validated benchmark. Proposed options include circulating biomarkers, direct measurement of filling pressure, and phenomapping, but so far, outcome-based studies are lacking. Other subspecialty communities in the field of atrial fibrillation or hypertrophic cardiomyopathy have invested a lot of effort and provided key evidence by targeting the validation of scores against hard outcomes. This approach made it easier to reach a consensus within the cardiology community and promoted the use of subsequent guidelines. Similar hard outcomes do exist for DD, including the occurrence of heart failure with preserved ejection fraction (HFpEF), defined as the need for an unplanned hospitalization for heart failure with normal ejection fraction in a population of patients without heart failure at baseline.

Criteria for diagnosing DD should take account of the subject's age, as indicated by the wide differences in DD prevalence according to age and definitions in our study, and, ideally, functional responses to stress. Reference values for diastolic variables should be based on large normative databases, allowing the continuous influences of risk factors to be considered; this would probably be more appropriate than using dichotomous diagnostic classes. A big-data approach could be used to develop DD diagnostic software that incorporates clinical decision trees developed by machine learning, which can test multiple diagnostic approaches and select the combination of variables that best predicts clinical events. Such a diagnostic tool could revolutionize the clinical utility of echocardiography in this field, by allowing therapeutic interventions to be tested in patients identified as at high risk to develop HFpEF.

In the setting of a worsening HFpEF epidemic, further research using such new strategies will be essential to characterize this entity better and to identify patients at risk for progression to overt HFpEF. The echocardiographic community should now accept this challenge and then provide diagnostic recommendations once they are supported by outcome-based studies.

Olivier Huttin, MD, PhD
Alan G. Fraser, MD
Stefano Coiro, MD, MSc
Erwan Bozec, PhD
Christine Selton-Suty, MD
Zohra Lamiral, MA
Zied Frikha, MD
Patrick Rossignol, MD, PhD
Faiez Zannad, MD, PhD
***Nicolas Girerd, MD, PhD**

*Centre d'Investigations Cliniques 1433
CHRU de Nancy
Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu
4 Rue du Morvan
54500 Vandoeuvre lès Nancy
France
E-mail: nicolas_girerd@yahoo.com

http://dx.doi.org/10.1016/j.jacc.2017.04.039

Please note: The STANISLAS study was sponsored by Nancy CHRU and supported by a public grant overseen by the French National Research Agency as part of the second Investissements d'Avenir program (ANR-15-RHUS-0004). Prof. Rossignol has received travel grants from Pfizer, AstraZeneca, Daiichi-Sankyo, Novartis, Roche, Takeda, Servier, and Fresenius; serves on the board for Gambro; has received speaking fees from AstraZeneca, Therval Medical, and Fresenius; and has prepared manuscripts for AstraZeneca. Prof. Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speaking fees from Pfizer and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors thank the entire Clinical Investigation Centre staff, all of whom are involved in the daily management of the STANISLAS cohort. The authors also thank Mr. Pierre Pothier for editing the manuscript.

REFERENCES

1. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.

2. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

3. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

4. Appleton CP. Doppler assessment of left ventricular diastolic function: the refinements continue. J Am Coll Cardiol 1993;21:1697–700.

5. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.

History Repeating?

The Logics of History

We read with interest the paper by Seitz et al. (1) focusing on mapping areas of spatiotemporal electrogram dispersion in patients with atrial fibrillation (AF). According to the authors, these areas represent "AF drivers" and their ablation is a personalized, more effective strategy than antral PVI (pulmonary vein isolation) or a stepwise ablation approach. This is a déjà vu: the use of a vague ablation target compared with a nonrigorous control group to draw

