Peripheral blood metabolite profiles associated with new onset atrial fibrillation

Ralf E. Harskamp, MD, PhD,[a,b] Thomas M. Granger, BA,[c] Robert M. Clare, MS,[b] Kyle R. White, MS,[b] Renato D. Lopes, MD, PhD,[b] Karen S. Pieper, MS,[b] Christopher B. Granger, MD,[b] Christopher B. Newgard, PhD,[d] Svati H. Shah, MD, MHS,[d] and L. Kristin Newby, MD, MHS[b,c] *Durham, NC*

Background Peripheral blood metabolite profiles have yielded mechanistic insights into various cardiovascular disease states. We hypothesized that peripheral blood metabolite profiles would be associated with new onset atrial fibrillation (AF).

Methods and results The study population comprised 1892 patients without AF at baseline, who, as part the MURDOCK Cardiovascular Disease Study molecular profiling cohort (n = 2023), had previously had determination of levels of 69 metabolites from frozen, fasting plasma specimens obtained during coronary angiography. We used Cox proportional hazards models to examine the association of 13 uncorrelated metabolite factors created from these data using principal components analysis (PCA) with new occurrences of AF during a median follow up of 2.8 (0.1–4.9) years. A total of 233 patients developed new AF (12.3%) during follow up. Patients with new onset AF were older (median 67 vs. 60 years); more often white (82 vs. 71%) and male (68 vs. 60%), and had more comorbidities than those who did not develop AF. After adjustment, PCA factor 1 (medium chain acylcarnitines; hazard ratio [HR]: 1.11 [1.01–1.22]), factor 2 (short chain dicarboxylacylcarnitines; HR: 1.21 [1.09–1.34]) and factor 5 (long chain acylcarnitines; HR: 1.19 [1.06–1.34]) were associated with new onset AF.

Conclusion Metabolite profiles were associated with new onset AF among patients referred for coronary angiography. Validation of these observations in broader patient populations may provide better mechanistic insight into the development of AF, and may provide new opportunities for prevention and treatment. (Am Heart J 2019;211:54-59.)

Atrial fibrillation (AF), the most common arrhythmia encountered in clinical practice, is associated with significant morbidity and mortality.[1] Between 2.7 and 6.1 million individuals in the United States alone have AF, and these numbers are increasing. In addition to the effect on quality of life, AF is also associated with direct and indirect costs estimated at approximately $3600 per patient year.[2,3] Current treatment strategies are centered at either "rhythm control" with medications or interventions or "rate control," in which patients remain in AF but ventricular rates are controlled.[4,5] In order to further improve management strategies or even prevent AF, a better means of identifying those at risk is needed. A number of studies have examined adaptation to and metabolic regulation of chronic AF at the tissue level.[6,7] The association of several circulating biomarkers with incident AF has been explored, including soluble ST2, growth differentiation factor-15, and troponin.[8] However, the relationship between plasma metabolite levels and risk for developing AF is an area of ongoing research that warrants further exploration. Therefore, we examined the association between peripheral blood metabolite factors and the development of new onset AF in a longitudinal cohort of patients who had been referred for coronary angiography.

Methods

Study population

For the current study we used data from a subset of participants in the Measurement to Understand Reclassification of Disease Of Cabarrus / Kannapolis (MURDOCK) Horizon 1 Cardiovascular Disease (Horizon 1 CV) Study, the methods of which have been previously described.[9] In summary, from 7015 patients enrolled in the Duke CathGen biorepository (https://dmpi.duke.edu/cathgen) at the time of cardiac catheterization for suspected coronary artery disease, 2023 sequential patients had all of plasma, DNA, and RNA samples collected and were included in the MURDOCK Horizon 1 CV Study

From the [a]Department of General Practice, Amsterdam UMC, University of Amsterdam, Amsterdam Public Health, Academic Medical Center, Duke University Medical Center, Durham, NC, [b]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, [c]Duke Clinical & Translational Science Institute, Duke University Medical Center, Durham, NC, and [d]Duke Molecular Physiology Institute, Duke University Medical Center, Durham, NC.

