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RESEARCH ARTICLE

Cardiac Heart Rate Dependence on Mitochondrial Deuterium ^2H Content

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ABSTRACT

Mitochondrial cardiac ATP production efficiency in beef hearts has been known to decrease with increasing systemic deuterium ^2H levels since the 1980's. Recently ketogenic diets which are known to decrease deuterium levels in humans were found to decrease both the resting and exercise heart rates in a volunteer. Furthermore, resting heart rates were found to systematically vary with the deuterium content from the previous meal consumed by six volunteers. A cardiac model is proposed showing extreme sensitivity of heart rate on the deuterium loading of the ATP synthase nanomotors. A predicted increase in heart rate by 28% is expected with a 5% decrease in ATP production. This finding strongly suggests that high deuterium levels in the fatty acids contribute to the diastolic dysfunction in heart failure not already attributed to direct structural damage, i.e., heart failure with preserved ejection fraction.

Keywords: ATP, ATPase nanomotor, cardiac, deuterium, deuterium-depletion, deuterium-depleted water; heart failure with preserved ejection fraction

1. Introduction

Deuterium ^{2}H is a natural heavy isotope of hydrogen with an abundance of one ^{2}H deuterium atom to every 6600 ^{1}H protium atoms on earth. Tritium ^{3}H is another heavy isotope of hydrogen but due to this isotope being radioactive with a decay half-life of 12.32 years, negligibly low levels are found in nature. When these deuterium hydrogen isotopes interact with the ATP synthase in living organisms, cellular ATP production rate decreases.[1-3] The replacement of protium with deuterium in biochemical processes is called deuteration and reducing the deuterium:protium ratio below 1:6600 is known as deuterium-depletion or deupletion. The discipline that studies and teaches how deuterium is discriminated and fractionated from protium in nature via biochemical reactions is called deutenomics. Figure 1 illustrates the basic atomic structure of these hydrogen isotopes. The total concentration of deuterium in the human body is 12-14 mmol/l which is higher than potassium 3.5-5.1 mmol/l indicating this isotope cannot be ignored in biochemical processes.

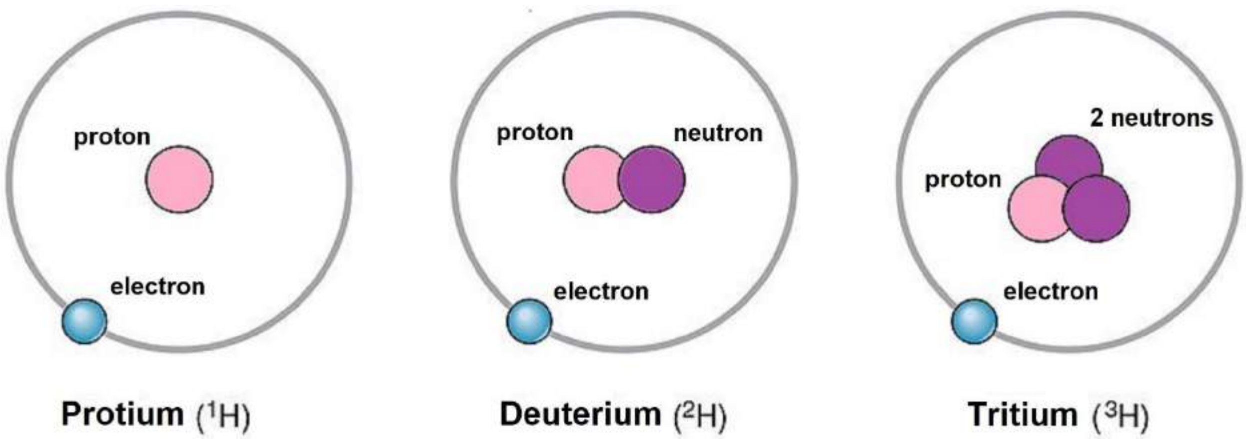

Figure 1. Isotopes of hydrogen. Protium is the most common isotope of hydrogen with an abundance of 99.98% on earth. Deuterium is the second most common isotope of hydrogen occurring with an abundance of 1:6600 hydrogens on earth. Tritium is a rare isotope due to being radioactive with a decay half-life, $\tau_{1/2}$, of 12.32 years. The total concentration of deuterium in the human body is 12-14 mmol/l which is notably higher than potassium at 3.5-5.1 mmol/l. Tritium is only found in trace amounts. The relative atomic masses are 1, 2, and 3, respectively.

The earliest known adverse effects of deuteration in living organisms was first reported in laboratory animals. In 1977, researchers reported that deuterium decreased the sensitivity of frog retinas to light.[4] By 1981, deuteration was found to decrease the ATP production in beef heart mitochondria. [1-3] This finding was instrumental in determining that a proton current along the electron-transport chain was directly involved in the production of ATP. However, the link between deuteration and human disease was not yet reported in the literature.

In 1997, the Nobel prize in chemistry was awarded to the chemists Jens Christian Skou, John E. Walker and Paul D. Boyer who discovered that the ATP synthase was a rotary nanomotor spinning at approximately 9000 rpm.[5] However, it would be another 10 years before the connection between deuteration and disease would begin to unfold. In 2007, Olgun calculated that the dissociation constant of deuterium from the Asp61 binding site of the ATP nanomotor was 35% that of protium indicating the ATP nanomotor would significantly slow down lowering the ATP production rate as deuterium levels increase within the mitochondria matrix.[6]

More recently, the metabolic effects of deuterium depletion have been studied in lung[7], rare childhood[8], renal cell[9], colorectal cancers[10] and diabetes mellitus.[11-12] In this report, the effect of deuteration on cardiac heart rate is presented. It will be shown that deuterium depletion via a keto diet significantly decreased both the resting and exercise heart rates in a volunteer. Low heart rates have also been previously reported in a body builder when he adopted a ketogenic diet to lower skeletal fat to 4.5% just prior to a contest.[13] The resting heart rates in six volunteers are then presented showing the resting heart rate systematically varies with the deuterium content from the last meal consumed.

A cardiac model explaining why the heart rate is susceptible to deuteration is presented. These findings raise the important question as to whether or not deuteration with aging is a factor associated with diastolic dysfunction in heart failure in the absence of structural damage. Decreased heart rates have also been associated with increased longevity[14] and this is likely due to lower deuterium levels in the fatty acids used to power the heart. These fatty acids are also needed to maintain the production of low deuterium "metabolic water" production in other organs.[15] Therefore, careful in-home heart rate measurements offer a technique for the monitoring of potential toxic deuterium exposure from foods and drinking water.

2. Materials and Methods

Volunteer 1 has hiking log books dating back to the age of 18. These logs include occasional peak exercise heart rates that were first recorded at the age of 24. Furthermore, resting ECG's from previous physicals that remained available date back to the age of 32. These data allowed the extraction of the historical resting and exercise heart rates over several decades which provided the hypothesis in Section 3.1. It was the observation that the change in resting and exercise heart rates with the initiation of a keto cycling diet in this volunteer that prompted a detailed correlation of resting heart rates with the meals consumed by six volunteers.

Six volunteers, three males and three females, were selected on the basis of good cardiac health. None were on any cardiac medications at the time of the food tests which would complicate the heart rate vs deuterium analysis. Their ECGs were all normal with no pathologic Q-waves, ST or T-wave abnormalities and none reported any angina. If admitted to a hospital, their GRACE scores would all fall between 34 and 98 indicating low risk for cardiac mortality.

The volunteers recorded resting heart rates over a period of two months minimum either immediately upon rising from sleep or three hours after dinner if they had a tendency to become hypoglycemic in the mornings. Volunteer 1 utilized an EMAY Model EMG-10 heart rhythm monitor to record 30 second rhythm strips indicating the resting heart rates. Volunteers 2-6 used an over-the-counter pulse-oximeter to record resting heart rates averaged over 30 seconds. These were manually recorded. All the heart rate data from all six volunteers have been recorded for future use. The technical specifications of the EMAY Model EMG-10 are listed in Table 1.

Lead	Standard 3 leads: Ⅰ Ⅱ Ⅲ
Calibration voltage	1mV±5%
Standard sensitivity	10mm/mV±5%
Amplitude frequency characteristic - standard	10Hz; 1Hz～20Hz; (+0.4dB, -3dB)
Noise level	≤30μV
Input impedance	≥50MΩ - CMRR: ≥60dB
Scanning speed	25mm/s±5%
Sampling rate	250 dots/s
HR measurement range	30bpm～300bpm, error: ±1bpm or 1%
Battery model	602540P DC 3.7V 530mAh
Type of protection against electric shock	Internal power device
Metal electrode degree of protection against electric shock	Type BF applied part
Degree of waterproof	IP22
Display	1.77" color TFT-LCD
Size	100mm (L)*45mm (W)*15mm (H)
Weight	about 60g

Table 1: EMAY Model EMG-10 Technical Specifications

Likewise, the technical specifications of the pulse oximeters are given in Table 2. These pulse oximeters are FDA and CE certified portable equipment featuring advanced technology, for measuring and displaying functional oxygen saturation of arterial hemoglobin (%Sp02) and pulse rate(PR) obtained from the fingertip.

Size	58mm x 36mm x 33mm, 2.3"x1.4"x1.3"
Color	White /Black and Gray
Batteries	2 x AAA
Resolution	±1%
Measurement range	SpO2 (70%-99%) & PR(30BPM~240BPM)
SpO2 Accuracy	±3% on the stage of 70% 99%
PR Accuracy	±1BPM or ±1%

Table 2: Finger Pulse Oximeter Blood Oxygen meter SpO2 Heart Rate Monitor Saturation.

Obtaining a typical data point is described as follows. Each volunteer would select a food item to test and would consume that item at dinner time. In order to maintain a balanced diet, breakfasts and lunches could be used to consume other food groups to maintain a proper daily intake. Each volunteer would consume enough food at dinner to allow the body to utilize this energy source throughout the night. This was roughly 600 kcal for most individuals or one-third of the basal metabolic rate per 24 hours. The resting heart rates would be measured after food is fully digested and before body enters a fully fasting state at which time fat stores begin to be mobilized. For most individuals, the ideal measurement time is immediately before rising from bed. However, for Volunteer 4, this was three hours after dinner while this volunteer was studying for classes. This was done because of his high metabolism would put this volunteer into a hypoglycemic episode by morning. The data from all six volunteers were recorded then copied into spread sheets which would allow for the production of the graphs presented in this report. Table 3 lists multiple factors that can influence heart rate and were not present in any of the volunteers during the time of heart rate data collection.

