Cardiac and vascular structural adaptation in experimental hypertension

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Various colonies of the spontaneously hypertensive rat (SHR) of the same age demonstrate different forms of the left ventricle (LV) in end-diastole. SHR from breeders in Australia and Switzerland exhibit concentrically hypertrophied LV, evident from an increased wall thickness to internal radius ratio (w/ri), while SHR from a Danish colony show an unchanged w/ri ratio, indicating eccentrically hypertrophied LV. These differences may be related to changes in arterial blood pressure and/or altered cardiac filling patterns.

A more favourable situation seems to prevail for the eccentrically hypertrophied SHR heart compared with the concentrically hypertrophied heart, the former demonstrating enhanced cardiac function. Thus, an LV with increased diastolic diameter, as in the eccentrically hypertrophied SHR heart, can produce an elevated stroke volume for a given degree of myocardial shortening. In renal hypertension, however, LV function was depressed, probably due to a factor, possibly released upon clipping of the renal artery, that has inherent negative inotropic properties. Here, the reduction of LV performance could be explained neither by the changed LV geometrical design nor by the altered myocardial myosin isoenzyme pattern.

At low aortic pressures and hence limited coronary perfusion, LV performance is attenuated in SHR and renal hypertensive rats, most likely due to the vascular structural changes within the coronary vascular bed.

Introduction

In response to a chronically increased pressure load, induced by aortic stenosis or by chronic systemic hypertension, left ventricular (LV) hypertrophy develops. The extent of LV hypertrophy in rat hearts has commonly been evaluated by relating LV weight to body weight. The structural configuration of the heart must, however, also be considered in terms of the end-diastolic volume or radius, and the wall thickness. The structural orientation of the heart can be determined by measuring end-diastolic volume at known distending pressures. Hence, internal radius and wall thickness can be calculated[1-3]. Accordingly, measurements of cardiac mass alone will not discriminate between cardiac adaptation in response to a pressure load (concentric hypertrophy) and that occurring in response to a volume load (eccentric hypertrophy). The former is characterized by generalized wall thickening at a largely unchanged internal radius, while the latter features an unaltered or slightly increased wall thickness at an increased internal radius.

The LV diastolic pressure volume (P-V) relationship has been extensively investigated, although mainly focused on changes in wall elasticity and stiffness[4-6]. Very few of these studies have examined the alterations in cardiac dimensions during growth and development of hypertension and what these changes do to cardiac performance.

Early primary hypertension, in man as well as in the spontaneously hypertensive rat (SHR), is characterized by elevations of both heart rate and cardiac output and a relatively normal total
peripheral resistance. This type of hyper-kinetic circulation induces an elevation in cardiac filling with a resultant increase in LV internal radius. This early phase appears to have different durations in various SHR colonies.

SHR, in the established phase of hypertension, are exposed to a sustained increase in arterial pressure. Comparison of age-matched SHR from different colonies reveals differences in the level of hypertension, cardiac mass and dimensions, and consequently in cardiac performance. Both female and male SHR obtained from a Danish breeder (Möllegaard, Skansved, Denmark) have a moderate pressure increase but show increased internal radii, while male SHR from a Swiss breeder (Klein Tierfarm, Switzerland) have greater arterial pressure elevation and an unchanged internal radius compared with normotensive control rats. Thus, depending on the SHR colony studied, the hearts of SHR with established hypertension demonstrate both eccentric and concentric LV hypertrophy at the same age.

An eccentric cardiac configuration should not indicate a reduced ventricular performance as long as myocardial contractility is preserved. On the contrary, a left ventricle with an increased diastolic diameter may be advantageous, the increased volume enabling it to expel an elevated stroke volume for a given degree of myocardial fibre shortening. In this respect, cardiac performance in SHR has been repeatedly shown to be well maintained or even enhanced.

Factors, in addition to the geometry of the heart, important for cardiac function are coronary flow and oxygen utilization. Coronary flow has been shown to be reduced and oxygen extraction augmented in SHR and in renal hypertensive rats. This decreased coronary flow is most likely due to structural autoregulation of the coronary resistance vessels, which develops in response to the raised arterial pressure. At normal perfusion pressure this increased coronary vascular resistance in the SHR heart will not limit cardiac performance whereas, at subnormal perfusion pressures, coronary flow and hence cardiac performance are compromised.

