Left Ventricular Mass and Functions in Normotensive Offspring of Hypertensive Parents: An Echocardiographic Study


Abstract
Objective: Published observations about cardiovascular alterations in normotensive individuals genetically predisposed to develop essential hypertension are conflicting. We tested the hypothesis that abnormalities in left ventricular mass and/or functions may be present in normotensive children of hypertensive parents.

Methods: One hundred normotensive offsprings (6 to 18 year age) of hypertensive parents (OHP) and an equal number of age- and sex-matched normotensive offsprings of normotensive parents (ONP) were studied with 2-dimensionally guided M-mode and Doppler echocardiography for left ventricular (LV) dimensions, mass, and systolic and diastolic functions.

Results: Both the groups had similar body mass index and blood pressure levels. LV dimensions and LV mass in OHP were higher than the corresponding values in ONP but the differences were not statistically significant. LV mass in male OHP was higher than in female OHP; LV mass was also higher when the mother rather than father was hypertensive. None of these differences were statistically significant, however. LV systolic functions were normal and identical in the two subject groups. Indices of LV diastolic function (peak early filling velocity and its deceleration time and late filling velocity) were also normal and similar in the two groups.

Conclusion: We conclude that children with a family history of essential hypertension have modest alterations in LV mass and these alterations might have a genetic basis separate from but possibly co-inherited with the trait of essential hypertension.

Introduction
Left ventricular (LV) hypertrophy is one of the pathological hallmarks of systemic hypertension with independent and important prognostic significance. However, echocardiography studies have failed to identify any critical level of cardiac mass at which compensatory hypertrophy ends and pathological hypertrophy begins. Further, the temporal relationship between the onset of clinical hypertension and the development of LV hypertrophy is also a matter of debate and discussion.1,2 There is no consensus either about the time of development of abnormalities in left ventricular diastolic functions during the evolution of systemic hypertension in individual patients. It is believed that increased LV mass and/or LV diastolic dysfunction might antedate the development of hypertension in the individuals destined to develop systemic hypertension in later life.

Since essential hypertension is thought to have an important genetic component in its causation and/or morphological expression, offspring of hypertensive parents represent an excellent opportunity to study the early subclinical phases of the syndrome of systemic hypertension.3,4 Additionally, offspring frequently share with their parents the predominant dietary practices, living habitat and the other environmental settings, which could otherwise potentially confound any attempts at comparison. The present study was, therefore, undertaken to assess LV functions and mass in offspring of hypertensive parents before the former would, if ever at all, qualify for the diagnosis of systemic hypertension.

Methods
Subjects
This study, which was accepted by the Ethical Science Committee of Sher-i-Kashmir Institute of Medical Sciences, Srinagar (Kashmir), was conducted in 200 normotensive Kashmiri children of 6 to 18 year age who had blood pressure equal to or less than 90th percentile for the age. Parents who visited the outpatient clinics of our institute for one or the other reason were recruited after informed consent and were directed to bring their eligible children on the next visit. The study group consisted of 100 children with one or both parents having hypertension (OHP) diagnosed as per the standard criteria.5 The control group was formed by an equal number of age- and sex-matched children who did not have hypertension or its history in either parent (ONP).

Blood pressure of children was recorded on two occasions, systolic and diastolic blood pressures were recorded twice at 5
Results

The basic demographic characteristics in cases and controls were comparable. There was no significant difference in the systolic or diastolic blood pressures either (Table 1). LV dimensions in OHP indexed to body surface area were higher than the corresponding dimensions in ONP. The mean LV mass index in OHP was also higher than that of the controls. None of these differences were statistically significant except for posterior wall thickness (Table 2).

LV systolic functions were normal in both the subject groups. No significant difference was found in the LV volumes or ejection fraction between the cases and controls. The parameters of diastolic function of LV were normal in all the subjects. Peak velocities of LV filling during the early rapid filling phase and the late atrial filling phase were similar in the two groups. Deceleration time of the early filling velocity was also normal and similar in the two subject groups (Table 3).

On multiple regression analysis, LV mass had a significant correlation with age, body mass index, blood pressure, and various LV dimensions but showed no significant correlation with indices of systolic or diastolic functions of LV in either the cases or the controls (Table 4). The mean LV mass index in the male OHP (64.4±20.31 gm/m²) was slightly but not significantly,
higher than the female children of such parents (57.36±17.51 gm/m²; p NS). The male and female ONP had more identical LV mass indices (57.40±17.26 versus 56.86±15.12; p NS).

In the situation of only one of the parents being hypertensive, LV mass index in children with a hypertensive mother (64.51±19.82) was higher than in the children with hypertensive father (57.16±17.81). The difference was not statistically significant (p=0.061).