1) Increased physical activity (exercise)
2) Medications/substances (sympathetic, parasympathetic, calcium channel blockers, alcohol, sedatives; opioids)
3) Infections
4) Pain
5) Hypoglycemia
6) Tissue Trauma
7) Overtraining
8) Hyper/Hypothermia
9) Smoking
10) Psychological (fear, anxiety, stress; anger)
11) Digestion of food
12) Implanted cardiac pacemakers

Table 3. Factors that can influence the heart rate.

3. Results

3.1 *Historical Findings*

In a recent study into the effect of deuterium depletion by a low carbohydrate intake and deuterium depleted water, a significant decrease in resting heart rate was observed with decreasing systemic deuterium.[12] The resting heart rate was found to drop by 20 bpm with a keto cycling diet with an additional 4 bpm drop after the initiation of deuterium depleted water intake four years later. This patient later volunteered as the first of six volunteers to look into the effect of various foods on the resting and exercise heart rates. Prior to age 53, the volunteer estimated an average carbohydrate (CHO) intake of 350 grams daily. After age 53, the primary energy source was changed to fats via a keto cycling diet described elsewhere.[16]

Figure 2 shows changes in the resting heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of Volunteer 1 between the ages of 31 and 60 years. Data prior to age 53 were obtained from routine physicals and resting ECG's. Data after age 53 were obtained from a portable EMAY Model EMG-10 ECG Monitor and portable automated blood pressure monitor. The most significant change occurred with a drop of 20 bpm in the resting heart rate when the keto cycling diet was initiated.[16] The addition of deuterium depleted water four years later decreased the resting heart rate by approximately 4 bpm. The weight of Volunteer 1 are given at several locations on the graph and the deuterium level of the drinking water in ppm are color coded. The blood pressures did vary slightly over time but no systematic connection to the deuterium level is obvious. However, there was a marked improvement to the c-peptide at age 55 which was previously reported following the initiation of the keto cycling diet.[16] There was also a gradual drop in the c-reactive peptide inflammatory marker (CRP) from 2.5 mg/l at the time the keto cycling diet was first initiated to <1.0 mg/l two years after the deuterium-depleted water (DDW) was added to the diet. These findings strongly suggest the largest factor in deuterium depletion is achieved with a low carbohydrate diet but further benefits do occur with the intake of deuterium depleted water (DDW). The DDW does seem to lower the CRP which could be beneficial in patients at risk of coronary artery disease where elevated CRP levels are a risk factor of coronary artery blockages or autoimmune disorders.

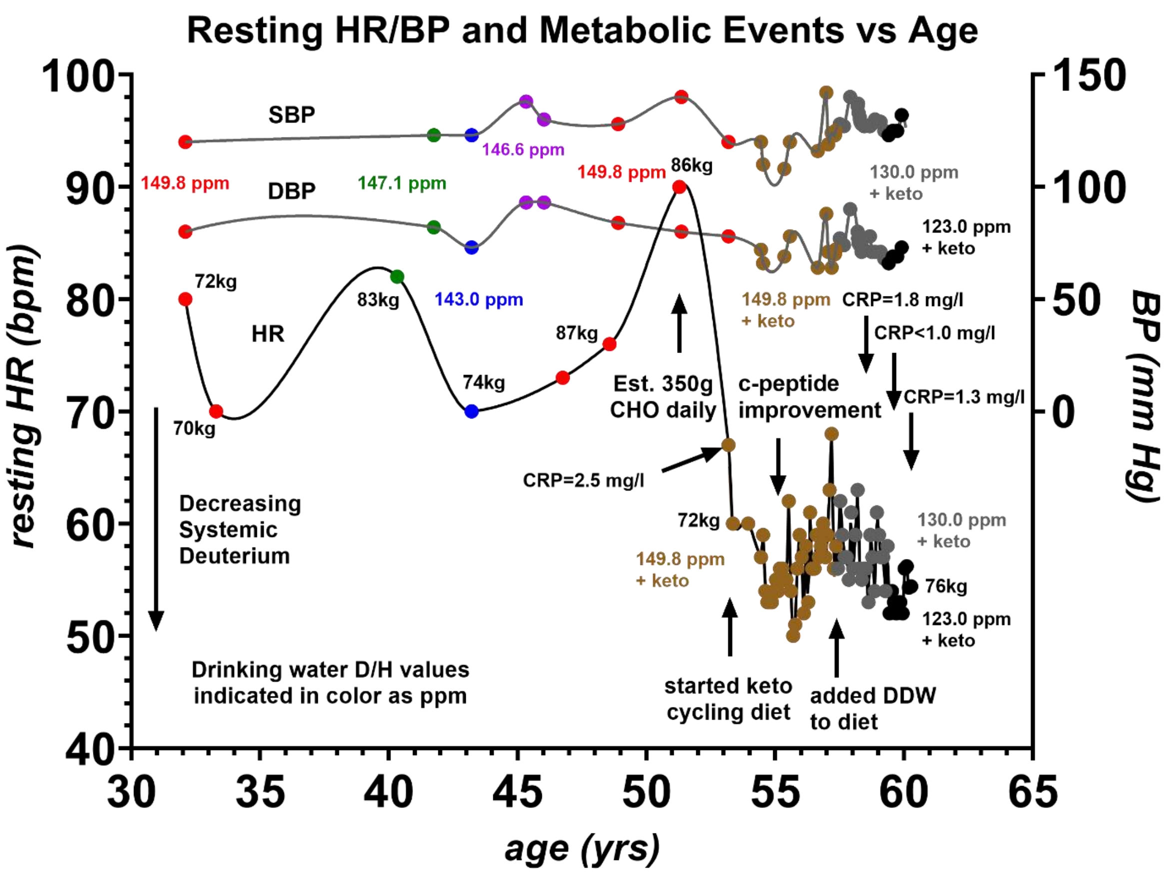

Figure 2. Resting heart rate (HR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) versus age. Volunteer 1 had a resting heart rate between 70 and 90 beats per minute (bpm) prior to adopting the keto cycling diet. This heart rate dropped by 20 bpm to 50 - 68 bpm after the keto cycling diet was initiated. A 74% ejection fraction (EF) measured with nuclear SPECT at age 57 indicates good contractility of the cardiac muscle. The addition of deuterium depleted water (DDW) at age 57.5 years appears to have lowered the resting pulse by an additional 4 bpm indicating that the keto diet had the most influence on the resting heart rate. The patient's weight indicated at seven ages do not correlate with the resting heart rate. The colors indicate the level of deuterium consumed in the drinking water as determined with mass spectroscopy. The C-reactive protein (CRP) inflammatory marker was measured at 2.5 mg/l when the keto cycling diet was initiated at age 53 and this gradually dropping to unmeasurable levels, <1.0 mg/l, by the age of 59. A slight rebound to 1.3 mg/l occurred following a COVID-19 infection at age 60.

Figure 3 indicates the systematic change in maximum recorded heart rates during strenuous climbs between the ages of 24 and 60. These exercise heart rates are recorded in Volunteer 1's hiking and climbing log books. The dates where diabetes type-II was diagnosed, c-peptide improvement occurred, keto cycling was initiated and DDW addition to the diet are indicated. Prior to age 53 the predominate energy source was carbohydrates (CHO) and after age 53 this was changed to fats via the keto cycling diet. Just above the x-axis, 13 rim to river backpacks in the Grand Canyon National Park are indicated to show that the drop in maximum heart rate was not due to a sudden improvement in physical fitness. Volunteer 1 has been in relatively good fitness his entire life. Both the resting and exercise heart rates appear to be strongly correlated to the primary energy source utilized, e.g. carbohydrates prior to age 53 and fats after age 53. Mass spectroscopy does indicate that deuterium is more concentrated in the plant storage sugars, e.g. carbohydrates, as compared to fats[15] suggesting these drops in heart rates are due to systemic deuterium depletion.

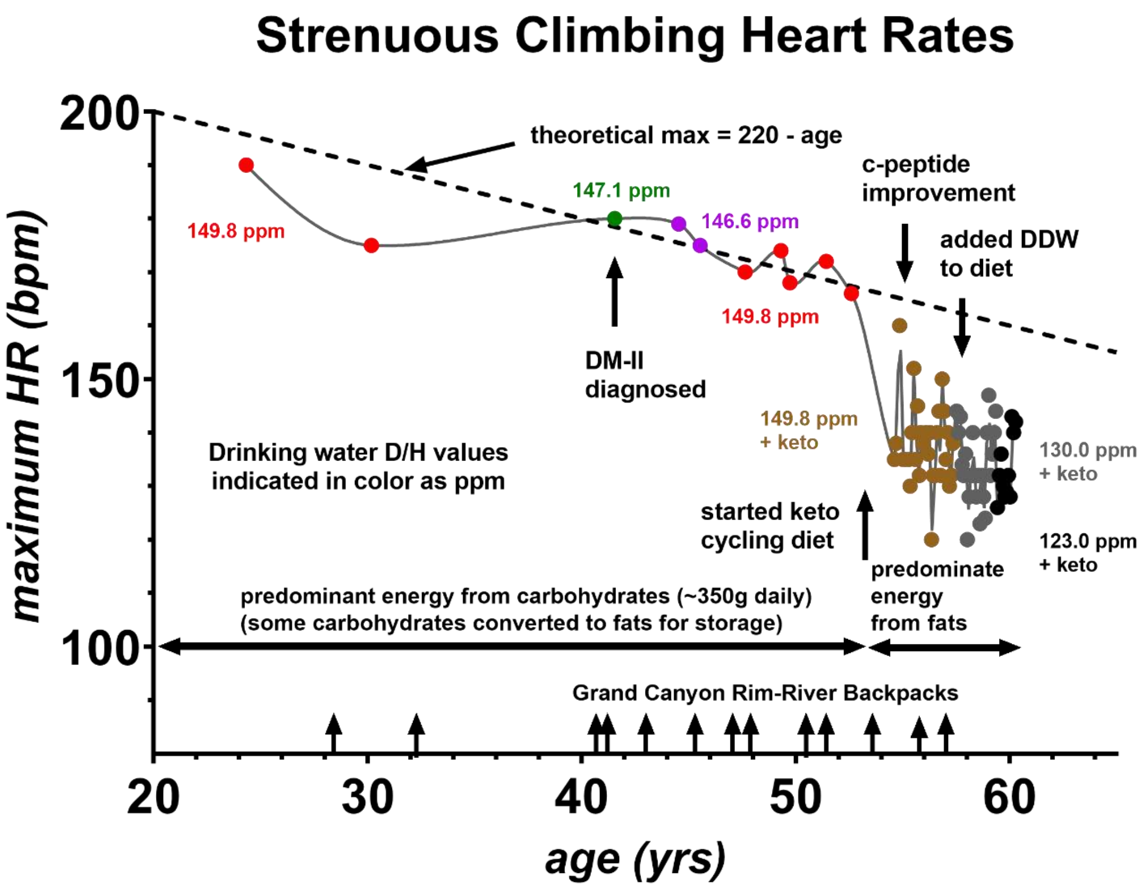

Figure 3. Peak exercise heart rates measured on steep climbs versus age. Volunteer 1 has hiking log books with peak heart rates dating back to age 24. Prior to age 53, the predominant energy source was carbohydrates estimated at 350g daily. Following age of 53, the predominant energy source was changed to fats at which time the peak exercise heart rates decreased below the theoretical maximum of 220-age. Between the ages of 28 and 57 years, Volunteer 1 made 13 backpacks in the Grand Canyon from the rim to the river and these trips are marked with the arrows just above the x-axis. These indicate that changes in overall physical fitness do not account for these maximum heart rate changes with age. Volunteer 1 was diagnosed with type II diabetes at age 41. Shortly after the keto cycling diet was initiated a significant improvement to the c-peptide was observed at age 55 which was previously published.[12;16]

