Review

Surgical animal models of heart failure related to coronary heart disease

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Abstract

Coronary heart disease is caused by atherosclerotic narrowing of coronary arteries. It accounts for about two-thirds of heart failure cases, which are frequently secondary to myocardial infarction. Despite considerable progress in the understanding and management of heart failure, its incidence, prevalence and economic burden are steadily increasing. Therefore, efficient preventive and therapeutic measures are urgently needed. In order to investigate the mechanisms involved in the pathogenesis of coronary heart disease-related heart failure and to develop therapies, appropriate animal models are indispensable. According to the aetiology of this disorder, surgical models are based on various methods allowing for the narrowing or occlusion of coronary arteries. Depending on the duration and extent of the impairment of coronary blood flow and its consequences for cardiac tissue, these are classified as models of myocardial infarction, cardiac ischemia/reperfusion injury, or chronic cardiac ischemia. In addition, factors such as species, strain, and gender of the laboratory animals also significantly contribute to the pathophysiology of the induced disorder and, therefore, have to be taken into consideration thoroughly when an animal model is to be established.

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1. Introduction

Current statistics from the British Heart Foundation [1] and the American Heart Association [2] show that cardiovascular disease is still the leading cause of deaths in Europe and the US, accounting for 49% and 37.3% of all deaths, respectively. Out of all cardiovascular deaths in Europe and in the US, coronary heart disease (CHD) is the single largest killer: More than 1 in 5 deaths are from CHD [1,2]. Moreover, CHD is also the leading cause of premature permanent disability in workers as well as of congestive heart failure (HF); more than 50% of all cases are attributed to CHD [3]. With the great improvement of diagnostis and therapies, more and more patients with acute coronary syndrome (ACS) and myocardial infarction (MI) survive, and in most cases inevitably develop HF. Despite considerable progress acquired in the understanding and management of HF, it remains associated with a one-year mortality of 20% and a 5-year mortality still above 50% [4].

In order to prevent and manage CHD-related HF more effectively, it is necessary to understand the pathophysiological mechanisms underlying this disorder more thoroughly and to develop novel therapeutic approaches. Therefore, animal models closely mimicking the characteristics and development of human MI and HF related to CHD are indispensable.

In an animal model the induced disorder should closely resemble the disorder in human with respect to structural and functional characteristics. The most important clues how to create an animal model fulfilling this condition as far as possible can be obtained from the aetiology of the disease. In the case of CHD it is the chronic narrowing by atherosclerotic plaques or the acute occlusion by thrombosis (MI) of...
coronary arteries, which finally lead to the development of HF [5]. Accordingly, various strategies and methods have been developed and applied in different species of laboratory animals to induce coronary artery narrowing or occlusion. These include the induction of hypercholesterolemia, which is the most important risk factor for atherosclerosis, by feeding a fat/cholesterol-rich diet. This caused the development of coronary atherosclerosis and subsequent occurrence of myocardial infarction at least in pigs [6], rats [7] and two non-human primate species [8]. However, time point and site of coronary occlusion(s) occur accidentally in such animals. Therefore, these models are inappropriate for scientific projects dealing with the characterisation of the secondary disorders MI and HF or with the development of novel therapeutic approaches for the treatment of these disorders. The lack of inducibility and predictable disease progression is also a problem associated with such models of atherosclerosis or HF based exclusively on specific gene manipulations by transgenic or gene targeting technologies (for a review see Chu et al. [9]). In addition, in the latter case the aetiology of HF is completely different from that of naturally occurring CHD-related HF.

In contrast, the surgical induction of MI or ischemia in an animal model has the advantage to facilitate a precise timing, location and extent of the coronary event, leading to more reproducible results. Therefore, this approach is indispensable in cardiovascular research. In the present review the most important surgical models of CHD-related MI and HF are described. Their advantages and disadvantages as well as animal-related factors significantly affecting the pathophysiological characteristics of the models such as species, strain and gender are discussed.