The purpose of the present studies was to assess further the relationship between the quantity and quality of the structural adaptation of the left heart in hypertension and changes in cardiac function. Implications of coronary vascular structural changes with respect to cardiac function will also be discussed.

Diastolic properties of hypertrophied hearts

In early, primary, experimental hypertension, 15-week-old male SHR obtained from Möllegaards breeding centre (Skansved, Denmark) showed a considerable, parallel shift to the right of the P-V curve compared with age-matched WKY (for methodological considerations c.f. Ref. 2). In these Danish rats, LV mass was proportionally increased in SHR whereas the w/ri ratio was similar in SHR and WKY (Table 1). In addition, Mirsky and coworkers demonstrated similar results in young SHR (US colony, not specified) by means of analysing the P-V curve, indicating that the hypertrophic structural adaptation of the LV in SHR is eccentric rather than concentric in nature. Similarly, 26-week-old female SHR also from the Danish colony showed eccentric LV hypertrophy, although more pronounced, since the w/ri ratio was even reduced compared with female WKY (Table 1). Arterial blood pressure was greater in the somewhat older female SHR; hence the wall thickness was correspondingly increased compared with the younger male SHR.

In a study performed on rats from an Australian colony, originally derived from Japan, 15-week-old SHR and age-matched WKY showed no difference in diastolic dimensions. In general, these Australian SHR have higher blood pressure than the SHR obtained from Möllegaard’s breeding centre (Table 1). Similarly, SHR obtained from Klein Tierfarm, Switzerland, demonstrated a pronounced LV mass with an unaltered end-diastolic volume resulting in an elevation of the w/ri ratio compared with matched WKY. These SHR had also significantly higher blood pressure than the Danish SHR (Table 1).

Six-week-old SHR from the same Australian colony demonstrated a significantly increased end-diastolic volume for a given end-diastolic pressure compared with age- and weight-matched WKY, suggesting an eccentric hypertrophy (Table 1). In these colonies, it is plausible that the initial increase in cardiac filling appears earlier and is of much shorter duration.
Table 1  Body weight, blood pressure, relative left ventricular weight and diastolic dimensions at an end-diastolic pressure of 7.5 mmHg

<table>
<thead>
<tr>
<th>Rat</th>
<th>Sex</th>
<th>Age (weeks)</th>
<th>BW (g)</th>
<th>BP (mmHg)</th>
<th>LV/BW (mg/g^-1)</th>
<th>EDV (μl/100 g^-1)</th>
<th>ri (mm/100 g^-1)</th>
<th>w (mm/100 g^-1)</th>
<th>w/ri</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-WKY</td>
<td>m</td>
<td>6</td>
<td>142±3</td>
<td>120±1</td>
<td>2.69±0.06</td>
<td>164±8</td>
<td>3.99±0.07</td>
<td>1.30±0.04</td>
<td>0.39±0.02</td>
</tr>
<tr>
<td>A-SHR</td>
<td>m</td>
<td>6</td>
<td>145±5</td>
<td>119±1</td>
<td>2.93±0.04***</td>
<td>194±6*</td>
<td>3.58±0.04*</td>
<td>1.29±0.03</td>
<td>0.36±0.01</td>
</tr>
<tr>
<td>A-WKY</td>
<td>m</td>
<td>15</td>
<td>336±8</td>
<td>141±1</td>
<td>2.41±0.04</td>
<td>156±3</td>
<td>3.34±0.02</td>
<td>1.22±0.02</td>
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</tr>
<tr>
<td>A-SHR</td>
<td>m</td>
<td>15</td>
<td>354±6</td>
<td>210±2***</td>
<td>2.83±0.05***</td>
<td>159±5</td>
<td>3.35±0.02</td>
<td>1.35±0.01*</td>
<td>0.40±0.00*</td>
</tr>
<tr>
<td>D-WKY</td>
<td>m</td>
<td>16</td>
<td>291±2</td>
<td>123±3</td>
<td>2.20±0.02</td>
<td>104±3</td>
<td>2.88±0.02</td>
<td>1.31±0.02</td>
<td>0.46±0.01</td>
</tr>
<tr>
<td>D-SHR</td>
<td>m</td>
<td>16</td>
<td>291±4</td>
<td>176±3***</td>
<td>2.55±0.03***</td>
<td>125±7*</td>
<td>3.06±0.05*</td>
<td>1.37±0.03</td>
<td>0.46±0.02</td>
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<tr>
<td>D-SHR</td>
<td>m</td>
<td>80</td>
<td>419±11</td>
<td>182±5</td>
<td>3.15±0.06***</td>
<td>120±3</td>
<td>3.03±0.02*</td>
<td>1.60±0.02***</td>
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<tr>
<td>D-WKY</td>
<td>f</td>
<td>25</td>
<td>250±2</td>
<td>125±2</td>
<td>2.29±0.04</td>
<td>97±5</td>
<td>2.84±0.05</td>
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<td>D-SHR</td>
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<td>25</td>
<td>208±2</td>
<td>186±2***</td>
<td>3.24±0.07***</td>
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<td>3.32±0.03**</td>
<td>1.52±0.02**</td>
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<td>S-WKY</td>
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<td>16</td>
<td>266±3</td>
<td>115±1</td>
<td>2.29±0.05</td>
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<td>S-SHR</td>
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<td>16</td>
<td>291±2</td>
<td>191±2***</td>
<td>2.94±0.06***</td>
<td>102±6</td>
<td>2.85±0.05</td>
<td>1.64±0.04***</td>
<td>0.59±0.02***</td>
</tr>
</tbody>
</table>

