Electrophysiological changes in heart failure and their relationship to arrhythmogenesis

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Abstract

This review focuses mainly on studies in non-ischemic animal models of heart failure. These animals develop ventricular arrhythmias, mostly non-sustained ventricular tachycardia, and often die suddenly. Clinical studies suggest that sudden death is due to ventricular tachycardia or fibrillation in about 50% of cases, the other half to bradyarrhythmias or electromechanical dissociation.

Electrophysiologic changes in heart failure are not confined to the ventricles: the intrinsic sinus rate is reduced due to a downregulation of If and sensitivity to acetylcholine is enhanced by upregulation of the muscarinic receptor. Reduction of heart rate may be a protective mechanism since at rapid rates contractility is reduced and the likelihood for triggered activity due to delayed afterdepolarizations is enhanced. The beneficial effect of β-adrenergic blockade in patients may be partly due to the reduction in sinus rate.

Although the results of different studies often vary, the most consistent electrophysiological changes in the ventricles are prolongation of the action potential, especially at slow rates, a reduction in the transient outward current Ito, the rapid and slow components of the delayed rectifier Ikr and Iks, and the inward rectifier Ik1. Abnormalities in intracellular calcium handling play a major role in the genesis of delayed afterdepolarizations. Triggered activity based on delayed afterdepolarizations has been demonstrated in failing myocardium and are caused by spontaneous release of calcium from the sarcoplasmic reticulum (SR), especially in the presence of noradrenaline. Three factors combine to the enhanced propensity for the occurrence of delayed afterdepolarizations: (1) increased activity of the Na/Ca exchanger, (2) a reduced inward rectifier, (3) residual β-adrenergic responsiveness required to raise the reduced sarcoplasmic calcium content to a level where spontaneous calcium release occurs.

Early afterdepolarizations have also been demonstrated, especially in human myocytes from failing hearts in the presence of noradrenaline.

Mapping experiments have shown that the ventricular arrhythmias are mainly due to non-reentrant mechanisms, most likely triggered activity based on delayed afterdepolarizations.

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1. Introduction

Several review articles on the mechanisms of arrhythmias in heart failure have appeared in the last 5 years or so [1–5], but there are quite a number of recent studies adding to our understanding that warrant a reappraisal.

In about half of patients with congestive heart failure, complex ventricular arrhythmias, including non-sustained ventricular tachycardia, are present and sudden death is common [6–14]. It is not clear whether there is a relationship between presence of arrhythmias and the subsequent occurrence of sudden death since there are both studies that support such a relationship [10,12,13] and studies that deny it [11,14]. It has been known for a long time that the most powerful predictor for sudden death is left ventricular dysfunction [15,16], and one therefore could expect that sudden death would be related to the severity of heart failure. But here there is controversy as well. Kjekshus [9] reported that in patients with New York Heart Association classes I and II heart failure, 50–60% of all deaths were sudden, whereas in patients with classes III and IV this was...
only 20–30%. In class IV, the most important cause of death was progression of heart failure. In patients hospitalized for end stage heart failure, awaiting cardiac transplantation, sudden death was due to ventricular tachycardia or fibrillation in about 50%, and due to bradycardia, asystole or electromechanical dissociation in the other 50% [17,18]. These findings contrast with those of recent randomized trials on the prevention of sudden death by implantable cardioverter defibrillator therapy, in which the device was most effective in patients with the lowest ejection fraction [19,20,21]. One cannot believe that a defibrillation shock would be helpful during asystole or electromechanical dissociation. In other words, there is still much to learn about arrhythmias and sudden death in heart failure.

Although atrial arrhythmias occur frequently in heart failure [22–24], for the sake of space, this review will primarily focus on ventricular arrhythmias and electrophysiological studies in animal models of heart failure.

