● Special Lecture

Mechano-Electrical Feedback: New Insights and Novel Therapies

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INTRODUCTION

The transduction of the cardiac electrical impulse into a heartbeat is well appreciated as excitation–contraction coupling. The reverse – contraction–excitation coupling or mechano-electrical feedback – is much less well studied or understood. Mechano–electrical feedback is defined as changes in electrophysiologic properties of cardiac tissue in response to contraction, changes in preload or afterload, and generally any mechanical force imposed onto the myocardium.

The first intracellular studies found stretch to shorten APD[1,2]. In MAP recordings from the left ventricular epicardium of the isolated canine heart[3-5], acutely increased mechanical load also resulted in a decrease of APD as well as effective refractory period (ERP). Similar results were found in isolated rabbit hearts[4]. Other investigators, however, reported a lengthening of APD in response to direct myocardial stretch[6-8]. Stretch–induced electrophysiological changes appeared to differ depending on whether acute mechanical stretch was applied in the form of increased preload or increased afterload[3,7,9,10]. The repolarization level at which APD was measured, as well as the mode of ventricular contraction, seemed to explain the conflicting results. Franz et al[7] studied stretch-induced changes in the isovolumically beating canine ventricle and demonstrated that an increase in ventricular volume load with a simultaneous increase in ventricular pressure shortened the APD at early repolarization levels while APD near complete repolarization was lengthened (**Fig. 1**)

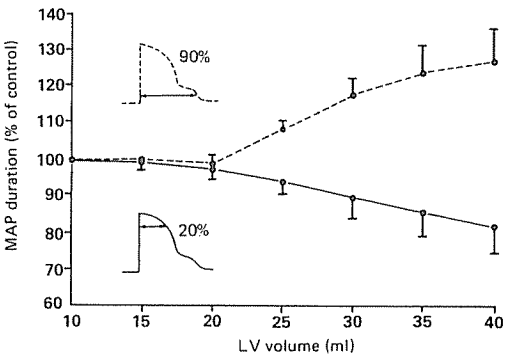

Fig. 1 MAP recordings were obtained from epicardium of isolated cross–perfused canine left ventricles (LV) instrumented with servo–controlled intra–cavity balloon. Data are average ± SD from 6 ventricles beating isovolumically at constant cycle length of 500 msec during 7 volume loading interventions. APD responded divergently depending on the level of repolarization. Plateau duration (APD at 20% repolarization) shortened with increasing volume while APD at 90% repolarization lengthened due to occurrence of afterdepolarizations (see also **Fig. 2**). From Franz et al [7] with permission.

OTHER ELECTROPHYSIOLOGICAL EFFECTS OF STRETCH

A decrease in the resting potential as well as

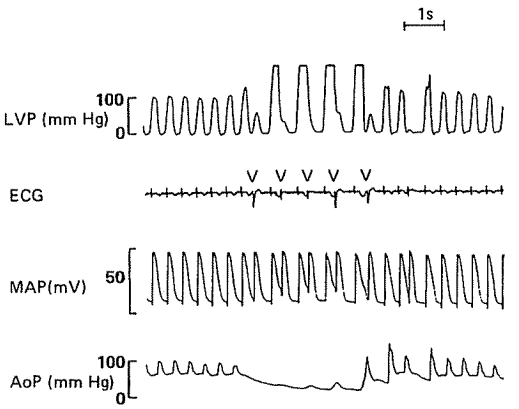

Fig. 2 Afterdepolarizations and ventricular arrhythmia with bigeminal pattern during transient aortic occlusion. See text for details. LVP = left ventricular pressure; AoP = aortic pressure. From Franz et al [7] with permission.

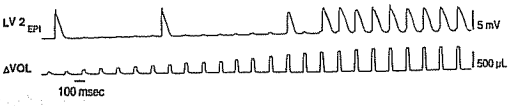

Fig. 3 Volume pulses of increasing amplitude applied to rabbit heart with intra-ventricular fluid-filled balloon. Note diastolic depolarizations during subthreshold pulses and ectopic beats during suprathreshold pulses. VOL denotes balloon volume changes; $LV2_{EPI}$ = one of two epicardial MAP recordings. From Franz et al [11] with permission.

action potential amplitude was reported under various conditions of isovolumic load in both dog[7] and rabbit[11] studies. These findings were in line with data reported from intracellular recordings in Purkinje and ventricular muscle fibers exhibiting both a decrease in resting and AP amplitudes under stretch[12,13]. The studies by Franz et al[7] and Hansen[9] also addressed the question whether preload (i.e. diastolic volume increase) or rather systolic outflow impedance (afterload) are more important for inducing stretch-induced electrophysiological changes. Both studies showed that only increased preload leads to acute stretch-induced electrophysiological changes described above[7].

The effects of suddenly increased afterload on MAP recordings were further demonstrated in *in-situ* hearts of open-chest dogs. When the ascending aorta was transiently occluded with large rubber-coated haemostats, the sudden increase in LVP resulted in afterdepolarizations and premature beats (**Fig. 2**). In this example, the first beat after the onset of the clamp is followed by a premature depolarization which generates relatively little pressure. The beat following the compensatory pause exhibits post-extrasystolic potentiation and an afterdepolarization that triggers another premature depolarization. This sequence repeats itself three times, until release of the aortic clamp.

Electrophysiological Effects of Short Transient Stretch-Importance of Timing during Systole or Diastole

Using a computer-controlled servo motor that drove intraventricular volume via a fluid filled latex balloon inserted in the left ventricle of an intact, isolated rabbit heart model with atrioventricular block and a slow escape rhythm, Franz et al[11] applied a series of volume pulses of successively increasing amplitudes. These volume pulses induced transient diastolic depolarizations that increased in parallel with increase in pulse volume. Above a certain amplitude or threshold, each transient depolarization was associated with a premature ventricular response, i.e. the preparation was "paced" by the volume pulses (**Fig. 3**).

Zabel et al[14] investigated the effects of short volume pulses administered at different times during systole and diastole, in comparison to longer, static stretch of the same amplitude. In this study, both repolarizing and depolarizing responses were observed with a remarkable dependence on the timing of the stretch pulse with respect to the AP phase. A short transient stretch pulse elicited either transient depolarizations when applied during late systole or diastole, or

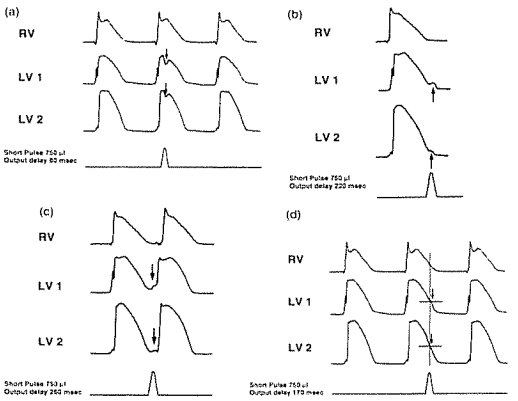

Fig. 4 Short stretch pulses evoke repolarizing during AP plateau (a) and depolarizing when applied during late phase 3 (b) or diastole (c). Minimal effects are seen when stretch pulse is given at mid of phase 3 (d, arrows and bars). RV = right ventricular MAP recording; LV1 and LV2=MAP recordings from 2 left ventricular sites (all epicardial). From Zabel et al [14] with permission.

transient repolarizations when applied during the plateau of the MAP. A stretch pulse placed towards the end of the MAP caused depolarizations that mimicked early afterdepolarizations or, if placed after the MAP, delayed afterdepolarizations. With sufficient amplitude of the stretch–induced (diastolic) depolarizations, premature ventricular contractions were caused.

Stacy et al[15] confirmed these results, however they postulated an accelerated phase 4 depolarization of Purkinje fibers as the mechanism for premature beats. In contrast to "classical" early or delayed afterdepolarizations, stretch–activated depolarizations did not depend on the trigger of a preceding AP. The studies by Zabel et al[14] and Stacy et al[15] could together demonstrate that the amplitude of an SAD is linearly correlated with the amplitude of the underlying stretch pulse. In addition to that, Zabel et al[14] found that the amplitude of a stretch–related *repolarization "dip"* during the plateau phase of the MAP exhibited a similar linear relationship to the stretch pulse amplitude as did the diastolic *depolarization "hump"* (**Fig. 4**). When applying the stretch pulse during early phase 3 of the MAP, the repolarizing deflection was less than during the plateau of the AP. Similarly, stretch–activated depolarizations became smaller when the pulse was moved from full repolarization levels towards a less complete repolarization level. Halfway between these opposing responses, a neutral response to stretch (stretch immunity) was found (**Fig. 4**). It is noteworthy that the peak ventricular pressure falls within the down–slope of the AP and thus within the window of electrophysiological "immunity" (**Fig. 4d**).

The study by Zabel et al[14] extended previous data by Lab[6] in isolated strips and whole frog ventricles also demonstrating opposite electrophysiological stretch effects dependent on the AP phase. Premature beats (excitations) were preceded by stretch–activated depolarizations in several studies in the intact beating canine heart[7,16] or pig heart[17], and man[18] involving a transient outflow tract obstruction as the acute mechanical stretch stimulus.

STRETCH AND ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common sustained arrhythmia, yet the mechanisms that lead to AF are incompletely understood. The occurrence of AF is often associated with hemodynamic or mechanical disorders of the heart, i.e. mitral valve disease, hypertension, or cardiac failure. Likewise, atrial dilatation is a common clinical finding and may play an important role for the susceptibility to AF. Atrial stretch caused by ventricular contraction modulates the atrial flutter cycle length in man[19]. We therefore hypothesized that SAC block by inhibitors such as gadolinium (Gd^{3+}) and GsMtx–4 (a novel peptide isolated from the Tarantula spider *Grammostola spatulata*) might antagonize proarrhythmic effects of myocardial

stretch in the intact heart and tested those effect in a rabbit heart model of stretch-facilitated atrial fibrillation[20,21]

Isolated Heart Preparation

In order to apply graded stretch to the atria, the heart was prepared according to a model previously described[22]. Endocardial electrograms were recorded from the right and left mid-atrial free wall by bipolar 4F catheters introduced through the orifice of the inferior caval vein and a pulmonary vein. To test the inducibility of atrial fibrillation, burst pacing was performed through bipolar epicardial hook electrodes attached to both atrial appendages. Stimuli of 1 ms pulse duration and threefold diastolic pacing threshold were applied for 15 sec at 50Hz. Intra-atrial pressure was increased progressively from 0 cmH_2O in steps of 2–3 cmH_2O. Hearts were allowed to adapt to each new pressure level for two minutes before a burst pacing sequence was delivered. AF was defined as inducible when a fast irregular rhythm was maintained $>$ 2 sec after cessation of burst pacing. Sustained AF was defined as a fast irregular rhythm that lasted for more than 60 sec after cessation of burst pacing and could only be terminated by lowering pressure. The pressure level was increased until sustained atrial fibrillation was induced, or a pressure level of 30 cmH_2O was reached.

Effect of Acute Stretch on AF Inducibility

In the un-dilated atrium at a pressure of 0 cm H_2O, burst pacing did not induce AF. After an increase in atrial pressure, AF could be induced in each preparation. The initial AF response seen during a stepwise pressure increase was predominantly non-sustained, while sustained AF emerged at greater pressure levels. AF inducibility in response to increasing pressure followed a sigmoidal curve (**Fig. 5**). On average, intra-atrial pressure needed to be raised to 8.8 ± 0.2 cmH_2O (P50) to produce AF after cessation of burst pacing. A further increase of intra-atrial pressure to 11.6 ± 0.6 cmH_2O ($p < 0.01$) was required to induce sustained AF (longer than 60s). Sustained

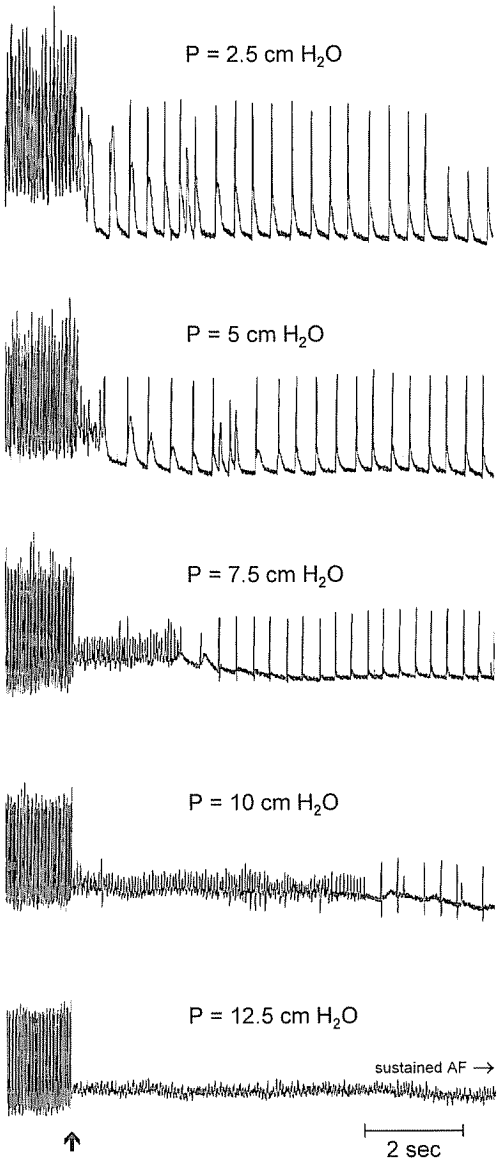

Fig. 5 Effect of atrial pressure (P) on AF inducibility and AF duration. Bipolar atrial electrograms after cessation of burst pacing during a stepwise increase in P. While no AF response to burst pacing was observed at P= 2.5 cmH_2O, the atrium maintained AF progressively longer after adaptation to higher P. AtP = 12.5 cmH_2O, AF became sustained[20].

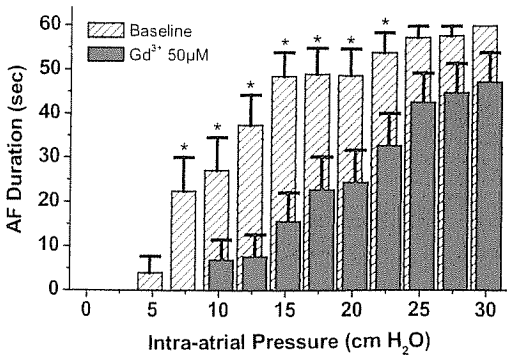

Fig. 6 Duration of induced AF in 16 hearts as a function of intra-atrial pressure (mean ± SE). Gd^{3+} 50 μM decreased average AF duration compared to baseline. * $p < 0.05$[20].

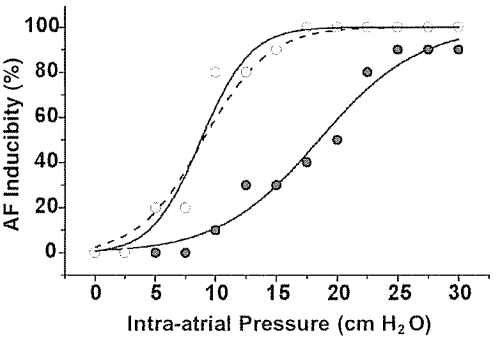

Fig. 7 Inducibility of AF induction (> 2s) plotted as a function of atrial pressure at baseline (○) and during application of GsMtx-4 0.75mg/L(●); n = 10[23].

AF terminated promptly upon pressure release. **Fig. 5** demonstrates how the average duration of AF episodes lengthened as intra-atrial pressure was increased. Spontaneous AF occurred in 5 hearts when intra-atrial pressure increased to 13.8 ± 3.3 cmH_2O. Premature depolarizations often preceded runs of AF.

Effect of Gd^{3+} on AF Inducibility

Gd^{3+} at 50 μM suppressed AF inducibility in all hearts studied. Subsequently, the dose-dependence of Gd^{3+} effects on AF inducibility was examined by adding Gd^{3+} to the perfusate in serial concentrations of 12.5, 25 and 50 μ M, allowing 15 min for equilibration. The AF response to burst stimulation with increasing atrial pressure was assessed at each concentration and after a 20 min washout period. In 6 hearts exposed to successive doses of Gd^{3+}, the vulnerability to AF decreased progressively (**Fig. 5**).

The intra-atrial pressure associated with a 50 % probability of AF induction (P50) showed a linear correlation ($r = 0.99$; $p < 0.005$) with Gd^{3+} concentration over the 0 to 50 μM dose range. P50 increased by 0.15 cmH_2O/ μ mol/L Gd^{3+}. P50 increased significantly during each step of increasing Gd^{3+} doses ($p < 0.01$). Each experiment lasted about 3 hours. Yet, time-related changes in the preparation could not have accounted for the observed reduction in AF vulnerability, since the effect of Gd^{3+} was largely reversible after 20 min of washout ($p < 0.01$ compared to Gd^{3+} 25 μM and 50 μM).

The effect of 50 μM Gd^{3+} was investigated in a total of 16 experiments. In each preparation, the lowest atrial pressure that had enabled AF induction in controls, was no longer sufficient to maintain AF during Gd^{3+}. Instead, intra-atrial pressure needed to be increased to significantly higher levels to obtain AF. P50 for AF induction was shifted to 19.0 ± 0.5 cmH_2O ($p < 0.001$). On average, atrial pressure needed to be elevated to 21.9 ± 0.4 cmH_2O to obtain sustained AF after Gd^{3+} ($p < 0.001$ versus baseline). Gd^{3+} (50 μM) markedly decreased the average duration of induced AF at pressures between 7.5 cm H_2O and 22.5 cmH_2O ($p < 0.05$; **Fig. 6**). Spontaneous AF was no longer observed during the stepwise increase in atrial pressure after Gd^{3+} was added.

Effect of GsMtx-4 on vulnerability to AF

After application of GsMtx-4 (0.75mg/L) in 10 hearts, induction of AF required a significantly higher atrial pressure of 18.5 ± 0.5 cmH_2O ($p < 0.001$; **Fig. 7**). This represented an increase of 9.7 ± 0.6 cmH_2O as compared to baseline ($p <$

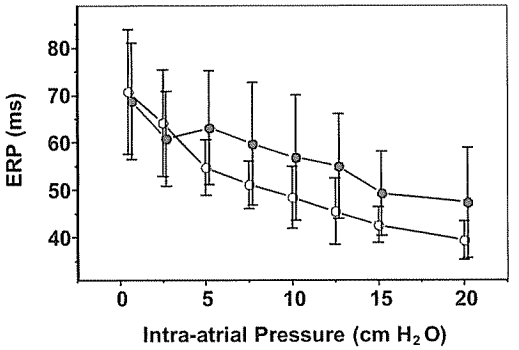

Fig. 8 Right atrial effective refractory period (ERP) measured in 7 hearts as a function of atrial pressure (mean ± SD). ERP progressively decreased with a rise in atrial pressure during control (○). ERP was unchanged after GsMtx-4 0.75mg/L(●)[23].

0.001). Sustained AF was obtained at 24.8 ± 0.6 cmH_2O after GsMtx-4, which was 13.2 ± 0.6 cmH_2O above baseline pressure ($p < 0.001$). The average duration of AF decreased significantly at intra-atrial pressures between 10 cmH_2O and 27.5 cmH_2O ($p < 0.05$). GsMtx-4 effects were reversible upon washout.

Atrial refractoriness

The effect of SAC-blockade on atrial refractoriness was evaluated in 15 hearts. The free right atrial mid wall was paced in close proximity to the recording electrode at twice diastolic threshold strength.

After a 10 beat train at 250 ms basic cycle length, a premature stimulus was introduced during electrical diastole. The coupling interval was shortened in 1 ms decrements until it failed to induce a propagated response, defining the effective refractory period (ERP). Measurements were performed at increasing atrial pressure levels during baseline and after a 15 min period of perfusion with Gd^{3+} 50 μM ($n = 8$) and GsMtx-4 0.75mg/L ($n = 7$), respectively. Again, atria were given two minutes to adapt to each pressure level before ERP determination. The right atrial ERP progressively shortened with an increase in atrial pressure (**Fig. 8**). On average, ERP shifted from 78 ± 3 ms at 0.5 cmH_2O to 52 ± 3 ms at 20 cmH_2O ($p < 0.05$). After application of 50 μM Gd^{3+}, this ERP-pressure relationship was maintained. ERP decreased from 73 ± 3 ms at 0.5 cmH_2O to 54 ± 2 ms at 20 cmH_2O. At each pressure step, ERP was unchanged from baseline. Likewise, ERP was not significantly altered compared to baseline after application of GsMtx-4. However, there was a slight tendency towards longer ERPs at atrial pressures above 2.5 cmH_2O (**Fig. 5**).

SAC BLOCKERS AS ANTIARRHYTHMIC AGENTS

In our studies, the most potent blockers of SACs, Gd^{3+} and GsMtx-4, reduced the vulnerability to AF during acute atrial dilatation. They impeded electrical burst initiation of AF, hampered maintenance of burst-induced AF and suppressed the generation of spontaneous AF during stretch. This is the first direct evidence that block of SACs counteracts the proarrhythmic effect of acute myocardial dilatation on the inducibility and maintenance of a sustained arrhythmia. It is also the first report to prove that the GsMtx-4 peptide modulates electrical tissue properties when employed in a whole heart model.