2. Surgical induction of MI or ischemia

According to the duration and extent of coronary blood flow impairment and cardiac ischemic injury, surgical models can be classified as related to MI, cardiac ischemia/reperfusion (I/R) injury and chronic cardiac ischemia.

2.1. Models of myocardial infarction

Various methods have been applied to induce MI and/or ischemia in animals via occlusions of coronary arteries (Fig. 1). The most common techniques will be described in the following sections.

2.1.1. Hydraulic occluder and ameroid constrictor

These methods are especially used in larger animals (e.g. pig) allowing for the complete or partial occlusion of coronary artery branches. Accordingly, they are suitable to induce MI and HF [10,11], as well as coronary stenosis for the investigation of hibernating myocardium (see Section 2.3). For occluder implantation a left anterolateral thoracotomy is performed. After incision of the pericardium, a branch of the left coronary artery (LCA) is dissected and the hydraulic occluder is placed around the vessel. It is then inflated to induce partial stenosis (see Section 2.3) or complete occlusion. To control the degree of occlusion and record the downstream flow through the LCA, an ultrasonic flow probe can be placed distally to the occluder during the same procedure [12].

An ameroid constrictor is implanted in a similar way but occlusion is achieved by a different mechanism. At body temperature, the ring around the vessel narrows gradually because of the hygroscopic property of the casein plastic material. As the hydraulic occluder the ameroid constrictor allows for the generation of big animal models for the investigation of MI-induced HF [10,11].

2.1.2. Coronary artery ligation

Coronary artery ligation was first applied in dogs for the investigation of HF [13]. Following orotracheal intubation and left thoracotomy, the proximal left anterior descending coronary artery (LAD) is dissected and ligated, and, thus, MI is induced. However, the mortality of this procedure was reported to be more than 50% due to malign ventricular tachycardias in the acute phase. Furthermore, infarctions are small in most cases (averaging 21% of the left ventricle), which is potentially due to a high number of sub-pericardial collaterals in this species. Therefore, only minor haemodynamic abnormalities were observed [13]. Moreover, the model is time-consuming, expensive and is facing increasing criticism with respect to animal protection efforts.

However, the application of this method in the pig caused a mortality of only 20%, mainly due to acute ventricular tachycardias and ventricular fibrillation [14]. Since Muller

Fig. 1. Schematic illustration of various techniques to induce myocardial ischemia and infarction. A: Occlusion of a coronary artery using a U-shaped occluder. While twisting the screw and pushing the plate, a stepwise occlusion can be induced. B: Stenosis induced by a ring-shaped occluder. Occlusion is achieved by hydraulic compression (hydraulic occluder) or by expansion of hygroscopic casein plastic material (ameroid constrictor). C: An intracoronary balloon catheter to induce embolism. D: Ligation of the coronary artery by a moistened band (large animals) or thin suture (laboratory rodents).
et al. [15] already demonstrated that the incidence of ventricular fibrillation and also the duration of ventricular tachycardias can be significantly decreased in the pig by the administration of the beta blocker Bucindolol 30 min prior and 10 min after ligation of the LAD, the mortality probably can be reduced further.

The induction of left ventricular MI in rats has been established by Pfeffer et al. [16]. In brief, after anaesthesia, oro-tracheal intubation and thoracotomy, the heart is rapidly exteriorised and the LCA is ligated in the proximal segment using a thin thread. The occlusion of the artery can be recognised by blanching of the tissue distal to the ligation. Rats with infarctions greater than 46% develop congestive HF after 21 days with elevated filling pressures, reduced cardiac output, and a minimal capacity to respond to pre- and after-load stress. The degree of impairment of LV function is directly related to the extent of myocardial loss [16]. The mortality seems to be strain-dependent. In a comparative study the mortality of Sprague-Dawley rats was 36%, whereas in Lewis inbred rats it was significantly lower (16%) [17] (see Section 3).