3.2 Resting Heart Rate Dependence on Deuterium Content of Food

Both resting and exercise cardiac heart rate data presented for Volunteer 1 strongly suggest that heart rates significantly drop when carbohydrates are replaced with healthy fats. This food shift suggests that deuterium might be playing a significant role in the heart rate especially when noting that ATP production in beef heart has been known to decrease with increasing deuterium levels since 1981. [1-3]

As a result, six volunteers agreed to make in-home recordings of their resting heart rates just before rising from bed to be compared to the dinner eaten the prior evening. Volunteer 1, a scientist, is the volunteer already discussed above and a 60-year-old male athletic individual who has had type-II diabetes mellitus since the age of 41.[12] Volunteer 2 is a 55yo female electrophysiologist technician who has had a history of Systemic Lupus Erythematosus (SLE) for 30 years. Volunteer 3, an engineer, was a 70yo less athletic male but very healthy with no underlying medical conditions. Volunteer 4 was a 29yo male PhD physics student with no known health conditions. He was the healthiest of the six volunteers remaining active with both cardio-exercises and weight lifting. Volunteer 5 was a 44yo female nurse with no known medical conditions who also remains physically active. Volunteer 6 was a 41yo female weight trainer with no known medical conditions who also remains physically active.

Volunteer 1 recorded his resting heart rates each morning for a period of ten months using an EMAY Model EMG-10 heart rhythm monitor. Four sample rhythms are shown in Figure 4. Volunteers 2-6 used a simple medical grade over-the-counter pulse ox meters to record their resting heart rates. These resting heart rate results are summarized below.

Figure 4. Two lead electrocardiogram (ECG) rhythms measured at lead position V4. The recordings were made with an EMAY Model EMG-10 just before rising from sleep. Resting heart rates recorded range from 46 bpm to 61 bpm depending on the meal eaten the night before. The top two ECG's compare a grass-fed bison ribeye to a grain-fed beef and the bottom two ECG's compare Argentine shrimp to grain-fed butter. Similar 30 second rhythm ECG's were recorded for each resting heart rate reported from Volunteer 1 in this report.

To assure that the heart is utilizing the food being tested by the time of rising from bed, the number of calories consumed had to be sufficient enough to span the number of hours slept each night by each volunteer. The volunteers have basal metabolic rates between 1600 kcal/day and 1800 kcal/day depending on age and weight. For instance, in order to span 6 hours sleep, a minimum of 400-450 kcal would be consumed for dinner. Furthermore, avoidance of other contaminants such as oils, e.g., fish in olive oil, was carefully followed. It was found that consumption of sardines in olive oil would consistently give the same heart rate readings as olive oil alone. The results from ten months of readings were recorded. Volunteer 1 recorded 30 second rhythm strips at the V4 lead position whereas Volunteers 2-6 used a pulse-ox meters averaged over 30 seconds. The time/date stamped ECG's were also saved for future use. The V4 position was chosen for the heart rate readings due to higher voltage making noise less of a problem. Furthermore, no medication changes were made during the time span of these experiments and the measurements were made immediately before rising from bed in the mornings when the heart rates are lowest. Volunteer 4, 29yo male, would be mildly hypoglycemic by the mornings so made his resting heart rate readings 3 hours post-prandial just prior to sleep.

A summary of 289 ECG derived resting heart rate data from Volunteer 1 are shown in Figure 5. The mean and standard deviations of the resting heart rates are indicated by the dots and bars, respectively. A minimum of ten readings were made for each group except for the two butters, canola oil, and HFCS (High Fructose Corn Syrup) which were tested two times each. Volunteer 1 preferred not to do additional measurements with these foods/additives since the higher heart rates suggested these were unhealthy. In Figure 5, the casein and whey protein shakes (40 grams protein each) led to the lowest resting heart rates followed by seafoods coded as blue, then grass-fed meats coded as green, cheeses coded as orange, then grain-fed meats coded as brown. The butters are coded as either grass-fed butter (green) or grain-fed butter (brown) with the latter showing the highest heart rates. Almonds, walnuts, L-glutamine, extra virgin olive oil and MCT virgin coconut oil are also included in the data. Volunteers 2-6 showed the same general heart rate patterns with whey protein resulting in the lowest resting heart rates followed by seafoods, grass-fed meats, cheeses, grain-fed meats then high fructose corn syrup. Volunteers 1 and 3 found much higher heart rates following the consumption of HFCS drinks suggesting these are high deuterium beverages. As a result, both of these volunteers rarely consume these beverages.

It will be pointed out here that none of the volunteers have an implanted cardiac pacemaker that determines the heart rate or heart medications that can alter the heart rate. Furthermore, no volunteer recorded any heart rates during any hypoglycemic episodes or after extreme exercise because these heart rates would be elevated due to the activation of the sympathetic nervous system. Furthermore, none of the factors that can influence the heart rate listed in Table 3 were present during the data collection. Volunteer 4, a 29yo male, made his recordings 3 hours post-prandial to avoid hypoglycemic episodes. Finally, the volunteers noted elevated heart rates with viral infections so food heart rate correlations did not include heart rate values during any viral infections. Volunteer 1 also noted a marked increase in resting heart rate to 70bpm during a COVID-19 infection. The technique of estimating deuterium levels in the foods under these three situations are not possible.

Figures 5-10 illustrate the summary of resting heart rates (left y-axis) as a function of meals (x-axis). The right y-axis is the estimated bioavailable deuterium level to be discussed in detail to follow. Seafoods are color coded as blue, grass-fed meats as green, cheeses as orange, oils as purple, grain-fed meats as brown, nuts as light-brown and others as black.

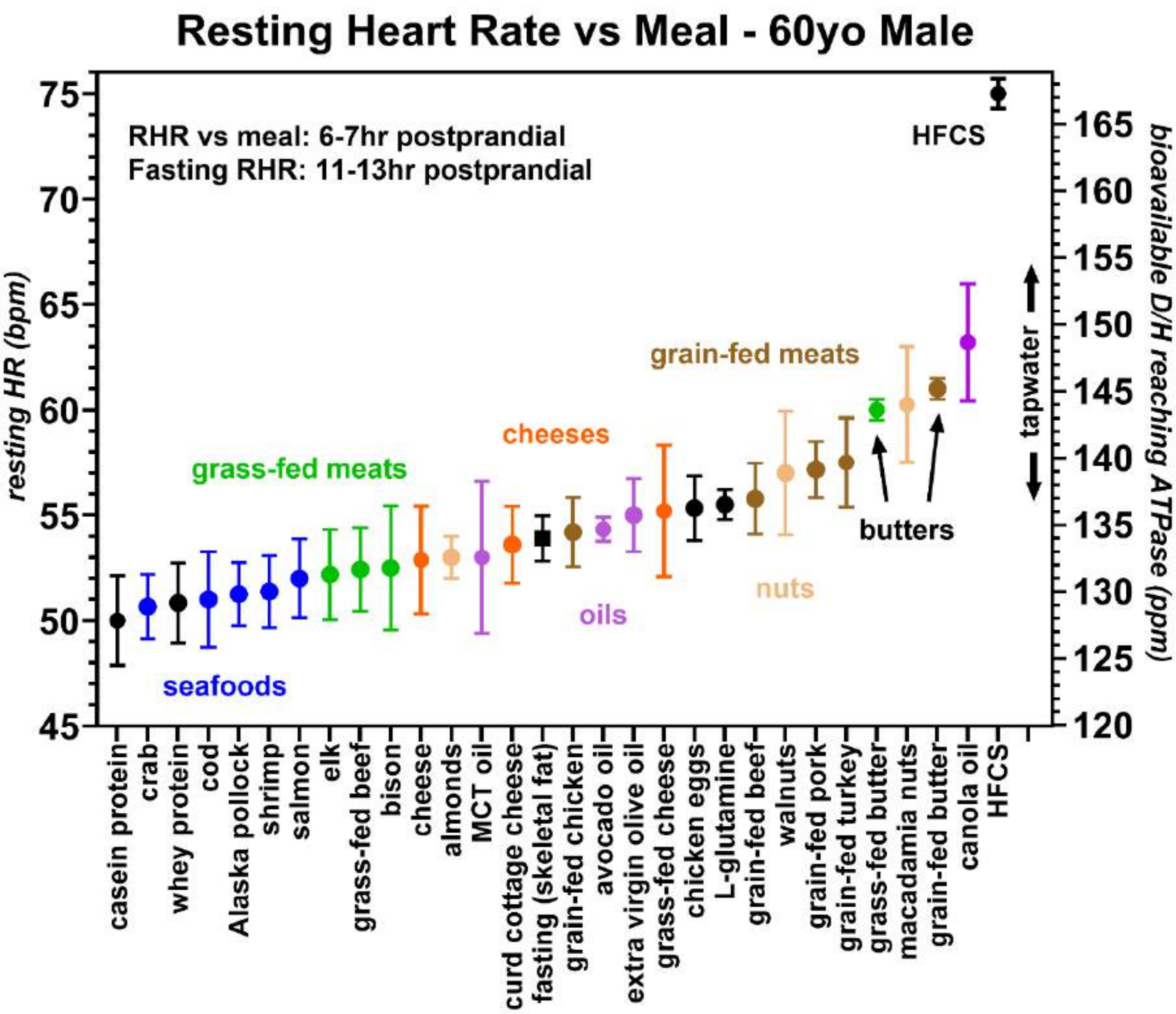

Figure 5. Resting heart rates recorded just prior to awakening over a ten-month period from Volunteer 1 (60yo male). In each food group, the average and standard deviations are shown by circles and bars, respectively. A minimum of ten runs were made with each food group except for the butters, canola oil, and HFCS (High Fructose Corn Syrup) which were two runs each. The lowest heart rates were seen with the casein protein shakes (black) followed by seafoods (blue), grass-fed meats (green), cheeses (orange) and then grain-fed meats (brown). Some nuts and tree oils are also shown. The right axis is the estimated bioavailable D/H ratio as described in the article. The black square near the center is the resting heart rate following fasting of 11-13 hours which is believed to measure the D/H ratio in the skeletal fat. This fasting heart rate (HR) is sensitive to average D/H intake, exercise level and medications. The D/H range for tap water in North America is also indicated.

