MESA Exam 6

VaSera
Thigh exams

Data preparation steps

Contents

July 2024

Equations

For <u>thigh</u> examinations, the following definitions apply:

tb_R: The time difference between the second heart sound and the dicrotic notch on the right brachial arterial waveform
tbt_R: The time difference between the feet of the right brachial and the right thigh cuff waveform
tbt_L: The time difference between the feet of the right brachial and the left thigh cuff waveform

L1: distance from the phonocardiogram probe over the middle of the sternum (2 intercostal spaces below the sternal notch) to the femoral pulsation on the right side
L2: Distance between the femoral pulsation to the middle of the thigh cuff (middle of the width of the cuff)

ρ is the blood density, with a fixed value of 1050 kg/m^3
P_s and P_d are systolic and diastolic blood pressure, respectively.

$$T_R \text{ (right transit time)} = tb_R + tbt_R \quad (1)$$
$$T_L \text{ (left transit time)} = tb_R + tbt_L \quad (2)$$

$$L = L1 + L2 \quad (3)$$

$$htPWV = \frac{L}{T} \quad (4)$$

$$ht\beta = \frac{2\rho}{P_s - P_d} . ln\left(\frac{P_s}{P_d}\right) . htPWV^2 \quad (5)$$

T_R is used to calculate R-htPWV, R-htβ
T_L is used to calculate L-htPWV, L-htβ

The overall htPWV and htβ are calculated as the average of the right and left (R- and L-) values.

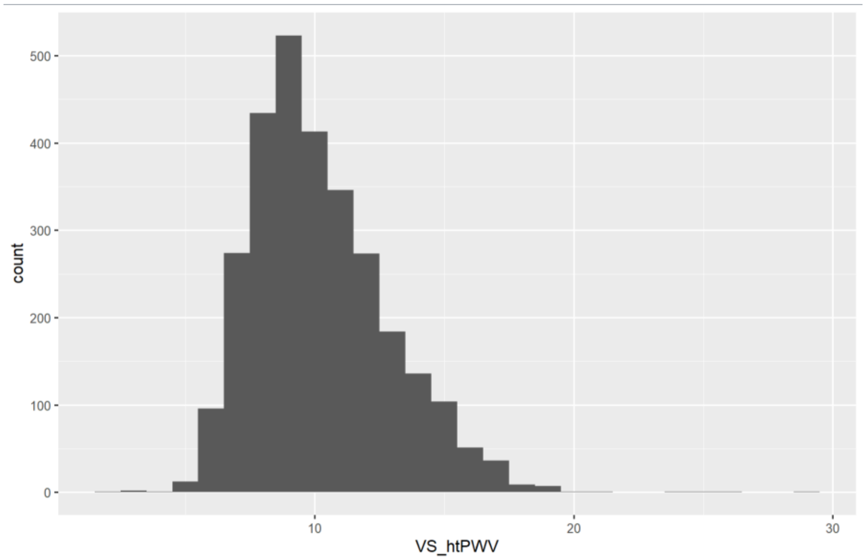
<u>**NOTE: For femoral data, we should not utilize a "cardiac-femoral vascular index" (CAFVI).**</u> For <u>**ankle**</u> data, the cardiac-ankle vascular index (CAVI) is computed from the heart-ankle beta index using the following formula:

