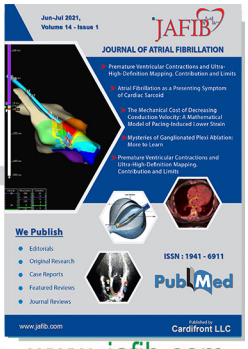
JAFIB
Original Research
Journal of Atrial Fibrillation




www. jafib.com

# The Mechanical Cost of Decreasing Conduction Velocity: A Mathematical Model of Pacing-Induced Lower Strain

*Ibrahim Marai[1,2], David Carasso[3], Shaqed Carasso[4], Shemy Carasso[1, 2]*

[1]Cardiovascular division, B Padeh Poriya Medical Center, Poriya, Israel
[2]The Azrieli Faculty of Medicine, Bar Ilan University, Zefat, Israel
[3]Faculty of Electrical Engineering, the Technion, Israel Institute of Technology, Haifa, Israel
[4]Department of Cell Biology and Cancer Science, The Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Technion Integrated Cancer Center, Haifa, Israel

## Abstract

**Purpose :** To simulate the effect of decreasing conduction velocity (Cvel) on average segmental myocardial strain using mathematical modeling.

**Method:** The simulation was run using MatLab version 7.4 (The MathWorks, Inc. Natick, Massachusetts). A normal strain-time curve pattern was sampled from a normal human echo study using the 2D strain imaging software (GE Healthcare, Milwaukee, Wisconsin). Contraction was simulated from simultaneous segmental activation (Cvel=∞) through normal activation (Cvel=400cm/sec) to pacing Cvel (100 to 10cm/sec). The simulation generated average segmental strain-time waveforms for each velocity and peak strain as a function of Cvel and time to peak strain as a function of Cvel curves.

**Result:** With decreasing Cvel, average peak segmental strain was found to be decreased and delayed. The following correlation equation represents the correlation between peak strain and Cvel : strain= $-20.12+27.65 \times e^{(-0.29 \times Cvel)}$. At the highest pacing Cvel (100cm/sec) average peak segmental strain dropped by 10%, at 50cm/sec by 30% and at the lowest pacing Cvel (10cm/sec) peak strain dropped by >90%. Time to peak segmental strain was minimally longer with decreasing Cvel down to 70cm/sec (pacing velocity range). Further decreased velocity dramatically increased time to peak strain of the simulated segment.

**Conclusion:** The simulation yielded a predictive correlation between slower conduction velocities and decreased and delayed segmental strain.

## Introduction

Cardiac resynchronization therapy (CRT) has proven helpful in patients with heart failure (HF) and ventricular dyssynchronization [1-4]. The major concept being an attempt to resynchronize early and delayed opposing wall contraction. It is easily understandable how dyssynchronized wall contraction results in lower average function . Right ventricular pacing has been shown to adversely affect left ventricular systolic and diastolic function [5,6]. However, biventricular pacing has not been universally successful and even detrimental in some patients [7,8].

Conduction velocity (Cvel) in the Purkinje system is 2 to 4 M/sec, while the Cvel in muscle is 0.5 to 1 [9]. As the Cvel during pacing is reduced by 4-10 fold, the electrical impulse propagates sequentially via myocardium causing intra-segmental delay. By applying similar reasoning that correlates reduced left ventricular function due to delayed wall contraction, sequential myocardial cell activation and contraction may result in less average shortening compared to the normal simultaneously activated segmental shortening. We used mathematical modeling to simulate average segmental strain to Cvel correlation.

## Methods

The simulation was run using MatLab version 7.4 (The Math Works, Inc. Natick, Massachusetts). A normal strain-time curve pattern was sampled from a normal human echo study using the Echo PAC PC 2D strain imaging software (GE Healthcare, Milwaukee, Wisconsin). It was generated from 10 healthy volunteers in sinus rhythm at a heart rate of 60-70 beats per minutes. Long axis echocardiographic views were analyzed using Siemens Velocity Vector Imaging (Mountain view, CA, USA) and generated 18 segments strain curves per subject.

## Key Words

Strain, Pacing, Conduction Velocity.