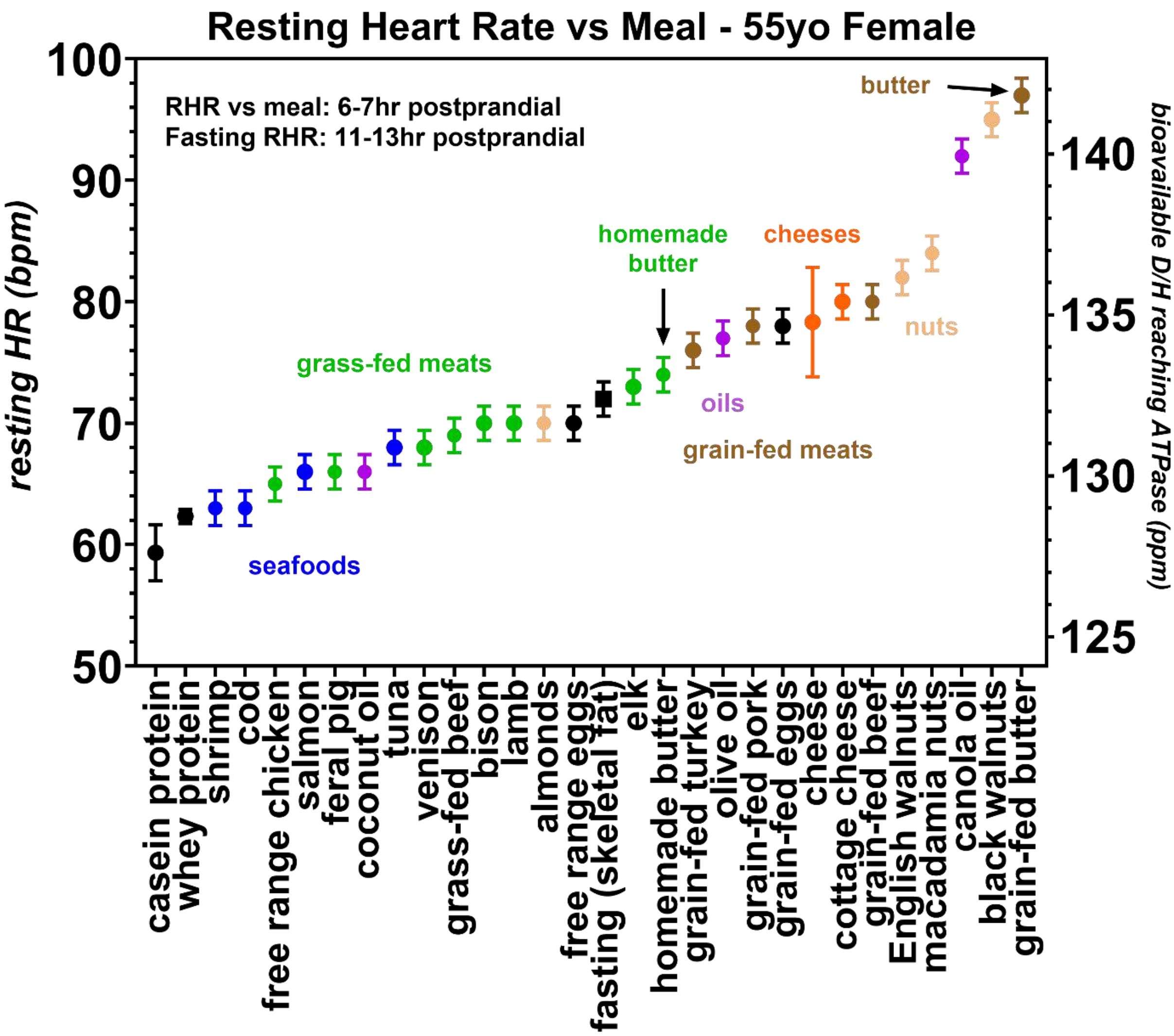

Figure 6. Resting heart rates recorded just prior to awakening over a three-month period from Volunteer 2 (55yo female). Similar to Volunteer 1, the lowest resting heart rates occurred with the protein shakes (black) followed by the grass or naturally-fed meats (green), grain-fed meats (brown), cheeses (orange) and nuts (light brown). Volunteer 2 also lived in a farming community and had access to free range chicken meat, feral pigs, venison and home-made butter. These four categories all fall into the grass- or natural-fed meat range of resting heart rates indicating lower deuterium levels than the commercially available meats. This volunteer had the greatest range in resting heart rates which is believed to be due to her long history of Systemic Lupus Erythematosus (SLE) as discussed in the article.

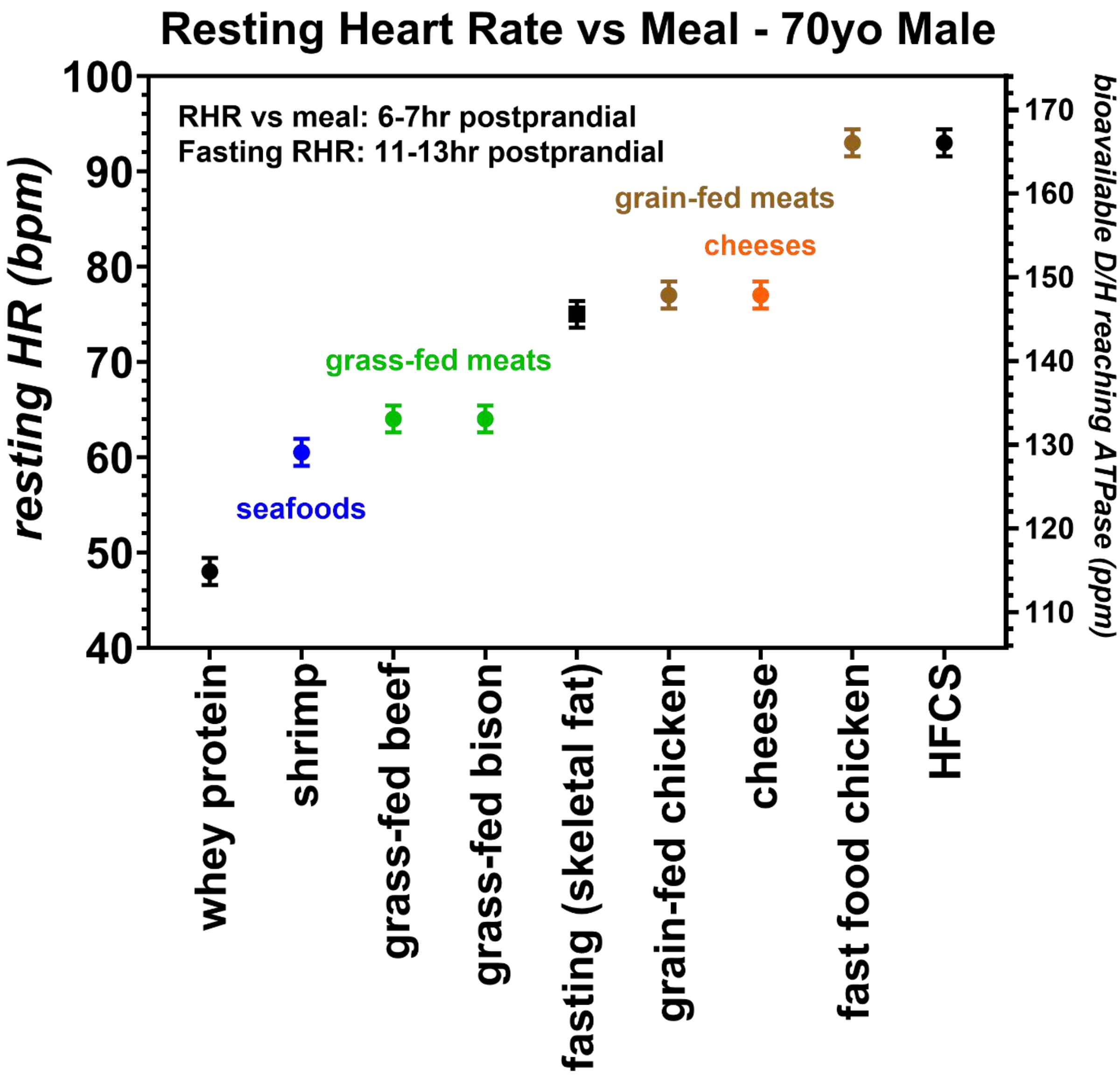

Figure 7. Resting heart rates recorded just prior to awakening over a five-month period from Volunteer 3 (70yo male). Volunteer 3 used an over-the-counter pulse-ox meter just before rising from bed in the mornings. The trend in resting heart rates were lowest in the whey proteins (black) followed by shrimp (blue), grass-fed meats (green), grain-fed chickens (brown), cheeses (orange) and HFCS (black). The estimated bioavailable D/H ratio is also given on the right y-axis. One of the fast food chickens tested led to an elevated resting heart rate suggesting this food may have been prepared with high-deuterium cooking oils or HFCS.

