Systemic Ventricular Function in Patients with Tetralogy of Fallot, Ventricular Septal Defect and Transposition of the Great Arteries Repaired During Infancy

KENNETH M. BOROW, M.D., JOHN F. KEANE, M.D., ALDO R. CASTANEDA, M.D., AND MICHAEL D. FREED, M.D.

SUMMARY Work-function curves relating systemic ventricular end-diastolic pressure (EDP) to minute work index (MWI) were used to assess ventricular performance in eight patients with tetralogy of Fallot (TOF), five patients with ventricular septal defect (VSD), and nine patients with d-transposition of the great arteries (TGA). All patients underwent repair when they were younger than 18 months of age and, when studied 13 months after surgery, were found to have satisfactory anatomic results by catheterization. Results were compared with seven control subjects. All patients had normal systemic ventricular hemodynamics at rest. A work-function curve for each patient was generated using a methoxamine infusion to increase afterload and measuring EDP, mean ventricular systolic pressure and cardiac index. Heart rate was maintained within a narrow range for each patient.

The systemic ventricle in the TGA patients responded to the afterload stress with a smaller increase in MWI than was noted for either the TOF (p < 0.05), VSD (p < 0.01) or control (p < 0.01) groups. This difference in MWI for the TGA patients occurred despite a comparable increase in systemic ventricular EDP for all groups. The net result was a highly significant difference in mean slope of the work-function curves for the TGA patients compared with the TOF (p < 0.02), VSD (p < 0.01) or control (p < 0.01) patients. There was no significant difference in mean slope for the TOF, VSD and control groups.

Thus, an afterload stress at early postoperative follow-up identified preclinical systemic ventricular dysfunction in TGA patients not evident in age-matched TOF and VSD patients. This finding takes on added significance with the recent development of alternative surgical approaches to repair of TGA that use the left ventricle as the systemic pumping chamber.

DYSFUNCTION of the systemic ventricle at rest and with exercise has been reported in older patients with tetralogy of Fallot (TOF),1-3 ventricular septal defect (VSD)4-8 and d-transposition of the great arteries (TGA).5-8 It is not known if repair of these lesions early in life can preserve ventricular function. Studies of patients corrected during infancy have used hemodynamic, echocardiographic or angiographic data derived from the resting, nonstressed ventricle to assess postoperative ventricular performance, with contradictory and often inconclusive results.5-17

The purpose of this investigation was to assess systemic ventricular function during cardiac catheterization at rest and during an afterload stress in patients with TOF, VSD and TGA repaired during infancy. We have reported the use of this technique to unmask latent left ventricular (LV) dysfunction in patients with TOF repaired during childhood.18 This study is the first detailed assessment of the functional reserve capacity of the systemic ventricle in patients with congenital heart disease repaired during infancy.

**Materials and Methods**

**Patients**

The Cardiology and Cardiovascular Surgery Departments of the Children's Hospital Medical Center has a policy that all patients with TOF, VSD with associated pulmonary artery hypertension, and TGA undergo cardiac catheterization approximately 1 year after surgical repair to assess the hemodynamic results. During the period of this study, 75% of our infants with these lesions underwent a 1-year follow-up catheterization. Our study population consisted of 22 such patients (eight with TOF, five with VSD and nine with TGA) surgically repaired when they were younger than 18 months of age. All had a preoperative cardiac catheterization within 9 months of operation and 77% (17 of 22) were catheterized within 2 months before surgical correction (table I). The age at preoperative catheterization was similar for all groups. Preoperatively, six of eight patients

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with TOF had cyanotic spells. All patients with VSD had large left-to-right shunts with a ratio of pulmonary-to-systemic blood flow greater than 3:1 and persistent congestive heart failure and/or failure to thrive. Seven of the nine infants with TGA had subvalvar or valvar pulmonic stenosis, but the LV pressure was less than two-thirds of systemic pressure in all nine. Two patients with TGA (nos. 14 and 22) had a VSD. At preoperative catheterization, the peak systolic and end-diastolic pressures in the systemic ventricle were slightly higher for the VSD patients than for either the TOF or TGA patients. Aortic blood oxygen saturation was 97 ± 1% (mean ± SEM) in the VSD patients, 76 ± 3% in the TGA patients and 89 ± 3% in the TOF patients at rest, falling to 68 ± 5% with crying.

