Evidence of Early Impairments in Both Right and Left Ventricular Inotropic Reserves in Children With Duchenne’s Muscular Dystrophy

Gilles Bosser, MD, Hugues Lucron, MD, Jean-Paul Lethor, MD, Guillaume Burger, MD, Françoise Beltramo, MD, Pierre-Yves Marie, MD, and François Marçon, MD

In Duchenne’s muscular dystrophy (DMD), cardiac function deteriorates with time and heart failure is one of the major causes of death. The aim of the study was to determine if a decrease in the ventricular inotropic reserves could be an early sign of cardiac dysfunction in these children. Nineteen children with DMD (aged 9 to 18 years, mean age 13.6 ± 2.4) underwent equilibrium radionuclide angiography at rest and during an inotropic stimulation with low-dose dobutamine perfusion (7.5 to 15 μg · kg⁻¹ · min⁻¹). In all patients, this investigation was short (<30 minutes), successful, and uncomplicated. At rest, left ventricular (LV) ejection fraction (EF) was normal (>0.50) in 79% of patients, and right ventricular (RV) EF was normal (>0.45) in 95%. There was a trend toward a decrease with age for rest LVEF (p = 0.051) but not for rest RVEF (p = 0.8). By contrast, marked declines with age could be documented for the increases (Δ) in LVEF and RVEF during dobutamine perfusion (p = 0.002 for ΔLVEF and p = 0.015 for ΔRVEF). Thus, by multivariate analysis, the best indicator of decline in cardiac function with age was LVEF determined with dobutamine. In children with DMD, low-dose dobutamine radionuclide angiography gives evidence of an early decline with age of the inotropic reserves of both ventricles. ©2004 by Excerpta Medica, Inc. (Am J Cardiol 2004;93:724–727)
appropriate. According to the recommendations of the American Society of Echocardiography, end-systolic and end-diastolic left ventricular (LV) diameters were measured in M-mode, and fractional shortening of the left ventricle was calculated.

Multiple-gated equilibrium radionuclide angiography: Radionuclide angiography was performed first at rest (baseline), after at least 10 minutes of rest in the supine position, and then at the maximal rate of dobutamine infusion. As already described in detail elsewhere, right (RV) and LV ejection fraction (EF) were calculated and determined at baseline (baseline RVEF and LVEF) and during low-dose dobutamine (dobutamine RVEF and LVEF) infusion. In addition, the inotropic reserves of right and left ventricles were calculated with the differences in EFs between dobutamine and baseline measurements (ΔRVEF and ΔLVEF, respectively).

Dobutamine infusion: Infusion of dobutamine through a brachial vein was begun immediately after the first radionuclide angiography acquisition had been performed at rest. Heart rate and systolic and diastolic blood pressures were recorded at 1-minute intervals, and an electrocardiographic lead was continuously monitored. Infusion was begun at a rate of 7.5 μg · kg⁻¹ · min⁻¹ during a 5-minute initial period, and thereafter the rate was increased by steps of 2.5 μg · kg⁻¹ · min⁻¹ at each 5-minute interval to obtain either a 20 mm Hg increase in systolic blood pressure or a 25% increase in heart rate versus baseline values. The final and maximal infusion rate was always in the range of 7.5 to 15 μg · kg⁻¹ · min⁻¹; this rate was constantly maintained for a 5-minute equilibration period and then during the second radionuclide angiography.

Statistical analyses: Continuous variables were expressed as mean ± SD, and were compared using unpaired or paired nonparametric tests according to the situation. Linear regression analyses were used to assess the relations between age and continuous variables. A p value <0.05 was considered statistically significant. Multivariate ascending linear regression analyses were applied stepwise on the radionuclide parameters (SPSS Inc., Chicago, Illinois) to determine the best indicators of the age-related decline in cardiac function. Variables were entered into the model at a p value <0.10 and were removed at a p value >0.15.

### RESULTS

**Patient characteristics:** Mean age of the patients (n = 19) was 13.6 ± 2.4 years (range 9 to 18), and 79% (15 of 19) were wheelchair bound. Muscular wasting worsened with age, as evidenced by the relation to age, documented for the minitent (12.3 ± 3.7 years; p = 0.004) and Brooke up (3.5 ± 1.1) and low (8.7 ± 1.0) (p = 0.02 and p = 0.06, respectively). Fractional shortening, determined at echocardiography was 29.6 ± 4.9% and abnormal (<28%,19) in 32% (6 of 19) of patients. This parameter was also greatly dependant on patients’ age (p = 0.0002). However, the evaluation of this parameter (difficult in patients with thoracic deformation) was based on the measurement of the LV diameter between anterior and posterior regions, and thus depends on the local motion of the posterior wall where the degenerative process of DMD starts and predominates.

