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ORIGINAL RESEARCH

Reducing Aortic Barotrauma and Vascular Extracellular Matrix Degradation by Pacemaker-Mediated QRS Widening

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BACKGROUND: The extent of pressure-related damage might be related to acceleration rate of the applied pressure (peak dP/dt) in the vascular system. In this study, we sought to determine whether dP/dt applied to the aortic wall (aortic dP/dt) and in turn vascular extracellular matrix degradation can be mitigated via modulation of left ventricular (LV) contractility (LV dP/dt) by pacemaker-mediated desynchronization.

METHODS AND RESULTS: First, in 34 patients, changes in aortic dP/dt values in 3 aortic segments in response to pacemaker-mediated stepwise QRS widening leading to gradual desynchronization of the LV contraction by means of steadily changed atrioventricular delay (AVD) with temporary dual-chamber pacing was examined before and after beta-blocker (15 mg IV metoprolol) administration. Second, serum matrix metalloproteinase-9 levels were measured in the 20 patients with permanent pacemaker while they were on sinus rhythm with normal QRS width and 3 weeks after wide QRS rhythm ensured by dual pacing, dual sensing, and dual response to sensing with short AVD. LV dP/dt substantially correlated with dP/dt measured in ascending (r=0.83), descending (r=0.89), and abdominal aorta (r=0.96). QRS width strongly correlated with dP/dt measured in ascending (r=−0.95), descending (r=−0.92), and abdominal (r=−0.96) aortic segments as well. In patients with permanent pacemaker, wide QRS rhythm led to a significant reduction in serum matrix metalloproteinase-9 levels (from 142.5±32.9 pg/mL to 87.5±32.4 pg/mL [P<0.001]) at the end of 3 weeks follow-up.

CONCLUSIONS: QRS prolongation by short AVD dual pacing, dual sensing, and dual response to sensing results in concomitant decreases in peak dP/dt values in the LV and in all aortic segments with or without background beta-blocker administration, which in turn led to a significant reduction in circulating matrix metalloproteinase-9 levels.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03665558.

Key Words: aortic aneurysm ■ dP/dt ■ matrix metalloproteinases ■ pacing

The extent of the pressure-related vascular injuries, in addition to individual susceptibility of the vascular structures, might be related not only to magnitude and duration but also acceleration rate of the applied pressure. In this regard, aortic peak dP/dt, maximum value of acceleration rate of aortic pressure, would be one of the principal determinants of mechanical stress applied to the aortic wall. Therefore, interventions aiming to reduce aortic peak dP/dt levels may open a new therapeutic avenue in the management of pressure-related vascular pathologies such as aortic aneurysms. Although beta-blockers (β-blockers) are the standard treatment for small aortic aneurysms and theoretical reasoning behind β-adrenergic blockage is logical, β-blocker therapy fails to consistently reduce aortic aneurysm growth in patients with aortic aneurysm.[1] In addition, poor tolerability of the β-blockers resulted in high dropout rate

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CLINICAL PERSPECTIVE

What Is New?

- Our study indicates that in patients with normal QRS width and left ventricle systolic function, QRS widening by short atrioventricular delay dual-chamber pacing decreases maximum value of acceleration rate of pressure (dP/dt) in the left ventricle and in all aortic segments either alone or additively on top of the background beta-blocker administration.
- A corresponding reduction of rate of rise in aortic pressure (aortic dP/dt) in response to constant wide QRS rhythm ensured by short atrioventricular delay permanent pacing for 3 weeks decreases serum matrix metalloproteinase-9, which is a well-known vascular extracellular matrix degradation marker, levels.
- Reducing vascular barotrauma by means of permanent pacemakers may be a new mode of therapy in the management of pressure-related vascular pathologies such as aortic aneurysms.

What Are the Clinical Implications?