All patients had total repair performed in the usual fashion, with the pericardial sac left open at surgery.

In infants with a VSD, the defect was closed through a right atriotomy with a Dacron patch. A pericardial or Dacron patch was placed across the right ventricular (RV) outflow tract and pulmonary valve annulus in seven of eight TOF patients, and the VSD was closed with a Dacron patch. All TGA patients were repaired using an intraatrial baffle; four of nine were repaired using Mustard’s technique and the remainder using a modified Senning procedure. Twenty of 22 patients were repaired using deep hypothermic circulatory arrest; the only exceptions, patients 8 and 22, were older than 1 year at the time of surgery. The temperature during cardiac arrest was not different for the three groups. The mean cardiac arrest time was 52 ± 8 minutes (± sd), 39 ± 5 minutes and 63 ± 12 minutes for the TOF, VSD and TGA groups, respectively (p < 0.05 for VSD vs TGA). Postoperatively, all TOF patients had complete right bundle branch block and
three of nine TGA patients experienced transient supraventricular rhythm abnormalities. No other significant perioperative events were noted for any group. The mean age at surgical repair, the interval from repair to postoperative cardiac catheterization, and the age at follow-up catheterization were comparable for all groups (table 1).

At postoperative catheterization, all patients were asymptomatic, in normal sinus rhythm, and had hemodynamically satisfactory repairs.

In the TOF patients, satisfactory repairs were defined as RV/LV systolic pressure ratio less than 0.6 and no evidence for a residual left-to-right shunt as determined by oxygen saturation measurements. In the VSD patients, satisfactory repairs were defined as a normal pulmonary artery mean pressure (< 16 mm Hg) and no evidence for residual left-to-right shunt at the ventricular level by oxygen saturation measurements or LV angiography. In the TGA patients, satisfactory repairs were defined as less than or equal to 5 mm Hg gradient across the inferior vena cava, superior vena cava and/or pulmonary venous baffle sites, no evidence for tricuspid regurgitation by right ventriculography and no residual shunts.

Only patients who fulfilled these criteria and in whom informed parental consent could be obtained were included in the study. The control group consisted of seven patients (ages 3.3–19.0 years, mean 11.0 years), six with isolated mild-to-moderate valvular pulmonary stenosis (RV/LV peak systolic pressure [PSP] ≤ 0.50) and one without significant heart disease.

Experimental Protocol

The methods used in this study have been described. All patients underwent routine right- and left-heart catheterization under light sedation with a combination of meperidine, 25 mg/ml, promethazine hydrochloride, 6.25 mg/ml, and chlorpromazine, 6.25 mg/ml, at a dose of 1.0 ml/30 lbs body weight to a maximum of 2.0 ml. Pressure measurements were made using Statham P23Db transducers zeroed at the patient’s mid-chest level. Pressure and oxygen saturation recordings were made. Cardiac output was determined either by the Fick technique using measured oxygen consumption by a Kipp diaferometer and oxygen saturation measurements or by thermodilution in the absence of pulmonary regurgitation. Systemic ventricular end-diastolic pressure (EDP) was measured 20–30 msec after the onset of the QRS complex with the transducer attenuation set at 2.0 mm Hg/cm paper. The EDP for a given set of loading conditions was taken as the mean value for 10 consecutive beats. After the resting hemodynamics were recorded, an i.v. infusion of methoxamine, a pure α agonist, was begun at a rate of 30 μg/kg/min. The infusion rate was slowly increased until the PSP in the systemic ventricle had increased to at least 40 mm Hg above the resting value. Cardiac slowing induced by methoxamine through baroreceptor stimulation was abolished by i.v. administration of atropine, 0.01–0.02 mg/kg.