Discussion

Kashmir valley is inhabited by a relatively homogenous inbreeding population with dietary practices and living conditions that do not differ significantly across the valley. Therefore, the normotensive offspring of the hypertensive parents examined in the present study, who have a moderate genetic risk for hypertension, stand naturally matched for many of the potentially confounding demographic and other characteristics and represent ideal subjects for studying the cardiovascular alterations that could precede the development of hypertension.

Previous studies about the morphological and/or functional cardiovascular changes in normotensive subjects at risk of developing systemic hypertension have yielded conflicting results. In the present study, cardiac dimensions and LV mass index in the normotensive OHP tended to be higher than the corresponding values in normotensive ONP. However, these differences did not reach the level of statistical significance except for LV posterior wall thickness (p<0.01). On regression analyses, body weight and height along with age and blood pressure level proved to be most important determinants of LV mass index. Graetinger, et al also reported the absence of any significant difference in LV mass index or wall thickness between normotensive healthy volunteers with or without genetic risk for hypertension. However, their contention that such a lack of difference could be due to a meaningful difference in diastolic blood pressure between the two groups can not be offered as a similar explanation for our observations since our subject groups were properly matched for the blood pressure level.10

In the Dutch Hypertension and Offspring Study, the thickness of LV posterior wall and interventricular septum were increased in the offspring of hypertensive parents but the difference from the offspring of normotensive parents was not significant. However, LV mass index and LV end-diastolic diameter were significantly increased in the former group. It would be prudent to mention that the mean age of the subjects in this study was higher than that of our subjects. Further, selection of subjects in the Dutch study was based on parental blood pressure level irrespective of the blood pressure of the individual participants.3 In some previous echocardiographic studies too, LV dimensions and LV mass index were found to be significantly higher in normotensive subjects at genetic risk for hypertension as compared to subjects without such risk.11-13 However, as in the Dutch study, the average age of the subjects examined in these studies was higher than that of the subjects in our study. It is possible and seems likely that our at-risk subjects might have been examined at an earlier stage in the natural history before the full expression of the morphological cardiovascular changes of the preclinical hypertension syndrome. Such inferences are also supported by the results of a previous echocardiographic study with similar age of the examined subjects as the present study.14

Longitudinal observations of the at-risk children are needed in this regard for a better understanding of the progression of LV morphological changes during the evolution of systemic hypertension.

In the present study, LV systolic functions were not different among the normotensive children with or without a genetic risk for hypertension. The indices of LV diastolic filling were also normal and identical among the two groups. Some previous echocardiographic studies too have been unable to document the presence of early diastolic dysfunction in hypertension - prone normotensive children and young adults.11,12 Aeschbacher, et al found that in the normotensive offspring of hypertensive parents, the peak early and late transmural flow velocities as assessed by Doppler echocardiography did not differ from those in the normotensive offspring of normotensive parents. Deceleration time of early diastolic flow and the isovolumic relaxation time were also identical in the two groups.15 Such observations are against the hypothesis that abnormalities in diastolic function may be the earliest cardiovascular changes in the natural history of hypertension and may be present in normotensive population with increased genetic risk for hypertension in the absence of increased LV mass. However, the later conclusions have been drawn mostly from studies in which only small numbers of subject were examined and the possible confounding effects of demographic characteristics and baseline blood pressure levels were not adequately considered.11,13,14

Our observation that male OHP have higher LV mass than the female OHP remains to be explained. Similarly, the greater contribution of maternal than paternal hypertension to increased LV mass in normotensive offspring is also poorly explained. It is possible that LV mass might be a separately determined genetic trait that is co-inherited with the trait of essential hypertension. Such inferences, although corroborated by observations made in experimental animals, are only speculative as of now.16 Significant genetic determination of LV mass was observed in the Framingham family cohort and has been revisited recently as well.17,18 Some longitudinal observations in untreated hypertensive patients also indicate that LV hypertrophy and diastolic dysfunction in hypertension are likely caused by different mechanisms.1 However, any dogmatic statements in
this regard shall have to await the investigations into potential candidate genes.

The results of our study indicate that young normotensive offspring of hypertensive parents have modest, albeit initially insignificant, morphological changes in LV wall thickness and LV mass. Such changes might progress with age and the difference from control subjects might become even more prominent. However, LV diastolic functions are not affected early on in the normotensive children at risk for hypertension. Conclusions drawn from the recently conducted HARVEST study also support the hypothesis that the changes in LV anatomy may occur earlier than diastolic filling abnormalities in the natural history of hypertension.20 Further, it seems likely that LV mass might be a separate genetic trait that is often co-inherited with hypertension.

Acknowledgements

We are thankful to our echocardiography technologists, Nazir Ahmad and Farooq Ahmad for their technical assistance and help.

References