2. Animal models of heart failure

There is a bewildering variety of animal models of heart failure (for details, see the excellent and exhaustive reviews of Hasenfuss [25] and Doggett and Brown [26]). A comparison of the different studies is difficult because not only do species differences have to be taken into account, but the way in which heart failure (with or without hypertrophy) was induced as well. Species used range from cow, baboon, dog, pig, sheep, cat, rabbit, turkey, ferret, guinea pig, Syrian hamster, rat and mouse [25,26]. Ways to induce heart failure range from coronary artery ligation, volume overload (aorta-caval fistulae, mitral regurgitation, aortic regurgitation, tricuspid regurgitation), pressure overload (aortic or pulmonary artery banding, salt-sensitive or spontaneous hypertension), combined volume and pressure overload, toxic cardiomyopathy (by, for example, doxorubicin or mononcrotaline administration), genetically determined (for example in Syrian hamsters and Doberman Pinscher dogs, or in transgenic mice in which dilated or hypertrophic cardiomyopathy can be induced), rapid pacing and hyperthyroidism [25,26].

For electrophysiologic studies, rat and mouse models have distinct disadvantages because the ventricular action potential lacks a plateau phase and calcium removal from the cytosol is predominantly via the activity of the sarcoplasmic reticulum (SR) calcium pump whereas activity of the Na/Ca exchanger is less relevant [25]. The species, which, as far as action potential characteristics are concerned, resemble humans most, appear to be rabbits and dogs.

Since hypertrophy in the absence of heart failure causes changes in the ventricular action potential, it is often difficult, if not impossible, to separate the changes due to heart failure per se and those due to hypertrophy. Furthermore, in patients, heart failure is a clinical syndrome characterized by signs and symptoms, and not by measurable parameters such as for example left ventricular ejection fraction or plasma levels of neurohormones. In animals, it is difficult to establish whether heart failure is present, and if so, to which degree. “Clinical” signs of heart failure include tachypnea, lack of appetite, lethargy, edematous extremities and piloerection. Vermeulen et al. [27] used a “heart failure index”, based on measurements of relative heart weight, relative lung weight, left ventricular end-diastolic pressure, presence of a third heart sound and ascites. Heart failure was considered to be present if at least three of the five parameters were abnormal.

3. Changes in sinus node function

Heart failure is associated with an enhancement of sympathetic nerve activity and a reduction in parasympathetic activity [28,29]. The resulting decrease in heart rate variability is associated with an increased risk for sudden death [30]. It is generally assumed that the autonomic imbalance, evident by changes in sinus node function, parallels the autonomic imbalance at the level of the ventricles. Only few studies have addressed the question whether sinus node function itself is affected by heart failure.

Opthof et al. [31] implanted transmitters for Holter recording in nine rabbits in which heart failure was induced by combined volume and pressure overload and documented changes in sinus cycle length and occurrence of arrhythmias during the development of heart failure for periods up to 490 days. Ventricular tachycardias developed in eight out of the nine rabbits. Three rabbits died suddenly; in these animals, sinus cycle length decreased shortly before death. In contrast, sinus cycle length increased in the surviving rabbits. In isolated right atrial preparations from these rabbits, the intrinsic sinus cycle length was significantly longer than in preparations from control rabbits (406 ± 13 vs. 353 ± 9 ms). Furthermore, in the isolated preparations from the failing rabbits, the response to acetylcholine was enhanced, while the response to norepinephrine was unchanged compared to control preparations. These results were corroborated in subsequent studies. Thus, Verkerk et al. [32] found that, in isolated sinus nodal cells from failing rabbits (same model as in Refs. [24,28]), intrinsic cycle length was decreased by 15% and diastolic depolarization rate by 30%, whereas other action potential parameters were unchanged. These effects were caused by a reduction of the hyperpolarization-activated pacemaker current I_f by 40%.

It is of interest to compare these data with in vivo data on cycle lengths in humans and dogs subjected to simultaneous sympathetic and parasympathetic blockade by propranolol and atropine, defined as intrinsic heart rate by Collignon [33]. This intrinsic cycle length is longer in patients with heart disease [33,34]. In conscious dogs with heart failure, sinus rate is faster than in control dogs (cycle lengths of 472 vs. 779 ms). However, in the presence of propranolol and
atropine, the intrinsic cycle length of failing dogs was 130 ms longer than in control animals [35]. Thus, it appears that in man and dog the intrinsic sinus node cycle length is also prolonged in heart failure, but that in vivo the enhanced sympathetic activity overrides this and actually decreases sinus cycle length.

