Review

Pacing-induced heart failure: a model to study the mechanism of disease progression and novel therapy in heart failure

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1. Introduction

Congestive heart failure (CHF) is a common clinical problem that confronts physicians and is often the final manifestation of many cardiovascular disorders. The diagnosis of CHF is accompanied by significant mortality and morbidity [1]. The syndrome is characterized by a relentless \textit{progressive} course that is often manifested as repeated hospital admissions imposing heavy economic burden on the health care delivery system [2,3]. Therefore, basic research into the fundamental mechanisms accounting for the \textit{progression} of CHF with the hope for developing novel therapeutic approaches to alter the progressive course has become a priority for many researchers. To facilitate these investigations, an animal model that closely mimics human CHF and also exhibits key components of what are now perceived to be important pathogenetic contributors to CHF progression is ideal. It is therefore the objective of this review to highlight how the model of pacing-induced cardiomyopathy has provided insights into the mechanisms of progression of CHF.

2. Mechanisms of the progression of heart failure: alterations in the biological properties of the failing heart

Clinicians have traditionally viewed CHF as being predominantly a haemodynamic disorder. Accordingly, haemodynamic descriptors such as elevated cardiac filling pressures, pulmonary venous and arterial hypertension, reduced cardiac output, and elevated systemic and pulmonary vascular resistance were used to characterize patients with CHF. While the haemodynamic descriptors can account for some of the clinical manifestations of CHF, such as dyspnea, fatigue and fluid retention, they do not adequately address the invariably progressive nature of the condition. In recent years, it has become apparent that CHF is a syndrome associated with a complex array of perturbations at multiple levels starting from the subcellular to the whole organ level. These alterations include profound structural and functional changes, which may culminate in the death of myocytes as well as major disruption of the cardiac extracellular matrix [4]. Both of these processes may contribute to progressive left ventricular (LV) remodeling and dysfunction. Compensatory mechanisms that are appropriately activated in the acute stage to combat systemic hypoperfusion may ultimately hasten disease progression. Several neurohormonal systems and the recently described proinflammatory cytokines have been incriminated in the process [5,6]. These mechanisms, through their direct toxic effects, their ability to alter myocardial gene expression, exhaust energy substrate, and increase oxidative stress [7] and probably through other mechanisms, will hasten cell death, possibly mediated by a combination of apoptosis and necrosis [8]. These major changes in the biological properties of the failing heart are probably the major contributors to the disease progression in CHF [9]. A proposed paradigm for the events leading to the progression of CHF is summarized in Fig. 1.

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interpretation of physiological data. Second, CHF evolves over a period of several weeks, which permits sequential observations [14,15]. Third, the magnitude of the provoking stimulus can be calibrated precisely by employing a programmable pacemaker. Fourth, rapid pacing produces a well-defined clinical syndrome of biventricular failure with cardiomegaly, hypoperfusion, pulmonary congestion, cachexia and ascites, all of which mimic the human state. Finally, the CHF induced in this fashion is reversible after cessation of pacing [16,17], a phenomenon that was described in the original report of Whipple et al. [13] and which our laboratory had examined closely to advantage [16]. A comprehensive description of the general aspects of this model, including the various methods of pacing, has previously appeared in several reviews [18–20]. In brief, the most commonly used method is right ventricular pacing in the dog using transvenous endocardial leads. In our laboratory, we employ programmable pulse generators and the pacing rate is programmed at 250 beats/min. Using this protocol, we have been able to consistently induce severe CHF in three to four weeks. With daily physical examination and weekly radiographic and echocardiographic assessments, premature mortality is seldom encountered. Other laboratories have induced CHF in the pig by chronic supraventricular tachycardia using atrial electrodes implanted after thoracotomy. The hemodynamic and neurohormonal changes induced in the pig model are quite similar to those of the canine model that uses endocardial right ventricular pacing. The pacing model has also been modified for use in the sheep and, more recently, in rabbits using epicardial electrodes. It is quite likely that other animal species and pacing protocols will be employed in the future. However, the current review will focus mostly on more specific aspects of CHF, and the contemporary experimental data derived from this model as well as on how these data provide further insights into our understanding of the mechanisms of progression of CHF.