Thomas Jared Bunch, MD served as guest editor for this article.
Submitted September 27, 2018; accepted January 31, 2019.

Reprint requests: L. Kristin Newby, MD, MHS, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC, 27715-7969.
E-mail: kristin.newby@duke.edu

0002-8703

https://doi.org/10.1016/j.ahj.2019.01.010

cohort. Targeted metabolite profiling was performed on all plasma samples. From this cohort, we subsequently excluded 131 patients who were admitted with AF, were diagnosed with AF during the index hospitalization, had a history of AF (defined as any prior episode of AF), or had missing follow-up data. The remaining patients (n = 1892), along with their clinical and molecular data, served as the study population for the current study. The Duke CathGen biorepository, the MURDOCK Horizon 1 CV Study, and the current analyses, were approved by the Duke University Medical Center Institutional Review Board. All patients provided written informed consent for the collection of biological samples and use of their clinical data.

Detection of new onset atrial fibrillation

New cases of AF during follow up were identified by examination of Duke medical records (electronic records, supplemented by chart review if indicated) for each patient from the time of his index catheterization (time of baseline sample collection; 2004 through 2007) through November 1, 2010. Hierarchical diagnostic evidence was used to assign a diagnosis of new onset AF as follows: 1) electrocardiographic evidence of new AF, 2) documentation of a new diagnosis of AF in physicians' notes, e.g. clinic notes, discharge summaries, admission notes, and 3) evidence by billing code. Patients with a history of coronary artery bypass grafting surgery (CABG) were not excluded; however, any AF that occurred in the post-CABG hospital setting (within 7 days) was not included as an endpoint for this analysis.

Metabolite profiling and metabolite factors

As described in prior work from the MURDOCK H1 CV cohort,[9] we used a targeted mass spectrometry-based approach to determine levels of 15 amino acids and 45 acylcarnitine species (byproducts of mitochondrial free fatty acid, carbohydrate, and amino acid catabolism) and routine chemistry methods to determine levels of nonesterified free fatty acids, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, ketones (total and B-hydroxybutyrate), and glucose. From these 69 metabolites, we created 13 uncorrelated factors using principal components analysis (PCA). In brief, these factors are unitless continuous variables that were created using linear combination of the various individual metabolites weighted based on the PCA results. These previously created factors, identified from the same baseline population (MURDOCK Horizon 1 CV cohort; n = 2023), were used for the current analyses.[10]

Statistical Methods

Baseline demographics, clinical characteristic, and medication use were described using medians with 25th and 75th percentiles for continuous variables and percentages for categorical variables. To examine the association of baseline PCA-derived metabolite factors with new onset AF during longitudinal follow up among patients without AF at baseline, we used Cox proportional hazards modeling. The 13 factor scores for each individual were included in the models as continuous variables. The factor scores are unitless, and the resulting Hazard Ratios (HR) reflect risk per unit increase. These models were adjusted for covariates previously reported as being associated with new onset AF or related to metabolite components understudy, including age, sex, race, body mass index, hypertension, diabetes mellitus, left ventricular ejection fraction (LVEF), chronic obstructive pulmonary disease (COPD), congestive heart failure, index clinical presentation (acute myocardial infarction [MI] vs. other), heparin use, and the Duke coronary artery disease severity index. Hazard ratios (HR) and corresponding 95% confidence intervals were reported. Proportional hazards assumptions were tested for all covariates using the method based on cumulative sums of martingale residuals over follow-up time. For covariates violating the assumption, cutoff points were selected based on assessment of log–log survival plots, and fitted with piecewise Cox models.[11]

