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Idiopathic Arterial Calcification of Infancy: Effectiveness of Prostaglandin Infusion for Treatment of Secondary Hypertension Refractory to Conventional Therapy: Case Report

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Abstract. A premature baby had severe hypertension associated with idiopathic arterial calcification of infancy. Despite the fact that there was laboratory evidence of renin-mediated hypertension, the disease was refractory to specific renin antagonist and failed to respond to conventional medical treatment. Prostaglandin E_1 (PGE_1) infusion (dosage range 0.017–0.068 μg/kg/min) promptly controlled hypertension on two occasions. The drug was given for a total of 65 days and then stopped after the appearance of severe thrombocytopenia; other side effects included sporadic hyperthermia and irritability. Blood pressure was then stabilized satisfactory by a multiple-antihypertensive regimen. In the light of these findings, we believe that PGE_1 infusion is a possible therapeutic alternative for babies with idiopathic arterial calcification complicated by severe hypertension refractory to conventional treatment.

Key words: Idiopathic arterial calcification — Hypertension — Prostaglandins

Idiopathic arterial calcification of infancy is a rare, usually fatal disease characterized by widespread subendothelial fibrosis in elastic and muscular arteries with focal calcification in the internal elastic membrane [3, 11, 14]. The clinical presentation is variable; respiratory distress usually associated with cardiac failure is the most common clinical finding, although in most reported cases the disease was diagnosed at autopsy [3, 11, 14]. Hypertension is usually present and may be refractory to medical therapy [1, 10]. In most cases, coronary artery involvement leads to death within the first 6 months of life due to myocardial ischemia with infarction or refractory cardiac failure [11]. We describe a premature baby affected by idiopathic arterial calcification of infancy with severe hypertension that responded only to prostaglandin E_1 (PGE_1) infusion.

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Case Report

S.M., a female infant, was delivered at 31 weeks by cesarean section because of acute fetal distress and polyhydramnios. At birth the baby was apneic (Apgar scores 2 and 5 at 1 and 5 minutes, respectively), and required resuscitation by endotracheal intubation and positive-pressure ventilation. The clinical features of fetal hydrops were present, and the birth weight was 1970 g. She was transferred to the Neonatology Center where intensive care was started.

On physical examination, a grade 3/6 pulmonary ejection murmur was heard, the femoral and brachial pulses were absent, and blood pressure was 80/50 mmHg. M-mode, two-dimensional, pulsed and continuous-wave Doppler examinations were performed with Hewlett-Packard Sonos 100 equipment, using 5.0- and 2.5-MHz transducers. The first echocardiograms showed pericardial effusion (8–10 mm posteriorly) and marked hyperechogenicity of the aortic and pulmonary arteries at the anulus and distally at arterial levels (Fig. 1). The ascending aorta and the aortic arch were narrow and the pulmonary artery appeared dilated, though its internal diameter was small according to standard values. Semilunar aortic and pulmonic valves were thin, with reduced opening. The tricuspid valve was echodense and showed low excursion of the leaflets (Fig. 1); the mitral valve appeared normal. The left ventricle was severely hypertrophic and hyperechogenic, and the right ventricle was dilated and poorly contracting; both atria were enlarged.

At pulsed Doppler examination a forward flow through the pulmonic valve was found with a low velocity (0.54 m/s); a small retrograde signal coming from a patent ductus arteriosus was detected in the pulmonary artery. A forward flow through the aortic valve and ascending aorta was detected with normal velocity (1 m/s). There was clear mitral regurgitation and short, single-peaked tricuspid forward flow with low velocity.

