Measures of Heart Rate Variability – Sherpa vs. Miami Students

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Context

Helaine Alessio, Department Chair, and Alex Claiborne, second year graduate student, from Miami University's Department of Kinesiology & Health, want to examine the association between heart rate variability and several predictors. Proposed as a sign of increased health, more heart rate variability is found in younger and more active individuals. Through a recent academic trip to Nepal, data were collected on both students and Sherpa (local mountaineers). This data is to be used to compare the two groups.

Data

Mr. Claiborne has provided us a dataset that contains several resting biological measurements and corresponding Heart Rate Variation (HRV) measurements for each of the Sherpa and students. The relevant data descriptions taken from the dataset can be found in **Table A.1** in the Appendix.

Notable features of the dataset:

1. There are 7 possible useful HRV measures for each individual, as described to us from Mr. Claiborne and discovered through the literature (Heart Rate Variability Standards of Measurement, Physiological Interpretation, and Clinical Use. Retrieved September 8, 2017, from http://circ.ahajournals.org/content/93/5/1043).
2. There are 3 possible variables included for each individual that could explain differences in HRV from individual to individual; those are oxygen saturation, mean resting heart rate, and if the individual is a Sherpa or student.
3. There are measurements for 7 Sherpa and 17 students.
4. The measurements were all recorded at 4500 meters above sea level.

Objectives

The objective of this study is to simply compare resting HRV between Sherpa and students at the given elevation of 4500 meters, while controlling for differences in oxygen saturation and resting heart rate. More directly, we will establish whether or not it is reasonable to assume there is a difference in HRV between the two groups; if so, we will then try to better quantify and understand this difference. Also, a large initial objective is to determine which of the 7 possible measures of HRV should receive more focus as a response.

Initial exploratory analysis of the data can give us a sense of the data, whether there are any outliers, and preliminary idea in determining if a difference between the two groups exists. Ultimately, we will use linear regression to examine the difference between the two groups while accounting for these covariates.

Exploratory Data Analysis

The first step in this project is narrowing down the 7 HRV measures, if possible. We discovered the standard deviation of the combined RR intervals recorded (SDNN) is not an ideal measure, as the total length of time over which RR intervals are measured can change, making this measurement unable to be traversable across different studies. This is why a measure such as RMSSD, which simply measures variation from RR-interval to RR-interval, is more preferable (Heart Rate Variability Standards of Measurement, Physiological Interpretation, and Clinical Use, et al., 2002). Thus, we did not even consider this SDNN at all. Below, in **Table 1**, is a summary of the remaining variables to give a general idea of their units and scale.

Table 1: Measures of center and spread for all variables given.

	RMSSD (ms)	pNN50 (ms)	FFT LF/HF (%)	AR LF/HF (%)	Poincare plot SD1 (ms)	SD2 (ms)
HRV Measures						
Sherpa	28.2 +/- 17.5	7.8 +/- 11.5	1.62**	0.86**	19.9 +/- 12.4	45.7 +/- 21.8
Students	57.7 +/- 40.6	19.6 +/- 18.8	1.22**	1.16**	40.8 +/- 28.7	97.6 +/- 52.1

	Mean HR/min (ms)	Oxygen Sat. (l/m)
Predictors		
Sherpa	80.8 +/- 12.7	86.1 +/- 5.1
Students	83.5 +/- 11.2	86.9 +/- 3.1

Values are Mean +/- St. Dev. except ** are medians

Values for the two LF/HF ratios are both medians because the distributions for both are extremely skewed with a few outliers. This is an early indication that taking the log of these responses might be a good idea. Another thing to notice is that the median for the FFT Ratio is higher for the Sherpa relative to students, but for the AR ratio, it is lower. This, along with the several outliers, immediately raises some concern with regard to the usefulness of the ratios for our objective.

The next step is to investigate the association of the potential predictors to the responses. **Figure 1** shows the scatterplot matrix of all our variables for all 24 observation points.

