Case report

Pathophysiology of narrow complex dilated cardiomyopathy insight derived from the velocity equation: velocity = distance/time

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SUMMARY

The pathophysiology of narrow complex dilated cardiomyopathy is not defined, so therapeutic options are limited. By utilising the velocity equation, the pathophysiology of narrow complex cardiomyopathy allows above normal conduction propagation velocities. There are two pathophysiological theories that allow above normal conduction velocities and failure to capture the myocardium: (1)insulating fibres of the conduction system extending beyond the apex and (2) reduction of axon branching. A patient with narrow complex cardiomyopathy was subjected to graded increase in amplitude and pulse width pacing to overcome the failure of native conduction to capture the myocardium. Peak systolic strain maps demonstrated a progressive increase in apical contractility with increasing pulse width and amplitude. Ejection fraction improved from 17% to 31%. Understanding the pathophysiology of narrow complex cardiomyopathy leads to proposed therapies. One potential pacing therapy is multi-lead pacing at high amplitude and pulse width to capture myocardial cells not captured by native conduction.

BACKGROUND

The definition of dilated cardiomyopathy is stated by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 'A myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to explain the observed myocardial abnormality'.[1] Dilated cardiomyopathy, an enlarged poorly contracting heart, can be further characterised by the duration of the electrocardiogram QRS greater than or less than 120 ms. Narrow complex dilated cardiomyopathy is a dilated cardiomyopathy with QRS duration less than 120 ms. From infancy to adolescence, both the QRS duration and size of the heart are linearly related.[2 3] Therefore, the conduction velocity, which is ratio of size of the heart to the QRS duration, is similar for all age groups in normal hearts.

The simple equation Velocity=Distance/Time can be used to propose new pathophysiological mechanisms of dilated narrow complex cardiomyopathy. Consider two racetracks with one track being twice as long. On each track, there are race cars that travel at the same speed. The race car on the longest course will finish the race in twice the time of the race car on the smaller track. This is the case of wide complex dilated cardiomyopathy with normal conduction velocity travelling a greater distance in an enlarged heart. If the race car on the longer course travelled at twice the velocity of the race car on the small track, the time to finish the race would be the same. The above normal speed is similar to narrow complex dilated cardiomyopathy with rapid propagation in an enlarged heart. The pathophysiology allowing above normal propagation velocities in narrow complex dilated cardiomyopathy associated with weak heart muscle needs explanation.

The QRS interval represents rapid propagation of electrical depolarisation through the conduction system composed of the bundle of His and Purkinje system with axons that are axial (parallel) and circumferential (perpendicular). The specialised conductive tissue interacts with the syncytium of myocardial cells. Myocardial cells contribute to cell to cell propagation. The velocity and synchrony of propagation depends on both. Anatomists and physiologists state that all myocytes have the potential to conduct cardiac impulse, and the actual morphological pathways of the conduction system are indistinguishable from surrounding cardiac myocytes. Clarification of the sinus node, bundle of His and the early branches of the bundles has been achieved. These appear as swellings or nodes. It was determined that conduction between the atria and ventricle had to be by specialised fibres that are insulated from surrounding tissues travelling through the fibrous annulus. The anatomy has been agreed on utilising the following three principles: (1) histologically discrete from adjacent working myocardium, (2) serially traceable from section to section and (3) insulated from the adjacent working myocardium by a sheath of fibrous tissue. Immunohistochemical techniques have helped to identify the insulation that determines the specialised conduction system.[4–7]

The timing sequence of cardiac conduction is intuitively from the base of the heart to the apex due to the anatomical direction of the fibres. There are axial and circumferential fibres; however, by means of insulation of the proximal fibres, the actual electrical mechanical dispersion is from apex to base.[8] In chick embryos during early development, the sequence of electromotive forces begins at the base and changes to apex to base during later

development.[9] This suggests the possibility of postdevelopment layering of insulation fibres in order to accomplish the switch from base to apical dispersion.

The propagation velocity of axons depends on the size of the axon and their direction of propagation (axial vs circumferential).[5] A larger fibre with an axial direction results in a faster depolarisation velocity. As a heart remodels to a large sphere, the specialised conduction system stretches and becomes thinner. The smaller diameter of fibres will result in a slower conduction and a wider QRS interval. Another component is the insulating fibres that form the sheath of specialised conducting tissue. The presence or absence of these insulating sheaths will change propagation velocities.

The QRS interval measured from the ECG can help characterise the pathophysiology of congestive heart failure by defining conduction velocity, that is, length of the conduction pathway divided by the QRS duration.