$$CAVI = a \times ha\beta + b \quad (6)$$

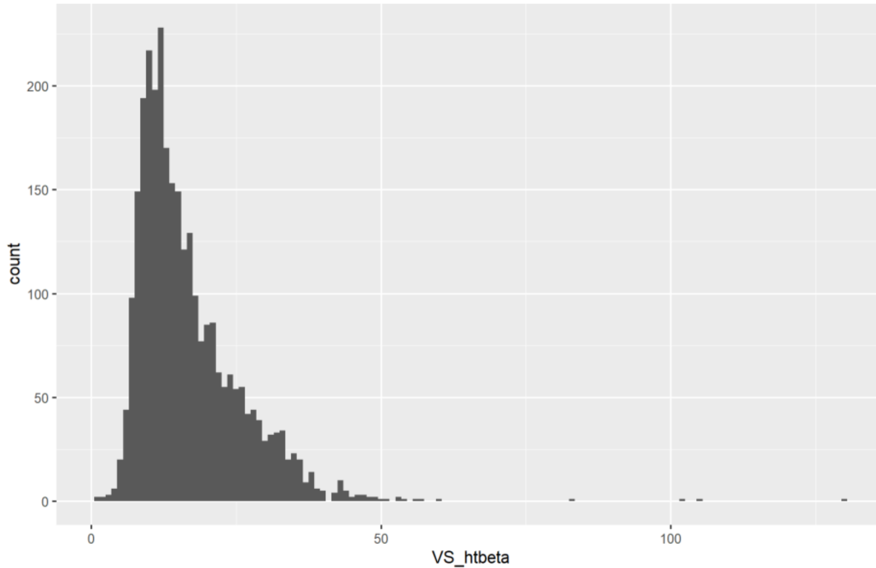
In equation (6), a and b are called "rescaling coefficients". Specific values for rescaling coefficients a and b have been developed for CAVI <u>**but not for the heart-thigh measurements**</u>, precluding an adequate computation of a "cardiac-femoral vascular index". Therefore, we recommend to utilize the heart-thigh beta index until such coefficients are developed for the thigh measurement. It should be noted, however, that all these rescaling coefficients do is to rescale the value in a linear transformation process, such that the values match the range of values of heart-ankle pulse wave velocity.

Descriptive statistics and histograms of htPWV and htβ

```
summary(data$VS_htPWV)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's
  1.984   8.283   9.717  10.206  11.754  29.308      67
```



```
summary(data$VS_htbeta)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
NA's
  0.5266  10.4674  14.2054  16.7369  20.8542 129.6887
65
```



* Extreme outliers were observed for htβ. Therefore, the measurements and calculation steps were rechecked for potential errors, and data curation steps were performed as documented in the following pages.

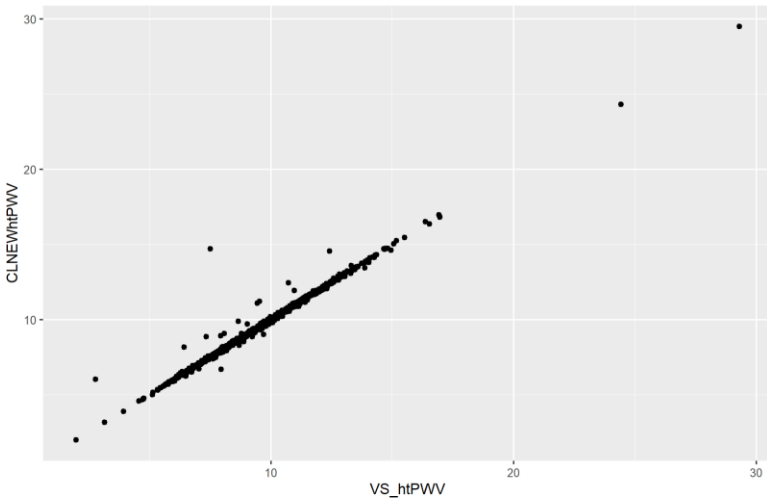
The Exam 6 VaSera dataset includes **2975** participants with completed examinations.

Assessment of the calculation steps

To recheck the results, htPWV and htβ were calculated based on the available transit times, path lengths distances, and blood pressure values, using the codes below. Calculated htPWV and htβ were then compared with values derived from the VaSera device to check whether the parameters were used in a similar way by the device software.

