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**Final version****Coronary blood flow by transthoracic echocardiography in children with endomyocardial fibrosis**

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**Abstract** We report herein the coronary flow (CF) pattern determined by transthoracic Doppler echocardiography (TTDE) in two white children with biventricular endomyocardial fibrosis (EMF). Endomyocardial biopsy showed various degrees of cardiac fibrosis in both patients as well as signs of chronic inflammation in one of the patients. TTDE showed a significant increase in CF in both the left anterior descending coronary artery and the posterior descending coronary artery compared with age-matched healthy controls. The diastolic flow in patients with EMF appeared to terminate earlier than in controls. The mechanisms and the potential significance of these novel findings are discussed.

**Keywords:** coronary flow. Endomyocardial fibrosis. Restrictive cardiomyopathy

### **Introduction**

Although common in the tropical and subtropical regions, endomyocardial fibrosis (EMF) or Davies' disease occurs only sporadically in Western countries (3). The main clinical features of this idiopathic disorder are primarily related to restrictive ventricular filling caused by obliteration of the apex and fibrosis in the endomyocardial layers of either one or both ventricles. The apical changes along with severe atrial enlargement are viewed as hallmarks by two-dimensional echocardiography (2).

Given the markedly decreased ventricular compliance secondary to EMF, the diastolic pressure in these patients is significantly increased. Because coronary flow (CF) mainly occurs in diastole, we investigated the coronary profile in two white children with biopsy-proven EMF. The data were compared with those from a control cohort of 14 age-matched healthy children.

## **Case Reports**

### Case No. 1

A 1-year old Caucasian girl born prematurely at 35 weeks of gestation presented with severe respiratory distress, cyanosis, and clinical signs of congestive heart failure. Since the age of six months, the patient had recurrent attacks of tiredness, vomiting and profuse sweating. Her mother had previously undergone heart transplant because of restrictive cardiomyopathy. The patient had an oxygen saturation of 85% with 5 l oxygen by face mask, a blood pressure of 73/46 (mean 53) mmHg, normal body temperature, and gallop rhythm. Laboratory tests indicated respiratory acidosis. Her and plasma pro-B-type natriuretic peptide (BNP) was 12422 ng/l (normal <153 ng/l).

### Case No. 2

A 4-year old girl was referred to our department because of history of dyspnoea and cardiac murmur. Her plasma pro-BNP was 65469 ng/l (normal <153) ng/l. Because she had severe tricuspid valve incompetence, the patient was first suspected of Ebsteins anomaly and she therefore underwent de Vega annuloplasty at the age of 5 years. Despite surgery, the tricuspid valve insufficiency progressed. She developed a moderate mitral insufficiency as well as signs of severe heart failure and pulmonary hypertension.

## **ECG and transthoracic echocardiography**

Both patients were in sinus rhythm, with peaked and prolonged P wave and incomplete right bundle branch block. Echocardiography showed markedly dilated atria with small ventricles caused by bilateral apical obliterations (Fig. 1). Both patients had moderate bilateral atrioventricular valve incompetence with right ventricular peak systolic

pressure over half of the systemic pressure, and a restrictive mitral inflow pattern. Pericardial effusion was present in the patient no. 2.

### **Coronary flow**

Peak flow velocity in diastole (PFVd), velocity time integral in systole and diastole (VTIs+d) and CF were measured in both the left anterior descending (LAD) and posterior descending (PD) coronary arteries as previously described (1). CF was calculated as follows:  $CF \text{ (ml/min)} = VTIs+d \times \text{Heart rate} \times \pi \text{ (coronary radius)}^2$ . As illustrated in Table 1, the coronary parameters were increased in patients compared with controls. In both patients, the diastolic flow terminated earlier than in controls (Figure 2).

### **Cardiac catheterization**

The hemodynamic data are listed in table 2. Coronary angiography was normal, and PD arising from the right coronary artery in both patients. Endomyocardial biopsy showed endocardial fibroelastosis and interstitial fibrosis in both patients with lymphocytic infiltration in patient number 2.

### **Discussion**

Transthoracic Doppler echocardiography (TTDE) represents a feasible and relatively inexpensive tool for non-invasive assessment of coronary flow (6). Our report is the first to suggest that CF as assessed by TTDE is increased in pediatric patients with EMF. The flow was found to be increased in both LAD and PD. The angiography-documented origin of PD from the right coronary artery and the biventricular affection in both patients may suggest a direct relation between flow changes and EMF. Another

finding is the distorted profile of CF with an earlier termination in end-diastole in patients compared with controls. Although not shown here, the vasodilator capacity of coronary arteries is inversely related to baseline flow. Therefore, our findings corroborate the hypothesis that coronary flow reserve is decreased in EMF.

The clinical course in EMF is often dramatic and is characterized by severe congestive heart failure at the time of presentation. Similar to other types of restrictive cardiomyopathies, EMF is commonly resistant to conventional heart failure therapy. The prognosis is poor and the mortality rate as high as 95% just 2 years after diagnosis (5).