In a rat model of right-sided heart failure caused by administration of monocrotaline, it was found that both pre- and post-ganglionic vagal nerve functions were diminished, but that the M2 receptor mediated response to acetylcholine of the sinus node was upregulated. The parasympathetic withdrawal was possibly due to a downregulation of neuronal nitric oxide synthase (nNOS) [36].

It therefore appears that in heart failure sinus rate can both be increased and decreased. An increase in sinus rate is a harbinger of sudden death and is most likely caused by an excess of sympathetic activity, and possibly circulating catecholamines, that overrides the intrinsic decrease of sinus cycle length caused by downregulation of If. The vagal withdrawal is partly compensated by an upregulation of the muscarinic receptor response to acetylcholine. In survivors, the decrease in sinus rate may be a protective response, since at rapid rates the likelihood for the occurrence of triggered arrhythmias is enhanced and contractility is decreased because of the reversal of the normal force–frequency relation [37,38]. That a relatively low heart rate is beneficial in heart failure is corroborated by clinical trials in patients with heart failure in which β-adrenergic blockade not only reduced all-cause mortality but also the incidence of sudden death [39,40]. Heart rate reduction per se in patients with heart failure is associated with survival improvement. However, for a given reduction of heart rate and for any level of baseline heart rate, bisoprolol further improved survival compared with placebo. Thus, heart rate reduction is not the only mechanism responsible for the beneficial effects on survival of β-blocking therapy [41].

4. Ventricular arrhythmias

There are few data on the incidence of ventricular arrhythmias in animals with heart failure based on pro-

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Fig. 1. Holter recordings of the electrocardiogram of a rabbit with heart failure obtained during the final minutes before sudden death. (A) At −10 min sinus tachycardia with a cycle length of 200 ms. (B) At −9 min, 30 s: sinus bradycardia with a cycle length of 410 ms followed by a ventricular escape rhythm (cycle length 610 ms). (C) At −7 min: widening of the QRS complex. (D) At −3 min: ST segment changes. (E) At −2 min: complete AV block. (F) Extreme bradycardia followed by ventricular fibrillation. (Reproduced with permission from Ref. [42].)
longed Holter monitoring. Of 23 failing rabbits (combined volume and pressure overload), 15 developed non-sustained ventricular tachycardias, while this was never seen in 9 control rabbits [42]. In another study, using the same model, non-sustained ventricular tachycardias occurred in 90% of failing rabbits [43]. In a dog model with pacing induced heart failure, Holter recordings revealed an increased incidence of non-sustained ventricular tachycardia as heart failure progressed, but it is unclear how many of the dogs developed this arrhythmia [44]. Approximately 10% of the rabbits died suddenly and 6 of the 25 dogs did so [31,42–44]. Holter recordings at the time of death were available in one dog and one rabbit. In the dog, the fatal arrhythmia was a polymorphic ventricular tachycardia degenerating into ventricular fibrillation. Fig. 1 shows the ECG of the rabbit that died suddenly, 122 days after induction of heart failure. Three hours before the terminal event, the animal suffered from supraventricular tachycardia (cycle length 170 ms) for 1.5 h (not shown); 10 min before the onset of ventricular fibrillation sinus rhythm prevailed (cycle length 200 ms (upper panel)), followed by sinus bradycardia (cycle length 410 ms) and sinus arrest with ventricular escape beats. Eventually, total atrioventricular block was present, ST segment elevation developed and finally ventricular fibrillation ensued. The animal certainly was dead during ventricular fibrillation, but might have been dead already during the period of extreme bradycardia. This is similar to what has been reported in patients with end stage heart failure who died suddenly [17,18].

In the combined volume–pressure overload rabbit model in which a 20-min period of coronary artery occlusion was added, ventricular fibrillation occurred in 76% of failing rabbits versus 27% in control animals [45]. Again, this seems to be similar to what happens in humans: in the Framingham study, cardiac failure alone increased the risk for sudden death fivefold. In those who also had coronary artery disease, there was a further doubling of risk [46].

5. Changes in action potential duration and ionic currents

One of the best documented changes in hypertrophy and heart failure, both in animal models and in humans, is the prolongation of the ventricular action potential, even though in most studies it was documented at unphysiologic long cycle lengths ranging from 1 to 5 s [41,44–50]. Vermeulen et al. [27] showed that, both in ventricular trabeculae from patients with terminal heart failure and from failing rabbits, action potential duration was particularly prolonged at long cycle lengths (i.e. longer than 700–1000 ms), whereas the differences with action potentials from control hearts became very small at shorter, more physiological cycle lengths. This has implications for arrhythmogenesis: failing hearts are not protected against reentry and the development of early afterdepolarizations due to the prolonged action potential is less likely to occur at rapid heart rates.

