We appreciate the acknowledgement that the foreign gas rebreathing method is highly accurate for measuring the effective cardiac output (the blood flow to ventilated lung). This technique and its development are reviewed in great detail in an outstanding paper by Laszlo (5). Investigators at our institution, UT Southwestern, developed the most common modification of this technique, which made it easy to use in exercising humans (6). We have further enhanced the technique by allowing the participant to determine his/her own inspiratory volume. The inert and soluble gases are inhaled directly from an upstream regulator through a turbine flow meter that directly measures inspiratory volume. This modification is described in great detail in the publication by Jarvis et al. (7), where it was validated against invasive techniques, including both direct Fick and thermodilution. During exercise, the normal increase in tidal volume (and respiratory rate) that occurred in these and most individuals allowed them to inspire an adequate tidal volume and mix the air in the bag with the air in the lung within 2 or 3 breaths. The typical error for repeat measurements of cardiac output during exercise in our laboratory is <5%. Thus, we feel that any change in venous return solely as a result of the rebreathing technique is likely to be small. Moreover, this technique was identical over all conditions, thus making the comparisons between conditions valid. Of note, our technique is similar although not identical to the technique used to differentiate APC versus TCPC Fontan mentioned earlier (3). However, as stated in our paper, this method of cardiac output measurement should be studied further in patients with congenital heart disease.

In our analysis of the data, we performed both the Bonferroni and Scheffe methods for multiple comparisons. With regards to minute ventilation, the results were identical using both methods. Given our study size, we believe that it was most appropriate to use conservative methods for testing, and we would need a larger study to more fully assess additional changes in respiratory patterns.

We appreciate the opportunity to further discuss our study, and it will serve as a springboard for additional studies evaluating the normal increase in respiratory patterns. This modification is described in great detail in the publication by Jarvis et al. (7), where it was validated against invasive techniques, including both direct Fick and thermodilution. During exercise, the normal increase in tidal volume (and respiratory rate) that occurred in these and most individuals allowed them to inspire an adequate tidal volume and mix the air in the bag with the air in the lung within 2 or 3 breaths. The typical error for repeat measurements of cardiac output during exercise in our laboratory is <5%. Thus, we feel that any change in venous return solely as a result of the rebreathing technique is likely to be small. Moreover, this technique was identical over all conditions, thus making the comparisons between conditions valid. Of note, our technique is similar although not identical to the technique used to differentiate APC versus TCPC Fontan mentioned earlier (3). However, as stated in our paper, this method of cardiac output measurement should be studied further in patients with congenital heart disease.

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We appreciate the opportunity to further discuss our study, and it will serve as a springboard for additional studies evaluating the complex physiology of the Fontan circulation both in our laboratory as well as those of others.

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Early Repolarization and Arrhythmia Death
Does it Need a Trigger?

We read with great interest the results of the recent meta-analysis performed by Wu et al. (1), in which the researchers suggested that early repolarization pattern (ERP), defined as an elevation ≥0.1 mV of the J point in the inferior and/or lateral leads, is consistently associated with higher risk for arrhythmia death but not cardiac death or all-cause death. Their findings also revealed a low to intermediate absolute incidence of arrhythmia death in patients with ERP. These findings are valuable to our current understanding of the true risk associated with ERP.

First, although an increased arrhythmic risk has once more been documented, the absolute increase in risk is low, supporting the notion that otherwise healthy patients are extremely unlikely to die from this condition. Therefore, cost effectiveness of primary prevention strategies may be very hard to attain.

Second, although bias due to misclassification may have played a role, the fact that only arrhythmic risk was shown to increase in the presence of early repolarization (ER) suggests that this electrocardiographic pattern was probably associated with a change in the mechanism underlying the fatal event rather than a higher risk for death.