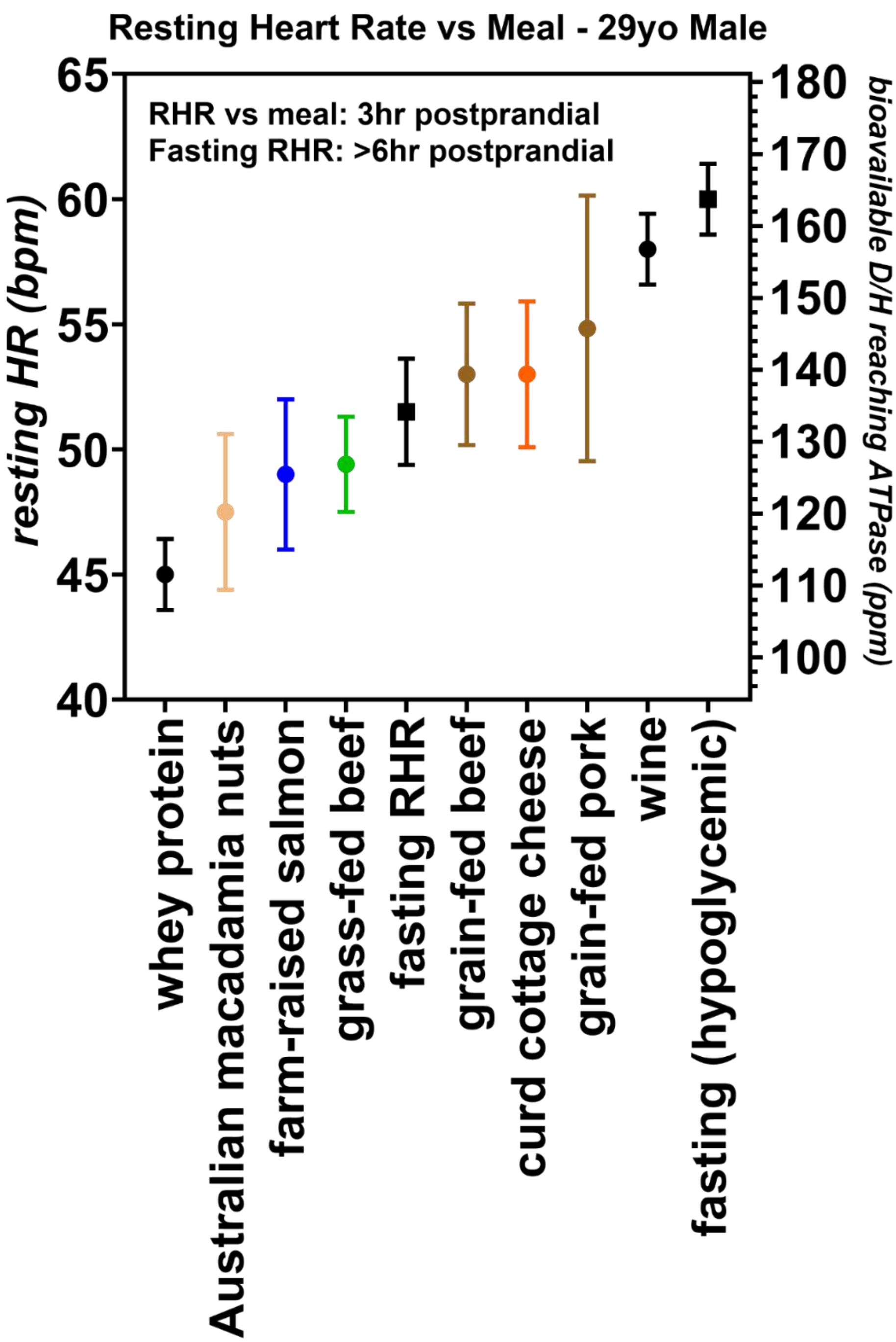

Figure 8. Resting heart rates recorded three hours postprandial over a three-month period from Volunteer 4 (29yo male). This volunteer was the most athletic and youngest of the six volunteers tested. His metabolism was sufficiently high enough that he would be mildly hypoglycemic in the mornings so he would collect the resting heart rates at 3 hours postprandial. His general patterns in resting heart rate trends for the whey proteins, salmon, grass-fed beef and grain-fed porks were the same as the previous three volunteers. His test of Australian macadamia nuts did reveal an unexpected low heart rate and he reported chills after consuming these nuts. It is unclear if these nuts are lower in deuterium due to the exact location of cultivation or some type of allergic reaction. This volunteer also tested some wine and found an increased heart rate that corresponds to a D/H ~ 156 ppm which is the same as mean seawater. His typical fasting hypoglycemic HR values are shown to the right of the figure.

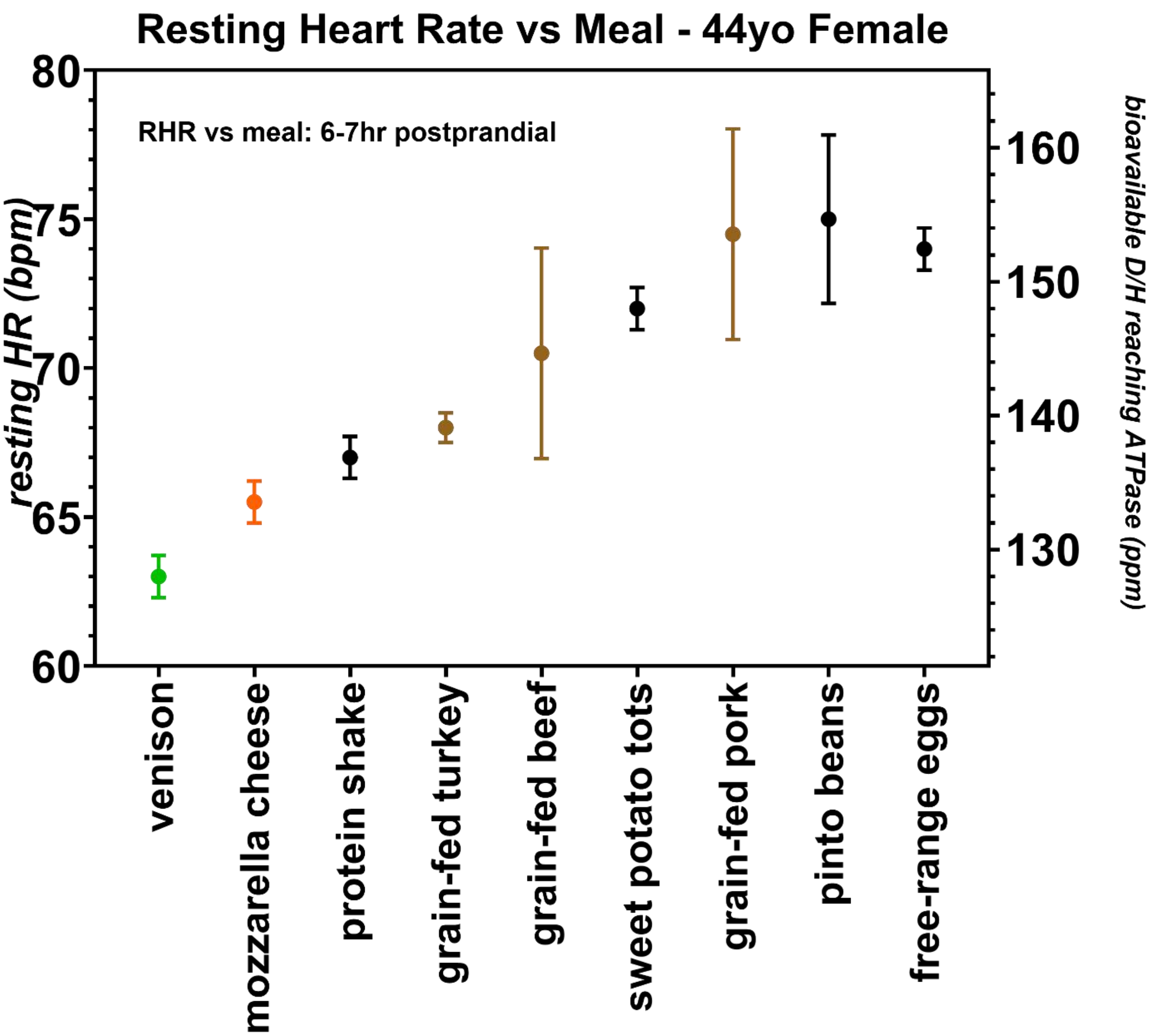

Figure 9. Resting heart rates recorded just prior to awakening over a two-month period from Volunteer 5 (44yo female). This female volunteer tested some naturally fed venison, grain-fed turkey, grain-fed beef and grain-fed pork for the purpose of determining if the resting heart rates varied as greatly as Volunteer 2 who was also female. The calibration slopes were different in these two volunteers ruling out sex as the cause of the increased resting heart rate range in Volunteer 2.