In recent years the mouse is the species increasingly used to characterise MI induced by coronary artery ligation (see Section 3). The surgical procedure to induce MI in the mouse is similar to the rat model [18]. However, a microscope is required to accurately detect and ligate the relatively small LCA of the mouse (Fig. 2A). Mortality associated with MI induction in mice is about 37–50% [19,20], but may be reduced by sublingual application of nitroglycerin (10–50 μg).

Fig. 2. Ligation of the left coronary artery (LCA) in the mouse. A: The ventilated mouse is placed on a heater mat (1) and the chest is opened left sided to have access to the left ventricle (2). After disruption of the pericardium one main branch of the LCA is ligated using thin Prolene suture (3,4). Sudden regional paleness indicates the ischemic area. The site of ligation is indicated by a yellow arrowhead (3). B: In the reperfusion model this technique is slightly modified. In order to facilitate the release of the ligation and to protect the site of occlusion during thread release, a small piece of polypropylene tube is inserted in the suture loop during occlusion.
after surgery (Nikol and coworkers, unpublished observation). Most cases of death occur within 1 h after ligation, probably due to ventricular fibrillation and severe acute HF.

2.1.3. Coronary artery embolisations

Another large animal model of ischemic cardiomyopathy is based on intracoronary embolisations with microspheres [21], agarose or polystyrene beads or the intracoronary injection of thrombin and autogenous blood with fibrinogen [22]. In the approach developed by Sabbah et al. [21] closed-chest dogs undergo 3 to 9 catheter-mediated intracoronary embolisations performed 1–3 weeks apart. Embolisations are discontinued when the left ventricular (LV) ejection fraction is less than 35%. In this model the LV end-diastolic pressure (LVEDP) increases, accompanied by a significant raise of pulmonary artery wedge pressure and systemic vascular resistance. At 3 months after the last embolisation, the animals exhibit patchy myocardial fibrosis and LV hypertrophy, as well as increased plasma levels of atrial natriuretic peptide (ANP) and norepinephrine. The number of β-AR and L-type calcium channels decrease [23] and the activity and protein levels of SR Ca²⁺-ATPase drops [24].

Coronary artery embolisations are induced percutaneously. Therefore, the risk of severe inflammatory complications following surgical interventions like thoracotomies is reduced. Moreover, this model resembles the clinical situation in patients with HF and acute coronary syndrome due to embolisation of atherosclerotic and thrombotic debris into the coronary microcirculation as well as the situation of patients with diffuse coronary artery disease such as in diabetes.

A limitation of the embolisation technique is the control of the exact location and length of coronary artery occlusion. Thus, Reffelmann et al. [25] recently developed a minimal-invasive approach to induce chronic myocardial infarctions in pigs: A flexible body comprising an open-cell foam sponge is percutaneously placed via a guide wire at a distinct position in the coronary artery. However, the follow-up period in this study was only one week and hence the safety of this method for a longer observation period has to be proven.

2.2. Model of myocardial ischemia or infarction followed by reperfusion

As thrombolysis and percutaneous transluminal coronary angiography (PTCA) are widely applied in the treatment of acute MI in human, cardiac dysfunction resulting from I/R injury – also called “myocardial stunning” – is a crucial problem to be solved. The same issue often occurs in cardiac surgery, since reperfusion is unavoidable in operations using extracorporal circulation and cardioplegia techniques. Models used for the study of I/R injury mainly include animal models as well as isolated perfused hearts. The duration of coronary artery occlusion is crucial for the pathophysiological outcome: With increasing duration of occlusion the risk for infarction of the stunned myocardium increases.