### 3. Pacing-induced cardiomyopathy

The search for experimental models that would simulate the human condition of CHF has captured the imagination of generations of investigators. The heterogeneous etiology of CHF and the uncertainty in defining its time of onset conspire to make CHF a difficult condition to investigate. A comprehensive review of different experimental models of CHF was published in Cardiovascular Research in 1985 [10], and was also the subject of several more recent reviews [11,12]. In brief, these models have involved the induction of pressure overload by the creation of aortic or pulmonary artery stenosis, volume overload by the creation of aortic insufficiency or arteriovenous shunt, induction of myocardial ischaemia by coronary ligation or embolism or use of myocardial toxins such as Adriamycin or catecholamines. While these models are extremely useful in evaluating particular aspects of CHF and, indeed, many seminal observations of CHF have been obtained from these models, they may not entirely mimic patterns of CHF in man. Furthermore, increasing knowledge of the pathophysiology of CHF and recognition of the progressive nature of the disorder call for an experimental model that not only simulates human cardiomyopathy but must also contain features that mediate disease progression in CHF.

In 1962, Whipple et al. [13] first reported that atrial pacing at over 330 beats/min can induce symptoms and physical signs of CHF in the dog. Although these investigators initially devised the model to reproduce the human condition of tachycardia-induced cardiomyopathy, over the past two decades, it has increasingly been used to evaluate broader questions in CHF. Several features make this model particularly suitable for the study of CHF. First, the model, at least when implemented in most laboratories including ours, avoids major surgical trauma, such as thoracotomy and pericardectomy, which may influence the interpretation of physiological data. Second, CHF evolves over a period of several weeks, which permits sequential observations [14,15]. Third, the magnitude of the provoking stimulus can be calibrated precisely by employing a programmable pacemaker. Fourth, rapid pacing produces a well-defined clinical syndrome of biventricular failure with cardiomegaly, hypoperfusion, pulmonary congestion, cachexia and ascites, all of which mimic the human state. Finally, the CHF induced in this fashion is reversible after cessation of pacing [16,17], a phenomenon that was described in the original report of Whipple et al. [13] and which our laboratory had examined closely to advantage [16]. A comprehensive description of the general aspects of this model, including the various methods of pacing, has previously appeared in several reviews [18–20]. In brief, the most commonly used method is right ventricular pacing in the dog using transvenous endocardial leads. In our laboratory, we employ programmable pulse generators and the pacing rate is programmed at 250 beats/min. Using this protocol, we have been able to consistently induce severe CHF in three to four weeks. With daily physical examination and weekly radiographic and echocardiographic assessments, premature mortality is seldom encountered. Other laboratories have induced CHF in the pig by chronic supraventricular tachycardia using atrial electrodes implanted after thoracotomy. The hemodynamic and neurohormonal changes induced in the pig model are quite similar to those of the canine model that uses endocardial right ventricular pacing. The pacing model has also been modified for use in the sheep and, more recently, in rabbits using epicardial electrodes. It is quite likely that other animal species and pacing protocols will be employed in the future. However, the current review will focus mostly on more specific aspects of CHF, and the contemporary experimental data derived from this model as well as on how these data provide further insights into our understanding of the mechanisms of progression of CHF.

