# A Mathematical Model for β-Thalassemia

**Team β AF**

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# 1 Executive Summary

β-thalassemia is a hereditary blood disorder that causes anemia and leads to approximately 25,000 deaths every year [1]. Our team has developed a multi-unit mathematical model of blood flow in individuals with and without β-thalassemia. The steady-state model utilizes mass balance equations and constituent percentages in order to calculate flow rates and concentrations of key blood components: red blood cells, hemoglobin A, other hemoglobin, oxygen, carbon dioxide, and iron (free flowing and stored in the liver). These components were tracked through organs that are significantly affected by β-thalassemia: the brain, liver, lungs, spleen, gastrointestinal tract, and bone marrow. In our model, blood flows continuously through the body. For the dynamic model, the steady-state model was perturbed in order to simulate the change in component flow rates and concentrations due to β-thalassemia. The dynamic model is able to simulate the three possible severities of β-thalassemia — major, intermedia, and minor — which makes the model tunable for varying severity levels. The model also tracks the time when the concentration of hemoglobin to the brain reaches dangerous levels and thus can be used to recommend a date for blood transfusion, which is important for ensuring that the β-thalassemic patient is treated in time before they develop serious complications or even die. For β-thalassemia major, our model calculates the time it takes after a blood transfusion for a patient to become cognitively impaired to be 44.6 days and for a patient to die to be 57.0 days. Additionally, our model shows that β-thalassemia intermedia and minor patients do not become cognitively impaired or die. Overall, our models adaptability to varying β-thalassemia severities, warning of dangerous hemoglobin levels to the brain, and illustration of the dynamic changes in key blood

components and organs of the body can significantly aid the monitoring and treatment of thalassemic patients symptoms as well as the development of more effective medications and treatments for individuals suffering from β-thalassemia.

# 2 Introduction

Anemia, or the lack of healthy red blood cells, is a medical condition that affects approximately 1.6 billion people, or 24.8% of the worlds population [2]. This disease has many variations, causes headaches, fatigue, and dizziness, and can lead to serious complications of the heart [3].

Thalassemia is an example of a slow, chronic, hemolytic anemia that causes approximately 25,000 deaths every year [4]. It is genetically inherited; a defect in globin producing genes causes a decrease in the rate of production of either α- or β-globin proteins, leading to a decrease in hemoglobin levels in the blood. Subsequently, this causes red blood cells to be destroyed faster than the bone marrow can produce them [5]. As it affects the production of hemoglobin, the oxygen carrying component of the red blood cell, β-thalassemia can have serious effects on oxygen delivery to organs. If left untreated, blood cells eventually break down at a rate that causes accumulation of iron in the patients liver and other organs [6]. This may lead to tissue damage, growth retardation, diabetes, and heart failure [6]. This is especially problematic because thalassemia is often misdiagnosed as iron deficiency anemia, and patients are often prescribed iron supplements that may worsen their condition [6].

There are two main types of thalassemia, α- and β-thalassemia, where either the α-globin genes or the β-globin genes, respectively, are affected. β-thalassemia, specifically, is classified

in one of three severities: minor, intermedia, and major [7]. β-thalassemia was chosen as the disease of focus because it has a wide range of severities which are inadequately covered by current research [7]. By modeling β-thalassemia, we are able to better manage current treatment of afflicted individuals.

By modeling essential organs affected by β-thalassemia — lungs, brain, spleen, liver, gastrointestinal (GI) tract, and bone marrow — and tracking crucial blood components — red blood cells (RBCs), hemoglobin A, other types of hemoglobin, oxygen, carbon dioxide, and iron — we can gain a better understanding of the differences between a healthy patient and a β-thalassemic patient. With this model, doctors or pharmaceutical companies will be able to determine which blood component rates in which organs are most affected by each severity of β-thalassemia. This information could lead to better management of current treatments including the frequency at which patients need blood transfusions.

# 3 Justification of Components

Our model tracks the following key components: red blood cells (RBCs), hemoglobin A, other hemoglobin (hemoglobin $A_2$ and hemoglobin F), oxygen ($O_2$), carbon dioxide ($CO_2$), and iron (free flowing iron and iron stored in the liver).

The body creates approximately 200 billion red blood cells per day which are responsible for the transport of $O_2$. Moreover, RBCs take in the waste product, $CO_2$, so that it can be exchanged in the lungs for $O_2$.

$O_2$ binds to hemoglobin, and without sufficient hemoglobin levels, cells throughout the body cannot receive enough $O_2$ to function properly. β-thalassemia reduces hemoglobin pro-

duction which, in turn, causes anemia. This insufficient supply of red blood cells in the body leads to increased risk of complications such as diabetes, heart failure, arrhythmia, and hypothyroidism as well as increased risk of mortality [7-8]. Approximately 97% of hemoglobin produced in healthy individuals is hemoglobin A, which is made up of two α-globin proteins and β-globin proteins [9]. However, the 3% of other hemoglobin (hemoglobin $A_2$ and F) are produced to an even greater extent in individuals with β-thalassemia. Hemoglobin $A_2$ is made up of two α-globin proteins and two δ-globin proteins [9]. Hemoglobin F, fetal hemoglobin, is made up of two α-globin proteins and two γ-globin proteins. Increasing severity of β-thalassemia correlates with increasing production of hemoglobin F [10]. Furthermore, individuals with β-thalassemia major produce no hemoglobin A and around 95-100% hemoglobin F [11]. Individuals with β-thalassemia minor have around 90-95% hemoglobin A, and individuals with β-thalassemia intermedia have approximately 30-50% hemoglobin A [11]. In practice, individuals with hemoglobin A levels between 5% and 90% are classified as having β-thalassemia intermedia. Therefore, tracking hemoglobin A, $A_2$, and F allows us to differentiate between the different severities of β-thalassemia. Additionally, tracking hemoglobin is important because it is necessary for the supply of $O_2$ to the cells.

Oxygen is necessary for aerobic cellular respiration. Because β-thalassemia decreases hemoglobin production, the supply of oxygen throughout the body decreases as well, leading to complications such as heart failure and death. Furthermore, $CO_2$ is the byproduct of cellular respiration and causes pH complications if not removed from the blood stream via gas exchange in the lungs [12].

In individuals with β-thalassemia, iron accumulates in organs due to blood transfusions and increased iron absorption by the gastrointestinal tract [13]. Since the body lacks the

means to excrete this excess iron, these individuals are at risk for developing iron-induced injuries in organs such as the liver, pancreas, and heart. Another important note is that iron is necessary for the production of RBCs. Free flowing iron bound to transferrin in the bloodstream and stored iron in the liver were tracked separately. Free flowing iron was tracked in order to show that it remains constant in all severities of β-thalassemia even though stored iron accumulates mostly in the liver. The significance of our selected components is summarized in Table 1 below.

Table 1: Summary of the Importance of our Mathematical Model's Selected Components

| **Components** | **Importance** |
|---|---|
| Red Blood Cells (RBCs) | Transport oxygen and carbon dioxide throughout the body. |
| Hemoglobin A | Located in red blood cells, binds to $O_2$ to be transported throughout the body. |
| Other Hemoglobin | Indicates the severity of β-thalassemia, since the production of hemoglobin $A_2$ and F increases with increasing β-thalassemia severity. |
| $O_2$ | Used in cellular respiration in order to create ATP necessary for cell function. |
| $CO_2$ | Waste product of cellular respiration that causes pH imbalance if not removed from the bloodstream by the lungs. |
| Iron (Fe) | Used to create RBCs. Although Fe is over accumulated in thalassemic patients, free Fe will remain constant. |

# 4 Justification of Units

In order to accurately simulate blood flow throughout the body in healthy and thalassemic individuals, our model includes the following key organs: the heart, lungs, brain, spleen, bone marrow, gastrointestinal (GI) tract, and liver.

The heart facilitates the transportation of blood components to and from the organs through cyclic pumping. It acts as a splitter by pumping blood and its key components to and from the organs throughout the body in order for cellular respiration and the production and destruction of RBCs to occur. Additionally, the heart acts as a mixer when the blood returns to the heart from the key organs.

The lungs, where gaseous exchange takes place, is also of importance in our model. Blood gets oxygenated while flowing through the capillaries, and carbon dioxide, the waste product of cellular respiration, is removed.

The brain directs and manages all processes necessary for human life. In the brain, oxygen from the blood is consumed and carbon dioxide is generated through cellular respiration in order to keep the body functioning properly. The brain requires a minimum of approximately 35 mL of $O_2$ per minute; if $O_2$ supply falls below this level, this could result in cerebral hypoxia, leading to severe brain damage and even death (Appendix B.2 Table 5) [14].

The spleen removes old and damaged red blood cells along with hemoglobin and recycles the iron bound to the hemoglobin back into the bloodstream [15]. This recycled iron is then used by the bone marrow to produce new hemoglobin.

The bone marrow is the site of red blood cell and hemoglobin production in the body [16]. Iron both absorbed by the GI tract and recycled from destruction of hemoglobin in the spleen is used to make new hemoglobin and in turn, functional red blood cells [17]. This maintains constant levels of red blood cells, hemoglobin, and iron in the body. In individuals with β-thalassemia, the lack of oxygen delivery to organs results in increased production of red blood cells, but mutations in the β-globin genes result in decreased hemoglobin A production.

All of the blood that leaves the GI tract flows to the liver [17]. The liver stores excess

iron in order to maintain constant iron levels in the bloodstream. Since the GI tract absorbs iron from the individuals diet, it contributes to the iron level in the blood flowing to the liver [17]. However, individuals with β-thalassemia have three to four times greater rates of iron absorption by the GI tract resulting from hypoxia [13]. This increased absorption of iron contributes to iron overload in the liver [18]. Consequently, it is important to take into account the GI tract and the liver and their roles in the absorption of iron. The significance of our selected units is summarized in Table 2 below.

Table 2: Summary of the Importance of our Mathematical Model's Selected Units

| **Unit (Organ)** | **Importance** |
|---|---|
| Heart | Pumps blood and acts as a splitter and mixer. |
| Lungs | Supplies the bloodstream with $O_2$ necessary for cellular respiration and removes the waste product, $CO_2$. |
| Brain | Requires a certain level of oxygen in order to keep the body functioning properly. |
| Spleen | Removes RBCs and recycles iron attached to hemoglobin for RBC production [15]. |
| Bone Marrow | Produces new RBCs and hemoglobin. |
| GI Tract | Absorbs iron used to form RBCs. |
| Liver | Stores iron and releases it into the blood when needed for processing hemoglobin. |

# 5 Basic System for Code

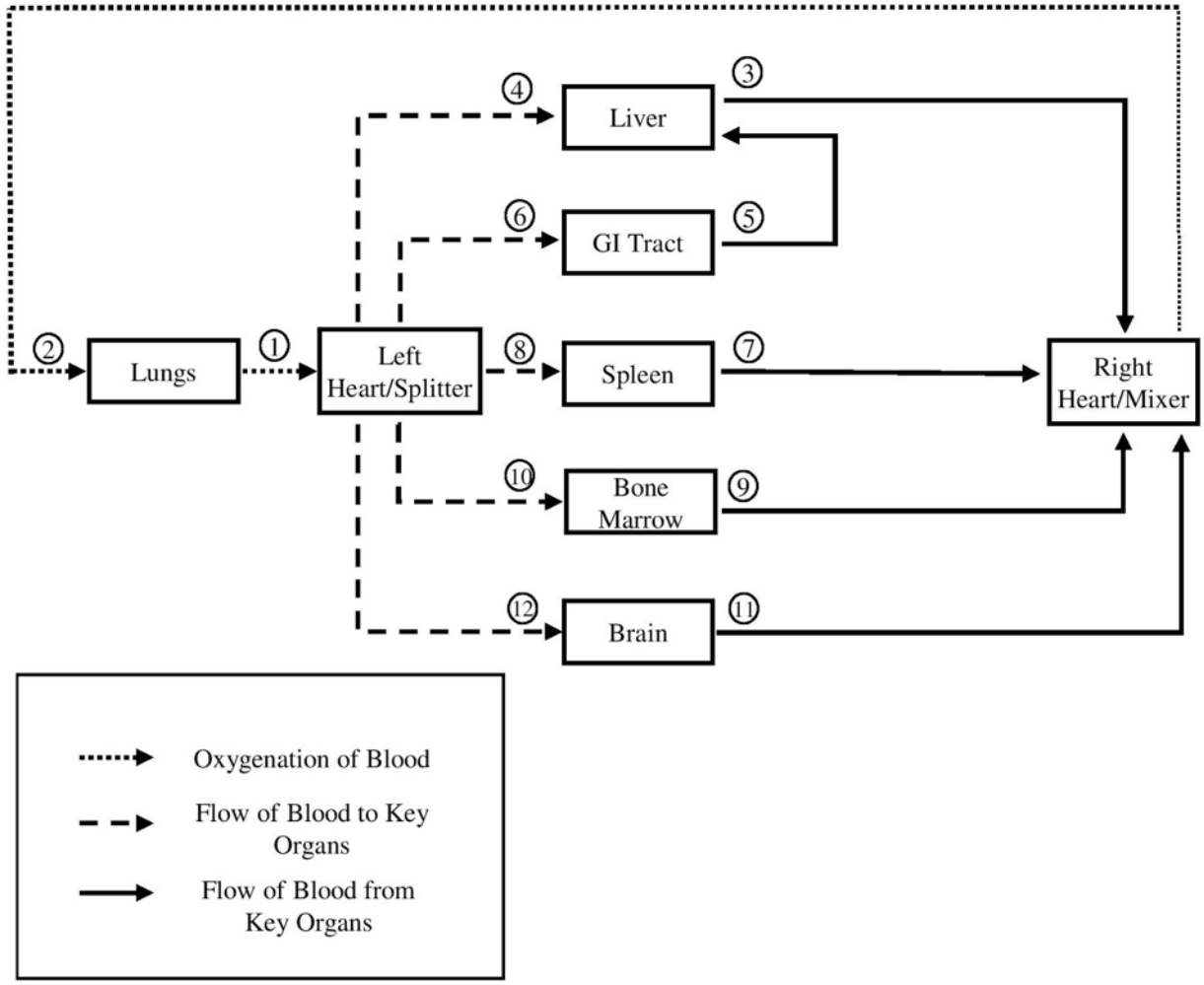


Figure 1: Multi-Unit System Stream Diagram of Blood Flow through Selected Organs of an Average 70 kg Adult Male

The seven key organs are modeled using a multi-unit system that contains twelve streams (Figure 1). For simplicity, our model simulates blood flow through the body of a 70 kg adult male. We assumed that the components tracked will not change in the heart and that the volumetric flow rates of blood in and out of each organ are the same. The model tracks the circulation of key blood components in three main steps: (1) oxygenation of blood, (2)

flow of blood to key organs, and (3) flow of blood from key organs back to the heart. This circulation of key blood components through the three step process takes one minute and constitutes one cycle. For simplicity, even numbered streams go out of the heart, and odd numbered streams go either into the heart, or in the case of stream 5, into the liver.

1. Oxygenation of Blood

   The first step, the oxygenation of blood, begins in the right side of the heart. The deoxygenated blood in the right side of the heart first goes to the lungs (stream 2). In the lungs, the metabolic waste product, $CO_2$, is exchanged for $O_2$ between the alveoli and capillaries. Afterwards, the newly oxygenated blood is sent to the left side of the heart (stream 1).

2. Flow of Blood to Key Organs

   The second step involves the flow of oxygenated blood from the heart to the organs where the blood components undergo generation and consumption specific to each organ. The left side of the heart acts as an ideal splitter that outputs streams of identical component composition to the liver (stream 4), GI tract (stream 6), spleen (stream 8), bone marrow, (stream 10) and brain (stream 12).

3. Flow of Blood from Key Organs Back to Heart

   During the third step, the deoxygenated blood from the liver (stream 3), spleen (stream 7), bone marrow, (stream 9) and brain (stream 11) return to the right side of the heart, which acts as an ideal mixer. Separately, the deoxygenated blood from the GI tract goes to the liver rather than the heart (stream 5). Afterwards, the process restarts from the first step, the oxygenation of the blood.

The code contains a driver function and nine other functions. Seven of these nine other functions represent the seven organs modeled. The inputs for each of the seven organ functions are the flow rates of the blood components entering each organ. In each function, some or all of the component levels change to model each organs function. These changed values are the output of each function. The eighth function, "oxygenator," calculates the amount of oxygen supplied to the streams from the heart, using the total amount of hemoglobin in the blood (both hemoglobin A and other hemoglobin) multiplied by the oxygen carrying capacity of hemoglobin, 1.34 mL of $O_2$ per gram of hemoglobin [15]. The last function, "getvalues," uses an input of severity of β-thalassemia and returns a variety of values, such as red blood cell lifespan and rate of iron absorption in the GI tract, for the provided severity level. These values are used by the organ functions to calculate the changes in components for different severity levels. Although the code itself is tunable to any time period of interest, we chose to model 86401 cycles, which is equivalent to the number of cycles of blood circulation in the body over two months. Total values of components were then plotted for steady-state and dynamic models to compare the levels of each tracked component in healthy individuals versus the levels in individuals with β-thalassemia.

## 5.1 Steady-State Model

In the steady-state model, the sum of all input, output, generation, and consumption terms is zero, meaning the accumulation term is zero as well. Therefore, none of the observed components change over time.

Total red blood cell count is maintained in the healthy model because the rate of red

blood cell production in the bone marrow, 150,000,000 red blood cells per minute, equals the rate of red blood cell destruction in the spleen (see Appendix B.6 Table 33). Since hemoglobin A and other kinds of hemoglobin are produced and destroyed at the same rate as red blood cells, concentrations of hemoglobin A and other hemoglobin remain constant.

Because hemoglobin is the primary oxygen carrying protein in the blood, maintaining constant levels of hemoglobin in the steady-state model means that the arterial oxygen content is constant as well. Since we assume a constant metabolic rate, there is no change in venous oxygen content, which also means that the change in carbon dioxide is constant.

Free flowing iron levels are also maintained at a constant level. There is no net increase in iron absorption in the GI tract because the same amount of iron is absorbed per day and leaves the GI tract. Because the rate of hemoglobin production and destruction are equal, there is no net change in free flowing iron levels.

## 5.2 Dynamic Model

The dynamic model, which addresses β-thalassemic patients, follows the same setup as the steady-state model and involves the same three steps. The model simulates the conditions immediately after a blood transfusion. For β-thalassemia major and intermedia, the initial levels of all components were set to those of a healthy individual, with the exception of total hemoglobin levels. Because the purpose of the model is to determine the frequency of blood transfusions in individuals with β-thalassemia, the total hemoglobin levels, the same constituent percentage of hemoglobin in the healthy model, were set to 12 g/dL, the target hemoglobin concentration in β-thalassemic individual [19]. Thus, setting

the hemoglobin levels to be the same as those following a blood transfusion allows the model to accurately predict when a consequent blood transfusion is necessary. Since individuals with β-thalassemia minor are not dependent on blood transfusions, the model sets all component levels as the same as those for the healthy model, in order to show the differences in component levels between healthy individuals and individuals with β-thalassemia minor. Considering β-thalassemia intermedia constitutes the wide range between major and minor, we assumed the red blood cell lifespan of β-thalassemia intermedia to be 67 days, the average lifespan between major and minor (Table 3).

Table 3: Initial Total Hemoglobin Level for Different Severities of Thalassemia

| **Severity of Thalassemia** | **Initial Total Hemoglobin Level (g/dL)** | **Average Red Blood Cell Lifespan (Days)** |
|---|---|---|
| **Minor** | 14.96 [15] | 120 [19] |
| **Intermedia** | 12 [19] | 67 |
| **Major** | 12 [19] | 14.5 [20] |

Furthermore, our code for the dynamic model also outputs the number of days after receiving a blood transfusion in which a β-thalassemic individual would become cognitively impaired and in which a β-thalassemic individual would die, if those states are reached in the specified time period. The model compares the total hemoglobin levels in the brain with 26.9 g/min in order to give the estimated death time for the patient and the hemoglobin level in the brain with 42.0 g/min to predict the cognitive impairment time (Appendix B.8 Table 41).

# 6 Results

Our steady state model for a healthy individual plots all constant component levels in each organ. Some selected component values are listed in Table 4 below.

Table 4: Selected Component Values for Healthy Individuals

| | $\mathbf{O_2}$ $\left(\mathbf{mL/min}\right)$ | **RBC Count** $\left(\times 10^{\mathbf{12}}\mathbf{/min}\right)$ | $\mathbf{H_A}$ $\left(\mathbf{g/min}\right)$ | $\mathbf{H_{Other}}$ $\left(\mathbf{g/min}\right)$ | $\mathbf{CO_2}$ $\left(\mathbf{mL/min}\right)$ | **Free Fe** $\left(\mathbf{mg/min}\right)$ | **Fe Stored (g)** |
|---|---|---|---|---|---|---|---|
| **Liver** | 60.1 | 1.56 | 43.5 | 1.35 | 155 | 0.270 | 0.254 |
| **Spleen** | 15.4 | 0.400 | 11.2 | 0.346 | 39.9 | 0.0693 | 0 |
| **Bone Marrow** | 50.1 | 1.30 | 36.3 | 1.12 | 129 | 0.225 | 0 |
| **Brain** | 140 | 3.64 | 102 | 3.14 | 363 | 0.630 | 0 |
| **GI Tract** | 210 | 5.46 | 152 | 4.71 | 544 | 0.945 | 0 |

Since each of these three separate severities of β-thalassemia creates a significant difference in component outputs from our model, we plotted each component and unit for each type of severity.

## 6.1 Stored Iron versus Free Flowing Iron

In our model, we tracked both free flowing iron and stored iron in order to show how these component levels change throughout the body. In β-thalassemia, iron accumulates in the liver over time because the rate of iron entering the liver is greater than the rate of iron leaving the liver through the bloodstream [7].

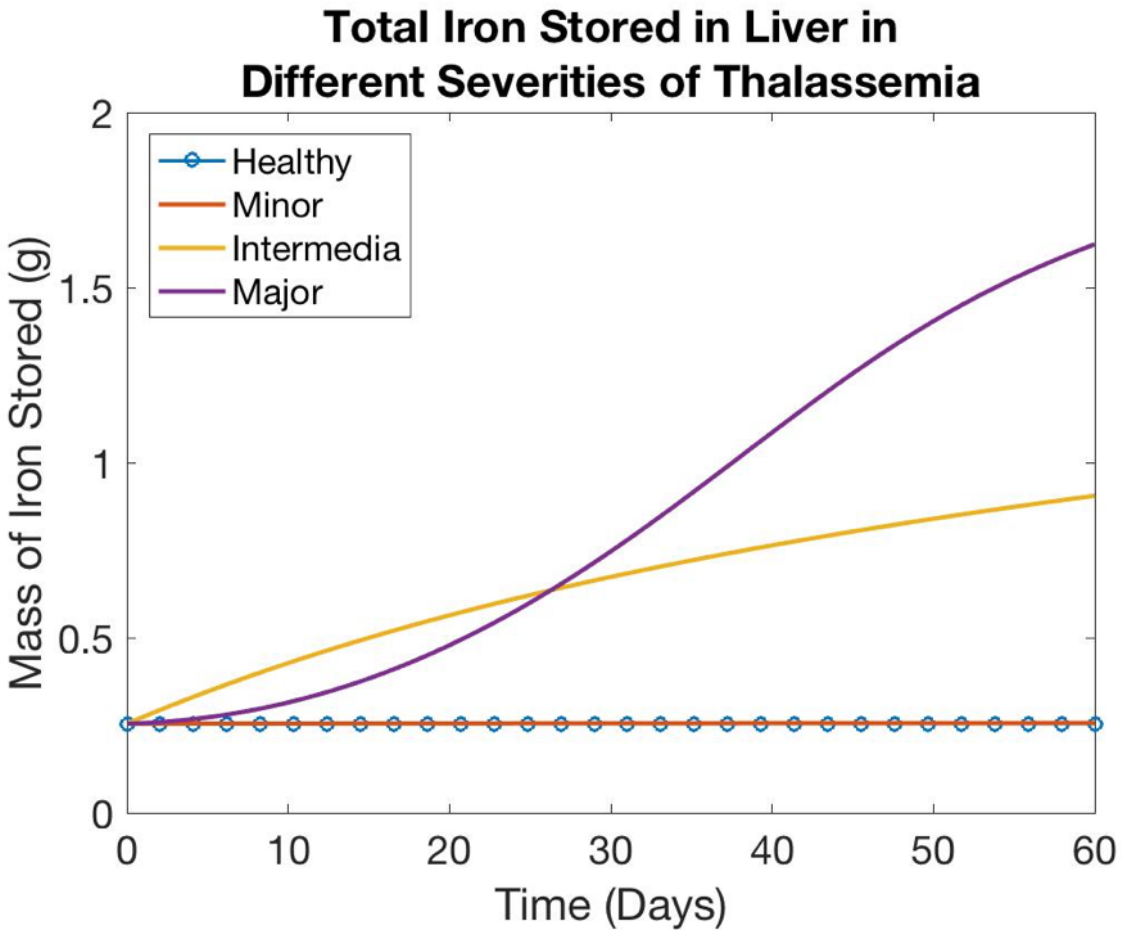


Figure 2: Graph of Iron Storage at the Liver in a Healthy Individual and Different Severities of β-Thalassemia

As shown by Figure 2 above, healthy individuals have a constant level of iron stored in the liver because no accumulation occurs in the steady-state (healthy) model, indicating that the rate of iron flowing into the liver equals the rate of iron flowing out of the liver. Additionally, β-thalassemia minor patients experience a very slight, 0.787%, increase in stored iron (see Appendix C.4.1 Table 57). Patients with β-thalassemia major, on the other hand, have the most extreme change of iron stored with a 538% increase after 60 days (see Appendix C.4.3 Table 59). β-thalassemia intermedia patients experience a less extreme but still significant 256% increase in stored iron after 60 days (Appendix C.4.2 Table 58).

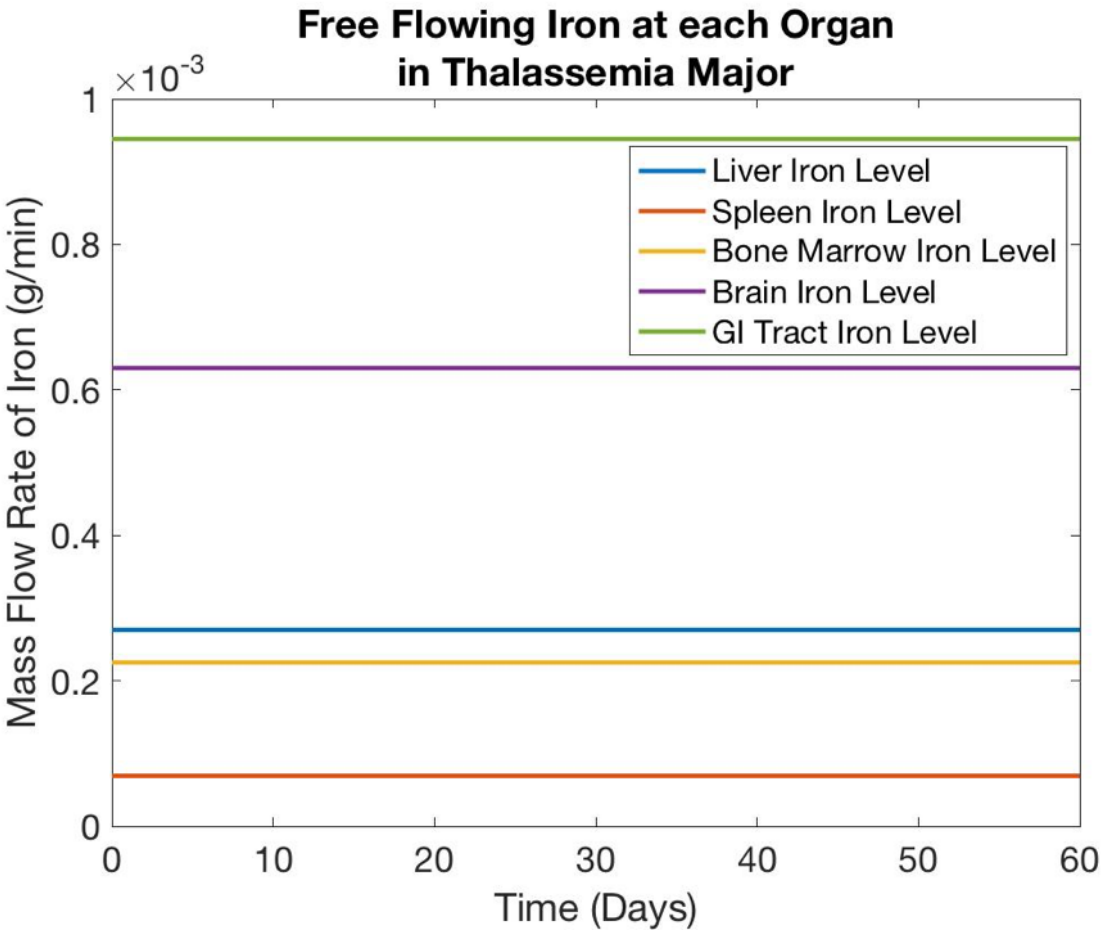


Figure 3: Graph of Free Flowing Iron at each Organ in β-Thalassemia Major

Figure 3 reiterates the idea that the body continuously maintains constant free flowing iron levels. Although this graph is of a -thalassemia major patient, the initial values for each organ are the same as the values of a healthy individual. This pattern continues for all severities of -thalassemia.

## 6.2 Red Blood Cell Accumulation

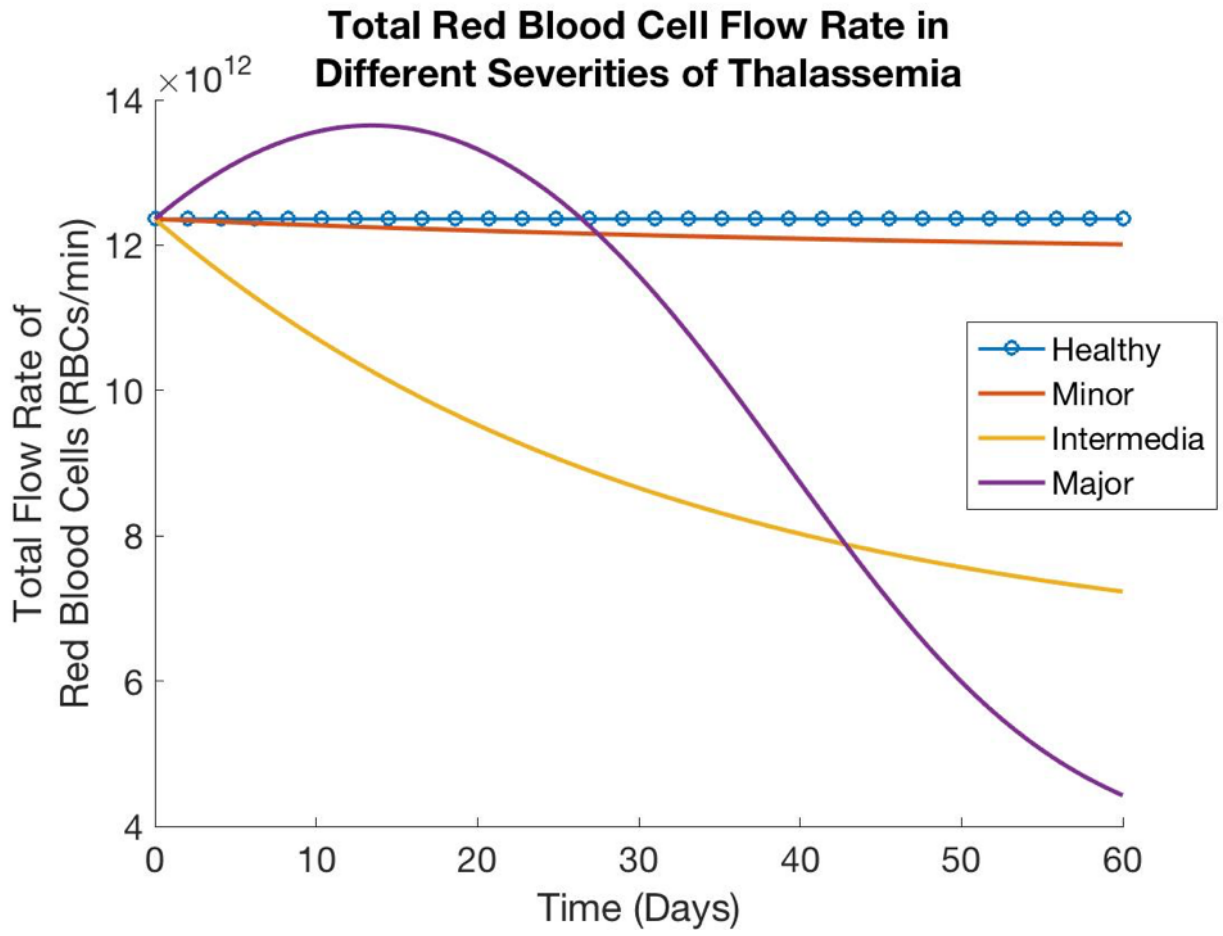


Figure 4: Graph of Total Red Blood Cell Flow Rate in a Healthy Individual and Different Severities of β-Thalassemia

In Figure 4, the decrease in red blood cell (RBC) flow rate is consistent with the fact that our mathematical model simulates an individual with β-thalassemia. For healthy individuals, total RBC flow rate remains constant since the model is at steady-state. For individuals with β-thalassemia, the count decreases over time at different rates for different severities. Individuals with β-thalassemia minor experience only a 2.76% decrease in RBC flow rate while β-thalassemia intermedia and major patients witness a 41.5% and 64.2% decrease, respectively, by the end of the 60 day period (Appendix C.4.1 Table 57, Appendix C.4.2

Table 58, Appendix C.4.3 Table 59).

Moreover, compared with the decrease of RBC flow rate in individuals with β-thalassemia intermedia, there is an initial increase in RBC flow rate in the β-thalassemia major model immediately after a blood transfusion. This is due to the fact that the transfused RBCs have a lifespan of 94 days and make up a larger percentage of the total RBCs [21]. As a result, the initial RBC production rate is greater than the destruction rate. However, these transfused RBCs eventually die out, resulting in an increase in RBC destruction rate, and thus, a general decrease in RBC flow rate overall.

## 6.3 Oxygen Levels

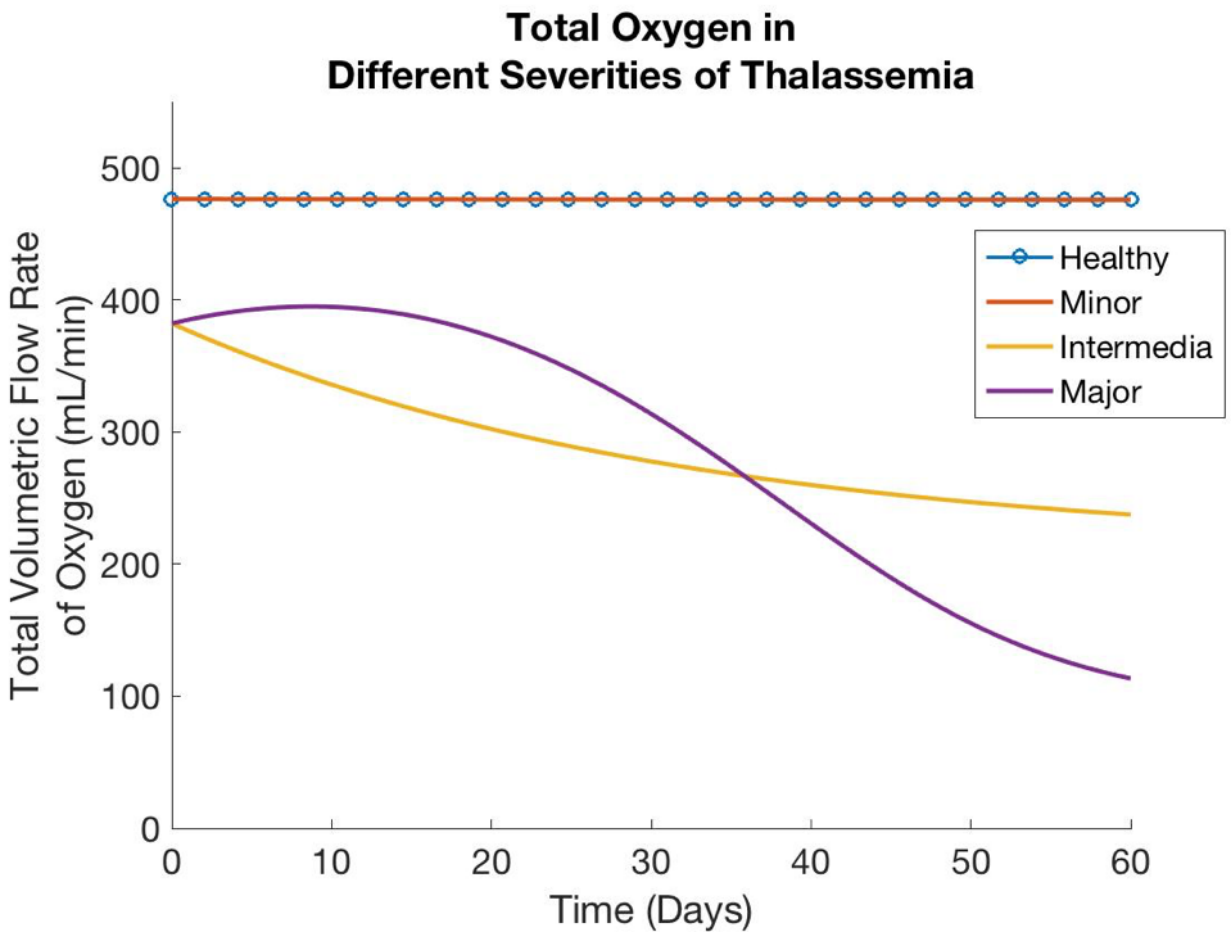


Figure 5: Graph of Total Oxygen Level in a Healthy Individual and Different Severities of β-Thalassemia

Since oxygen binds to hemoglobin within the blood, $O_2$ levels (shown in Figure 5) correlate with the amount of RBCs in the bloodstream (shown in Figure 4). Our model assumes that the oxygen level consumption is constant for healthy individuals. Individuals with β-thalassemia minor show similar stable levels of $O_2$. In β-thalassemia intermedia, however, total $O_2$ levels show a 37.9% decrease after 60 days due to the reduction of RBC levels (see Appendix C.4.2 Table 58). β-thalassemia major shows an initial 4.49% (slight) increase in $O_2$

due to the transfused RBCs from the last blood transfusion the patient received. After the initial increase, the $O_2$ levels decrease by 70.41% due to the natural destruction of transfused RBCs (Appendix C.4.3 Table 59).

## 6.4 Hemoglobin A

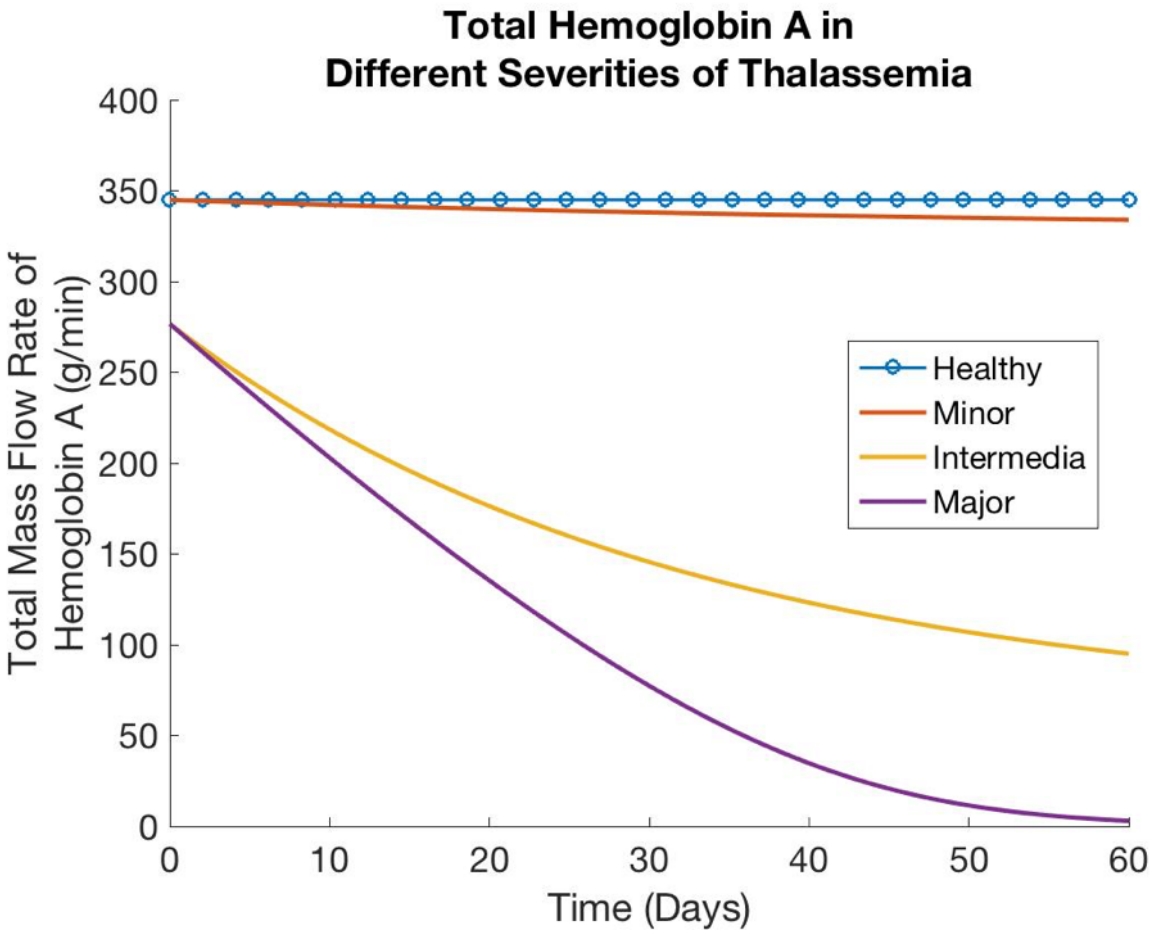


Figure 6: Graph of Total Hemoglobin A Level in a Healthy Individual and Different Severities of β-Thalassemia

Figure 6 shows that level of hemoglobin A remains at 345 g for a steady-state model (see Appendix B.4 Table 8). On the other hand, individuals with β-thalassemia do not produce as much hemoglobin A because of defective β-globin genes. Consequently, our model shows

a decrease in hemoglobin A level for all three severities of β-thalassemia. Moreover, with increasing severity of β-thalassemia, the hemoglobin A levels decrease to a greater extent because of impaired hemoglobin A production. While the hemoglobin A level of the β-thalassemia minor model only decreases to 335 g over 60 days, our β-thalassemia intermedia model drops to 95.1 g while β-thalassemia major declines to 3.01 g (Appendix C.4.1 Table 57, Appendix C.4.2 Table 58, Appendix C.4.3 Table 59).

## 6.5 Other Hemoglobin

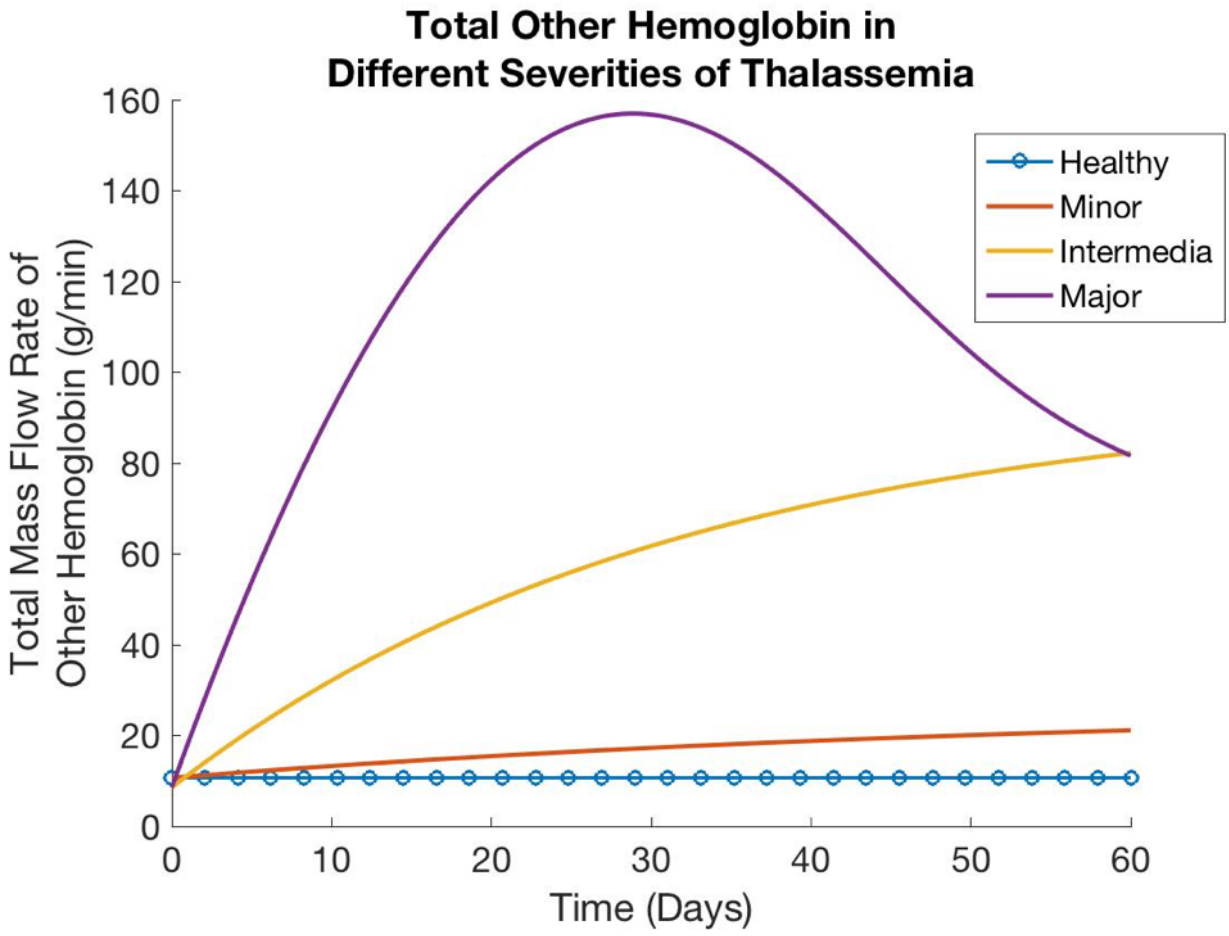


Figure 7: Graph of Total Other Hemoglobin Levels in a Healthy Individual and Different Severities of β-Thalassemia

An important indicator of β-thalassemia is the level of other hemoglobin level. Compared to the constant level of other hemoglobin in the healthy model, our β-thalassemia model displays an increase in other hemoglobin levels because of the increase in hemoglobin $A_2$ and F production in Figure 7. With increasing severity of β-thalassemia, the levels at 60 days after transfusion increase from 21.1 g for individuals with β-thalassemia minor, to 82.2g for β-thalassemia intermedia and 81.6 g to β-thalassemia major (Appendix C.4.1 Table 57, Appendix C.4.2 Table 58, Appendix C.4.3 Table 59).

## 6.6 Line of Complications and Death

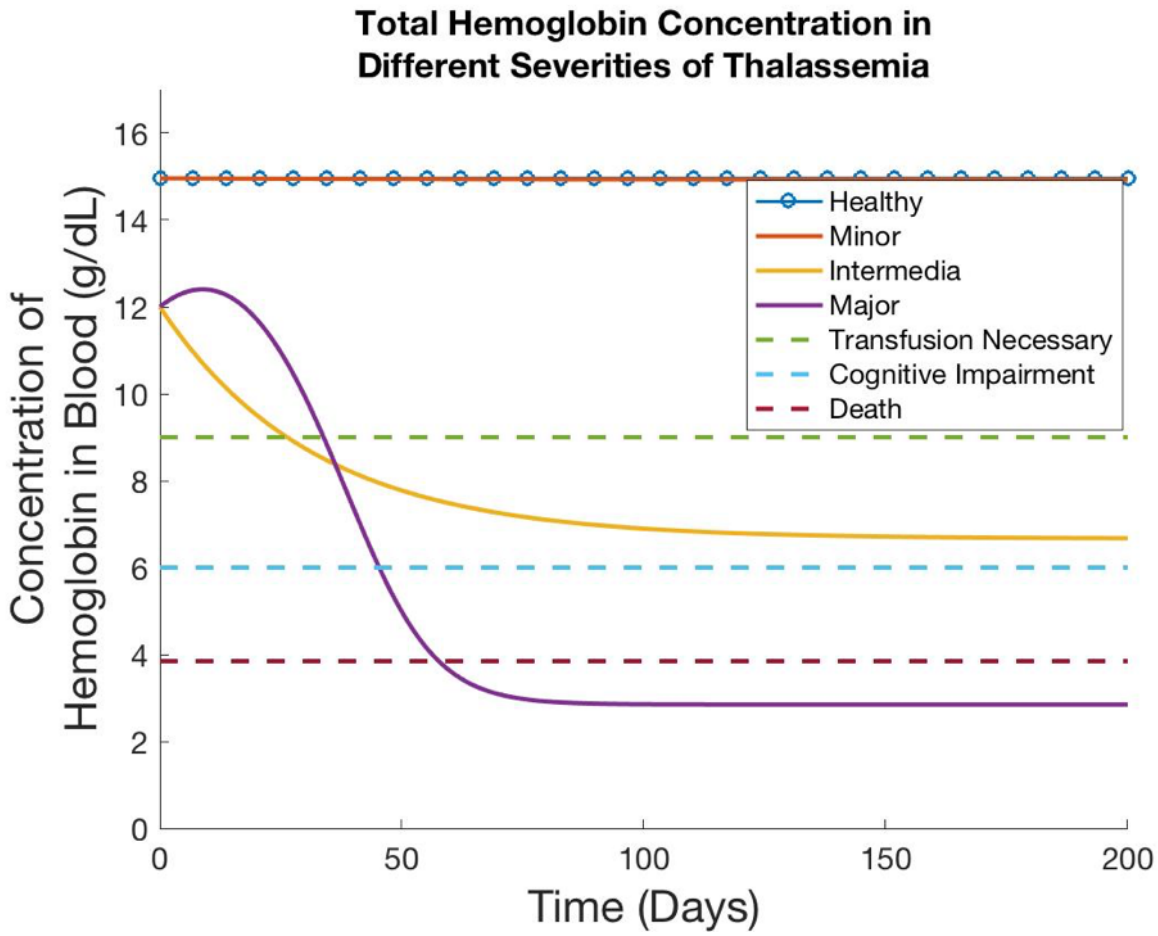


Figure 8: Graph of Total Hemoglobin Concentrations in a Healthy Individual and Different Severities of β-Thalassemia

As shown in Figure 8, our model outputs whether or not the individual will become cognitively impaired or dead if not given a second blood transfusion. More specifically, the threshold hemoglobin concentration value for recommended blood transfusion is 10 g/dL, 6 g/dL for cognitive impairment, and 3.84 g/dL for death (Appendix B.1, Appendix B.8 Table 41). Healthy individuals and individuals with β-thalassemia minor and intermedia do not need to receive blood transfusions within 100 days. However, individuals with β-thalassemia

major will become cognitively impaired at 44.6 days post-transfusion and will die in 57.0 days post-transfusion according to our mode. Thus, another transfusion is recommended at 30.0 days after the previous one.

# 7 Strengths & Weaknesses

Although the model outputs a clear and accurate level for the six important components for various severities of β-thalassemia, it still has some limitations. Our model assumes that the red blood cells are only destroyed in the spleen and do not otherwise leave the system. This means that our model does not take into account external injuries or other factors that may result in blood loss or RBC destruction. This, in turn, means that our RBC flow rate graphs may have higher values than in reality.

Another limitation stems from the assumption that iron is stored only in the liver. As a result, our models stored iron levels in the liver are also higher than realistic values and underestimates the time that iron overload occurs.

We also assumed 100% of all hemoglobin is broken down only in the spleen. The hemoglobin is then recycled back to the bone marrow. This assumption does not account for hemoglobin broken down in other organs such as the liver which is not physiologically accurate. However, it does not affect our final results because total hemoglobin destruction is still accounted for.

Despite our models limitations, it still provides physicians and researchers an interactive model that can take in different severities of β-thalassemia and various time periods to track the changes of various components affected by β-thalassemia.

The model was written so that it is easily tunable and is generalized enough to be applied to specific patients with varying levels of component values. For example, the user could change the initial levels of hemoglobin, percentage of hemoglobin A produced in the body, and lifespan of red blood cells in the function "getvalues" to obtain personalised results.

Likewise, our model is accurate in terms of iron overload and the day that the next blood transfusion is necessary. Calculating the time needed for blood transfusions is especially important in β-thalassemia major because patients would die without transfusions approximately every 2-5 weeks [22]. This time period is similar to our models calculated value of around 30 days.

Furthermore, our model accurately portrays not only the blood transfusion time, but hemoglobin, $O_2$, and $CO_2$ levels. These values can help improve the management of β-thalassemic treatments, such as the frequency that a patient needs to undergo blood transfusions.

Additionally, there is limited research on β-thalassemia intermedia partly because it includes all of the severities between β-thalassemia major and β-thalassemia minor. Despite this, our model generalizes intermedia so that we can account for and calculate blood component values for individuals with β-thalassemia intermedia.

Moreover, healthy individuals and β-thalassemia minor individuals both have nearly constant component values and are very indistinguishable from each other. However, our model can distinguish between a healthy and β-thalassemia minor individual by tracking the levels of other hemoglobin (Hemoglobin $A_2$ and F).

# 8 Conclusion

Our multi-unit model simulates blood flow through the steady-state system of a healthy individual as well as through the dynamic system perturbed by β-thalassemia. It calculates and outputs the flow rates and concentrations of key blood components affected by β-thalassemia. These components include $CO_2$, $O_2$, hemoglobin A, other hemoglobin, red blood cells, including free flowing iron and iron stored in the liver. We tracked these components through the liver, gastrointestinal tract, lungs, bone marrow, brain, and spleen. These outputs indicate the levels of the three types of β-thalassemia (minor, intermedia, and major) and provide the approximate post-transfusion day β-thalassemic patients will become cognitively impaired or die. When looking at a time period of 200 days, our model shows that healthy, minor, and intermedia individuals do not require blood transfusions. However, β-thalassemic major patients will become cognitively impaired after 44.6 days and die after 57 days if not given a subsequent blood transfusion. Consequently, this model can be used by physicians and researchers to not only predict when thalassemic patients need treatments such as blood transfusion, but also to provide data for the research and development of β-thalassemia treatments and medications.

# Appendices

## A Assumptions

1. The thalassemic patients we are modeling do not lose any blood other than through blood flow through the organs. Therefore, the amount of the red blood cells lost is higher in our model than in actual β-thalassemic patients patients.
2. We assume all hemoglobin is being broken down in the spleen and is consequently recycled back to the bone marrow. This assumption does not account for hemoglobin recycling in other organs such as the liver. Consequently, our model may have inaccurate hemoglobin levels in certain organs.
3. We assume iron is stored in only the liver. However, other organs such as the brain and pancreas may store iron as well. As a result, our models iron levels are higher than realistic levels. Therefore, our blood transfusion time is shorter than what is accurate.
4. Red blood cell production is constant.
5. The heart acts just as a pump, splitter, and mixer. It also does not take in $O_2$ or release $CO_2$.
6. Since approximately 95% of $CO_2$ is converted into bicarbonate ions or bound to the hemoglobin within the RBCs, we assume that all of the $CO_2$ is taken up by the RBCs, and the amount of $CO_2$ dissolved in the plasma is negligible [23].
7. There is no evidence in the literature to suggest decreased RBC lifespan in β-thalassemia minor. However, there is evidence of decreased RBC lifespan in β-thalassemia inter-

media [24]. Quantitative data on RBC lifespan in β-thalassemia intermedia is limited. Therefore, RBC lifespan in β-thalassemia minor is assumed to be equal to that of a healthy individual, and the RBC lifespan in β-thalassemia intermedia is assumed to be the average of the RBC lifespan in β-thalassemia minor and the RBC lifespan in β-thalassemia major.

# B Calculations

## B.1 Raw Data

Brain VFR (Volumetric Flow Rate) = 700 $^{\text{mL}}/_{\text{min}}$ [25]

Heart VFR = 0 $^{\text{mL}}/_{\text{min}}$

Lungs VFR = 2377 $^{\text{mL}}/_{\text{min}}$

Liver Hepatic Artery VFR = 300 $^{\text{mL}}/_{\text{min}}$ [25]

GI Tract VFR = 1050 $^{\text{mL}}/_{\text{min}}$ [25]

Spleen VFR = 77 $^{\text{mL}}/_{\text{min}}$ [26]

Bone Marrow VFR = 250 $^{\text{mL}}/_{\text{min}}$ [25]

$O_2$ Carrying Ability of Hemoglobin = 1.34 $^{\text{mL } O_2}/_{\text{min}}$ [15]

Healthy Hemoglobin Concentration = 14.96 $^{\text{g}}/_{\text{dL}}$ [15]

Thalassemia Minor Hemoglobin Concentration = 12 $^{\text{g}}/_{\text{dL}}$ [11]

Thalassemia Intermedia Hemoglobin Concentration = 8 $^{\text{g}}/_{\text{dL}}$ [11]

Thalassemia Major Hemoglobin Concentration = 4.5 $^{\text{g}}/_{\text{dL}}$ [11]

$O_2$ Consumption of Blood = 0.05 $^{\text{mL } O_2}/_{\text{mL blood}}$ [25]

Arterial $O_2$ Saturation = 0.97 $^{\text{mL } O_2}/_{\text{mL blood}}$ [15]

Arterial $CO_2$ Saturation = 0.492 $^{\text{mL } CO_2}/_{\text{mL blood}}$ [25]

Respiratory Quotient = 0.8 [25]

Healthy Fraction of Hemoglobin A = 0.97 [11]

Thalassemia Minor Fraction of Hemoglobin A = 0.925 [11]

Thalassemia Intermedia Fraction of Hemoglobin A = 0.4 [11]

Thalassemia Major Fraction of Hemoglobin A = 0 [11]

Healthy RBC (Red Blood Cell) Lifespan = 172,800 min [15]

Thalassemia Minor RBC Lifespan = 172,800 min

Thalassemia Intermedia RBC Lifespan = 96,840 min

Thalassemia Major RBC Lifespan = 20,880 min [20]

Transfused RBC Lifespan = 135,460 min [21]

Blood Volume = 5000 mL [25]

Thalassemia Intermedia MCV (Mean Corpuscular Volume) = 75 fL [11]

Thalassemia Major MCV = 70 fL [11]

Healthy RBC Count = 5,200,000,000 $^{\text{RBCs}}/_{\text{mL blood}}$ [15]

Thalassemia Minor RBC Count = 5,240,000,000 $^{\text{RBCs}}/_{\text{mL blood}}$ [27]

Thalassemia Intermedia MCH (Mean Corpuscular Hemoglobin)= 25 pg [11]

Thalassemia Major MCH = 19 pg [11]

Total Iron in Body = 4.5 g [15]

Iron Bound to Transferrin = 0.0000009 $^{\text{g Fe}}/_{\text{mL blood}}$ [15]

Iron Bound to Hemoglobin = 0.00391 $^{\text{g Fe}}/_{\text{g Hemoglobin}}$ [15]

Thalassemia Intermedia Iron Absorption in GI Tract = 0.00000260 $^{\text{g}}/_{\text{min}}$ [28]

Thalassemia Major Iron Absorption in GI Tract = 0.00000665 $\frac{g}{min}$ [16]

Threshold Concentration of Hemoglobin to Brain to prevent Cognitive Impairment = 6 $\frac{g}{dL}$ [29]

Threshold Concentration of Hemoglobin for Blood Transfusion = 10 $\frac{g}{dL}$ [29]

Note: VFR of Lungs is equal to the sum of the VFR's of the liver, spleen, bone marrow, GI tract, and brain.

## B.2 Oxygen

**General Equation**

Accounting Equation: $IN - OUT + GEN - CON = ACC$

**Healthy:**

$$\frac{VFR * Healthy\,Hemoglobin\,Concentration}{100 * Hemoglobin\,O_2\,Carrying\,Capacity * Arterial\,O_2\,Saturation} - (O_2\,IN - O_2\,CON) +$$
$$0 - VFR * O_2\,Consumption\,of\,Blood = O_2\,ACC = 0$$

**Thalassemia Minor:**

$$\frac{VFR * Minor\,Hemoglobin\,Concentration}{100 * Hemoglobin\,O_2\,Carrying\,Capacity * Arterial\,O_2\,Saturation} - (O_2\,IN - O_2\,CON) +$$
$$0 - VFR * O_2\,Consumption\,of\,Blood = O_2\,ACC = 0$$

**Thalassemia Intermedia:**

$$\frac{VFR * Intermedia\,Hemoglobin\,Concentration}{100 * Hemoglobin\,O_2\,Carrying\,Capacity * Arterial\,O_2\,Saturation} - (O_2\,IN - O_2\,CON) +$$
$$0 - VFR * O_2\,Consumption\,of\,Blood = O_2\,ACC = 0$$

**Thalassemia Major:**

$$\frac{VFR * Major\,Hemoglobin\,Concentration}{100 * Hemoglobin\,O_2\,Carrying\,Capacity * Arterial\,O_2\,Saturation} - (O_2\,IN - O_2\,CON) +$$
$$0 - VFR * O_2\,Consumption\,of\,Blood = O_2\,ACC = 0$$

Table 5: Steady-State Oxygen Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 136 | 101 | 0 | 35 | 0 |
| **Minor** | 109 | 74 | 0 | 35 | 0 |
| **Intermedia** | 72.8 | 37.8 | 0 | 35.0 | 0 |
| **Major** | 40.9 | 5.9 | 0 | 35.0 | 0 |

Table 6: Steady-State Oxygen Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 462 | 462 | 0 | 0 | 0 |
| **Minor** | 371 | 371 | 0 | 0 | 0 |
| **Intermedia** | 247 | 247 | 0 | 0 | 0 |
| **Major** | 139 | 139 | 0 | 0 | 0 |

Table 7: Steady-State Oxygen Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 210 | 195 | 0 | 15 | 0 |
| **Minor** | 158 | 143 | 0 | 15 | 0 |
| **Intermedia** | 87.9 | 72.9 | 0 | 15.0 | 0 |
| **Major** | 26.5 | 11.5 | 0 | 15.0 | 0 |

Table 8: Steady-State Oxygen Level in the Gastrointestinal Tract in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 204 | 151 | 0 | 53 | 0 |
| **Minor** | 164 | 111 | 0 | 53 | 0 |
| **Intermedia** | 110 | 56.7 | 0 | 53 | 0 |
| **Major** | 61.4 | 8.92 | 0 | 52.5 | 0 |

Table 9: Steady-State Oxygen Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 15.0 | 11.1 | 0 | 3.9 | 0 |
| **Minor** | 12.0 | 8.15 | 0 | 3.9 | 0 |
| **Intermedia** | 8.01 | 4.16 | 0 | 3.85 | 0 |
| **Major** | 4.50 | 0.654 | 0 | 3.85 | 0 |

Table 10: Steady-State Oxygen Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$O_2$ IN** ($\mathbf{mL/min}$) | **$O_2$ OUT** ($\mathbf{mL/min}$) | **$O_2$ GEN** ($\mathbf{mL/min}$) | **$O_2$ CON** ($\mathbf{mL/min}$) | **$O_2$ ACC** ($\mathbf{mL/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 48.6 | 36.1 | 0 | 12.5 | 0 |
| **Minor** | 39.0 | 26.5 | 0 | 12.5 | 0 |
| **Intermedia** | 26.0 | 13.5 | 0 | 12.5 | 0 |
| **Major** | 14.6 | 2.1 | 0 | 12.5 | 0 |

## B.3 Carbon Dioxide

**General Equation**

Accounting Equation: $IN - OUT + GEN - CON = ACC$

**Healthy:**

$$VFR * Arterial\, CO_2\, Saturation - (CO_2\, IN + CO_2\, CON) + VFR * O_2\, Consumption\, of\, Blood * Respiratory\, Quotient\, -\, 0 = CO_2\, ACC\, =\, 0$$

**Thalassemia Minor:**

$$VFR * Arterial\, CO_2\, Saturation - (CO_2\, IN + CO_2\, CON) + VFR * O_2\, Consumption\, of\, Blood * Respiratory\, Quotient\, -\, 0 = CO_2\, ACC\, =\, 0$$

**Thalassemia Intermedia:**

$$VFR * Arterial\, CO_2\, Saturation - (CO_2\, IN + CO_2\, CON) + VFR * O_2\, Consumption\, of\, Blood * Respiratory\, Quotient\, -\, 0 = CO_2\, ACC\, =\, 0$$

**Thalassemia Major:**

$$VFR * Arterial\, CO_2\, Saturation - (CO_2\, IN + CO_2\, CON) + VFR * O_2\, Consumption\, of\, Blood * Respiratory\, Quotient\, -\, 0 = CO_2\, ACC\, =\, 0$$

Table 11: Steady-State Carbon Dioxide Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** $(\mathbf{mL/min})$ | **$CO_2$ OUT** $(\mathbf{mL/min})$ | **$CO_2$ GEN** $(\mathbf{mL/min})$ | **$CO_2$ CON** $(\mathbf{mL/min})$ | **$CO_2$ ACC** $(\mathbf{mL/min})$ |
|---|---|---|---|---|---|
| **Healthy** | 344 | 372 | 28 | 0 | 0 |
| **Minor** | 344 | 372 | 28 | 0 | 0 |
| **Intermedia** | 344 | 372 | 28 | 0 | 0 |
| **Major** | 344 | 372 | 28 | 0 | 0 |

Table 12: Steady-State Carbon Dioxide Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** **(mL/min)** | **$CO_2$ OUT** **(mL/min)** | **$CO_2$ GEN** **(mL/min)** | **$CO_2$ CON** **(mL/min)** | **$CO_2$ ACC** **(mL/min)** |
|---|---|---|---|---|---|
| **Healthy** | 1260 | 1260 | 0 | 0 | 0 |
| **Minor** | 1260 | 1260 | 0 | 0 | 0 |
| **Intermedia** | 1260 | 1260 | 0 | 0 | 0 |
| **Major** | 1260 | 1260 | 0 | 0 | 0 |

Table 13: Steady-State Carbon Dioxide Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** **(mL/min)** | **$CO_2$ OUT** **(mL/min)** | **$CO_2$ GEN** **(mL/min)** | **$CO_2$ CON** **(mL/min)** | **$CO_2$ ACC** **(mL/min)** |
|---|---|---|---|---|---|
| **Healthy** | 706 | 718 | 12 | 0 | 0 |
| **Minor** | 706 | 718 | 12 | 0 | 0 |
| **Intermedia** | 706 | 718 | 12 | 0 | 0 |
| **Major** | 706 | 718 | 12 | 0 | 0 |

Table 14: Steady-State Carbon Dioxide Level in the Gastrointestinal Tract in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** **(mL/min)** | **$CO_2$ OUT** **(mL/min)** | **$CO_2$ GEN** **(mL/min)** | **$CO_2$ CON** **(mL/min)** | **$CO_2$ ACC** **(mL/min)** |
|---|---|---|---|---|---|
| **Healthy** | 516 | 558 | 42 | 0 | 0 |
| **Minor** | 516 | 558 | 42 | 0 | 0 |
| **Intermedia** | 516 | 558 | 42 | 0 | 0 |
| **Major** | 516 | 558 | 42 | 0 | 0 |

Table 15: Steady-State Carbon Dioxide Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** ($mL/min$) | **$CO_2$ OUT** ($mL/min$) | **$CO_2$ GEN** ($mL/min$) | **$CO_2$ CON** ($mL/min$) | **$CO_2$ ACC** ($mL/min$) |
|---|---|---|---|---|---|
| **Healthy** | 37.9 | 41.0 | 3.1 | 0 | 0 |
| **Minor** | 37.9 | 41.0 | 3.1 | 0 | 0 |
| **Intermedia** | 37.9 | 41.0 | 3.1 | 0 | 0 |
| **Major** | 37.9 | 41.0 | 3.1 | 0 | 0 |

Table 16: Steady-State Carbon Dioxide Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$CO_2$ IN** ($mL/min$) | **$CO_2$ OUT** ($mL/min$) | **$CO_2$ GEN** ($mL/min$) | **$CO_2$ CON** ($mL/min$) | **$CO_2$ ACC** ($mL/min$) |
|---|---|---|---|---|---|
| **Healthy** | 123 | 133 | 10 | 0 | 0 |
| **Minor** | 123 | 133 | 10 | 0 | 0 |
| **Intermedia** | 123 | 133 | 10 | 0 | 0 |
| **Major** | 123 | 133 | 10 | 0 | 0 |

## B.4 Hemoglobin A

### General Equation

Accounting Equation: $IN - OUT + GEN - CON = ACC$

**Healthy:**

$$\frac{VFR * Healthy\,Hemoglobin\,Concentration * Healthy\,Fraction\,of\,Hemoglobin\,A}{100} -$$

$$(Hemoglobin\,A\,IN + Hemoglobin\,A\,GEN - Hemoglobin\,A\,CON) +$$

$$\frac{Healthy\,Hemoglobin\,Concentration * Healthy\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Healthy\,RBC\,Lifespan} -$$

$$\frac{Healthy\,Hemoglobin\,Concentration * Healthy\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Healthy\,RBC\,Lifespan}$$

$$= Hemoglobin\,A\,ACC = 0$$

**Thalassemia Minor:**

$$\frac{VFR * Minor\,Hemoglobin\,Concentration * Minor\,Fraction\,of\,Hemoglobin\,A}{100} -$$

$$(Hemoglobin\,A\,IN + Hemoglobin\,A\,GEN - Hemoglobin\,A\,CON) +$$

$$\frac{Minor\,Hemoglobin\,Concentration * Minor\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Minor\,RBC\,Lifespan} -$$

$$\frac{Minor\,Hemoglobin\,Concentration * Minor\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Minor\,RBC\,Lifespan}$$

$$= Hemoglobin\,A\,ACC = 0$$

**Thalassemia Intermedia:**

$$\frac{VFR * Intermedia\,Hemoglobin\,Concentration * Intermedia\,Fraction\,of\,Hemoglobin\,A}{100} -$$

$$(Hemoglobin\,A\,IN + Hemoglobin\,A\,GEN - Hemoglobin\,A\,CON) +$$

$$\frac{Intermedia\,Hemoglobin\,Concentration * Intermedia\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Intermedia\,RBC\,Lifespan} -$$

$$\frac{Intermedia\,Hemoglobin\,Concentration * Intermedia\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Intermedia\,RBC\,Lifespan}$$

$$= Hemoglobin\,A\,ACC = 0$$

**Thalassemia Major:**

$$\frac{VFR * Major\,Hemoglobin\,Concentration * Major\,Fraction\,of\,Hemoglobin\,A}{100} -$$

$$(Hemoglobin\,A\,IN + Hemoglobin\,A\,GEN - Hemoglobin\,A\,CON) +$$

$$\frac{Major\,Hemoglobin\,Concentration * Major\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Major\,RBC\,Lifespan} -$$

$$\frac{Major\,Hemoglobin\,Concentration * Major\,Fraction\,of\,Hemoglobin\,A * Blood\,Volume}{100 * Major\,RBC\,Lifespan}$$

$$= Hemoglobin\,A\,ACC = 0$$

Table 17: Steady-State Hemoglobin A Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 102 | 102 | 0 | 0 | 0 |
| **Minor** | 77.7 | 77.7 | 0 | 0 | 0 |
| **Intermedia** | 22.4 | 22.4 | 0 | 0 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

Table 18: Steady-State Hemoglobin A Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 345 | 345 | 0 | 0 | 0 |
| **Minor** | 264 | 264 | 0 | 0 | 0 |
| **Intermedia** | 76.1 | 76.1 | 0 | 0 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

Table 19: Steady-State Hemoglobin A Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 196 | 196 | 0 | 0 | 0 |
| **Minor** | 150 | 150 | 0 | 0 | 0 |
| **Intermedia** | 43.2 | 43.2 | 0 | 0 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

Table 20: Steady-State Hemoglobin A Level in the Gastrointestinal Tract in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 152 | 152 | 0 | 0 | 0 |
| **Minor** | 117 | 117 | 0 | 0 | 0 |
| **Intermedia** | 33.6 | 33.6 | 0 | 0 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

Table 21: Steady-State Hemoglobin A Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 11.174 | 11.694 | 0 | 0.004 | 0 |
| **Minor** | 8.547 | 8.544 | 0 | 0.003 | 0 |
| **Intermedia** | 2.464 | 2.462 | 0 | 0.002 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

Table 22: Steady-State Hemoglobin A Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **$H_A$ IN (g/min)** | **$H_A$ OUT (g/min)** | **$H_A$ GEN (g/min)** | **$H_A$ CON (g/min)** | **$H_A$ ACC (g/min)** |
|---|---|---|---|---|---|
| **Healthy** | 36.278 | 36.282 | 0.004 | 0 | 0 |
| **Minor** | 27.750 | 27.753 | 0.003 | 0 | 0 |
| **Intermedia** | 8.000 | 8.002 | 0.002 | 0 | 0 |
| **Major** | 0 | 0 | 0 | 0 | 0 |

## B.5 Other Hemoglobin

### General Equation

Accounting Equation: $IN - OUT + GEN - CON = ACC$

**Healthy:**

$$\frac{VFR * Healthy\,Hemoglobin\,Concentration * (1 - Healthy\,Fraction\,of\,Hemoglobin\,A)}{100} -$$

$$(Hemoglobin\,Other\,IN + Hemoglobin\,Other\,GEN - Hemoglobin\,Other\,CON) +$$

$$\frac{Healthy\,Hemoglobin\,Concentration * (1 - Healthy\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Healthy\,RBC\,Lifespan} -$$

$$\frac{Healthy\,Hemoglobin\,Concentration * (1 - Healthy\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Healthy\,RBC\,Lifespan}$$

$$= Hemoglobin\,Other\,ACC = 0$$

**Thalassemia Minor**

$$\frac{VFR * Minor\,Hemoglobin\,Concentration * (1 - Minor\,Fraction\,of\,Hemoglobin\,A)}{100} -$$

$$(Hemoglobin\,Other\,IN + Hemoglobin\,Other\,GEN - Hemoglobin\,Other\,CON) +$$

$$\frac{Minor\,Hemoglobin\,Concentration * (1 - Minor\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Minor\,RBC\,Lifespan} -$$

$$\frac{Minor\,Hemoglobin\,Concentration * (1 - Minor\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Minor\,RBC\,Lifespan}$$

$$= Hemoglobin\,Other\,ACC = 0$$

**Thalassemia Intermedia**

$$\frac{VFR * Intermedia\,Hemoglobin\,Concentration * (1 - Intermedia\,Fraction\,of\,Hemoglobin\,A)}{100}$$

$$-(Hemoglobin\,Other\,IN + Hemoglobin\,Other\,GEN - Hemoglobin\,Other\,CON) +$$

$$\frac{Intermedia\,Hemoglobin\,Concentration * (1 - Intermedia\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Intermedia\,RBC\,Lifespan} -$$

$$\frac{Intermedia\,Hemoglobin\,Concentration * (1 - Intermedia\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Intermedia\,RBC\,Lifespan}$$

$$= Hemoglobin\,Other\,ACC = 0$$

**Thalassemia Major**

$$\frac{VFR * Major\,Hemoglobin\,Concentration * (1 - Major\,Fraction\,of\,Hemoglobin\,A)}{100} -$$

$$(Hemoglobin\,Other\,IN + Hemoglobin\,Other\,GEN - Hemoglobin\,Other\,CON) +$$

$$\frac{Major\,Hemoglobin\,Concentration * (1 - Major\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Major\,RBC\,Lifespan} -$$

$$\frac{Major\,Hemoglobin\,Concentration * (1 - Major\,Fraction\,of\,Hemoglobin\,A) * Blood\,Volume}{100 * Major\,RBC\,Lifespan}$$

$$= Hemoglobin\,Other\,ACC = 0$$

Table 23: Steady-State Other Hemoglobin Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 3.14 | 3.14 | 0 | 0 | 0 |
| **Minor** | 6.30 | 6.30 | 0 | 0 | 0 |
| **Intermedia** | 33.6 | 33.6 | 0 | 0 | 0 |
| **Major** | 31.5 | 31.5 | 0 | 0 | 0 |

Table 24: Steady-State Other Hemoglobin Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 10.7 | 10.7 | 0 | 0 | 0 |
| **Minor** | 21.4 | 21.4 | 0 | 0 | 0 |
| **Intermedia** | 114 | 114 | 0 | 0 | 0 |
| **Major** | 107 | 107 | 0 | 0 | 0 |

Table 25: Steady-State Other Hemoglobin Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 6.06 | 6.06 | 0 | 0 | 0 |
| **Minor** | 12.2 | 12.2 | 0 | 0 | 0 |
| **Intermedia** | 64.8 | 64.8 | 0 | 0 | 0 |
| **Major** | 60.8 | 60.8 | 0 | 0 | 0 |

Table 26: Steady-State Other Hemoglobin Level in the Gastrointestinal Tract in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 4.71 | 4.71 | 0 | 0 | 0 |
| **Minor** | 9.45 | 9.45 | 0 | 0 | 0 |
| **Intermedia** | 50.4 | 50.4 | 0 | 0 | 0 |
| **Major** | 47.3 | 47.3 | 0 | 0 | 0 |

Table 27: Steady-State Other Hemoglobin Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 0.3456 | 0.3454 | 0 | 0.0002 | 0 |
| **Minor** | 0.6930 | 0.6927 | 0 | 0.0003 | 0 |
| **Intermedia** | 3.696 | 3.693 | 0 | 0.003 | 0 |
| **Major** | 3.465 | 3.454 | 0 | 0.011 | 0 |

Table 28: Steady-State Other Hemoglobin Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | $\mathbf{H_{Other}}$ **IN** (g/min) | $\mathbf{H_{Other}}$ **OUT** (g/min) | $\mathbf{H_{Other}}$ **GEN** (g/min) | $\mathbf{H_{Other}}$ **CON** (g/min) | $\mathbf{H_{Other}}$ **ACC** (g/min) |
|---|---|---|---|---|---|
| **Healthy** | 1.1220 | 1.1222 | 0.0002 | 0 | 0 |
| **Minor** | 2.2500 | 2.2503 | 0.0003 | 0 | 0 |
| **Intermedia** | 12.000 | 12.003 | 0.003 | 0 | 0 |
| **Major** | 11.25 | 11.26 | 0.011 | 0 | 0 |

## B.6 Red Blood Cells

### General Equation

Accounting Equation: $IN - OUT + GEN - CON = ACC$

### Healthy:

$$Healthy\,RBC\,Count * VFR - (RBC\,IN + RBC\,GEN - RBC\,CON) + \frac{Healthy\,RBC\,Count * Blood\,Volume}{Healthy\,RBC\,Lifespan} - \frac{Healthy\,RBC\,Count * Blood\,Volume}{Healthy\,RBC\,Lifespan} = RBC\,ACC$$

$$= 0$$

**Thalassemia Minor**

$$Minor\,RBC\,Count * VFR - (RBC\,IN + RBC\,GEN - RBC\,CON) + \frac{Minor\,RBC\,Count * Blood\,Volume}{Minor\,RBC\,Lifespan} - \frac{Minor\,RBC\,Count * Blood\,Volume}{Minor\,RBC\,Lifespan} = RBC\,ACC = 0$$

**Thalassemia Intermedia**

$$\frac{Intermedia\,Hemoglobin\,Concentration * VFR}{Intermedia\,MCH * 10^{-10}} - (RBC\,IN + RBC\,GEN - RBC\,CON) + \frac{Intermedia\,Hemoglobin\,Concentration * Blood\,Volume}{Intermedia\,MCH * 10^{-10} * Intermedia\,RBC\,Lifespan} - \frac{Intermedia\,Hemoglobin\,Concentration * Blood\,Volume}{Intermedia\,MCH * 10^{-10} * Intermedia\,RBC\,Lifespan} = RBC\,ACC = 0$$

**Thalassemia Major**

$$\frac{Major\,Hemoglobin\,Concentration * VFR}{Major\,MCH * 10^{-10}} - (RBC\,IN + RBC\,GEN - RBC\,CON) + \frac{Major\,Hemoglobin\,Concentration * Blood\,Volume}{Major\,MCH * 10^{-10} * Major\,RBC\,Lifespan} - \frac{Major\,Hemoglobin\,Concentration * Blood\,Volume}{Major\,MCH * 10^{-10} * Major\,RBC\,Lifespan} = RBC\,ACC = 0$$

Table 29: Steady-State Red Blood Cell Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 3.64 | 3.64 | 0 | 0 | 0 |
| **Minor** | 3.67 | 3.67 | 0 | 0 | 0 |
| **Intermedia** | 2.24 | 2.24 | 0 | 0 | 0 |
| **Major** | 1.66 | 1.66 | 0 | 0 | 0 |

Table 30: Steady-State Red Blood Cell Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 12.4 | 12.4 | 0 | 0 | 0 |
| **Minor** | 12.5 | 12.5 | 0 | 0 | 0 |
| **Intermedia** | 4.67 | 4.67 | 0 | 0 | 0 |
| **Major** | 3.25 | 3.25 | 0 | 0 | 0 |

Table 31: Steady-State Red Blood Cell Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 7.02 | 7.02 | 0 | 0 | 0 |
| **Minor** | 7.07 | 7.07 | 0 | 0 | 0 |
| **Intermedia** | 2.08 | 2.08 | 0 | 0 | 0 |
| **Major** | 1.39 | 1.39 | 0 | 0 | 0 |

Table 32: Steady-State Red Blood Cell Level in the Gastrointestinal Tract in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 5.46 | 5.46 | 0 | 0 | 0 |
| **Minor** | 5.50 | 5.50 | 0 | 0 | 0 |
| **Intermedia** | 1.12 | 1.12 | 0 | 0 | 0 |
| **Major** | 0.675 | 0.675 | 0 | 0 | 0 |

Table 33: Steady-State Red Blood Cell Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 0.4004 | 0.4002 | 0 | 0.000150 | 0 |
| **Minor** | 0.4035 | 0.4033 | 0 | 0.000152 | 0 |
| **Intermedia** | 0.0821 | 0.0819 | 0 | 0.000165 | 0 |
| **Major** | 0.0495 | 0.0489 | 0 | 0.000567 | 0 |

Table 34: Steady-State Red Blood Cell Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **RBC IN** ($\times 10^{12}$/min) | **RBC OUT** ($\times 10^{12}$/min) | **RBC GEN** ($\times 10^{12}$/min) | **RBC CON** ($\times 10^{12}$/min) | **RBC ACC** (RBC/min) |
|---|---|---|---|---|---|
| **Healthy** | 0.4004 | 0.4002 | 0.000150 | 0 | 0 |
| **Minor** | 0.4035 | 0.4033 | 0.000152 | 0 | 0 |
| **Intermedia** | 0.0821 | 0.0819 | 0.000165 | 0 | 0 |
| **Major** | 0.0495 | 0.0489 | 0.000567 | 0 | 0 |

## B.7 Iron

### General Equation

Accounting Equation: $IN - OUT + GEN - CON = ACC$

### Healthy:

$$VFR * Iron\,Bound\,to\,Transferrin - (Iron\,IN + Iron\,GEN - Iron\,CON) + \frac{Healthy\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Healthy\,RBC\,Lifespan} - \frac{Healthy\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Healthy\,RBC\,Lifespan}$$

$$= Iron\,ACC = 0$$

**Thalassemia Minor**

$$VFR * Iron\,Bound\,to\,Transferrin - (Iron\,IN + Iron\,GEN - Iron\,CON) + \frac{Minor\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Minor\,RBC\,Lifespan} - \frac{Minor\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Minor\,RBC\,Lifespan}$$

$$= Iron\,ACC = 0$$

**Thalassemia Intermedia**

$$VFR * Iron\,Bound\,to\,Transferrin + Intermedia\,Iron\,Absorption\,in\,GI\,Tract - (Iron\,IN + Iron\,GEN - Iron\,CON) + \frac{Intermedia\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Intermedia\,RBC\,Lifespan} - \frac{Intermedia\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Intermedia\,RBC\,Lifespan}$$

$$= Iron\,ACC$$

**Thalassemia Major**

$$VFR * Iron\,Bound\,to\,Transferrin + Major\,Iron\,Absorption\,in\,GI\,Tract - (Iron\,IN + Iron\,GEN - Iron\,CON) + \frac{Major\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Major\,RBC\,Lifespan} - \frac{Major\,Hemoglobin\,Concentration * Blood\,Volume * Iron\,Bound\,to\,Hemoglobin}{100 * Major\,RBC\,Lifespan}$$

$$= Iron\,ACC$$

Table 35: Steady-State Iron Level in the Brain in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 0.63 | 0.63 | 0 | 0 | 0 |
| **Minor** | 0.63 | 0.63 | 0 | 0 | 0 |
| **Intermedia** | 0.63 | 0.63 | 0 | 0 | 0 |
| **Major** | 0.63 | 0.63 | 0 | 0 | 0 |

Table 36: Steady-State Iron Level in the Lungs in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 2.14 | 2.14 | 0 | 0 | 0 |
| **Minor** | 2.14 | 2.14 | 0 | 0 | 0 |
| **Intermedia** | 2.14 | 2.14 | 0 | 0 | 0 |
| **Major** | 2.14 | 2.14 | 0 | 0 | 0 |

Table 37: Iron Level in the Liver in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 1.215 | 1.215 | 0 | 0 | 0 |
| **Minor** | 1.215 | 1.215 | 0 | 0 | 0 |
| **Intermedia** | 1.218 | 1.215 | 0 | 0 | 0.003 |
| **Major** | 1.222 | 1.215 | 0 | 0 | 0.007 |

Table 38: Steady-State Iron Level in the Gastrointestinal in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 0.945 | 0.945 | 0 | 0 | 0 |
| **Minor** | 0.945 | 0.945 | 0 | 0 | 0 |
| **Intermedia** | 0.948 | 0.948 | 0 | 0 | 0 |
| **Major** | 0.952 | 0.952 | 0 | 0 | 0 |

Table 39: Steady-State Iron Level in the Spleen in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 0.0693 | 0.0862 | 0.0169 | 0 | 0 |
| **Minor** | 0.0693 | 0.0829 | 0.0136 | 0 | 0 |
| **Intermedia** | 0.0693 | 0.0855 | 0.0162 | 0 | 0 |
| **Major** | 0.0693 | 0.111 | 0.0421 | 0 | 0 |

Table 40: Steady-State Iron Level in the Bone Marrow in a Healthy Individual and Different Severities of β-Thalassemia

| **Severity** | **Iron IN** ($\mathbf{mg/min}$) | **Iron OUT** ($\mathbf{mg/min}$) | **Iron GEN** ($\mathbf{mg/min}$) | **Iron CON** ($\mathbf{mg/min}$) | **Iron ACC** ($\mathbf{mg/min}$) |
|---|---|---|---|---|---|
| **Healthy** | 0.225 | 0.208 | 0 | 0.0169 | 0 |
| **Minor** | 0.225 | 0.211 | 0 | 0.0136 | 0 |
| **Intermedia** | 0.225 | 0.209 | 0 | 0.0162 | 0 |
| **Major** | 0.225 | 0.183 | 0 | 0.0421 | 0 |

## B.8 Threshold Values

### Equations

$$Total\,Flow\,Rate\,of\,Hemoglobin\,to\,Brain\,to\,prevent\,Death\ = \frac{O_2\,Consumption\,of\,Blood * Brain\,VFR}{Arterial\,Hemoglobin\,Saturation * O_2\,Carrying\,Ability\,of\,Hemoglobin}$$

$$Total\,Flow\,Rate\,of\,Hemoglobin\,to\,Brain\,to\,prevent\,Cognitive\,Impairment\ = \frac{Brain\,VFR * Threshold\,Concentration\,of\,Hemoglobin\,toBrain\,to\,prevent\,Cognitive\,Impairment}{100}$$

$$Hemoglobin\,Concentration\,to\,prevent\,Death\ = \frac{Total\,Flow\,Rate\,of\,Hemoglobin\,to\,Brain\,to\,prevent\,Death * 100}{Brain\,VFR}$$

Table 41: Threshold Values in Brain for Cognitive Impairment and Death

| | **Total Flow Rate of Hemoglobin to Brain** $(\mathbf{g/min})$ | **Hemoglobin Concentration** $(\mathbf{g/dL})$ |
|---|---|---|
| **Cognitive Impairment** | 42.0 | 6 |
| **Death** | 26.9 | 3.84 |

# C Results

## C.1 Thalassemia Minor

Table 42: Component Levels over 60 Days in the Liver in β-Thalassemia Minor

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 60.1 | 1.56 | 43.5 | 1.35 | 155 | 0.270 | 0.254 |
| **Day 20** | 60.1 | 1.54 | 42.9 | 1.97 | 155 | 0.270 | 0.255 |
| **Day 40** | 60.1 | 1.53 | 42.5 | 2.36 | 155 | 0.270 | 0.256 |
| **Day 60** | 60.1 | 1.52 | 42.2 | 2.67 | 155 | 0.270 | 0.256 |

Table 43: Component Levels over 60 Days in the Spleen in β-Thalassemia Minor

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 15.4 | 0.400 | 11.2 | 0.346 | 39.9 | 0.0693 | 0 |
| **Day 20** | 15.4 | 0.395 | 11.0 | 0.505 | 39.9 | 0.0693 | 0 |
| **Day 40** | 15.4 | 0.392 | 10.9 | 0.606 | 39.9 | 0.0693 | 0 |
| **Day 60** | 15.4 | 0.389 | 10.8 | 0.685 | 39.9 | 0.0693 | 0 |

Table 44: Component Levels over 60 Days in the Bone Marrow in β-Thalassemia Minor

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 50.1 | 1.30 | 36.3 | 1.12 | 129 | 0.225 | 0 |
| **Day 20** | 50.1 | 1.28 | 35.7 | 1.64 | 129 | 0.225 | 0 |
| **Day 40** | 50.1 | 1.27 | 35.4 | 1.97 | 129 | 0.225 | 0 |
| **Day 60** | 50.1 | 1.26 | 35.1 | 2.22 | 129 | 0.225 | 0 |

Table 45: Component Levels over 60 Days in the Brain in β-Thalassemia Minor

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 140 | 3.64 | 102 | 3.14 | 363 | 0.630 | 0 |
| **Day 20** | 140 | 3.59 | 100 | 4.59 | 363 | 0.630 | 0 |
| **Day 40** | 140 | 3.56 | 99.1 | 5.51 | 363 | 0.630 | 0 |
| **Day 60** | 140 | 3.54 | 98.4 | 6.23 | 363 | 0.630 | 0 |

Table 46: Component Levels over 60 Days in the Gastrointestinal Tract in β-Thalassemia Minor

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 210 | 5.46 | 152 | 4.71 | 544 | 0.945 | 0 |
| **Day 20** | 210 | 5.39 | 150 | 6.88 | 544 | 0.945 | 0 |
| **Day 40** | 210 | 5.34 | 149 | 8.26 | 544 | 0.945 | 0 |
| **Day 60** | 210 | 5.31 | 148 | 9.34 | 544 | 0.945 | 0 |

## C.2 Thalassemia Intermedia

Table 47: Component Levels over 60 Days in the Liver in β-Thalassemia Intermedia

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 48.2 | 1.56 | 34.9 | 1.08 | 155 | 0.270 | 0.254 |
| **Day 20** | 37.9 | 1.19 | 22.0 | 6.34 | 155 | 0.270 | 0.572 |
| **Day 40** | 32.9 | 1.02 | 15.7 | 8.87 | 155 | 0.270 | 0.758 |
| **Day 60** | 30.0 | 0.913 | 12.0 | 10.4 | 155 | 0.270 | 0.905 |

Table 48: Component Levels over 60 Days in the Spleen in β-Thalassemia Intermedia

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 12.4 | 0.400 | 8.96 | 0.227 | 39.9 | 0.0693 | 0 |
| **Day 20** | 9.73 | 0.306 | 5.64 | 1.63 | 39.9 | 0.0693 | 0 |
| **Day 40** | 8.45 | 0.261 | 4.03 | 2.28 | 39.9 | 0.0693 | 0 |
| **Day 60** | 7.70 | 0.234 | 3.08 | 2.66 | 39.9 | 0.0693 | 0 |

Table 49: Component Levels over 60 Days in the Bone Marrow in β-Thalassemia Intermedia

| | $O_2$ $(mL/min)$ | RBC Count $(\times 10^{12}/min)$ | $H_A$ $(g/min)$ | $H_{Other}$ $(g/min)$ | $CO_2$ $(mL/min)$ | Free Fe $(mg/min)$ | Fe Stored (g) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 40.2 | 1.30 | 29.1 | 0.9 | 129 | 0.225 | 0 |
| **Day 20** | 31.6 | 0.995 | 18.3 | 5.28 | 129 | 0.225 | 0 |
| **Day 40** | 27.4 | 0.848 | 13.1 | 7.40 | 129 | 0.225 | 0 |
| **Day 60** | 25.0 | 0.761 | 10.0 | 8.65 | 129 | 0.225 | 0 |

Table 50: Component Levels over 60 Days in the Brain in β-Thalassemia Intermedia

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 113 | 3.64 | 81.5 | 2.52 | 363 | 0.630 | 0 |
| **Day 20** | 88.5 | 2.79 | 51.2 | 14.8 | 363 | 0.630 | 0 |
| **Day 40** | 76.8 | 2.37 | 36.6 | 20.7 | 363 | 0.630 | 0 |
| **Day 60** | 70.0 | 2.13 | 28.0 | 24.2 | 363 | 0.630 | 0 |

Table 51: Component Levels over 60 Days in the Gastrointestinal Tract in β-Thalassemia Intermedia

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 169 | 5.46 | 122 | 3.78 | 544 | 0.945 | 0 |
| **Day 20** | 133 | 4.18 | 76.9 | 22.2 | 544 | 0.945 | 0 |
| **Day 40** | 115 | 3.56 | 55.0 | 31.1 | 544 | 0.945 | 0 |
| **Day 60** | 105 | 3.19 | 42.0 | 36.3 | 544 | 0.945 | 0 |

## C.3 Thalassemia Major

Table 52: Component Levels over 60 Days in the Liver in β-Thalassemia Major

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 48.2 | 1.56 | 34.9 | 1.08 | 155 | 0.270 | 0.254 |
| **Day 20** | 46.6 | 1.67 | 16.6 | 18.2 | 155 | 0.270 | 0.493 |
| **Day 40** | 29.8 | 1.13 | 4.66 | 17.6 | 155 | 0.270 | 1.06 |
| **Day 60** | 14.3 | 0.559 | 0.379 | 10.3 | 155 | 0.270 | 1.62 |

Table 53: Component Levels over 60 Days in the Spleen in β-Thalassemia Major

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 12.4 | 0.400 | 8.96 | 0.277 | 39.9 | 0.0693 | 0 |
| **Day 20** | 12.0 | 0.429 | 4.25 | 4.68 | 39.9 | 0.0693 | 0 |
| **Day 40** | 7.66 | 0.289 | 1.20 | 4.52 | 39.9 | 0.0693 | 0 |
| **Day 60** | 3.67 | 0.143 | 0.0973 | 2.64 | 39.9 | 0.0693 | 0 |

Table 54: Component Levels over 60 Days in the Bone Marrow in β-Thalassemia Major

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 40.2 | 1.30 | 29.1 | 0.900 | 129 | 0.225 | 0 |
| **Day 20** | 38.9 | 1.39 | 13.8 | 15.2 | 129 | 0.225 | 0 |
| **Day 40** | 24.9 | 0.939 | 3.89 | 14.7 | 129 | 0.225 | 0 |
| **Day 60** | 11.9 | 0.466 | 0.316 | 8.59 | 129 | 0.225 | 0 |

Table 55: Component Levels over 60 Days in the Brain in β-Thalassemia Major

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 113 | 3.64 | 81.5 | 2.52 | 363 | 0.630 | 0 |
| **Day 20** | 109 | 3.90 | 38.6 | 42.6 | 363 | 0.630 | 0 |
| **Day 40** | 69.9 | 2.63 | 10.9 | 41.1 | 363 | 0.630 | 0 |
| **Day 60** | 33.4 | 1.30 | 0.884 | 24.0 | 363 | 0.630 | 0 |

Table 56: Component Levels over 60 Days in the Gastrointestinal Tract in β-Thalassemia Major

| | $\mathbf{O_2}$ $(\mathbf{mL/min})$ | **RBC Count** $(\times 10^{12}\mathbf{/min})$ | $\mathbf{H_A}$ $(\mathbf{g/min})$ | $\mathbf{H_{Other}}$ $(\mathbf{g/min})$ | $\mathbf{CO_2}$ $(\mathbf{mL/min})$ | **Free Fe** $(\mathbf{mg/min})$ | **Fe Stored (g)** |
|---|---|---|---|---|---|---|---|
| **Day 0** | 169 | 5.46 | 122 | 3.78 | 544 | 0.945 | 0 |
| **Day 20** | 163 | 5.85 | 57.9 | 63.8 | 544 | 0.945 | 0 |
| **Day 40** | 104 | 3.95 | 16.3 | 61.6 | 544 | 0.945 | 0 |
| **Day 60** | 50.1 | 1.96 | 1.33 | 36.1 | 544 | 0.945 | 0 |

## C.4 Percent Change in Total Component Values

### C.4.1 Thalassemia Minor

Table 57: Total Component Values and Percent Changes in β-Thalassemia Minor

| | $\mathbf{O_2}$ $(\mathbf{mL/min})$ | **RBC Count** $(\times 10^{12}\mathbf{/min})$ | $\mathbf{H_A}$ $(\mathbf{g/min})$ | $\mathbf{H_{Other}}$ $(\mathbf{g/min})$ | $\mathbf{CO_2}$ $(\mathbf{mL/min})$ | **Free Fe** $(\mathbf{mg/min})$ | **Fe Stored (g)** |
|---|---|---|---|---|---|---|---|
| **Day 0** | 476 | 12.4 | 345 | 10.7 | 1230 | 0.945 | 0.254 |
| **Day 20** | 476 | 12.2 | 340 | 15.6 | 1230 | 0.945 | 0.255 |
| **Day 40** | 476 | 12.1 | 337 | 18.7 | 1230 | 0.945 | 0.256 |
| **Day 60** | 476 | 12.0 | 335 | 21.1 | 1230 | 0.945 | 0.256 |
| **Percent Change from Day 0 to Day 60** | 0% | -2.76% | -3.04% | +98.2% | 0% | 0% | +0.787% |

### C.4.2 Thalassemia Intermedia

Table 58: Total Component Values and Percent Changes in β-Thalassemia Intermedia

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 383 | 12.4 | 276 | 8.51 | 1230 | 2.14 | 0.254 |
| **Day 20** | 301 | 9.46 | 174 | 50.3 | 1230 | 2.14 | 0.572 |
| **Day 40** | 261 | 8.06 | 124 | 70.4 | 1230 | 2.14 | 0.758 |
| **Day 60** | 238 | 7.23 | 95.1 | 82.2 | 1230 | 2.14 | 0.905 |
| **Percent Change from Day 0 to Day 60** | -37.9% | -41.5% | -65.6% | +866% | 0% | 0% | +256% |

### C.4.3 Thalassemia Major

Table 59: Total Component Values and Percent Changes in β-Thalassemia Major

| | $O_2$ ($mL/min$) | RBC Count ($\times 10^{12}/min$) | $H_A$ ($g/min$) | $H_{Other}$ ($g/min$) | $CO_2$ ($mL/min$) | Free Fe ($mg/min$) | Fe Stored ($g$) |
|---|---|---|---|---|---|---|---|
| **Day 0** | 383 | 12.4 | 276 | 8.56 | 1230 | 2.14 | 0.254 |
| **Day 20** | 370 | 13.2 | 131 | 144 | 1230 | 2.14 | 0.493 |
| **Day 40** | 236 | 8.94 | 37.0 | 140 | 1230 | 2.14 | 1.06 |
| **Day 60** | 113 | 4.43 | 3.01 | 81.6 | 1230 | 2.14 | 1.62 |
| **Percent Change from Day 0 to Day 60** | -70.4% | -64.2% | -98.9% | +854% | 0% | 0% | +538% |

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