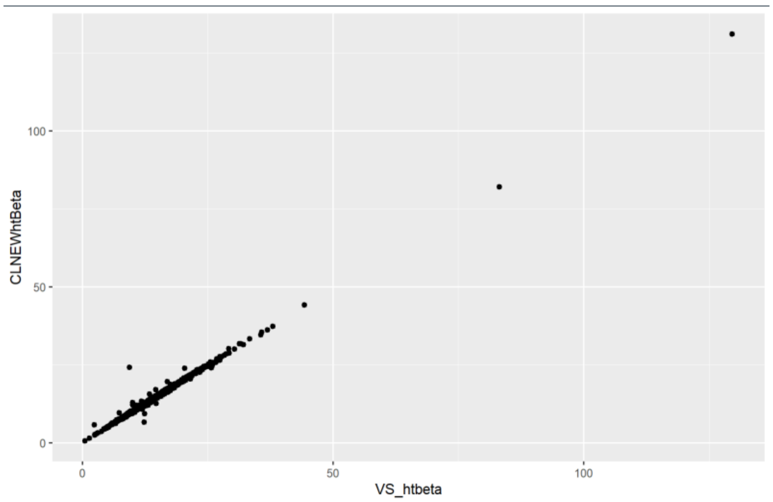
R code utilized for this process was as follows:

```
# Define variables based on VaSera measurements of length, transit time, and blood
pressure
data <- data %>%
  mutate(
        tpathlen6 = vasera_vtvsl16 + vasera_vtvsl26,
        left_T = vasera_vtvsrtb6 + vasera_vtvsltbt6, #tbR + tbaL
        right_T = vasera_vtvsrtb6 + vasera_vtvsrtbt6, #tbR + tbaR
        sbp = vasera_vtvssyst6,
        dbp = vasera_vtvsdiast6,
        VS_htPWV = vasera_vtvshtpwvfin6,
        VS_htbeta = vasera_vtvshtbetafin6)



# Define calculated htPWV
data <- data %>%
  mutate(CLNEWhtPWV =
         ((tpathlen6/left_T)+(tpathlen6/right_T))/2)

# comparisons between VaSera htPWV (VS_htPWV) and calculated htPWV
(CLNEWhtPWV)
```



- The difference between VS_htPWV and CLNEWhtPWV was less than 1 unit in 99.5% of cases (excluding missing values)

```
# Define calculated htβ
data <- data %>%
  mutate(CLNEWhtBeta =
         (2*1050)*(CLNEWhtPWV^2)/((sbp-dbp)*133.322368)*log(sbp/dbp))

# comparisons between VaSera htβ (VS_htbeta) and calculated htβ (CLNEWhtBeta)
```



- The difference between VS_htbeta and CLNEWhtBeta was less than 1 unit in 98.8% of cases (excluding missing values)

* The high concordance between calculated htPWV and htβ with VaSera estimated values shows that the same values were used by the VaSera device software to calculate these indices and the VaSera values. Some small differences are occasionally present, which is likely due to internal processes in the VaSera device (such as beat parameter computations followed by averaging of values vs. averaging intervals followed by parameter computations). We consider these differences negligible in practice.

Cases with irrational path length measurements

Assessment of measured distances

Among many cases, the values of L entered by the site staff (estimated pulse travel length from the heart to the thigh cuff) was unreasonably high compared to body height. In some cases, the L was even higher than the value of the body height.

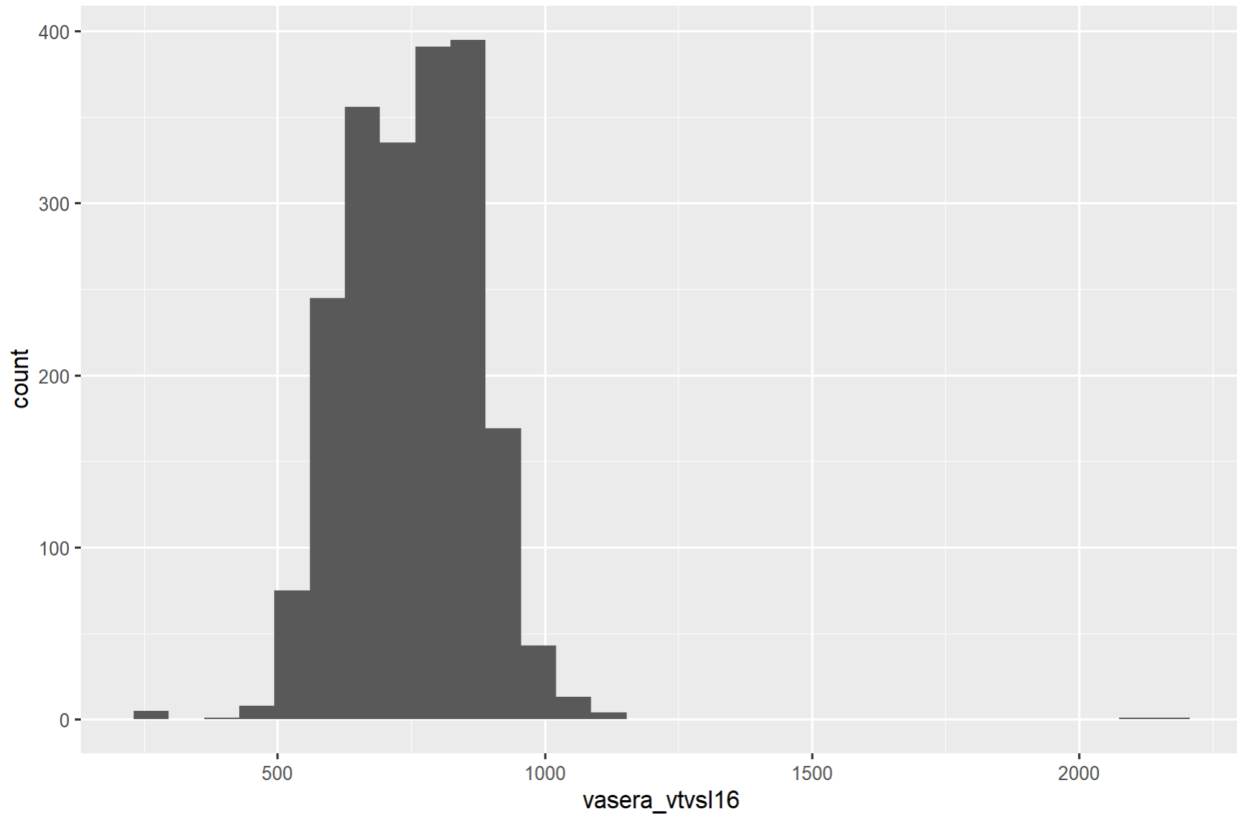
```
> summary((data$tpathlen6/data$EXAM6_htcm6*10))
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  30.98   51.91   57.29   59.18   65.06  135.92     875 
```