#### 3.1. Fluid retention in pacing-induced cardiomyopathy

Pulmonary congestion and edema formation are two major components of the syndrome of CHF. The mechanisms for fluid retention in CHF are multiple and include the development in the kidney of Starling forces, such as increased venous capillary pressure and decreased oncotic pressure, as well as the effects of local and systemic neurohormonal activation [21]. In our laboratory, chronic right ventricular pacing in dogs at 250 beats/min for >3 weeks invariably produces severe radiographic pulmonary congestion [14,17]. Peripheral edema occurs and is often manifested as ascites [14]. Significant changes in body weight may or may not occur [15,16], which probably reflect the net balance between accumulation of edema fluid and loss of lean body mass. In an earlier study, we made detailed comparisons of the sequential changes of plasma neurohormonal parameters during evolving pacing-
induced CHF to gain insights into the role of neurohormonal activation on fluid retention. Atrial natriuretic peptide (ANP) was activated early during the course of evolving CHF, suggesting that this vasodilator, natriuretic neurohormone played an important role in early CHF. Presumably, it acts to prevent fluid retention at this early stage when the other neurohormones, such as norepinephrine, renin and aldosterone, were not significantly increased [22]. At the time of severe CHF, hyponatremia developed, possibly related in part to the intense activation of the renin–angiotensin system, which is apparent at this advanced stage. Others have reported that the glomerular filtration rate, renal blood flow and urinary Na excretion all decreased significantly [23]. Using a modified pacing protocol in which the pacing rate was increased at weekly intervals from 200 to 210, 220 and 240 beats/min, Stevens et al. [23] and colleagues described the serial changes in urinary Na excretion in relation to plasma neurohormonal parameters from early LV dysfunction to the development of overt CHF. At early LV dysfunction, plasma ANP and brain natriuretic peptide (BNP), nitric oxide (NO) and cGMP levels were all increased whereas the levels of the vasoconstrictor neurohormones such as norepinephrine and renin were not increased. Urinary excretion of cGMP was increased and urinary Na excretion was maintained. At overt CHF (38 days of pacing), plasma cGMP and natriuretic peptide levels remained increased but the plasma NO level and urinary cGMP excretion were reduced from levels at early and moderate LV dysfunction. Urinary Na excretion was markedly reduced only in moderate LV dysfunction and overt CHF. These data indicate an important functional role of the natriuretic peptides and NO, which are activated early during evolving CHF and that their ability to stimulate cGMP may serve to maintain volume homeostasis and prevent fluid retention, at least in the earlier stages of CHF. Further support of this concept has been derived from observations that intrarenal administration of the inhibitor of the natriuretic peptide receptor antagonist HS-142-1 to dogs with acute CHF induced by rapid pacing resulted in reduced urinary cGMP and Na excretion accompanied by a reduced glomerular filtration rate [24]. Our laboratory has demonstrated that in spite of increased circulating levels of ANP and BNP, the release of these peptides to an acute further increase of atrial pressures, and the natriuretic responses to exogenous administration of ANP and BNP are both attenuated at CHF [25,26]. These probably constitute additional mechanisms contributing to the fluid retention.

In order to evaluate whether the response to hypertonic saline challenge can predict the propensity for fluid retention in CHF, we classified normal dogs according to whether they drank more or less water than required to dilute the saline challenge to isotonicity [27]. These dogs were then paced for one or three weeks. At CHF, the fluid retention score was higher in dogs that drank more after the saline challenge at baseline. Indeed, as shown in Fig. 2, there was a direct correlation between water intake following saline challenge at baseline and subsequent fluid retention. There was also an inverse correlation between the ability to concentrate urine at baseline and the degree of fluid retention at CHF. These data suggest that the ability to regulate a salt load may be a useful predictor of the propensity for fluid retention in CHF.

