Experimental models of heart failure

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Background Most successful and reproducible animal models of chronic heart failure (HF) include: increased peripheral resistance, rapid ventricular pacing, arteriovenous shunt, supravalvular stenosis, chronic heart block, repetitive transmyocardial direct current (DC) shock. The main limitation of all these approaches was the lack of stability of the left ventricular (LV) dysfunction.

Methods We have described a stable and reproducible animal model of LV dysfunction mediated by ischemic loss of contractive myocardium, which is suitable for chronically studying the complex pathophysiology of HF. This model incorporates conscious dogs with a chronic anterior myocardial infarction (MI). Once the MI is stabilized the progression of the ischemic disease is produced by injecting into the circumflex coronary artery 1–2 cc of latex microspheres to cause embolization of microcirculation. This procedure is repeated 3–5 times over several weeks and, at the end, it results in a spread ischemic damage and a significant loss of ventricular systolic function.

Results The healed MI results in a depression of heart rate variability and baroreflex sensitivity in a subgroup of dogs. In these dogs the depressed vagal control of the heart is associated with elevated arrhythmic risk. On the contrary in dogs with preserved cardiac reflexes the arrhythmic risk is low. In the high risk group a profound electrophysiological remodelling occurs with the MI and progresses once LV dysfunction is created while the low risk dogs tolerate the embolization procedure with a loss in LV function but without the changes in the cardiac electrical stability.

Conclusion Experimental preparations based on a chronic MI and progression of the ischemic damage toward a chronic LV dysfunction has provided important information concerning autonomic and electrophysiologic alterations associated with sudden cardiac death.

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KEYWORDS
Experimental; Ischemia; Heart failure

Introduction

Despite significant progress in the prevention and treatment of cardiovascular diseases, the incidence and prevalence of congestive heart failure (CHF) have been increasing steadily in recent years, especially in the elderly. The most common cause of chronic heart failure is no longer hypertension or valvular heart disease, as it was in past decades, but rather coronary artery disease (CAD). Heart Failure is the consequence of multiple pathophysiological alterations and adaptations, leading to left ventricular (LV) hypertrophy, dysfunction and dilatation, increased systemic vascular resistance and activation of the neuroendocrine system. This latter seems to be most critical component of all as the only

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currently effective pharmacological therapies are b-adrenergic receptors blockers\textsuperscript{6,7} and inhibitors of the angiotensin converting enzyme\textsuperscript{8,9} while other interventions targeted to other important factors of heart failure (HF) such, for instance, TNF had failed to show any efficacy.\textsuperscript{10} The role of the various mechanisms responsible for HF progression is difficult to ascertain in humans because of uncertainty associated with the identification of when HF in fact begins. An added difficulty is the usual confounding influence of concomitant pharmacological therapies. The understanding of left ventricular remodelling and dysfunction is fundamental to describe the natural history of the disease and the efficacy and timing of interventions needed to positively interfere with all the processes leading to HF and, ultimately, cardiac death. In this context it is important to remember that mortality in the early stages of HF is strongly determined by arrhythmic mechanisms while in more advanced stages pump failure is a more frequent mechanism. Because of these many difficulties, animal models of chronic HF are fundamental to describe the complex nature of this disease process and a number of experimental model systems have been generated in various species (see Table 1).\textsuperscript{11} Hereafter, we will briefly review some aspects of the many experimental models of heart failure described in recent years. We will then describe a stable and reproducible animal model of LV dysfunction mediated by ischemic loss of contractive myocardium, which is suitable for studying the complex pathophysiology of this disease process with a specific focus on the electrophysiologic alterations leading to sudden arrhythmic death.

**Experimental approaches to heart failure**

Experimental preparations of HF have involved various interventions including trauma\textsuperscript{12} and toxic depression of cardiac function.\textsuperscript{13} However, these interventions may directly affect neuro-humoral factors independently from the primarily influence of HF, while the experimental preparation should allow quantifiable results that can be extrapolated to the clinical reality of the disease. Others approaches to the creation of an animal model of HF were more successful and reproducible. Such models include increased peripheral resistance,\textsuperscript{14} rapid ventricular pacing,\textsuperscript{15} creation of an arteriovenous shunt,\textsuperscript{16} supravalvular stenosis,\textsuperscript{17} chronic heart block,\textsuperscript{18} repetitive transmyocardial direct current (DC) shock,\textsuperscript{19} but, again, very few of these models generated data that could be consistently translated into human applications.