Propagation velocity=distance/QRS duration

Propagation velocity has two primary directional components: (1) circumferential velocity branching, perpendicular to the main fibres and (2) axial velocity parallel to the main fibres. Contributions to the two directional components are the conduction system with branching fibres that are perpendicular and axial and the myocardial cells that are elongated axially giving preference to rapid longitudinal conduction and slower circumferential conduction. The axial velocity parallel to conduction fibres has been experimentally shown to be higher than the circumferential velocity perpendicular to the conduction fibres.[10] Figure 1 demonstrates the propagation velocity in the axial and circumferential directions using normal heart geometry and normal QRS duration. The axial and circumferential distances are measured from the echocardiogram's apical long axis view and parasternal short axis at the papillary muscle level view. The time is the QRS interval determined from the ECG. The axial propagation velocity is faster (125 cm/s) than the circumferential velocity (106 cm/s).

Figure 2 demonstrates the propagation velocity in the axial and circumferential directions in a wide QRS dilated cardiomyopathy. For both the normal heart and dilated heart examples, the distance and QRS are measured, and the propagation velocity is calculated. The first normal example demonstrated the increased propagation velocity in the axial direction as expected. The second diseased heart, with a 10% ejection fraction and a wide QRS duration dilated cardiomyopathy, demonstrates a lower circumferential propagation velocity and an even lower axial velocity. The heart remodels as a sphere because of slowed conduction, primarily in the axial direction with axial velocity approaching the same velocity of circumferential.

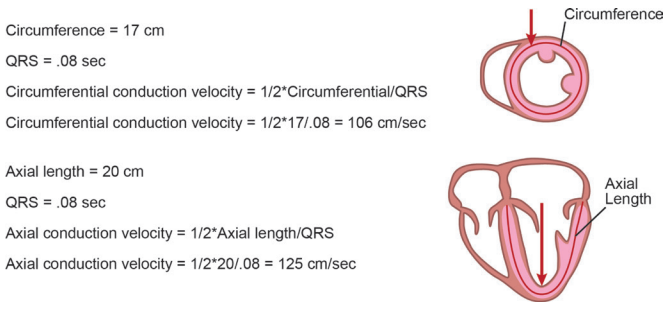

Figure 1 Circumferential and axial velocities of normal heart (top=parasternal short axis view; bottom=apical four-chamber view).

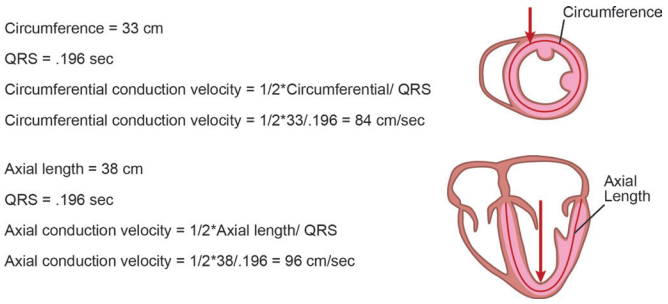

Figure 2 Circumferential and axial velocities of wide QRS dilated cardiomyopathy (top=parasternal short axis view; bottom=apical four-chamber view).

Figure 3 represents a dilated cardiomyopathy with a narrow QRS. The conduction velocities reflect a nearly spherical heart with above normal circumference and axial velocities of 206 and 238 cm/s, respectively. This is compared with the normal conduction velocities of 106 and 125 cm/s. This demonstrates that diseased heart with narrow QRS has nearly twice the conduction velocity of a normal heart. Table 1 illustrates actual measurement of patients with normal hearts, dilated hearts with different QRS duration, the conduction velocities that changed during myocarditis and recovery. For comparison, a mouse and humpback whale mammalian hearts are included which represent a size variation of six orders of magnitude. The calculated propagation velocity varies by less than one order of magnitude.[11–13] The humpback has above normal conduction velocities as compared with the mouse. The velocities are similar to a dilated narrow complex cardiomyopathy. There is debate over the existence of above normal conduction velocity. The humpback whale has propagation velocities of 300 cm/s. The simple velocity equation is strongly evident that the pathophysiology of narrow complex dilated cardiomyopathy is above normal conduction velocities. The anatomy and physiology of the heart have to explain why abnormal conduction velocity exists in the setting of weak cardiac contraction.

The hypothesis

Narrow complex dilated cardiomyopathy requires above normal conduction velocities and failure to capture myocardial cells. Two anatomical theories of above normal conduction are proposed:

Theory 1: Insulating fibres extending beyond the apex allowing above normal conduction but failure to capture myocardial cells due to the insulation of distal fibres.