**Corresponding Author**
Ibrahim Marai MD, Cardiovascular division, B PadehPoriyaMedical Center, Poriya, Israel.

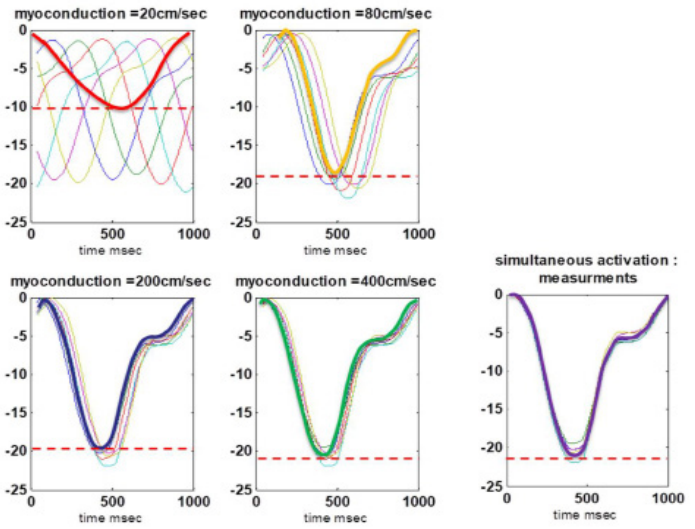



**Figure 1:** **Strain-time waveforms within a segment in different conduction velocities (Cvel) are showed. With low Cvel of the pacing range (less than 100 cm/sec), the waveforms (dashed lines) within a segment were sequentially generated, while with increasing Cvel (≥200 cm/sec), the waveforms became more and more overlapped until being simultaneously generated when the velocity is within or above the range of normal Cvel (≥400 cm/sec). The bold curve generated from the summation of the strain-time waveforms within a segment represents the average strain-time waveform of the segment in each Cvel.**

All 180 segmental curves were normalized to cycle length to generate an average strain curve for the model. This pattern was set as the single sarcomere (oscillator) shortening waveform. The following parameters were entered for segmental representation in the simulation : segmental length of 5cm, myocardial cell length 120μm, 50% longitudinal overlap between cells, and 60 oscillators per cell[10]. All oscillators within a single cell were activated simultaneously. Contraction was simulated from simultaneous segmental activation (Cvel=∞) through normal activation (Cvel=400cm/sec) to pacing conduction velocities (100 to 10cm/sec). The simulation generated sequential strain-time waveforms within a segment and average segmental strain-time waveform for each velocity (figure 1). This simulation also generated average peak segmental strain as a function of Cvel and time to average peak segmental strain as a function of Cvel curves.

### Statistical evaluation

Strain and time-to-peak strain relationship to Cvel was assessed using curve-fitting quadratic regression analysis.

## Results

The strain-time waveforms within a segment are showed in figure 1. With low Cvel of the pacing range (less than 100 cm/sec), the waveformswithin a segment were sequentially generated, while with increasing Cvel (≥200 cm/sec), the waveforms became more and more overlapped until being simultaneously generated when the velocity is within the range of normal Cvel( ≥400 cm/sec) .

With decreasing Cvel the average peak segmental strain decreased and was increasingly delayed (Figure 1,2 ). The decrease in average peak segmental strain followed the following correlation equation (Figure 3): strain= -20.12+27.65 x $e^{(-0.29 \times Cvel)}$. The first part of the formula (-20.12) represents normal peak strain and the second part (27.65 x $e^{(-0.29 \times Cvel)}$) represents a negative exponential function. Maximal average peak strain plateaued at Cvel conduction of 400 cm/sec. Increasing the velocity above 400 cm/sec did not further increase strain. However, decreasing Cvel caused an exponential reduction in strain. At the highest pacing Cvel (100cm/sec) the average peak segmental strain dropped by 10%, at 50cm/sec it dropped by 30% and at the lowest Cvel (10cm/sec) strain dropped by more than 90%.

Figure 4 represents time-to-average peak segmental strain correlation with Cvel, following the equation: time-to-peak strain = 360+ 406 x $e^{(-0.04 \times Cvel)}$. Time to peak strain was minimally longer with decreasing Cvel down to 70cm/sec (within the pacing velocity range). Further decreased velocity dramatically elongated time-to-peak strain of the simulated segment.

## Discussion

### Simulation and experimental results

The simulation yielded a predictive correlation between slower conduction velocities and decreasing peak segmental strain and increasing delay in its timing, resulting from intra-segmental, or microscopic dyssynchrony. This is very similar to wall (macro) dyssynchrony found in some of the dilated cardiomyopathy patients. It is easily understandable how misaligned wall peak contractions cause a decrease in global strain, forming the basis for resynchronization therapy. Our simulation demonstrates that the same phenomenon may happen microscopically within a single segment, adversely affecting its potential maximal strain in a predictable way related to Cvel. Pacing reduces Cvel to levels that would reduce peak segmental strain in the range of 10% to 90%. As the simulation is not linear an average pacing velocity of 50 cm/sec would be expected to decrease strain by 30%.