**Radionuclide angiography at baseline and during low-dose dobutamine infusion:** In all cases, this investigation was short in duration (<30 minutes), successfully conducted, and well tolerated, without any significant side effects. At baseline, only 21% (4 of 19) of patients had an abnormal baseline LVEF (<50%20–22) and only 5% (1 of 19) had an abnormal baseline RVEF (<45%.20–22). With low-dose dobutamine, the expected increases in heart rate and/or blood pressure have always been achieved. The modifications in heart rate, systolic blood pressure, diastolic blood pressure, LVEF, and RVEF during dobutamine infusion for the group are listed in Table 1. LVEF and RVEF increased significantly (p <0.0001 for both groups). On average, the inotropic reserves, determined with the differences in EF between dobutamine and baseline measurements, were 12.4 ± 6.4% for the left ventricle (ΔLVEF) and 9.7 ± 3.7% for the right ventricle (ΔRVEF).

**Age-related impairments in LV and RV functions (Figures 1 and 2):** There was no relation between baseline RVEF and patient’s age (p = 0.76). There was a trend toward a decrease with age for baseline LVEF (p = 0.051); each 1-year increase in patients’ ages was associated with only a 1.8 ± 0.9% absolute decrease in baseline LVEF (95% confidence interval 0.0% to 3.6%). A trend (p = 0.10) toward a decrease with age of dobutamine RVEF could be found, whereas this relation was highly significant for dobutamine LVEF (p <0.001); each 1-year increase in patients’ ages was associated with a 3.6 ± 0.8% absolute decrease in dobutamine LVEF (95% confidence interval 1.9% to 5.4%).

Finally, the inotropic reserves of left and right ventricles were highly dependent on patient’s age (p = 0.002 for ΔLVEF and p = 0.02 for ΔRVEF).

By multivariate analysis, the best indicator of the decline in cardiac function with age was dobutamine LVEF (p <0.001), and when this parameter was excluded, 2 independent variables were selected: ΔLVEF (p = 0.001) and baseline LVEF (p <0.022).

**DISCUSSION**

In the present study, LVEF and RVEF determined with radionuclide angiography were normal at base-

| TABLE 1 Radionuclide Angiography and Dobutamine Infusion (n = 19) |
|---------------------------------|----------------|--------------|
|                                | Baseline       | Dobutamine   |
| Heart rate (beats/min)         | 98 ± 12        | 119 ± 17*    |
| Systolic blood pressure (mm Hg)| 113 ± 14       | 141 ± 17*    |
| Diastolic blood pressure (mm Hg)| 70 ± 11         | 76 ± 10*     |
| LVEF (%)                        | 55 ± 9         | 67 ± 12*     |
| RVEF (%)                        | 53 ± 5         | 62 ± 6*      |

*p <0.0001; †p = <0.001; ‡p = 0.09.
FIGURE 1. Relations between age (years) and RV parameters provided by low-dose dobutamine radionuclide angiography. (A) Baseline RVEF, (B) dobutamine RVEF, and (C) \( \Delta \)RVEF.

FIGURE 2. Relations between age (years) and LV parameters provided by low-dose dobutamine radionuclide angiography. (A) Baseline LVEF, (B) dobutamine LVEF; and (C) \( \Delta \)LVEF.
line in most children with DMD (79% and 95%, respectively). Furthermore, there was no evidence of an age-related decline of baseline RVEF and only a slight decline for baseline LVEF. These results have already been documented in previous reports, and they may be explained by a decrease in baseline global cardiac performance known to occur at an older age than the mean age of our population (13.6 ± 2.4 years).

By contrast, there were marked declines with age for the inotropic reserves of both ventricles (ΔRVEF and ΔLVEF), and LV inotropic reserve is a known important parameter for prognostic evaluation in other nonischemic cardiomyopathies. Moreover, LVEF determined during the inotropic stimulation by dobutamine (dobutamine LVEF) was the best indicator of the age-related impairment in cardiac function. Each 1-year increase in patients’ ages was associated with an absolute decrease: as much as 3.6 ± 0.8% in dobutamine LVEF, a rate that was twofold higher than that documented for baseline LVEF. Therefore, it may be postulated that dobutamine LVEF is a sufficiently sensitive index for assessing the cardiac effects of early therapeutic interventions in young children with DMD. This could be a helpful tool in evaluating early therapeutics, such as angiotensin-converting enzyme inhibitors or β blockers (drugs that are proposed to delay the development of cardiac dysfunction in these children); however, to date, no study has demonstrated such a property.

An additional and original observation is that age-related impairment in the inotropic reserve was not only documented in this study for the left ventricle, but also for the right ventricle. Although an early impairment in RV function is often documented in Becker’s muscular dystrophy, this point is much more debated for DMD. Our observation suggests the presence of an early diffuse cardiac involvement, including the right ventricle, although the process begins and predominates in the left ventricle. This last point is supported by our finding that dobutamine LVEF is the most reliable indicator of age-related impairment in cardiac function in the present study.