Mean ± SEM. BW = body weight, BP = blood pressure, EDV = end-diastolic volume expressed per 100 g bw, ri = internal radius per 100 g bw, w = wall thickness per 100 g bw, w/ri = wall thickness to internal radius ratio, m = male, f = female, WKY = Wistar Kyoto normotensive control rats, SHR = spontaneously hypertensive rats, A = Australian colony, D = Danish colony, S = Swiss colony. Levels of statistical significance are indicated as */P<0.05, **P<0.01, ***P<0.001 between the respective SHR group and its WKY control group, and *P<0.05, **P<0.01, ***P<0.001 between D-SHR 16 week-old and D-SHR 80 week-old SHR.

Table 1: Body weight, blood pressure, relative left ventricular weight and diastolic dimensions at an end-diastolic pressure of 7.5 mmHg.

Mean ± SEM. BW = body weight, BP = blood pressure, EDV = end-diastolic volume expressed per 100 g bw, ri = internal radius per 100 g bw, w = wall thickness per 100 g bw, w/ri = wall thickness to internal radius ratio, m = male, f = female, WKY = Wistar Kyoto normotensive control rats, SHR = spontaneously hypertensive rats, A = Australian colony, D = Danish colony, S = Swiss colony. Levels of statistical significance are indicated as */P<0.05, **P<0.01, ***P<0.001 between the respective SHR group and its WKY control group, and *P<0.05, **P<0.01, ***P<0.001 between D-SHR 16 week-old and D-SHR 80 week-old SHR.

As the young Australian rats demonstrated eccentric rather than concentric LV hypertrophy as not fully understood. In part, this adaptation may result from a response to an elevated cardiac output in young SHR emanating mainly from an increased heart rate[9], and from a neurogenic and/or structural-based centralization of their blood volume[10,20].

An eccentric structural adaptation of the LV implies that there will be an increased stroke volume for any given degree of myocardial shortening; or alternatively, stroke volume is maintained at a reduced level of myocardial muscle shortening[9]. This type of structural alteration, in contrast to concentric changes, represents another mechanism by which the circulation copes with a moderately increased pressure load.

Taken together, different colonies of SHR show marked variation in LV dimensions and blood pressure at different ages. In addition, the quality of the LV adaptation ranges between degrees of concentric and eccentric hypertrophy brought about by increased cardiac filling, resulting from the hyperkinetic circulation that is present in young SHR.

Induction of renal hypertension in both Wistar rats and in SHR (with prevailing eccentric hypertrophy), produces a marked concentric hypertrophy, as indicated by 13% and 44% increases of the w/ri ratio, respectively[21]. In
both strains of rats there was a substantial increase in external radii. In the renal hypertensive SHR, the internal radius also was reduced, which might explain the very pronounced increase in w/ri ratio. In the Wistar rat but not in the SHR the percentage increase in the w/ri ratio was proportional to the rise in blood pressure (60% and 45% respectively).\(^{121}\)

In renal hypertensive rats, seven days following surgical removal of the renal artery clip, left ventricular weight had regressed, while w/ri ratio remained unaltered (Fig. 2). This indicated that the type of adaptation that had occurred could not be reversed in a similar period of normotension.