Most importantly, ERP has never been shown to consistently increase arrhythmic risk in the absence of additional proarrhythmic triggers. Depression of the epicardial action potential plateau in ER may create a transmural repolarization gradient that is not arrhythmogenic by itself, but further increases in the net repolarizing current, with additional loss of the action potential dome, and dispersion of repolarization may create an electric substrate conducive to malignant ventricular arrhythmias. Under certain conditions known to predispose to ST-segment elevation, such as ST-segment elevation myocardial infarction (MI), or to additional repolarization heterogeneity,
such as hypokalemia and heart failure, patients with ERP may be at increased arrhythmic risk. Recent studies support the important role of additional proarrhythmic triggers in the pathogenesis of ER, especially in the case of acute myocardial ischemia (2–5). A prospective study composed of patients at high coronary risk could add some robustness to these theses in the event that a higher arrhythmic risk was detected in those with ERP. Moreover, inclusion of low-risk coronary patients only, eventually based on Framingham risk stratification, could help us better evaluate the potential intrinsic arrhythmogenic nature of ER.

Although the authors highlighted that increased transmural heterogeneity of ventricular repolarization may be the mechanism involved, it is of note that some researchers have reported that repolarization abnormality markers, such as T-wave alternans and QT dispersion, do not differ between patients with and without J-waves, whereas the incidence of late potentials (a depolarization abnormality marker) in idiopathic ventricular fibrillation J-wave groups is higher than in non–J-wave groups (6). The contribution of various pathophysiological mechanisms in ER syndrome seems as likely as in the Brugada syndrome.

In the first 2 forest-plots, the I² is more than 90%, illustrating a very high heterogeneity. Interpretation of data arising from pooling of such a heterogeneous group of studies may compromise the overall validity of the meta-analysis. Moreover, the fact that there are no funnel-plots provided makes us wonder about a potential publication bias in this meta-analysis.

Although physicians should be aware of the potential arrhythmogenic role of ERP, there is no evidence to support different primary prevention strategies for patients with ER. Nevertheless, prevention of arrhythmic triggers, such as acute myocardial ischemia, through more aggressive prevention of coronary artery disease might mitigate the apparent association between ER duration and arrhythmic mortality.

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http://dx.doi.org/10.1016/j.jacc.2013.02.037

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The early repolarization pattern (ERP), which is characterized by an elevation of ≥0.1 mV of the QRS–ST junction (J point) with either QRS slurring or notching in the inferior and/or lateral leads on 12-lead electrocardiography (ECG), has recently been associated with vulnerability to ventricular fibrillation in case-control studies. However, the prognostic significance of ERP in the general population remains controversial. We conducted a meta-analysis to summarize all published prospective studies and case-control studies to date on the risk and incidence of cardiac death, arrhythmia death, and all-cause death in the general population with ERP. The results from our meta-analysis showed that ERP was associated with increased risk of arrhythmia death (risk ratio: 1.70; 95% confidence interval [CI]: 1.19 to 2.42; p = 0.003) but not with cardiac or all-cause death. At the same time, we found that the absolute risk differences of the patients with ERP were 70 cases of arrhythmia death per 100,000 patients per year (1).

Although our meta-analysis included large sample sizes, long durations of follow-up, and well-established prospective studies or case-control studies and our pooled estimates were based on prospective analyses with detailed adjustment for confounding variables, there were some limitations. First, the relatively small number of studies limited our ability to identify which subgroups were at higher risk for reported events. Second, the small number of studies also limited our ability to determine whether heterogeneity in summary estimates was explained by factors related to study quality. Heterogeneity among studies was formally assessed using Q and I² statistics, and risk ratios and 95% CIs were pooled in random-effects models in our meta-analysis because of big I² values. Third, we cannot exclude the possibility of patient confounding and publication bias due to misclassification, although there was no evidence of publication bias (p = 0.22) in the patient risk estimates for arrhythmia death. At the same time, sensitivity analysis in our study showed that none of the individual studies substantially influenced the pooled risk ratios for any of the outcomes.

How the ERP increases the risk of arrhythmia death is unclear. Experimental studies have shown that a prominent transient outward current (Ito)–mediated action potential notch in ventricular epicardium, but not endocardium, causes a transmural voltage gradient during early ventricular repolarization that produces J-point elevation on the ECG. An increase in net repolarizing current, due either to a decrease of inward currents or augmentation of outward currents, accentuates the action potential notch and leads to augmentation of the J-point elevation. The prominent Ito responsible for the ERP may facilitate the development of ventricular fibrillation (2–5). The genetic basis for ERP remains unclear.

We consider ERP to have a cardiac electrophysiological unstable and potential intrinsic arrhythmogenic nature that increases the