**Tachycardia-induced cardiomyopathy**

Among the many approaches, the tachycardia induced model has been one of the most used. Sympathetic dependent increased heart rate is a typical initial mani-

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**Table 1**

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<tr>
<th>Techniques</th>
<th>Species</th>
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<td>Naturally occurring models</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>Hamster\textsuperscript{a}, dog, turkey</td>
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<td>Salt-sensitive hypertension</td>
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<td>Experimentally Induced Models</td>
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<td>Myocardial ischemia</td>
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<td>Coronary ligature</td>
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<td>Coronary embolism</td>
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<td>Chronic rapid cardiac pacing</td>
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<td>Ventricular pacing</td>
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<td>Supraventricular pacing</td>
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<td>Pressure overload</td>
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<td>Aortic banding</td>
<td>Rat, guinea pig</td>
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<td>Pulmonary artery banding</td>
<td>Mouse, rat, cat, dog, pig</td>
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<td>Volume overload</td>
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<td>Arteriovenous shunt</td>
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<td>Mitral regurgitation</td>
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<td>Aortic regurgitation</td>
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<td>Toxic cardiomyopathy</td>
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<td>Doxorubicin</td>
<td>Rat, rabbit, dog, pig</td>
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<td>Alcohol</td>
<td>Rat, turkey</td>
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<td>Genetically altered animals</td>
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<td>Dilated cardiomyopathy</td>
<td>Mouse</td>
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\textsuperscript{a} Most frequently used models.
festation of LV dysfunction evolving into HF and high heart rate is indicated as a marker but also a mechanism of the failing heart.

The effect of tachycardia on ventricular structure and function is an important area of research because incessant or chronic elevated heart rate, as it may occur in patients with atrial fibrillation with elevated ventricular responses not adequately modulated by the therapy, produces ventricular dysfunction and dilation. Experimental tachycardia-induced cardiomyopathy was first described by Whipple et al. in 1962. In 1986 Armstrong et al. examined rapid ventricular cardiac pacing as a means of inducing HF in the dog. They instrumented 15 mongrel dogs with a unipolar pacemaker lead placed in the right ventricular apex. Seven animals were paced at 250 beats/min for 3 weeks (VP1 group), an additional series of six animals (VP2 group) was paced until a clear biologic end point for HF was reached. The changes in cardiac size and hemodynamics in the VP1 and VP2 group were compared with those obtained in parallel studies of 10 sham-operated animals. The VP1 group showed an increase in cardiac size, a reduction in mean arterial pressure, a fall in cardiac index and an increase in left ventricular filling pressure. The VP2 group showed similar but more advanced changes. The changes in these two groups were significantly different from those in the group of the sham-operated animals. A neurohumoral evaluation on the animals showed that plasma norepinephrine and renin activity were unchanged in the sham operated animals, whereas in the VP1 group, plasma norepinephrine rose but plasma renin activity did not change. In the VP2 group both norepinephrine and plasma renin rose. In this prospective the tachycardia model reproduces some of the conditions associated with HF and indeed, a large number of animal models including the one we have just described, support the concept that incessant or chronic tachycardia can lead to severe bi-ventricular systolic and diastolic dysfunction characterized by hemodynamic and cardiac structural changes. These changes occur as soon as 24 h after rapid pacing, with continued deterioration in ventricular function for up to 3–5 weeks resulting in end-stage HF. The main limitation of this preparation is that all the mechanical alterations induced by rapid pacing reverse in few days after stopping the treatment. Such a recovery from pacing-induced cardiomyopathy demonstrates that the myopathic process associated with rapid heart rates is largely reversible. Within 48 h after stopping pacing, hemodynamic variables approach control levels, and left ventricular ejection fraction shows significant recovery with subsequent normalization after 1–2 weeks.

