Intra-uterine growth retardation results in increased cardiac arrhythmias and raised diastolic blood pressure in adult rats

X.W. Hu\textsuperscript{a,b}, A. Levy\textsuperscript{a}, E.J. Hart\textsuperscript{a}, L.A. Nolan\textsuperscript{a}, G.R. Dalton\textsuperscript{b}, A.J. Levi\textsuperscript{b,*}

\textsuperscript{a}Division of Medicine, University of Bristol, Bristol, BS2 8HT, UK
\textsuperscript{b}Department of Physiology, Cardiovascular Research Laboratories, University of Bristol, University Walk, Bristol, BS8 1TD, UK

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Abstract

Objectives: Epidemiological evidence in humans suggests that intrauterine growth retardation is associated with an increased risk of hypertension and coronary heart disease in later life. To begin to understand the mechanisms involved, we developed and exploited a rat model of intrauterine growth retardation to assess predisposition to arrhythmias and resting blood pressure levels at defined ages from 4 to 18 months. Methods: Isolated working heart experiments were carried out on rats that had been subjected to intrauterine growth retardation by prenatal protein deprivation and age-matched male Wistar controls to measure susceptibility to wall stress-induced arrhythmias. In addition, resting systolic and diastolic blood pressures were measured in conscious rats via an indwelling arterial catheter. Results: Hearts from intrauterine growth retarded animals showed significantly more ventricular premature beats and more episodes of ventricular tachycardia at all ages examined (4, 9 and 18 months), and at 4 and 18 months, a reduction in coronary blood flow. Diastolic pressure was significantly raised by intrauterine growth retardation in both groups examined (4 and 9 months). Conclusions: Protein malnutrition during the intrauterine period results in profound intrauterine growth retardation that is associated with a raised diastolic blood pressure and an increased predisposition to cardiac arrhythmias in later life. These results are consistent with epidemiological observations made in human populations, and as similar pathophysiological changes may operate in both situations, intrauterine protein deprivation may be a useful model to help define some of the mechanisms involved. © 2000 Published by Elsevier Science B.V.

Keywords: ECG; Coronary circulation; Blood pressure; Ventricular arrhythmias

1. Introduction

Severe under-nutrition during pregnancy causes intrauterine growth retardation (IUGR) and delivery of a small-for-dates neonate. Epidemiological studies by Barker and others [1–9] have suggested that there is a relationship between IUGR and later lifetime incidence of hypertension, ischaemic heart disease, glucose intolerance and non-insulin-dependent diabetes mellitus. There has, however, been little experimental investigation of these observations so far. The long-term consequence of IUGR must result from some programming event or events that occur in utero [10,11]. Whilst maternal protein deficiency remains the major cause of IUGR in some parts of the world, other factors like low maternal plasma zinc levels [12], iodine deficiency [13], the existence of preeclampsia [14] and particularly impaired placental development and utero-placental circulation [15] are also thought to be responsible. It is difficult, however, to separate multiple influences during normal human foetal development and subsequent growth to adulthood. Animal models provide an opportunity to control the period of nutritional intervention and allow the later life effects of a highly defined intrauterine insult to be examined. The IUGR rat model used restricted protein intake during gestation only and as pups were immediately cross fostered onto normal dams after birth and control and IUGR rats housed in mixed groups after weaning, postnatal conditions were as near identical as possible.
The isolated working heart preparation has been used extensively in the past to investigate whole heart function independent of blood pressure or the hormonal and nervous influences that exist in vivo [16–19]. By abruptly changing outflow pressures in this model for defined periods — a stress similar to the physiological effects of changes in systolic blood pressure — the effects of a brief increase in ventricular wall stress on cardiac rhythm could be assessed. We also measured resting blood pressure and ventricular morphology in each animal group.