A factor predisposing to reentry is the increased dispersion in action potential duration and refractoriness, as has been reported in several studies [54–57].

The changes in ionic currents, underlying the changes in action potential duration, have recently been reviewed in detail by Armoundas et al. [5] and by Tomaselli and Marban [53].

Na⁺ currents were found to be unchanged in heart failure, both in dogs [51] and in humans [58] and the same is true for the L-type Ca⁺ current [51,59–61], although in the pig and the rabbit a reduction by 40% was found [62,63]. The response of the Ca⁺ current to isoproterenol was blunted, possibly reflecting downregulation of the β-adrenergic receptor and/or distal changes in signal transduction. More recent studies on canine and human myocytes found that the density of the L-type Ca⁺ channels was reduced [64,65], but that the basal density of the calcium current was maintained by increased phosphorylation of the channels [65]. The blunted response to adrenergic stimulation could be due to the reduced density of the channels [65].

The most consistent change in ionic currents is a reduction in the density of the transient outward current [51,63,67–69], but there are studies reporting no change or even an increase (for further details, see the reviews by Armoundas et al. [5] and by Tomaselli and Marban [53]). Downregulation of the transient outward current is unlikely to produce large effects on action potential duration in the ventricles of large mammals such as dog and man [53]. Moreover, in the guinea pig, in which the transient outward current is not expressed in the ventricles, the action potential is prolonged in hypertrophy and heart failure, and is attributed to changes in calcium cycling proteins: upregulation of the Na/Ca exchanger, downregulation of the calcium pump of the sarcoplasmic reticulum (SERCA) and phospholamban will decrease SR load and lead to a reduction of calcium-dependent inactivation of the L-type calcium channel. The resulting increase in inward current will prolong the plateau phase of the action potential [70]. The same mechanism accounts for the action potential prolongation in the model study of Winslow et al. [66].

The inward rectifier Ik1 has been found to be reduced [51,67,69], but other studies found no change [63]. There are few studies on the delayed rectifier: Chen et al. [65] reported that it was hardly detectable and if it could be detected it was very small in both diseased and normal myocytes. In a dog model of heart failure, Ik1 was found to be decreased, while Ikr remained unchanged [69]. Veldkamp et al. [71] were able to record single channel currents of the rapid component of the delayed rectifier, Ikr, from myocytes from patients with cardiomyopathy, but could not detect the slowly activating component Iks. No comparisons with normal human myocytes could be made.

Very often, measurements of membrane currents are made at room temperature and action potentials at physio-
logic temperatures, albeit at unphysiologically long cycle lengths. This hampers understanding of the relationship between changes in action potential duration and ionic currents. An exception is the study by Tsui et al. [63], in which in a pacing-induced heart failure model in the rabbit, measurements were made at physiological temperatures and cycle lengths. Action potentials were prolonged, densities of the transient outward current, and both E-4031-resistant and -sensitive components of the delayed rectifier (Iks and Ikr) were reduced, as was the L-type calcium current, whereas Ik1 was unchanged.

It is difficult to arrive at a general conclusion as to which changes in ionic currents are most important in determining the action potential prolongation, which has been found in all models of hypertrophy and heart failure. Species differences, the various models of heart failure and the experimental conditions (temperature, cycle length, presence of calcium buffering internal solutions) have to be taken into account. In this respect, computer simulations are helpful. In the model of Priebe and Beuckelmann [72], the major mechanisms for action potential prolongation in human heart failure were the reduction in the rapid and slow components of the delayed rectifier, the reduction of the inward rectifier Ik1, the enhanced activity of the Na/Ca exchanger, the slowed diastolic decay of the intracellular calcium transient and the reduction of the Na/K-pump activity. The reduction in the transient outward current had only a small effect on action potential prolongation. The simulation study of Winslow et al. [66] also arrived at the conclusion that reduction of potassium currents alone cannot account for the action potential prolongation and that alterations in calcium handling must be incorporated.