Although first devised to mimic tachycardia-induced cardiomyopathy in humans, the model has been invaluable to the general study of heart failure by providing a predictable, although unstable, model of low output biventricular failure. Of specific importance is the information that this model has provided on ionic changes in HF. Marban and Tommaselli indeed documented repolarization abnormalities leading to sudden death due to a significant reduction in the expression of repolarizing currents, namely $I_{to}$ and $I_{k1}$. This loss in repolarizing currents explains the abnormal prolongation of repolarization and its dispersion and describes a potential arrhythmogenic mechanism in HF. Overall, the tachycardia-induced HF models have provided a number of important information concerning cellular and hemodynamic changes occurring in HF. Nonetheless, this model suffers the limitation of being unstable. This feature has made impossible, for instance, a substantial understanding about autonomic mechanisms in HF as they can be derived from the analysis of heart rate. Additionally, fast heart rate is, now a days, an infrequent cause of HF and, thus, some important aspects of this syndrome may be overlooked by using this model. One for all is the fact that the myocardial damage induced by fast pacing is homogeneous and thus, those many aspects that are dependent upon the typical mechanical and electrical dysomogeneity of the failing heart cannot be assessed in this type of preparation. Based in these considerations the attention of experimental investigators has focused on ischemic models of heart failure. This considering that the ethology of LV dysfunction and heart failure is mostly ischemic.

Multiple coronary microembolizations

Initial attempts in the use of microembolization implied a single intracoronary injection of microspheres to produce an extensive myocardial damage. This approach to cause a sustained LV dysfunction was, in most cases, lethal and thus, not suitable for chronic models. However, if the same amount of damage was produced by intermediate steps so that partial recovery was allowed between each ischemic insult, the changes for a longer survival would have been higher. Based on this idea, Sabbah et al. developed a stable model of CHF performing multiple sequential intracoronary embolization with polystyrene latex microspheres. The initial study was performed in 20 dogs in which 3–9 embolizations were performed 1 week apart. The first 3 embolizations consisted of 2 ml of microsphere suspension injected subselectively into either the left anterior descending or left circumflex coronary artery in an alternating fashion. Subsequent embolizations consisted of 3–6 ml of microspheres divided equally between the left anterior descending or left circumflex coronary artery until LV ejection fraction was <35%.

Among the 20 dogs studied six (30%) died before full completion of the study. One dog died 24 h after the first embolization from a rupture posterior wall infarction. The remaining five deaths were due to anesthesia in one dog, cardiac decompensation in two, and sudden and unexpected cardiac death, presumably due to arrhythmias in two dogs. The dogs developed a chronic HF mediated by a loss of contractile myocardium and manifested many of the sequelae of HF including marked depression of LV systolic and diastolic function, LV dilation and hypertrophy, reduced cardiac output, development of mitral regurgitation and elevation of systemic vascular resistance. The depression of LV
function is accompanied, in this model, by activation of the sympathetic nervous system and by increased secretion of ANF. An important feature of this model of HF is the observation of a lack of recovery of LV function once coronary embolization were discontinued. It is likely that multiple embolization, repeated over time, gradually exhausts the compensatory mechanisms to counteract the loss of viable tissue and, therefore, leads to a sustained depression of cardiac function. In the present model plasma norepinephrine concentration increased substantially while plasma renin activity (PRA) remained within normal limits throughout the course of evolving HF. This was at variance from studies in tachycardia induced HF in which both PRA and norepinephrine plasma levels increased. The basis for this disparity is unclear but may reflect the differences in the etiology of HF in these two animal models. It is also possible that in the present model, normal levels of PRA could indicate a state of adequate compensation.

This model may be well suited for studying the pathophysiology of heart failure mediated by loss of contractile myocardium and for the evaluation of the efficacy of pharmacological and other therapeutic interventions. For instance, this model has been used to examine the effects of long-term monotherapy with enalapril, metoprolol and digoxin on the progression of LV systolic dysfunction and LV chamber enlargement. This study proved that in dogs with reduced LV ejection fraction, early long-term monotherapy with enalapril or metoprolol prevents the progression of LV systolic dysfunction and arrests, or attenuates, the process of progressive chamber enlargement. In contrast, early therapy with digoxin, while preventing the progressive decline in LV ejection fraction, does not impede the process of progressive chamber dilation. On the other hand, this experimental preparation has not provided major information about the arrhythmias mechanisms responsible for sudden death in ischemic HF. This mainly because no risk stratification for arrhythmic death has been described in this preparation. The analysis of the arrhythmia pattern in this model has shown that some dogs will develop ventricular tachyarrhythmias but no information has emerged, so far, from studies in this model that had enhanced the understanding of arrhythmic sudden death in HF.

An experimental model of spontaneous sudden death in chronic post-MI ischemic LV dysfunction

The microembolization technique has been applied in a canine model for post-MI sudden death described by Schwartz and Stone. In this earlier model the interaction between acute myocardial ischemia and disturbances in the autonomic nervous system plays a key role in sudden cardiac death, particularly when these factors occur in a myocardium that is electrically unstable because of pre-existing ischemic damage.

The model consists of two stages. In the first stage an anterior wall myocardial infarction (MI) is produced by a permanent ligation of the anterior intraventricular branch of the left coronary artery immediately proximal to the first major diagonal artery perforator. During the same surgical session a pneumatic occluder is placed
around the circumflex branch of the left coronary artery. After thirty days recovery from the MI the dogs are studied and characterized for developing ventricular fibrillation during an exercise and myocardial ischemia test on a motor-drive treadmill. Each dog is exercised submaximally for 12–15 min while the work load increases progressively every 3 min until heart rate reaches a target range of 215–225 beats/min. At that time, left circumflex artery is occluded for 2 min; the treadmill is stopped after the first min of occlusion, while ischemia is maintained for an additional minute. The occurrence or not of ventricular fibrillation (Fig. 1) during the two min of exercise and myocardial ischemia clearly defines two groups of dogs at high risk (SUSCEPTIBLE) and at low risk for sudden cardiac death (RESISTANT). The availability of two groups of dogs with opposite arrhythmia risk profile makes this model unique and allowed the understanding of critical autonomic mechanisms in sudden death. This model indeed generated the first experimental evidence that the analysis of reflex control of heart rate could provide meaningful prognostic information for risk stratification of post-MI individuals.39,40 This finding has been successfully applied clinically and, now a days, baroreflex sensitivity and heart rate variability have a class I A indication for risk stratification of sudden death.42 The unique feature of this chronic animal model has been recently exploited into the major issue of chronic LV dysfunction and HF adding a chronic ischemic damage by multiple microembolizations.43 Sudden cardiac death risk was assessed in 15 dogs with a healed anterior MI by the sub-maximal exercise and brief acute circumflex ischemia test: six dogs were susceptible to SCD (i.e. they developed VF) and were successfully defibrillated and nine were resistant. Baroreflex sensitivity (BRS) was assessed in dogs after MI and proved to be lower in susceptible dogs compared with the resistant group as already described.

Afterwards, ischemic left ventricular dysfunction was induced in the same dogs by repetitive microembolization of the circumflex coronary artery until LV ejection fraction reached 35%. Once stable LV dysfunction was obtained, the incidence of SCD was significantly higher in susceptible dogs. This group developed premature ventricular contractions (PVCs) within days of reaching an LVEF of 35% and progressed rapidly to nonsustained then sustained ventricular tachycardia. By eight weeks, all susceptible dogs died suddenly after having sustained or nonsustained ventricular tachycardia before their death (Fig. 2). Resistant dogs developed only PVCs over a much longer period of time and only one dog died suddenly three weeks after reaching the target LV ejection fraction.

A first major difference that distinguished the two groups was that arrhythmias progression in susceptible dogs was associated with a persistent sinus tachycardia, thus reflecting a significant chronic elevated sympathetic drive. On the other hand, resistant dogs, despite an identical cardiac damage, did not change heart rate throughout the six month follow-up. Susceptible dogs had significantly lower vagal reflex activation measured by baroreflex sensitivity (9.71.5 ms/mmHg susceptible vs. 28 ± 9.8 ms/mmHg, p < 0.01). Furthermore, susceptible dogs had a marked sympathetic activation in response to acute myocardial ischemia as indicated by the fact that heart rates went from 220 ± 19 bpm at coronary occlusion to 265 ± 18 bpm at 30 s of ischemia (p < 0.05). In contrast, resistant animals had controlled heart rates during exercise and coronary occlusion (from 218 ± 14 bpm at coronary occlusion to 231 ± 19 bpm at 30 s of ischemia, p = ns).

Another aspect that differentiated the two groups concerned the ventricular repolarization. QT intervals from susceptible dogs were longer after MI and prolonged within eight weeks after LV dysfunction was established (from 246 ± 26 to 274 ± 56 ms, p < 0.01). In contrast, QT intervals in resistant dogs prolonged to a lesser degree only after 24 ± 6 weeks (from 231 ± 20 to 247 ± 20 ms, p = 0.03).

