

Review

## Rat models of hypertension, cardiac hypertrophy and failure

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### 1. Introduction

Animals have been used by humans for centuries to understand their own biology. In cardiovascular research, animal models have allowed the study of cardiovascular disease in the early stages, as well as the investigation of the mechanisms of the pathogenesis of cardiovascular disease and the effects of drug intervention. The aim of these studies is to provide clear concepts for selected investigations in humans. An ideal animal model for any cardiovascular disease in humans should have five characteristics: (i) mimic the human disease, (ii) allow studies in chronic, stable disease, (iii) produce symptoms which are predictable and controllable, (iv) satisfy economical, technical and animal welfare considerations, and (v) allow measurement of relevant cardiac, biochemical and haemodynamic parameters.

The use of rats as animal models is rational from the economic viewpoint and many techniques have been developed to measure relevant functional parameters. However, there is often insufficient consideration as to whether the other criteria, especially the mimicry of human disease, are satisfied with the choice of rat models of cardiovascular disease. Three examples illustrate the problems. Firstly, cardiovascular diseases such as hypertension and heart failure in humans are usually slowly developing with wide-ranging neurohumoral adaptations in contrast to the acute onset of symptoms in many surgical or drug-induced rat models of these important diseases. Secondly, cardiovascular disease is uncommon in young humans but

markedly increases with age [1] yet most models of hypertension and heart failure only use young adult rats. Animal models of ageing have been recently reviewed [2]. Thirdly, the development of atherosclerosis is very unusual in most strains of rats, even in the presence of sustained high blood lipid levels, in contrast to humans where atherosclerosis is common and an important risk factor in hypertension and heart failure.

Although this review discusses almost exclusively experiments in living animals, such studies are not appropriate for all investigations of the cardiovascular system. Cell dispersion from adult hearts and the culture of neonatal or adult cardiac fibroblasts or neonatal cardiomyocytes have replaced some animal studies since these allow studies of a single cell type in the absence of homeostatic mechanisms over a wider range of experimental conditions than easily obtained *in vivo*. However, while these studies have allowed characterisation of cell properties, they cannot reproduce the working heart muscle. The use of animal models may be limited by ethical concerns and legislation, as a reaction to the diametrically opposed opinions within the community on the necessity for the use of animals in research [3]. Some rats will develop severe illness and death due to the procedures described in this review; this is inevitable if these rats are valid models of human diseases with high morbidity and mortality. This review aims to present the commonly used and some recently introduced rat models of hypertension, cardiac hypertrophy and heart failure to allow rational discussion of the advantages and disadvantages of each model.

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## 2. Hypertension

Human hypertension is usually a slowly-developing disorder of middle to old age which predisposes to the cardiovascular disorders that cause most of the morbidity and mortality in the elderly [2]. The incidence and sequelae of hypertension vary markedly by patient subgroup, particularly by gender and race [4]. The prevalence of hypertension is higher in men than age-matched premenopausal women, but similar for 70-year-old men and postmenopausal women [4]. Physiological levels of oestrogen exert a cardioprotective effect, with postmenopausal women being two to three times less likely to develop heart disease if receiving oestrogen replacement therapy [5].

Human hypertension is probably triggered by environmental influences such as increased salt intake, obesity and lack of exercise acting on a genetic predisposition [6]. The specific genes responsible for hypertension have not been identified but epidemiological, family and twin studies suggest that a substantial portion of the phenotypic variation in blood pressure is genetically determined [7].

Long-term hypertensives often have other cardiovascular risk factors including elevated cholesterol levels, reduced high-density lipoproteins, diabetes, left ventricular hypertrophy and obesity [2]. Untreated hypertensives present acutely with stroke, coronary artery disease leading to myocardial infarction or acute renal failure. Most patients have essential hypertension, where no cause can be determined, which leads to many abnormalities in the physiological regulatory systems for blood pressure including neurotransmitters and humoral factors with abnormalities of the cardiac and vascular smooth muscle and endothelium. It is often unclear which of these changes are causative and which are secondary to the hypertension [6]. These are the characteristics of human hypertension which rat models should mimic. Many studies have been undertaken using rat models of hypertension and heart failure since an earlier comprehensive review [8]. Our review of hypertension is mainly of the rat models of systemic hypertension, but some consideration of renal and pulmonary hypertension is inevitable (Table 1). Excessive vasoconstriction, commonly involving the endogenous peptides, angiotensin II and endothelin, or deficient vasodilat-

Table 1  
Some rat models of hypertension, cardiac hypertrophy and failure

| Syndrome                | Model  |
|-------------------------|--|
| <i>Hypertension</i>     |  |
| Systemic                | Spontaneously Hypertensive Rats (SHRs)<br>Stroke-prone SHR (SHR-SP)<br>Mineralocorticoids (DOCA-salt)<br>NO synthase inhibition (L-NAME administration)<br>Transgenics (TGR(mREN2)27 rats)<br>Diabetic hypertensive rats (STZ-SHR, Zucker) |
| Renal                   | Renal artery occlusion (1K1C, 2K1C)  |
| Pulmonary               | Monocrotaline<br>Hypoxia (normobaric, hypobaric)   |
| <i>Hypertrophy</i>      |  |
|                         | Spontaneously Hypertensive Rats (SHRs)<br>Renal artery occlusion<br>Pressure loading (aortic banding)<br>Catecholamines (noradrenaline, isoprenaline)<br>Transgenics   |
| <i>Heart failure</i>    |  |
| Systemic hypertension   | Spontaneously Hypertensive Rats (SHRs-F)<br>Hypertensive HF prone rats<br>Dahl/Rapp salt-sensitive rats  |
| Ischaemic heart failure | Non-occlusive coronary ligation  |
| Myocardial infarction   | Coronary ligation<br>Microembolization of coronary vessels   |
| Cardiomyopathy          | Toxins (adriamycin, ethanol)   |
| Myocarditis             | Autoimmune<br>Chagas' disease  |
| Pulmonary hypertension  | Monocrotaline<br>Hypoxia   |
| Miscellaneous           | Aortocaval fistula (shunts)  |

ation, often involving nitric oxide (NO), are common mechanisms in hypertension, whether defined as systemic, pulmonary or renal.

## 2.1. Systemic hypertension

### 2.1.1. Spontaneously hypertensive and stroke-prone rats (SHRs and SHR-SP)

The most commonly used model of cardiovascular disease, with over 4000 Medline references in the last 10 years, is the Spontaneously Hypertensive rat (SHR) often with the Wistar Kyoto rat (WKY) as the normotensive control. SHRs are descendants of an outbred Wistar male with spontaneous hypertension from a colony in Kyoto, Japan, mating with a female with an elevated blood pressure, and then brother×sister mating continued with selection for spontaneous hypertension, defined as a systolic blood pressure of over 150 mm Hg persisting for more than one month [9]. From 1968, this inbred strain of SHRs was further developed in the USA (reviewed in [10]). The various colonies of SHR are pre-hypertensive for the first 6–8 weeks of their lives with systolic blood pressures around 100–120 mmHg [11], and then hypertension develops over the next 12–14 weeks [12]. As in humans, hypertension develops more rapidly and becomes more severe in male than female SHR [13]. *In vivo* studies have shown that, in the early stages of hypertension, SHRs have an increased cardiac output with normal total peripheral resistance. As the SHR progresses into the established hypertension state, the cardiac output returns to normal and the hypertrophied blood vessels produce an increase in the total peripheral resistance [14].