conclusions that are not reasonably supported by the data. There are many problems with this study. First and foremost, there is no experimental model supporting the assumption that spatiotemporal electrogram dispersion is a stable and reproducible phenomenon, holding a significant role in maintaining or driving AF. As electrophysiologists, we have been there before: it is important to experimentally validate the study hypothesis before translating it into clinical practice (2,3). This is the strongest defense against the many biases that inevitably affect clinical studies: whenever mapping/ablation studies preceded mechanistic studies, this has led to years before a "promising" ablation strategy is finally recognized as ineffective. Among the other problems are the following: 1) the use AF termination, a frequently used but often misunderstood surrogate endpoint (its occurrence in paroxysmal AF is common with any ablation strategy, and it has been shown not to correlate with AT (atrial tachycardia)/AF recurrence in nonparoxysmal patients) (4,5); 2) the control group is inexplicably not contemporaneous or consecutive (47 out of 98 patients ablated between November 2008 and March 2010 vs. 105 consecutive patients enrolled between September 2013 and March 2014), which raises the question of selection bias; and 3) the most relevant long-term outcome (single-procedure freedom from AT/AF off AAD [antiarrhythmic drugs]) is reported tangentially, with no comparison with the control group (nevertheless, the derived success rate of the intervention group is about 31%, which is far from laudatory). In conclusion, it is important to understand and highlight the limitations of this study, because we should learn from the past, not forget it.

*Carola Gianni, MD, PhD
Sanghamitra Mohanty, MD
Luigi Di Biase, MD, PhD
Andrea Natale, MD
*Texas Cardiac Arrhythmia Institute
St. David's Medical Center
3000 N. IH-35, Suite 720
Austin, Texas 78705
E-mail: carola.gianni@gmail.com

http://dx.doi.org/10.1016/j.jacc.2017.02.077

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Seitz J, Bars C, Théodore G, et al. AF Ablation guided by spatiotemporal electrogram dispersion without pulmonary vein isolation: a wholly patient-tailored approach. J Am Coll Cardiol 2017;69:303–21.

2. Atienza F, Calvo D, Almendral J, et al. Mechanisms of fractionated electrograms formation in the posterior left atrium during paroxysmal atrial fibrillation in humans. J Am Coll Cardiol 2011;57:1081–92.

3. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510-512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. Circulation 2015;132:2108–17.

4. O'Neill MD, Wright M, Knecht S, et al. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. Eur Heart J 2009;30:1105–12.

5. Elayi CS, Di Biase L, Barrett C, et al. Atrial fibrillation termination as a procedural endpoint during ablation in long-standing persistent atrial fibrillation. Heart Rhythm 2010;7:1216–23.

REPLY: History Repeating?

The Logics of History

We appreciate the interest of Dr. Gianni and colleagues in our paper (1) and their invitation to a careful consideration of history. Classic anatomy-based approach may be insufficient for treating persistent atrial fibrillation (AF) (reference #1 in our article [1]). Gianni and colleagues seem to acknowledge this limitation and recommend extensive ablation strategies in persistent AF (Figure 1 from [2]). These authors posit that extensive ablation approaches, which mostly rely on probabilistic ablation in pre-defined atrial regions, are solidly grounded in experimental findings. Conversely, their viewpoint is that mechanistic evidence is lacking for nonextensive ablation using spatiotemporal dispersion of abnormal electrograms to identify regions driving fibrillation.

Since the initial descriptions reported by Garrey in 1924 (3), the medical literature is replete with reports (in silico, in ex vivo experiments, and in patients) on the clustering of abnormal electrical or contractile manifestations in the regions where AF electrical sources can be found. AF single or multiple drivers indeed sprawl over well-delineated atrial regions, which spatial arrangement during sustained AF widely varies from patient to patient (references 6-24 in our article [1]). Therefore, our understanding of history is that it overwhelmingly supports nonextensive and mechanism-based ablation.

Besides, Dr. Gianni and colleagues have overlooked several aspects of our contribution:

1. We show that the time stability and the interoperator and intraoperator reproducibility of mapped dispersion regions are very robust (Online Figure 2 in our article [1]).
2. AF termination has been shown to be correlated with outcomes (4,5). Importantly, our AF termination rates and long-term outcomes were not different between patients presenting in sinus rhythm and patients "spontaneously" in AF.