A model of early transient pressure overload simulating repair of aortic coarctation in childhood

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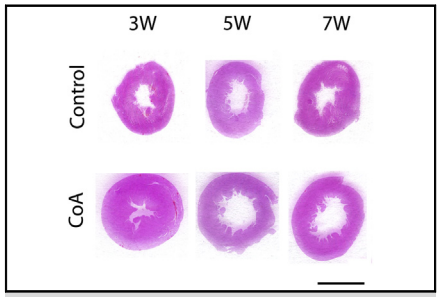

Early-life transient pressure overload elicits a complex response from the left ventricle.

Central Message

A novel animal model to explore late complications of aortic coarctation that occur despite successful early-life repair.

Aortic coarctation (CoA) is a congenital disorder characterized by severe narrowing of the aorta near the insertion point of the ductus arteriosus. Despite early and successful intervention, those who have undergone repair of CoA are predisposed to developing numerous cardiovascular complications later in life. Particularly prevalent are hypertension and left ventricular hypertrophy. Almost half of the patients who develop left ventricular hypertrophy do so in the absence of residual aortic narrowing.[1] To explore potential mechanisms to explain these findings, our novel animal model mimics key features of CoA and its repair: aortic constriction during early life and its relief in the equivalent of human childhood. The use of spontaneously hypertensive rats additionally allowed us to determine how the left ventricle (LV) responds to late systemic hypertension.

METHODS

Male, 3-week-old spontaneously hypertensive rats were purchased from the Animal Resources Centre in Perth, Australia. All animal studies conformed to Australian National Health and Medical Research Council (NHMRC) regulations and were approved by the University of Sydney Animal Ethics Committee. Spontaneously hypertensive rats underwent a modified transverse aortic constriction procedure described previously.[2] The transverse aorta was banded between the left common carotid artery and the left subclavian artery with a 2-0 Vicryl Plus (polyglactin 910) absorbable suture (Cat No. VCP615; Ethicon, Inc, Somerville, NJ), which retains 75%, 50%, and 25% of its tension at 2, 3, and 4 weeks, respectively. To constrict the aorta to a consistent diameter, the suture was looped around the aorta and a 21G needle and tightened, after which the needle was slipped out of the loop. A control group was sham-operated with a nonconstricting loose loop.

Weekly transthoracic echocardiographs were used to monitor changes in LV geometry and function. At 3, 5, and 7 weeks postconstriction, subsets of animals underwent arterial catheterization. In vivo pressure measurements were collected from the LV, ascending aorta, and abdominal aorta. Subsequently, spontaneously hypertensive rats were euthanized, and their hearts were harvested. The LV was weighed, fixed in 10% buffered formalin, embedded in paraffin, and sectioned. Tissue sections were stained with hematoxylin and eosin, and average myocyte area was calculated as described elsewhere.[3] Other sections were stained with Milligan's Trichrome stain (Sigma Aldrich, Sydney, Australia) to determine the collagen content of the myocardium as a percentage of total myocardium area.[3] Data are presented as mean ± standard error of the mean. Comparisons were made using a 2-tailed Student *t* test.

RESULTS

Constriction of the transverse aorta with an absorbable suture established a transient systolic blood pressure gradient between the upper and lower body, resulting in temporary LV pressure overload (Figure 1). At 3 weeks postconstriction, aortic constriction established a mean systolic blood pressure gradient of 83 mm Hg. The pressure gradient was more than halved at 5 weeks postconstriction; by 7 weeks, it was no longer significantly different from controls (Figure 1, *A*). Correspondingly, posterior wall thickness at end-systole in the CoA group was significantly larger than that for controls at 2 to 4 weeks postconstriction, but it was no longer significantly different from 5 weeks onward (Figure 1, *D*).

Hematoxylin and eosin–stained LV cross-sections at the level of the papillary muscle showed transmural thickening in the CoA group, compared with controls (Figure 2, *A*). The mean cardiomyocyte area in the CoA groups was increased at 3 weeks postconstriction, and regressed to sham levels by 5 weeks (Figure 2, *B*).

