EDITORIAL COMMENT

Four Decades of the Fontan Operation

Did We Ever Have a Leg to Stand on?*

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Experimental research on dogs enabled us to check the technical feasibility of this procedure, but there were no survivors for more than a few hours.

—Fontan and Baudet (1971) (1)

The Concept

Claudius Galen (circa AD 129 to 200) held that there were 2 separate blood systems, nutritive and respiratory, with fuel supplied by the liver and fumes exiting through the windpipe (2). The concept of the heart as a pump would wait another 1,500 years. In 1628, William Harvey (3) put forth the idea of the heart as a source of propulsion when he observed the auricles and 2 ventricles beating in a living mammal (2). With the advent of human dissections, Harvey's experiments in the forearm led him to conclude that "since the Blood could not well, because of the interposing Valves, be sent by the Veins to the Limbs, it should be sent through the Arteries, and return though the Veins, whose valves did not oppose its course that way" (3). Harvey is thus credited for his discovery of the circulation: "I began privately to consider if it [the heart] had movement in a circle" (3). These cornerstone observations escorted us into 3 centuries of research that would expand our understanding of the normal cardiovascular circulation.

After birth, the aortic and pulmonary circulation are arranged in series with pulsatile subpulmonary and subaortic ventricles. In the occurrence of a functional single ventricle because of tricuspid atresia or a double-inlet single ventricle, the systemic and pulmonary circulation are connected in parallel with complete admixing of oxygenated and deoxygenated blood (4). Over 300 years after Harvey's discovery, Sewell and Glenn (5) would construct a pump to divert caval

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return into the pulmonary artery, bypassing the right heart and giving rise to the Glenn anastomosis.

In Fontan and Baudet's initial report (1), they state, "We were of the opinion that a hypertrophied right atrium as in tricuspid atresia, could supply the additional work represented by a pulmonary arterial pressure higher that the left atrial pressure . . . it seemed indispensible to provide the right atrium with valve homografts." The opinion turned out to be erroneous, but the idea was an important departure point. The valves in a low-pressure, nonpulsatile circulation were a source of thromboembolism and were replaced by the direct right atrial–to–pulmonary anastomosis, or "modified Fontan" procedure (6). In its last reiteration, the right heart was bypassed altogether, with an extracardiac conduit steering blood from the head and the feet directly into the pulmonary artery via the superior and inferior vena cavae (7).

Thus, in Fontan patients, a circulation in series is surgically re-established, but in the absence of a pulsatile subpulmonary ventricle, blood must flow down a pressure gradient from the cavae to the left atrium. Necessarily, the pulmonary pressures must remain low as must the pressure in the left atrium. Under such circumstances, the goals of the Fontan procedure are realized: to relieve cyanosis and to maintain cardiac output; reduce volume loading of the systemic ventricle.

The Patient

In 2006, I was privileged to host a small group of medical students who had requested to visit our congenital heart disease unit. I invited a patient to speak about living with lifelong disease. A young woman explained that she had been planning her departure to the University of California, Los Angeles, to study film when she survived a cardiac arrest and required an implantable defibrillator. She described a "heart-stopping experience," indicating that "we had been waiting 20 years for something to go wrong." With wit, she shared her existential dilemmas. The tone of the conversation was much like what one hears in any number of coffee shops concentrated around college campuses. I watched with pleasure as the patient and students of the same age exchanged ideas. When the meeting ended, I saw the young women walk down the corridor in continued discourse with one of the students. The next day, I received a call. One of the students wanted to meet with me. She walked into my office, tall with a lot of thick dark hair and large, inquisitive brown eyes. She looked fit and happy but restless. She sat down and pulled out of her large bag a small sealed envelope that she handed to me. By way of easing conversation, I asked her what she had enjoyed most in medicine to date. She indicated her definite desire to be a cardiac surgeon. After a few minutes, I asked her if I could open the envelope. A single sheet of paper revealed an operative report of the Fontan operation she underwent at 4 years of age. She had not gone back to a cardiologist since the age of

16 years. I asked her why she came on this day. She said that that she had been inspired by the film student she had met. A patient with tetralogy of Fallot (TOF) having survived cardiac arrest thus inspired a physician in training with a Fontan operation to become a patient again. The story is moving for many reasons beyond the scope of this editorial. It does, however, underscore the extraordinary motivation for our work and highlight several characteristics of Fontan patients worthy of mention.

Complications and mortality vary with underlying anatomy, the year of operation, and the type of Fontan anastomosis (8). For patients operated before 1985, 10-year survival was 60% to 70% (9). Twenty-five-year survival was almost 80% in patients with tricuspid atresia (10). With the more recent lateral tunnel and extracardiac Fontan procedures, 10- to 25-year survival has varied from 80% to 90% (11). Of patients undergoing the Fontan operation for tricuspid atresia from the 1970s to the 1990s, nearly 90% are in New York Heart Association functional class I or II on long-term follow-up (10). In the functionally single ventricle, echocardiographic indexes of systolic and diastolic dysfunction are well documented (12). Beyond 20 years, deterioration in functional class can occur rapidly with the onset of complications (13).