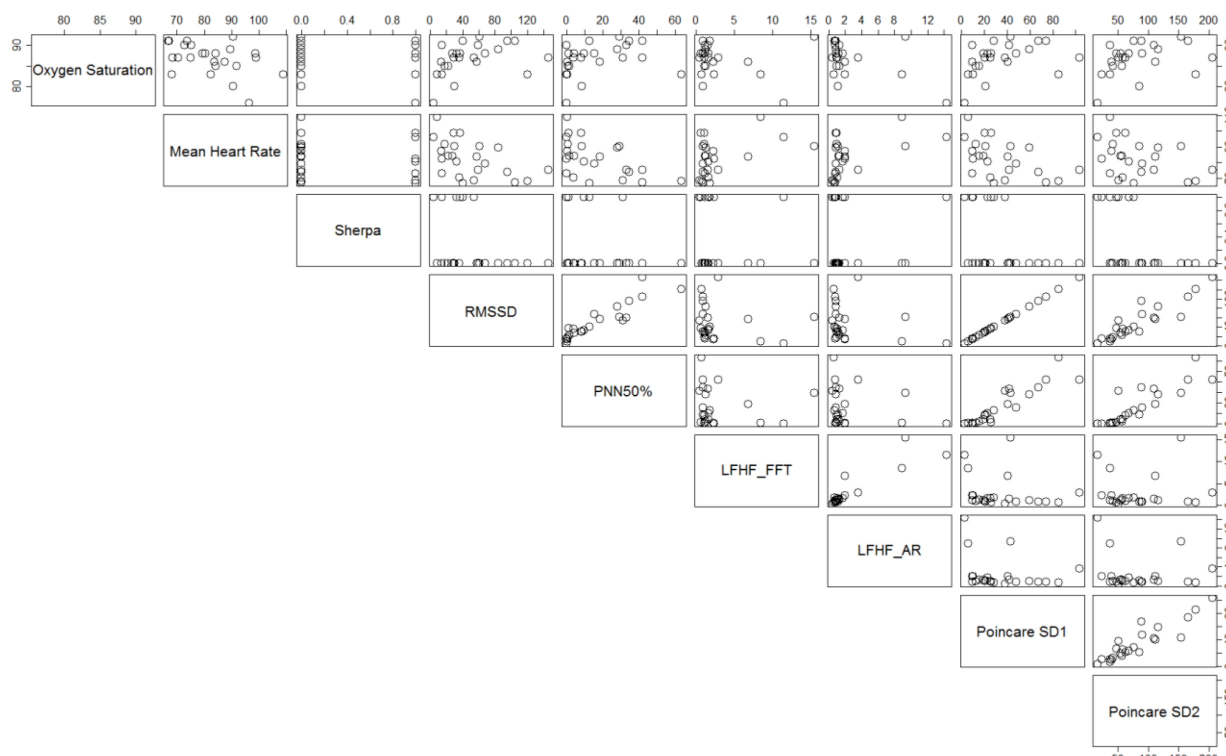


Figure 1: Scatterplot matrix of 3 predictors and 6 responses.

Intuitively, mean heart rate should have a negative relationship with HRV. We see this, at least weakly with all the predictors except the ratios, which also is intuitive because the ratios should have an inverse relationship with HRV, as we traditionally think about it (Brennan, et al., 2002). As for oxygen saturation, it appears to have a logarithmic relationship with our responses. Taking the log is a common approach when using HRV as a response (Heart Rate Variability Standards of Measurement, et al., 1996). Taking the log of the ratios might have merit as well because of the pattern and clustering displayed in **Figure 1**. The figure also demonstrates that RMSSD and Poincare plot SD1 are perfectly correlated, which makes sense as SD1 is a measure of successive RR interval variation. Poincare plot SD2 is a measure relative to the variation of RR intervals in the overall time domain and thus presents the same inconsistency issue SDNN presented (Brennan, et al., 2002). So, both Poincare plot standard deviations will be ignored for the purposes of the study.

Figure 2 displays the scatterplot matrix including the log of the four remaining response variables. Due to the association and research, we can be fairly confident in using both *log(RMSSD)* and *log(pNN50)* as responses representative of HRV, and it is shown that no noticeable association exists between these two and either the log of the ratio. We will still briefly consider the ratios in models, but it seems that there is probably no significant information to be gained about them using the two predictors given in the two subject groups.