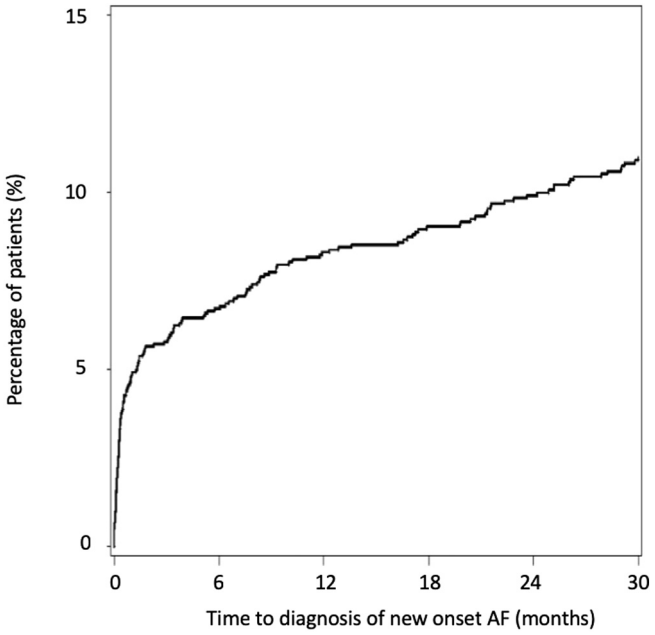
To assess the incremental predictive value of the metabolite factors that were associated with new onset AF, we estimated the Net Reclassification Index (NRI) among patients who did and who did not develop AF during a 1-year follow-up period. The NRI measures the change in risk classification brought about by adding the metabolite factors to a predictive model that contained the baseline clinical variables noted above. For the purposes of this analysis and in the absence of an a priori categorization scheme, we categorized patients according to their predicted risk of AF (i.e., predicted risk above the overall rate for the whole cohort or less than or equal to the overall rate for the whole cohort) using the variables in our adjustment model. We also assessed the improvement in discrimination of the model with metabolite factors, by calculating the difference in the C-Index for the baseline model with or without addition of metabolite factors. Bootstrap sampling was used to derive a 95% confidence interval for the increase in the C-index brought about by adding metabolite factors. This study was focused on generating hypotheses, rather than developing a validated risk prediction model; thus, we did not perform external validation. For all statistical analyses, the significance level was set at 0.05. All analyses were done in SAS v9.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

The study population comprised 1892 patients without AF who underwent coronary angiography for evaluation for suspected coronary artery disease. The majority had stable ischemic symptoms, but 11% presented with an acute MI. As shown in Figure 1, 12.3% of patients (n = 233) were diagnosed with AF during a median of 2.8 (0.1–4.9) years of follow up.

Figure 1



Cumulative incidence of new onset atrial fibrillation in the study population.

Patients with new onset AF were generally older (median 67 vs. 60 years), more often white (82 vs. 71%) and male (68 vs. 60%), and more frequently presented with NYHA class III/IV heart failure (17.6% vs. 7.7%) than those who did not have AF during follow up (Table I). Patients who developed AF during follow-up were more frequently taking beta-blockers, statins, aspirin and warfarin (without evidence of prior atrial fibrillation and with a documented non-AF indication for anticoagulation) at baseline. Coronary angiography revealed that patients who later developed AF also had more advanced coronary artery disease at baseline.

Association of metabolite factors and new onset AF

Table II displays unadjusted and adjusted associations of PCA-derived metabolite factors with new onset AF. After adjustment for clinical factors, PCA factor 1 (medium chain acylcarnitines; HR 1.11 [1.01–1.22]), factor 2 (short chain dicarboxylacylcarnitines; HR 1.21 [1.09–1.34]), and factor 5 (long chain acylcarnitines; HR 1.19 [1.06–1.34]) were significantly associated with new onset AF during follow up. A trend was observed for factor 6 (branched-chain amino acids and catabolites: HR 1.14 [1.00–1.31], P = .054) and new onset AF during follow-up.

Additionally, there was 1 PCA factor (factor 11; lipids) for which the hazard was not constant across time (P = .006 for proportional hazards). There was a trend for decreasing risk with increases in Factor 11 during the first 30 days after hospital admission (HR 0.82 [0.66–1.03], P = .081). However, there was no evidence of an association between Factor 11 and outcome after 30 days (HR: 1.05 [0.89–1.23], P = .60). Since the p-values for both HRs are >0.05, the average across all time is displayed in the table (HR 0.93 [0.82–1.05]).

