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RNA Biomarkers for Heart Failure: Is There a Correlation Between Heart and Blood Transcriptomics?

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Biomarkers play a crucial and growing role in diagnosing and managing cardiovascular disease. Currently, there are several well established biomarkers employing Elisa detection of serum peptides such as Troponin I (TnI), Troponin T (TnT), Natriuretic Peptide B (BNP), C-Reactive Protein (CRP), Creatine Kinase (CK-MB), Myeloperoxidase (MPO), Lipoprotein(a), and Myoglobin (Mgb). While RNA signature-based biomarkers have become standard of care in cancer, notably breast cancer[1], this approach has yet to fully emerge in cardiovascular medicine, although studies in patient tissues[2-5] _ENREF_2, preclinical models, and recent clinical studies[6, 7] support their utility.

To date clinical transcriptomic cardiac studies have employed gene/mRNA arrays[2-5, 8-10], exonic arrays[11, 12] _ENREF_6, microRNA arrays[13-17] _ENREF_8_ENREF_6, and it is expected that data on sequencing of long non-coding RNAs (lncRNAs) will emerge and grow rapidly in the coming few years. Whereas, RNAs in these studies were extracted either directly from heart tissue or peripheral blood, few studies have compared simultaneously global transcript profiles from heart tissue with peripheral blood, to determine whether there is a sufficient correlation between heart and blood transcriptomics to support the use of RNA blood biomarkers for diseases of the myocardium.

In the current issue of JACC Heart Failure, Gerling *et al*[18] address this important issue by comparing the global mRNA expression profiles from heart tissue to peripheral blood mononuclear cells (PBMCs) in an aldosterone rat model of heart failure. Their findings in

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gene expression and molecular pathway analysis supported a correlation between the blood and heart transcriptomics. The mRNA data was also supported by similar correlation in the increase of cytosolic calcium and zinc cations and the elevation of 8-isoprotane in cardiac myocytes and PBMCs. These findings add an important data point to the discussion of whether RNA blood biomarkers can serve as an appropriate surrogate for cardiovascular disease.

Several studies have shown that expression profiles obtained from myocardium provide highly accurate biomarkers of disease etiology and prognosis. Almost a decade ago, Kittleson and colleagues performed microarray analysis on tissue obtained from explanted hearts and revealed that ischemic cardiomyopathy (ICM) could be distinguished from non-ischemic cardiomyopathy (NICM) and that that the hearts of patients with NICM who do not undergo LVAD implantation resemble non-failing (NF) hearts more than those of the sicker NICM patients who require an LVAD before cardiac transplantation[2, 3] ENREF 2. Heidecker and co-workers identified a unique myocardial gene signature that distinguished patients with myocarditis with 100% sensitivity and specificity among a broad range of secondary cardiomyopathies including stress-induced cardiomyopathy, sarcoidosis, peripartum cardiomyopathy, arrhythmogenic right ventricular dysplasia, giant-cell myocarditis, and systemic lupus erythematosus[5]. Other investigators have shown the value of transcriptomic biomarkers for a variety of other cardiovascular disorders, including atherosclerotic coronary artery disease[10] and asymptomatic left ventricular dysfunction (ALVD)[9]. The question remains, however, can blood based transcriptomic biomarkers accurately substitute for those obtained directly by the affected tissue. Due to its amorphous nature, blood is rarely referred to as tissue. In reality, blood is tissue that is in direct physical contact with all organs (except the brain). Unsurprisingly, in a thoughtful study by Liew *et al*[19] who queried the absolute transcript levels of global mRNAs from 248 human blood samples on 248 microarray chips, and compared the results with publicly available microarray data from different human tissues, blood was shown to express tissue-specific transcripts. For example, the β-MHC transcript which is heart specific, was found to be expressed in the blood (Figure 1). Similarly, Adachi *et al*[20] reported based on global miRNA profiling of various human tissue and miRNA qPCR of cardiac patient sera, that miR-499 is heart specific and is up-regulated in the plasma of Myocardial Infarct (MI) patients, respectively.

In order for RNA transcripts to become clinically useful blood biomarkers in the future (Figure 2), there are several important studies that need to be performed:

1. Comparison between heart and blood transcripts in cardiac patients

Such studies will be ground breaking in screening for and identifying the transcripts that are potential biomarkers. It is possible that the transcripts to be identified could be previously unrelated to cardiac disease. In a study comparing the transcriptomics of brains and blood in Parkinson's disease patients, we identified an RNA splicing molecule among others to be dysregulated in both the brain and blood[21]. Taken into consideration the blood brain barrier, we anticipate that the comparison in heart disease to be much more direct and informative. In addition, these studies should not be limited to gene/mRNA expression, but rather include global miRNA expression, exonic expression/alternative splicing, and sequencing of lncRNAs.

2. The transcriptomic data from cardiac patients need to be correlated with clinical/functional measures

As in the informative study by Smih *et al*[9] where blood transcriptomic microarray data from ALVD patients was correlated with echocardiography data to predict clinical outcome, it will be important to use clinical data as the basis for hierarchical clustering of the transcriptomic data.