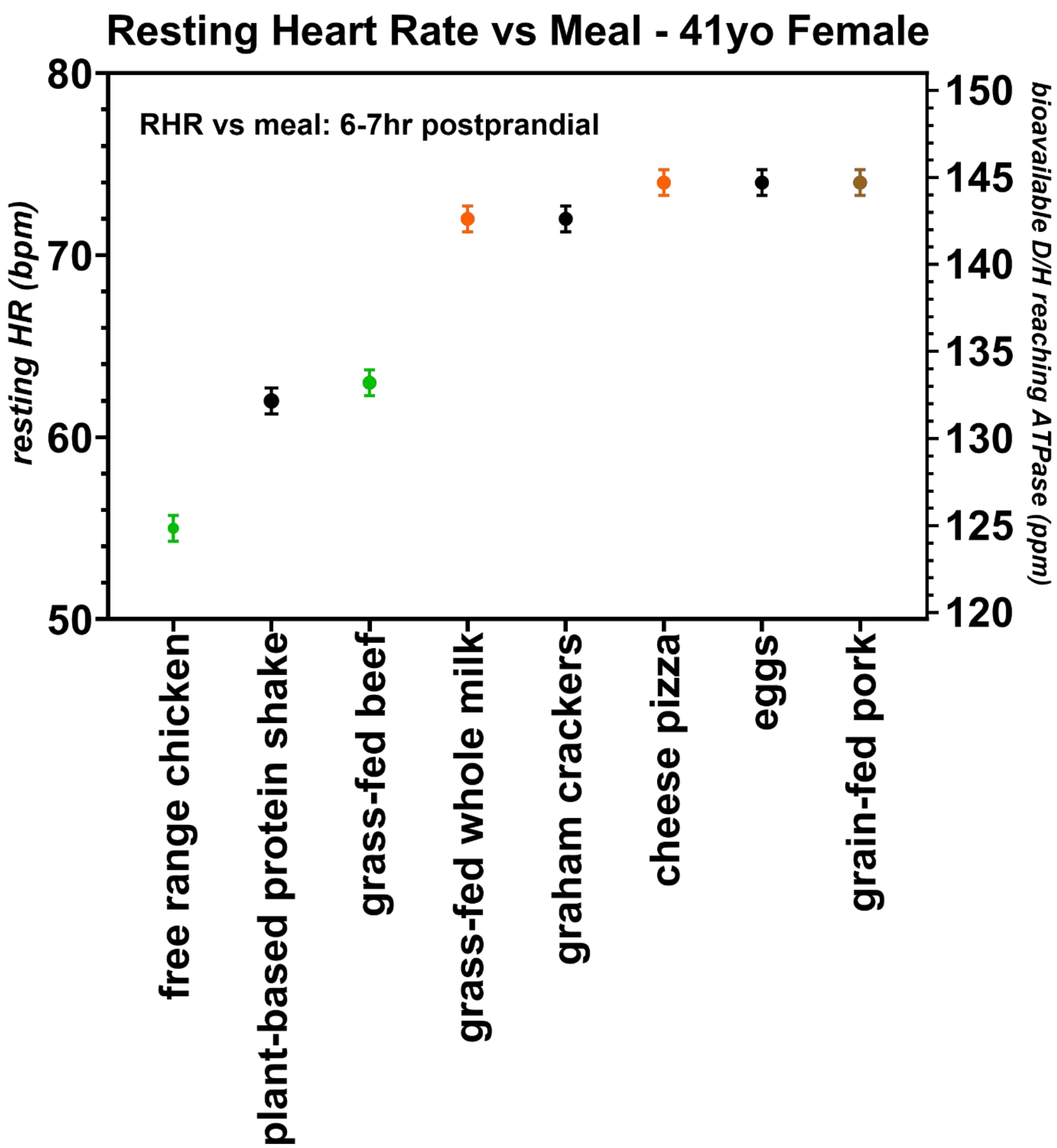

Figure 10. Resting heart rates recorded just prior to awakening over a two-month period from Volunteer 6 (41yo female). This female volunteer was tested and found to have a different heart rate dependence on deuterium from the other volunteers. This volunteer tested free range chicken, grass-fed beef and grain-fed pork and found the same general resting heart rate increase with deuterium level. All six volunteers were found to have unique resting heart rate vs deuterium levels as discussed in more detail in the article.

Intermittent strenuous hiking was also performed by Volunteer 1 who found a loss of 0.045% skeletal fat per kilometer hiked.[12] This was followed by a low carbohydrate intake early in the week to help regenerate the skeletal fat under a ketogenic environment.[16] This is believed to assist at lowering the overall deuterium content stored in the skeletal fat.

Volunteer 3 recalled no episode in his life where a heart rate below 60 bpm was ever recorded. However, after an increased consumption of shrimp and whey protein shakes for two weeks his heart rates began dropping below 59 bpm. Furthermore, a resting heart rate of 47 was recorded following a day where he consumed a total of five whey protein shakes.

No symptomatic hypotensive symptoms were ever observed in any volunteer. Furthermore, all volunteers did notice a slightly larger impulses on their chest during these lower heart rates suggesting higher stroke volumes. This would be consistent with the body builder who developed heart rates dropping to a low of 27 bpm at the time of their body building contest. In that case study, an ultrasound echocardiogram clearly indicated those lower heart rates corresponded with increases in the cardiac stroke volumes.[13]

Using mass spectrometry data with some data obtained from Boros and Somlyai[21], the estimated deuterium levels can be estimated from a linear fit between these published D/H ratios and the recorded resting heart rates for food sources with known deuterium levels. Mass spectroscopy reveals the D/H (deuterium/hydrogen) ratio in a number of foods used in the calibrations in this report: lard 116 ppm, casein protein shake 128 ppm, venison 128 ppm, grass-fed beef/elk fat 128 ppm, pea-based protein shake 129 ppm, extra virgin olive oil 130 ppm, free range chicken 130 ppm, grain-fed turkey 133 ppm, curd cottage cheese 136 ppm, grain-fed pork meat 148 ppm and high fructose corn syrup 166 ppm. These were curve fit to each volunteer's data to obtain the estimated fatty acid D/H level shown at the right axis of the graphs in Figures 5-10 and right column in Figure 7.

Volunteer 1: D/H (ppm) = 1.5791 P + 48.852,
Volunteer 2: D/H (ppm) = 0.3773 P + 105.22,
Volunteer 3: D/H (ppm) = 1.1374 P + 60.28,
Volunteer 4: D/H (ppm) = 3.4786 P – 44.984,
Volunteer 5: D/H (ppm) = 2.2222 P – 12.00,
Volunteer 6: D/H (ppm) = 1.0456 P + 67.334,
where P = resting heart rate.

The differences in the slopes are best explained as differences in autonomic tone of the peripheral vascular system for each volunteer. The healthiest volunteer had the lowest change in resting heart rate with deuterium while the volunteer who has a 30-year history of Systemic Lupus Erythematosus (SLE) had the largest resting heart rate change with deuterium. SLE is well known to adversely impact the peripheral vascular tone.

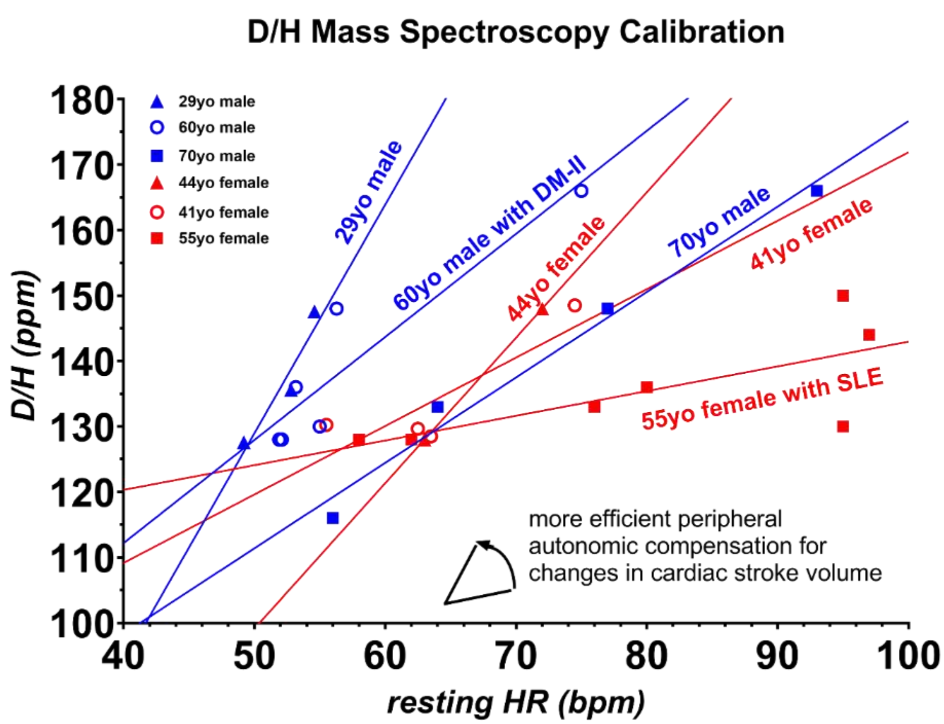

Figure 11. The deuterium calibrations for the six volunteers are shown as the D/H ratio in parts per million deuterium content vs resting heart rates (HR) in beats per minute (bpm). The deuterium content in a number of foods were measured by mass spectroscopy and plotted as a function of recorded resting heart rate in each of the volunteers. The male volunteers are shown as blue and female volunteers are shown as red. All volunteers had different calibration patterns implying differences in the autonomic tone of the peripheral vascular system effects the heart rate. The greatest heart rate range occurred in the volunteer with a long history of Systemic Lupus Erythematosus (SLE) and smallest heart rate range occurred in the youngest, healthiest volunteer.

It is noted that the heart primarily runs from fatty acids which is likely an evolutionary development to provide the heart with the lowest deuterium fuel source. Amino acids also appear to provide the cardiac muscle with an alternative energy source when the other substrates are in lower supply. Deuterium may be located at locations on the amino acids or locations of the fatty acid chains that are not bioavailable to the production of ATP in the mitochondria. The heart rate is believed to be a more sensitive test for determining the actual bioavailability of deuterium seen at the ATPase, while the mass spectroscopy is more sensitive for measuring the true structural D/H level. However, it is unclear how the deuterium in the food that doesn't reach the ATPase effects other functions of the human cellular functioning such as DNA synthesis.

Finally, Volunteer 1 recorded 20 fasting resting heart rates over a ten-month period. The resting heart rates would slowly approach and stabilize at 53.1 bpm after 11-12 hours following the last meal. At that time, all the calories consumed from the meal would be completely consumed placing the volunteer into a fasting state revealing the D/H stored within the adipose tissue. Interestingly, this is also the average resting heart rate made over the previous two months.

4. Discussion of a Model for Cardiac Output

It is well established that cardiomyocytes obtain the majority of their energy from the β-oxidation of fatty acids.[17] The data presented in this report strongly suggest that deuterium ^2H in these fatty acids supplying the heart lower the ATP production rate. A simple model is presented which shows how much the heart rate (pulse) is predicted to change in order to maintain a constant cardiac output as the ATP production rate decreases due to deuterium loading. These predicted changes are calculated separately for both males and females.

Assuming the left ventricle is roughly spherical for the purpose of estimating the stroke volume, the volume of a sphere V from mathematical textbooks is given as

$V = (4/3)\,\pi r^3$, where r = radius of the sphere.

The circumference of the sphere c from mathematical textbooks is $c = 2\pi r$. If the left ventricle is assumed to be roughly spherical, this mathematical circumference is the circumference of the left ventricle. In this model, standard left ventricular volumes of an average healthy person averaged over ages 10-89 are used.[18]

Define V1 = end diastolic volume = 76.8ml ± 15.4ml (male) or 63.9ml ± 14.7ml (female), and V2 = end systolic volume = 27.6ml ± 7.1ml (male) or 22.1ml ± 6.3ml (female).

The cardiac stroke volume ΔV is given as ΔV = V1 – V2. Substituting r with $r = c/2\pi$, the stroke volume of this "standard person" becomes

$\Delta V = (c_1^3 - c_2^3) / 6\pi^2$, where

c_1 = end diastolic ventricular circumference and c_2 = end systolic ventricular circumference.

Define CO = cardiac output per minute = ΔV x P, where

P = pulse in beats per minute (bpm).

Now take patient whose fatty acid deuterium levels are elevated leading to a decrease in ATP production rates. Define e = efficiency of the ATP synthase nanomotors (range 0-1 with 1 = 100% efficiency). The increase in deuterium slows the rate of ATP production which in turn lowers the amount of ca^{++} ions that can be pumped back into the sarcoplasmic reticulum (SR) during diastolic filling.[19] As a result, the stroke volume decreases due to a decrease in end diastolic ventricular circumference. Assuming this decrease is related to the ATP synthase efficiency e in a linear fashion, the values V1 and c1 in our standard patient are replaced by eV1 and ec_1, respectively.

In order for the cardiac output to remain constant, the pulse P has to increase to compensate for a decrease in the stroke volume ΔV = eV1 – V2. Define the standard patient cardiac output as CO and the compensated cardiac output as CO_e. Unless heart failure occurs, CO = CO_e. Also define the standard patient pulse as P and the compensated pulse as P_e. Solving for c_1 and c_2 from the standard volumes[18] above, c_1 = 11.909cm and c_2 = 8.467cm (male) or c_1 = 11.201cm and c_2 = 7.862cm (female). The corrected pulse becomes

$P_e = P \{(c_1^3 - c_2^3) / [(ec_1)^3 - c_2^3]\} = P \{1082 / [(11.909e)^3 - 607]\}$ (male);

$P_e = P \{(c_1^3 - c_2^3) / [(ec_1)^3 - c_2^3]\} = P \{919 / [(11.201e)^3 - 486]\}$ (female).

These equations are plotted in Figure 12 with the pulse P plotted along the x-axis and corrected pulse P_e along the y-axis for various ATP production rate efficiencies which are also color coded from 75% to 100% efficiency. Males are shown as solid lines and females as dashed lines. Note that there is less than a 1% difference predicted for the sexes in healthy patients.

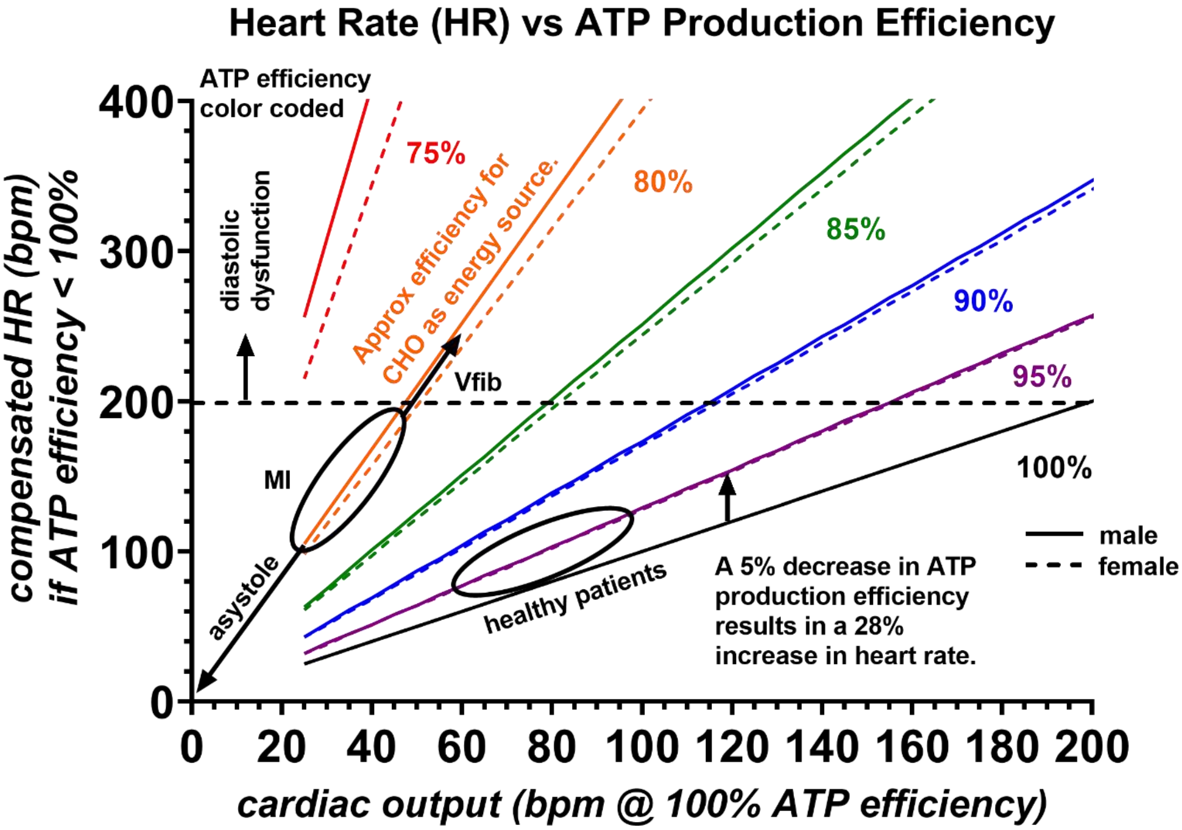

Figure 12. Compensated heart rates (y-axis) needed to maintain various cardiac outputs (x-axis) shown for different ATP production rate efficiencies (colors) assuming no changes occur in peripheral vascular tone. The cardiac outputs are in units of bpm at 100% ATP production efficiency. The vertical arrow indicates a 28% increase in heart rate with a 5% decrease in ATP production rate, e.g. 100% to 95%. Carbohydrates typically contain more deuterium than fatty acids and are estimated to be 20% less efficient at producing ATP (orange). Compensated heart rates > 200 bpm are unsustainable for the dimensions of the human heart due to finite cardiac conduction velocities. This range in heart compensation will lead to diastolic dysfunction over time. When ischemia occurs during a MI, ATP production efficiency drops due to the cardiomyocytes being forced to utilize carbohydrates as a backup energy source via anaerobic metabolism. The higher deuterium levels in carbohydrates increase the compensated heart rates and if this becomes excessive the conduction system cannot fully depolarize the ventricle causing the ventricle to enter a state of contraction fasciculations, i.e. Ventricular fibrillation. If the ATP production suddenly drops due to a energy shift completely into the inefficient lactate cycle, the heart goes into asystole. The region of cardiac output for a resting healthy individual is labelled in the figure. The prediction for males and females are shown as solid and dashed lines, respectively. Compensation in the peripheral vascular system tone will decrease the amount of SA node elevation that will be needed to maintain a constant cardiac output.

It will be pointed out that the left ventricle is better described by a cylinder hemiellipsoid.[20] The volume V_h of a hemiellipsoid is $(2/3)\pi abc$, where a, b and c are the radius along the different axis of the hemiellipsoid. In the human heart, r=a=b and r=c/η, where η is the degree of relative elongation along the longer axis of the left ventricle and a constant. Therefore, $V_h = (2/3)\pi\eta r^3$ where the cubic function in the volume remains. As a result, the calculation for a corrected heart rates for a sphere are the same for the hemiellipsoid.

Changes in the peripheral vascular tone implied from the different D/H calibrations between the six volunteers shown in Figure 11 decrease the amount of compensation required by the SA node pacing needed to maintain constant cardiac output. In other words, individuals with peripheral vascular disease are unable to maintain adequate systemic blood pressure as easily as other individuals as the stroke volume decreases from increasing deuterium levels. As a result, these individuals will show a greater increase in SA node heart rate to maintain adequate cardiac output.

In conclusion, the heart rate is extremely sensitive to the ATP production efficiency due to the cubic function of the ventricular circumference in the mathematical volume equation. This is likely the reason we evolved to use fatty acids as the predominant cardiac energy source since fatty acids tend to be lower in deuterium than carbohydrates.[12] If carbohydrates were the primary energy source, the higher deuterium levels and resulting lower ATP production efficiencies e would lead to very high heart rates. When the heart rates reach the level where complete purkinje depolarization cannot occur within systole, diastolic dysfunction is the result. For healthy individuals, less that a 1% difference in compensated heart rates are expected between the sexes.

5. Conclusions

Heart failure with preserved ejection fraction has been studied by multiple researchers since 2015. The most common stated etiology of this class of heart failure is a decrease in ATP production within the mitochondria.[23-26] However, no specific substrate defect could be identified in any of these studies. Early studies of beef heart identified a decrease in beef heart ATP production with increasing deuterium levels within the mitochondria.[1-3] At the time of these studies, the significance of these discoveries on the health of the cows was mostly unknown. Figure 13 shows the basic metabolic pathways for energy production with the red arrows indicating the higher deuterium level pathways. Black arrows can be either high or low deuterium routes depending on the deuterium content within the fatty acid storage. Blue arrows indicate where deuterium depleted water can enter the metabolic pathways.

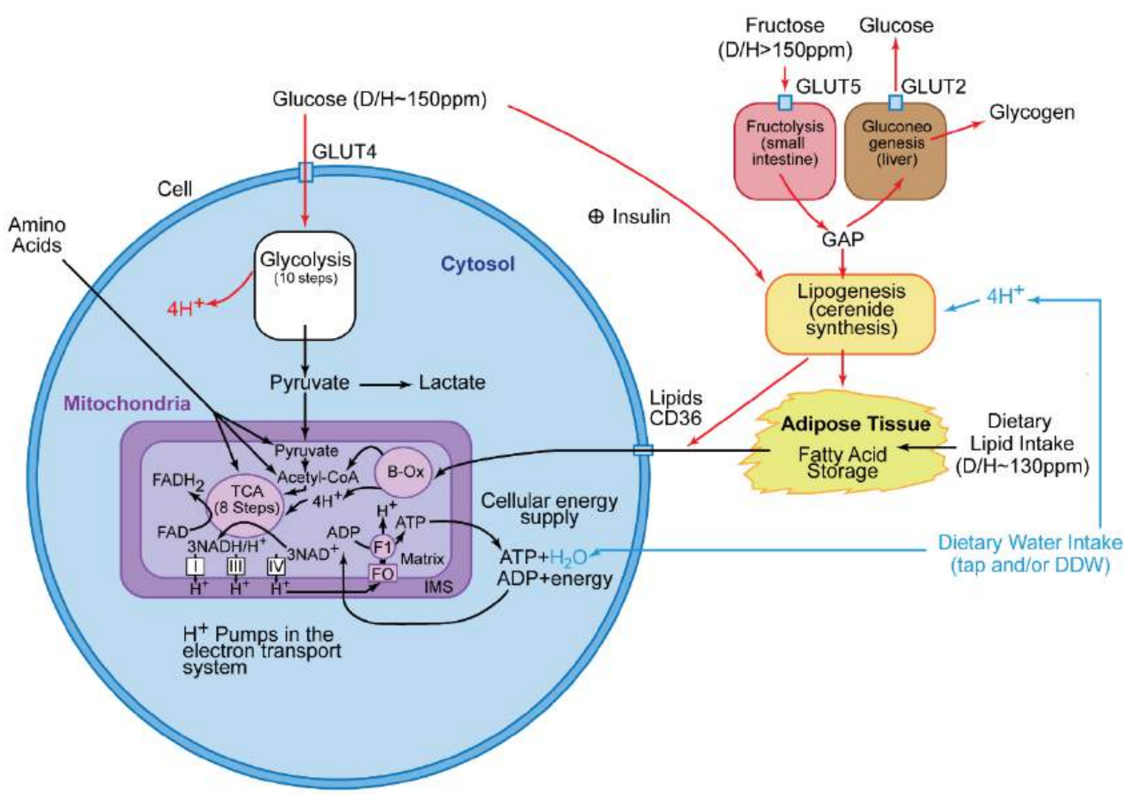

Figure 13. The basic metabolic pathways leading to the ATP production inside the mitochondria. These pathways are found in standard biochemistry textbooks; however, this plot is different in that the high deuterium/hydrogen ratio (D/H) pathways are coded in red whereas the typically lower D/H pathways are coded as black. Furthermore, when deuterium depleted water (DDW) is consumed the very low deuterium enters the metabolism at the pathways coded as blue. In non-insulin resistant individuals or individuals maintaining relatively low carbohydrate intakes, the glucose is primarily processed via the 10-step glycolysis pathway which strips off four hydrogens per glucose molecule having higher deuterium levels, e.g. ~150 ppm for glucose, leading to the pyruvate production. This then feeds the TCA cycle with lower deuterium pyruvate. When glucose intakes are excessive, insulin spikes occur pushing the high D/H glucose towards the production of high deuterium fats, e.g. ceramides. Fructose bypasses this insulin requirement and enters the lipogenesis cycle freely. Notably, high fructose corn syrup is particularly high in deuterium averaging ~166 ppm D/H based on mass spectroscopy.[21] Low deuterium levels are needed in the lipids since lipids ultimately provide a large proportion of the hydrogens that ultimately rotate the ATP nanomotors embedded in the inner matrix membrane of the mitochondria decreasing their efficiency. Typical lipids from healthy fats average ~ 130 ppm D/H ratios as opposed to the unhealthy 150-166ppm D/H ratios found in sugars and high fructose corn syrups.[21] Amino acids can also serve as substrates to pyruvate, acetyl-CoA or the TCA cycle and the entry site is dependent on the specific amino acid involved. Under aerobic conditions, pyruvate enters the TCA cycle and undergoes oxidative phosphorylation leading to a net production of 32 ATP molecules. Under anaerobic conditions or high mitochondrial deuterium levels stalling the ATP nanomotors, pyruvate converts to lactate through anaerobic glycolysis in the cytoplasm only resulting in the production of 2 ATP molecules. This also lowers the cytoplasm pH which is believed to contribute to cancer,[7-10;27] metabolic disorders including diabetes[11-12] and diminished immunity.[28]

In the current study, both the resting heart rate and exercise heart rate of a volunteer recorded over a 35-year period are presented. The data clearly show that upon adopting a keto cycling diet,[16] i.e., switching the primary energy source from carbohydrates to fats, lowered both the resting and exercise heart rates. Fats are also known to be lower in deuterium than carbohydrates as found in mass spectroscopy.[11,12,15;21] These findings alone suggest that increases in the cardiac ejection volumes with deuterium depletion occurs since the blood pressures remain normal. These findings also suggest deuterium as the etiology of the heart failure with preserved ejection fraction studied by cardiac researchers.[23-26] At high levels of deuterium oxide exposure, mongrel dogs were found to develop stone hearts during cardiopulmonary bypass surgeries in 1984.[29]

A study looking at the specific effect of various foods on the resting heart was designed to further elucidate the effect of deuterium on these cardiac findings. Six volunteers recorded resting heart rates for comparison to the foods consumed during the previous meal. Volunteer 1 used a 30 second ECG monitor to record the heart rate while Volunteers 2-6 used a pulse oximeter to record the heart rate. The results showed the general trend in resting heart rates for all six volunteers:

casein protein < whey protein < seafoods < grass-fed animals < cheese<grain-fed animals < grain-fed butter < high fructose corn syrup,

with the grain-fed butters being in the range of tap water. The deuterium levels in these food groups do trend in the same direction with the mass spectroscopic findings of the D/H ratios[21] with grass-fed animal meats being lower in deuterium than the grain-fed animal meats which is expected from other deutenomics studies.[30] However, there is an exception in this trend in regards to butter. The D/H ratio reported in butter is 124 ppm,[21] but, the resting heart rates are relatively higher in the commercially available butter compared to the home-made butter tested by Volunteer 2. Differences in these resting heart rates with different butter types suggest different hydrogenation levels incorporated during the manufacturing process. Seafoods and grass-fed animal meats show lower resting heart rates and these are known to generally have lower deuterium levels as measured by mass spectroscopy.[21] These foods are also higher in the omega-3 fatty acids suggesting a possible link between the need of lower deuterium to biochemically produce these omega-3 fatty acids. The findings also suggest an excessive consumption of carbohydrates, high fructose corn syrup and grain-fed animal meats are likely contributing to the development of heart failure in individuals with preserved ejection fraction.

Differences in the rate of heart rate increase with substrate deuterium level between the six volunteers strongly suggest peripheral vascular tone also plays a role in heart failure. In individuals with peripheral vascular disease, the peripheral vascular tone is less able to compensate for decreases in cardiac stroke volumes with increasing deuterium levels. As a result, the SA node compensation is more pronounced in these individuals increasing the rate of heart failure.

The distribution of deuterium within the substrate is a likely a determinant of the relative bioavailability of deuterium reaching the ATP nanomotor. This could explain why many butters sampled led to higher heart rates despite having lower D/H as measured by mass spectroscopy.[21] Interestingly, deuterium NMR was used to determine the relative deuterium depletion at the C(2) position in carbon bound hydrogens of glucose taken from various parts of bean and spinach plants.[31] The authors found that the deuterium was found to vary depending on which part of the plant was sampled. It is possible that deuterium is less likely to favor the carbons that share a double bond with an adjacent carbon. If true this would explain why omega-3 fatty acids have less deuterium than the omega-6 fatty acids as measured by mass spectroscopy.[21] Therefore, while the mass spectroscopy provides good guidance as to the deuterium levels in foods the final evaluation of metabolic impact of deuterium should be determined by the actual effect of foods on the resting heart rate.

Different responses in heart rate to different amino acid production sources suggest that amino acids are feeding the TCA cycle in the cardiomyocytes as a substrate. The substrate entry points depend on the specific amino acid involved and these entry points are discussed in standard biochemistry textbooks. Most volunteers have found their energy levels can be maintained throughout the day with a high intake of whey and/or casein protein. Volunteer 1 has also found that both exercise and resting heart rates decrease following the consumption of high protein, low carbohydrate, low fat protein shakes. On the contrary, the consumption of L-glutamine was found to increase the resting heart rate rather than decrease the heart rate. L-glutamine, the most common amino acid found in meat, is produced by bacterial fermentation of glucose suggesting a different D/H value than the D/H level found in protein shakes. This difference in heart rate response is strongly suggesting these amino acids are being directly utilized by the TCA cycle as a substrate in the heart.

Athletes, including body builders and long distance endurance cyclists, routinely experience low resting heart rates during training.[32] The data presented here strongly suggest that the high intake of whey/casein protein are partly responsible for these low heart rates. Around the time of a body building contest one case report reports resting heart rates as low as 27 bpm and ultrasonography shows this corresponds to significant increases in cardiac stroke volumes.[13;33] Low deuterium in the energy substrate is the likely the true cause for these low heart rates in athletes rather than increased vagal tone sometimes taught in medical schools. The cyclical burn off of skeletal fat with intermittent strenuous exercise also assists at eliminating the higher deuterium stored body fats.

A special case of increased heart rates can be found among alcohol users. Many people who use alcohol have been found to have elevated heart rates.[34] Volunteer 4 did record a relatively higher resting heart rate following the consumption of wine. These heart rates likely reflect the deuterium load that occur in the alcohol molecule which is produced by the fermentation of high deuterium sugars, rice, corn and potato starches. A deuterium load placed on the liver during the metabolism of any high deuterium alcohol is likely contributing to the hepatocyte damage that occurs in the alcohol use disorders. Recently researchers in China have begun studying the effect of deuterium depleted alcohol in lab rats to better elucidate these cellular damage mechanisms.[35]

Our hearts have likely evolved to use fatty acids as the primary fuel rather than carbohydrates because fatty acids are generally found to be lower in deuterium content than plant storage sugars.[21] As suggested in the data presented here, amino acids can also be utilized by the heart if readily available. Furthermore, high-deuterium toxic ceramides, especially those made from fructose sources are believed to accumulate over a life time especially in sedentary individuals. These ceramides gradually increase the heart rate with age and once the cardiac conduction system can no longer provide the impulses to keep the muscle contracting in synchrony heart failure is said to occur. A good exercise program can help burn off these high deuterium ceramides helping keep them below the toxic levels found in heart failure with preserved ejection fraction.

Deep space missions will need to consider the level of deuterium in the foods consumed because the deuterium will ultimately increase the D/H ratio ending up in the waste water that must be recycled back into drinking water. Due to the increased risk of heart failure, cancer,[7-10,27] metabolic disorders,[11-12] and decreased immunity[28] with increasing deuterium levels, success of long space missions will depend on maintaining low deuterium levels in the food eaten by the crew.

Finally, the use of resting heart rate data is a technique that brings deuterium food analysis into every household without the need of expensive mass spectroscopic testing. Such testing offers a simple means for people to improve their diets to optimize their health status thereby improving their longevity. The increase in longevity reported in low resting heart rates[14] is likely the result of lower systemic deuterium levels.

Consent: A written informed consent was obtained from the six volunteers for publication of this report.

Author's Contributions: Analysis of the deuterium depletion data, ECJ and JEP; endocrinology guidance, CLJ. All authors have read and agreed to the published version of the manuscript.

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Abbreviations: CHO = carbohydrates; CRP = C-reactive protein; D = deuterium; DDW = deuterium-depleted water; D/H = deuterium hydrogen ratio; DM-II = type-II diabetes mellitus; ^1H = protium hydrogen isotope; ^2H = deuterium hydrogen isotope; NMR = nuclear magnetic resonance; $\tau_{1/2}$ = half-life.

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