The male SHR is commonly used as a model of established human hypertension, for example to define hypertension-induced changes in signalling mechanisms [15] and to test new antihypertensive medication, for example felodipine [16]. Human hypertension is difficult to study as there is substantial individual variation in the two triggering elements of hypertension, polygenetic disposition and excitatory environmental factors, leading to many variations in the direct and indirect effects on the cardiovascular system that are difficult to differentiate. Researchers in hypertension have commonly resorted to the use of SHRs which have, within each colony, uniform polygenetic disposition and excitatory factors which produce uniform changes in the indirect and direct effects on the cardiovascular system. This lack of inter-individual variation is one of the major advantages of the SHR [17] but it means that the SHR can only model one of many possible causes of human hypertension. As the specific genes responsible for developing hypertension have not been identified, one of the most valuable contributions of inbred genetic models is the mapping and identification of these genes [7]. Extensive investigations have identified several quantitative trait loci for hypertension and diabetes [18–21], although the identity of the genes and the

pathophysiological basis for the observed linkages remain largely unknown. Another advantage of the SHR is that it follows the same progression of hypertension as human hypertension with pre-hypertensive, developing and sustained hypertensive phases with each phase lasting at least several weeks [22]. However the SHR differs from human hypertension in that SHRs reproducibly develop hypertension in young adulthood rather than in middle age as in humans. Because SHRs have a pre-hypertensive state, they have the important potential to be used in studies of the cause and development of hypertension. It is somewhat surprising that SHRs are rarely used for such studies. The SHR model is also suitable for gender studies in hypertension but only a few recent studies have considered gender differences in SHR responses [23,24]. In addition, the normal life spans of normotensive and SHRs are comfortably short, 2.5–3 years and 1.5–2.5 years, respectively, to make it relatively easy to follow ‘cradle to grave’ [25].

The WKY controls were established later, in 1971, as a normotensive control strain by the National Institutes of Health (USA) as an inbreed of the Wistar Kyoto colony via brother×sister mating [10]. The degree of genetic difference between the SHR and WKY strains and within different colonies of each strain is substantial and comparable to the maximum divergence possible between unrelated humans [26,27] and thus unlikely to be related solely to hypertension. Differences between SHRs and Wistar normotensive rats other than WKY may be more likely to be hypertension-related than differences between SHR and WKY because the SHRs were derived from the WKY, hypertension may develop spontaneously in the WKY, and the WKY may share some of the genes responsible for hypertension with the SHR [28]. Significant pathophysiological or pharmacological differences between SHR and normotensive rats may not be related to hypertension but rather represent differences between various colonies of normotensive rats [29].

The SHR is a useful model as compounds which lower blood pressure in SHR also lower blood pressure in hypertensive humans. The SHR is a chronic stable model producing symptoms which are predictable and controllable and avoiding difficult or life-threatening technical interventions. Thus it is not surprising that SHRs have been used extensively and successfully for 30 years to test medicines for their effectiveness in lowering blood pressure, and to study the mechanisms of established hypertension. The common criticism of the SHR model is that it has been around for a long time yet we still know little about the cause of the onset of hypertension. One reason is that the appropriate studies with prehypertensive rats have not been done. Another reason is the difficulties in undertaking and interpreting the appropriate genetic mapping studies.

Experience with other genetic hypertensive strains of rats has been limited by comparison with the SHR yet these strains may be useful in determining the genes

involved both in hypertension and in associated risk factors such as an elevated fibrinogen; some examples are the New Zealand [30], Milan [31], Prague [32], Lyon [33] and San Juan [34] hypertensive rats.

### 2.1.2. Stroke-prone spontaneously hypertensive rat (SHR-SP)

Hypertension is the major risk factor for stroke, a cerebrovascular incident causing disability. Stroke in humans is uncommon under age 40 but increases markedly over age 65 with 65% due to atheroma and thrombosis, 15% to haemorrhage and 15% to embolism [35]. The SHR-SP strain was developed following separation of the SHR into three substrains, A, B and C, in 1971 with the A strain having a higher incidence of cerebrovascular disease, followed by selective mating of offspring with at least one parent with spontaneous stroke [36]. The SHR-SP are hypertensive at 5 weeks and systolic blood pressure rises to at least 250 mmHg in males, in contrast to pressures of around 200 mmHg in SHR, with a positive correlation between the incidence of cerebral lesions and blood pressure [36]. Salt-loading accelerates the development of hypertension and the occurrence of stroke [36,37]. The initial signs of stroke are excitement, hyperirritability, paroxysm, followed by behavioural and psychological depression and motion disturbances, apathy, coma and death [36]. Consistent post-mortem findings are lesions in the cortex or subcortex of the frontal, medial and occipital areas of the telencephalon with thromboses in the arterioles around the lesions [36]. Since these lesions are similar to humans, SHR-SP have been used to investigate preventive strategies for both stroke (for example, mibefradil [37] or endothelin receptor blockade [38]) and cardiac hypertrophy due to severe hypertension [39]. However, SHR-SP die in early to mid-adulthood (52–64 weeks [40] or around 14–20 weeks old following salt-loading [37]), in contrast to SHR (around 2 years), and WKY (around 3 years); thus this model does not mimic the most common age of onset of stroke in humans. Further, there is insufficient evidence that effective therapeutic regimes in the SHR-SP can be translated into effective prevention of stroke in humans. No studies were found which used the SHR-SP to investigate treatment regimens for stroke.

### 2.1.3. Mineralocorticoid hypertension

Salt retention is characteristic of human hypertension and can be achieved rapidly in uninephrectomised rats by mineralocorticoid administration, for example by weekly subcutaneous injections of deoxycorticosterone acetate (DOCA), and salt loading as 1% NaCl in the drinking water [41–43]. Nephrectomised rats given deoxycorticosterone or NaCl alone do not show any major changes in blood pressure, and it is only the combination of deoxycorticosterone and NaCl that produces a major increase in blood pressure with increases in cardiac and renal weight [41]. Hypertension develops more quickly and becomes

more severe in male than female DOCA–salt rats [44]. DOCA–salt rats have no signs of congestive heart failure at 6 weeks (hepatic or pulmonary congestion or effusion; [41]). Initially there was about a 20% mortality associated with unilateral nephrectomy [41] but the mortality in our recent studies is around 1–2% within the first 4 weeks after surgery (Brown, unpublished observations).