There are a number of conditions (i.e. DOCA-salt hypertension) that cause a volume load in combination with a pressure load. A 10-week DOCA treatment in 4-week-old WKY rats resulted in a mixture of an eccentric and a concentric LV hypertrophy, produced from both a volume and a pressure overload (Fig. 3). In this situation, wall thickness (as influenced by the pressure load) and internal radius (as influenced by cardiac filling) are increased, the former to a greater extent, which results in a significantly enhanced w/ri ratio (Fig. 3). In these DOCA studies, blood pressure increased by 25% and the w/ri ratio by only 14% compared with control WKY. The less than proportional effect on the w/ri ratio suggests a dissociation between the haemodynamic and the structural parameters. This separation could, at least in part, be explained by the effect of increasing end-diastolic volume originating from the adaptation to the enhanced cardiac filling.

In contrast, 26-week-old female SHR (Møllegaard) showed both increases in wall thickness and internal radius (similar to DOCA rats) but w/ri ratio was here reduced. In these rats, this adaptation suggests that the eccentric LV hypertrophy is due to a volume load as being the dominant haemodynamic stimulus (Table 1).\(^{21}\)

**Systolic function of hypertrophied hearts**

As mentioned earlier a large LV end-diastolic diameter does not necessarily imply depressed cardiac function, at least not in early, uncomplicated hypertension. Several investigations have demonstrated a maintained or even enhanced LV performance\(^{11-14}\) in SHR working at high

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**Figure 2** Peak cardiac work represents the maximal value of the product of heart rate \(\times\) stroke volume \(\times\) (aortic pressure-left atrial pressure). Values are given for 10 renal hypertensive rats of 4 weeks' duration (2K1C), 10 2K1C rats in which the renal artery clip has been removed for 7 days (DC-2K1C) and normotensive control (Wistar) rats \((n = 14)\). Below is indicated wall thickness to internal radius ratio (w/ri) at an end-diastolic pressure of 7.5 mmHg from groups treated the same way \((11\text{\textsuperscript{NCR}},\ 11\text{\textsuperscript{2K1C}},\ 12\text{\textsuperscript{DC-2K1C}})\). Mean ± SEM. *\(P<0.05\), **\(P<0.01\). ***\(P<0.001\).

**Figure 3** End-diastolic pressure (EDP)- and end-diastolic volume (EDV)-relationships obtained in arrested hearts from normotensive Wistar Kyoto rats (open squares, \(n = 12\)) and DOCA-hypertensive rats (filled squares, \(n = 9\)). Internal radius (ri) and wall thickness to internal radius ratio (w/ri) are indicated at an EDP of 7.5 mmHg. Mean values, SEM is indicated for EDP 7.5 mmHg. *\(P<0.05\), **\(P<0.01\), ***\(P<0.001\).
pressures. For example, measurements of cardiac performance in 16-week-old SHR obtained from the Swiss breeder Kleine Tierfarm, with a concentric LV hypertrophy, demonstrated that ejection fraction and maximal stroke volume were similar to that of matched WKY rats. Using similar techniques maximal LV function was found to be significantly increased in Danish 16-week-old SHR with prevailing eccentric LV hypertrophy, compared with matched WKY rats. Comparison of maximal cardiac function between these two colonies of SHR suggests that eccentric LV hypertrophy may in fact be superior to concentric LV hypertrophy in managing increased arterial pressure as long as the pressure load is not too severe. It may be that, in spite of the increased wall stress in eccentric LV hypertrophy, maximal stroke work may be augmented since an increased stroke volume can be delivered for a given degree of myocardial fibre shortening.

With progression of hypertension in the Danish SHR (from 16 to 80 weeks), a concentric LV adaptation develops beyond the prevailing eccentric hypertrophy (Table 1). Whereas young SHR from this breeder demonstrate an increased LV function and maximal cardiac function in 78-week-old SHR is approximately equal to that of age-matched WKY rats (Fig. 4). This indicates a significant reduction in LV function with time in SHR since LV performance was unchanged in young and old WKY rats (Fig. 4). It may be that once the w/r ratio exceeds a critical 'threshold', LV performance may be impaired in SHR.