Incremental value of metabolite factors in a clinical model for prediction of atrial fibrillation

The C-index for the baseline model was 0.719. When the metabolite factors were added, the C-index of the model improved to 0.731. The bootstrap-derived confidence interval around the absolute increase in C-index (0.012 [95% CI -0.047 – 0.072]) suggests random variation as the source of difference in discrimination between the two models cannot be ruled out. We found a net increase in the attribution of risk (NRI = 0.012) to patients who subsequently developed AF, and a net decrease in the attribution of risk (NRI = 0.024) to patients who did not develop AF during a 1-year follow-up period (for details see Supplement 1).

Discussion

In this study we demonstrated that certain byproducts of cellular metabolism were independently associated with future onset of non-operative AF during longitudinal follow up in a cohort of patients referred for coronary angiography. More specifically, after multivariable adjustment for known AF risk factors (listed in the Statistical Methods section), medium chain and long chain acylcarnitines (factors 1 and 5)

Table I. Baseline characteristics of the study population

	No AF	AF	P-value
N	1659	233	
Demographics			
Age, years	60 (53, 69)	67 (60, 74)	<0.001
Female, %	40.1 (666)	31.8 (74)	0.014
White, %	70.6 (1171)	82 (191)	<0.001
Presentation Characteristics			
BMI	29 (25, 33)	28 (25, 32)	0.14
SBP, mmHg	144 (130, 161)	145 (131,164)	0.46
Heart rate, bpm	69 (60, 79)	71 (60, 81)	0.099
AMI at presentation, %	10.7 (178)	12.0 (28)	0.56
NYHA			<0.001
0	81.7 (1355)	70.0 (163)	
1	1.7 (28)	3.0 (7)	
2	9.0 (149)	9.4 (22)	
3	6.3 (104)	15.0 (35)	
4	1.4 (23)	2.6 (6)	
Past Medical History			
History of smoking, %	46.8 (776)	50.2 (117)	0.33
Hypertension, %	67.1 (1114)	69.1 (161)	0.55
COPD, %	5.2 (87)	8.2 (19)	0.070
Diabetes, %	29.6 (491)	24.9 (58)	0.139
Prior MI, %	27.6 (458)	27.0 (63)	0.86
Prior PCI, %	21.8 (361)	24.0 (56)	0.43
Prior CABG, %	20.1 (334)	23.2 (54)	0.28
Results of Diagnostic Testing			
Ejection fraction, %	58 (52, 66)	56 (45, 65)	0.001
Duke CAD severity index	31 (0, 52)	39 (20, 71)	<0.001
No of diseased vessels			0.005
0	39.2 (612)	29.8 (67)	
1	24.3 (380)	21.8 (49)	
2	15.9 (249)	20.0 (45)	
3	20.6 (321)	28.4 (64)	
Medications at Baseline			
Anti-arrhythmic drugs*, %	1.0 (17)	1.7 (4)	0.32
Beta-blocker, %	63.6 (1054)	81.5 (190)	<0.001
ACE inhibitor, %	36.6 (607)	39.9 (93)	0.33
Statin, %	55.6 (921)	70.0 (163)	<0.001
Aspirin, %	68.4 (1133)	83.3 (194)	<0.001
Warfarin/Coumadin*, %	1.0 (16)	2.6 (6)	0.044

* these medications were confirmed by medical record review to be for non-AF indication.

and short chain dicarboxylacylcarnitines (factor 2) were associated with a de novo diagnosis of AF during a median follow-up of 3.5 years. Trends were seen for branched-chain amino acids and catabolites (factor 6). These findings suggest that discordant regulation of cellular metabolism, measured by metabolite levels in peripheral blood, may be detectable before the onset of atrial fibrillation. However, the additive benefit of these markers for predicting new onset AF appears to be modest.