Cardiac output, heart rate, aortic pressure and systemic ventricular pressure measurements were repeated at peak methoxamine effect and at several intermediate points at which hemodynamics were stable. A heart rate variation from baseline of greater than 10% was the criterion for exclusion.

Work-function curves for the systemic venous pressure were constructed by plotting the relationship between EDP and minute work index (MWI, kg-m/m²/min) for the systemic ventricle at rest and during the afterload stress. MWI was calculated as

\[ (CI) (MSP - EDP) \times 0.0136 \]

where CI = cardiac index (l/min/m²), MSP = mean systolic pressure for the systemic ventricle (mm Hg) obtained by planimetry of the area under the systolic phase of the aortic pressure tracing recorded at a paper speed of 100 mm/sec, and 0.0136 = conversion factor from mm Hg-cm² to g-m, having the units g-m/mm Hg-cm².

Biplane cineangiography of the systemic ventricle was performed at 64 frames/sec in all patients. The area-length method described by Dodge et al. was used to determine left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) in the TOF and VSD patients; RV volumes in the TGA patients were determined using Simpson’s rule. Volumes were determined except in patients 18 and 22, in whom it could not be calculated because of technical reasons. Ejection fraction (EF) was calculated as (EDV – ESV)/EDV.

The hemodynamic measurements were compared using the t test for unpaired data.

Results

Resting Postoperative Hemodynamics and Anatomy

Table 2 is a summary of the resting postoperative hemodynamics for the control and study patients. There was no significant difference in mean heart rate, systemic vascular resistance or CI between the study and control groups. PSP and MSP, ventricular EDP and MWI were slightly higher for the control patients than for the patients with repaired TGA. Postoperatively, three of nine TGA patients had mild subpulmonary stenosis (patient 14, 10 mm Hg; patient 18, 49 mm Hg; patient 22, 25 mm Hg). Seven of nine patients had this finding preoperatively, demonstrating the dynamic rather than fixed nature of the LV outflow tract obstruction frequently seen in TGA patients before repair. Of the 15 patients with preoperative VSDs, only two, patients 2 and 6, had evidence of small residual defects on ventricular angiography. No patient had a pulmonary-to-systemic blood flow ratio greater than 1.2:1.0.

Cineangiographic Volume Data

Figure 1 shows the resting cineangiographic volume data for the systemic ventricle in the TOF, VSD and TGA groups. The EDV and ESV indexes were larger and the EF lower for the TGA patients than for either
TABLE 2. Resting Hemodynamics in Control and Postoperative Study Patients

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<td>EDP (mm Hg)</td>
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<td>MWI (kg-m/min/m²)</td>
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All values are mean ± SEM.

Abbreviations: HR = heart rate; CI = cardiac index; PSP = peak systolic pressure; MSP = mean systolic pressure; SVR = systemic vascular resistance; EDP = end-diastolic pressure in systemic ventricle; MWI = minute work index; TOF = tetralogy of Fallot; VSD = ventricular septal defect; TGA = d-transposition of the great arteries.

the TOF or VSD groups. There were no significant differences in the volume data between the TOF and VSD patients.

Work-Function Curves for the Systemic Ventricle

The response to the afterload challenge was evaluated using work-function curves. Heart rate and CI did not substantially change with the methoxamine infusion. The individual patient's responses to the afterload stress are shown in Table 3. The systemic ventricle in the TGA patients responded to the afterload stress with a smaller increase in MWI than was noted for either the TOF (p < 0.05), VSD (p < 0.01) or control (p < 0.01) groups (fig. 2A). This difference in MWI for the TGA patients occurred despite comparable increases in systemic ventricular EDP for all groups (fig. 2B). The net result was a highly significant difference in the mean slope of the systemic ventricular work-function curves for the TGA patients (0.59 ± 0.06, mean ± SEM) compared with the TOF (0.97 ± 0.10; p < 0.02), VSD (0.95 ± 0.07; p < 0.01) or control patients (1.13 ± 0.12; p < 0.01). The slopes for the TOF, VSD and control groups did not significantly differ. Figure 3 shows the relationship between initial EDP and the slope of the MWI-EDP relation. Of the 20 patients with a left ventricle as the systemic pump (including the seven controls), 19 had slopes greater than 0.65. In contrast, only one of nine TGA patients had a slope greater than 0.65. This finding was independent of the patient's initial systemic ventricular EDP.