Regional I/R in the anaesthetised animal is the standard model. Similar to the MI animal models, the coronary artery is ligated with a strip of moistened umbilical tape (for big animals) or thread (for small animals), but a small plastic tube is placed between the ligated vessel and the node allowing for easier and safe relief of the occlusion (Fig. 2B). Ischemia can be verified by the sudden regional paleness of the myocardium and ECG changes. Reperfusion is verified by the appearance of hyperaemia in the previously pale region. During the period of occlusion, the chest incision is covered with moistened gauze to prevent drying and loss of heat. In comparison to the permanent occlusion model, the reperfusion MI model leads to a higher infiltration of inflammatory cells, attenuated fibrotic remodelling and enhanced neovascularisation in the area of infarction [26].

In order to minimize interfering inflammatory effects induced by surgery, a “closed chest” ligation model of myocardial I/R injury in the mouse has been developed by
Nossuli et al. [27]: After thoracotomy, a thin suture is passed under the LAD and the ends of the suture are threaded through a 0.5-mm piece of PE-10 tubing resulting in a loose snare around the LAD. The ends of the suture are exteriorised through each side of the chest wall, the chest is closed and finally the suture ends are tucked under the skin. The ultimate I/R experiment is performed a few days later, when inflammatory cytokines have returned to baseline. By pulling the free suture ends in opposite directions the LAD is occluded and releasing them enables reperfusion.

The hydraulic occluder together with ultrasonic flow probe has also been applied to induce I/R injury in large animal models like the pig [28].

An ex vivo system especially used for the analysis of pathophysiological and electrophysiological consequences of I/R injury induced in vivo is the reperfusion chamber introduced in 1895 by Langendorff and firstly used to investigate the isolated sheep heart [29]. The construction and functional principle of this device are illustrated in Fig. 3. After explantation of the heart, the aorta is rapidly cannulated above the aortic valves and then mounted in a perfusion system with perfusion solution (i.e. Krebs–Henseleits bicarbonate buffer gassed with 5% CO₂ and 95% O₂) that supplies substrates for energy metabolism. The perfusion solution is led retrogradely into the aorta and the ends of the suture are threaded through a 0.5-mm piece of PE-10 tubing resulting in a loose snare around the LAD. The ends of the suture are exteriorised by pulling the free suture ends in opposite directions the LAD is occluded and releasing them enables reperfusion.

In pigs, the hydraulic occluder technique was used to cause partial coronary artery stenosis, hence providing a model of chronic myocardial hibernation [35–37]. With the help of a Doppler flow probe placed proximally to the occluder, alterations of artery blood flow can be evaluated and consequently controlled by the occluder. Left ventricular and aortic pressures are measured via a double-sensor Millar catheter. The implantation of a pair of ultrasonic crystals at midmyocardial depth allows for the measurement of regional wall contractility [37]. Hibernating myocardium is characterised as in patients by increased glucose uptake measured by 18FDG positron emission tomography (PET). During fasting and after dobutamine-induced stress this rise is proportional to the reduction of blood flow at rest [38]. However, two days after replacement of the occluder after a 24 h period of coronary artery stenosis histological analysis revealed various foci of myocardial tissue loss similar to the corresponding rat/mouse model (see above) [36]. Another study showed that trans-myocardial laser revascularization (TMR) improved myocardial perfusion, regional and global contractile reserve in this model [39].

The amiodar constrictor has also been used to provoke chronic coronary artery stenosis in the pig [10]. However, in comparison with the hydraulic occluder technique it lacks the predictability and reliability. The degree and progress of stenosis cannot be adjusted and after several weeks a complete occlusion of the coronary artery typically occurs [10,40]. However, the slowly and gradually increasing stenosis allows for the formation of collaterals therefore mimicking the situation seen in some patients.