The electrical vulnerability to stretch has been attributed to concurrent reductions in APD and ERP resulting in decreased wavelength of atrial excitation. A high correlation between ERP shortening and AF inducibility in a recent study by Ravelli and Allessie[22] supports this hypothesis. Our data confirm these previous results by demonstrating a decrease in ERP and increased AF manifestation with progressive atrial stretch. Yet, we found the local atrial ERP response largely unaltered after application of Gd^{3+} and GsMtx-4, while the vulnerability to AF was significantly reduced. Apparently, shortening of ERP alone is

insufficient to explain the increased susceptibility to AF during stretch. Acute atrial dilatation increases the spatial dispersion of atrial refractoriness[24]. The inhomogenous structure and wall thickness of the atria can create regional differences in wall stress during elevated intra-atrial pressure. The nonuniform distribution of local atrial ERP due to heterogeneous wall stress could provide a basis for the initiation and maintenance of atrial reentry during stretch[24]. SAC block by Gd^{3+} or GsMtx-4 might interfere with local electrical properties dependent on the magnitude of regional wall stress and possibly reduce ERP dispersion.

The wavelength of the atrial impulse is also determined by myocardial conduction properties. The effect of acute myocardial stretch on intra-atrial conduction time has recently been evaluated in the rabbit atrium. Uniform conduction was observed in the unstretched atrium[24]. With an increase in atrial pressure, conduction velocity decreased in areas of delayed conduction, and local conduction block occurred. Alterations in conduction time depending on atrial load could influence the susceptibility to atrial reentry. If SAC were to be involved in stretch-dependent changes in atrial conduction time, SAC block can be expected to mitigate them. This needs to be further elucidated.

The increased atrial irritability during stretch manifested in spontaneous onset of AF. A rise in atrial pressure elicited non-sustained runs of AF initiated by premature depolarizations. This is in accordance with previous observations in dog hearts that developed spontaneous atrial arrhythmias upon atrial balloon dilatation[25]. A possible explanation for premature depolarizations is the occurrence of afterdepolarizations. Sustained atrial stretch induced afterdepolarizations that were abolished by SAC blockade[25]. Afterdepolarizations have been reported to account for onset of polymorphic atrial tachycardia degenerating into AF[26,27].

SUMMARY

The electrophysiological effects of pulsatile stretch, stretch generated by increased preload and afterload, and acute static mechanical stretch can be explained by the existence of SACs. As expected from the known characteristics of these channels, stretch generates a repolarizing response during systole, a neutral response in the middle of phase 3 near the reversal potential of SACs, and a depolarizing response during diastole. The latter response may mimic early afterdepolarizations that can induce propagated ventricular excitation. Sustained stretch increases the dispersion of ventricular excitability, refractoriness, and electrical load. This causes variations in conduction velocity, facilitating re-entrant arrhythmias. There appears to be ample experimental evidence that mechanical load alters electrophysiology in a way that is likely to facilitate the induction and/or sustenance of ventricular arrhythmias.

Recent studies show that SAC blockade modulates the electrical properties of the intact rabbit atrium during acute dilatation, with minimal effects on normal excitability. Despite the differences in chemical structure, both GsMTx-4 and Gd^{3+} suppressed fibrillation in a similar manner without altering the stretch-dependence of the ERP. A decrease in the stretch-induced vulnerability to AF was consistent with the concept that facilitation of AF is mediated by SACs. Blocking SACs may therefore represent a novel antiarrhythmic approach to specifically diminish the proarrhythmic effect of acute atrial stretch towards AF. While Gd^{3+} lacks specificity and cannot be used under physiological conditions, GsMtx-4 should prove useful for studying mechanical transduction from the level of molecules

to organisms and may be the first member of a new class of antiarrhythmic agents.