Theory 2: Reduction of axon branching lessens resistance to propagation but failure to capture myocardium.

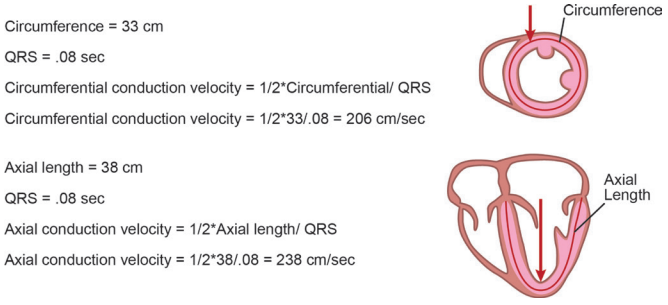

Figure 3 Circumferential and axial velocities of narrow QRS dilated cardiomyopathy (top=parasternal short axis view; bottom=apical four-chamber view).

Table 1 Actual measurement of normal, diseased myocardium, mouse and humpback

Condition	QRS duration (milliseconds)	Axial perimeter (centimemters)	Circumferential perimeter (centimeters)	Axial velocity (centimeters/second)	Circumferential velocity (centimeters/second)
Normal	80	20	17	125	106
Dilated wide QRS	196	38	33	96	84
Dilated narrow QRS	80	38	33	238	206
Dilated narrow QRS patient	84	25.5	22.8	151	135
Myocarditis new onset	102	23	18.9	113	92
Myocarditis recovered	98	19.3	16.9	98	86
Mouse	8–11		0.95		43–59
Humpback whale	150–200		55 (Estimated length of conduction system)		275–366

CASE PRESENTATION

Evaluation of the hypothesis

Both of these theories allow for above normal conduction and development of weak heart muscle due to failure to recruit myocardial cells. Pacing with greater pulse amplitude and duration, thereby recruiting more cells by the greater electromotive force, tests both of these theories. By recruiting more denervated cells, the immediate result would be an increase in contractile force. Echocardiographic strain imaging could confirm an increase in contractility with an increase in electromechanical coupling. As the electromotive forces decrease farther from the pacing electrode, the increase in contractility should diminish.

We describe a case report of a 68-year-old woman with a narrow QRS complex (figure 4), dilated cardiomyopathy in whom we implanted a defibrillator for ejection fraction less than 35%, unresponsive to 3 months of optimum medical therapy. The patient met the criteria for dilated cardiomyopathy and had no coronary disease, hypertension or primary valvular disease. Medication list and echo measurements are listed in table 2. It should be noted that the patient did not have significant functional mitral regurgitation.

1. Severe left ventricular dilatation with severely reduced global systolic function.
2. Grade indeterminate LV diastolic dysfunction.
3. Normal RV size and function.
4. No significant haemodynamic cardiac valvular disease, mild mitral regurgitation.
5. No pericardial effusion.

With Institutional Research Board Approval and appropriate patient consent, the patient with narrow complex cardiomyopathy had a clinically indicated defibrillator implanted and came to the echocardiographic laboratory the next day. Biventricular pacing was not offered due to intact AV node and low likelihood of ventricular pacing on a chronic basis. The patient underwent echocardiographic imaging in native conduction and with pacing at three different pulse waves and amplitudes increasing the electromotive forces progressively. The baseline heart rate was elevated and then fell serendipitously, so the pacing heart rate was identical to the baseline heart rate. At each increase in pacing pulse width and amplitude, at the same heart rate, strain imaging and ejection fraction were recorded.

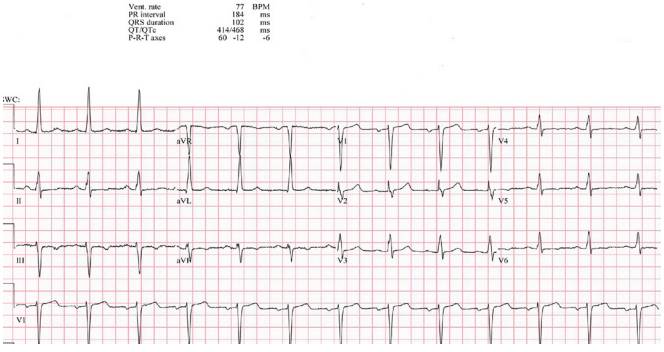

Figure 4 Subject ECG.