2. Methods


2.1. Development of the IUGR model

Wistar rats weighing 225–250 g were time mated with young males and the presence of a vaginal plug taken as positive mating (day zero). The females, once plugged, were randomly assigned to control or IUGR groups. IUGR was induced by allowing pregnant dams free access to a powdered protein-free diet (Harlan Teklad Premier. Purina Mills, St. Louis, MO, USA) until delivery. Control dams were allowed free access to a similar, but complete powdered diet containing 22% protein. Further groups of IUGR animals were generated at intervals throughout the study to minimize the effects of subtle changes in animal housing conditions over the 18-month duration of the breeding programme. Specifically, a group of animals were bred half way through the study (to contribute to the 9-month group) and several breeding cycles to generate 4-month-old animals were undertaken, the last occurring 4 months before the end of the 18-month study.

Immediately after birth, both IUGR and control pups were cross-fostered onto dams fed a normal pelleted diet with the litter sizes limited to six pups. After weaning, male pups from the two groups were provided with identical feeding and living conditions in mixed cages in normal 12 h light/dark cycles with temperature maintained at 26°C and free access to water. Although both sexes are adversely affected by IUGR [1,4], for practical reasons and as male individuals with IUGR have a higher incidence of cardiovascular disease and glucose intolerance than females [20], we confined the study to male animals. To identify age-related changes, experimental procedures were carried out in control and IUGR animals at 4, 9 and 18 months of age.

2.2. Working heart studies

2.2.1. Experimental solutions

Tyrode’s was used as the perfusion solution throughout the experiment. It was made fresh each day with Milli-Q water and contained: NaCl 114 mM; NaHCO₃ 25 mM; NaH₂PO₄ 1.0 mM; CaCl₂ 2.6 mM; glucose 11.1 mM and KCl at either 6 mM or 3 mM (see below). It was gassed continuously during perfusion with 95% O₂–5% CO₂ (pH 7.4) and maintained at 37°C.

2.2.2. Preparation of the hearts for the perfusion

Rats were anaesthetised with an induction mixture of 4% halothane vaporized in 95% O₂–5% CO₂, and maintained with 2% halothane for 2–3 min. The heart was excised with one cut through the ascending aorta and pulmonary veins, and immediately placed in 4°C Tyrode’s solution containing 5 I.U./ml heparin. The heart was quickly mounted onto a cannula by the aorta and perfusion started in Langendorff mode (i.e. retrograde perfusion). The pulmonary veins were identified and mounted onto a separate cannula connected to the preload chamber, allowing Tyrode’s solution to flow via the left atrium to the left ventricle. A small incision was made in the proximal pulmonary artery to ensure free coronary drainage. The volume of drainage was used as a direct measure of coronary flow. When the pulmonary veins were sealed tightly round the cannula, Langendorff perfusion was discontinued and anterograde perfusion (working heart mode) was commenced at a constant preload of 20 cm water.

2.2.3. Perfusion apparatus and induction of arrhythmia

The working heart apparatus was described previously [18,19]. In brief, fresh, warmed, oxygenated Tyrode’s solution was fed via the left atrium into the left ventricle, which pumped fluid into a compression chamber then into a column of defined height (Fig. 1). A Gould diaphragm pressure transducer (model P23 ID; Gould Nicolet Technologies, Ilford, UK) was used to monitor pressure distal to the compression chamber and its signal was recorded continuously on a chart recorder (Gould 8000 series). Preload was set at 20 cm water, and baseline afterload was set at 60 mmHg. The increments in afterload that we applied above the baseline level were preset at 20, 40, 60 and 80 mmHg by adjusting the height of a second outflow column.