2.3. Models of chronic myocardial ischemia

In the rat a model of incomplete narrowing of coronary arteries similar to the coronary artery occlusion model was established. After thoracotomy, a probe or copper wire (275 μm in diameter) is placed onto the epicardium along the LCA, and the LCA together with the probe is ligated 1–2 mm from its origin followed by removal of the probe, which results in an average reduction in luminal diameter by 42% [32]. During coronary occlusion, the ST segment of the electrocardiogram (ECG) is transiently elevated. Persisting ST segment elevation after removal of the probe suggests unwanted complete coronary artery occlusion. HF may occur as a result of chronic cardiac ischemia in this model, which has been also established in the mouse [33]. During the procedure of coronary ligation it is inevitable to include within the ligature some muscle mass, which may affect vessel stenosis. The actual level of constriction measured at death varies from a minimum of 18% to a maximum of 69% [32]. Already forty-five minutes after non-occlusive constriction in the rat, the ischemic heart exhibits increased LVEDP and LV volume, decreased thickness of LV wall and cardiac cell damage [32]. After 5–7 days, the maximal resting coronary blood flow decreases by 43% [34], foci of reparative fibrosis and myocytolytic necrosis and myocyte hypertrophy are found [34].

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3. Significance of species, strain and gender

Apart from the choice of the technique to induce the type of CHD-related disorder to be investigated the most suitable animal species has to be selected. Small laboratory rodents have the advantages of being cheap, easy to breed and exposed to fewer criticism regarding animal protection. Accordingly, larger numbers of animals can be used. Techniques such as high resolution echocardiography allowing for the accurate evaluation of heart function, determination of infarct size and quantitative characterisation of post-
infarct remodelling are already available for these small species [19,20]. In addition, haemodynamic function and electrophysiological aspects of heart rhythm of the failing or infarcted rodent myocardium can also be examined in the isolated perfused organ (ex vivo) in the Langendorff apparatus (see also Section 2.2 and Fig. 3) [20]. Recently the mouse has become the most important laboratory rodent species because of the availability of a large and further increasing number of transgenic strains, offering the analysis of the significance of certain gene functions for the aetiology and pathophysiology of CHD-related HF (see Section 4). However, there are significant physiological differences between the hearts of laboratory rodents and humans (Fig. 4). For example, cardiomyocyte action potentials of rat and mouse are characterised by a very short duration normally lacking a plateau phase; the resting heart rate is about 5 times higher than in humans and the force–frequency relation is inverse [41]. The calcium removal from the cytosol is predominated by the activity of the SR Ca\(^{2+}\)-ATPase in human and rodents. However, the Na\(^{+}/Ca^{2+}\)-exchanger activity is less relevant in rodents than in human (Fig. 4) [42].

Compared with rodents, the hearts of large animals are more similar to human hearts, both in anatomy and physiology. In pigs, the coronary vasculature is right-dominant as in 80% of human hearts. Therefore, the pig hydraulic occluder or ameroid model is often used to study ischemic heart disease. Species characterised by a collateral-rich coronary system like the dog hardly develop extensive MIs. Nevertheless, even between species with minimal coronary collateral circulation there are significant differences: Under the same conditions of I/R, the size of MI is significantly less in baboons compared to pigs [43].

The anatomy of the coronary artery system is not only different between species but may also vary significantly between individuals of a single species. Liu et al. reported that the branching and position of the LAD in Sprague-Dawley outbred rats is more heterogeneous than in Lewis inbred rats. Accordingly, LAD ligation resulted in more uniform infarct sizes in the latter indicating that the use of inbred animals is favourable over that of outbred animals to keep the degree of variance between animals as low as possible [17]. However, for the mouse specific approaches have been established which may be instrumental to keep the variability of infarct sizes as low as possible [44,45].

Besides inter- and intra-species specific variability affecting the outcome of animal studies gender-specific effects on CHD have to be considered. The cardio-atheroprotective effect of estrogens is well known from various hypercholesterolemic animal models (reviewed under special consideration of mouse models by Hodgson and Maeda [46]. Estrogens lead to a reduction in plasma cholesterol [47], inhibit vessel wall LDL accumulation [48] and reduce vascular smooth muscle cell proliferation and extracellular matrix deposition after endothelial damage [49]. Targets of estrogens may also be immunoinflammatory components of atherogenesis [50]. Consequently, an influence of estrogens on inflammatory processes and remodelling following MI cannot be excluded. Thus, male animals may more easily develop HF secondary to CHD, particularly in atherosclerotic animal models. However, modern gender medicine requires the investigation of both, males and females.