The DOCA–salt model shows a markedly depressed renin–angiotensin system and thus has been used in hypertension research as an angiotensin-independent model in the characterisation of new antihypertensive compounds (for example, [45,46]). Mineralocorticoid overactivity, especially hypersecretion of deoxycorticosterone, is rarely observed in humans [47] and is generally the result of a genetic defect [48]. Although it may be more appropriate to administer aldosterone since this is the major mineralocorticoid in humans, an aldosterone–salt model has been less widely used than the DOCA–salt model although it produces similar responses [47,49].

Both the DOCA– and aldosterone–salt models rely on impairment of kidney capacity and salt loading to rapidly induce hypertension and hypertrophy. This is not a very realistic model for many human hypertensive patients: how many have hypersecretion of aldosterone, one kidney and eat huge amounts of salt to develop acute hypertension? These models progress quickly to severe hypertension and hypertrophy, and therefore are not suited for long-term studies in chronic, stable disease. The model is economical, with the technical requirements of this model being such that, with experience, there should be minimal mortality due to the procedures alone.

### 2.1.4. NO synthase inhibition

Nitric oxide (NO, endothelium-derived relaxing factor), a paracrine vasodilator, has been implicated in regulating vascular tone and myocardial contractility, and inhibiting platelet aggregation, and therefore may be critical in the development of hypertension and atherosclerosis [50]. There are at least three forms of the NO synthase (NOS) [51]; the cytokine-inducible NOS2 cosegregates with an increased blood pressure in the Dahl salt-sensitive rat [52] but endothelial cell NOS3 seems uninvolved in human essential hypertension [53]. NO synthesis can be blocked by inhibitors such as L-NAME (N<sup>ω</sup>-nitro-L-arginine methyl ester) and nitro-L-arginine. Chronic administration of L-NAME increased systolic blood pressure and heart weight and decreased renal function; the ACE inhibitor ramipril reversed all changes [54]. Chronic administration of L-NAME to rats during gestation induces the development of a pre-eclamptic syndrome similar to humans [55]. Since the role of decreased NO production in human hypertension is unclear, it is too early to decide whether NO synthase inhibition is an appropriate model. However, this model deserves more attention as it is technically easy and the procedure should have low mortality.

### 2.1.5. Transgenic rats

Transgenic rats develop hypertension, hypertrophy and heart failure, and are considered as models of hypertrophy in this review.

### 2.1.6. Diabetic hypertensive rats

Diabetes is an important risk factor in patients with hypertension and heart disease; further, diabetics have a high incidence of cardiovascular disease, especially hypertension, atherosclerotic coronary disease, cardiomyopathy and microvascular damage [56,57]. Rapid injection of streptozotocin to adult rats produces many of the characteristic cardiovascular and renal features of humans with uncontrolled insulin-dependent diabetes [58], even though these rats can survive without exogenous insulin for at least 12 weeks and are usually normotensive. Streptozotocin administration to SHR produces a model of hypertensive insulin-dependent diabetic humans; these rats show progressive cardiac deterioration [59] and have been used to measure responses of antihypertensive drugs on hypertrophy and vascular permeability [60]. Similar studies have been undertaken in the Cohen–Rosenthal diabetic hypertensive rat, a crossbreeding of the Cohen diabetic and SHR [61]. Since at least 85% of diabetics are non-insulin-dependent with many of these patients being hypertensive and obese, models of non-insulin-dependent diabetic hypertension are more relevant. The genetically-determined obese Zucker rat [59,62,63] fulfils the criteria as a relevant model of non-insulin-dependent diabetes [59] with moderately elevated blood pressure, progressive kidney damage [64] and hypercholesterolaemia. Lean, age-matched littermates are the appropriate control for the obese Zucker rat. A newer genetic model of human non-insulin-dependent diabetes is the Otsuka Long-Evans Tokushima fatty rat which develops mild hypertension with typical cardiac and renal complications such as perivascular fibrosis and glomerulosclerosis [65]. Obesity appears to be an independent risk factor for cardiovascular disease [66]; the JCR:LA-cp rat is obese and develops atherosclerotic and myocardial lesions [67]. Further studies are essential to determine the specific cardiovascular changes caused by chronic obesity, diabetes and mild hypertension.

## 2.2. Renovascular hypertension

The kidney is vital in cardiovascular homeostasis yet renal damage is a relatively minor cause of human hypertension. Renovascular hypertension develops in response to renal ischaemia; models involve restricting blood flow by clips on the renal arteries [68,69]. The one-kidney, one clip model (1K1C), where one kidney is removed and a clip placed on the renal artery of the remaining kidney, and the corresponding two-kidney two-clip (2K2C) model are volume overload forms of hypertension, as there is

stimulation of the renin–angiotensin–aldosterone system in the absence of renal excretion or fluid loss. 2K2C hypertension mimics bilateral renal artery stenosis in humans while the clinical equivalent of the 1K1C model is unclear.

Renovascular hypertension occurs in humans due to renal artery constriction, usually from atherosclerotic or fibromuscular dysplastic renal disease, since this lowering of renal perfusion pressure causes the kidney to overproduce renin and leads to a continual activation of the renin–angiotensin–aldosterone system [69] similar to the two-kidney, one-clip (2K1C) model of hypertension. In contrast to 1K1C and 2K2C rats, 2K1C rats where the contralateral kidney remains untouched are a pressure overload model of hypertension as there is activation of the renin–angiotensin–aldosterone system and vasoconstriction in the presence of renal excretion and fluid loss. These models of renovascular hypertension cause a sudden increase in blood pressure, unlike the slow onset of human hypertension with the development of homeostatic mechanisms.

In the rat, 2K1C hypertension is characterised by sharp increases in plasma renin activity due to the decreased renal arterial pressure in the clipped kidney, and increased circulating angiotensin II concentrations and blood pressure within 2–4 weeks. Plasma renin activity and angiotensin II levels return to near normal levels around 4 weeks with interstitial fibrosis now evident in the heart, especially around the intramural coronary arteries. After several months, a chronic phase develops characterised by elevated plasma renin activity and perivascular and interstitial fibrosis of the myocardium [70]. These results are broadly consistent in rat and man [69]. 2K1C rats have been widely used as a high renin model of hypertension, for example in the evaluation of angiotensin receptor antagonists [71]. The 2K1C procedure in rats is not uniformly successful; for example, of 105 rats, 19 did not develop hypertension, 27 developed malignant hypertension and 12 died; only 47 (45%) developed stable hypertension [72].

Cardiac diseases remain the major cause of death in patients with end-stage renal failure. The reduced renal mass model of chronic uraemia in rats, produced by 5/6 nephrectomy, is characterised by impaired cardiac function after 28 days [73] as well as hypertension, cardiac hypertrophy and fibrosis after 16 weeks which can be significantly improved by the ACE inhibitor, enalapril [74]. After 14 months of uraemia, the cardiac hypertrophy in these rats was not accompanied by a commensurate increase in the number of capillaries [75]. This model certainly allows the investigation of hypertension following renal failure but it is hard to envisage the applicability to essential hypertension in humans.