Table 2 Patient medication list and baseline echocardiographic measurements

Aspirin 81 milligram (mg) chewable tablet	One tablet daily		
Carvedilol (COREG) 12.5 milligram tablet	Take one tablet (two) times daily.		
Gabapentin (NEURONTIN) 300 mg	Gabapentin 300 mg two times daily.		
Insulin Glargine LANTUS 100 U/mL	Inject 42 Units into the skin nightly.		
Magnesium oxide (MAG-OX)	Take one tablet (400 mg total) daily.		
Metformin 1000 mg	Take one tablet (two) times daily.		
Sacubitril-Valsartan (ENTRESTO) 24–26	Take one tablet (two) times daily.		
Simvastatin (ZOCOR) 10 mg	Take one tablet nightly.		
Sitagliptin (JANUVIA) 100 mg	Take one tablet daily.		
Spironolactone (ALDACTONE) 25 mg	Take one tablet daily.		
Measurements 2D echo			
Interventricular Septum diastolic thickness	1.1 cm	Left Ventricular outflow diameter	2.0 cm
Left ventricular Posterior Wall diastolic thickness	1.1 cm	Left Atrial volume index	48.9 mL/m^2
Left Atrial systolic diameter	5.0 cm	ejection fraction	22.8%
Left Ventricular diastolic diameter	6.7 cm		
Left Ventricular systolic diameter	5.6 cm		

INVESTIGATIONS

Empirical data

Table 3 illustrates the experiment performed under a protocol approved by the Institutional Review Board. With progressive increase in electromotive forces produced by increasing pulse width and amplitude, there was progressive increase in peak systolic strain in the apical segment and the ring proximal to the apex. These segments are adjacent to the pacing impulse. The strain measurements obtained further from the electrode demonstrated no effect or a decline in strain. In addition, pacing dyssynchrony showed a preference to increasing posterior strain implying the electromotive forces travelled in that direction. The global systolic strain fell from baseline of −11.3% to −9.6%; however, the ejection fraction in the four-chamber view increased from 17% to 31% and in the two-chamber view from 22% to 25%. The experiment demonstrates increased strain in segments closest to the pacing electrode with the effect decreasing at greater distance. This suggests that a clinical device will need multiple leads with increased electromotive force to capture isolated contractile elements and prevent dyssynchrony of contraction.

Consequences of the hypothesis

The hypothesis suggests that the anatomical conduction system has a fundamental role in cardiac performance providing synchrony and efficiency of contraction. Failure of these fibres to interact with myocardial cells can lead to decreased contractile function, inefficient pumping function. Rapid propagation of conduction velocity has not been previously considered. Understanding mechanisms for these failures can lead to better understanding of pathophysiology and new therapies to correct these deficiencies. The hypothesis of abnormal insulation or abnormal budding of axons has not only implication for the heart, but also for every organ system that malfunctions, degenerates or ages since all organs are innervated.

TREATMENT

After the study protocol was completed, the defibrillator was reprogrammed to its pre-study settings. There were no changes made to the patient's medical regime and she returned to the advanced heart failure clinic for follow-up treatment.

OUTCOME AND FOLLOW-UP

Two years later, the patient remains alive with guideline directed therapy with symptoms of heart failure and an ejection fraction that has not changed. She is awaiting new therapies that may give her benefit.

Table 3 Effect of changing pacing pulse width and amplitude in narrow complex dilated cardiomyopathy

	Baseline no Pacing	Initial pacing	Mid-range pacing	Max- range pacing
Left Ventricular Ejection fratciton in the 4 chamber and 2 chamber %	17/22	27/22	23/19	31/25
Apex strain	–10	–12	–12	–13
Proximal ring strain	–10.25	–11.5	–11.75	–12.75
Global strain	–11.3	–11.7	–8.6	–9.6
Pacing amplitude/pulse width	0/0 no pacing	2.5/.5	5/1.0	7.5/1.5
Peak systolic strain maps figures	Figure 5A	Figure 5B	Figure 5C	Figure 5D

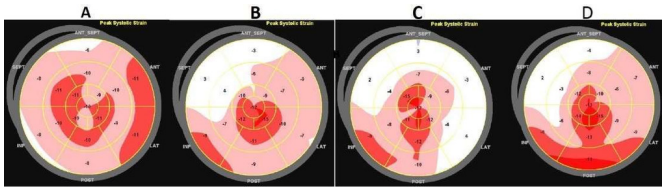

Figure 5 Peak systolic strain maps for table 3. (A) Baseline, (B) initial low energy pacing, (C) mid energy pacing, (D) maximum energy pacing.