Reduced Cvel and dyssynchrony may cause molecular changes including ion channels and electrical alterations that are similar in

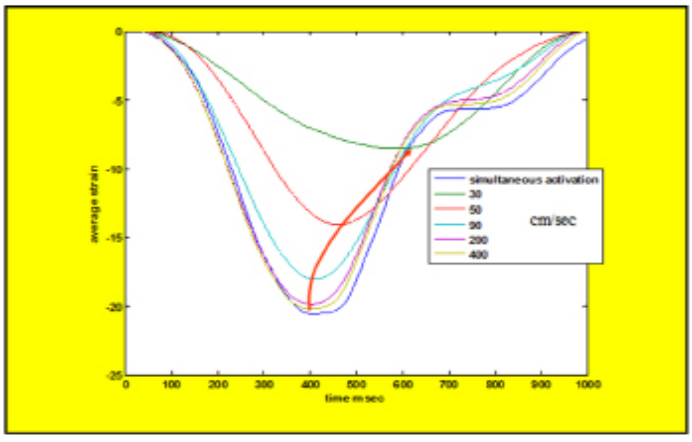



**Figure 2:** **Average longitudinal segmental strain-time curve patterns at various conduction velocities from simultaneous segmental activation (conduction velocity =∞) through normal activation (400cm/sec) to pacing conduction velocities (<100cm/sec). With decreasing conduction velocity, the average peak longitudinal segmental strain decreased and delayed.**

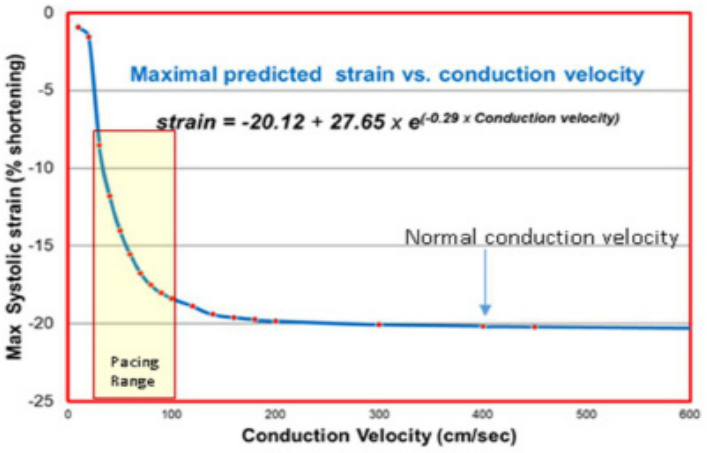



**Figure 3:** **Average peak longitudinal segmental strain (max systolic strain) to conduction velocity correlation. The decrease in average peak strain with decreasing conduction velocity followed the following correlation equation : strain (%)= -20.12+27.65 x e [-0.29 x conduction velocity (cm/sec)]**

some aspects to those in HF and reduced ejection fraction. Chronic left ventricular dyssynchrony due to regionally delayed electrical activation can induce regional and global molecular signalling that alters excitation –contraction coupling, energetics, arrhythmia susceptibility, and myocardial survival [11]. Moreover electrical conduction delay and mechanical dyssynchrony can trigger complex biomolecular changes beyond the known changes in HF [11]. Spragg et al [12] found in animal model that left ventricular dyssynchrony in failing hearts generates myocardial protein dysregulation concentrated in the late-activated, high-stress lateral endocardium. Such molecular polarization within the left ventricle creates transmural and transchamber expression gradients of calcium handling and gap junction proteins that may worsen chamber function and arrhythmia susceptibility.In another study [13], it was demonstrated that left ventricular dyssynchrony induces regional differences in potassium and calcium currents, which increased action potential duration in the lateral wall. Early after depolarizations were increased in the dyssynchronous failing heart.