Discussion

Primary repair of TOF, VSD and TGA early in life is generally accepted as a safe procedure. Several authors have emphasized the need for detailed follow-up of these patients not only in regard to survival, but also with regard to ventricular performance. Resting hemodynamics alone, however, may fail to detect abnormalities in ventricular function. Often, the ventricle's response to an additional work load must be established if latent dysfunction is to be identified. The stress method most commonly used involves dynamic exercise testing. However, this was not feasible in our study because our patients were 2 years of age or younger. In addition, the cardiac response to dynamic exercise is frequently difficult to interpret because of a complex interaction between preload, afterload, intrinsic contractile state, heart rate and autonomic tone. By choosing an experimental design using pharmacologic manipulation of afterload to assess performance, we could circumvent the problem of inadequate cooperation. In addition, methoxamine has virtually no effect on myocardial contractile force, while producing only minimal changes in peripheral and pulmonary venous tone. Atropine successfully blocked the parasympathetic nervous system response to carotid baroreceptor stimulation and helped maintain heart rate within a narrow range (table 3). Thus, a relatively isolated afterload challenge to ventricular...
### Table 3. Preinfusion Hemodynamics and Response to an Afterload Challenge

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reserve capacity was possible without significant reflex chronotropic or inotropic changes.

The normal response to an acute increase in afterload is maintenance of cardiac output while ventricular work and EDP increase.27 Our TOF, VSD and control patients demonstrated this response while showing comparable increases in MWI and EDP and similar values for the slopes of their respective work-function curves. The VSD patients, despite the presence of congestive heart failure and failure to thrive before repair, showed normal LV function and reserve capacity 1 year after correction. This correlates well with their marked clinical improvement postoperatively. The TOF patients repaired during infancy also appear to have normal LV systolic function and compliance. This is in marked contrast to our previous findings in TOF patients repaired later in childhood, in whom LV dysfunction was unmasked with an afterload stress.18 By 1.3 years of age, the left ventricle in our VSD and TOF patients appears to have attained a functional status comparable to that noted in our older control patients. The systemic ventricle for the TGA patients had lower resting EDP and MWI than the control patients. This suggests that the systemic ventricle in the TGA patients may be operating on the lower portion of the ascending limb of its Starling curve and therefore may have substantial preload reserve available to meet situations requiring additional work. Nine of the 10 TGA patients, however, had a value for the slope of their work-function curve that was less than that found for the TOF, VSD and control patients. This was primarily due to a smaller increase in MWI relative to the associated rise in EDP. A ventricle that performs more work while

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Abbreviations: PSP = peak systolic pressure in the systemic ventricle; MSP = mean systolic pressure in the systemic ventricle; EDP = end-diastolic pressure in the systemic ventricle; CI = cardiac index; MWI = net minute work index; TOF = tetralogy of Fallot; VSD = ventricular septal defect; TGA = d-transposition of the great arteries.

**FIGURE 2.** Systemic ventricle's minute work index (MWI) and end-diastolic pressure (EDP) response to the afterload challenge in patients with tetralogy of Fallot (TOF), ventricular septal defect (VSD), transposition of the great arteries (TGA), and control (C) patients. The change (Δ) in MWI and EDP was calculated by subtracting pre-methoxamine (pre) values from values at peak methoxamine (peak) effect. Bars represent mean ± SEM.
Figure 3. Relationship between initial end-diastolic pressure (EDP) for the systemic ventricle and the slope of the minute work index (MWI)-EDP relation. Patients with a left ventricle as their systemic pumping chamber are represented by circles and those with a right ventricle as the systemic ventricle are indicated by squares.

