A number of studies have investigated premature ventricular contractions (PVC) to reflect mortality of patients with heart failure (HF) caused by ischemic or dilated cardiomyopathy. The origin, morphology and frequency of the PVC are the main interest, with the coupling interval (CI) drawing less attention because it is believed to be constant under the stable basic cycle length. In the last century, Thanavaro et al reported the relationship between the CI and type of PVC (ie, repetitive PVC tends to occur at the optimal CI range in myocardial infarct patients). On the other hand, Lowery et al indicated that a variable CI leads to multiform and repetitive PVC. In this century, advances in ambulatory data analysis have clarified the CI dynamics as they relate to the following ventricular arrhythmia mechanism and underlying heart disease severity. However, the relationship between CI variability and fatal ventricular arrhythmia occurrence and prognosis are complicated (ie, Sosnowski et al demonstrated high CI variability, whereas Lerma et al concluded low CI variability as a new risk factor of fatal ventricular arrhythmias). Therefore, the role of CI variability in mortality is still in dispute.

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In this issue of the Journal, Lee et al report the prognostic value of variable CI in patients with ischemic or dilated cardiomyopathy showing low left ventricular (LV) function associated with frequent PVC. They set counts and morphologies of the PVC, and time-domain parameters of heart rate variability such as the average of all normal sinus beat (N-N) intervals (MEANNN) and the standard deviation of these intervals (SDNN) as ambulatory monitoring parameters. With respect to CI variability, the average of all coupling (N-V) intervals (MEANNV) and the standard deviation of the N-V intervals (SDNV) were set. They demonstrated that the MEANNN, SDNN and the ratio of SDNV to SDNN in the group reaching the primary endpoint of cardiac mortality were significantly greater than those of the group who were alive during the same follow-up period of 63 months. Regardless of the intergroup differences in age, LV function and prescriptions, their finding has clinical importance for the management of patients with HF associated with frequent PVC.

The CI of PVC arising from the same origin is theoretically constant. Therefore, CI variability indicates different mechanisms of PVC occurrence or modulation of PVC propagation. Three major mechanisms of tachyarrhythmia including PVC development are reentry, triggered activity and abnormal automaticity. In the case of ordered reentry, the impulse propagates around an anatomical obstacle. Altered conduction velocity within the circuit or switching exit causes variable CI (Figure B). In the case of functional reentry, there is no fixed obstacle. When the excitation travels within damaged tissue, an impulse with a short wavelength is fragmented, functionally blocked, pursuing the tail of relative refractory tissue. Therefore, the CI of PVC exiting from multiple reentrant circuits shows wide variation (Figure C). CI variability is also implicated in the case of nonreentrant mechanisms. Diseased myocardium with fibrosis, stretch or dilatation is associated with focal arrhythmogenic mechanisms. Triggered activity is observed in damaged tissue with less Ca²⁺ handling capacity. Intracellular Ca²⁺ overloading evokes delayed afterdepolarization at the end of a regular action potential, leading to triggered PVC. Inhomogeneous Ca²⁺ overloading causes focal PVC with different CI (Figure D). The same is true in the case of abnormal enhanced automaticity in depolarized tissue. Resting membrane potential is less negative in the diseased ventricle, where the Na current is inactivated, and the Ca current is counterbalanced by a hyperpolarizing background K current. Variable extent of the counterbalance causes abnormal automaticity and PVC with different CI. These focal arrhythmogenic mechanisms are likely based on the lack of electrotonic effect in damaged but viable myocardium. Intracellular Ca²⁺ overloading causes degradation of gap junctional proteins. Considering that myocardial cells are coupled to each other through gap junctions, which play a pivotal role in maintaining electrotonus and preventing membrane potential fluctuation, focal mechanisms may be related to gap junctional impairment characterized by the ischemic or failing heart.

Contrary to the outstanding new findings, this article has a few limitations (ie, CI variability cannot be evaluated by routine clinical ambulatory monitoring, and the reproducibility of measurement of this unique parameter remains unanswered). Furthermore, the strict relationship between PVC morphology and CI variability was not tested in the study, in which the number of PVC morphologies showed marginal significance (P=0.051) as a determinant of SDNV in their multiple linear
prevalence and proportion of individual causes of sudden cardiac death (SCD) in Asia are very different from those in Western countries. Taking these differences into account is of great clinical importance when screening high-risk patients and hence the best candidates for prophylactic implantable cardioverter-defibrillator (ICD), under the current unresolved status of primary prevention of SCD with ICD in HF patients.

regression analysis. If PVC morphology was the major determinant of CI variability, PVC likely may have propagated by switching the exit of the reentrant circuit (Figures B, C). On the other hand, if the CI was random under constant PVC morphology, the PVC might have reflected electrical instability leading to focal discharge (Figure D). Nevertheless, there is value publishing this study from Far East Asia, because the prevalence and proportion of individual causes of sudden cardiac death (SCD) in Asia are very different from those in Western countries. Taking these differences into account is of great clinical importance when screening high-risk patients and hence the best candidates for prophylactic implantable cardioverter-defibrillator (ICD), under the current unresolved status of primary prevention of SCD with ICD in HF patients.
Disclosures

The authors have no potential conflicts of interest to disclose.

References