Mitochondrial fatty acid metabolic byproducts and cardiac arrhythmias

Under physiologic conditions, the majority of cardiac cellular energy produced in the mitochondria comes from free fatty acids (60%) and to a lesser extent from carbohydrates (35%), amino acids and ketone bodies (5%).[12] L-carnitine assists the transport of fatty acids into mitochondria, where they are oxidized as a major source of energy. L-carnitine functions through reversible esterification and translocation of acylcarnitines, including medium chain acylcarnitines and long chain acylcarnitines. Increased metabolite byproducts of mitochondrial energy production, such as short-chain and long-chain dicarboxylated acylcarnitines (factors 2 and 3) and fatty acids (factor 12) have previously been associated with premature coronary artery disease, myocardial infarction, and mortality.[11] These effects may not be limited to ventricular myocardium, but also occur the atrial myocardium and skeletal muscle or other tissues. The relationships that were observed between metabolite factors and later development of AF may suggest a link with changes in lipid metabolism that originate at a myocellular level in the atria or other tissues. Prior studies showed that in the presence of (acute) myocardial ischemia, the accumulation of fatty acids in myocardial cells was a cause of ventricular arrhythmias.[13] Particularly, long chain, but also short chain acylcarnitines, rapidly increase in ischemic tissue and elicit electrophysiologic derangements and may also lead to left ventricular dilation.[14,15]

In our study, patients who later developed AF had greater ischemic burden at baseline as well as accumulation of fatty acids. Sustained fatty acid accumulation in the myocardial tissue of these patients subsequently may have triggered atrial arrhythmias, including AF. We also found that major constituents of lipid metabolism (Factor 11: glutamine/glutamate, triglycerides, high density lipoprotein cholesterol) tended to be associated with new onset of early AF. In a recent study among ischemic patients with metabolic syndrome, metabolic profiles were measured from atrial appendages that were obtained while these patients underwent CABG surgery.[16] The investigators found that palmitoyl-L-carnitine (a medium chain acylcarnitine) was associated with new onset of post-operative AF. While these mechanisms may indeed be active locally, it is also possible that the metabolic profiles we measured in the blood are a signal of a more global metabolic state that is associated with adverse clinical manifestations such as AF, and explain overlapping associations of some factors with risk for more than one cardiovascular endpoint (e.g., factor 2 with both future AF and coronary disease).

Mitochondrial carbohydrate metabolic byproducts and cardiac arrhythmias

When acutely or chronically stressed, the mitochondria in myocardial cells switch from fatty acid oxidation to the energetically more efficient carbohydrates as the preferred fuel for oxidative energy production.[17,18] In animal studies, glycolytic inhibition may predispose to AF.[19]A clinical study provided support for these findings, demonstrating that the ratio of glycolytic end products (lactate, alanine) to end products of lipid metabolism (acetate) in tissue samples from atrial appendages positively correlated with the occurrence of post-operative AF.[20] In our study we did

Table II. Unadjusted and adjusted association of metabolic factors with new onset AF

	Unadjusted		*Adjusted*	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Factor 1 (Medium-chain acylcarnitines)	1.18 (1.08–1.29)	**<0.001**	1.11 (1.01–1.22)	**0.033**
Factor 2 (Short-chain dicarboxylacylcarnitines)	1.17 (1.07–1.29)	**0.001**	1.21 (1.09–1.34)	**<0.001**
Factor 3 (Long-chain dicarboxylacylcarnitines)	1.04 (0.89–1.22)	0.60	0.97 (0.81–1.15)	0.69
Factor 4 (Ketone related)	1.13 (1.01–1.27)	**0.04**	1.07 (0.95–1.21)	0.29
Factor 5 (Long chain acylcarnitines)	1.26 (1.13–1.41)	**<0.001**	1.19 (1.06–1.34)	**0.004**
Factor 6 (Branched-chain amino acids and catabolites)	1.15 (1.02–1.30)	**0.027**	1.14 (1.00–1.31)	**0.054**
Factor 7 (Cholesterol)	0.97 (0.86–1.10)	0.67	1.09 (0.96–1.24)	0.19
Factor 8 (Amino acids)	0.97 (0.85–1.10)	0.62	0.97 (0.85–1.11)	0.66
Factor 9 (Short-chain acylcarnitines)	1.12 (1.00–1.26)	**0.049**	1.04 (0.93–1.18)	0.47
Factor 10 (Medium-chain acylcarnitines)	1.09 (0.97–1.22)	0.14	1.05 (0.93–1.19)	0.40
Factor 11 (Lipids)	0.93 (0.82–1.05)	0.24	0.96 (0.84–1.11)	0.59
Factor 12 (Fatty acids)	1.03 (0.91–1.17)	0.65	1.01 (0.89–1.14)	0.93
Factors 13 (Glucose)	0.98 (0.87–1.11)	0.74	1.03 (0.89–1.18)	0.73

not find an association between ketone-related metabolites (ketones; Hbut; beta-hydroxybutyrate; alanine) or glucose and new onset AF. However, it may be that such a signal measurable in tissue was not strong enough to be detected in blood.