In this equation, tpathlen6 = L1 + L2

Furthermore, in some cases, the measured L1 and L2 both had implausible/nonsensical values.

L1

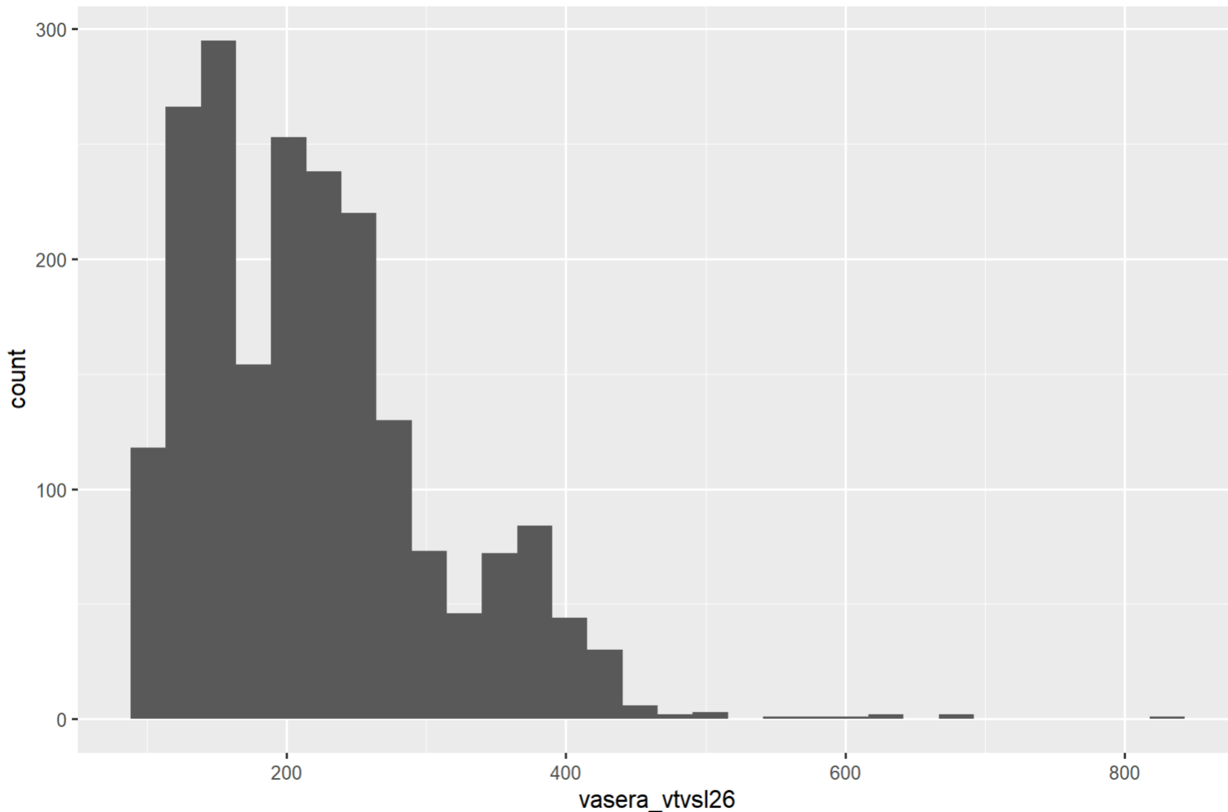
```
> summary(data$vasera_vtvsl16)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  260.0   663.0   754.0   753.7   845.0  2171.0     933 
```