DISCUSSION

The scientific method requires an observation. In this paper, the observation is dilated heart with narrow QRS. The scientific method then requires a theory to explain the observation. There are two theories proposed: abnormal insulating fibres or failure of terminal budding of neurons. Both theories are consistent with rapid conduction and weak contraction due to lack of myocardial recruitment. Other theories may exist that explain the observation. An experiment needs to be performed to test the theory. The experiment was to provide greater electromotive forces by increasing the pulse width and amplitude within the limits of the device to see if more myocardial cells could be recruited. Strain imaging demonstrated that cells closest to the pacemaker lead had increased contractility as expected by the theory. It did not elucidate which theory was correct. Both conditions may be present.

Electromechanical coupling is a combination of depolarisation of the myocardial cell by the conducting axon and propagation through the syncytium of myocardium. The paper by Kléber and Rudy[14] is a review of propagation of an individual action potential through a single cell and syncytium of cells by ionic channels and gap junctions. These findings describe action potential speed, altered by various conditions. The paper clearly describes how arrhythmias are generated and unilateral conduction blocks occur within the AV node and in cardiac muscle altered by geometrical boundaries. Anisotropic re-entry occurs when there is non-uniformity in electrical propagation. In the heart, the elongated cells have different conduction velocities along the breath and length of the myocardium. These different velocities can cause re-entry. Both of the proposed theories of above normal conduction velocities can also contribute to anisotropic re-entry by variable conduction velocities within the conduction system. A new non-pharmacological antiarrhythmic device could be conceived, if the abnormal differences in conduction velocity can be normalised by multi-lead high output pacing correcting the anisotropy.

The myocardial syncytium propagation velocity can be estimated through the pathophysiological condition of complete heart block which eliminates the conduction system. As the area of block descends through the conduction system, the QRS becomes wider and spontaneous depolarisation decreases with a lower heart rate. The end result is the ventricle tends to dilate to some degree constrained by the pericardium and the QRS duration becomes wider with a significant slowing propagation velocity. Therefore, rapid propagation velocity cannot be explained by the myocardial syncytium in the setting of dilated cardiomyopathy. In addition, there may be both rapid and slow conduction within a single heart, so a narrow QRS morphology can still have delayed septal activation resulting in cardiac dyssynchrony.

Cardiac re-synchronous therapy in narrow QRS dilated cardiomyopathy was ineffective in a randomised multicenter trial.

Therefore, current guidelines do not recommend re-synchronous therapy implantation when QRS duration is <130 ms.[15 16] This experiment indicates that increasing electromotive force can increase contractility. Theory 1 or 2 could be the underlying pathology. The pathologist with meticulous scrutiny and special stains could evaluate specimens for lack of axonal budding or excessive axon-insulating sheaths. The work is tedious and has not been accomplished.

Cardiac contractility modulation delivers a non-capture electric current during the refractory period. The current delivered is much greater than the pulse delivered by pacing and is thought to modify the entry of calcium into the myocardium and improve contractility. The actual mechanism is unknown.[17–19] The authors propose that this current allows capture of more myocardium by altering the resistance of insulating fibres or sensitising myocardial cells not captured by the altered native conduction system.

Treatment of any disease process must begin with an understanding of the anatomy and pathophysiology of the disease. Narrow complex dilated cardiomyopathy represents above normal conduction propagation velocities as defined by the simple velocity equation. The proposed pacing strategy for narrow complex dilated cardiomyopathy is multi-lead pacing at high amplitudes with increased pulse width to achieve cardiac synchrony and recruitment of myocardial cells not activated by native conduction system.

Learning points

Treatment of any disease process must begin with an understanding of the anatomy and pathophysiology of the disease.

- Any disease process should have first principles applied. Narrow complex dilated cardiomyopathy represents above normal conduction propagation velocities as defined by the simple velocity equation.
- Abnormal insulating sheaths or failures of axonal budding are two theories for failure to couple electrical forces with myocardial cells.
- Cardiac contraction modulation may alter the electromechanical coupling between the conduction system and myocardial cells increasing contractile forces.
- The proposed pacing strategy for narrow complex dilated cardiomyopathy is multi-lead pacing at high amplitudes with increased pulse width to achieve cardiac synchrony and recruitment of myocardial cells not activated by native conduction system.

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Contributors All authors have contributed in design, execution and writing of this report. PDH made the observation that conduction velocity is increased in narrow complex cardiomyopathy and designed the study protocol. GO is the electrophysiologist who implanted the defibrillator. RP is the cardiology fellow who managed the research protocol. BJ is a cardiologist who provided insight and review. PDH is the first author who conceived the notion after losing a patient with narrow complex cardiomyopathy.

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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect