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Editorial commentary:

Substrate for development of atrial fibrillation in patients with congestive heart failure: Are we close to the answer?

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Development of atrial fibrillation (AF) in patients with congestive heart failure (CHF) remains one of the leading causes of their clinical deterioration [1]. About 15-20% of patients with CHF have AF and it is more common in patients with advanced cardiac disease achieving 50% in patients with grade IV CHF according to New York Heart Association[2]. According to the data from controlled clinical trials, the annual incidence of AF in patients with CHF is in the range of 3% to 5% [3,4,5,6]. While analyses of AF impact on mortality in CHF trials show conflicting findings, new onset AF during follow-up has consistently been associated with poor prognosis and more than twofold increase in all-cause mortality [3,5,6].

Despite the undisputable clinical importance, surprisingly little is known about clinical and/or electrophysiological predictors of AF in patients with CHF. Though shortened atrial effective refractory period (ERP) and reduced conduction velocity, both essential components of the fibrillatory wavelength, have been linked to the maintenance of AF [7], it is not clear whether the same mechanism underlies development of AF in CHF.

In an elegant study presented in this issue of *Heart Rhythm*[8], Workman et al. came one step closer to unveiling electrophysiologic characteristics of atrial myocardium in patients with CHF *without* prior history of AF. Using whole-cell-patch clamp technique on an impressive number of atrial tissue samples collected during open heart surgery, the authors have studied differences in ion channel expression associated with CHF and demonstrated shortening of atrial cellular ERP associated with left ventricular systolic dysfunction (LVSD). This is the first study that provides information on cellular ERP in patients with CHF or LVSD. This finding fits as a logical explanation of the increased predisposition to AF in CHF patients. It is therefore intriguing that a couple of years ago a clinical study by Sanders et al. performed on a similar, though smaller in number, group of patients with CHF came to the opposite result[9]. Using conventional electrophysiological approach, Sanders et al. have demonstrated consistently longer ERP in patients with CHF compared to healthy controls at all paced atrial sites and at all pacing cycle lengths (600 ms, 500 ms and 400 ms). The reason for this discrepancy is rather unclear. Patients in the study of Sanders et al. were ten years younger and had lower mean LVEF than subjects from the current study (26% vs 36%) but it is unlikely to be the sole explanation. In animal experiments, increase in atrial filling pressure, which is commonly observed in CHF, produced heterogeneous effects on the atrial refractory periods [10, 11, 12]. However, it was the shorter atrial ERP that was associated with higher inducibility of AF[11]. Yet another recently published study on patients with mitral stenosis without history of AF evaluated the effect of chronic increase in left atrial filling pressure on electrical remodeling and found no change or an increase in ERP in this group of patients[13].

Another variable in the reentrant wavelength equation, i.e. conduction velocity, appeared to be increased rather than reduced in patients with CHF in the study of Workman et al.[8]

Atrial cellular action potential maximum upstroke velocity (dV/dt_{max}) was greater in patients with LVSD compared with those without. The authors suggest that the net effect of the observed conduction velocity and refractoriness would still be a shortening of the reentrant wavelength by ~20% since *“the dV/dt_{max} increase was smaller (11%) than ERP decrease (24%) and... should increase conduction velocity by only 4% according to a mathematical model”*. Animal data indicate that CHF causes localized disorganization of atrial conduction rather than its overall slowing[12]. In clinical studies, conduction velocity was slower compared to healthy controls both in patients with CHF[9] and mitral stenosis[13].

The differences in findings between the work of Workman et al. and the clinical studies mentioned above may be explained by the fact that the CHF-induced atrial remodeling is not limited to the change in electrophysiological properties of atrial myocytes and cellular electrophysiology cannot be directly extrapolated to the tissue or the organ level. Autonomic imbalance, accumulation of fibroblasts and collagen between atrial myocytes [12] and connexin dysfunction [14] caused by CHF result in disturbed local conduction and may contribute to increased predisposition to AF in a greater extent than the observed change in dV/dt_{max} .

These observations illustrate the need for more studies in order to understand the nature of the AF substrate in patients with CHF. Workman and colleagues should be congratulated for their significant contribution to our knowledge on the electrophysiological substrate that may predispose patients with CHF to develop AF. This knowledge is crucial for the development of new pharmacological AF therapies that have cellular ion channels as targets. Currently available class III antiarrhythmics amiodarone and dofetilide recommended for

rhythm control in CHF patients, both prolong ERP and slow conduction. However, they are only modestly effective and are not better than rate control strategy as recently shown in AF-CHF trial[15].

This knowledge is also important for identification of the reliable predictors of AF in CHF. It is important to bear in mind that the findings in the present study concern patients with CHF who had *never* had any documented or symptomatic AF episode. What makes some of them more prone to develop AF is still a puzzle. There is no controlled clinical study on CHF population that would evaluate any individual electrophysiological predictor of AF in a prospective fashion. Our group has retrospectively studied baseline P-wave duration and morphology in MADIT-II cohort[16] and observed that abnormal P-wave morphology was associated with new onset AF while no differences in P-wave duration at baseline could be seen between those who developed the arrhythmia during follow-up and those who did not. More analyses from similar large-scale studies are clearly needed. It is also obvious that only through the multidisciplinary approach, by combining information from electrophysiological studies, analyses of ECG-based markers of abnormal atrial electrophysiology applied on the large-scale trials and experimental assessment of cellular electrophysiology like the one by Workman et al.[8], we will be able to say why some CHF patients develop AF and what can be done to prevent it.

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