3.2. Myocardial remodeling and dysfunction

In almost all species studied, chronic atrial or ventricular rapid pacing both produce marked dilatation of all cardiac chambers [16,28,29]. This profound cardiac chamber dilatation is surprisingly accompanied by little or no cardiac hypertrophy at the whole organ level. Indeed, in both dog and pigs subjected to fixed-rate pacing, ventricular wall thinning without increased heart weight appears to be the rule [16,30,31]. Interestingly, at four weeks after cessation of pacing, whereas all haemodynamic and neurohormonal parameters returned to the baseline values, both systolic and diastolic chamber volume remained increased from baseline while heart weight actually increased from the time of CHF [16,32]. We initially believed that these findings reflected a relative metabolic deficiency induced by rapid pacing. Thus, chronic rapid pacing resulted in severe depletion of myocardial high-energy phosphate [33], potentially impairing the development of hypertrophy. The dramatic recovery of haemodynamic and clinical parameters as well as the development of hypertrophy after cessation of pacing appeared to support this hypothesis. To test this hypothesis, we devised a seven-week protocol of intermittent pacing, consisting of 48 h of rapid pacing alternating with 24 h of resumption of sinus rhythm, reasoning that there would have been intermittent recovery of energy substrate to permit the development of hypertrophy [34]. However, both the continuously paced and intermittently paced dogs failed to develop cardiac
hypertrophy during the evolution of heart failure. Although the reasons why cardiac hypertrophy at a whole-organ level does not develop in this model remain unclear, these unique features of this model suggest that the insult is sufficiently intense such that these paced animals never enter a stage of compensated LV hypertrophy [35]. Furthermore, the persistent chamber dilatation in spite of haemodynamic recovery at four weeks would suggest that structural remodeling is ongoing in spite of cessation of pacing.

In contrast to the left ventricle, our laboratory had observed a significant increase in left atrial dimension in conjunction with an increase in left and right atrial appendage weights, indicating the development of significant biatrial hypertrophy [36,37]. The basis for the dissociation between atrial and left ventricular hypertrophy is unclear, given a similar systemic haemodynamic and neurohumoral environment. It could, however, relate in part to the different atrial and ventricular rates and, therefore, high atrial wall stress and the different oxygen requirements of these chambers under the stress of rapid ventricular pacing. Interestingly, it has been shown recently that the differential wall stress of the left atrium and left ventricle is accompanied by higher increased collagen content in the left atrium but not in the left ventricle of the paced dogs [37]. The features described thus far suggest that the model may be best suited for studying the mechanisms of the rapid progression of heart failure and partly prompted investigators to examine this model in detail at the myocyte and the extracellular matrix level.

3.3. Structural and functional alterations of the myocytes

Considerable information is now available concerning the structural and functional alterations of the myocytes in pacing-induced cardiomyopathy. Using elegant enzymatic dissociation methods from perfusion-fixed LV myocardial sections taken from pigs with supraventricular tachycardia-induced CHF, Spinale et al. [38] observed that the cross-sectional area of myocytes was significantly reduced whereas the length of the resting was increased. There was a net reduction in total myocyte volume and myofibril content. These important observations indicate myocyte remodeling, which could account for the LV wall thinning, increased globularity and the lack of hypertrophy observed at the whole-organ level in this model. The altered myocyte geometry may in turn be mediated by alterations in myofibril alignment, orientation of contractile proteins and structures of the cytoskeleton [39]. The remodeled isolated myocyte had markedly impaired steady-state contractile function [40] as well as a blunted response to β-adrenergic stimulation [41]. The impaired myocyte function may in turn account for the impaired resting LV inotropic function and contractile reserve, which are well-documented in this model [31,42,43]. In dogs with CHF induced by LV pacing, morphometric analysis of the myocardium in situ revealed a significant loss in the number of myocytes but an increase in the volume of the remaining myocytes, which were characterized by a marked increase in the cell length to cell diameter ratio [44]. These data suggest that myocyte cell loss and reactive hypertrophy of remaining myocytes are the major components of canine pacing-induced cardiomyopathy. The differences in techniques of analysis and experimental preparation may have accounted for the different observations in the changes in myocyte cross-sectional area and the presence or absence of myocyte hypertrophy [38,44]. Nevertheless, alteration in myocyte geometry appears to be a consistent finding in this model and, indeed, myocyte remodeling may be an important contributor to the progression of CHF.

