MicroRNAs As Circulating Biomarkers for Heart Failure: Questions About MiR-423-5p

To the Editor:

With great interest, we read the recent article by Tijsen et al., who claimed to have identified several miRNAs (miRNAs) that may serve as attractive biomarker candidates for heart failure (HF), among which miR-423-5p was most highly related to the clinical diagnosis of HF. We have concerns regarding the validity and completeness of presentation of statistical analyses, as well as regarding the study population that limit information gained from this publication.

One of the major limitations of this study is sample size. Even the highest number of cases in any analysis in the study (which seems to be receiver–operator characteristic analysis for HF versus non-HF plus healthy controls) is not large enough to draw a conclusion using the receiver–operator characteristic curve. Authors have used c statistic, which represents the area under the receiver–operator curve, a plot of sensitivity versus 1 specificity, to determine the potential of the miRNAs as candidate biomarkers. Although the c statistic provides an estimate of prognostic accuracy, its appropriateness in identifying biomarkers of potential clinical utility was questioned recently. This approach is relatively insensitive for detecting moderate effects with potential clinical relevance. Another drawback of this study is that authors did not provide the net reclassification improvement for certain or combination of miRNAs on top of the traditional markers. No data are provided whether miRNAs as potential biomarkers for HF are of independent and/or superior diagnostic value to traditional BNP or NT-BNP. Clearly, this would require significantly more patients and work.

There is a significant difference in age between the healthy controls and HF patients in both the experiments, ie, microarray and real-time PCR. It is known that miRNA expression can significantly change with age. Other reasons could be the incidence of single-nucleotide polymorphisms, which are known to influence the expression of mature miRNAs. Incidentally, an association between a single-nucleotide polymorphism in miR-423 and age was previously noted, and it could be possible that the differences in miR-423 expression between HF patients and healthy controls are merely attributable to differences in age. It is therefore required to include age-matched controls to eliminate the influence of confounding factors in biomarker discovery studies.

We completely agree with the authors that there is a need to identify simple and reliable circulating biomarkers as objective measures of HF. MiRNAs indeed could serve as highly interesting and exciting candidates, and the authors are congratulated to have performed one of the first pilot studies in the field of miRNA research. However, given the issues mentioned above, further research is urgently needed with appropriate controls, sample size, and tests before putting miRNAs to the forefront of clinical biomarkers in cardiovascular medicine.

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Regalla Kumarswamy

Department of Molecular and Translational Therapeutic Strategies
Medical School Hannover
Hannover, Germany

Stefan D. Anker

Department of Cardiology
Charité Medical School
Berlin, Germany

and

Centre for Clinical and Basic Research
IRCCS San Raffaele
Rome, Italy

Thomas Thum

Department of Molecular and Translational Therapeutic Strategies
Medical School Hannover
Hannover, Germany

E-mail: Thum.Thomas@mh-hannover.de


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