4. Recent applications of CHD-related HF animal models

The models of CHD-related HF most widely used in the last years were those based on coronary artery ligation in mice or rats primarily leading to MI or I/R injury. The most remarkable investigations were those using such models in combination with transgenic or gene-targeting technologies (Section 4.1.). However, HF models based on coronary artery ligation in rodents were also extensively used for the preclinical development of therapeutic approaches (Section 4.2.).
4.1. Use of transgenic and gene-targeted animals to study CHD-related HF

A very recent example for investigations aimed at the disclosure of the significance of single genes for the pathophysiology of CHD-related HF is the demonstration of the implication of matrix metalloproteinase 7 (MMP-7) in post-MI remodelling and arrhythmogenesis [51]. Applying permanent coronary artery ligation in constitutive MMP-7 knockout (KO) mice and wildtype (WT) control animals it was shown that MMP-7 degrades connexin 43 in post-infarction remodelling. Accordingly, a decrease of conduction velocity was found in infarcted WT hearts but not in MMP-7 KO hearts. The revelation of the role of cardiac S100A1 protein in heart failure [52] is another example for the employment of surgical MI induction in mice with constitutively effective genetic alterations. In this work the use of gene-targeted S100A1 KO mice as well as transgenic mice overexpressing S100A1 revealed that S100A1 attenuates the loss of contractile performance and progression towards heart failure. Numerous similar investigations with constitutive gene-targeted or transgenic rodents have been published so far.

However, constitutively effective genetic alterations have some disadvantages. They may provoke long-term adaptations, which can render the responsiveness of the organism to stimuli such as ischemia or they may be even lethal. Another specific disadvantage of constitutive gene targeting consists in the lack of cell type selectivity, which makes it more difficult to relate pathophysiological effects to certain cell types. To provide solutions for such problems systems for conditional trangene expression and gene targeting have been developed (reviewed by Mallo [53] and Heine et al. [54]). So far, only few investigations based on their application in combination with surgical induction of MI or ischemia have been published. For example, Sheikh et al. [55] demonstrated that alpha-E-catenin is required for cardiomyocyte adherens junction integrity using cardiacspecific alpha-E-catenin conditional KO mice: Upon induction of MI by permanent LAD ligation these mice displayed a predisposition to ventricular free wall rupture. Since this protein is required for early embryonic development the gene had to be deleted specifically in cardiomyocytes to prevent lethality. An investigation based on a conditional (inducible) transgene expression system (tet off system) [56] revealed that the protection of mouse myocardium from I/R injury by preceding brief episodes of I/R (preconditioning) was compromised by the induced expression of a transgene encoding the Frizzled-related protein FrzA.

However, also such conditional systems appear to have disadvantages. Adverse effects on the heart of the proteins mediating the induction of transgene expression or gene deletion, i.e. the tetracycline transactivator (tTA) or the Cre recombinase, respectively, have been demonstrated. High level expression driven by the cardiac alpha-myosin heavy chain promoter of both, tTA [57] as well as Cre recombinase [58] in transgenic mice caused cardiomyopathy. These data suggest that non-transgenic mice are not suitable to serve as controls in experiments where conditional systems are used. Instead, transgenics expressing tTA or Cre recombinase, but without induction of the respective conditional effect should serve as control animals (for details see McCloskey et al. [57] and Buerger et al. [58]).