## Significance of the results

The understanding that pacing has a contractility cost may be very important to decision making related to pacemaker implantation in various indications, weighing mechanical cost vs. benefit of pacing. Moreover, as our simulation does not simulate pacing per-se, but rather the effect of decreasing Cvel, it can be generalized to the effect of native conduction defects. Thus, bundle branch blocks would be assumed to decrease contractility at segmental level above and beyond the creation of overall left ventricular dyssynchrony. Importantly, average Cvel at pacing sites adjacent to the conduction system (the conduction system could be early invaded by the electrical impulse generated by the pacing site and thus activates directly part of the myocardium) could be higher than at sites far from the conduction system. This may explain the differences that could be in contraction in different pacing sites and different forms of fascicular blocks and intraventricular conduction delays.

Specifically in patients candidates for biventricular pacing, higher baseline lateral strain would seem important to identify as pacing may decrease it beyond the power gain from realigning dyssynchronized walls. Moreover, the Cvel at the pacing segment can be measured during implantation to try to predict the mechanical cost of pacing. Finally this predictable loss of contractility could be used in situations where it me be desirable as in obstructive cardiomyopathy.

Beyond the understanding that pacing may reduce myocardial function and work efficiency, the results of this model support contemporary trends of engaging the conduction system in pacing. This may be especially important in patients with reduced ejection fraction before pacing to avoid further functional impairment. This could be assessed during lead positioning by echocardiographic strain imaging to assure best activation patterns with the least impact on contraction. However, the clinical benefit of this strategy should obviously be validated in a clinical trials. Recently, conduction system pacing (His bundle pacing or left bundle branch pacing) has been suggested to restore and retain normal electrical activation of the ventricles or to achieve electrical synchrony of the left ventricle [14,15]. His bundle pacing and left bundle branch area pacing have emerged as alternative method for CRT in patients with HF and left bundle branch block [16,17]. Our simulation suggests yet another advantage for that procedure maximizing contraction and timing of the paced segments. It may help selecting patients for this new procedure.

Theoretically, this model can be applied to atrial myocardium. Pacing at different sites in the atria may cause to different strains as the Cvel is not similar on all parts of atria. For example, Cvel along Crista Terminalis and Bachmann's bundle is relatively higher compared to other sites, and Cvel may be lower at fibrotic sites compared to normal sites. The clinical significance of pacing from different sites is not clear. Indeed, small studies have previously indicated that atrial pacing may precipitate atrial fibrillation [18,19]. Two large randomized studies have shown that low inter atrial septal pacing is superior to right atrial appendage pacing in preventing persistent or permanent atrial fibrillation in patients with sinus node dysfunction and intra-atrial conduction delay [20,21].In the other hand, no association between the

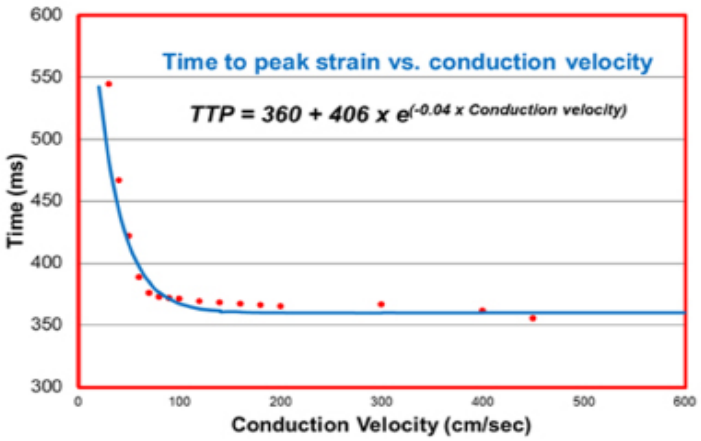



**Figure 4:** **Time to average peak longitudinal segmental strain (TTP) to conduction velocity correlation. The correlation followed the equation: TTP (msec)= 360+ 406 x e [-0.04 x conduction velocity (cm/sec)].**

percentage of atrial pacing and the development of atrial fibrillation was found in patients with sick sinus syndrome in other study [22].

## Limitations

The simulation does not incorporate cellular pre-stretching by earlier activated cells. This is hard to account for, as it is dependent on tissue compliance that may vary according to left ventricular dysfunction etiology. Pre-stretching would adversely affect strain even more, thus the simulation may underestimate the effect of conduction velocity on strain.