Otherwise, there will continue to be a gap between transcriptomic data and its clinical translation. Additionally, transcriptomic data can be correlated with the currently acceptable standard clinical assays used for cardiac diseases. For, example, Cheng *et al*[22] found that plasma miR-1 transcripts were correlated with plasma CK-BM levels in patients with MI.

3. Mathematical models need to be created to fit the blood transcriptomic data and the clinical data

Mathematical models need to be created integrating clinical data and the newly identified blood transcripts (which hopefully at this level would be screened down to hundreds rather than tens of thousands of genes or isoforms, and tens rather than hundreds of microRNAs and lncRNAs). Based on the combinatorial values of the absolute transcript levels, different models would be built to fit the expression data onto the clinical data. The final desired outcome is a simple readout/score of blood transcript data that, based on the built models, can predict the kind and level of cardiac disease as in Figure 2. These mathematical models will require validation in clinical populations, in a manner similar to the transcriptomic biomarkers developed using myocardial tissue[2-5, 17].

In conclusion, while further studies are warranted to make blood RNA transcripts as clinical biomarkers for cardiac diseases, we agree with Liew *et al*[19] that “blood cells can act as sentinels of disease”, and therefore we could capitalize on this property of blood for the diagnosis/prognosis of cardiac diseases. The current study by Gerling *et al*[18] _ENREF_15_ENREF_15_ENREF_15 provides additional supportive data for this concept. While direct sampling of myocardium might offer advantages for biomarker application, using peripheral blood has obvious benefit in terms of broader application and generalizability of transcriptomic biomarkers as they emerge in cardiovascular medicine.

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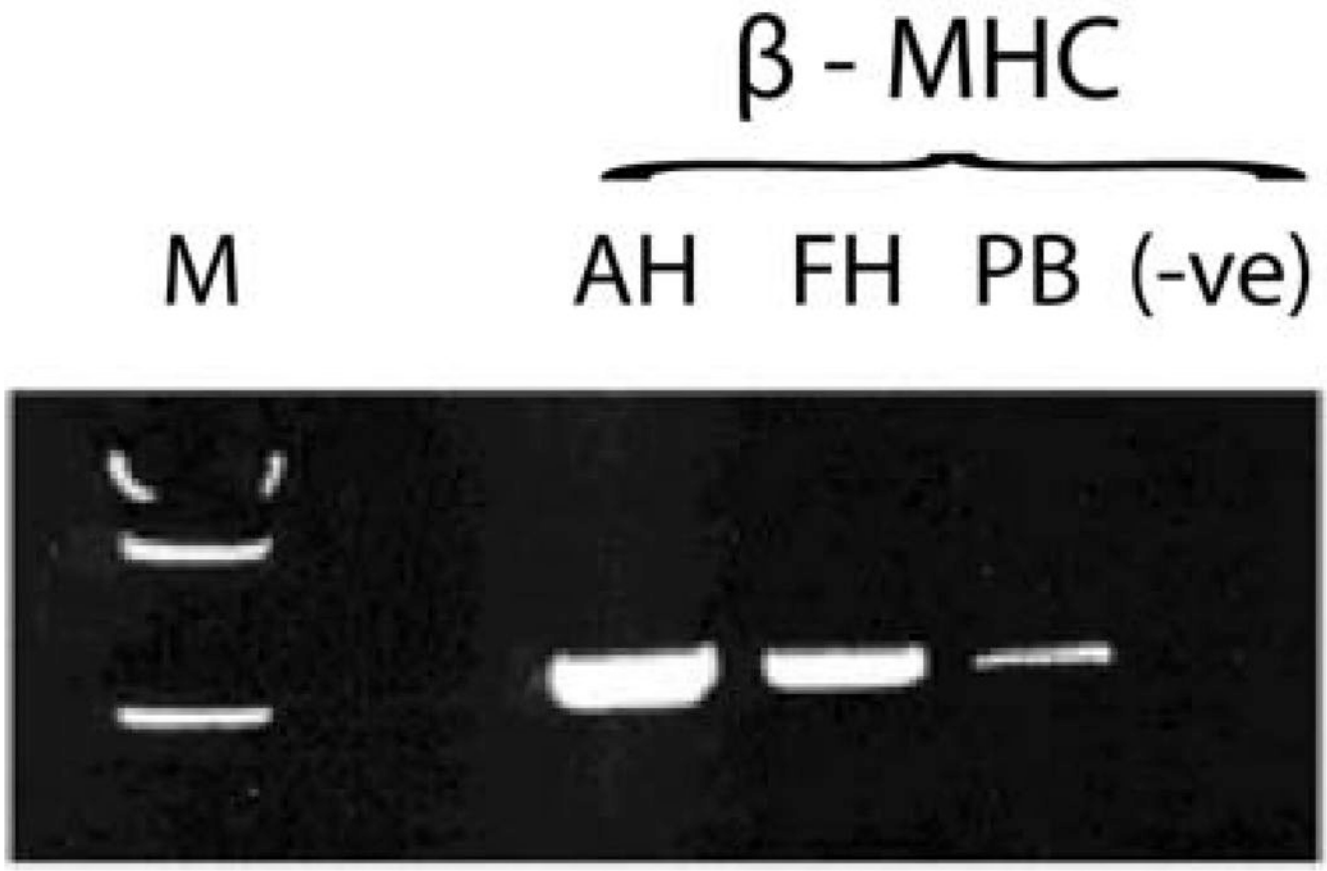