The underlying mechanisms remain largely unknown. Extensive perivascular and interstitial fibrosis is paralleled by inflammation, necrosis, and formation of microthrombi with subsequent ischemia. In addition of being an important source of heart failure and arrhythmias, particularly in already diseased hearts, ischemia leads to release of vasoactive metabolites such as adenosine, which dilates the coronary microcirculation. Similar vasodilator effects may be exerted by inflammatory mediators such as cytokines. Inflammatory infiltrates were identified by endomyocardial biopsy only in patient no. 2, but this does not exclude such changes in patient no. 1 given the pattern of patchy inflammation in EMF. The significant atrial enlargement seen in EMF is an important stimulus for increased release of BNP, another substance with vasodilator properties. BNP may also be secreted in response to cytokines (4). The increased myocardial work to counteract fibrosis could also contribute to vasodilatation and increased CF. Both patients had pulmonary hypertension, which may increase the right ventricular work and CF.

Despite the overall increase of diastolic flow, the decreased and early termination of flow in end-diastole in patients with EMF may jeopardize myocardial viability by

exposing the cardiomyocytes to inadequate perfusion. This abnormal flow distribution is probably caused by decreased ventricular compliance with increased end-diastolic pressure subsequent to EMF (*Figure 3*). This mechanism might be particularly manifest at terminal stages, when systolic failure also occurs, with subsequent decrease in aortic blood pressure and further increase in the end-diastolic pressure.

We hypothesize that the observed CF abnormalities in patients with EMF might impede appropriate adjustment of myocardial perfusion to the metabolic need in stress situations, accompanied by increased myocardial oxygen demand, leading to ischemia and subsequent further fibrosis. This hypothesis must be verified in future studies.

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**TABLE 1**

Coronary flow parameters in left anterior descending coronary artery (LAD) and posterior descending coronary artery (PD) in patients with EMF and in controls (n=14). Data in controls are presented as mean±standard deviation.

	<b>Patient # 1</b>		<b>Patient# 2</b>	<b>Controls</b>		
	LAD	PD		LAD	PD	
PFVd (cm/s)	76	39	95	42	46±11	31±5
CF (ml/min)	48	25	91	32	31±7	20±2
VTI <sub>d+s</sub> (cm)	18	8	24	10	10±2.5	11±2

CF=coronary flow, PFV=peak flow velocity, VTI<sub>d+s</sub>=velocity time integral in diastole and systole

**TABLE 2**

Haemodynamic data obtained via catheterization in patients with EMF versus normal values.

	Age years	LVM gram	RAp mean mmHg	RVEDp mean mmHg	PAP mean mmHg	PAWp mean mmHg	Cardiac Index l/min/m <sup>2</sup>
Patient # 1	1.3	40	16	20	26	20	2.2
Patient # 2	7	50	21	18	37	19	1.75
Normal	2-8	54	2-6	3-6	15	6-9	3.5

RAp = right atrial pressure, RVEDp= right ventricular end diastolic pressure, PAP=pulmonary artery pressure, PAWp=pulmonary artery wedge pressure.

**FIGURE LEGENDS****Figure 1**

Transthoracic echocardiography in patient with EMF showing dilated left (LA) and right (RA) atria with bilaterally small ventricles caused by apical obliterations.

**Figure 2**

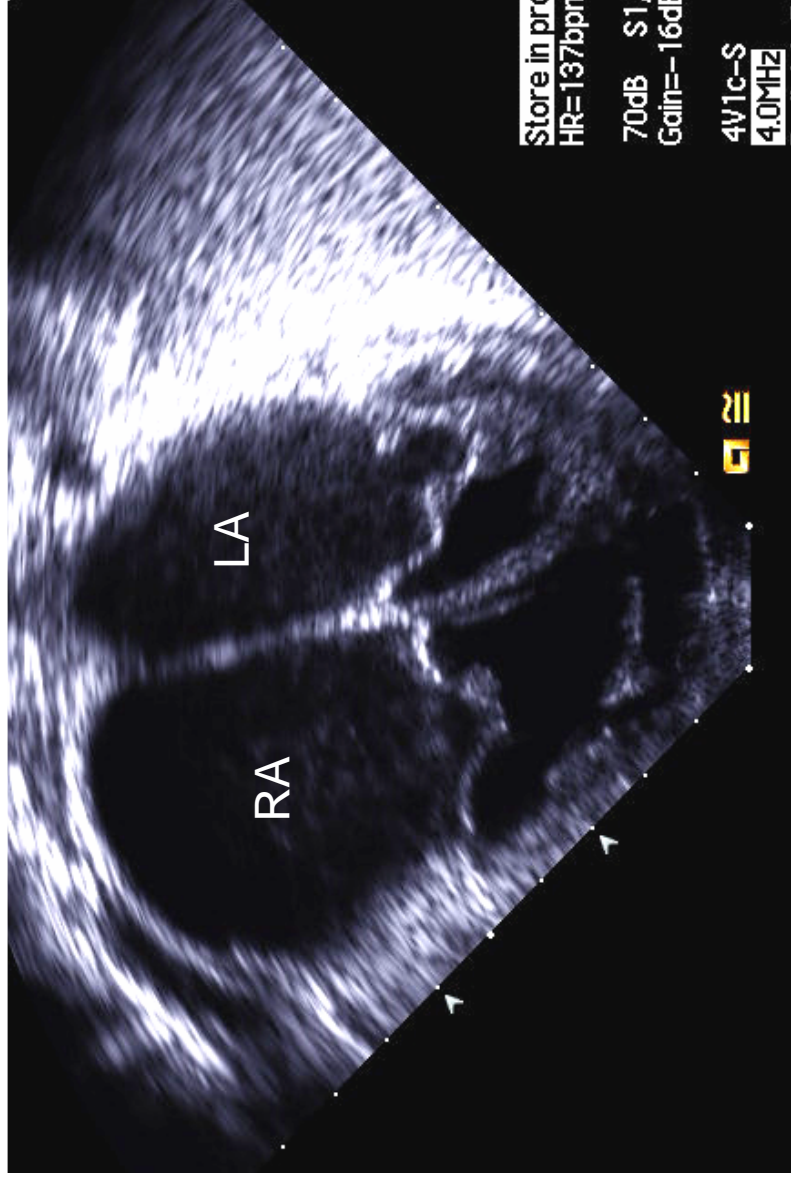
Coronary flow in LAD by TTDE in a patient with endomyocardial fibrosis (left panel) and in age-matched healthy control (right panel).