References

1) Dudel J, Trautwein W. Das Aktionspotential und Mechanogramm des Herzmuskels unter dem Einfluss der Dehnung. Cardiologie 1954;25:344.
2) Kaufmann R, Lab MJ, Hennekes R, Krause H. Feedback interaction of mechanical and electrical events in the isolated ventricular myocardium (cat papillary muscle). Pfluegers Arch 1971;332:96.
3) Lerman BB, Burkhoff D, Yue DT, Franz MR, Sagawa K. Mechanoelectrical feedback: independent role of preload and contractility in modulation of canine ventricular excitability. J Clin Invest 1985;76:1843–50.
4) Calkins H, Maughan WL, Kass DA, Sagawa K, Levine JH. Electrophysiological effect of volume load in isolated canine hearts. Am J Physiol 1989;256:H1697–706.
5) Calkins H, Maughan WL, Weisman HF, Sugiura S, Sagawa K, Levine JH. Effect of acute volume load on refractoriness and arrhythmia development in isolated, chronically infarcted canine hearts. Circulation 1989;79:687–97.
6) Lab MJ. Mechanically dependent changes in action potentials recorded from the intact frog ventricle. Circ Res 1978;42:519–28.
7) Franz MR, Burkhoff D, Yue DT, Sagawa K. Mechanically induced action potential changes and arrhythmia in isolated and in situ canine hearts. Cardiovasc Res 1989;23:213–23.
8) Costard-Jackle A, Franz M. Indication of myocardial "memory". Gradual, persisting modulation of myocardial decrease in excitation following change in the activation sequence. Z Kardiol 1989;78:797–803.
9) Hansen DE. Mechanoelectrical feedback effects of altering preload, afterload, and ventricular shortening. Am J Physiol 1993;264:H423–32.
10) Coulshed DS, Cowan JC. Contraction–excitation feedback in an ejecting whole heart model–dependence of action potential duration on left ventricular diastolic and systolic pressures. Cardiovasc Res 1991;25:343–52.
11) Franz MR, Cima R, Wang D, Profitt D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias [published erratum in Circulation 1992; 86:1663]. Circulation 1992;86:968–78.
12) Penefsky ZJ, Hoffman BF. Effects of stretch on mechanical and electrical properties of cardiac muscle. Am J Physiol 1963;204:433.
13) Boland J, Troquet J. Intracellular action potential changes induced in both ventricles of the rat by an acute right ventricular pressure overload. Cardiovasc Res 1980;14:735–40.
14) Zabel M, Koller BS, Sachs F, Franz MR. Stretch-induced voltage changes in the isolated beating heart: importance of the timing of stretch and implications for stretch-activated ion channels. Cardiovasc Res 1996;32:120-30.
15) Stacy GP, Jr, Jobe RL, Taylor LK, Hansen DE. Stretch-induced depolarizations as a trigger of arrhythmias in isolated canine left ventricles. Am J Physiol 1992;263:H613–21.
16) Benditt DG, Kriett JM, Tobler HG, Gornick CC, Detloff BL, Anderson RW. Electrophysiological effects of transient aortic occlusion in intact canine heart. Am J Physiol 1985;249:H1017–23.
17) Dean JW, Lab MJ. Effect of changes in load on monophasic action potential and segment length of pig heart in situ. Cardiovasc Res 1989;23:887–96.
18) Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Changes in myocardial repolarization in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction–excitation feedback in humans. Circulation 1988;77:70–7.
19) Ravelli F, Disertori M, Cozzi F, Antolini R, Allessie MA. Ventricular beats induce variations in cycle length of rapid (type II) atrial flutter in humans. Evidence of leading circle reentry. Circulation 1994;89:2107–16.
20) Bode F, Katchman A, Woosley RL, Franz MR. Gadolinium decreases stretch-induced vulnerability to atrial fibrillation. Circulation 2000;101:2200–5.
21) Bode F, Kilborn M, Karasik P, Franz MR. The repolarization–excitability relationship in the human right atrium is unaffected by cycle length, recording site and prior arrhythmias. J Am Coll Cardiol 2001; 37:920–5.
22) Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff–perfused rabbit heart. Circulation 1997;96:1686–95.
23) Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation. Nature 2001;409:35–6.
24) Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol 1996;7:833–42.
25) Tavi P, Laine M, Weckstrom M. Effect of gadolinium on stretch-induced changes in contraction and intracellularly recorded action- and afterpotentials of rat isolated atrium. Br J Pharmacol 1996;118:407–13.
26) Bers DM, Li L, Satoh H, McCall E. Factors that control sarcoplasmic reticulum calcium release in intact ventricular myocytes. Ann N Y Acad Sci 1998; 853:157–77.
27) Kirchhof P, Eckardt L, Monnig G, Johna R, Loh P, Schulze-Bahr E, Breithardt G, Borggrefe M, Haverkamp W. A patient with "atrial torsades de pointes". J Cardiovasc Electrophysiol 2000;11:806–11.