3.4. Continuing myocyte loss

Another potentially important mechanism mediating the relentless progression of CHF is the continuing loss of myocytes. Apoptosis, or programmed cell death, is a mechanism of cell death in which developmental or environmental factors trigger a genetic program that activates a specific series of events, resulting in the disposal of the cell [45]. Unlike necrosis, another mechanism of cell death, apoptosis is a tightly regulated and energy-requiring process [46]. It is interesting that cellular environments that are known to trigger apoptosis, such as exposure to hypoxia, oxidative stress, cytokines and abnormal gene expression [47–49], may also be the same environment that surrounds the failing myocytes.

Apoptosis has recently been reported in the canine model of pacing-induced CHF. In dogs who were paced for four weeks, apoptosis was detected in 4/1000 myocyte nuclei and associated with enhanced p53 DNA binding activity to the Bax promoter, increased expression of Bax protein and attenuation of Bcl-2 [50].

Our laboratory has recently examined the time course of development of apoptosis during evolving pacing-induced CHF [51]. LV myocardium from normal dogs (controls), dogs paced for one week (early CHF) and three weeks (severe CHF) were examined for apoptosis using TUNEL staining and DNA laddering. As shown in Fig. 3, apoptosis was detected in the myocardium in the dogs at three weeks and even after one week of pacing. These data suggest that apoptosis occurs early and persists during the course of development of CHF and may be one of the mechanisms mediating the progression of CHF.

3.5. Extracellular matrix remodeling

In both patients and animal models, the development of cardiac dilatation and altered LV geometry are associated with significant alterations in the cardiac fibrillar collagen network [52]. In the canine pacing model, we first reported
the appearance of interstitial edema and disruption/disappearance of collagen fibers in the hearts of these animals as early as 6 h after pacing, with persistence for the ensuing weeks [53]. Furthermore, these disruptions were still evident at 48 h after cessation of pacing. The disruption of collagen removes the mechanical support for adjoining myocytes, as manifested by muscle fiber disorientation, which then contributes to the cardiac remodeling process and the impaired systolic and diastolic function [54,55]. While we initially reported an increase in collagen content in the paced-dogs [53], others have shown that the collagen content was unchanged in the dog [54], or reduced in paced-pigs [55]. The reasons for these differences in observations are uncertain and may relate in part to methodological differences and the limitations of small sampling sites.

In an earlier study, we reported an increase in 92 kDa gelatinase, as assessed by zymography in the LV samples of the paced dogs, whereas the 72 kDa gelatinase was unchanged [56]. The increase in 92 kDa gelatinase was closely related to the LV chamber dilatation. At that time, we hypothesized that, in this canine model, there might be a selective activation of myocardial tissue matrix metalloproteinas (MMPs), which would mediate the changes in cardiac geometry. Subsequently in other studies, the serial changes in myocardial MMPs during evolving CHF were examined in the pig model of supraventricular pacing-induced CHF [57]. After only seven days of atrial pacing, the LV myocardial collagen content fell by >25%, accompanied by a two-fold increase in interstitial collagenase (MMP-1), stromelysin (MMP-3) and 72 kDa gelatinase (MMP-2). These changes persisted at three week of pacing.

We recently assessed MMPs in the left atrium in conjunction with those from the left ventricle in the canine pacing model [58]. After one week of pacing, MMP-2 was significantly increased in the left atrium but not the left ventricle. After three weeks of pacing, MMP-3 was increased in the left atrium whereas MMP-9 was increased in the left ventricle. These data suggest that there is differential regulation of the MMPs between the left atrium and the left ventricle in response to rapid pacing. Therefore, the canine and pig data both support the concept that enhanced expression and/or activity of MMPs may contribute to the progression of LV remodeling and dysfunction in CHF.