Abrupt rises in left ventricle pressure and thus rises in ventricular wall stress are known to be arrhythmogenic [21,22]. In each experiment the arrhythmias induced by an abrupt increase in afterload for 20 s were assessed using a 3-way tap to divert outflow to a preset higher pressure. The sequence of afterload increments was randomly selected and the effects of three episodes of each afterload increment were recorded by continual ECG monitoring using three electrodes attached to the apex, proximal aorta and left atrium via the metal cannulae (Fig. 1) and pressure monitoring on a chart recorder. Hearts were allowed to recover for 2 min between each change of afterload. Between each working heart study, the apparatus was flushed with 2 l of ultrapure boiling water. The entire
arrhythmia responses to afterload changes. Aortic flow was measured from a flow meter in the aortic outflow line. Adding aortic flow and coronary flow gave the cardiac output. Ventricular premature beats (VPB) and ventricular tachycardia (VT) could be observed on the ECG recording and were counted and analysed in accordance with the Lambeth convention [23]. VPB were defined as discrete and identifiable premature QRS complexes having bizarre morphologies, and VT was defined as four or more consecutive VPB. Ventricular fibrillation (VF) was also noted. Arrhythmias of atrial origin were excluded from analysis as they were uncommon and did not occur reliably in response to afterload increases. The body weight of each rat was measured and at the end of working heart testing, hearts were thoroughly blotted dry and weighed as follows: (1) weight of whole heart, left and right ventricles and the whole atrium; (2) inner diameter of the ventricular cavity and the outer diameter of the whole heart; (3) thickness of the left ventricular wall and interventricular septum.

2.4. Statistical analysis

To compare VPB and VT between IUGR and control animals, the average value for three runs during each 20-s rise of afterload were compared. Results were expressed as mean±standard error of mean (S.E.). Mann–Whitney tests, Student’s t-test and analysis of variance (ANOVA) were used where appropriate.

2.5. Measurement of blood pressure

Groups of IUGR and control animals that were not used for working heart studies were induced and maintained on an anaesthetic consisting of 2% halothane in a mixture in nitrous oxide (1 l/min) and oxygen (0.5 l/min) throughout surgery. The right carotid artery was identified, isolated and its distal end closed with sutures. A fine polythene cannula (Dow Corning, Middle Land, MI, USA; 0.96 mm O.D.× 0.50 mm I.D., Portex, Hythe, UK) occluded at the distal end with a stainless steel pin was inserted approximately 20 mm into the carotid artery and secured with sutures. Before insertion, the proximal half of the cannula (approaching the heart) was prefilled with 50 I.U. heparin saline and the remainder with 5000 I.U. heparin saline to prevent coagulation. The free end of the cannula was tunneld through subcutaneous connective tissue, exteriorised through a scalp incision and fed into a protective steel spring secured to the parietal cranium with screws and dental cement [24]. Once animals had recovered, they were returned to individual cages and the end of the spring attached to a mechanical swivel. This allowed 360° movement in a horizontal plane and 180° in a vertical plane to give animals maximum freedom of movement. To avoid the unpredictable effects of high dose heparin on blood pressure, heparin saline left in the cannula was allowed to drain out in 0.1 ml blood after removal of the pin, and the cannula flushed with 0.2 ml of 50 I.U. heparin.
saline before it was connected to a pressure transducer. Before any measurements were made, the animals were allowed at least 10 min to recover from the brief handling stress and the continued presence of the operator in the room. In each case, resting systolic and diastolic pressures and heart rate were recorded 24 h after recovery from surgery.

3. Results

3.1. IUGR model

Switching females to a protein-free diet immediately before mating completely prevented successful pregnancy, hence the introduction of protein-free diet after mating. The incidence of positive mating that failed to litter was 14% in the dams fed a protein-free diet compared to none in the control dams. The gestation period in protein-free diet fed dams was longer than control dams (22.8 ± 0.2 vs. 22.2 ± 0.2 days, \( P < 0.029 \)). Weight loss during gestation in protein-free diet fed dams was 69.6 ± 3.3 g, compared to a weight gain of 43.7 ± 6.5 g in controls. In keeping with this, there was a dramatic difference in pup birth weights between the two groups. Control pups averaged 6.7 ± 0.8 g compared to IUGR pups which weighed 3.9 ± 0.5 g (\( P < 0.001 \)). Thus IUGR pups were only 58% of the weight of control pups at birth. Furthermore, the growth of IUGR rats remained slightly below that of control rats over 9 months (Fig. 2A and B) and even after 18 months the weight of IUGR rats remained significantly below control (Table 1). Differences in birth weight and body weight over the first month are shown in Fig. 2A. Fig. 2B shows body weight measured at 1-week intervals up to 4 months, then at monthly intervals up to 9 months. There was a 20% death rate among IUGR pups at birth followed by a further 16% until weaning (i.e. a 36% death rate by 1 month), compared to a 6% mortality at birth and 0% until weaning in controls. There was no significant difference in litter sizes or in the ratio of male to female rats delivered between IUGR and control groups.

