

## Supporting Information - Table.

### RBC survival for all participants compared to normal individuals.<sup>1</sup>

Measurement	Mean (SD)		Median (IQR)		Range	
	HbSS	Normal	HbSS	Normal	HbSS	Normal
Mean survival (days) <sup>2</sup>	31.9 (12.5)	110.7 (8.8)	30.5 (23.3 - 41.3)	111 (105-118)	14.1 - 53.6	96 - 121
Median survival (days) <sup>3</sup>	28.2 (11.9)	118.7 (9.0)	24.8 (19.5 - 38.9)	118.5 (113.5- 126.8)	12.0 - 50.2	103 - 129
Mean RBC age (days) <sup>4</sup>	17.6 (5.6)	61 (3.8)	17.4 (14.2 - 22.5)	62 (58.5 - 64)	8.4 - 26.6	54 - 64

Abbreviations: HbSS, homozygous sickle cell anemia; IQR, interquartile range; RBC, red blood cell; SD, standard deviation.

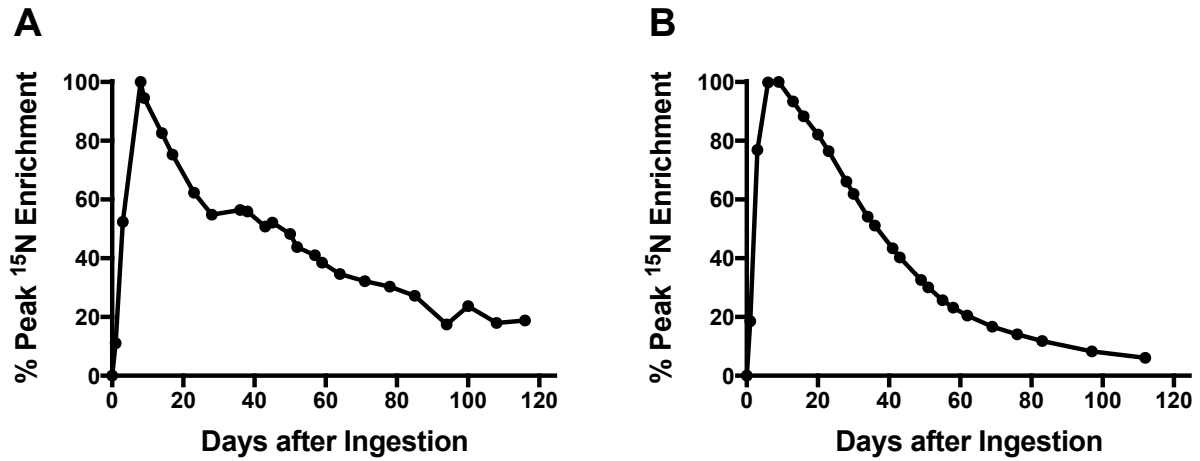
<sup>1</sup>RBC survival in normal individuals (N=6) measured using the same <sup>15</sup>N-glycine stable isotope method as the study participants.<sup>11</sup>

<sup>2</sup>The mean RBC survival across the entire cell population calculated by integration of the survival curve. The mean survival is impacted by non-uniformity of the distribution of lifespans across the RBC population.

<sup>3</sup>The time point obtained by interpolation at which cell labelling has fallen from its maximum to half maximum, where half the RBCs have longer survival and half have shorter survival. This may differ from mean RBC survival when there is non-uniformity of the population.