	vasera_vtvsl16 THIGH: VS L #1	vasera_vtvsl16_new	EXAM6_htcm6 HEIGHT (cm)	EXAM6_bmi6c BODY MASS INDEX (kg/m^2)	EXAM6_bsa6c BODY SURFACE AREA
1519	2171	NA	176.0	25.18698	1.943314
1466	2080	NA	162.6	29.50940	1.834884
1452	1131	1131	182.5	27.64670	2.140662
1587	1118	1118	178.5	33.59763	2.245805
2635	1118	1118	157.2	57.08583	2.303021
1783	1092	1092	174.2	36.24837	2.232077
2881	1079	1079	173.4	42.84431	2.379127
1747	1053	1053	194.5	27.33812	2.355243
2826	1053	1053	177.5	39.01626	2.372070
2828	1053	1053	170.0	44.57522	2.345214
1657	1040	1040	158.2	34.79856	1.884840
1676	1040	1040	168.3	32.82908	2.026997
1736	1040	1040	182.5	32.14099	2.282180
2572	1040	1040	182.4	33.53965	2.321866
2644	1040	1040	179.0	41.47960	2.467084
2905	1040	1040	175.6	37.29082	2.287798
1534	1027	1027	184.0	33.62878	2.356682
1706	1027	1027	161.5	28.34755	1.784644
2602	1027	1027	172.6	35.93383	2.191739
1582	1014	1014	171.0	33.35180	2.092451
2577	1014	1014	152.6	39.54213	1.880224
2637	1014	1014	171.0	34.12742	2.112995
2457	1001	1001	160.2	35.26070	1.933316
2533	1001	1001	175.4	37.96567	2.301169
2543	1001	1001	185.8	30.35244	2.291078
2848	1001	1001	167.8	34.23324	2.053754

L2

```
> summary(data$vasera_vtvsl26)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  100.0   150.0   207.0   218.8   260.0   830.0     933 
```

