Nourin miRNAs: Novel Blood Biomarkers For Early Identification Or Exclusion Of Myocardial Ischemia In Women Suspected Of Having Coronary Artery Disease (CAD)

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INTRODUCTION

Women are frequently present with questionable angina and more difficult to diagnose for stable CAD, contributing to many are under-diagnosis and under-treated, with worse outcomes. Nourin is an ***early*** inflammatory mediator that is released within 5 minutes by myocardial ischemia and its release is associated with post-ischemic cardiac inflammation (***Fig. 1***) [1]. We demonstrated that the Nourin regulatory miRNAs [miR-137 (a marker of cell damage) and miR-106b (a marker of inflammation)] can identify Myocardial ischemia in patients with UA and stratify severity of ischemia, with higher expression in acute STEMI patients compared to UA patients [2-5].

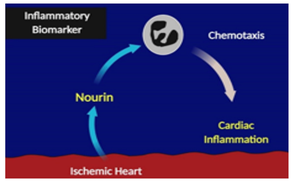
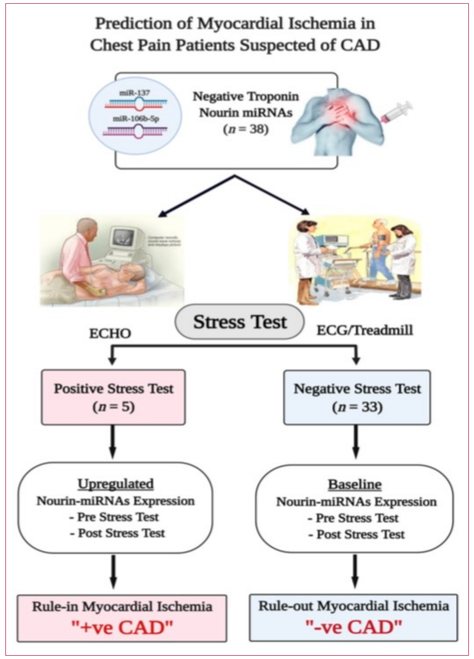


Fig. 1: **Nourin and ischemic hearts**

SUBJECTS / METHODS

Fig. 2: **Study Workflow**



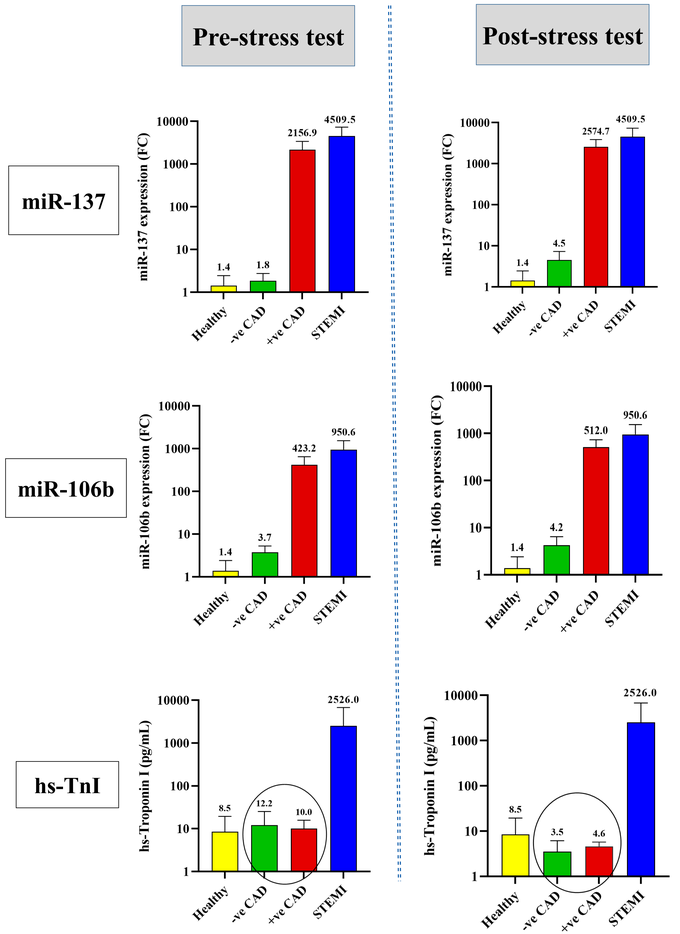
We tested the **hypothesis** that unlike high-sensitivity Troponin I (hs-TnI), Nourin-dependent miR-137 and miR-106b can identify or exclude myocardial ischemia in chest pain patients who are suspected of having CAD, as proven by stress ECHO/ECG test results.