- In patients with aortic aneurysm, short atrioventricular delay dual-chamber permanent pacing may decrease the magnitude of vascular barotrauma, may allow the use of higher dosages of betablocker and its effect can be adjusted simply by programming externally according to the patient's needs during follow-up.
- Given the limited and controversial efficacy of available medical therapies, this mode of intervention may help prevent the progression of barotrauma susceptible aortic pathologies, particularly aneurysms, and can increase the effectiveness and safety of existing medical treatments.

Nonstandard Abbreviations and Acronyms

dP/dt	the first derivative of LV or aortic pressure with respect to time
DDD	pacing mode of dual pacing, dual sensing, and dual response to sensing
AVD	atrioventricular delay time of DDD pacemaker
MMP-9	matrix metalloproteinase-9

in the treatment.[2] Therefore, a big potential exists for successful medical/interventional therapies that may halt or reduce aneurysm progression and hence alleviate or postpone the need for surgical repair.

Because it is the major determining factor of the aortic peak dP/dt,[3] changing left ventricular (LV) contractility, thereby LV peak dP/dt, may lead to a change in aortic peak dP/dt in the same direction. However, unlike LV peak dP/dt, aortic peak dP/dt emerges after aortic valve opening in early systolic ejection phase. Moreover, LV and aortic peak dP/dt values are required to be assessed at various contractility levels yet to conclude the existence and magnitude of the potential association between them. In this context, shortening of QRS duration was shown to be associated with increased maximum rate of LV pressure rise (peak dP/dt) and with augmented LV contractile performance in patients undergoing cardiac resynchronization therapy.[4,5] On the basis of this physiological background, QRS duration widening, that is, by dual-chamber pacing with short atrioventricular delay (AVD) can contrarily reduce LV contractility and, correspondingly, LV and aortic peak dP/dt.

From mechanobiological point of view, as a potential biomarker of biomechanical strain and therefore pressure-related aortic damage, matrix metalloproteinases (MMP) have been implicated in the pathogenesis of aortic aneurysm because of the important role they play in connective tissue homeostasis.[6–8] In particular, compared with healthy controls, a significant reduction demonstrated in initially elevated serum MMP-9 concentrations after the aortic repair in patients with abdominal aortic aneurysm[9,10] implies the critical role of MMPs in aortic aneurysms setting. Besides, due to an active and ongoing degradation and repair processes taking place in the vascular wall, which is governed by the balance between MMP enzymes and their inhibitors,[11,12] MMPs can be detectable to some extent in the serum of healthy subjects. It has been shown that mechanical stretch-induced upregulation of genes and their products seem to stimulate MMP expression in the vascular wall,[13] which is responsible for extracellular matrix degradation and, therefore, disruption of aortic elastic fibers. MMPs are activated in vascular smooth muscle cells in response to increased mechanical stretch[14] and longitudinal tension.[15] However, acceleration rate of the mechanical stress submitted to aortic wall, in addition to its magnitude,[16] can also contribute to the aortic wall stress. Herein, we hypothesized that decreasing the acceleration rate of aortic pressure (aortic peak dP/dt) may contribute to reducing overall mechanical stretch on the aortic wall, which may, in turn, reduce the vascular expression and circulating concentrations of MMP-9.

The aim of this study was to analyze the acute changes in peak dP/dt values in all 3 aortic segments in response to gradually altered LV peak dP/dt values by means of stepwise QRS widening via shortening of AVD with temporary dual-chamber temporary pacing. Second, effect of the wide QRS rhythm ensured for a given period of time by short

AVD permanent pacing on the circulating levels of a vascular extracellular matrix degradation marker, MMP-9, was examined.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

A total of 34 patients, 15 patients admitted to the cardiac catheterization laboratory for routine angiogram and 19 undergoing routine electrophysiological study, were included in the first part of the study. For the second stage of the study, 20 patients with permanent dual-chamber pacemaker implanted due to sick sinus syndrome who had ventricular pacing rate <10% in the last 6 months detected at the interrogation of their pacemakers were prospectively included. Patients with normal LV systolic function (ejection fraction >50%), healthy conduction systems, and noncritical coronary stenoses or normal coronary arteries were enrolled in the study. Patients with intraventricular conduction abnormalities (baseline QRS >100 ms), mild to moderate aortic or mitral valve disease, or atrial fibrillation were not included.