Figure 1. Heart specific transcripts expressed in blood

β-MHC transcripts were detected in human peripheral blood (PB). Positive controls used were human adult and fetal heart tissue (AH and FH respectively). No template/blank (-ve) was used as a negative control. M =molecular weight marker. Adapted from Liew et al (2006).

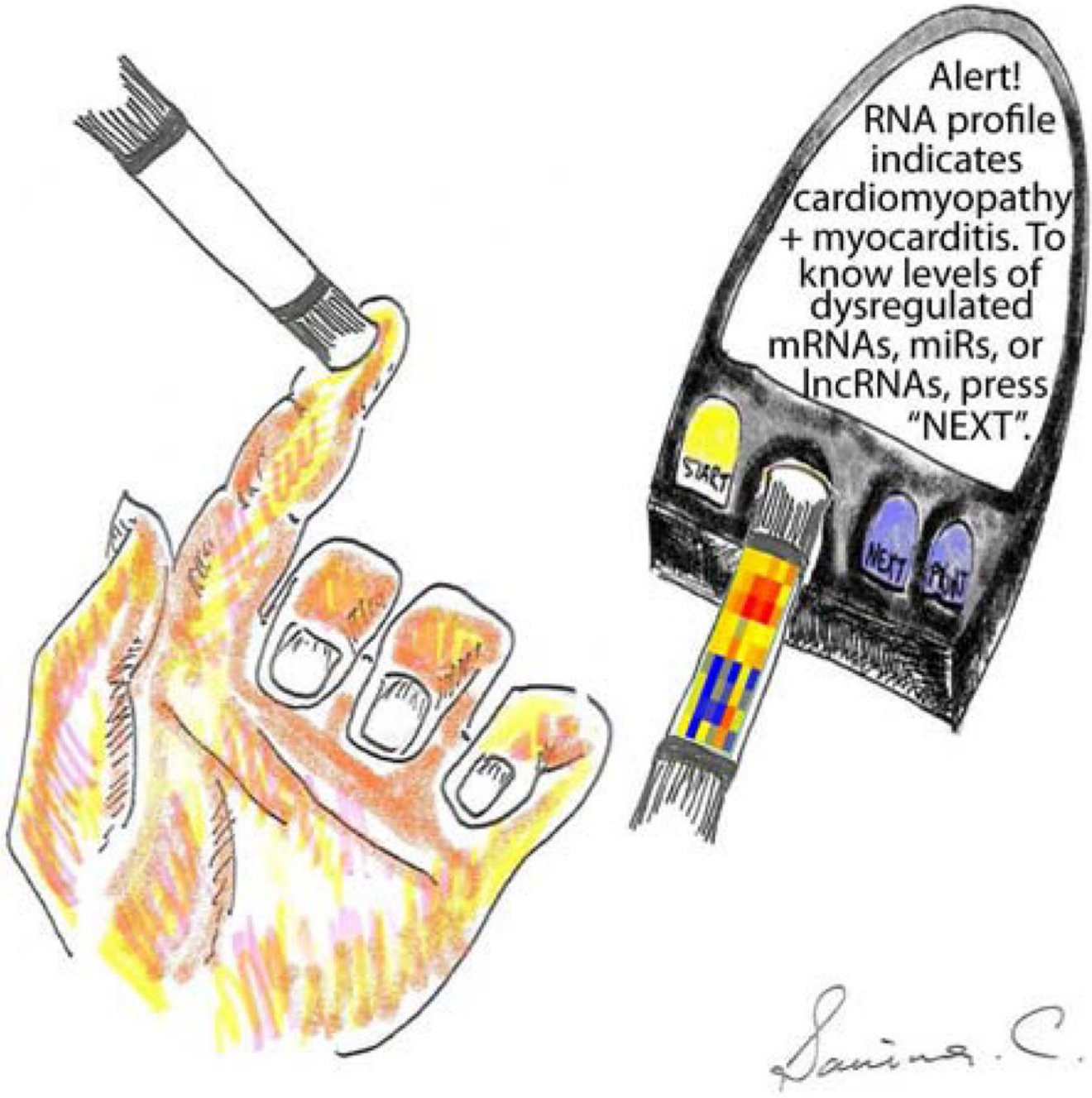

Figure 2. A look into the future

RNA blood transcripts will be translated into scores that can predict the kind and degree of cardiovascular disease.