This first study described a new chronic animal model of ischemic LV dysfunction in which dogs at high risk for spontaneous SCD can be reliably identified. The main findings are that autonomic imbalances (depressed vagal and elevated sympathetic control of heart rate) present before HF develops in subjects with ischemic heart disease, are associated with lethal arrhythmias as LV dysfunction progresses. Moreover abnormal repolarization (QT interval prolongation and the loss of repolarization adaptation to short cycle lengths) complete the high-risk matrix. The implication of this study is that the autonomic and electrophysiological conditions resulting from an MI, even in cases in which the degree of LV damage is limited as in the present model, are critical in determining the outcome once LV dysfunction occurs. It seems that an elevated sympathetic reflex response to ischemia determines a marked hypertrophic response and
electrophysiological derangements that ultimately create the condition for an elevated arrhythmic risk.

The important issue of abnormal ventricular repolarization has been addressed in a very recent study in this same model. Endocardial repolarization has been analysed in detail by the use of electrical mapping.44

In a group of 12 dogs surface QT intervals were obtained at similar cycle lengths to avoid the need of correction algorithms 30 days after MI. The mean RR intervals used for the measurements were 421 ± 21 ms for susceptible and 423 ± 21 ms for resistant dogs. Surface QT intervals were longer in susceptible dogs (240 ± 10 ms) compared to resistant animals (222 ± 7 ms, p = 0.04).

Electrophysiological studies were performed through a femoral arteriotomy during anesthesia (propofol 10 mg bolus induction followed by 2–5 mg boluses for maintenance) using sterile technique. Descriptions of the electroanatomic mapping system (CARTO, Biosense Webster) are.46,47 With the use of a magnetic sensor, the system displayed the location of the mapping catheter relative to the location of a reference sensor taped to the posterior chest (spatial accuracy < 1.0 mm). One hundred to 300 local electrograms were obtained by first confirming adequate catheter contact. Local repolarization time was defined as the interval between the R wave peak and the end of the local T wave. This method was used to decrease the chance for error in identifying local activation. Each electrogram was visually examined and repolarization time was calculated by examining the digitally acquired signal using cursors to measure the time from R wave peak to the end of the local T wave. Regional repolarization kinetics were reconstructed in a 3-D color-coded map (longest-purple, shortest-red). Two operators, blinded to the dog status, determined local repolarization from the local electrograms.

Local repolarization times were recorded from four regions within the LV, which were chosen based on the characteristics of regional remodeling following the anterior MI: (1) the basal anterior wall, which was not directly involved with LAD ligation or acute circumflex ischemia; (2) the anteroapical area, which was chosen to examine repolarization characteristics of the chronic infarct; (3) the lateral wall was evaluated as the area previously exposed to acute ischemia; (4) the anteroseptum, which was chosen as a transition area between the apical infarct and the basal anterior wall.

Histologically unique areas were also evaluated using bipolar upstroke voltage as an indirect marker. Areas with voltages < 1.5 mV were considered scar tissue and > 10.0 mV were considered as hypertrophied areas. Repolarization duration was examined using five measurements selected from each histologic region.

Sinus cycle lengths during endocardial mapping were similar in resistant (400 ± 44 ms) and susceptible (397 ± 31 ms, p = 0.8) dogs. Average endocardial repolarization times using all regions were significantly longer in susceptible (217 ± 36 ms) compared to resistant (196 ± 21 ms, p < 0.001) dogs. Prolonged ventricular repolarization in susceptible dogs was accounted for by a significant delay in the hypertrophied basal anterior wall (239 ± 42 ms), which was longer than other areas of the susceptible ventricle (scar 212 ± 26 ms, p < 0.01, septum 222 ± 28 ms, p < 0.05 and lateral wall 197 ± 35, p = 0.001, Fig. 3). The basal anterior wall of resistant dogs did not have echocardiographic or electrophysiological (electrograms with voltage > 10 mV) evidence of hypertrophy and repolarization was shorter (200 ± 21 ms, p < 0.001) when compared to susceptible dogs. In resistant dogs, repolarization was also shorter in the septum (203 ± 21 ms resistant vs. 222 ± 28 ms susceptible, p < 0.05). No significant regional repolarization differences were found in resistant dogs (Fig. 3). This study demonstrated that regional heterogeneity of ventricular repolarization after MI is an important component of the matrix conducive to development of ischemia dependent lethal arrhythmias. The current data set provides a direct link between post-MI adverse remodeling, enhanced by augmented sympathetic activation, and the electrical consequences on ventricular repolarization associated with high sudden death risk. QT intervals on the surface electrocardiogram were prolonged in high-risk animals as previously demonstrated,45 and are prolonged in humans at high SCD risk.48,49 However, the extent of repolarization heterogeneity was not evident by the mild QT interval prolongation observed.