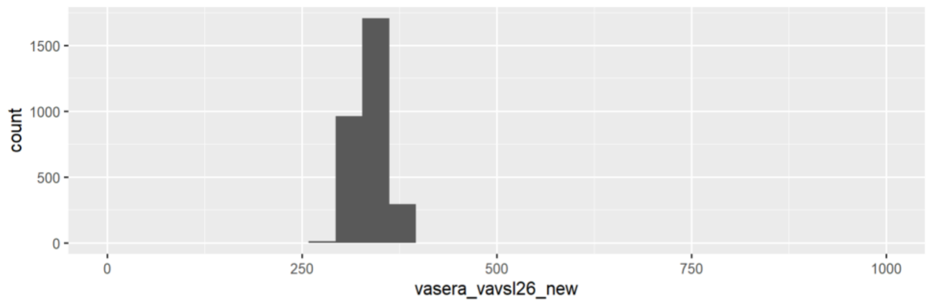


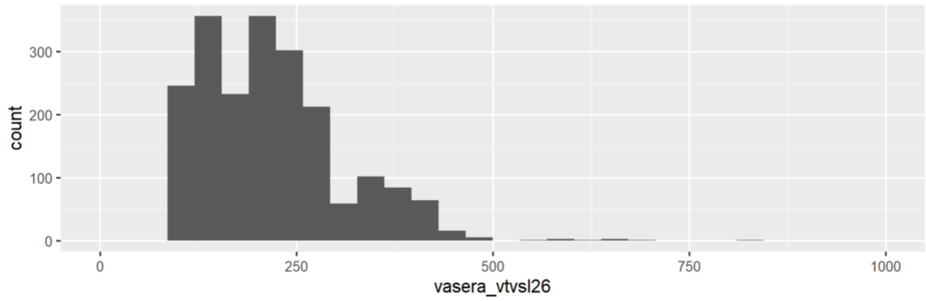
Moreover, a comparison between the L2 from thigh exams and the L2 from ankle exams further suggests possible errors in measuring the L2 distance in thigh examinations.

In ankle measurements, the L2 is defined as the distance between the femoral artery pulsation in the groin and the popliteal artery in the knee. This L2 is estimated by the VaSera automated mode regression equation (See *Takahashi et al., Journal of Atherosclerosis and Thrombosis, DOI: 10.5551/jat.44834*).

In thigh exams, the L2 is defined as the distance between the femoral artery pulsation in the groin and the middle point of the thigh cuff width.

Therefore, the maximum possible distance for thigh measurement L2 must be lower than the ankle measurement L2 minus half the length of the thigh cuff, as shown in the Figure below.





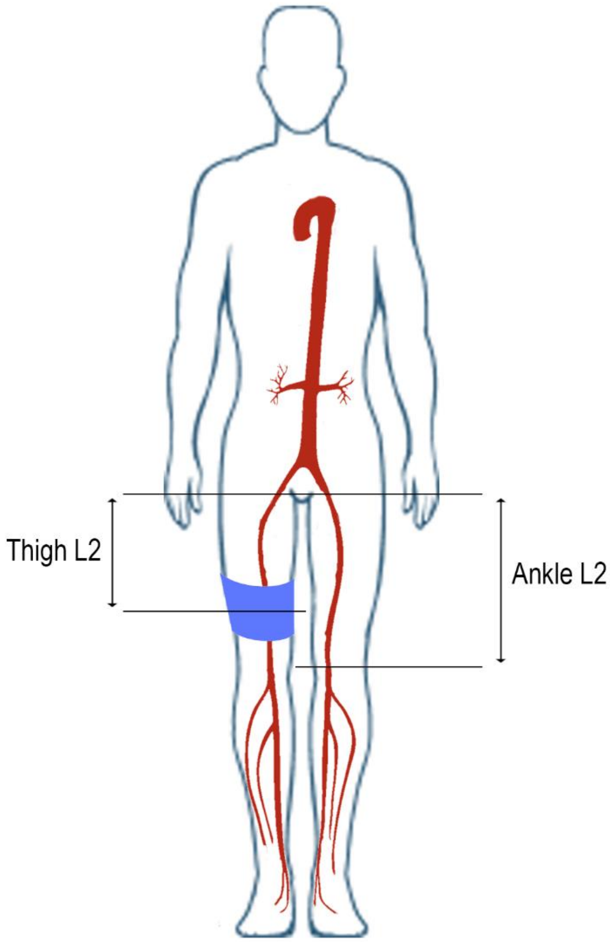


Figure – Even if the thigh cuff was placed directly above the knee, the maximum possible thigh L2 would be less than the ankle procedure L2. In this scenario, the difference between the thigh and ankle L2 would be at least half the width of the thigh cuff.

The standard thigh cuff used in the VaSera examinations had a width of 9.4 cm.

However, for 358 cases, the thigh L2 was implausibly higher than the ankle L2 minus half the width of the ankle cuff, as shown below:

```
> data %>%
+   mutate(count = vasera_vtvsl26 >= vasera_vavsl26_new
- (94/2)) %>%
+   summarize(sum = sum(.$count, na.rm=T))
  sum
1 358
```

Due to the inconsistencies in the measurements of distances in thigh exams, and the high number of cases with missing values of path length, which is essential for computation of arterial stiffness indices derived from thigh exams, we decided to directly estimate the path length (L) for thigh exams using a regression equation based on body height. This would be similar to the approach used for estimating path length in the calculation of heart-ankle β and CAVI in ankle examinations. Therefore, an advantage of this approach is that it makes pulse transit path lengths comparable between ankle and thigh indices. The development of this equation is described below.