Mitochondrial amino-acid metabolic byproducts and cardiac arrhythmias

In prior clinical studies, higher levels of beta-hydroxybutyrate (a ketone body) and the ketogenic amino acids tyrosine and leucine in the blood were observed among patients who developed post-operative AF.[6] Similarly, in our study with non-operative AF, we found that branched-chain amino acids and related catabolites (phenylalanine, tyrosine, methionine, (iso)leucine, valine) were associated with the new onset AF, and a trend remained after multivariable adjustment (P = .059). Additionally, short-chain dicarboxyacylcarnitines (factor 2), which can also be derived from CoA esters generated during oxidation of amino acids, were also associated with new onset of AF.[11]

Implications of metabolic findings

Many mitochondrial metabolic changes observed among patients with AF are shared with patients who present with acute myocardial ischemia and heart failure,[9,10,21,22] and AF is more common among patients with these conditions. The shifts from fatty acid-dominated metabolism to a more glycolytic state or protein and amino acid metabolism in the heart and/or peripheral tissues that are measured in peripheral blood, may therefore be a global harbinger of disease progression on a (intra)cellular level that ultimately leads to overt cardiovascular disease. The early identification of such alterations of metabolism through peripheral blood sampling may be of clinical importance, holding potential to identify patients at risk for developing AF.

Limitations

Our study population only included patients who underwent coronary angiography. As such, patients without suspicion for significant coronary artery disease, but who may be at risk for developing AF, were not included. Second, this is an observational study and subject to selection biases and the effects of unmeasured confounders or confounding by covariates for which we could not adjust. Because they were not systematically available, we did not measure or adjust for other blood biomarkers like natriuretic peptides or imaging parameters like left atrial size that may predict atrial fibrillation. We did not account for the use of beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers or antihypertensive medications at baseline. However, we adjusted for the clinical conditions for which these medications are typically used (e.g., hypertension, heart failure, and coronary artery disease). Because we studied peripheral blood, we may have missed changes in myocardial tissue that could provide other insights into disease processes, and our results could reflect more global metabolic derangements associated with AF, rather than local mechanisms. A cause and effect relationship between metabolite factors and new onset AF or the biological relevance of the findings cannot be established from this study. Confirmatory studies in other patient populations are needed.

Conclusion

Alterations in metabolic profiles are associated with future onset of non-operative AF among patients referred for coronary angiography. Although these associations were modest, with further study, their association with new onset AF could lead to novel mechanistic understanding of AF risk and may provide opportunities to identify new prevention and treatment strategies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.01.010.

Funding Sources

Funding for the statistical analysis on this manuscript was provided for by the Duke Clinical Research Institute, Durham NC. The MURDOCK Horizon 1 Cardiovascular Disease Study was funded by a gift to Duke University from the David H. Murdock Foundation for Business and Culture and a grant from the National Center for Research Resources (UL1RR024128–01). Salary support for Dr. Harskamp was provided by a Rubicon fellowship provided by the Netherlands Organization for Scientific Research (NWO). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Disclosures