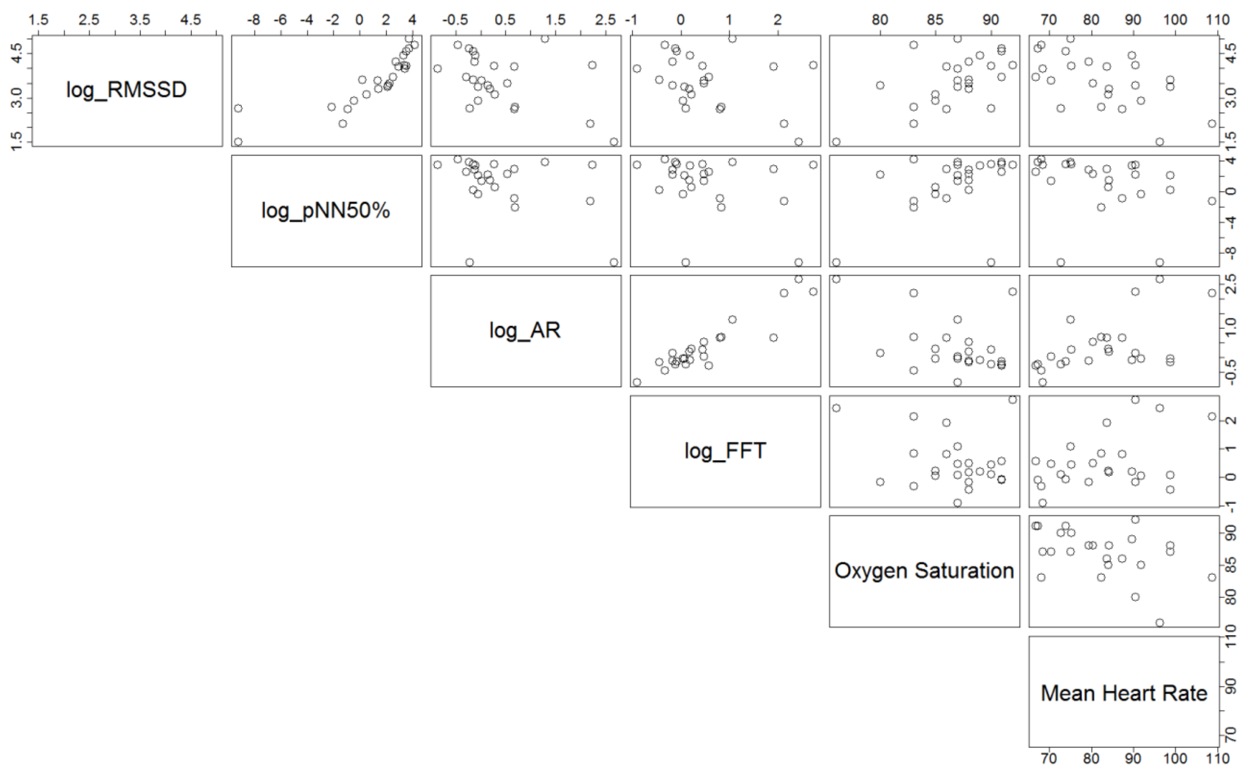


Figure 2: Scatterplot matrix with possible responses after *log* transformation.

So, at this point, we are most intrigued with the effect the two covariates have on *log(RMSSD)* and *log(pNN50)* in the two subject groups. Separate scatterplot matrices for those 4 variables, separated by Sherpa and students, can be found as **Figure B.1** and **Figure B.2** in the *Appendix B*. Boxplots for those 4 variables can be seen below in **Figure 3**. Since the responses will have a log-transformation, the boxplots for those can be seen in **Figure B.3** in *Appendix B*.

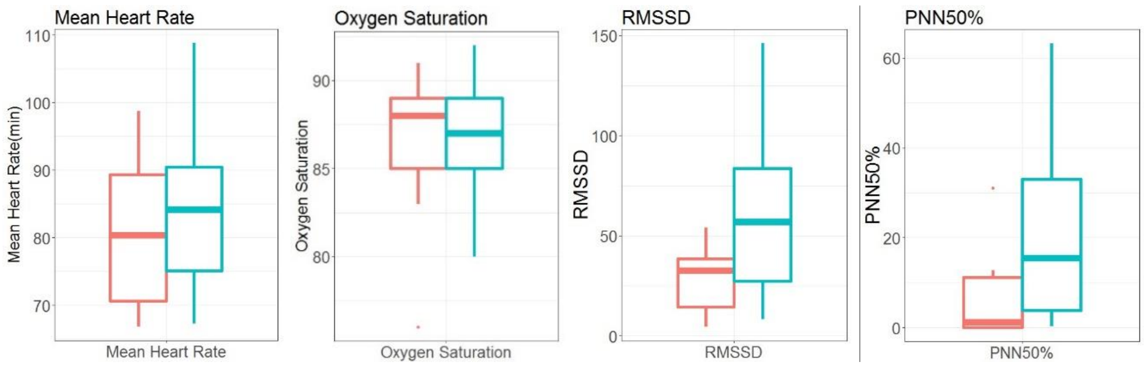


Figure 3: Boxplots of the four variables of interest. Sherpa in Red, Students in Blue.

There seems to be visual evidence in **Figure 3** that HRV differs between Sherpa and students, as Sherpa tend to have less variation. Further, it seems that the spread of the HRV measures for students seems to be larger, extending much further in the positive direction. This would further suggest there is a multiplicative or exponential relationship between HRV between the two groups and further support the need for a log transformation. Mean heart rate and oxygen saturation are at similar levels for both groups.

Visual evidence for inclusion of interactive terms was also explored, and none was found. This can be shown by similar associations for Sherpa and students for both mean heart rate and oxygen saturation against HRV in **Figures B.4** and **B.5** in the *Appendix B*.

Model Presentation

Initially, we want to establish statistical confidence in the difference of HRV between Sherpa and students that we see in the boxplots of *RMSSD* and *pNN50*. The results of the two sample *t*-test for *RMSSD* for the two groups results in a significant *p*-value of 0.021. Statistical output is included in the *Appendix C* as **Output C.1** and **Output C.2**, respectively. This simple statistical procedure is inadequate, however, because it does not account for oxygen saturation and mean heart rate. Now, we shall focus on a model that can control for these covariates.

We use a linear regression model to model the linear relationship between the response variable and three predictors.

Our regression model can be written in the form of:

$$Y = \beta_0 + \beta_1 * \textit{Oxygen Saturation} + \beta_2 * \textit{Mean Heart Rate} + \beta_3 * \textit{Sherpa} + \varepsilon,$$

where β_0 is the intercept, β_1, β_2, β_3 are parameters, *Sherpa* is an indicator variable (1 if individual is a student, 0 if Sherpa), and ε is the error term.

We plan on investigating the basic linear model for a few of the different responses, as well as confirming the lack of necessity for interaction terms that we saw visually in the exploratory analysis of the dataset.

Analysis, Part I

We build the linear regression model in which the response variable is the *log(RMSSD)* and the predictors are oxygen saturation, mean heart rate, and the sherpa/student indicator variable.

log(RMSSD) was the preferred response because the response *pNN50* had one extreme value and two values of zero, which is difficult to deal with when transforming, especially with such a small sample. We found some evidence that each predictor is statistically associated with the response, with an R-squared of 59.67%. This latter quantity measures the variation in response that is explained by the linear relationship between the response and the predictors. The fitted model can be written as follows:

Predicted(*log(RMSSD))* = -0.98215 + 0.07975**Oxygen Saturation* – 0.03464**Mean Heart Rate* + 0.72117**Sherpa*

The exponentiated coefficient exp(β_4) for *Sherpa* is the expected multiplicative change between the Sherpa and students RMSSD when oxygen saturation and mean heart rate are held at some fixed value. Of course, the expected difference for the Sherpa and students will be different for different levels of oxygen saturation and mean heart rate because the coefficients for those covariates are exponential as well. Thus, one can think of the exp(β_4) as a multiplicative change in RMSSD between the two groups. For example, let us say that an individual has a mean heart rate of 85 and oxygen saturation of 87, both around the average for an individual in this study. Then, according to our model, for Sherpa, you have estimated *log(RMSSD)* = 3.012, making expected *RMSSD* 20.322 for students. For students, you have estimated *log(RMSSD)* = 3.012 + 0.72117; so estimated *RMSSD* is 41.799. We can say that *RMSSD* will be exp(0.72117)=2.05 about two times higher for students relative to Sherpa It may be better to express this relationship as a percentage chance from Sherpa to students. Thus, for a student and Sherpa that have the same mean heart rate and oxygen saturation, the student's RMSSD will be (exp(0.72117)-1)*100% = 105% larger. This helps quantify the difference in RMSSD that we saw in the boxplot in **Figure 3**.

<u>*Analysis, Part II*</u>

Next, we wanted to explore including the ratios as the response in the same model. Using the log(*FFT LF/HF)* ratio as the response, the model becomes much less informative; the R-squared value drops to 17.89%; see **Model Output C.3** in *Appendix C*. Using the *log*-transformation of the other ratio as the response yields similar results, **Model Output C.4** in *Appendix C*, and we can confirm what the exploratory analysis showed; we cannot confidently quantify a difference between the two groups for the LF/HF ratios.

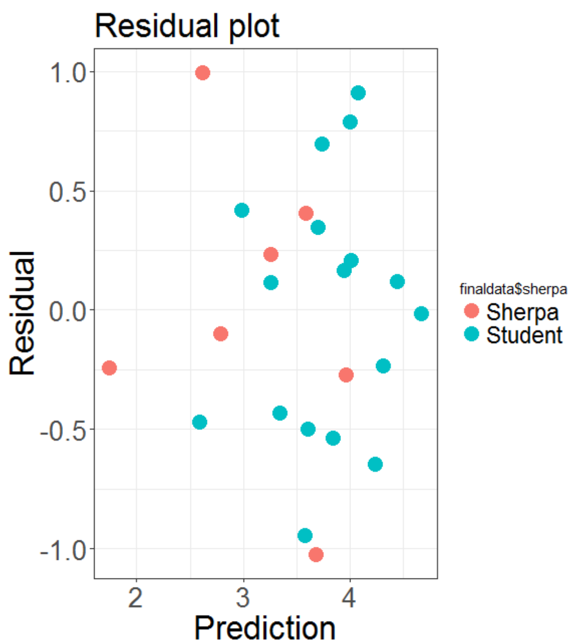
<u>*Analysis, Part III*</u>

The next step in the analysis is to look for interactions using the models. We do not expect to find any significant interactions, based upon our exploratory graphical analysis. Since *log(RMSSD)* is the response we have established as the better HRV measure, it will be used as the response in a model including all three possible two-way interactions from our three predictors. The resulting model is as follows:

Predicted(*log(RMSSD)*) = 31.203641 - 0.314271**Oxygen Saturation* - 0.430339**Mean Heart Rate* + 5.937032**Sherpa* + 0.004870**Oxygen Saturation*Mean Heart Rate* - 0.028591**Oxygen Saturation*Sherpa* - 0.034903**Mean Heart Rate*Sherpa*

However, the interactions, and any of the main effects in presence of those interactions for that matter, are not statistically significant. A similar result occurs when using *log(pNN50)* as the response. See **Model Output C.5 – C.6**. We can now conclude that interactions do not appear to play a significant role in the relationships between the response and the three predictors. Most pertinently, the relationship between Sherpa/student and the response appears to be the same regardless of the level of oxygen level or heart rate.

In terms of better understanding the difference in HRV between Sherpa and students, our best model seems to be the first explored, the basic linear regression model using *log(RMSSD)* as the response. **Figure 8** below shows two residual analysis plots that further support the legitimacy of the model.



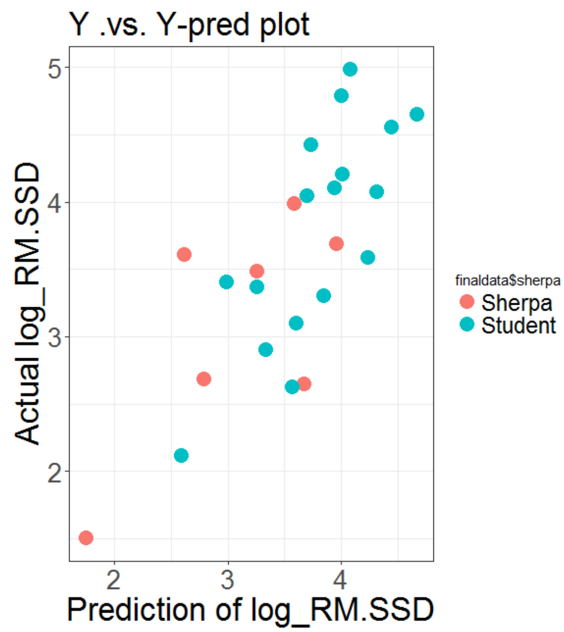


Figure 8: Residual plot (left) and Prediction vs. Actual (right)

The residual plot shows no concerning patterns, and the Actual vs. Predicted plot for our model shows an obvious positive relationship along the y = x line.

<u>Discussion</u>

Entering the study, it was believed that more, or higher, heart rate variability is found in both younger and more active individuals. So, from an age standpoint, the students are assumed to have the advantage. As for fitness level, it is a little more unclear, as Sherpa exercise for a living; however, the amount of fitness for both groups is unknown. Thus, the result that the students generally have more HRV initially makes us believe the age difference was either relatively larger or served as more weight toward the subjects' HRV measures.

We would like to caution that this analysis was strictly exploratory, and the results should be taken with "a grain of salt," as we did not enter the study with a particular model in mind to test. Confirming the results would require another set of data from the same populations, along with an analysis using the log(RMSSD) model we have suggested.

Appendix A

Table A.1: Descriptions and units of the variables for each observation

Variable	Units	Description
Independent Variables		
SDNN (SD RR)	**ms**	**Standard deviation of total ms between RR intervals. Not used, as the length of time is not defined and set for each measurement. So, this is simply an estimate of overall HRV and not specific enough.**
RMSSD	**ms**	**Square root of the mean squared differences between successive RR intervals.**
pNN50	**%**	**Number of interval differences of successive RR intervals that are greater than 50 ms divided by the total number of intervals.**
FFT LF/HF ratio		**FFT stands for fast Fourier Transformation. LF and HF represent the relative value of power in proportion to the total power minus VLF (Very Low Frequency). Helps control for the change in total power that can be found between RR intervals. The ranges for qualifying as LF or HF are (.04-.15 Hz) and (.15-.4 Hz), respectively.**
AR LF/HR ratio		**AR stands for auto-regressive modeling. It uses an order J prior that is selected before hand. It allows for measurement without pre-specified intervals**
Poincare plot, SD1	**ms**	**<--Same information as RMSSD*** **
Poincare plot, SD2	**ms**	**These two measure the distribution of signal in 2D space (SD1 consecutive interval measure, and SD2 more overall measure for whole time domain)**
Predictor Variables		
Oxygen Saturation	**%**	**Amount of oxygen in blood**
Mean RR	**ms**	**Average ms of RR interval**
Sherpa		**1 if individual is a Sherpa, 0 is student**