Estimation of pulse transit path length for thigh examinations (L)

We derived equations to estimate L1 (distance from the heart to the femoral artery pulsation in the groin) and L2 (distance from the femoral artery pulsation in the groin and the middle of the thigh cuff) based on body height.

To increase consistency with ankle measurements, we took an approach of estimating L1 and L2 separately, since L1 is identical for both measurements.

We first derived a regression equation for estimating L1 based on height. In developing this regression, we used ankle exam estimations of L. Since L1, L2, L3, and the total L in ankle exams were estimated based on the VaSera automated mode regression equation using body height, our regression shows a linear relationship between body height and L. The only difference between our equation and the VaSera automated mode equation is that our coefficients are derived to estimate the L1, whereas VaSera coefficients directly estimate the total L, which is the pulse travel distance between the heart and the ankle, and corresponds to the sum of L1, L2, and L3 in the ankle exams.

The results of the regression model used to derive the equations for L1 and L2 using ankle examination data are shown below:

```
Call:
lm(formula = vasera_vavsl16 ~ vasera_vavsheight6, data = data)

Residuals:
    Min      1Q  Median      3Q     Max
-6.1949 -2.4075 -0.1017  2.6206  7.1062

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)        24.056373   0.939985   25.59   <2e-16 ***
vasera_vavsheight6  3.760411   0.005706  659.05   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 3.071 on 2072 degrees of freedom
  (901 observations deleted due to missingness)
Multiple R-squared:  0.9953,	Adjusted R-squared:  0.9953
F-statistic: 4.344e+05 on 1 and 2072 DF,  p-value: < 2.2e-16
```

L1 (mm) = 3.76 * Height (cm) + 24.056

```
data <- data %>%
 mutate(vasera_vtvsl16_clnew =
      3.76*EXAM6_htcm6 + 24.056)
```

```
> summary(data$vasera_vtvsl16)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  260.0   663.0   754.0   753.7   845.0  2171.0     933 
> summary(data$vasera_vtvsl16_clnew)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  542.9   615.9   642.6   644.1   670.8   770.4       3 
```

We repeated a similar process to predict the ankle L2 based on body height:

```
Call:
lm(formula = vasera_vavsl26 ~ vasera_vavsheight6, data = data)

Residuals:
    Min      1Q  Median      3Q     Max 
-5.7383 -2.6438 -0.2154  2.7321  5.7372 

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)    
(Intercept)        30.438935   0.909300   33.48   <2e-16 ***
vasera_vavsheight6  1.862456   0.005519  337.43   <2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 2.971 on 2072 degrees of freedom
  (901 observations deleted due to missingness)
Multiple R-squared:  0.9821,	Adjusted R-squared:  0.9821 
F-statistic: 1.139e+05 on 1 and 2072 DF,  p-value: < 2.2e-16
```

L2 (mm) = 1.862 * Height (cm) + 30.439

```
data <- data %>%
  mutate(vasera_vavsl26_clnew = (EXAM6_htcm6*1.862 + 30.439))
```

```
> summary(data$vasera_vavsl26)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
   60.0   320.0   340.0   336.5   350.0   500.0     901 
> summary(data$vasera_vavsl26_clnew)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  287.4   323.5   336.7   337.5   350.7   400.0       3 
```

The ratio of thigh L2 and ankle L2

The L1 has the same definition between ankle and thigh exams. However, the definition of L2 is different. To calculate the estimated thigh L2, we needed to derive a plausible estimate of the ratio of thigh L2 and ankle L2.

First, we removed the implausible and nonsensical thigh L2 values in the dataset, using the code below:

```
data <- data %>%
  mutate(vasera_vtvsl26_cleaned = case_when(
    vasera_vtvsl26 >= vasera_vavsl26_clnew - (94/2) ~ NA_real_,
    T ~ vasera_vtvsl26
  ))
```

```
> summary(data$vasera_vavsl26_new)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  287.4   323.5   336.7   337.5   350.7   400.0       3 
> summary(data$vasera_vtvsl26)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  100.0   150.0   207.0   218.8   260.0   830.0     933 
> summary(data$vasera_vtvsl26_cleaned)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.    NA's 
  100.0   140.0   190.0   187.3   230.0   320.0    1291 
```