Maximal cardiac performance during experimental renal hypertension has previously been evaluated both in rats and in dogs, to some extent with conflicting results. In contrast to the maintained and improved LV function in SHR, LV performance is clearly depressed in renal hypertensive rats, regardless of whether renal hypertension was induced in ordinary Wistar rats or in SHR. Seven days after unclipping, however, maximal LV performance improved dramatically compared with the clipped rat, rising above the level found in the unclipped control rat (Fig. 2). Furthermore, cardiac dimensions 1 week after unclipping were not significantly changed compared with the clipped, hypertensive rats, thus not explaining the marked increase in LV function found 1 week following unclipping (Fig. 2). We speculate that some factor, of renal or non-renal origin, exerts a negative inotropic influence, since neither the blood pressure nor the myosin isoenzymes is able to account for the reduced LV function in the renal hypertensive rat.

Influence of the coronary vasculature on systolic function in hypertrophied hearts

The functional importance of hypertensive coronary structural changes has often been neglected when LV function has been evaluated in hypertrophied hearts. The extent of vascularization in relation to the myocardial growth and the structural vascular changes (i.e. increased wall thickness to lumen ratio) will markedly influence coronary blood flow. In response to a volume overload the heart develops eccentric hypertrophy but as long as the arterial pressure is not increased, no

**Figure 4** Peak stroke volume obtained at four different perfusion pressure levels (afterloads) in isolated perfused hearts from young (16-week-old WKY rats, n = 10 and SHR, n = 10) and old (78-week-old WKY, n = 11 and SHR, n = 8). Note the reduced stroke volumes in both the young and the old SHR at afterload = 50 mmHg and the enhanced left ventricular function in young SHR challenged at the highest afterload, which deteriorates with aging. Mean ± SEM. *P<0.05, **P<0.01, ***P<0.001.
structural narrowing of the coronary vessels should occur. In this particular situation the outgrowth of the coronary vessels will match that of the myocardial muscle mass, similar to blood vessel growth in compensatory renal hypertrophy from a uni-nephrectomized normotensive rat.

Previous studies have demonstrated a reduced coronary flow at maximal dilatation for any given aortic pressure in both SHR and in renal hypertensive rats compared with respective normotensive control rats. The finding that there is an enhanced coronary vascular resistance in these hypertensive rats is in accordance with the findings of an elevated vascular resistance at maximal dilatation in other vascular circuits, such as the hindlimb or in the kidneys. These results suggest that the coronary blood vessels, as do other vascular beds, develop a structurally determined, luminal narrowing.

The positive correlation between reduction of maximal LV function and coronary flow at low aortic pressures, suggests that the decrease in flow may be responsible for the decreased LV performance in SHR at low perfusion pressures. When coronary flow was elevated by means of increasing the perfusion pressure, maximal stroke volume is better maintained in SHR than in WKY, in spite of a 'relatively' lower coronary flow in the SHR (Fig. 4). This fact has also been supported by findings in renovascular hypertensive dogs, in which indices of contractility became depressed at moderately low aortic pressure levels, which were well-tolerated by the normal hearts. Thus, the hypertensive structural changes within the coronary vascular bed exert adverse effects on cardiac pumping performance if the prevailing perfusion pressure is too low.

Although the use of antihypertensive treatment in hypertensive patients reduces the risk of cardiovascular complications, concern has been expressed that excessive reduction of blood pressure, as might be caused by antihypertensive therapy, may precipitate myocardial ischaemia and infarction. Hence, the critical link here may be the coronary structural changes, which by reducing coronary flow capacity, will lead to a mismatch between demand and supply of nutrients. Therefore, a slow reduction in arterial pressure, allowing for a gradual regression of coronary vascular changes may be advantageous.

In summary, cardiac function in primary hypertension is greatly influenced by the end-diastolic design of the LV. Eccentrically hypertrophied hearts with an unchanged w/ri ratio compared with controls, show an augmented LV function (Danish bred SHR), whereas concentrically hypertrophied hearts with an elevated w/ri ratio (Australian and Swiss bred SHR), show a reduced/unchanged LV performance. This is probably because the eccentrically hypertrophied LV needs less myocardial muscle shortening to produce a given stroke volume than does the concentrically hypertrophied LV. No relationship between diastolic design and LV function seems to exist in renal hypertension, in which instead a negative inotropic influence is suggested.

Hypertrophied hearts from both primary and renal hypertensive states show marked impairment of LV function when perfused at low coronary perfusion pressures, which most likely is caused by the presence of coronary vascular structural changes. These changes will be a limiting factor for coronary flow and LV function at a low transmural pressure, since LV function is well-maintained at higher perfusion (transmural) pressures.

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