## In Summary

The simulation yielded a predictive correlation between slower conduction velocities with a decreasing segmental strain and with increasing delay in its timing, resulting from intra-segmental, or microscopic dyssynchrony. Clinical studies are needed to confirm the clinical significance of this model

## References


1. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al. Longterm clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 2002;39:2026-33.
2. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
3. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. MIRACLE Study Group. Cardiac resynchronization in chronic heart failure.N Engl J Med 2002;346:1845-53.
4. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L and Tavazzi L. for the Cardiac Resynchronization — Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in Heart Failure.N Engl J Med 2005;352:1539-49.
5. Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J III, Schalij MJ, Bax JJ. Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. J Am Coll Cardiol. 2007;50:1180–1188.
6. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol. 2006;48:1642–1648.
7. Bax JJ, Van der Wall EE, Schalij MJ. Cardiac resynchronization therapy for heart failure. N Engl J Med 2002;347:1803-4.
8. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, et al. Tissue Doppler imaging is superior to strain rate imaging and post systolic shortening on the prediction of reverse remodeling in both ischemic and non ischemic heart failure after cardiac resynchronization therapy. Circulation 2004;110:66-73.
9. Lister JW, Klotz DH, Jomain SL, Stuckey JH, Hoffman BF. Am J Cardiol 1964:14:494-503.
10. Masuda H, Yamauchi M, Yoshida M, Takahashi M, Nanjo H, Asari Y, Sugita A: Side-to-side linking of myocardial cells in hypertrophic cardiomyopathy: whole heart microscopic observation with tangential sections. Path Int 2005, 55:677–687.
11. Cheng A, Helm RH, Abraham TP. Pathophysiological mechanisms underlying ventricular dyssynchrony. Europace 2009; 11: v10–v14.
12. Spragg DD, Leclercq C, Loghmani M, Faris OP, Tunin RS, DiSilvestre D et al. Regional alterations in protein expression in the dyssynchronous failing heart. Circulation 2003;108:929–32.
13. Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K et al. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation 2009;119:1220 –30.
14. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, Tung R, Tada H, Koneru JN, Bergemann T, Fagan DH, Hudnall JH, and Vijayaraman P. Permanent His-bundle pacing: a systematic literature review and meta-analysis. Europace 2018;20: 1819- 1826.
15. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. Heart Rhythm 2019;16:1791–1796.
16. Ajijola OA, Upadhyay GA, Macias C, Shivkumar K, Tung R. Permanent His-bundle pacing for cardiac resynchronization therapy: Initial feasibility study in lieu of left ventricular lead. Heart Rhythm 2017;14:1353–1361.
17. Zhang W,, Huang J, Qi Y, Wang F, Guo L, Shi X, Wu W, Zhou X, Li R. Cardiac resynchronization therapy by left bundle branch area pacing in patients with heart failure and left bundle branch block. Heart Rhythm 2019;16: 1783–1790.
18. Adelstein E, Saba S. Right atrial pacing and the risk of post implant atrial fibrillation in cardiac resynchronization therapy recipients. Am Heart J 2008;155:94-9.
19. Elkayam LU, Koehler JL, Sheldon TJ, Glotzer TV, Rosenthal LS, Lamas GA.The influence of atrial and ventricular pacing on the incidence of atrial fibrillation: a meta-analysis. Pacing Clin Electrophysiol 2011;34:1593-9.
20. Verlato R, Botto GL, Massa R, Amellone C, Perucca A, Bongiorni MG, Bertaglia E, Ziacchi V, Piacenti M, Rosso AD, Russo G, Baccillieri MS, Turrini P, Corbucci G. Efficacy of low interatrial septum and right atrial appendage pacing for prevention of permanent atrial fibrillation in patients with sinus node disease: results from the electrophysiology-guided pacing site selection (EPASS) study. Circ Arrhythm Electrophysiol 2011;4:844-850.
21. Lau CP , Tachapong N, Wang CC, Wang JF, Abe H, Kong CW, Liew R, Shin DG, Padeletti L, Kim YH, Omar R, Jirarojanakorn K, Kim YN, Chen MC, Sriratanasathavorn C, Munawar M, Kam R, Chen JY, Cho YK, Li YG, Wu SL, Bailleul C, Tse HF. Prospective randomized study to assess the efficacy of site and rate of atrial pacing on long-term progression of atrial fibrillation in sick sinus syndrome: Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) Study.Circulation 2013;128:687-693.
22. Hjortshøj S, Riahi S, Nielsen JC, Skjøth F, Lundbye-Christensen S, Andersen HR, DANPACE Investigators. Does atrial pacing lead to atrial fibrillation in patients with sick sinus syndrome? Insights from the DANPACE trial. Europace 2014;16:241-245.