Then, we calculated the average ratio of this cleaned thigh L2 variable to the estimated ankle L2:

```
data %>%
  mutate(TL2_AL2_raito = vasera_vtvsl26_cleaned/vasera_vavsl26_clnew) %>%
  select(TL2_AL2_raito, vasera_vtvsl26_cleaned, vasera_vavsl26_clnew) %>% summary(.)
```

```
TL2_AL2_raito    vasera_vtvsl26_cleaned vasera_vavsl26_clnew
 Min.   :0.2772   Min.   :100.0          Min.   :287.4       
 1st Qu.:0.4067   1st Qu.:140.0          1st Qu.:323.5       
 Median :0.5622   Median :190.0          Median :336.7       
 Mean   :0.5560   Mean   :187.3          Mean   :337.5       
 3rd Qu.:0.6909   3rd Qu.:230.0          3rd Qu.:350.7       
 Max.   :0.8599   Max.   :320.0          Max.   :400.0       
 NA's   :1291     NA's   :1291           NA's   :3           
```

We took the median of this ratio (0.56) and estimated the thigh L2 as 0.56 * ankle L2.

Calculation of htPWV and htβ

We estimated thigh exam pulse travel distance (L) based on the steps explained above.

```
data <- data %>%
  mutate(vasera_vtvsl16_clnew =
        3.76*EXAM6_htcm6 + 24.056) %>%
  mutate(vasera_vtvsl26_clnew = .56*(EXAM6_htcm6*1.862 + 30.439))

data <- data %>%
  mutate(vasera_vtvsl6_clnew =
        vasera_vtvsl16_clnew + vasera_vtvsl26_clnew)
```

Using this estimation, we then calculated htPWV and htβ using the R codes below:

```
# htpwv
data <- data %>%
  mutate(vasera_vtvslhtpwvfin6 =
        vasera_vtvsl6_clnew/(vasera_vtvsrtb6 + vasera_vtvsltbt6)) %>%
  mutate(vasera_vtvsrhtpwvfin6 =
        vasera_vtvsl6_clnew/(vasera_vtvsrtb6 + vasera_vtvsrtbt6))

data <- data %>%
  mutate(vasera_vtvshtpwvfin6 =
        (vasera_vtvslhtpwvfin6 + vasera_vtvsrhtpwvfin6)/2)

attr(data$vasera_vtvslhtpwvfin6, which = "label") <-
  "THIGH: VS L HT PWV Recalculated by Core Lab"
attr(data$vasera_vtvsrhtpwvfin6, which = "label") <-
  "THIGH: VS R HT PWV Recalculated by Core Lab"
attr(data$vasera_vtvshtpwvfin6, which = "label") <-
  "THIGH: VS HT PWV Recalculated by Core Lab"



#htbeta
data <- data %>%
  mutate(vasera_vtvslhtbetafin6 =
        (2*1050)*(vasera_vtvslhtpwvfin6^2)/((vasera_vtvssyst6-
vasera_vtvsdiast6)*133.322368)*log(vasera_vtvssyst6/vasera_vtvsdiast6)) %>%
  mutate(vasera_vtvsrhtbetafin6 =
        (2*1050)*(vasera_vtvsrhtpwvfin6^2)/((vasera_vtvssyst6-
vasera_vtvsdiast6)*133.322368)*log(vasera_vtvssyst6/vasera_vtvsdiast6))
```

```
data <- data %>%
  mutate(vasera_vtvshtbetafin6 =
         (vasera_vtvslhtbetafin6 + vasera_vtvsrhtbetafin6)/2)

attr(data$vasera_vtvslhtbetafin6, which = "label") <-
  "THIGH: VS L HT BETA Recalculated by Core Lab"
attr(data$vasera_vtvsrhtbetafin6, which = "label") <-
  "THIGH: VS R HT BETA Recalculated by Core Lab"
attr(data$vasera_vtvshtbetafin6, which = "label") <-
  "THIGH: VS HT BETA Recalculated by Core Lab"
```

The main variables of interest are:

	Variable name	Label
Heart-thigh PWV	vasera_vtvshtpwvfin6	THIGH: VS HT PWV Recalculated by Core Lab
Heart-thigh β stiffness index	vasera_vtvshtbetafin6	THIGH: VS HT BETA Recalculated by Core Lab