Reply to the Editor:

We thank Takagi and colleagues for their interest in our work and their update, which completes and supports our results.¹ Among the RAPCO reports published during the years covered by our research (January 1966–March 2009), we chose to include the study by Buxton and colleagues² published in 2003 and exclude the report by Hayward and collaborators³ published in 2007 because the latter study included patients undergoing serial angiography and, more importantly, because in that analysis saphenous vein was grafted to second-, third- and fourth-order coronary vessels, thus affecting overall patency rate.

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**FONTAN HEMODYNAMICS:
WHAT IS THE PROBLEM?**
To the Editor:

Congratulations to Dasi and coauthors¹ for their valuable study on Fontan hemodynamics. Eleven patients underwent lateral tunnel procedures, and 11 underwent total cavopulmonary connection through an extracardiac Fontan operation. We have previously proposed that contractility and ventricular stress tests should be reevaluated

with different measurement methods,² although our opinions do not coincide with those of some other authors.³ We think that there should be a consensus regarding methods used to measure contractility and ventricular stress with respect to Fontan hemodynamics. Consideration of our opinions on this issue by Dasi and coauthors¹ would be appreciated and would help us in solution of this enigma.

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Reply to the Editor

We thank Kestelli and colleagues for their letter on this important topic. Fontan failure^{1,2}—defined here as poor prognosis after the Fontan operation—may occur at either an early or a late stage. Most late failures are in older patients with the classic atriopulmonary connection, with problems including arrhythmias, thromboembolism, heart failure, and pulmonary venous blockage. Early failures include arteriovenous malformations and protein-losing enteropathy, occurring mostly in patients with a total cavopulmonary connection. Heart failure appears eventually if no other failure mode manifests. These

varying failure modes clearly show that the problem is complex, multifactorial, and still unfolding as more and more patients who underwent total cavopulmonary connection in the mid 1990s are now reaching adulthood. Even though all these patients have a single-ventricle physiology that is inherently preload limited with increased afterload,³ it is not yet clear whether preload limitation is the only cause. There are other independent factors (quality of connection, afterload, underlying congenital defect).

The specific modes of failure for a given patient depend on the severity of the underlying congenital heart defect, efficacy of the palliative approach chosen, and the health and composition of the interacting organ system, including the lungs and abdominal viscera. We have just begun a National Institutes of Health–funded predictive study to help determine the specific criteria for efficient management of these patients. For instance, patients in whom the hepatic flow return is biased toward a single lung may have arteriovenous malformations develop. Those with a highly energy-dissipating total cavopulmonary connection may have decreased preload, poor exercise tolerance, or high central venous pressure, leading to protein-losing enteropathy or heart failure. There is no predictive model currently available that can determine the precise contributors to and mechanisms of failure in a given patient, even when all hemodynamic information is available. We hope that our ongoing research will provide more definite answers to these questions in the coming years.

In the final analysis, for many patients with Fontan circulation, survival into the 4th or 5th decade may require innovative solutions, such as that proposed by Kestelli and associates.⁴ There are many concerns regarding the proposed solution, however, which may be trading one problem for many others. The proposed solution is energy neutral (energy available to drive the circulation is still the same,

although it is used differently) but requires the single ventricle to pump significantly more volume to maintain the same cardiac output, thus decreasing net cardiac output. The theoretic gains in pulsatility and pulmonary vascular resistance must be balanced by the risks of low cardiac output, ventriculotomy, and thrombosis related to the valves in the pulmonary circuit. Nevertheless, these are just theoretic predictions, and detailed in vitro and in vivo studies are necessary to assess the true efficacy of this and other novel solutions. Venous and mechanical supports that provide an additional energy source are being studied through progressing animal models and may offer the best hope for some patients.⁵

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THE MURINE MONOCLONAL ANTIBODY ANTI-CYTOKERATIN CAM 5.2 IS SPECIFIC FOR INTRACELLULAR CYTOKERATIN 8, NOT CYTOKERATIN 18 To the Editor:

We read with great interest the contribution by Grotenhuis and colleagues regarding the article entitled "The sentinel node concept in adenocarcinomas of the distal esophagus and gastroesophageal junction."¹ However, the authors might have inadvertently annotated the NCL 5D3 clone to be the source of the murine monoclonal antibody CAM 5.2 and unsuitably suggested CAM 5.2 to be specific to cytokeratins 8 and 18 in their experiment as well.¹

We would like to comment and clarify that anti-cytokeratin CAM 5.2 was different from cytokeratin 8/18 monoclonal antibody. Monoclonal antibody to cytokeratin 8/18, instead of anti-cytokeratin CAM 5.2, was originally developed and manufactured by Novocastra Laboratories Ltd (Newcastle Upton Tyne, United Kingdom) using the brand Novocastra. The company grew and in 2003 was integrated into Vision Biosystems (Wetzlar, Germany). Today, Novocastra has become an important part of the overall histology range of Leica Microsystems' Biosystems Division through this definitive merger.

Therefore, monoclonal antibody to cytokeratin 8/18 is produced by Leica Microsystems' Biosystems Division, which is derived from the 5D3 clone.

This clone reacts with human cytokeratin-intermediate filament proteins at 52.5 and 45 kd, which are identified as cytokeratins 8 and 18, respectively.² On the other hand, anti-cytokeratin CAM 5.2 reagent is produced by Becton Dickinson Biosciences (Franklin Lakes, NJ) and is derived from the clone CAM 5.2. This clone reacts with human cytokeratin-intermediate filament proteins at 48 and 52 kd, which are identified as cytokeratins 7 and 8, respectively.³ In addition, Becton Dickinson Biosciences (1977) revised the data sheet for anti-cytokeratin CAM 5.2 to have a primary reactivity with cytokeratin 8 and, in addition, a weaker but distinct reactivity with cytokeratin 7. The data sheet also shows that there is no reactivity with cytokeratins 18 or 19. As a result, CAM 5.2 is not synonymous with cytokeratins 8 and 18.⁴ We concluded that the murine monoclonal antibody CAM 5.2 will not be specific for intracellular cytokeratins 8 and 18.

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