Integrative diagnosis of sickle cell disease patients for personalized medicine

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INTRODUCTION

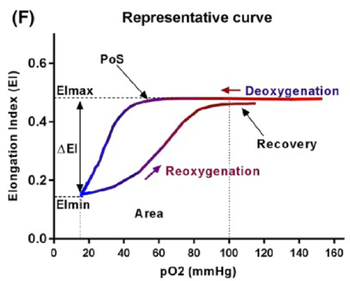
- Sickle cell disease (SCD) is a chronic life threatening disorder, caused by the presence of structurally abnormal adult hemoglobin S (HbS) that under low oxygen saturation forms polymers damaging the RBC structure, referred to as 'sickling'. Sickled erythrocytes result in hemolytic anemia and recurrent vaso-occlusive crisis, leading to long-term morbidity and ultimate early death.
- Although this is a monogenic disorder, the phenotypic characterization of the disease is highly heterogenous and unpredictable.
- Laser Optical Rotational Red Cell Analyzer (LoRRca) is the next generation ektacytometer that measures RBC deformability as function of pO2 and allows monitoring of sickling behavior in SCD patients.
- In the GenoMed4ALL project, oxygen gradient ektacytometry data will be integrated with genomics, metabolomics and clinical data of 1000 SCD patients. This will allow better characterization of SCD and development of Artificial Intelligence (AI) algorithms for personalized medicine.

OBJECTIVE(S)

To analyze the correlation of Lorrca parameters (PoS, EImax and EImin) with:

- SCD genotypes (SS, Sβo , SC and Sβ+)
- Hydroxyurea treatment (HU-, HU+)
- Levels of HbF

METHOD(S)



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- **Maximum EI (Eimax**) represents the baseline position reflecting the overall deformability of the total RBC population at ambient air.
- **Minimum EI (Eimin**) represents minimal deformability after deoxygenation and reflects changes in the shape and orientation of RBCs upon deoxygenation
- **Point of Sickling (PoS)** is the pO_2 at which a 5% decrease of EI_{max} during deoxygenation is measured and represents the oxygen tension where the sickling process starts.

This is a longitudinal observational study and our fist results were analysed as following :

1st All patients with SS, Sβo , SC and Sβ+ genotypes, older than 1yo at steady state with no transfusion in the last 3 months were analyzed by oxygen gradient ektacytometry. Derived parameters were correlated with genotypes.

2nd In patients with severe genotype (SS, Sβ°) the oxygen gradient ektacytometry parameters were correlated with hydroxyurea options (HU-, HU+) and HbF.

RESULT(S)

49 samples were analyzed: 32 SS, 2 Sβo , 12 SC and 3 Sβ+.

- PoS and EImin allowed patients' clustering in 2 groups according to genotype: SS vs. Sβo , SC and Sβ+ SS.
- EImin showed statistically significant Scheffe test value in discriminating SS vs Sßo and SS vs SC, while PoS was statistically significant only in discriminating SS vs SC.

Genotype	n	PoS Mean±SD	EImax Mean±SD	EImin Mean±SD
SS	32	34,34 ± 5,0	0,45 ± 0,1	0,23 ± 0,1
Sβ0	2	25,13 ± 0,2	0,53 ± 0,0	0,39 ± 0,0
SC	12	23,83 ± 3,9	0,44 ± 0,1	0,33 ± 0,0
Sβ+	3	27,40 ± 2,9	0,54 ± 0,0	0,33 ± 0,0
Sβ0,SC,Sβ+	17	24,62 ± 3,7	0,47 ± 0,1	0,34 ± 0,1

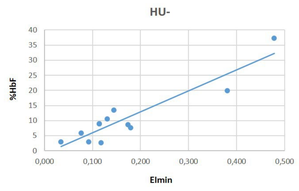
Pos, Eimax and Eimin Mean and Stndard Deviation (SD) values in relation to different SCD genotypes.

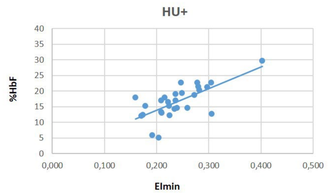
31 samples from severe SCD patients (SS, Sβo) were further analyzed for correlation with HU and HbF.

- The best correlation between Lorrca parameters and HbF was found in group of patients without treatment (HU-).
- EImin showed the highest correlation being 93% in HU- and 81% in HU+ group.

Pararmeter	n	HU in SS,Sß⁰	Mean±SD	HbF %correl
PoS	7	HU-	38,08 ± 9,5	-81%
EImax	7	HU-	0,39 ± 0,1	84%
Eimin	7	HU-	0,17 ± 0,1	93%
PoS	24	HU+	32,63 ± 5,0	-71%
Eimax	24	HU+	0,47 ± 0,1	46%
Eimin	24	HU+	0,25 ± 0,1	81%

Pos, Eimax and Eimin Mean and Stndard Deviation (SD) values in relation to Hydroxyurea (HU) and their coefficient of correlation with HbF.





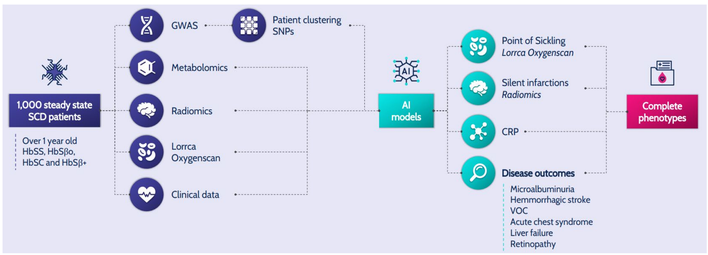
CONCLUSION(S)

Our results demonstrate the value of oxygen gradient ektacytometry to the characterization of SCD patients.:

- PoS and EImin were able to distinguish between SS and other genotypes, regardless of HU treatment.
- PoS, EImax and EImin all showed differences between HU+ and HU- groups, being EImin the most valuable one. EImin also showed the highest correlation with HbF.

It is highly likely that PoS could be impacted by other variables: 2,3 DPG, pH, RBC hydration, genetic variants or metabolomics.

Pooling data of 1000 SCD patients from at least 10 EU centers in the GenoMed4LL project is needed to improve results robustness. Standardization of Oxygenscan data generation should be ensured for data comparison and development AI algorithms for personalized medicine.



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