Therapy with dopamine, digoxin, diuretics, and PGE_1 (0.017–0.019 μg/kg/min) was started. During the next few days serial echocardiographs showed reabsorption of the pericardial effusion, two-dimensional features of hyperechogenic great arteries substantially un-

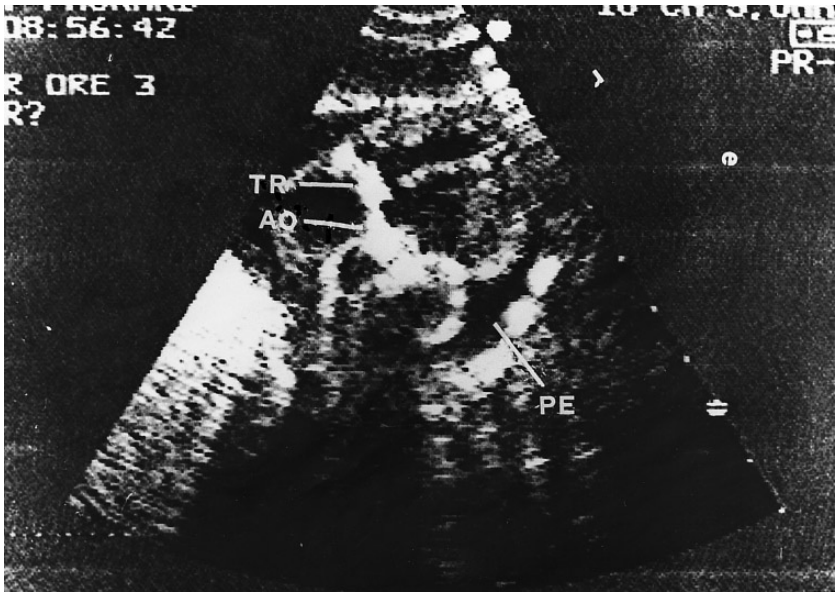

Fig. 1. Echocardiogram at 1 day of age showing marked hyperechogenicity of the aorta (*AO*) and tricuspid valve (*TR*) with a pericardial effusion (*PE*).