The major cause of end-stage renal failure is insulin-dependent diabetes with hypertension being an additional risk factor. This can be reproduced in uni-nephrectomised rats with streptozotocin-induced diabetes; these rats develop hypertension and renal failure within 8 months

which can be improved by treatment with an ACE inhibitor or an angiotensin AT1 receptor antagonist [76].

Perinephretic hypertension, an unusual variant in humans, can be produced by encapsulation of one or both kidneys with a cellulose acetate wrap (cellophane wrap model, [77]). These rats develop left ventricular hypertrophy, reactive cardiac fibrosis and increased cardiac stiffness [78]. Functional studies have not been reported in this model of hypertension.

### 2.3. Pulmonary hypertension

In human pulmonary hypertension, pulmonary artery systolic and mean pressures exceed 30 and 20 mm Hg, respectively, at rest or pulmonary artery mean pressure exceeds 30 mm Hg during exercise [79]. Primary (unexplained) pulmonary hypertension is a rare but serious disorder that occurs predominantly (73%) in young women (mean age 34) who develop prominent central pulmonary arteries and right ventricular hypertrophy followed by failure. Survival is poor with only 21% surviving to 5 years [80]. Secondary pulmonary hypertension is more common and has many causes such as left ventricular systolic failure, chronic obstructive pulmonary disease, pulmonary thromboembolism and hypoventilation, and is characterised by swelling of the pulmonary capillary endothelial cells, thickening of endothelial cells basal lamina and interstitial oedema [80]. The fundamental molecular mechanisms which may contribute to the pathophysiology of pulmonary hypertension have recently been reviewed [81].

#### 2.3.1. Monocrotaline

Subcutaneous administration of a single dose of the Crotalaria alkaloid, monocrotaline (60–105 mg/kg), to rats has been used as a non-invasive, slowly-developing, haemodynamically relevant model for primary pulmonary hypertension leading to right ventricular hypertrophy [82,83]. Right ventricular performance was enhanced in monocrotaline-treated rats without heart failure, yet  $\beta_1$ -adrenoceptor density and adenylate cyclase activity were selectively decreased in the right ventricle [84] as were isoprenaline-induced responses in isolated right ventricular myocytes [85] and noradrenaline-induced positive inotropic responses in right ventricular papillary muscles [86]. Similar changes have been reported in the failing right ventricle of patients with primary pulmonary hypertension [87]. The systemic effects of monocrotaline killed about 20% of rats within the first few days [88]; this experience does not appear to be general.

#### 2.3.2. Hypoxia

Secondary pulmonary hypertension caused by hypoventilation can be produced in rats as a model for humans

by prolonged exposure to normobaric hypoxia (for example, 2 weeks with 10% O<sub>2</sub>, [89]). Hypoxia in rats produces characteristic morphological changes in the pulmonary vasculature, especially an extension of smooth muscle into more peripheral pulmonary arteries and reduction in their number [90]. The synthesis of the vasoconstrictor, endothelin, is increased and its actions on local ET<sub>A</sub> receptors induces hypertension, vascular remodelling and right ventricular hypertrophy [89]. The role of the endogenous vasodilator, NO, in hypoxia-induced pulmonary hypertension is unclear: both low NO due to hypoxia-induced inhibition of uptake of its precursor, L-arginine [91], and upregulation of endothelial NO synthase [92] have been reported.

Right ventricular hypertrophy develops in humans living at high altitude. This has been simulated in rats in a barochamber, for example at 7000 m for 8 h/day, 5 days a week for 24 exposures [93] or continuously for 14 days [94]. Rats subjected to hypobaric hypoxia develop pulmonary hypertension and right ventricular hypertrophy with increased peak indices of mechanical performance [95] and an increased collagen deposition partly reversible by enalapril treatment [93].

Both monocrotaline treatment and hypoxia appear to produce similar cardiac changes, especially selective right ventricular hypertrophy, as in human pulmonary hypertension, although the pulmonary changes do not seem to be comparable in rats and humans [96]. Since alveolar hypoxia is often the stimulant of the pulmonary vasoconstriction that underlies the hypertension in humans, the hypoxia models probably better mimic the human disease. These models fulfil the other criteria as useful models of human pulmonary hypertension.

## 3. Cardiac hypertrophy and failure

Cardiac hypertrophy is an increase in the mass of the contractile and ancillary proteins of the heart above that which is normal for the given stage of its maturation growth [97]. In its initial stages, the hypertrophied ventricle is able to compensate in the face of an increased workload, but in the later stages, the diastolic and eventually the systolic properties of the left ventricle become impaired causing decompensation, and this leads to heart failure [97]. The commonest cause of cardiac hypertrophy is hypertension, and hypertrophy is an independent risk factor for sudden death of unknown origin, and also increases the risk of myocardial ischaemia and of ventricular arrhythmias [97].

The common definition of heart failure is the inability of the heart to provide an adequate nutrient supply to metabolising tissues [98]. Heart failure in humans can be acute, for example immediately after a myocardial infarction, in hypertensive crises or in cardiotoxicity, but heart

failure usually refers to the chronic condition following long-term hypertension or coronary heart disease [99]. Hypertension-induced heart failure is preceded by hypertension-induced cardiac hypertrophy. Valvular heart disease and cardiomyopathy are also causes of chronic heart failure. Left heart failure is the most common initial symptom and is associated with an increased pulmonary capillary pressure which in turn causes an increase in the pulmonary venous system pressure to impair respiration [100]. This progression is modified by reactive pulmonary vasoconstriction and obliteration of small pulmonary arteries which helps to decrease pulmonary capillary pressure and to protect the lungs from oedema but has the disadvantage of causing an increase in pulmonary artery pressure (pulmonary hypertension) that ultimately causes right heart failure [100]. The heart responds to pressure overload by hypertrophy in the form of wall thickening and a reduced cavity size. In the hypertrophied heart, the heart cells start to die and this myocyte necrosis is associated with fibroblast proliferation and expansion of the extracellular matrix. Programmed cell death (apoptosis) rather than necrosis has been shown to be the key event in end-stage human heart failure [101–103]. The heart is dilated in the final stages of heart failure [100]. This chronic condition develops slowly in humans and is associated with compensatory changes in other organs including the kidney, as well as in the peripheral vasculature and skeletal muscle. In human heart failure, neuro-humoral systems become activated increasing the circulating levels of noradrenaline, angiotensin, aldosterone and atriopeptin [98].

Reviews of animal models of heart failure [104–106] have all generally concluded that no one animal model can mimic entirely any one pattern of human heart failure. Nevertheless many different models have been developed and most are useful in evaluating particular aspects of failure (mechanisms in pathogenesis, drug intervention) and can provide information not available in the clinic. The choice of model, established or new, should be based on a particular question. Kept in perspective, and used in this way, models complement clinical experience and extend our understanding of cardiovascular disease. Most humans with heart failure present in the later stages; thus models can be particularly useful as they allow study in the early stages.

In this review, we will consider whether some of the presently used rat models of heart hypertrophy and failure (Table 1) are appropriate as models of the human disease. We have chosen to emphasise models that attempt to produce heart failure by hypertension and coronary artery disease, the most common causes of human heart failure, which occur together in 80% of patients with heart failure [99]. The major problems with all heart failure models are controlling the onset, rate of progression and degree of heart failure, with particular difficulty in producing a stable level of failure.

## 4. Hypertrophy

### 4.1. Spontaneously hypertensive rats

The SHR is a commonly-used model of chronic hypertension (see above) which progresses to heart failure during the last six months of their lifespan of about 2 years [107]. Thus, SHR should not be overlooked as a model to study the mechanisms of hypertension-induced hypertrophy as it progresses to heart failure. Electrophysiological studies have shown that action potentials from hypertrophied SHR left ventricular slabs or myocytes are prolonged [108,109]. Ion channel studies have shown impaired function of cardiac inward rectifying K channels without changes to transient or delayed outward rectifying K channels or L-type Ca channels in SHR hypertrophy [109]. Apoptosis is observed in the hearts of 8 and 16 week old SHRs [110]. Studies with multicellular SHR ventricular preparations usually show impaired contractility and responses to  $\beta$ -adrenoceptor stimulation [108] whereas hypertrophied SHR myocytes have increased contractility [111].

As hypertrophy in humans is usually associated with chronic hypertension, the SHR is a realistic model of human hypertrophy. This model also fulfils the other criteria in that it allows studies in chronic, stable disease, produces symptoms which are predictable and controllable, and allows measurement of relevant cardiac, biochemical and haemodynamic parameters.

### 4.2. Renal artery occlusion

Renovascular hypertension resulting from renal ischaemia (see above) leads progressively to left ventricular hypertrophy and failure. Hypertension in the adult heart induces concentric ventricular hypertrophy, in which wall thickness increases without chamber enlargement. This hypertrophy is characterised by a lateral increase in the size of the myocytes rather than an increase in the number of cells or average myocyte length [112]. About 12 weeks after surgery, 2K1C rats show left ventricular heart failure with a 35% increase in left ventricular weight, increased left ventricular end-diastolic pressure and wall stress with reduced stroke volume and cardiac output together with marked ventricular fibrosis [113,114].

### 4.3. Pressure loading by outflow constriction

Partial aortic constriction by aortic banding leads to a rapid increase in cardiac load and therefore cardiac hypertrophy. Under anaesthesia, a left thoracotomy is performed to expose the ascending aorta which is constricted to about 30% of the original cross-sectional area with a silver clip or a Weck hemoclip [115–118]. Alternatively, a spirally cut polyethylene catheter tube is placed around the abdominal aorta to produce the aortic stenosis [119]. The

heart weight is increased by 47% in 28 days by banding [115], and a low mortality of 10–15% is associated with the operation [115,119]. This model has been used to define the changes occurring during hypertrophy, for example in cell size, myofibrils and myosin isoforms [120], incidence of apoptosis [121] and altered adrenoceptor responsiveness [122]. There is no evidence of chronic heart failure as liver enlargement or pleural or peritoneal effusions are not observed following short term banding [117]. However, superimposition of streptozotocin-induced diabetes on the hypertension of abdominal aortic constriction led to ascites, liver and lung congestion and reduced heart noradrenaline levels as signs of heart failure [123].

Outflow constriction by aortic banding is clearly a model of cardiac hypertrophy and not of heart failure, although several of the above studies have suggested it is a model of heart failure. The operative procedure is relatively easy and has a high success rate in generating cardiac hypertrophy in a short time. This model does not mimic a clinical condition and one cannot be certain that the hypertrophy associated with this short sharp pressure overload is similar to that observed with the more gradual process of essential hypertension in humans.

Right ventricular hypertrophy independent of pulmonary hypertension can be produced by increasing right ventricular pressure following pulmonary artery banding. In 7 week old rats, banding to an internal diameter of 1.4 mm for twelve weeks led to right ventricular hypertrophy and an increased collagen fraction in the right ventricle [124]. This model would appear to mimic a minor cause of right ventricular dysfunction in humans.

#### 4.4. *Catecholamines (isoprenaline and noradrenaline)*

Heart failure is characterised by activation of the sympathetic nervous system leading to high circulating noradrenaline concentrations which correlate with cardiovascular morbidity [125]. High noradrenaline concentrations are associated with  $\beta$ -adrenoceptor downregulation [126]. Noradrenaline as the sympathetic neurotransmitter would seem to be the only relevant catecholamine for comparison with humans. Noradrenaline infusion leads to selective left ventricular hypertrophy; cAMP-mediated positive inotropic responses were reduced in the hypertrophied left ventricle [127]. Unlike noradrenaline, isoprenaline is a nonselective  $\beta$ -adrenoceptor agonist producing no  $\alpha$ -adrenoceptor-mediated vasoconstriction. The isoprenaline-infused rat has been used to study desensitization of the adenylate cyclase signalling pathway [128,129]. Isoprenaline-treated rats developed myocardial necrosis and a progressive enlargement of the left ventricular cavity out of proportion to mass, as in humans with discrete myocardial infarction [130]. These studies have not measured circulating noradrenaline or isoprenaline concentrations and therefore a comparison with levels in human heart failure is not possible. Further, there are no chronic

studies of catecholamine-infused rats to determine whether these rats develop heart failure.

Phaeochromocytomas produce very high catecholamine concentrations, usually much higher than in heart failure. Thus, rats with this transplantable tumour may be a suitable model for the pathological effects of chronic excess catecholamine concentrations but are unlikely to be relevant for chronic heart failure research. These rats develop cardiomyopathy and a functional desensitisation of  $\beta$ -adrenoceptor function [131] but have not been further studied as models of heart failure.

#### 4.5. *Transgenic rats*

Transgenic techniques are now increasingly used since they offer the possibility of analysing responses by selected genes [132]. The most commonly used species for transgenic experiments is mice but their small size limits their usefulness in cardiovascular research as few techniques are available for functional studies. Since the renin-angiotensin system is pivotal in controlling the cardiovascular system, the murine Ren-2 gene was chosen to generate transgenic rats [133]. Male rats have a sustained angiotensin II-dependent increase in blood pressure with low circulating renin levels thus providing convincing evidence for the physiological significance of tissue renin-angiotensin systems. At 12–14 weeks, male transgenic rats have concentric cardiac hypertrophy but no dilatation or any signs of heart failure, and downregulation of  $\beta_1$ -adrenoceptors [134]. Female Ren-2 transgenic rats have been used to study the interplay between the renin-angiotensin system and oestrogen in the pathogenesis of hypertension [135,136]. Since this transgenic rat line [TGR(mREN2)27] is a rat model of hypertension with a precisely defined monogenetic defect, it therefore cannot be considered as a genuine model of polygenic human hypertension [133]. Further, human hypertension is usually associated with normal or high plasma renin concentrations. However, this model may allow a clearer understanding of the role of local renin-angiotensin systems in cardiovascular disease [137]. Transgenic rats expressing the human angiotensinogen gene have been used to test the functional importance of the local human renin-angiotensin system [138]. These results indicate that transgenic rats are becoming an important tool in understanding hypertension.