Based on these observations, a potentially new target of intervention in the treatment of CHF may be to inhibit MMPs. The pacing model provides an ideal substrate to study this potentially exciting therapeutic intervention. In a recent study using pigs paced for three weeks to CHF, the administration of a non-specific inhibitor of MMPs was associated with a modest improvement in LV whole organ and myocyte function and a reduction in LV chamber volume and wall stress [59]. These preliminary results obtained from the pacing model strongly support the concept of the pathologic role of MMPs in the LV remodeling process and may open up new therapeutic strategies in the treatment of LV remodeling and CHF.

3.6. Neurohormones and cytokines

The development of CHF is associated with the activation of several neurohormonal systems. The neurohormone hypothesis states that prolonged neurohormone activation not only explains the clinical, hemodynamic and metabolic perturbations but also contributes to disease progression in CHF [5]. The model of pacing-induced cardiomyopathy is ideal for studies of the pathophysiological role of neurohormonal activation in CHF because of its ability to produce intense stimulation of almost every neurohormonal system, including the more recently described endothelin system [21,23,60]. The pronounced alterations in the sympathetic nervous system, the renin–angiotensin system and the natriuretic peptide system in this model have previously been described comprehensively in several reviews [18,19,61]. This section will focus mainly on recent observations relating to the changes in endothelin-1 and the cytokine tumor necrosis factor-α (TNF-α) and how the pacing model may provide insights into the pathophysiological role of these systems.

Endothelin-1 (ET-1) is one of the most potent vasoconstrictor peptides with diverse biological properties, which have recently been implicated in the pathogenesis of CHF [62,63]. In dogs with pacing-induced CHF, plasma ET-1 levels are consistently elevated [60,64]. To elucidate some of the mechanisms for the increased circulating ET-1 level, we recently studied pulmonary clearance of ET-1 in dogs with pacing-induced CHF [60]. Compared to baseline, the capacity of the lung to clear ET-1, as measured by the permeability–surface product, was markedly reduced at CHF. This was accompanied by a reduced binding affinity of the type B endothelin receptors in the lungs. Our novel findings suggest that reduced pulmonary clearance of ET-1 is likely to contribute to the increased circulating ET-1 levels observed in this model. Using a ribonuclease
protection assay, we have recently demonstrated markedly increased mRNA expression of preproET-1 in the left ventricle and the lungs of paced dogs [65]. The increased cardiac expression of ET-1 raises the possibility that ET-1 may play an important paracrine role in CHF. The increased pulmonary expression strongly supports the hypothesis that increased ET-1 mediates the pulmonary hypertension in CHF, as suggested by previous reports of a strong correlation between plasma ET-1 levels and pulmonary vascular resistance observed in the placebo-treated dogs [65]. The beneficial hemodynamic effects were obtained with no adverse effects on neurohormonal parameters such as norepinephrine and ANP. In a rabbit model of pacing-induced CHF, administration of another ET₄ antagonist was accompanied by a restoration of function of the isolated myocytes [69]. Therefore, data derived to date from the canine and rabbit pacing-induced CHF models suggest that an activated endothelin system may mediate the pulmonary and systemic vasoconstriction and impairment of myocyte function in CHF. Accordingly, the endothelin receptor antagonists may hold great promise as therapeutic agents in CHF.

There is increasing evidence in support of a pathological role of the proinflammatory cytokines such as TNF-α in the pathogenesis of CHF [70]. Several studies have reported, in patients with advanced CHF, elevated circulating levels of TNF-α and its soluble receptors (sTNF-R1 and sTNF-R2) [71,72]. In the canine pacing-induced CHF model, we recently reported serial changes of plasma TNF-α levels during evolving CHF [73]. As early as one

![Graphs showing hemodynamic effects](image-url)