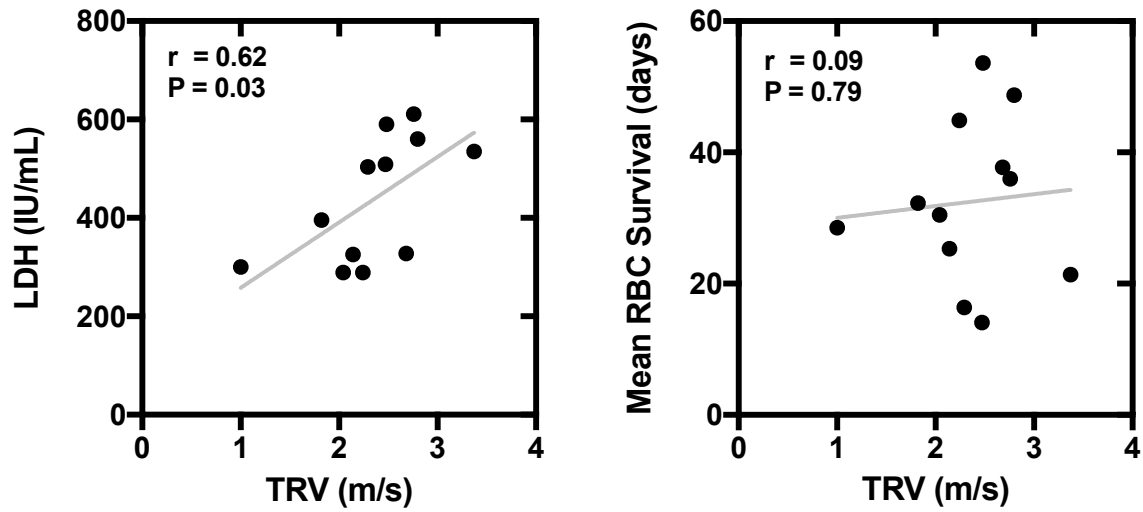
<sup>4</sup>The mean age of all RBCs in circulation, derived from the survival curve. The mean age is impacted by the distribution of cells across their lifespan, from release into the blood stream to removal from the blood stream. Under ideal circumstances with normal cells at steady state, it will be near but not necessarily equivalent to half of the mean red cell survival.

## Supporting Information - Figure 1.



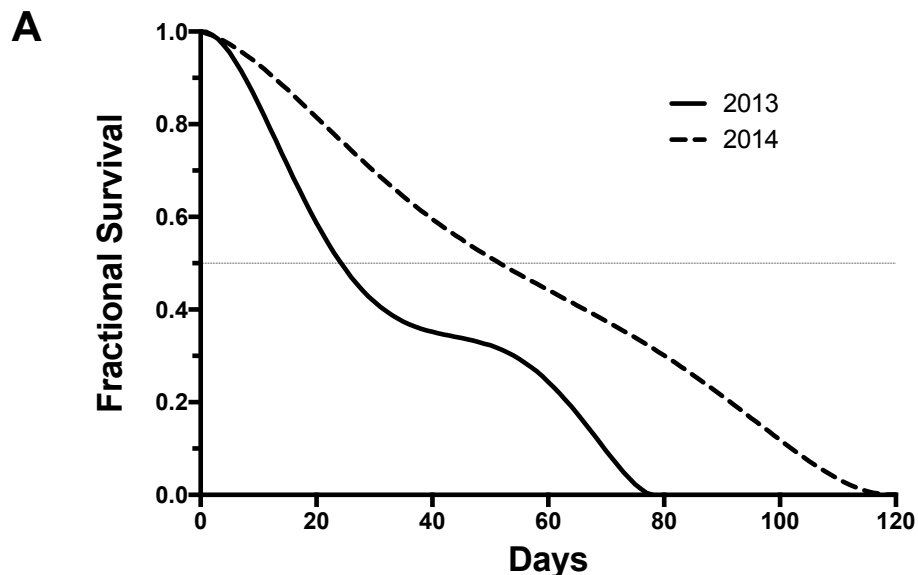
**Representative percent atom percent excess (%APE) curves.** For all subjects, baseline (pre-ingestion)  $^{15}\text{N}/^{14}\text{N}$  ratios were subtracted from ratios obtained after administration of stable isotope to calculate the atom percent excess (APE). A relative atom percent excess (%APE) was derived for each time point using the maximum value as 100%. Panel A shows participant #2 performed on a Europa Scientific 20/20 gas isotope ratio mass spectrometer. Panel B shows participant #10 performed on a Thermo Finnigan Delta V gas isotope ratio mass spectrometer.

Supporting Information - Figure 2.

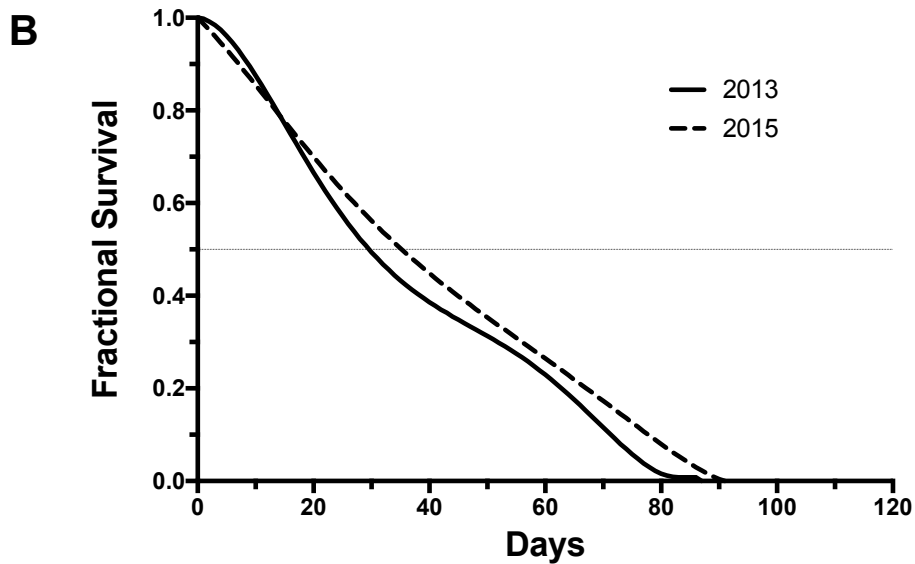


Tricuspid jet regurgitant velocity (TRV) correlates with LDH but not directly measured mean RBC survival. We found a positive linear correlation between TRV and LDH. However, we found no correlation between TRV and directly measured RBC survival in the same individuals. Therefore, the relationship between TRV and LDH is not explained by hemolytic rate.

Supporting Information - Figure 3.



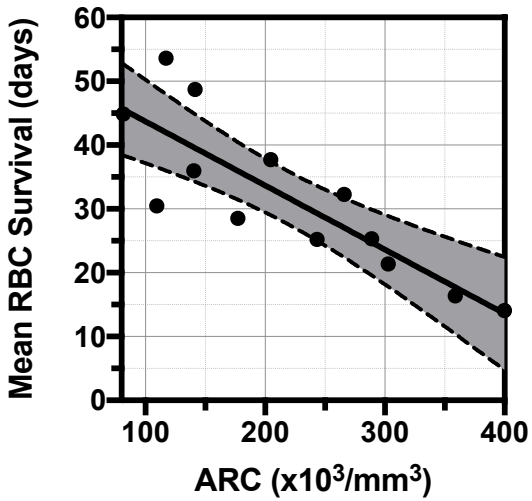
Year	Mean RBC Survival (days)	HbF (%)	MCV (fL)	WBC (/mm <sup>3</sup> )	ANC (/mm <sup>3</sup> )	Platelets (/mm <sup>3</sup> )	Hb (g/dL)	ARC (x10 <sup>3</sup> /mm <sup>3</sup> )	Hydroxyurea (mg/kg/day)
2013	33.9	19	119	6,400	2,400	330,000	10.1	109.5	29
2014	54.8	23.7	127	4,300	1,800	271,000	9.6	81.6	31



Year	Mean RBC Survival (days)	HbF (%)	MCV (fL)	WBC (/mm <sup>3</sup> )	ANC (/mm <sup>3</sup> )	Platelets (/mm <sup>3</sup> )	Hb (g/dL)	ARC (x10 <sup>3</sup> /mm <sup>3</sup> )	Hydroxyurea (mg/kg/day)
2013	36.1	25	104.7	6,200	5,950	312,000	10.9	140.3	23
2015	39.4	26.9	106	5,300	2,600	246,000	10.5	141.6	23