Based on findings from this study it is possible that surface ECG analysis methods may underestimate the degree of ventricular repolarization abnormalities that contribute to arrhythmogenesis, thus decreasing the measurements’ predictive value.50 Furthermore, the data underscore the need for an accurate understanding of repolarization alterations in the ischemic heart in light of the extensive use of antiarrhythmic and non-cardiovascular drugs that act on repolarizing currents.

The spontaneous ventricular arrhythmia observed in this experimental preparation is most consistent with a reentrant mechanism. Reentrant arrhythmias require unidirectional block and a path of slowed conduction.51 Regional differences in repolarization found in susceptible dogs provide the potential for unidirectional block and the increased refractory gradient in susceptible dogs theoretically increased the likelihood of unidirectional block leading to reentry.

Post-MI depression of BRS and the tachycardic response to acute ischemia documented that susceptible dogs respond to perturbations with sympathetic activation, whereas resistant dogs had stronger vagal reflexes that controlled heart rate during the same acute stimuli following the similar coronary ligation. These observations, obtained in dogs with comparable LV dysfunction, suggest that individual differences in post-MI neural activation are critical to development of a myocardial substrate conducive for lethal arrhythmias. Adverse remodeling after MI is well known, and it is traditionally described in terms of histological52–54 or architectural changes55 over time. Only a few data sets focus on the possibility that the electrical properties of the ventricle remodel after MI or how this remodeling leads to sudden death.56,57 Integrating all the changes resulting from the stimulus of myocardial injury may help elucidate the mechanisms responsible for
Fig. 3 Endocardial repolarization duration maps from a resistant dog (left) and a susceptible animal (right) showing an anteroposterior projection (AP, top), right anterior oblique (RAO, middle) and left anterior oblique (LAO, bottom). Local repolarization durations are color coded with dark-blue and purple representing the longest duration (up to 200 ms) and orange representing the shortest repolarization duration (140 ms). Endocardial repolarization duration was longest in the basal anterior wall of susceptible dogs (From ref.44). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
clinical observations that beta-blocker and ACE inhibitor therapy after MI not only reduce adverse remodeling of the ventricle and progression of ischemic heart disease, but also reduce sudden death.

In the present experimental preparation differences in repolarization heterogeneity between susceptible and resistant dogs may be accounted for by two mechanisms: (1) different tissue responses to autonomic changes associated with the MI. Indeed, autonomic markers (heart rate, baroreflex sensitivity and heart rate variability) in susceptible animals are different compared to resistant dogs even before MI19,60 and respond differently to both acute ischemia38 and chronic infarction over time;58 (2) development of myocardial hypertrophy. This is important since downregulation of repolarizing K+ currents is associated with left ventricular hypertrophy59 resulting in heterogeneity of repolarization currents. Simulation models predict that action potential duration would be prolonged with heterogeneity of Ikr and Ik1 expression.60 It is conceivable that the differences in neural activation seen in this study are key mechanisms in the electrical and histological remodeling that led to high VF risk. In this model, interruption of local sympathetic input to the heart by left stellectomy reduces the incidence of VF61 suggesting that imbalanced sympathetic input to the ventricles is an important factor in arrhythmogenesis.62 It is possible to speculate, therefore, that increased sympathetic activity in susceptible dogs resulted in regional hypertrophy and downregulation of repolarizing potassium channels in specific areas, which lead to heterogeneity of repolarization. These findings represent a bridge between the large body of data primarily focusing on tissue and structural remodeling following MI and how the remodeling itself creates risk for lethal arrhythmias in the context of autonomic imbalance due to a previous MI.

References