Serum levels of Nourin miRNAs (qPCR) and plasma hs-TnI were measured blindly in:

1. Patients presenting with *chest pain* who are suspected of having CAD (n=38) both before stress ECHO/ECG test ("pre-test") and 30 minutes after test completion ("post-test") (***Fig. 2***). Five patients were stress test positive & 33 were test negative (miRNAs were measured in only 7 out of the 33 negative).
2. Acute STEMI patients (n=16).
3. Healthy subjects (n=16).

RESULTS

Fig. 3: **Nourin miRNAs are novel diagnostic biomarkers for myocardial ischemia in stable CAD patients. Hs-TnI was not elevated in positive stress test patients.**



1. Very low baseline levels of Nourin miRNAs were detected in healthy subjects (range: 1.38 to 1.43) and CAD negative (range: 1.84 to 4.53);
2. Significant upregulation of miR-137 (2,156 **pre** and 2,574 **post**) and miR-106b (423 **pre** and 521 **post**) in CAD positive (n=5) compared to low levels in CAD negative (n=7) (range: 1.84 to 4.53) both **pre** (*due to continuous release in response to chronic myocardial ischemia*) and **post**;
3. Higher levels in acute STEMI patients (4,509 for miR-137 & 950 for miR-106b **pre**) compared to CAD (2,156 & 423 **pre**);
4. Hs-TnI was <u>not</u> elevated in chest pain patients with positive stress test (value of 10.0 **pre** & 4.6 **post**), but was elevated in acute STEMI patients (2526);
5. As indicated in Table 1, both ***miRNAs have 85.7% sensitivity pre, while 100% post, with 100% specificity that can rule out myocardial ischemia.***

Table 1. Diagnostic efficacy of Nourin miR-137, miR-106b, and hs-TnI to discriminate stress test-positive patients (CAD) (n=5) from test-negative patients (no CAD) (n=7), both pre- & post-stress test.

Parameters	Pre-stress test (n=12)			Post-stress test (n=12)		
	miR-137 (FC)	miR-106b (FC)	Hs-TnI (ng/mL)	miR-137 (FC)	miR-106b (FC)	Hs-TnI (ng/mL)
AUC / p-value	1.0 /<0.005	1.0 / <0.005	0.5 /0.94	1.0 /<0.005	1.0 /<0.005	0.6 /0.78
Sensitivity (%)	85.7	85.7	---	100	100	---
Specificity (%)	100	100	---	100	100	---

CONCLUSIONS

Nourin miRNAs are novel blood-based biomarkers that:

1. Can ***early*** identify myocardial ischemia *in* ***women*** before it progresses to infarction, despite ambiguous/minimal symptoms;
2. Can be used as a ***negative test*** *with strong negative predictive value* to *promptly* exclude *myocardial ischemia in patients with chest pain*, thus ***avoiding further testing***; *in the same way as NT-proBNP is used for heart failure and D-dimer for thrombosis;*
3. Can be used for **routine screening** for early diagnosis of myocardial ischemia in patients *without injury or infarction,* thus allowing appropriate therapy, while still in the **stable state;**
4. Potentially improve the ***treatment algorithms for women***, patients' outcomes, quality of life, and **saving lives**.

REFERENCES

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