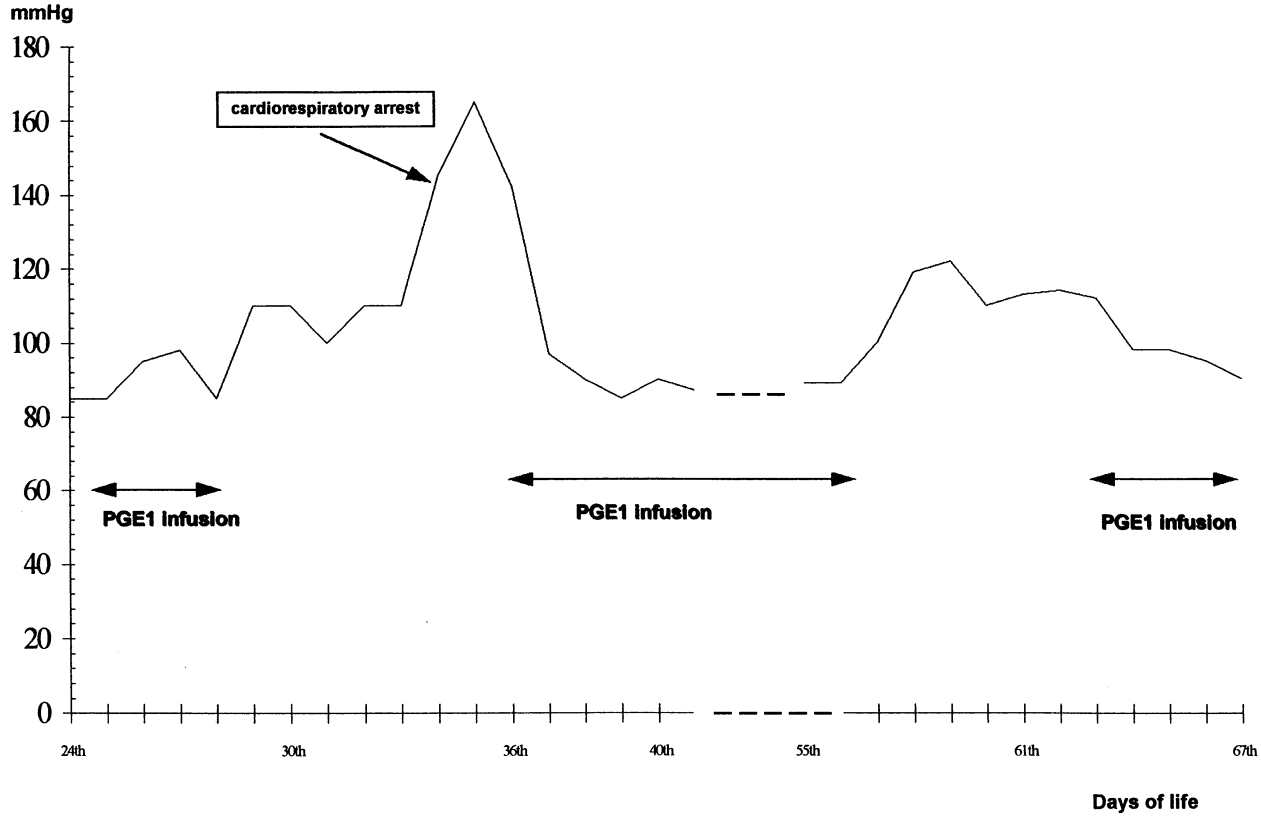

Fig. 2. Daily maximum systolic blood pressure.

changed, and marked improvements of right ventricle contractility with high velocity tricuspid regurgitation, suggesting pulmonary hypertension.

Additional examinations during the first month of life showed progressive reduction of the aortic and pulmonary hyperechogenicity, marked concentric hypertrophy of the left ventricle with good function, persistent patency of the ductus arteriosus with a small left-to-right shunt, and mild mitral insufficiency. By the end of the fourth week the

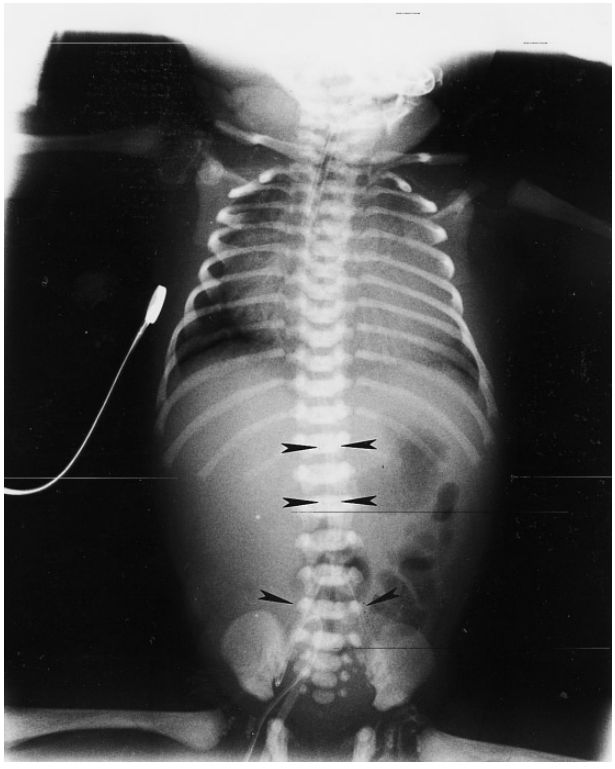

Fig. 3. Radiograph of the thorax and abdomen at birth, showing a double line of calcification on the distal aorta and iliac bifurcation (*arrowheads*).

infant's condition stabilized, and she was weaned from ventilatory support. Therapy with dopamine and prostaglandin was discontinued without problem.

Within a week the baby became hypertensive (systolic blood pressure >100 to 110 mmHg) and developed acute heart failure followed by cardiac arrest that required resuscitation and mechanical ventilation. An electrocardiogram (ECG) showed ST depression but no Q waves. Therapy with dopamine (5 μg/kg/min) and captopril (0.3 mg/kg/day) was started. The following 48 hours were characterized by high blood pressure values (average systolic pressure >110 mmHg with peaks of >140 mmHg and a maximum of 163 mmHg) despite increasing doses of captopril (up to 2 mg/kg/day) and sodium nitroprusside infusion (up to a maximum dose of 6 μg/kg/min). The peripheral plasma renin value was 39.2 ng/ml/h (normal <2.7 ng/ml/h), suggesting a renin-mediated hypertension. Urinary vanillylmandelic acid excretion was normal.