Angiotensin converting enzyme (ACE) produces the physiologically active peptide, angiotensin II. Local expression of ACE in the rat carotid artery [139] and of NO synthase in cardiomyocytes [140] were achieved using *in vivo* gene transfer techniques. These techniques may become important for defining the role of paracrine or autocrine substances in vascular biology and hypertension by making possible the comparison of segments with overexpression of these factors and adjacent nontransfected vessel or muscle segments.



## 5. Heart failure

### 5.1. Spontaneously hypertensive rats with failure (SHRs-F)

The SHR-F has been long known to have many similarities to human essential hypertension-induced heart failure [141] including the important feature that impaired myocardial performance is a late feature that precedes overt failure. More recently, Bing et al. [142] have shown that at 18–24 months, 57% of the SHRs have cardiac decompensation and they have further compared these animals to age-matched SHR without failure (SHR-NF) and Wistar Kyoto normotensive (WKY) rats. The SHR-F can be identified outwardly as they become less active and well groomed and develop occasional tachypnoea which becomes more persistent and turns into laboured respiration. Left, but not right, ventricular hypertrophy is a feature of the young adult SHR while hypertrophy of the right ventricle is a reliable marker in the cardiac decompensation of failure [142]. Pleuropericardial effusions and atrial thrombi are also commonly observed in SHR-F. Echocardiography was used to show that the SHR-F had increased diastolic and systolic volumes and decreased ejection fractions with cardiac catheterization demonstrating an increased left ventricular end-diastolic pressure [142]. Increased apoptosis of cardiomyocytes is observed in the SHR-F compared with the SHR-NF [143] which may be caused by increased endothelial cell NO synthase in cardiomyocytes [140]. The biochemical changes underlying the pathophysiology of heart failure are unclear; however, alterations in NO synthesis by myocardial NO synthase have been implicated [144].

The SHR-F model is a good model of human hypertension-induced heart failure as these conditions have many features in common, and thus will allow measurement of relevant cardiac, biochemical and haemodynamic parameters. In the SHR, failure occurs around 2 years of age and may therefore be compromised by the effects of ageing [142]. This may make the interpretation of the rat data more difficult but it could also be argued that, since human heart failure is also commonly complicated by the effects of ageing, the aged SHR is the more realistic model. As this is a non-intervention model, there is no need for skilled technical assistance or mortality associated with surgery. The major disadvantage of the SHR-F model is the extended time frame and therefore increased costs of these experiments compared with other models of heart failure.

### 5.2. Hypertensive HF-prone rats (SHHF)

A hypertensive heart failure-prone rat strain, SHHF/Mcc-cp or SHHF, that develops failure at a younger age than SHR was created by mating Koletsky rats heterozygous for the corpulent gene with SHR [145]. These rats are spontaneously hypertensive, 25% are obese and mani-

fest hyperinsulinaemia and diabetes (males) or abnormal glucose tolerance (females). Obese rats develop fatal dilated cardiomyopathy between 10 and 12 months (males) or 14 and 16 months (females) of age while lean male SHHF develop hypertension and left ventricular hypertrophy by 3 to 5 months of age and overt heart failure by 16 to 20 months of age [146–148]. The circulating levels of noradrenaline, renin, aldosterone and atriopeptin are all raised [146] and there are abnormalities in cardiac structure such as biventricular hypertrophy, myocyte enlargement and increased interstitial fibrosis [145]. Echocardiography showed eccentric hypertrophy in 10–12 month old non-failing male SHHF rats in contrast to the concentric hypertrophy in SHRs of the same age [149]. Expression of the genes for the enzymes controlling mitochondrial fatty acid  $\beta$ -oxidation was reduced both in heart failure stages of SHHF rats and in human heart failure [150].

This model seems to have many similarities to the human disease when it is a slowly developing mix of hypertension, hyperinsulinemia and diabetes. The model needs to be more fully characterised but, because of its time course, neurohumoral changes and lack of technical intervention, has considerable potential as a model of the development of human heart failure. The disadvantages of this model are the variable expression of symptoms and expense as it is a slowly developing model, although age-induced changes should play a lesser role than in the SHR-F.

### 5.3. Dahl/Rapp salt-sensitive rats

Understanding salt-sensitive hypertension in humans has been helped by the introduction of inbred rat models, especially the Dahl/Rapp salt-sensitive and salt-resistant rats [151]. The development of hypertension and heart failure in the Dahl/Rapp salt-sensitive rat can be controlled by titration of the amount of salt in their diet, and is more rapid and greater in male than female rats [152]. Addition of 8% NaCl to the diet at 6 weeks of age leads to concentric left ventricular hypertrophy at 11 weeks, and marked left ventricular dilation at 15–20 weeks which leads to laboured respiration, left ventricular hypokinesia and sudden death [153]. In human heart failure, specific organ (heart, lung, liver) enlargement is a feature and this is also observed in this salt-sensitive model of heart failure. The isometric contractions of the isolated left papillary muscle of the Dahl/Rapp salt-sensitive rat heart are decreased and prolonged in the hypertrophied muscle and further decreased and prolonged in end-stage failure [153]. There is also a reduction followed by a loss in response of the left papillary muscle to isoprenaline in this model [153]. These contractile parameters are very similar to those reported in end-stage human heart failure. The corresponding normotensive control strain is the Dahl/Rapp salt-resistant rat; as with SHR and WKY rats, Dahl rats show more genetic polymorphism than expected [26]. Recent studies have shown that modulation of NO pro-

duction from L-arginine is integrally involved in the development of hypertension in these salt-sensitive rats [151,154].

Salt is considered to be one of environmental triggers for human hypertension. However, the appropriateness of the model may be questioned as the parallel group of humans who are as exquisitely salt-sensitive as the Dahl/Rapp salt-sensitive rat may be a subset of African-Americans with inherited hypertension, salt sensitivity and a predisposition to kidney damage [151] rather than a significant proportion of hypertensive humans. The symptoms of the model do however have many characteristics in common with the human disease. Other advantages are that it is easy, non-invasive, relatively quick and consistent. This model is potentially useful in studies of the role of the L-arginine:NO pathway as a mechanism by which a well-compensated hypertrophied heart eventually decompensates.