3.2. Heart morphology and function

At all ages the absolute body and whole heart weights in IUGR animals was significantly lower than controls (Table 1). Whole heart weight and body weight were, however, reduced in proportion and therefore there were no significant differences in the heart/body weight ratios between the two groups at any of the ages examined (Table 1). In all groups the weight of the left ventricle tended to be lower in IUGR rats than in controls (Table 2): this reached statistical significance in the 4- and 18-month groups (\( P < 0.01 \) and < 0.05, respectively). There were no differences in the thickness of the left ventricular wall between IUGR and control (Table 2) and no significant differences in the thickness of the interventricular septum between IUGR and control at 4 months of age. At 9 and 18 months, IUGR animals had significantly less thick interventricular

<table>
<thead>
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<th>Age (months)</th>
<th>Control</th>
<th>IUGR</th>
<th>( P ) value</th>
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</thead>
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<tr>
<td>Body weight</td>
<td>4 472.4 ± 13.80 410.5 ± 18.20 0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 534.2 ± 9.17 487 ± 6.92 0.00018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 679 ± 18.68 588.8 ± 17.50 0.0001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heart weight</td>
<td>4 1.23 ± 0.04 1.06 ± 0.04 0.0035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 1.34 ± 0.03 1.25 ± 0.02 0.036</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 1.63 ± 0.04 1.49 ± 0.04 0.022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart/body×1000</td>
<td>4 2.55 ± 0.04 2.61 ± 0.06 0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 2.50 ± 0.05 2.57 ± 0.03 0.21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 2.42 ± 0.06 2.57 ± 0.09 0.26</td>
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<table>
<thead>
<tr>
<th>Animal numbers</th>
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<th>( n = 15 )</th>
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<tr>
<td>9  ( n = 21 )</td>
<td>( n = 29 )</td>
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</tr>
<tr>
<td>18  ( n = 21 )</td>
<td>( n = 25 )</td>
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Table 2
Comparison of ventricular weights, wall thickness, septal thickness and left ventricular radius

<table>
<thead>
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<th>Age (months)</th>
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<th>IUGR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of left ventricle</td>
<td>4</td>
<td>0.87±0.03</td>
<td>410.5±18.20</td>
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<td></td>
<td>9</td>
<td>0.91±0.02</td>
<td>0.87±0.02</td>
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<tr>
<td></td>
<td>18</td>
<td>1.13±0.03</td>
<td>1.03±0.03</td>
</tr>
<tr>
<td>Left ventricular wall thickness</td>
<td>4</td>
<td>4.09±0.17</td>
<td>4.24±0.19</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4.41±0.06</td>
<td>4.36±0.07</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4.07±0.06</td>
<td>4.25±0.09</td>
</tr>
<tr>
<td>Radius of left ventricular cavity</td>
<td>4</td>
<td>4.94±0.16</td>
<td>3.78±0.24</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>4.19±0.12</td>
<td>4.14±0.08</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4.03±0.09</td>
<td>4.25±0.08</td>
</tr>
<tr>
<td>Septal thickness</td>
<td>4</td>
<td>3.26±0.12</td>
<td>3.49±0.23</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3.4±0.08</td>
<td>3.14±0.05</td>
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<tr>
<td></td>
<td>18</td>
<td>3.54±0.09</td>
<td>3.26±0.07</td>
</tr>
<tr>
<td>Weight of right ventricle</td>
<td>4</td>
<td>0.24±0.009</td>
<td>0.22±0.006</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.24±0.008</td>
<td>0.22±0.004</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.25±0.007</td>
<td>0.25±0.006</td>
</tr>
<tr>
<td>Whole atrium weight</td>
<td>4</td>
<td>0.091±0.003</td>
<td>0.076±0.004</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.11±0.005</td>
<td>0.10±0.003</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.51±0.005</td>
<td>0.13±0.005</td>
</tr>
</tbody>
</table>

We found no difference in the inner diameter of the left ventricular cavity between IUGR and controls at any age.