At this point a decision was made to reinstitute PGE_1 therapy considering its known hypotensive effect [7] and, more importantly, the fact that during a previous PGE_1 infusion the infant was normotensive. PGE_1 was started at an initial dose of 0.017 μg/kg/min, increasing to 0.068 μg/kg/min, and the hypertension promptly resolved (average systolic blood pressure <100 mmHg) (Fig. 2). Slowly the infant's condition improved, and she could be extubated.

Cardiac catheterization and aortography, carried out at age 6 weeks, showed that the abdominal aorta progressively narrowed under the diaphragm, becoming thread-like near the origin of the renal arteries. At this level there was an extended tortuous collateral circle. Catheterization of renal arteries was obviously not possible, and a study of the venous side was not performed. A review of the first day radiographs showed a double line of calcification on the distal aorta and iliac bifurcation (Fig. 3), indicating a diagnosis of idiopathic arterial calcification of infancy. Other laboratory investigations revealed normal serum urea and creatinine concentrations. The serum calcium concentration was 9.3 mg/dl, inorganic phosphorus 4.6 mg/dl, and alkaline phosphate 300 U/L; the urinary calcium/creatinine ratio was 0.23. Thyroid function tests, autoantibodies, and TORCH (toxoplasma, rubella, cytomegalovirus, and herpes virus) were normal.

At 8 weeks of life oral therapy with hydrochlorothiazide (2 mg/kg/day), nifedipine (1.5 mg/kg/day), and amlodipine (1 mg/kg/day) was started with the aim of stopping the PGE_1 infusion, but as the PGE_1 was discontinued the patient's blood pressure rose again despite a brief attempt with epoprostenole infusion (PGI_2) (up to a dose of 10 ng/kg/min). PGE_1 therapy was restarted (initial dose 0.02 μg/kg/min increased up to 0.026 μg/kg/min), with prompt resolution of the hypertension (Fig. 2). Echocardiography at this point was consistent with the diagnosis of hypertensive cardiopathy (severe concentric left ventricle hypertrophy and mitral insufficiency) (Fig. 4). The ductus arteriosus had closed.

After 65 total days, prostaglandin therapy was definitively suspended owing to severe thrombocytopenia that required two platelet transfusions. The only other side effects noted during this period were irritability and sporadic hyperthermia. The infused dose ranged from 0.017 to 0.068 μg/kg/min.

At this point polytherapy including captopril, furosemide, nifedipine, and amlodipine was effective in maintaining her blood pressure within acceptable values (systolic pressure near 100 mmHg, with rare peaks of 120 mmHg). The baby was discharged at 5 months of life. At present, she is 1 year old; she is on captopril and nifedipine only, and her blood pressure is acceptable (110/60 mmHg in all four limbs). The arterial radiologic calcifications are no longer visible.

Discussion

Idiopathic arterial calcification is a rare disease. Its incidence is unknown, but around 100 cases have been reported so far. The clinical presentation is variable, during the early perinatal period it may manifest as hydrops fetalis, presumably arising from cardiac failure [8]. Cardiac failure caused by myocardial ischemia due to coronary artery obliteration is frequently observed and is undoubtedly accelerated by the presence of hypertension. Poor vascular compliance due to fibrosis of medium-sized arteries is thought to be an important factor in the pathogenesis of the hypertension, although sometimes a renovascular component is recognized [10, 15]. Fetal hypertension, possibly due to diffuse arterial calcification, was suspected to be the cause of in utero cardiac failure and subsequent hydrops in our case: The echocardiographic feature of left ventricle hypertrophy with normal contractility excludes myocardial ischemia of coronary origin. Conventional antihypertensive therapy can be used, although some cases of hypertension have been refractory to all medical treatment [1, 10]. Our patient became increasingly hypertensive on two occasions after prostaglandin infusion was stopped, and her hypertension difficult to control despite combined therapy with a specific renin antagonist (captopril) and a powerful vasodilator (sodium nitroprusside) at the doses usually rec-