#### 5.4. Coronary artery ligation

The most commonly used model of heart failure is complete coronary artery occlusion by ligation. A left thoracotomy is performed under ether anaesthesia; gentle pressure on the right side of the thorax exteriorizes the heart, and then the left coronary artery is ligated [155]. In this initial and more recent studies (for example [156–158]), a high rate of mortality, up to 50%, occurred following this drastic surgery. In Pfeffer's study, 46 of the surviving 90 rats at 3 weeks did not have signs of myocardial infarction at autopsy, and 44 had infarcts of 4–59% of the left ventricular endocardial circumference. This variation in infarct size observed after 3–4 weeks usually results in the grouping of rats into a small infarct group, about 20% of the left ventricular circumference which is considered a model of myocardial infarction, and a major infarct group, about 40–50%, which is considered the model of heart failure [156–158]. In their original study, Pfeffer et al. [155] noted that the rats that had small infarcts did not have outward signs of myocardial infarction and heart failure (no ascites, peripheral oedema, respiratory distress or failure to groom). There was also no change in body weight or left ventricular weight and heart rate was normal but there was a gain in the weight of the right ventricle, an increase in ventricular and right atrial pressures, and a decrease in arterial pressure. In those rats with a large infarct, the right and left ventricle filling pressures were increased and cardiac output was decreased after 3–4 weeks indicating that the rats were in failure [155,156]. In these large infarct rats, there is hypertrophy of the septum but no weight gain of the left ventricle due to loss of viable myocardium [156]. Both necrosis and apoptosis are associated with the infarct in the coronary artery ligation model [159]. Large myocardial infarcts are also associated with increased circulating level of atriopeptins and renin [158].

In their original report, Pfeffer et al. [155] acknowledged that coronary artery ligation was not analogous to the pathogenesis of coronary artery disease or to infarction in humans as the model initially contained an otherwise normal myocardium and coronary arteries. The inability of coronary artery ligation to model any common cause of heart failure is a major disadvantage. Other problems with this model are the high mortality of the rats and the variation in infarct size, and that it does not have a progression from compensation to endstage heart failure. These disadvantages are much less obvious following coronary ligation in Lewis inbred rats in comparison with Sprague-Dawley rats [160]. The advantage to this model is that it quickly, and therefore economically, produces some rats with some of the symptoms of heart failure. However, we consider that the disadvantage of not modelling any cause of human heart failure far outweighs any advantages.

Ischaemic heart disease in humans results from chronic non-occlusive coronary artery narrowing. This can be reproduced in rats by ligation of a probe held in contact with the left coronary artery and then removal of the probe resulting in an average 53% reduction in luminal diameter and 43% mortality within 1 month [161]. The reduction in coronary blood flow leads to a predictable progression to impairment of left ventricular haemodynamic performance and heart failure [162]. Although the major cause of the chronic narrowing of human coronary arteries is atherosclerosis, usually of several vessels, rather than partial ligation, this model allows a slower, more realistic development of ischaemic heart failure than complete coronary ligation.

#### 5.5. Microembolization of coronary vessels

A more appropriate model of human heart failure may be produced by blockage of smaller intramyocardial vessels, for example by microspheres, rather than blockage of one of the larger epicardial coronary arteries. In the anaesthetised rat, a catheter is placed into the left ventricle by way of the external right carotid artery in order to deliver a suspension containing about 150–200 000 plastic microspheres of 15  $\mu\text{m}$  diameter to the coronaries during a temporary occlusion of the ascending aorta [163]. The embolized rats have a small decrease in heart rate, stroke volume and cardiac index and an increase in total peripheral resistance and left ventricular end-diastolic pressure [163].

This model of heart failure is relatively new and only a preliminary characterisation has taken place. It seems likely that the model created by this technique will have similar characteristics, advantages and disadvantages to the coronary ligation model, and in the absence of a diseased myocardium cannot be considered an appropriate model. It would be of interest to compare mortality and variability data in both microembolization and coronary ligation models.

### 5.6. Adriamycin (doxorubicin)

The use of adriamycin in the treatment of human cancers is associated with the side effect of cardiotoxicity that can lead to congestive heart failure and death [164–166]. Rats treated with adriamycin are usually used to investigate the mechanisms of cardiotoxicity and ways of preventing it [167–169] but occasionally used as a model of heart failure [170]. Treatment of rats with adriamycin, 2 mg/kg/week, for 12 weeks results in a decreased cardiac output, decreased blood pressure, pleural effusions, ascites and hepatic congestion [170]. There is no change in heart weight but there are pathological changes in the myocytes such as cytoplasmic vacuolation, disorganisation of myofibrils and some necrosis; adriamycin toxicity is not all as a result of cardiotoxicity, as anaemia, thrombocytosis and decreases in serum albumin are also observed [170]. 21 of 41 rats did not survive the 12 week treatment with adriamycin because of gross pathological changes consistent with heart failure [170].

The main advantages of this model is that it is a simple technique, non-invasive, economical and has a short time course. It is an appropriate model of adriamycin cardiotoxicity but does not model any other type of heart failure. Thus this model is not useful in determining the mechanisms or prevention of heart failure following decompensation following chronic hypertrophy.

### 5.7. Alcoholic heart disease

Chronic ingestion of ethanol by humans is often associated with alcoholic heart disease resulting in ventricular dysfunction and heart failure; alcohol abuse may be a major cause of cardiomyopathy [171]. Male rats maintained chronically on oral ethanol (30% in their drinking water for 8 months) developed myocardial damage, especially multiple areas of myocyte loss and replacement fibrosis, and ventricular wall remodelling resulting in ventricular dysfunction; all necessary ingredients in the development of alcoholic heart disease [172]. Chronic ethanol treatment in rats produced moderate hypertrophy with significantly decreased responses to phenylephrine, glucagon and dobutamine [173]. Short-term ethanol treatment for 8 weeks produced no signs of heart failure but showed early decreases in  $\alpha_1$ -adrenoceptor and muscarinic receptor densities without any changes in  $\beta$ -adrenoceptor density or adenylate cyclase activity [174].

This would seem to be an ideal model of alcoholic cardiomyopathy demonstrating slowly-developing symptoms similar to those in humans but, like the adriamycin model, would not be useful in determining the mechanisms of the more common forms of heart failure due to either coronary artery disease or hypertension or both.

