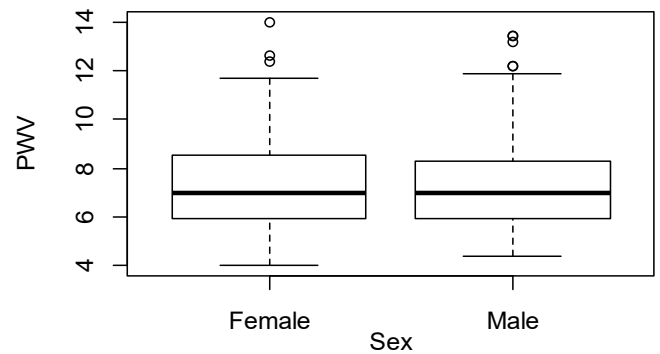


Fig. (1). Comparison of PWV parameter between female and male.

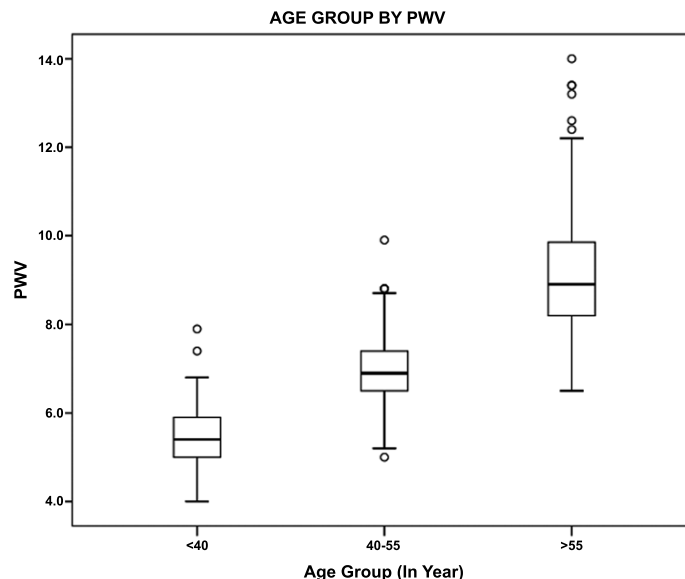


Fig. (2). Comparison of the PWV parameter of different age groups.

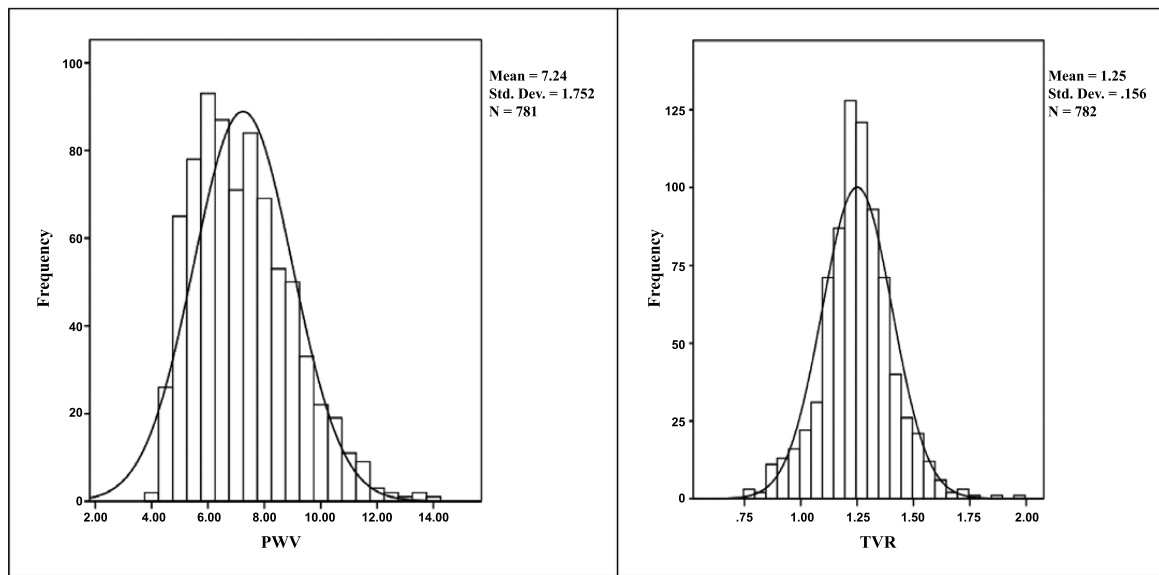


Fig. (3). Histogram plot of PWV and TVR.

Table 1. Characteristics of study populations.