6. Abnormal intracellular calcium handling

A prominent feature of myocytes from failing hearts is the alteration in intracellular calcium handling [73,74], and many studies have investigated changes in the activity of the Na/Ca exchanger, SERCA, the ryanodine receptor and the Na/H exchanger. As is the case for the studies on ionic currents, the results are not always consistent. As reviewed by Sipido et al. [75], 14 out of 29 studies report on an increase in the function and/or expression of the Na/Ca exchanger, 10 found a decrease and 5 no change. This is in part related to the species examined, for of the 16 studies on rats, only 5 found an increase, whereas 9 show an increase in the 13 studies on other animal species. Another factor accounting for the inconsistencies is the way in which heart failure was induced: in the rabbit model of failure caused by rapid pacing, the Na/Ca exchanger was downregulated [76], whereas in the combined pressure and volume overload rabbit model it was upregulated [77]. Presence or absence of signs of heart failure, although infrequently considered, do not appear to play a role: in guinea pigs subjected to aortic banding increased protein levels and larger exchange currents were found in both the compensated hypertrophy stage and the failure stage [70], although with time currents became smaller. In rats with myocardial infarction-induced failure, mRNA levels of the exchanger also decreased with time [78]. In a recent study, the function of the Na/Ca exchanger was examined in ventricular myocytes form normal human hearts and from hearts in end stage heart failure [79]. In nonfailing myocytes, the exchanger extrudes calcium nearly throughout the cardiac cycle. In failing myocytes, calcium enters the cell through the exchanger during the action potential, as a result of a lower [Ca++]i, a prolonged action potential and a higher [Na+]i [79].

Downregulation of SERCA seems a more constant finding [80–82]. The same holds true for the finding of an increased open probability of the ryanodine receptor (the calcium release channel of the SR) [83,84]. Activity of the Na/H exchanger is increased in hypertrophy and heart failure [85,86]. In one study [86], this led to an increase in intracellular sodium, which via the Na/Ca exchanger caused intracellular diastolic calcium to increase as well. Another study in the same rabbit model of heart failure, however, found an unaltered diastolic calcium [77], possibly because failure was less severe [86]. It was suggested that inhibition of the Na/H exchanger might be a promising approach to prevent spontaneous calcium release from the SR [86].

The abnormalities of intracellular calcium handling have recently be summarized by Bers et al. as follows: reduced SERCA function, enhanced Na/Ca exchanger function and enhanced SR calcium leak all contribute to the reduced SR calcium load, and thus to the reduced intracellular calcium transient. The relative contributions of these three mechanisms may vary in different models of heart failure and with different degrees of severity of failure [87].

7. Delayed afterdepolarizations

The basis for delayed afterdepolarizations are the calcium-after transients resulting from spontaneous calcium release from the SR [77,81–91]. The after transient associated calcium is removed from the cell by the electrogenic Na/Ca exchanger [43,77,90–92] or by a calcium-activated chloride current [93], providing the transient inward current that causes the delayed afterdepolarization. Delayed afterdepolarizations have indeed been recorded from failing myocardium or isolated myocytes from failing hearts [27,89,90]. In the study by Vermeulen et al. [27] noradrenaline needed to be present in order to elicit delayed afterdepolarizations, and the same was true for the occurrence of calcium-after transients and delayed afterdepolarizations in the study by Baartscheer et al. [88] (see Fig. 2). Pogwizd et al. [89] concluded that three factors combine to enhance the propensity for the occurrence of delayed afterdepolarizations: (1) increased Na/Ca exchanger, providing more transient inward current for any given SR calcium release; (2) a
reduced inward rectifier Ik1, allowing more depolarization for any given transient inward current; (3) residual β-adrenergic responsiveness, required to raise the low SR calcium content to the point at which more spontaneous calcium release occurs. They [89,90] noted the paradox that normally a high SR calcium content is required for spontaneous calcium release, whereas in heart failure, SR calcium content is reduced [77,88,94,95]. Pogwizd et al. [43,89,90] resolved this paradox by the preserved β-adrenergic responsiveness which allows, in the presence of adrenergic drive, the calcium content of the SR to reach the threshold for spontaneous calcium release. As already mentioned, delayed afterdepolarizations and calcium-after-transients only occur in the presence of noradrenaline [27,88], and it is well known that in patients with heart failure catecholamine levels are increased [96]. Another factor facilitating SR calcium release is the increased open probability of the ryanodine receptor [88].