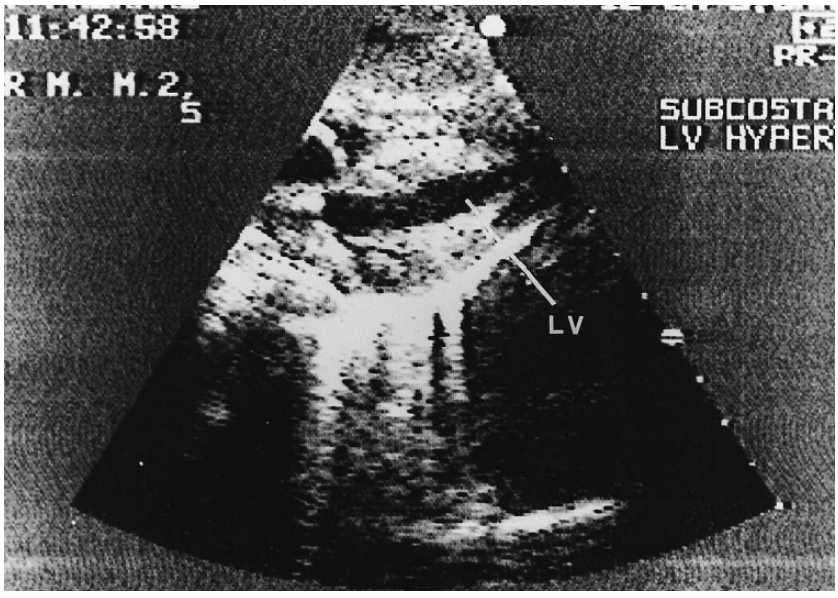

Fig. 4. Echocardiogram at 2 months of age showing marked hypertrophy of the left ventricle (*LV*).

ommended for newborns [2, 4, 6, 12]. Her blood pressure fell only after PGE_1 infusion was recommenced.

The mechanism of the hypotensive effect of PGE_1 is not clear. Some authors have suggested that with idiopathic arterial calcification the refractoriness to antihypertensive therapy—and more specifically to vasodilatory drugs—might be due to the diminished vascular compliance caused by diffuse arterial calcification [10]. Prostaglandins are potent vasodilators, and the dilatation appears to involve arterioles, precapillaries, sphincters, and postcapillary venules, whereas large veins are not affected [5]. It was still difficult to understand why this drug was able to lower blood pressure, whereas the other vasodilators initially used did not. One possible explanation is that PGE_1, by increasing pulmonary blood flow through the ductus arteriosus, was able to lower blood pressure by diminishing cardiac output in the systemic circle. By contrast, at the time of the second successful course of PGE_1, no ductal shunt was visible by echocardiographic examination. Moreover, it was surprising that PGI_2, a vasodilator as potent as PGE_1, infused at a dose up to 10 ng/kg/min failed to control blood pressure, whereas PGE_1 did it at relatively low doses. When the baby was 2.5 months of age, the PGE_1 infusion had to be suspended because of serious side effects. Fortunately, it was possible to achieve satisfactory control of her blood pressure with multidrug therapy, slowly tapered up to the present. A gradual spontaneous resolution of hypertension might also be possible, as previously shown [15]. A reduction of arterial calcification, at least in some districts, is also suggested by radiologic findings and measurement of the pulsatility of the radial and femoral arteries, which became evident after the first month of life. Spontaneous resolution of arterial calcification has been noted [13], as has resolution associated with diphosphonate therapy [1, 9]. On the basis of the pharmacologic actions of prostaglandin [5], we think that the disappearance of radiologic calcification in our case was not related to the use of this drug.

Prostaglandin E_1 is a drug now widely accepted for treatment of babies with complex cardiac malformations and those awaiting cardiac transplantation. Its infusion is frequently performed over extended periods, with well known and acceptable side effects [7, 16]. In our patient PGE_1 was infused for a total of 65 days. Cortical hyperostosis, recently shown in 100% of infants who were given PGE_1 for >60 days [17], was not evident.

In the light of our data, we believe that PGE_1 infusion represents an efficient, reasonably safe alternative treatment for babies with idiopathic arterial calcification complicated by hypertension refractory to conventional therapy.

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