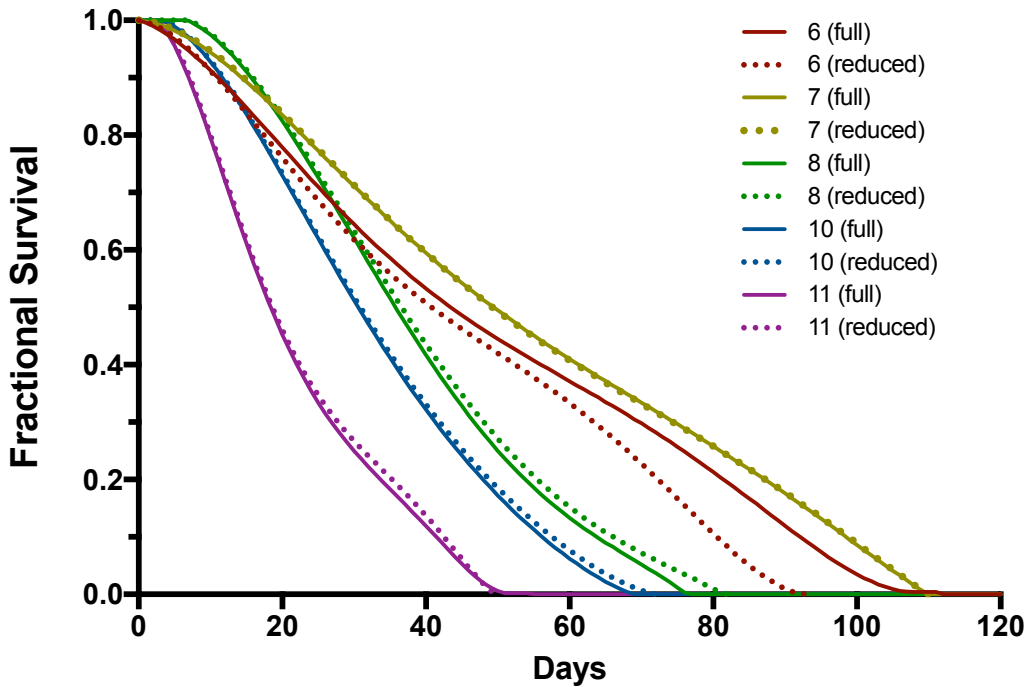
**Repeated RBC survival measurements.** Two participants completed two separate labeling studies. Panel A: the hydroxyurea dose of participant #5 was increased to maximal tolerated dose between the two studies. The HbF level increased from 19 to 24%, and this was associated with a 20.9-day increase in RBC survival. Panel B: participant #6 received the same dose of hydroxyurea during both studies. The HbF level increased from 25 to 26.9%, and this was associated with a 3.3-day increase in RBC survival.

Supporting Information - Figure 4.



**Linear relationship between ARC and mean RBC survival.** A linear regression line with 95% confidence limits is shown. An ARC of 300,000/ $\mu$ L, for example, would be consistent with an RBC lifespan of 18 - 29 days, which represents a 61% difference in RBC lifespan. Accordingly, ARC is not a robust surrogate marker of hemolytic rate for individual patients, but it may be useful in large population studies.

Supporting Information - Figure 5.



**Comparison of full and reduced data sets for calculation of RBC survival curves.** For 5 participants, we retrospectively omitted several measurements of atom percent excess (APE) beginning with the fifth week of the labeling study for the calculation of RBC survival curves, reducing the number of APE time-points from 26 (“full”) to 18 (“reduced”). The survival curve from the full (solid lines) and reduced (dotted lines) datasets are shown. The reduced dataset produced reasonably concordant results. For these 5 studies the mean absolute difference in mean RBC survival ( $|\text{mean RBC survival}_{\text{full}} - \text{mean RBC survival}_{\text{reduced}}|$ ) was 1.4 days with a standard deviation of 1.7 days.