### 5.8. Myocarditis

Giant cell myocarditis is a lethal inflammatory heart

disease characterized by the appearance of multinucleated giant cells in lesions. This disorder is not associated with preceding infection and no pathogen has been isolated, and thus it is presumed that autoimmune mechanisms are involved. Myocarditis is frequently characterised by congestive heart failure and is occasionally lethal. Recently a new rat model of both acute and chronic heart failure following autoimmune myocarditis has been described in which the myosin fraction, extracted from the human heart at autopsy from patients who had no history of myocarditis or heart failure and no inflammatory lesions, is mixed with Freund's adjuvant supplemented with *Mycobacterium tuberculosis* and injected subcutaneously into the foot pads of Lewis rats [175]. In order to get a more effective sensitisation, *Bordetella pertussis* vaccine was also given i.v. [175]. This procedure does not produce myocarditis in mice, guinea-pigs or other strains of rats. In the acute phase (after 4 weeks), there is massive pericardial effusion, mild to moderate pleural effusion, gray swollen patch areas on the cardiac surface, an increase in heart weight with interstitial oedema and cellular infiltration, and inflammation with the accumulation of neutrophils, lymphocytes and macrophages [175]. The chronic phase (after 3 months) is characterized by diffuse myocardial fibrosis without significant inflammation [176]. In vivo haemodynamic measurements have shown left ventricular systolic and diastolic dysfunction [176]. The inflammation and course of myocardial damage appear to be modulated by cytokines and excessive amounts of NO produced by inducible NO synthase [177,178]. This model has been used in a study to evaluate the usefulness of cyclosporin, prednisolone and aspirin in the treatment of myocarditis [179]. The advantage of this model of myocarditis is the production of severe symptoms unlike earlier models which gave mild lesions without congestive heart failure [175]. This model is useful in evaluating the mechanisms and treatment of myocarditis but has little or no relevance to heart failure of other etiologies.

Chronic Chagas disease, produced decades after infection with the parasite, *Trypanosoma cruzi*, is the leading cause of heart failure in South and Central America. The heart is the most commonly affected organ showing lymphocytic myocarditis, diffuse interstitial fibrosis and myocyte hypertrophy. These pathological changes were reproduced in rats chronically infected for 8 months with *T. cruzi* [180]. This model deserves further investigation since adequate treatment of the symptoms of chronic Chagas' disease would ameliorate this major public health problem in South America.

### 5.9. Pulmonary hypertension

The monocrotaline model is commonly used as a model of pulmonary hypertension (see above) and occasionally used as a model of heart failure. Right ventricular heart failure develops as accumulation of liquid in the peritoneal and pleural spaces in about 4 weeks after monocrotaline

injection [88,181,182]; at six weeks, heart failure is severe with laboured respiration and often large volumes of fluid in the chest [86]. Positive inotropic responses to noradrenaline but not calcium chloride are reduced six weeks after monocrotaline treatment [86], as in human heart failure [183]. However, several conditions not normally associated with human heart failure have been reported in monocrotaline-treated rats such as hepatic cirrhosis and megalocytosis, venoocclusive disease [182] and thrombocytopenia [184]. The major advantages are the ease and rapidity of producing the model. The disadvantages of the monocrotaline model are the effects not associated with heart failure. As a model of one of the lesser causes of heart failure, the monocrotaline model may be useful in evaluating pharmacological interventions for pulmonary hypertension-induced right heart failure, but it is hard to see how this could be of benefit to the majority of patients with heart failure associated with systemic hypertension and coronary artery disease. No studies of heart failure induced by chronic hypoxia in rats were found, although this may be a relevant model of secondary pulmonary hypertension-induced failure.

#### 5.10. Aortacaval fistula (shunts)

Volume overloading produces cardiomegaly in humans [185]; substantial volume overload-induced cardiac hypertrophy can be produced in rats following large arteriovenous shunts. A mid-line incision is made in the anaesthetised rat to expose the abdominal artery and vena cava, which are then isolated using bulldog clamps [186]. Under a dissection microscope, 1 mm openings are made in each vessel and then the opposing edges are stitched together. The clamps are removed and the patency of the fistula is confirmed visually by the presence of mixing arterial blood in the vena cava [186]. End-to-side anastomoses between the left ilio-lumbar vein and the aorta produced shunts of about 1.25 mm diameter [187,188]. Similar shunts can be achieved by puncturing the aorta with an 18 gauge needle, perforating its opposite wall and penetrating the vena cava. The aorta is then clamped, the needle taken out and a drop of cyanoacrylate glue used to seal the aorta puncture point [189]. Shunts have also been created in SHR rats [190]. Aortacaval fistula below the renal arteries produced either compensated or decompensated heart failure after 6 days with 35 or 65%, respectively, increases in heart weight and all signs of heart failure such as ascites, oedema and dyspnoea [191]. Rats with aortacaval fistula are a model of high cardiac output with decreased mean arterial blood pressure, increased right atrial pressure, increased left ventricular end-diastolic pressure and marked hypertrophy of both ventricles with dilation of the ventricular cavities [186–189]. Ligation of the shunt led to significant, but not complete, reversal of the cardiac hypertrophy showing that myocytes can remove recently added series sarcomeres [192].

Aortacaval fistula procedures have a very high mortality rate (77%, 133; 47% 134) but this is much reduced with the revised procedure [189] to less than 5% [193]. Flaim et al. [186] claim that aortacaval fistula is a form of heart failure because it met the current definition as ‘that condition in which the heart is no longer able to pump an adequate supply of blood in relation to the venous return and in relation to the metabolic needs of the body at the particular moment’. They did however concede that the performance of these hearts is normal and that the production of aortacaval fistula was a model to study compensatory mechanisms associated with heart failure [186]. Most indexes of cardiac function were normal or elevated 5 months after surgery despite renal and hepatic congestion [188] although echocardiography showed abnormalities in left ventricular filling at 18 weeks [194]. The combination of hypertension (SHR) and rats with aortacaval fistula did not appear to be a relevant model of congestive heart failure and provided no new concept or idea compared with aortacaval fistula in normotensive rats [190]. It seems unlikely that the compensatory mechanisms following aortacaval fistula mimic the compensatory mechanisms in human heart failure [186].

## 6. Conclusions

Cardiovascular disease remains the major cause of death in Western countries. The use of relevant models for human cardiovascular disease may provide useful information allowing an understanding of the cause and progression of the disease state as well as potential therapeutic interventions. The most common pathophysiological changes in the human cardiovascular system – hypertension, cardiac hypertrophy and heart failure – have been successfully reproduced in rat models. There is an extensive range of rat models; most mimic some aspects of the relevant human disease. No model mimics exactly all the symptoms of the human disease, partly because many of the changes in the human disease are not thoroughly understood, and this aim is probably illusory. As human hypertension, hypertrophy and heart failure have many different genetic and environmental causes, it may be appropriate to study different rat models. The major deficiency in many rat models is reproducing the slow onset of human disease; important exceptions are the SHR-F and SHHF as models of heart failure. Several models do not reproduce the concurrent activation of homeostatic mechanisms in humans, especially neuro-humoral changes during heart failure. Further, many rat models produce pathophysiological changes which are rarely seen in the human disease state. However, a thorough understanding of both the advantages and disadvantages of each model is necessary if the results are to be extrapolated to humans. This requires further studies on

both rats and humans and critical evaluation of the results of these investigations.

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