Thus, although complete bypass of the right heart in the absence of a subpulmonary pump was not achievable in animals with horizontal bodies, it was realized in humans, who were vertical most of the time (14). Was it really possible for blood to flow from the ankles back up to the heart without a pump or heart valves (14)? Evidently yes, but what are the clinical consequences on the lower extremities?

The Present Study

In this issue of the *Journal*, Valente et al. (15) address this question, which has not been asked to date, with the well-named CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients) study. The investigation, driven by astute clinical observation, describes the risk for chronic venous insufficiency (CVI) in patients with the Fontan operation. Fontan patients are compared with normal subjects and a group of patients with TOF repair to determine if those with the Fontan operation are at increased risk for CVI.

The investigators performed a multicenter, prospective, cross-sectional observational study recruiting 159 stable Fontan patients age >18 years, 40 patients with TOF, and 25 normal controls. A standardized clinical examination of the lower extremities was performed using the clinical, etiological, anatomical, and physiological (CEAP) classification of CVI. Severe CVI was defined as CEAP grade ≥4. The observations were photographed to record the CEAP grade. Validation was obtained in a subgroup of patients, demonstrating 100% correlation for those with severe CVI between the CEAP grade assigned by a vascular medicine specialist blinded to the record and the grade determined by the clinical investigators.

The Fontan group had a mean age of 30.6 ± 9.1 years. The single ventricle was predominantly of the left ventricular type, and the Fontan procedures were mostly atriopulmonary anastomosis and lateral tunnel types. Of the Fontan patients, 27% had histories of thrombotic complications. The prevalence of CVI in the Fontan population was twice that in the controls, and 22% of Fontan patients had severe CVI compared with none of the healthy controls. In multivariate analysis, more than 5 cardiac catheterizations, leg symptoms, and deep venous thrombosis were independently correlated with severe CVI. The investigators observed no correlation between CVI and cardiac factors considered to be risk factors for adverse Fontan outcomes, including the morphology of the underlying ventricle and the type of Fontan anastomosis. In all likelihood, the small numbers preclude the ability to demonstrate specific Fontan features that would help identify the subgroup of patients at high risk for severe CVI. Furthermore, there are no reported data on hemodynamic or biochemical markers of thrombotic risk.

The investigators postulate that as a result of a chronically high caval pressure, an elevation in systemic venous hydrostatic pressure may occur, inducing venous remodeling, hypertension, and inflammation. In the Fontan circulation, systemic venous return is closely dependant on peripheral venous properties (16). In a study of 6 Fontan patients and controls, Kelley et al. (16) measured peripheral venous pressure, venous pooling, and changes in vasomotor tone under normal conditions and with the induction of graded orthostatic stress. In these patients, all of whom had residual right atrial tissue, the baroreceptor-mediated ability to limit venous pooling was preserved (16). Fontan patients also showed a smaller capacity for venous pooling and an increase in venomotor tone (16). Furthering these observations, Krishnan et al. (17) investigated what effect this might have on microvascular filtration. Using strain-gauge and impedance plethysmography during the head-up tilt test in 9 Fontan patients, they documented a measurable increase in lower limb venous pressure associated with a higher threshold for microvascular filtration in Fontan patients compared with controls (17). Taken together, these findings suggest that in Fontan patients, adaptive mechanisms are in place to enhance the gradient for venous return to the heart, prevent an excessive drop in systemic venous pressure with orthostasis, and prevent the onset of peripheral vascular changes that would be observed in normal patients at the same venous pressures.

In the group of Fontan patients reported by Valente et al. (15), what then differentiates the 22% of Fontan patients who exhibited severe CVI from those who did not? Is it that the elevation in systemic pressures exceeded the adaptive mechanisms seen in Fontan patients without CVI? Is it that a subgroup of Fontan patients exhibited lower filtration thresholds in their limbs? Would we find a difference in those with and without residual right atrial mechanoreceptor tissue in the Fontan circulation? Interest-

ingly, perhaps the answer lies not only in the peripheral Fontan circulation but also in the function of the single ventricle. It is remarkable to note that in the present study (15), the prevalence of CVI was not significantly different in Fontan patients and in those with TOF repair known for right ventricular dysfunction (18). There are no data in the present study that would allow us to speculate as to the reason for this finding. We are not provided with information on ventricular function in either the Fontan or the TOF group. If ventricular dysfunction is the final common pathway for CVI in both patient groups, the investigators may have uncovered an important finding applicable to a wide range of patients with congenital heart disease with right ventricular dysfunction. A prospective study with quantitative data on ventricular function and hemodynamic conditions using the method established by the CALF investigators, targeting patients with CVI who have single-ventricle, systemic, and nonsystemic right ventricular dysfunction, would help answer these questions.

Four decades after the first description of the Fontan operation (1), in answer to the question of whether we ever had a leg to stand on, the answer is probably no. It has been said of William Harvey's scientific genius that it resulted from his ability to see the implications of even rough approximation (2). Quite possibly, the work of Sewell, Glenn, and Fontan espoused the same cognitive course (1,5). Like many things in nature, although the results are not perfect, they are no less remarkable. Fontan patients have captured the imagination of their surgeons and cardiologists for a long time. Valente et al. (15) provide a novel, thought-provoking set of observations that, as with many good studies, leave us with a new set of questions and wanting for more answers.

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