Appendix B

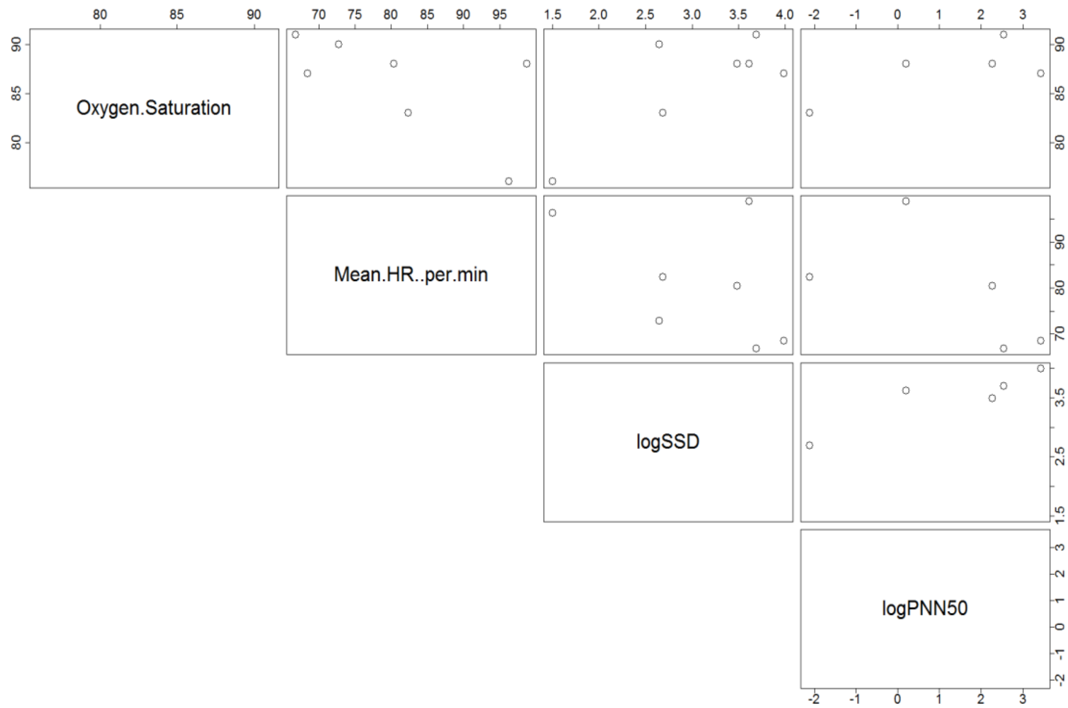


Figure B.1: All variables are measurements from Sherpa

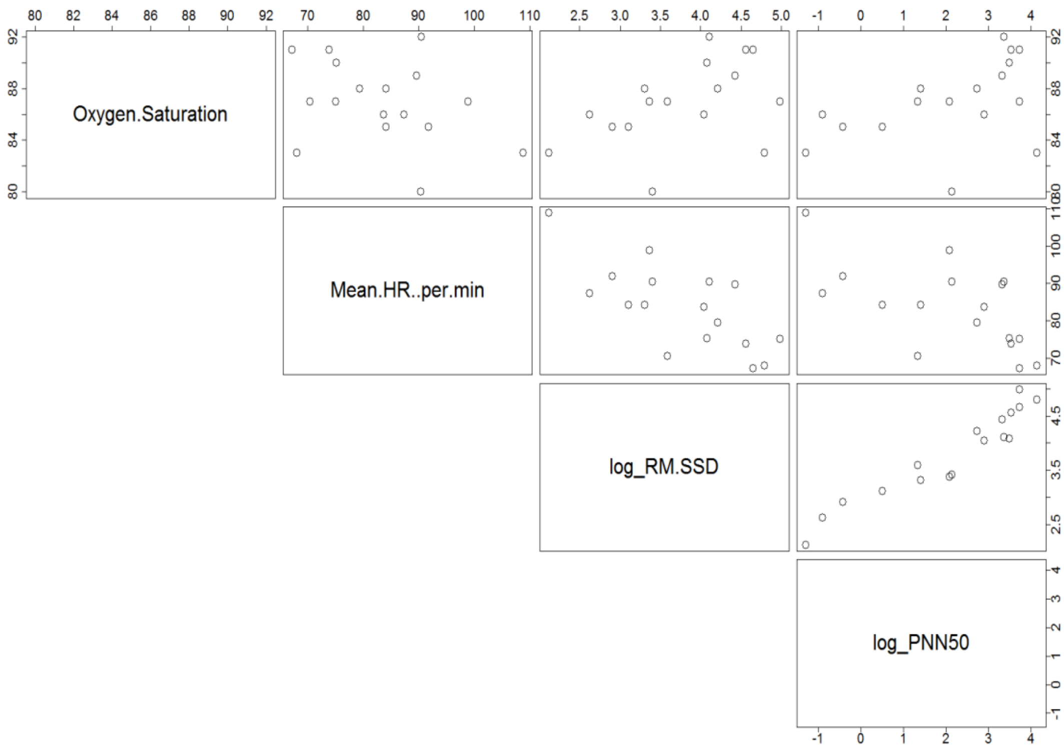


Figure B.2: All variables are measurements from students

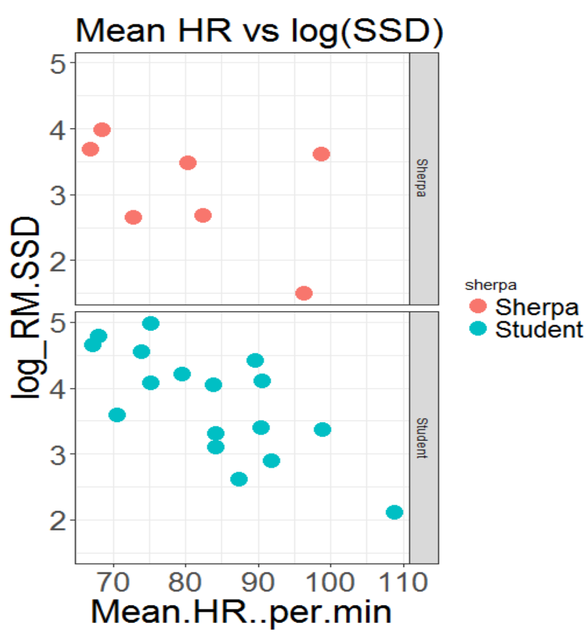


Figure B.4: Interaction plots, *log(RMSSD)* x *Mean Heart Rate* separated by the two groups

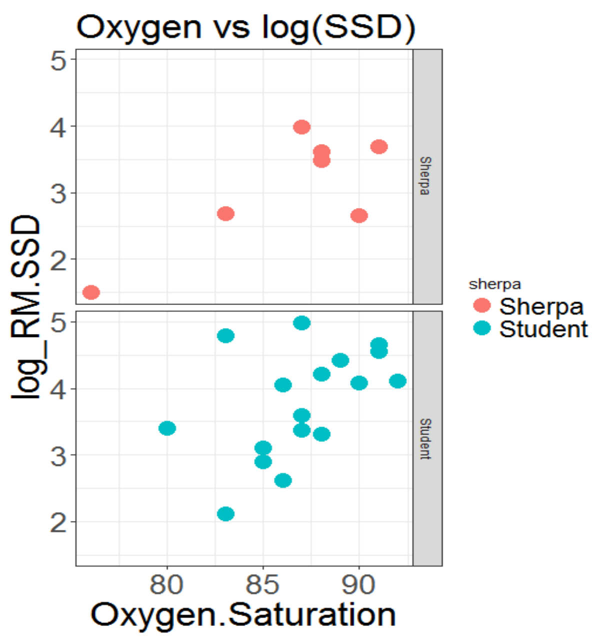


Figure B.5: Interaction plots, *log(RMSSD)* x *Oxygen Saturation* separated by the two groups

Appendix C

Output C.1: Basic Model, *log(RMSSD)* as the response

```
Call:
lm(formula = finaldata$log_RM.SSD ~ finaldata$Oxygen.Saturation +
    finaldata$Mean.HR..per.min + finaldata$sherpa)

Residuals:
     Min       1Q   Median       3Q      Max 
-1.02506 -0.44157  0.05149  0.36204  0.99608 

Coefficients:
                            Estimate Std. Error t value Pr(>|t|)   
(Intercept)                 -0.98215    3.71943  -0.264  0.79444   
finaldata$Oxygen.Saturation  0.07975    0.03687   2.163  0.04283 * 
finaldata$Mean.HR..per.min  -0.03464    0.01209  -2.866  0.00955 **