8. Early afterdepolarizations

The role of early afterdepolarizations in heart failure is unclear. They have been observed in isolated ventricular myocytes from dogs with rapid pacing induced heart failure [52,69] and in myocytes from rabbits with left ventricular hypertrophy [57], but only at unphysiologic long cycle lengths ranging from 2000 to 5000 ms. Normally, early afterdepolarizations occur at very long cycle lengths, but in normal canine myocytes, a type of early afterdepolarizations has been described that occurs at cycle lengths between 400 and 1000 ms during β-adrenergic stimulation and disappears at long cycle lengths [97]. In the same myocytes, delayed afterdepolarizations occurred as well, and both types of afterdepolarizations were related to SR calcium release and activation of the Na/Ca exchanger. As pointed out by Sipido et al. [75,98], when the Na/Ca current is inward during the action potential plateau, the increased Na/Ca exchange current might prolong the action potential and set the stage for early afterdepolarizations. It is possible that such early afterdepolarizations might occur in failing hearts. Indeed, Veldkamp et al. [99] found in isolated myocytes from patients with heart failure, stimulated at 1 Hz in the presence of 1 μmol noradrenaline that action potentials prolonged and early afterdepolarizations occurred in 50% of cells. Noradrenaline increased the calcium current, but had no effect on potassium currents. These findings contrast with those of Vermeulen et al. [27]: in isolated rabbit trabeculae from both failing and normal hearts, early afterdepolarizations were found in about 30% of preparations, in the presence of noradrenaline and a low extracellular potassium concentration (3 mM) during slow pacing or after long pauses. In ventricular trabeculae from human hearts, in the same conditions, early afterdepolarizations were never found, not even in preparations from patients that had used class III antiarrhythmic agents in which action potentials were greatly prolonged.
9. Automaticity

Two studies documented automaticity in either ventricular trabeculae [27] or isolated myocytes [52] from failing hearts. In the study by Vermeulen et al. [27], automaticity only occurred when the extracellular milieu had a K⁺ concentration of 3 mM and contained noradrenaline. Unstimulated preparations became automatic, with distinct diastolic depolarization, at a maximal diastolic potential close to −90 mV. The rhythm was slow, with cycle lengths in the order of seconds. In the study of Nuss et al. [52], spontaneous depolarizations that were irregular also had very long cycle lengths in the order of seconds. The spontaneous depolarizations were not likely to be caused by the hyperpolarization-activated current If, since they occurred more frequently when the cells were exposed to cesium, which blocks If. It is possible that the instability of the resting membrane potential, because of the reduction in Ik1 [52,67,69], plays a role, enabling an as yet unidentified inward current to depolarize the membrane. The clinical significance of these spontaneous depolarizations is unclear, but since the rhythms are so slow, it is doubtful whether they could play a role in the intact heart.

10. Mechanisms of ventricular tachycardia

Delayed afterdepolarizations can induce triggered activity leading to sustained rhythms [27]. However, the salvos of triggered activity in in vitro preparations have longer cycle lengths than the ventricular tachycardias in the in vivo animals. It is likely that in the intact animal or human, triggered activity due to delayed afterdepolarizations might initiate reentrant rhythms. Early afterdepolarizations do not trigger new action potentials but can induce dispersion of repolarization, which favors reentry [97].

The major cause for heart failure is coronary artery disease, and a distinction must be made between ventricular tachycardias occurring in failing hearts with a healed infarct, in failing hearts with ischemic cardiomyopathy and in hearts with non-ischemic failure.