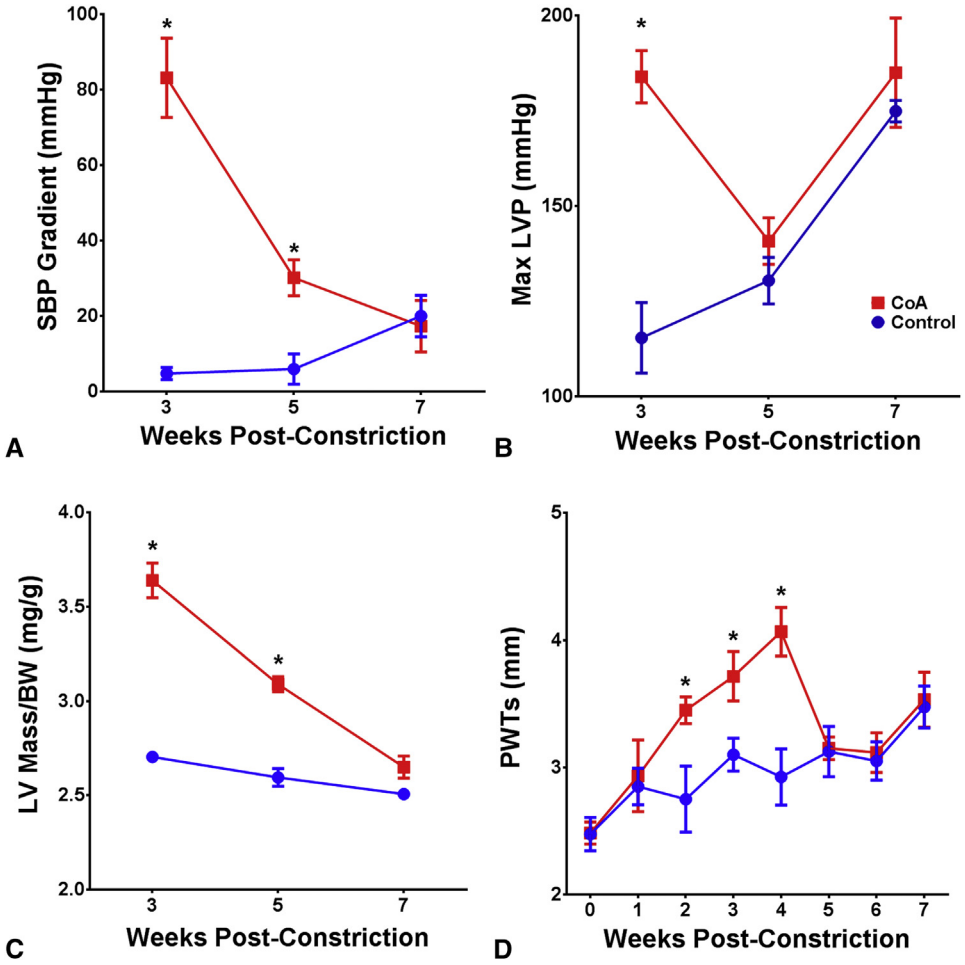

FIGURE 1. Transient SBP gradient established between upper and lower body by transverse aortic constriction and resulting LVP overload. A, SBP gradient; (B) maximum LVP; and (C) LV mass indexed to BW at 3, 5, and 7 weeks postconstriction in CoA (*red*) and sham-operated controls (*blue*). D, PWTs observed by transthoracic echocardiography. Observations at 0 weeks were made immediately before surgery. *SBP*, Systolic blood pressure; *LVP*, left ventricular pressure; *CoA*, aortic coarctation; *LV*, left ventricle; *BW*, body weight; *PWT*, posterior wall thickness at end-systole. *Indicates significant difference between the groups ($P < .05$).

Segments of stained LV show collagen deposition (Figure 2, *C*) and indicate increased fibrosis in CoA animals. Although the fibrosis partially regressed after relief of aortic constriction, it remained significantly elevated, compared with that of controls, for the duration of the study (Figure 2, *D*).

DISCUSSION

Constriction of the aorta established a marked upper–lower body pressure gradient, which was relieved as the suture degraded. Further, the hemodynamic changes produced were similar to those reported previously in children who have CoA, with pre-repair gradients of 66 ± 18 mm Hg, and postrepair gradients of 17 ± 4 mm Hg.[4] Thus, this model potentially is useful for studying changes associated with early relief of coarctation and later responses to hypertension.

In our study, left ventricular hypertension in early life occurred both with and without contributive increases in myocyte size or collagen content, underscoring the complexities of ventricular remodeling. In addition, our data show that histologic changes in the LV may persist after transient aortic constriction, despite an initially normalized geometry. However, no early difference was seen in response of the LV to onset of systemic hypertension. Further studies are needed to determine if differences in LV histology do persist, and if so, whether they elicit a differential response to prolonged systemic hypertension.