Factors	Frequency	Percent (%)
<b>Sex of the patients</b>		
Male	551	70.46
Female	231	29.54
<b>Age group</b>		
< 40 years	219	28.00
40- 55 years	298	38.10
>55 years	265	33.90

### 2.1. Measurement of Blood Pressure, Arterial Stiffness, and Hemodynamics

Measurement was carried out by using a Mobil-O-Graph instrument (Mobil-O-Graph (IEM, Stolberg, Germany) Mobil-O-Graph® PWA v 4.8.2 IEM-Hypertension Management Software) in a temperature controlled (23-26°C) quiet room during morning. Subject was made to sit in upright and peripheral and central blood pressure, Augmentation Index (AIX) and Pulse Wave Velocity (PWV) were measured with Mobil-O-Graph. Signal from brachial artery was detected by this system. Pulse wave initiated by the contraction of the left ventricle, travel through the aorta. This running 1<sup>st</sup> pulse wave gets reflected from distal branching point of aortic wall and generates 2<sup>nd</sup> reflected wave. Arterial stiffness mainly determines the morphology of reflected 2<sup>nd</sup> wave. AIX and PWV were obtained with the help of algorithm and mathematical model in the inbuilt software by using amplitude and time difference of 1<sup>st</sup> and 2<sup>nd</sup> wave. We recorded the peripheral and central blood pressure, pulse pressure and arterial stiffness by this instrument. The detailed variables used in model are given in the appendix (Table A1).

### 2.2. Statistics

Data are presented as mean  $\pm$  Standard Deviation (SD) for continuous observations, and as percentage for categorical observations. A stepwise multiple linear regression model was used to determine the significant factors associated with PWV and TVR. The factors which are found to be significant in the univariate analysis were included in the final model, and also the final model was adjusted for all the confounding variables. The results of the regression model have been presented in the form of coefficients, standard error, and corresponding p-value. In all cases a p-value <0.05 was considered statistically significant. R version 3.0.2 statistical software was used for the analysis.

## 3. RESULTS

### 3.1. Different Subgroup and Clinical Characteristics of the Participants

A total of 782 patients participated in this study. Details of the age and sex distribution of the participants are shown in Table 1.

### 3.2. Correlation Between Pulse Wave Velocity and Other Variable

In order to study the association between the PWV and other variables, we have used a bivariate linear regression model as a first step of analysis, to determine the significant factor associated with PWV. In the model incorporating one by one variable, we have found that most of the factors are statistically significant affecting the PWV ( $p$ -value  $< 0.05$ ), excluding the factors *i.e.*, sex and Pulse Pressure (PP) Amplification. All the significant factors showed a positive association. Now in the second step of analysis, we have conducted a stepwise multiple linear regression approach to account the confounding effect, just by extending the bivariate analysis into a multivariate set-up where we included only those variables in the model which came out significant in the bivariate analysis. The factors *viz.*, age, systolic blood pressure, heart rate, Aug Pr, Aug Ind, BMI, and BSA were significantly affecting the PWV (Table 3).

Age was found to be the most influential factor, the old age ( $> 55$  years) had a greatest impact (3.301) on PWV as compared with younger age group. In this study SBP, HR, augmentation pressure and BSA had a positive association

with the PWV. Augmentation Index and BMI had a negative impact on the PWV (Table 3), whereas SBP, DBP, cSBP, PP amplification, AIX, and PWV show a positive association with TVR. HR and CO negatively correlate with the TVR (Table 4).

Our model shows high  $R^2$  value (*i.e.* 86%) *i.e.* the factors *viz.*, age, systolic blood pressure, heart rate, Aug Pr, Aug Ind, BMI, and BSA together explain 86% variance in PWV. The corresponding adjusted  $R^2$  is 85%.

### 3.3. Correlation Between Total Vascular Resistance and other Variable

The factors *viz.*, systolic blood pressure, diastolic blood pressure, heart rate, central systolic blood pressure, pulse pressure amplification, cardiac output, cardiac index, augmentation pressure, augmentation index, reflection magnitude, PWV, and BSA are significantly associated with the Total Vascular Resistance ( $p$ -value  $< 0.05$ ). SBP, DBP, cSBP, PP amplification, Augmentation Index, and PWV had a positive association with the TVR. HR, CO, and BSA had a significant negative impact on the TVR (Table 4). The adjusted  $R^2$  is found to be 90%.

