We congratulate Shafer et al. (1) on their recent publication. Pressures in Patients With Relationship of Cardiac Output

We like to raise some points and would be grateful to the researchers if clarification could be provided to better understand their methodology and results. With regards to the patient population, we were somewhat surprised to see that young patients, seemingly undergoing operations in the last decade or so, all underwent atriopulmonary Fontan. Total cavopulmonary connection has been the surgery of choice in the last 2 decades because it provides a better hemodynamic profile and reduces the risk of arrhythmia generated by an enlarging right atrium.

The results of this study were obtained in young and asymptomatic patients a few years post-Fontan operation. We wonder whether the conclusions can be generalized to the whole population of patients with Fontan circulation, including those with very large right atria and those with a “failing Fontan.”

The inert gas rebreathing method is indeed one of the most accurate methods for noninvasive assessment of cardiac output. This method requires appropriate and strict adjustment of respiratory pattern. A rebreathing bag of a volume of 1.5 to 2.5 liters should be used for several breaths and should be emptied at each breath for the technique to provide accurate results (2). Such adjustment of breathing pattern during exercise produces little change in cardiac output in healthy individuals but could significantly affect cardiac output in patients with Fontan circulation. In fact, an optimal respiratory breathing pattern during exercise has been suggested in Fontan patients, resulting in the most efficient pulmonary augmentation of blood flow (3). The lack of a significant increase in cardiac index from “exercise” to “exercise plus inspiratory load,” as seen in this study, would appear to contradict previous data on the beneficial effects of negative inspiratory pressure in Fontan patients (4). We wonder whether this relates to the technique used for measuring cardiac output.

Furthermore, it appears unclear to us whether the increase in stroke volume in these patients was accounted for entirely by the skeletal muscle and ventilatory pumps. Complete separation of the effects of the muscle and ventilatory pumps is difficult to achieve, even with such a carefully designed protocol such as the one used in this paper, as demonstrated by the change in minute ventilation in both patients and controls on “zero-resistance cycling” (Fig. 4 of their paper [1]). The latter proved to be statistically nonsignificant, but we wonder whether this was due to the Bonferroni post hoc adjustment for multiple comparisons, which is known to inflate type II errors.

References


Reply

We appreciate the interest and thoughtful comments regarding our recently published paper and are pleased to take this opportunity to discuss our techniques and data further (1).

As stated, our study was performed exclusively in patients with the atriopulmonary connection (APC) Fontan. Although this is not the more contemporary type of Fontan circulation, our design did allow for study of a relatively homogenous population, limiting the amount of unmeasured confounding. Although there is evidence of less efficient flow dynamics at rest and lower effective pulmonary blood flow at peak exercise in the APC Fontan versus the total cavopulmonary connection (TCPC), the changes during exercise as they would apply to our findings are unknown (2,3). We agree that there is a need for additional investigation of our results in the TCPC Fontan and hope to do so in the future.

In part because of the work of Shekerdemian et al. (4), the inspiratory load was included in our study and designed to impose an enhancing and inhibitory (from the expiratory load) stimulus on the ventilatory pump. However, it is worth highlighting a few key differences between the Shekerdemian et al. (4) study and ours. First, their patients were intubated and paralyzed and thus by definition without thoracic or skeletal muscle pump activity. Their study showed that negative-pressure ventilation was able to counteract some of the untoward effects of positive-pressure ventilation in the absence of respiratory muscle pump activity. It is important to emphasize that we showed a decline in stroke volume even in the presence of muscle pump activity, highlighting the need for caution when using this type of ventilatory support. Although our study failed to show significant additional benefit of negative intrathoracic pressure during exercise above the increase in stroke volume due to the muscle pump, we agree that the design did not evaluate the ventilatory pump without simultaneous action of the muscle pump. If we had added an isocapnic hyperpnea condition in the absence of zero resistance cycling to our study, we could have commented more fully on this concept. With our data, we would suggest that unless antagonized, the effects of change in intrathoracic pressure are less critical than the muscle pump in maintaining the stroke volume in the nonparalyzed patient with Fontan circulation.

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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 complex physiology of the Fontan circulation both in our laboratory as well as those of others.

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REFERENCES


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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,