As already mentioned in the introduction the suitability of genetically engineered mice prone to develop atherosclerosis to serve as models of CHD-related HF is impaired by the unpredictable timing and location of intracoronary plaque formation and occlusion. However, the experimental induction of MI or ischemia in such genetic models might contribute to the understanding of the influences of the basic disorder on the progression of its fatal consequences and vice versa. Accordingly, Pons and coworkers [59] induced MI by LAD ligation in apolipoprotein E (ApoE) KO mice and WT mice to reveal whether atherosclerosis influences the development of post-ischemic HF. Their results suggest that atherosclerosis does not aggravate HF development in mice. On the other hand, Tokuno et al. [60] showed that hearts of atherosclerotic low density lipoprotein receptor (LDLr)/ApoE double KO mice are more susceptible to I/R injury than hearts of normal mice. However, in this investigation I/R was applied in explanted hearts in the Langendorff reperfusion chamber.

4.2. Development of therapeutic approaches

Mouse or rat models of MI or I/R injury induced by coronary artery ligation were also extensively used to evaluate (gene) therapeutic approaches. Since the basic cause of HF secondary to MI is the massive loss of myocytes, which is at least partially due to apoptosis [61], many therapeutic approaches concentrate on the attenuation of cardiomyocyte apoptosis. For example, the infection of mice with an adenovirus encoding soluble Fas (sFas), a competitive inhibitor of the pro-apoptotic Fas ligand, on the third day of MI induced by LCA ligation led to the inhibition of apoptosis in granulation tissue. Consequently, a cell-rich infarct scar with many vessels and bundles of smooth muscle cells developed and displayed a contractile phenotype [62].

As an alternative to cardioprotective strategies, approaches leading to cardiac regeneration are extensively pursued using surgical models of MI/HF. For example, the adenoviral delivery of cyclin A into the infarct border zone of rat hearts subjected to LCA ligation initiated endogenous regeneration by the stimulation of cardiomyocyte proliferation and thereby improved cardiac function [63]. On the other hand the transplantation of exogenous cell types potentially providing regenerative capacity such as embryonic [64] or adult, bone marrow-derived stem cells [65], appeared promising.

As an alternative to the transplantation of bone marrow-derived stem cells their mobilisation by the cytokine granulocyte-colony stimulating factor (G-CSF) has been
applied in mouse models of myocardial infarction [20,66,67]. This treatment has been demonstrated to prevent apoptotic cell death [68], to stabilise electrophysiological coupling between cardiomyocytes in the border zone of the infarcted area and to improve vascularisation in the area of infarction in the mouse [20,66,68]. Similar results were obtained in a pig coronary artery ligation model [14].

Studies using rat or mouse models of LCA ligation-induced HF for the evaluation of classical, pharmacological therapy approaches are still being performed. For example, a recently published investigation indicated that cerivastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, improves left ventricular remodelling and function in rats with heart failure and may retard its progression [69].

5. Conclusions

Because of the epidemiological and socio-economic impact of CHD-related HF extensive efforts to counteract this disease are required. Since the understanding of disease mechanisms is essential to be able to develop efficient therapies the use of animal models is indispensable. However, every animal model has advantages and specific limitations and none of them is suitable to study all aspects of CHD-related HF. Besides the technical determinants of a certain model, species, strain and gender affect the pathophysiology of the manipulated heart and, therefore, have to be considered when an animal model shall be established.

At present, the most widely used animal models of CHD-related HF are rat and mouse models. The mouse in particular has the advantage to offer numerous transgenic and gene-targeted strains. In combination with the surgical methods reviewed in this paper these strains allow for the investigation of the significance of specific gene functions for the disorders secondary to CHD and for the simulation of (gene-)therapeutic approaches. Transgenic mice prone to develop the disorders usually associated with or preceding CHD, such as atherosclerosis, are particularly valuable to understand the influence of these disorders on the progression of CHD-related HF when used in combination with the surgical induction of cardiac ischemia.

Nevertheless, large animal models will be used further on because they often provide the advantages of a high degree of physiological similarities to human and the easier applicability of complex technical manipulations.

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