**Table 2. Descriptive statistics of study populations (n=782).**

Variables	Male		Female		Overall	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
Age (in years)	48.16	13.80	50.03	13.87	48.72	13.84
SBP (mm Hg)	125.77	17.41	126.33	19.63	125.94	18.09
DBP (mm Hg)	85.53	12.53	83.27	13.75	84.86	12.94
PP (mm Hg)	40.31	11.87	42.97	13.28	41.1	12.36
HR (beats/min)	84.58	13.79	84.52	13.29	84.56	13.63
CSys (mm Hg)	116.47	15.92	116.69	17.86	116.53	16.5
CDia (mm Hg)	87.09	12.74	84.86	13.81	86.43	13.09
Cpp (mm Hg)	29.39	9.16	31.85	10.48	30.12	9.63
PP Amplification	1.38	0.17	1.37	0.16	1.38	0.17
Stroke vol. (ml)	60.57	11.47	60.53	12.48	60.55	11.77
CO (L/min)	5.03	0.75	5.04	0.83	5.03	0.77
Total vas resistance (mmHg x l <sup>-1</sup> x min <sup>-1</sup> )	1.25	0.15	1.24	0.16	1.25	0.16
Cardiac index (L/min/m <sup>2</sup> )	2.89	0.50	3.01	0.57	2.93	0.53
AugPr (mm Hg)	5.94	4.57	7.30	5.28	6.35	4.83
Reflection Magnitude (%)	60.15	8.36	62.12	7.83	60.74	8.25
AUGInd (%)	23.45	11.17	26.21	12.29	24.27	11.58
PWV (m/s)	7.18	1.71	7.38	1.84	7.24	1.75
BMI (kg m <sup>-2</sup> )	25.18	4.08	25.04	4.16	25.14	4.1
BSA (m <sup>2</sup> )	1.75	0.18	1.69	0.19	1.73	0.18

**Table 3. Results of stepwise multiple linear regression models assessing the factors affecting the PWV.**

Parameters	Estimate	95% C.I.	Std. Error	t-value	P- value
Intercept	0.805	(0.185, 1.424)	0.316	2.551	0.011
Age (<40 years)	Ref.	-	-	-	-
40- 55 years	1.337	(1.216, 1.456)	0.061	21.91	0.001
>55 years	3.301	(3.174, 3.428)	0.065	51.026	0.001
Systole	0.029	(0.026, 0.033)	0.002	17.713	0.001
HR	0.007	(0.001, 0.014)	0.003	2.434	0.015
AugPr	0.064	(0.043, 0.085)	0.010	6.151	0.001
AUGInd	-0.016	(-0.025, -0.007)	0.005	-3.534	0.000
BMI	-0.028	(-0.043, -0.011)	0.008	-3.397	0.001
BSA	0.667	(0.307, 1.025)	0.183	3.648	0.000
<b>R<sup>2</sup></b>	<b>0.866</b>				
<b>Adjusted R<sup>2</sup></b>	<b>0.854</b>				

**Table 4. Results of stepwise multiple linear regression models assessing the factors affecting the total vascular resistance.**

Parameters	Estimate	95% C.I.	Std. Error	t value	P-value
(Intercept)	1.317	(1.189, 1.445)	0.065	20.260	0.001
Systole	0.003	(0.001, 0.005)	0.001	3.183	0.002
Diastole	0.005	(0.003, 0.006)	0.000	9.942	0.001
HR	-0.001	(-0.001,-0.000)	0.000	-2.997	0.003
cSys	0.004	(0.001, 0.006)	0.001	3.233	0.001
PP_Amplification	0.048	(-0.000, 0.096)	0.025	1.962	0.050
CO	-0.213	(-0.231, -0.194)	0.010	-22.219	0.001
Cardiacindex	-0.025	(-0.053, 0.004)	0.015	-1.702	0.089
Aug Pressure	-0.002	(-0.004, 0.000)	0.001	-1.472	0.141
Reflection Magnitude	-0.001	(-0.001,0.000)	0.000	-1.652	0.099
AUG Index	0.001	(0.000, 0.002)	0.000	2.077	0.038
BSA	-0.044	(-0.096, 0.009)	0.027	-1.625	0.105
PWV	0.004	(0.001, 0.006)	0.001	3.000	0.003
<b>R<sup>2</sup></b>	<b>0.890</b>				
<b>Adjusted R<sup>2</sup></b>	<b>0.901</b>				

#### 4. DISCUSSION

In the present study comprising a relatively large population (n = 782), age and SBP showed strong correlation with PWV. In higher SBP, chronically elevated distending pressure increase the arterial stiffness and hence PWV. No gen-

der difference was observed in PWV. Several parameters have been shown to positively associate with PWV, including systolic pressure and body surface area. In CVD patients with several cardiovascular risk factors, damage large and small arteries. Alteration of large artery property modulates

the function of small arteries and arterioles [14]. Recently, transcranial doppler profile of patients with chronic subcortical cerebrovascular disease reveals that diffused vascular pathology also develop from small vessel and then extend to large vessel [15].

The increased HR reduces the recoiling time of arteries and trigger vessel stiffening [16]. Like previous result [17-19], present result also shows significant positive trends between HR and PWV. PWV is also determined by BSA. Generally, body weights of taller individual are more than shorter. Higher BSA likely to increase the distance between the heart and sites of wave reflection, consequently decreasing it. Body height diminishes somewhat with age. We also observed a negative correlation between PWV and AIX as well as PWV and BMI in this study, which is consistent with the previous literature [20-24].