Fig. 4. Hemodynamic effects of chronic treatment with LU 135252, selective endothelin type A receptor antagonist versus placebo in dogs paced for two weeks to heart failure. † P<0.001 versus baseline; § P<0.05 versus placebo. Reproduced from ref. [68] with permission of the European Society of Cardiology.
week after the onset of pacing, there was a trend of the plasma TNF-α levels increasing from baseline. At three weeks of pacing, the plasma TNF-α level was markedly elevated. Immunohistochemical studies of the LV tissue demonstrated intense staining of TNF-α, which was not observed in the control normal dogs. Furthermore, there were very few inflammatory cells in the paced dogs. The spleen stained only mildly positive. Our findings therefore suggest that, in the canine model of pacing-induced CHF, there is a marked activation of the proinflammatory cytokine TNF-α. Furthermore, the heart is one source of production of cytokines in CHF and this activation may occur in the absence of any major concurrent immune activation.

One of the mechanisms by which the cytokines exert an adverse effect on the failing heart may be through an increased expression of inducible nitric oxide synthase (iNOS) [74]. In vitro studies in myocytes [75] and in vivo studies in animals [76] have demonstrated that NO decreases myocardial contractility and attenuates the contractile response to β-adrenergic stimulation. We have previously demonstrated that, in the canine model of pacing-induced CHF, the inotropic response to β-adrenergic stimulus is attenuated [41]. It is therefore conceivable that enhanced myocardial NO may mediate in part the β-adrenergic hyporesponsiveness in heart failure in this model. To test the hypothesis, a recent study examined the effects of NOS inhibitor on contractile function in myocytes isolated from dogs with pacing-induced cardiomyopathy [77]. Total myocardial NOS activity, as measured by the conversion of arginine to citrulline, was temporary interruption of pacing. Also, unlike most other diomyopathy [77]. Total myocardial NOS activity, as necessary to acquire physiological measurements during pacing. Because of this limitation, it is frequently observed in the control normal dogs. Furthermore, there NMMA), indicating that increased NOS in the coronary arteries enhances endothelium-dependent relaxation in the coronary arteries in the paced dogs. Notwithstanding differences in observations between different studies, the data obtained from the pacing model, on balance, suggest that increased NO may play a "protective role" by down-regulating the inotropic response of the heart to β-adrenergic stimulation, counteracting hypertrophy while preserving coronary blood flow.

Some more aspects, including the limitations of the pacing model, warrant further discussion. Although the various mechanisms that contribute to the progression of CHF are well understood, the mechanisms initiating the depression of myocardial function remain poorly defined. Our laboratory has provided some evidence that a reduction in myocardial high-energy phosphate content and an inadequate increase in myocardial blood flow in response to increased metabolic demand may play a role [33,34]. Even though the CHF syndrome induced by this model simulates human heart failure in many respects, major differences exist. Unlike human heart failure, the heart failure produced is dependent upon continuous pacing at rapid rates and is at least partially reversible after cessation of pacing. Because of this limitation, it is frequently necessary to acquire physiological measurements during temporary interruption of pacing. Also, unlike most other CHF states, left ventricular hypertrophy does not occur at the whole-organ level. The issue of steady-state definition arises since continuous ventricular pacing at rapid rates produces inexorable clinical deterioration within three to four weeks of the initiation of pacing. Some investigators, including our laboratory, however, have circumvented the rapid deterioration and ultimate mortality by reducing the ventricular rate to 160–180 beats/min, once clear-cut clinical CHF has developed. Indeed, the opportunity to calibrate the degree of insult by using externally programmable pacemakers potentially avoids the high mortality as well as the risk of inducing mild heart failure, as observed in other preparations such as the myocardial infarction models [12]. The limitations notwithstanding, the rapid pacing model has been extremely useful in providing the opportunity to study pathogenetic insights into compensatory mechanisms and the basis for disease progression in heart failure. A variety of treatment modalities have been explored in this model and opportunities exist for the development of new prognostic markers arising from the study of the hemodynamic, neurohumoral, cardiac structural and tissue correlates of heart failure. Its wide acceptance in multiple laboratories globally is an indication of its utility to investigators and of its promise for the future.