Dr. Harskamp, Mr. Granger, Mr. Clare, Mr. White, Ms. Pieper, and Dr. Shah reported no potential conflicts of interest. Dr. Lopes reports consulting honoraria and advisory board membership of Boehringer-Ingelheim and Bristol-Myers Squibb, and receiving grants from AstraZeneca, Boehringer-Ingelheim, and Daiichi Sankyo. Dr. Newgard has received financial support from Pfizer and research support from Pfizer and Eli Lilly. Dr. Granger reports research funding and salary support from Boehringer-Ingelheim, Bristol Myers Squibb, Glaxo SmithKline, Hoffmann-La Roche, Medtronic Foundation, Merck&Co, Pfizer, Sanofi-Aventis, Takeda, The Medicines Company, and Daiichi Sankyo. Dr. Newby reports research funding and salary support from Glaxo SmithKline, Verily Life Sciences, MURDOCK Study, PCORI, and NIH; and consulting honoraria from BioKier, Roche Diagnostics, Metanomics, and Ortho-Clinical Diagnostics, and other services for National Institute of Health.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics–2012 Update: A Report From the American Heart Association. Circulation 2012;125:e2-e220.
2. Li J, Solus J, Chen Q, et al. Role of inflammation and oxidative stress in atrial fibrillation. Heart Rhythm 2010;7:438-44.
3. Conway DS, Buggins P, Hughes E, et al. Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. J Am Coll Cardiol 2004;43:2075-82.
4. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257-354.
5. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-47.
6. Mayr M, Yusuf S, Weir G, et al. Combined metabolomic and proteomic analysis of human atrial fibrillation. J Am Coll Cardiol 2008;51:585-94.
7. De Souza AI, Cardin S, Wait R, et al. Proteomic and metabolomic analysis of atrial profibrillatory remodelling in congestive heart failure. J Mol Cell Cardiol 2010;49:851-63.
8. Rienstra M, Yin X, Larson MG, et al. Relationship between soluble ST2, growth differentiation facto-15, and high-sensitivity troponin I and incident atrial fibrillation. Am Heart J 2014;167:109-15.
9. Shah SH, Granger CB, Hauser ER, et al. Reclassification of cardiovascular risk using integrated clinical and molecular biosignatures: Design of and rationale for the Measurement to Understand the Reclassification of Disease of Cabarrus and Kannapolis (MURDOCK) Horizon 1 Cardiovascular Disease Study. Am Heart J 2010;160:371-379.e2.
10. Shah SH, Sun JL, Stevens RD, et al. Baseline metabolomic profiles predict cardiovascular events in patients at risk for coronary artery disease. Am Heart J 2012;163:844-850.e1.
11. Lin DYW, L.J., Ying Z. Checking the Cox Model with cumulative sums of martingale-based residuals. Biometrika 1993;80:557-72.
12. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785-9.
13. Ferrari R, Merli E, Cicchitelli G, et al. Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular diseases: a review. Ann N Y Acad Sci 2004;1033:79-91.
14. Rizzon P, Biasco G, Di Biase M, et al. High doses of L-carnitine in acute myocardial infarction: metabolic and antiarrhythmic effects. Eur Heart J 1989;10:502-8.
15. Iliceto S, Scrutinio D, Bruzzi P, et al. Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM) Trial. J Am Coll Cardiol 1995;26:380-7.
16. Montaigne D, Marechal X, Lefebvre P, et al. Mitochondrial dysfunction as an arrhythmogenic substrate: a translational proof-of-concept study in patients with metabolic syndrome developping post-operative atrial fibrillation. J Am Coll Cardiol 2013;62:1466-73.
17. Goodwin GW, Taylor CS, Taegtmeyer H. Regulation of energy metabolism of the heart during acute increase in heart work. J Biol Chem 1998;273:29530-9.
18. Taegtmeyer H. Cardiac metabolism as a target for the treatment of heart failure. Circulation 2004;110:894-6.
19. Ono N, Hayashi H, Kawase A, et al. Spontaneous atrial fibrillation initiated by triggered activity near the pulmonary veins in aged rats subjected to glycolytic inhibition. Am J Physiol Heart Circ Physiol 2007;292:H639-48.
20. Mayr M, Madhu B, Xu Q. Proteomics and metabolomics combined in cardiovascular research. Trends Cardiovasc Med 2007;17:43-8.
21. Huang Y, Zhou M, Sun H, et al. Branched-chain amino acid metabolism in heart disease: an epiphenomenon or a real culprit? Cardiovasc Res 2011;90:220-3.
22. Shah AA, Craig DM, Sebek JK, et al. Metabolic profiles predict adverse events after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2012;143:873-8.