Augmentation Pressure (AP) is the increase in SBP by the return of peripheral reflected wave. PWV increases along with the increase in arterial stiffness which also increases the wave reflection from periphery. Earlier return of reflected wave adds Additional Pressure (AP) to forward wave and ultimately increases the SBP [25-27]. In our study, the arterial PWV is significantly and positively correlated with AP. Interestingly many factors defining the PWV are subjected to age-dependent alterations.

Another key aspect of cardiovascular function analysis is Total Vascular Resistance (TVR). Vascular resistance is highest in arterioles (41%), followed by capillaries (27%), small arteries and branches (16%), aorta and larger arteries (9%), venules (4%), large veins (2%) and small veins (1%) [28]. In this study, multiple linear regression model shows that TVR has significant positive association with PWV and AIX. Like previous report in our study, TVR are positively correlated with SBP and DBP [29, 30]. Elevated TVR increases the amplitude of reflected wave and increases SBP. Furthermore, TVR has significant negative correlation with HR and CO. Previous study also reported the negative correlation between HR and CO [31]. In the patients with CVD because of increase in TVR, blood accumulates in arterial side of circulation; consequently, elevated the aortic pressure against which heart pumps. Similarly increases in TVR also decrease the amount of blood in the venous side of circulation. As per Starling's law the reduction in right atrial pressure trigger reduction in CO. The  $\beta$ -blockers, like atenolol treatment, also increase TVR and decrease CO [32]. In contrast when TVR decreases; more blood is allowed to flow to the venous side of circulation, resulting in fall of the aortic pressure against which heart pumps. Our result shows significant relationship of TVR with Cardiac index, AP, reflection magnitude and BSA.

Our study had some limitations. The first difference between the proportion of male and female may partially influence the association of PWV with other factors like age, sex, AIX, BMI, and BSA. Another limitation is wide variation of age in subjects which may not be ideal for study of the association between different hemodynamic parameters. Finally, in this study, we tried to get a global view of the influence of different hemodynamic and non-

hemodynamic parameters on PWV and TVR as well as their interaction. Analyzing association of too many factors at a time may not reflect the in detail interaction of these parameters. Further, in-depth study of specific age groups, equal isolation of gender ratio and limited parameters may resolve these drawbacks.

## CONCLUSION

Despite the limitation, our large community-based study shows blood pressure and pulse pressure depending on complex interaction between large arteries and arterioles. Understanding this interplay and their association with other hemodynamic and non-hemodynamic parameters are the key to understand the pathophysiology of different cardiovascular diseases. The macro and microcirculatory structure of arterial tree are the target for several cardiovascular disease therapeutics. This study shed light on the relationship between proximal and distal part (PWV and TVR) of the arterial tree as well as their association with different hemodynamic and non-hemodynamic parameters. Arterial stiffness is a manifestation of the cumulative effect of all the harmful factors acting on the vascular wall. Recently, Puglisi *et al.* reported that subclinical changes of arterial stiffness and hypoperfusion can be monitored by ultrasound technique [15]. Arterial stiffness also can be measured directly by PWV. PWV is also the target of several drugs. So PWV value may be considered as a predictor of future cardiovascular event of an individual and indicator of the outcome of the treatment. Result of this study also shows the correlation between PWV and different cardiovascular factors. Considering this, measurement of PWV and arterial stiffness will help to develop a cost-effective technique for risk stratification in a resource-limited setting. By its own right, PWV and arterial stiffness measurement will help in massive health screening.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institute Ethics Committee of AIIMS Bhubaneswar, India.

## HUMAN AND ANIMAL RIGHTS

No animals used in this study. All the experiments conducted on humans were in accordance with the declaration of Helsinki and Indian Council of Medical Research Guideline, India.

## CONSENT FOR PUBLICATION

Informed consent was obtained from all the patients included in the study.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

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## Appendix

**Table A1. Variables used in the model.**

Variables	Descriptions
Age	Age of the participant
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
PP	Pulse Pressure
HR	Heart Rate
CSys	Central Systolic Blood Pressure
CDia	Central Diastolic Blood Pressure
Cpp	Central Pulse Pressure
PP_Amplification	Pulse Pressure Amplification
Stroke_vol	Stroke Volume
CO	Cardiac Output
Totalvasresistance	Total Vascular Resistance
Cardiac index	Cardiac Index
Aug Pr	Augmentation Pressure
ReflectionMagnitude	Reflection Magnitude
AUG Ind	Augmented Index
PWV	Pulse Wave Velocity
BMI	Body Mass Index
BSA	Body Surface Area

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