finaldata$sherpaStudent      0.72117    0.27153   2.656  0.01517 * 
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.5934 on 20 degrees of freedom
Multiple R-squared:  0.5967,	Adjusted R-squared:  0.5362 
F-statistic: 9.864 on 3 and 20 DF,  p-value: 0.000335
```

Output C.2: Basic Model, *log(pNN50)* as the response

```
Call:
lm(formula = finaldata$log_PNN50 ~ finaldata$Oxygen.Saturation +
```

```
    finaldata$Mean.HR..per.min + finaldata$sherpa)

Residuals:
    Min      1Q  Median      3Q     Max 
-9.1846 -0.9672  0.1553  1.2827  4.0315 

Coefficients:
                             Estimate Std. Error t value Pr(>|t|)   
(Intercept)                 -21.15498   17.94344  -1.179  0.25224   
finaldata$Oxygen.Saturation   0.29244    0.17788   1.644  0.11580   
finaldata$Mean.HR..per.min   -0.07130    0.05831  -1.223  0.23568   
finaldata$sherpaStudent       3.79349    1.30994   2.896  0.00894 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 2.863 on 20 degrees of freedom
Multiple R-squared:  0.4496, Adjusted R-squared:  0.367 
F-statistic: 5.446 on 3 and 20 DF,  p-value: 0.006666
```

