Changes in plasma extracellular RNAs: Independent associations with left and right ventricular reverse remodeling

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Introduction

Right ventricular (RV) systolic dysfunction is a prognostic marker in chronic heart failure (HF). However, reliable assessment of RV function remains a challenge. We examined the correlation of commonly used RV function parameters with i) markers of left ventricular (LV) remodeling and ii) dynamic changes in levels of plasma extracellular RNAs (exRNAs) in patients with chronic HF. We then created models using linear regression, regression trees and random forests in order to investigate the association between changes of exRNAs with the dynamic process of cardiac remodeling.

Sample

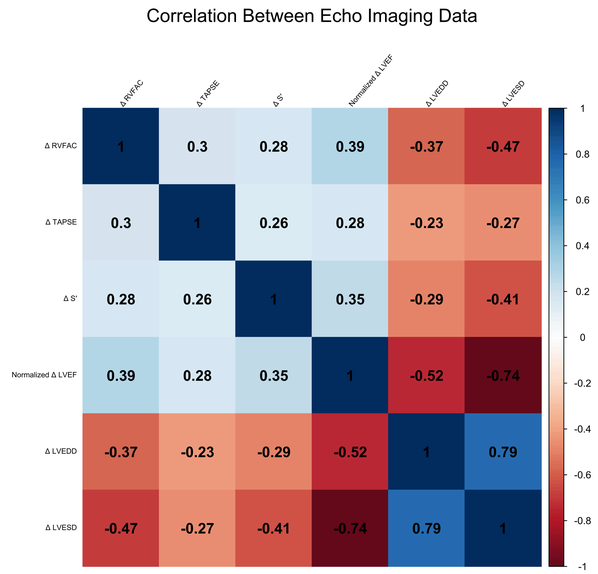
For PEARL–HF, we recruited 153 patients with chronic heart failure . The mean age of our sample was 66 years of age and 77% of the population were men. Heart failure was due to ischemic causes in 53% of our population.

PEARL-HF	N=153
Age(mean,SD)	66(11)
Gender (male)	118(77%)
Cause of Cardiomyopathy (ischemic)	81(53%)

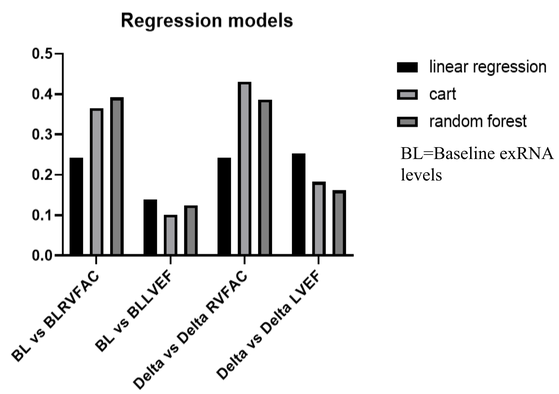
Methodology

RV function was assessed at 2 sequential time points using standard and tissue Doppler echocardiography by measuring RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), right ventricle systolic pressure (RVSP)and S prime. LV function was assessed by measuring ejection fraction (EF), left ventricle end systolic diameter (LVESD) and left ventricle end diastolic diameter (LVEDD). ExRNAs previously identified as associated with LV remodeling were assessed by a microfluidics-based PCR assay on plasma from 2 sequential visits.

We utilized Pearson correlation to discover our strongest candidates for associating exRNAs with right and left ventricular reverse remodeling. We then employed multivariate linear regressions to understand the miRNA's predictive strength. A LASSO linear regression was performed, and the most important miRNA were kept in the model. Using the selected miRNAs, three models were created i) Linear regression, ii Cart (regression trees), iii) Random forests. Regression Trees (CART) and Random Forests were used to understand any non-linear relations. We then proceeded to an internal validation of our models, bootstrapping with 90% training sets and 10% testing sets, running loops of 1000, 5000, and 10000 times, every time with a different random split.

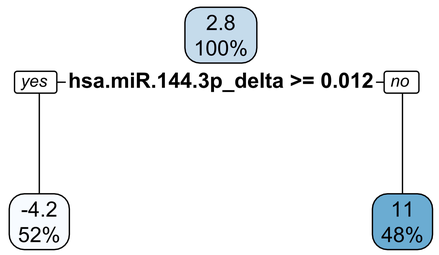


RVFAC correlates better with LVEF, LVESD and LVEDD when compared to TAPSE and S prime



BL=Baseline exRNA levels

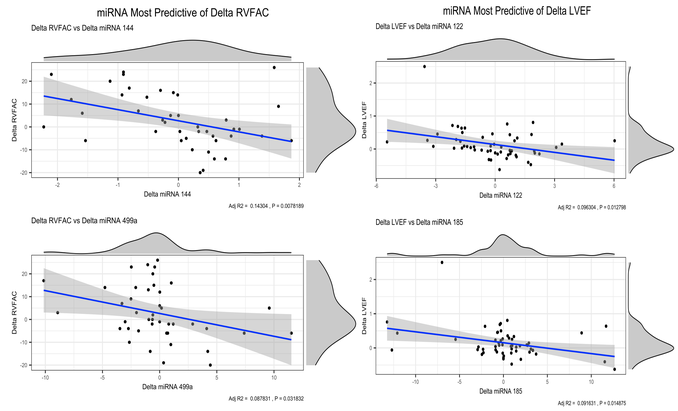
Comparison of R^2 between our models



Decision tree created using mir144. A change in CT value of 0.012 and more is associated with increase of LVEF by 11%. A change in miR144 less than 0.012 is associated with a decrease in LVEF by 4.2%.

Results

Among the RV function assessment modalities in the context of cardiac reverse remodeling, we found that an improvement in RVFAC was most strongly associated with an increase in LVEF. We created a linear regression model predicting delta in RVFAC using miR.1228.5p, miR.144.3p, miR.144.3p, miR.185.3p,and miR.499a.5p with adj R2 = 0.2037, $p < 0.02$. These findings were independent of delta LVEF. We then created a similar regression model predicting delta LVEF using miR.122.5p, miR.1228.5p, miR.185.3p, miR.193a.5p, and pir.57322 with adj R2 = 0.5015 $p < 0.001$. When we performed our internal validation using the 90/10 splits we observed similar results in the predictive power of our models.



Correlation plots for the ''top'' miRNAs used in our models

Conclusion

Changes in RVFAC better reflect changes in left ventricular remodeling. Changes in RVFAC were associated with changes in plasma levels of miR.1228.5p, miR.144.3p, miR.144.3p, miR.185.3p,and miR.499a.5p. Changes in LVEF were associated with changes in miR.122.5p, miR.1228.5p, miR.185.3p, miR.193a.5p, and pir.57322. ExRNAs could be used for the creation of models that could independently "predict" a change in right and left ventricular function. Further validation in complimentary datasets is needed.

Acknowledgments

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