### 3.2.1. Aortic flow, coronary flow and cardiac output

Aortic flow, coronary flow and cardiac output were normalised to whole heart weight and results are shown in Fig. 3A–C. For the 4-month group, coronary flow (Fig. 3B) was significantly lower in IUGR animals than in control (P<0.007), however there were no significant differences in either aortic flow or cardiac output (Fig. 3A and C). In the 9-month group both aortic flow (Fig. 3A) and cardiac output (Fig. 3C) were significantly reduced in IUGR hearts (aortic flow: P<0.025; cardiac output: P<0.02), however there was no significant difference in coronary flow at this age. The 18-month group showed results similar to the 4-month group — a significant reduction in coronary flow for IUGR hearts (P<0.02) with no significant difference in aortic flow or cardiac output.

### 3.2.2. Arrhythmias

Representative ECGs and pressure recordings from a control heart (top panel) and an IUGR heart (bottom panel) are shown in Fig. 4. The lower trace of each panel shows pressure changes recorded distal to the aorta. Each recording starts with a baseline afterload (60 mmHg), and after a few seconds the afterload was increased by 40 mmHg for a period of 20 s. The upper trace shows the simultaneous ECG recording. At the start of each recording, the heart was in sinus rhythm. The control heart continued to beat in sinus rhythm for the whole period of afterload increase. In contrast, within a few seconds of afterload increase, the ECG recorded from the IUGR heart showed abnormal and wide complexes of ventricular origin. Sometimes these abnormal complexes alternated with complexes of atrial origin as in this case. In other hearts there were repeated complexes of ventricular origin. The abnormal ventricular complexes subsided within a few seconds of return to the baseline afterload.

### 3.2.3. Ventricular premature beats

The number of VPB observed in control and IUGR...
hearts are shown in Fig. 5A–C. The major conclusion from the analysis is that at each age, and with most pressure steps, IUGR hearts developed more ventricular arrhythmias. Hearts from IUGR animals developed significantly more arrhythmias with pressure steps of 60 and 80 mmHg. It is also clear that for both control and IUGR hearts, the number of arrhythmias developed was graded with the amplitude of the imposed pressure step and tended to increase with age (although not significantly).

The most striking result was in the 9-month group. Although the number of arrhythmias that developed at each pressure step in control hearts was not different between the 4- and 9-month animals, IUGR hearts at 9 months developed a much larger number of arrhythmias compared to controls — a difference that was highly significant at each pressure step. In the 18-month group, there appeared to be a larger number of arrhythmias in the control hearts compared to 9- and 4-month control groups, indicating that arrhythmias tend to increase with age (although not significantly). Nevertheless, in the 18-month group the IUGR hearts developed significantly more arrhythmias at each pressure step than the 18-month controls. As for the other groups, the number of arrhythmias was graded with the amplitude of the pressure step for both IUGR and control groups.

### 3.2.4. Ventricular tachycardia

The number of episodes of ventricular tachycardia (VT) in IUGR and control hearts in each age group is shown in Fig. 6A–C. The overall picture was similar to that for VPB with IUGR displaying more VT with each pressure step, and in each age group. In the 4 month group very few episodes of VT were observed in control hearts and there was a clear increase in VT developed in IUGR hearts with...
the difference becoming significant for 60- and 80-mmHg pressure steps. It was also notable that the number of VT complexes and number of episodes of VT increased in proportion to the amplitude of pressure step for IUGR hearts. For the 9-month group VT was also relatively uncommon for the control hearts, and there was a striking increase in VT developed in IUGR hearts, with the difference being significant for each pressure step. In the 18-month group there appeared to be a trend towards increased VT in the control hearts, especially for 60- and 80-mmHg pressure steps. This was similar to the VPB results, once again suggesting that there is an age-related increased predisposition to arrhythmias. As in the other groups IUGR hearts developed more VT compared to control, with the difference becoming significant for all pressure steps except 20 mmHg.
3.2.5. Ventricular fibrillation