Only minimally increasing its EDP has better function than a ventricle that responds to a similar stress with a smaller increase in ventricular work and the same elevation in EDP. 27

Because EDP has been substituted for end-diastolic fiber length as an approximation of preload, differences in elastic stiffness properties between the two ventricles must be considered. If the right ventricle in the TGA patients is more stiff than the LV in the TOF, VSD and control patients, one would expect to find an excessive rise in EDP associated with a small change in end-diastolic fiber length (true preload). This reduction in diastolic fiber length for a given EDP would result in less ventricular work being performed per unit increase in ventricular EDP. In our study, the RV EDV index in the TGA patients was larger than the LV EDV index in either the TOF or VSD groups, but despite its larger size, the right ventricle in the TGA patients had a lower diastolic filling pressure than the left ventricle in the TOF or VSD patients. Ventricular stiffness depends on the chamber's pressure-volume relation, 28 so a larger EDV at a lower EDP suggests that the right ventricle in the TGA patients may have less rather than more elastic stiffness properties than the normal left ventricle. One cannot account for the depressed MWI-EDP relation in the TGA patients on the basis of increased RV chamber stiffness, nor can one account for this difference on the basis of pericardial factors, because the pericardium was left open postoperatively in all patients. The most likely explanation is a difference in systolic function between the right ventricle in the TGA patients and the left ventricle in the TOF, VSD and control patients, a finding independent of EDP over the physiologic range of ventricular filling pressures.

The right ventricle in the physiologically repaired TGA patients could maintain a normal cardiac output despite the afterload challenge, and is thus hemodynamically well compensated, at least at this early age. There has been much concern, however, about the long-term function of the right ventricle in patients with TGA because the right ventricle must eject blood into the high-resistance circulation both before and after surgical repair. Godman and co-workers studied 14 patients 4-10 years after the Mustard operation. 29 Using pressure-velocity indexes of ventricular function at rest, they found decreased RV contractility in only one patient. They concluded that the right ventricle could function at a level of contractility comparable to that of the left ventricle. This conclusion has recently become suspect; other investigators have noted a poor correlation between pressure-volume indexes and pump function indexes of ventricular performance. Several authors have reported abnormal systemic ventricular function in patients repaired using Mustard’s procedure. These abnormalities have included depressed RV EF in the face of normal or increased RV EDV and normal or low RV CI. 6, 10, 18, 19 In addition, exercise stress testing has identified decreased endurance indexes in some of the patients. 7 Thus, our findings of mild RV systolic dysfunction as early as 1 year after repair of TGA takes on additional importance because alternative surgical approaches using the left ventricle as the systemic ventricle have been described. 80, 81

Differences between RV and LV myocardial fiber array or contraction pattern may in part account for the depressed RV function in the TGA patients in our study. Hypoxemia and chronic myocardial ischemia before physiologic repair may cause irreversible cellular and metabolic damage. In addition, the detrimental effect of the relatively long cardiac arrest time required to perform either the Mustard or Senning operation is unknown. Recently, at our institution, several TGA patients have been repaired during the first few weeks of life using the modified Senning procedure. If this subgroup of TGA patients has normal functional reserve capacity at the 1-year follow-up study, it would strongly suggest that myocardial hypoxemia rather than intrinsic anatomic or geometric factors is the underlying cause of the RV systolic abnormality.

Our findings show that patients with TOF, VSD and TGA successfully repaired during infancy have normal resting hemodynamics in their systemic ventricle 1 year after repair. The TOF and VSD patients, when afterload stressed, had normal work-function curves relating LV MWI to EDP and normal LV reserve capacity. Patients with physiologically repaired TGA, however, showed evidence of systemic ventricular dysfunction with failure to appropriately
increase ventricular work in response to the methoxa-
mine challenge. Only long-term follow-up study will
determine if the right ventricle in TGA patients shows
further reduction in ventricular function associated
with clinical deterioration and death.

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