Studies in isolated, Langendorff-perfused human hearts with a healed infarction have demonstrated that reentry is the mechanism that maintains ventricular tachycardia [100–103]. Since these studies were performed on isolated hearts of patients that underwent cardiac transplantation because of end-stage heart failure in which the trigger for sustained reentry was a well timed premature electrical stimulus, it is unknown what was the trigger for the tachycardia when the heart was still in the patient. It could well have been one, or several non-reentrant premature beats based on afterdepolarizations. The reentrant circuit was made up of surviving myocardial fibers within the infarct [101], and action potentials and conduction velocity parallel to the long axis of the surviving fibers were normal [100,103]. Sometimes, a macroreentrant circuit could be demonstrated [101,102], but in other hearts, the myocardial fibers and the strands of fibrous tissue were intertwined in such a complex way that reconstruction of the reentrant pathway in the whole heart was impossible. Studies on infarcted isolated muscle showed that excitation proceeded in a zigzag way through surviving fibers embedded in a complex network of connective tissue, and that very “slow” conduction was caused by the greatly prolonged pathway of the excitatory wave [103]. In other words, the structural changes caused by the infarct seemed more important as determinants of arrhythmias than changes in cellular electrophysiology of the myocardium remote from the infarct. That these changes do play a role is shown by a study on dispersion of refractoriness in the remote myocardium of patients with myocardial infarction and either monomorphic ventricular tachycardia, or tachycardia that rapidly degenerated into ventricular fibrillation [104]. In the ventricular fibrillation group, dispersion in refractoriness was several times larger than in the ventricular tachycardia group.

In dogs with prolonged ischemic cardiomyopathy, caused by intracoronary embolization, in which patchy fibrosis was present but no well defined infarct, monomorphic ventricular tachycardia was due to repetitive focal activation of subendocardial sites. Polymorphic tachycardia was due to sequential focal activation from multiple sites. Moderate conduction delays were found, but only when fibrosis was transmural, and no evidence for reentry could be demonstrated [105].

In failing human hearts with dilated or hypertrophic cardiomyopathy, fractionated electrograms and conduction delay, especially of premature beats, could be correlated to sites where there were long, compact strands of fibrotic tissue. However, reentrant excitation could not be demonstrated, nor could tachycardias be induced by premature stimulation [106,107]. In another study on patients with dilated cardiomyopathy, three-dimensional intraoperative mapping was performed, just before cardiac transplantation [108]. Both spontaneous and induced ventricular tachycardia arose from a focal mechanism in either the endocardium or epicardium, and no evidence for macroreentry was found. Similar findings had been reported earlier, although in that study only epicardial mapping was performed [109].

Three-dimensional mapping was also carried out in rabbit hearts in which failure was caused by combined pressure and volume overload. Again, spontaneous ventricular premature beats and ventricular tachycardia were due to non-reentrant mechanisms [110].

11. Summary and conclusions

Heart failure not only causes electrical remodelling on the ventricles but affects sinus node function as well. The intrinsic sinus cycle length is decreased, due to a down-regulation of If, and the muscarinic receptor mediated response to acetylcholine is upregulated. This may be a
protective mechanism since in heart failure, a relatively low heart rate is beneficial. At rapid rates, there is an increased likelihood for the occurrence of delayed afterdepolarizations, and a decreased contractility. The beneficial effects of β-blockers seem to be due in part to the reduction in sinus rate.

Electrical remodeling of ventricular myocytes involves membrane currents that are important for repolarization, and ion exchangers and pumps that regulate intracellular calcium handling. Although the results of the various studies are often inconsistent, Ito, Ik1, Ik, Iks and ICa-L have been found to be decreased, and repolarization, especially at slow heart rates, is delayed. The Na/Ca exchanger and the Na/H exchanger are upregulated, SERCA, is downregulated, and the open probability of the ryanodine receptor is increased. Despite a reduced SR calcium content, spontaneous release of calcium from the SR occurs, especially in the presence of noradrenaline, and activates the Na/Ca exchanger (or possibly a calcium activated chloride current) which causes a transient inward current responsible for delayed afterdepolarizations which can serve as triggers for reentrant rhythms. The role of early afterdepolarizations is less clear, but the prolonged action potential of failing myocardium predisposes to early afterdepolarizations, especially at slow rates, and noradrenaline has been shown to induce early afterdepolarizations in isolated myocytes.

In failing hearts with a healed infarct, ventricular tachycardias are caused by reentrant excitation within the network of surviving myocardial fibers in the infarct. In non-ischemic cardiomyopathies, both in humans and in animal models, ventricular tachycardias are predominantly due to non-reentrant mechanisms, most likely triggered activity caused by delayed afterdepolarizations.

References