Output C.3: Basic Model, *log(FFT LF/HF* ratio) as the response

```
Call:
lm(formula = log(finaldata$LFHF_FFT) ~ finaldata$Oxygen.Saturation + 
    finaldata$Mean.HR..per.min + finaldata$sherpa)

Residuals:
     Min       1Q   Median       3Q      Max 
-1.42213 -0.53606 -0.04986  0.40876  2.04276 

Coefficients:
                            Estimate Std. Error t value Pr(>|t|)
(Intercept)                 -0.69027    5.67099  -0.122    0.904
finaldata$Oxygen.Saturation -0.01641    0.05622  -0.292    0.773
finaldata$Mean.HR..per.min   0.03148    0.01843   1.708    0.103
finaldata$sherpaStudent      0.04646    0.41401   0.112    0.912

Residual standard error: 0.9048 on 20 degrees of freedom
Multiple R-squared:  0.1789, Adjusted R-squared:  0.05575 
F-statistic: 1.453 on 3 and 20 DF,  p-value: 0.2575
```

Output C.4: Basic Model, *log(AR LF/HF* ratio) as the response

```
Call:
lm(formula = log(finaldata$LFHF_AR) ~ finaldata$Oxygen.Saturation + 
    finaldata$Mean.HR..per.min + finaldata$sherpa)

Residuals:
     Min       1Q   Median       3Q      Max 
-1.04988 -0.51431  0.03923  0.24011  1.80893 

Coefficients:
                             Estimate Std. Error t value Pr(>|t|)  
(Intercept)                  1.356323   4.855984   0.279   0.7829  
finaldata$Oxygen.Saturation -0.045806   0.048139  -0.952   0.3527  
finaldata$Mean.HR..per.min   0.036201   0.015781   2.294   0.0328 *
finaldata$sherpaStudent      0.007164   0.354507   0.020   0.9841  
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.7748 on 20 degrees of freedom
Multiple R-squared:  0.3354, Adjusted R-squared:  0.2357 
F-statistic: 3.364 on 3 and 20 DF,  p-value: 0.03906
```

Output C.5: Model with interaction terms, *log(RMSSD)* as the response

```
Call:
lm(formula = finaldata$log_RM.SSD ~ finaldata$Oxygen.Saturation + 
    finaldata$Mean.HR..per.min + finaldata$sherpa + 
finaldata$Oxygen.Saturation * 
    finaldata$Mean.HR..per.min + finaldata$Oxygen.Saturation * 
    finaldata$sherpa + finaldata$Mean.HR..per.min * finaldata$sherpa)

Residuals:
    Min      1Q  Median      3Q     Max 
-0.9701 -0.3035  0.1218  0.2545  0.7969 

Coefficients:
                                                        Estimate Std. Error t 
value
(Intercept)                                            31.203641  26.280087  
1.187
finaldata$Oxygen.Saturation                            -0.314271   0.294543 
-1.067
finaldata$Mean.HR..per.min                             -0.430339   0.279548 
-1.539
finaldata$sherpaStudent                                 5.937032   8.106697  
0.732
finaldata$Oxygen.Saturation:finaldata$Mean.HR..per.min  0.004870   0.003157  
1.543
finaldata$Oxygen.Saturation:finaldata$sherpaStudent    -0.028591   0.076924 
-0.372
finaldata$Mean.HR..per.min:finaldata$sherpaStudent     -0.034903   0.027122 
-1.287
                                                       Pr(>|t|)
(Intercept)                                               0.251
finaldata$Oxygen.Saturation                               0.301
finaldata$Mean.HR..per.min                                0.142
finaldata$sherpaStudent                                   0.474
finaldata$Oxygen.Saturation:finaldata$Mean.HR..per.min    0.141
finaldata$Oxygen.Saturation:finaldata$sherpaStudent       0.715
finaldata$Mean.HR..per.min:finaldata$sherpaStudent        0.215

Residual standard error: 0.56 on 17 degrees of freedom
Multiple R-squared:  0.6947,	Adjusted R-squared:  0.587 
F-statistic: 6.447 on 6 and 17 DF,  p-value: 0.0011
```

References

Task Force from the European Society of Cardiology and the North American Society of Pacing Electrophysiology (1996, March 1). Heart Rate Variability Standards of Measurement, Physiological Interpretation, and Clinical Use. Retrieved September 8, 2017, from http://circ.ahajournals.org/content/93/5/1043

Brennan, M., Palaniswami, M., & Kamen, P. (2002, November 1). Poincaré plot interpretation using a physiological model of HRV based on a network of oscillators. Retrieved September 08, 2017, from http://ajpheart.physiology.org/content/283/5/H1873