The incidence of more complex ventricular arrhythmias such as ventricular fibrillation (VF) are shown in Fig. 7. In the working heart VF was usually caused by one of the higher pressure steps and was almost always irreversible, such that it resulted in no cardiac output and cardiac death. There was no difference in the incidence of VF between IUGR and control hearts at 4 months, but a clear increase in the incidence of VF in IUGR hearts for both the 9- and 18-month groups (Fig. 7). Overall, 18 of 51 hearts from IUGR animals developed terminal VF, compared to 7 of 50 control hearts. These results were generally consistent with the higher incidence of VPB and VT that we found in IUGR.

3.2.6. Arterial blood pressure

Systolic blood pressure, diastolic blood pressure and average blood pressure (diastolic + 1/3 (systolic – diastolic)) were significantly higher in IUGR than in control rats at 4 months (Fig. 8). At 9 months, only the diastolic pressure was statistically higher in IUGR. We found no significant difference in resting heart rate between IUGR and controls in either age group. Animals were not available for study of arterial blood pressure at 18 months.

4. Discussion

In this study we have demonstrated that protein depriv-
reduced compared to control. The resulting pups were less than two thirds of the weight of control pups and even though their postnatal treatment was identical to controls, their growth curves tracked but did not catch up with control animals even after 18 months. We were unable to address the possibility that IUGR resulted in a shorter lifespan in these animals after they had survived infancy. The 20% death rate amongst IUGR pups at birth (compared to only 6% of control animals) was mainly due to the protein deprived dams consuming the IUGR pups immediately after birth. A further 16% of IUGR pups died in the period until weaning, compared to zero in control groups. The increased death rate in IUGR pups after that time, amounting to 16% from the neonatal period until weaning, was mostly due to their reduced ability to compete for sucking.

4.1. Effect of IUGR on heart parameters

In the 4-, 9- and 18-month groups whole heart weight in IUGR animals was reduced compared to control overall, but this was always in proportion to body weight. Atrial weight was less for IUGR at all age points, however we found no difference in weight of the right ventricle between IUGR and control. At all age groups left ventricular weight was lower in IUGR animals than in controls, consistent with their reduced heart weight (reaching statistical significance at 4 and 18 months but not 9 months). We did not, however, detect a difference in left ventricular wall thickness or cavity diameter. In the context of this study, this was an important result, since it was a central issue to ascertain whether left ventricular wall stress might be different between IUGR and controls. A step increase in afterload increases cavity pressure in the left ventricle and the resulting left ventricular wall stress is determined by Laplace’s law

\[
\text{Left ventricular wall stress} = \frac{\text{left ventricular pressure} \times \text{mean internal radius of the cavity}}{\text{free left ventricular wall thickness}}
\]

Since left ventricular internal radius and wall thickness were similar in IUGR and control hearts and the same afterload increments were applied to each, stepped increases in left ventricular wall stress were similar in each group. A difference in wall stress alone is therefore very unlikely to account for the large differences seen between the response of the IUGR hearts and controls. While the weight of the left ventricle in IUGR animals was generally less than control, against our expectations we did not detect a difference in left ventricular wall thickness. The explanation might be found in arterial blood pressure differences. In both of the groups we were able to examine (at 4 and 9 months), diastolic pressure was raised in the IUGR animals. At 4 month systolic pressure was also raised in the IUGR groups. It is conceivable this might have resulted in slight compensatory hypertrophy of the left ventricle in IUGR, such that left ventricular wall thickness (relative to left ventricular weight) might have become slightly larger in IUGR compared to control.