**Figure 3**

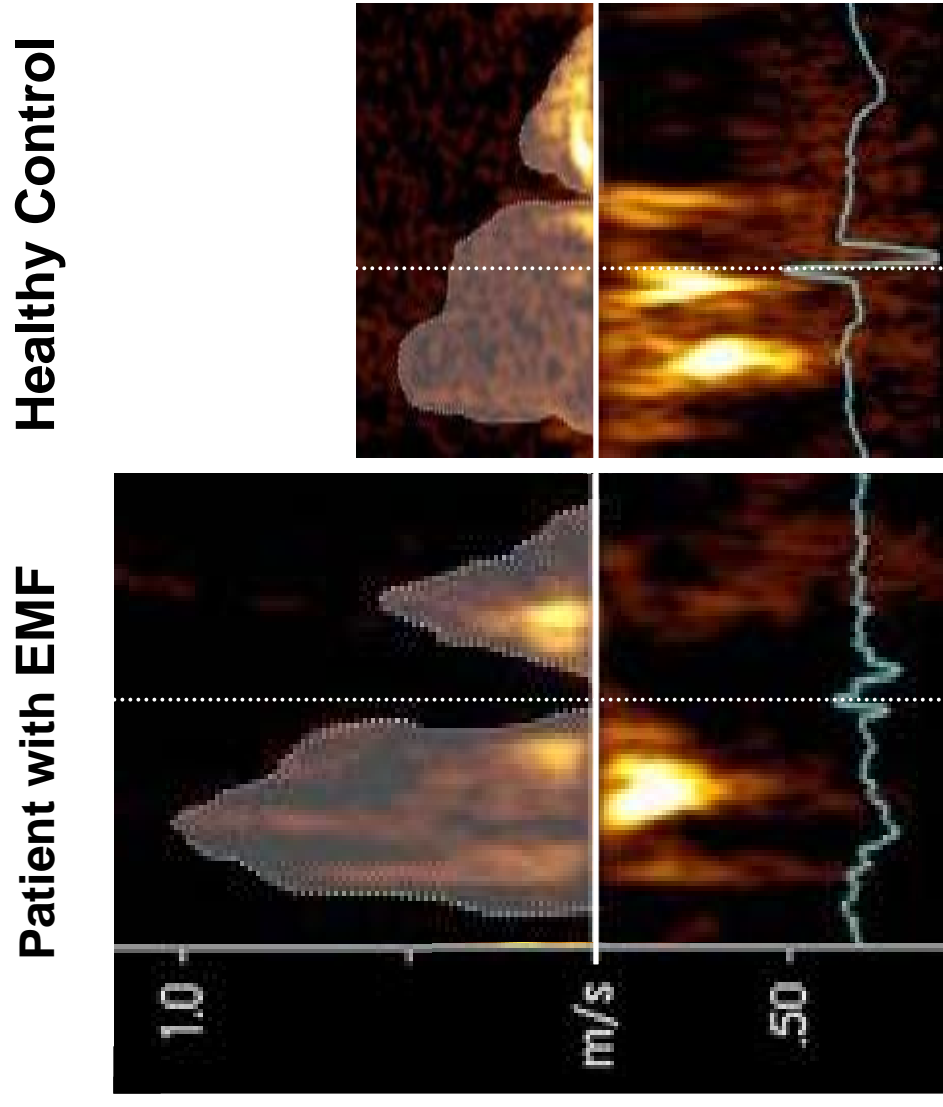
Schematic illustration of coronary flow in relation to left ventricular and aortic pressures. Decreased ventricular compliance causes increase in left ventricular end-diastolic pressure (LVEDP) with subsequent downward shift (as indicated by arrow) of coronary flow in end-diastole. DPTI=diastolic pressure time integral.

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**FIGURE 1**



**FIGURE 2**



**FIGURE 3**