4.2. Effect of IUGR on cardiac arrhythmias

One of the most striking results of this study was the dramatic excess of afterload-induced arrhythmias in IUGR hearts compared to controls, particularly in view of the data showing that ventricular wall stress was likely to have been similar between the two groups. Even at 4 months we could already detect an increase in VPB in the IUGR group in response to each pressure step. As the animals aged, the number of VPB induced by a given pressure step increased in both the control and IUGR groups, but at each age the corresponding increase in VPB in the IUGR group was higher. It seems likely that IUGR resulted in physiological changes in the left ventricle and perhaps the whole heart which predisposed it to developing more VPB in response to an increase in wall stress. An ischaemia-induced mechanism may also have contributed to the arrhythmias, but seems unlikely in view of the short duration of increased afterload. A similar profile was observed with episodes of VT where in addition to a slight increase with advancing age, similar afterload pressure steps in IUGR animals produced a two fold or higher incidence of VT compared to control. This difference generally carried through to the incidence of terminal VF, where although there were no differences in the rates of VF induction in the 4-month group, there was a 2- to 4-fold increase in VF at 9 and 18 months.

4.3. Effect of IUGR on arterial blood pressure

Pilot studies of blood pressure measurements using the tail cuff method [25,26] or acute arterial cannulation under anaesthetic [27] were, in our hands, found to be more susceptible to confounding factors and much less repeatable than measurement via chronic intra-arterial cannulation [28]. Given the changes in blood pressure observed at 4 and 9 months, it is particularly unfortunate that insufficient animals were available for this part of the study to be repeated at 18 months. The significant increase in systolic and diastolic pressures noted at 4 months (each by 10 mmHg) and the significantly increased diastolic pressure at 9 months (again 10 mmHg) demonstrate firstly that IUGR might result in more general changes in the cardiovascular system than those confined to the heart. It is possible that IUGR alters arterial vascular tone or has effects on the nervous control of the cardiovascular system. Secondly, there may be a connection between these data and the coronary flow results mentioned previously. If an increase in vessel tone is involved in the change of arterial blood pressure in IUGR, then this might also account for
reduced coronary flow observed in the 4- and 18-month groups [29].

Marked effects of IUGR on diastolic blood pressure and on the predisposition to age-related and afterload-induced arrhythmias have not previously been observed. The purpose of this study was to investigate the effect of IUGR, if any, on the heart and as such, it was not designed to address specific mechanisms that might underlie these changes. We can only speculate at the present time about how IUGR might have altered the pathophysiology of hearts to make them susceptible to wall stress-induced arrhythmias. One possibility suggested by these data is that there might be a reduction in coronary flow relative to whole heart weight in IUGR that might predispose them to arrhythmias [30,31]. The observation that coronary flow at baseline (60 mmHg) afterload was significantly reduced in the 4- and 18-month groups but not in the 9-month group in which arrhythmias were most marked does not entirely exclude this possibility as it was not possible to measure coronary flow during the pressure step increases. It is during each of the afterload steps that reduced coronary flow would have to become inadequate for cardiac requirements if resulting ischaemia were to underlie the arrhythmias. Further possibilities include altered intracellular calcium ion regulation in IUGR hearts [32±34], an altered action potential [35,36] or perhaps abnormal conduction pathways leading to circus electrical movements [37–39].

4.4. Relation to human studies

The stimulus for the present study was the finding in humans that IUGR predisposes to hypertension, ischaemic heart disease, glucose intolerance and non-insulin-dependent diabetes [4,6–8]. At least for the cardiovascular findings in humans, there appear to be some similarities between the data presented here and epidemiological studies of human populations. However, we did not identify a progressive rise in blood pressure between 4 and 9 months, and this does not appear wholly consistent with the pattern of development of hypertension in man.

There may also be a parallel between the increase in arrhythmias we found, especially the potentially dangerous ones such as VT and VF, and ischaemic heart disease in humans with IUGR [5,20,40,41]. Clearly an increase in the probability for VT and VF will predispose animals under normal conditions to sudden cardiac death, and this might account for a proportion of the premature mortality noted in low birth weight humans. The potential similarities between our IUGR rat model and the human situation call for a more detailed investigation of the effects of IUGR on different body systems, and an investigation of the mechanisms of these striking effects on the heart and cardiovascular system. It is conceivable that with more insight into the mechanisms we may be able to prevent and treat some of the ill health suffered by humans with IUGR.

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