Written informed consent was obtained from all patients. Studies were conducted in accordance with the Declaration of Helsinki, and study protocols were approved by our hospital ethics committee (Ethical Committee of Istanbul University, Faculty of Medicine). Clinical trial registration number=NCT0366555, November 1, 2018.

Study Protocol

In patients undergoing routine coronary angiogram, subsequent to angiography, a pigtail catheter was placed into the left ventricle and temporary pacing leads were placed in the right atrium and the right ventricle (Group I, n=15). Ventricular pressure waveforms were initially recorded while external pacemaker generator (Dr Osypka GmbH Medizintechnik PACE 201 External Dual Chamber Pacemaker) was turned off and afterwards while dual-chamber pacing (dual pacing, dual sensing, and dual response to sensing; DDD) with stepwise incremental lengthening of AVD starting from 30 ms up to 150 ms with 10 ms increments at each step. Two-minute pacing was performed during each pacing period. Then the pigtail catheter was pulled back into the ascending aorta and aortic pressure waveforms were recorded before pacing and at each pacing step in the same order (13 steps, beginning from 30 ms of AVD). Thereafter, an intravenous β-blocker (metoprolol), a prototypical pharmacological agent used in reducing LV dP/dt, was administered (a total of 15 mg; three 5 mg IV boluses, 5 minutes apart) and pressure waveforms were recorded from the LV and aorta. Then, the same pacing protocol (stepwise incremental lengthening of AVD starting from 30 ms up to 150 ms with 10 ms increments at each step) was applied under background β-blocker therapy. Pressure waveforms were again recorded from the LV and then from the aorta during each 2 minutes of the pacing period under background β-blocker therapy.

Changes in peak dP/dt values in ascending, descending, and abdominal aortic segments in response to gradually changed AVD by DDD pacing were examined in 19 patients undergoing electrophysiological study (Group II). In this group of patients, electrophysiology catheters that were already placed in the right atrium and the right ventricle connected with the same external dual-chamber pacemaker generator used for dual-chamber pacing. Pressure waveforms were recorded in the left ventricle and in the 3 aortic segments by means of a pigtail catheter while in baseline condition (without pacing) and during temporary DDD pacing with gradually changed AVD. In this group of patients, pacing was initiated with AVD 10 ms shorter than patients' native PR interval. Then, AVD was gradually decreased with 10 ms intervals until when it was 60 ms shorter than patients' native PR interval. LV and then aortic pressure waveforms were collected at baseline condition and during each 2-minute pacing period (6 steps) in each aortic segment.

In Group I, having patients prediagnosed with coronary artery disease, PR interval was normal with low variability. In these patients, pacing started at 30 ms with 10 ms increments until 150 ms was adequate to examine varying QRS intervals. In this group, aortic pressures were measured from the ascending aorta. To observe whether this difference in aortic peak dP/dt reached further aortic segments would inordinately delay length of the procedure; hence this examination was carried out in a different patient group (Group II) after electrophysiological study was performed. The PR interval was longer in this group and had higher variability. As pacing applications performed with fixed AVD would not provide similar QRS interval, pacing was performed with AVD 10 to 60 ms shorter than the PR interval to widen native QRS by 10 to 60 ms on each stage to achieve similar QRS interval on the same stage. These 2 groups constituted the first cohort of the study.

LV and aortic peak dP/dt values were calculated by introducing all pressure waveform data (LV and aortic) to the main hemodynamic console, which allows automatic calculation of dP/dt for LV pressure waveforms using standard formula, as LV pressure (Figure 1).

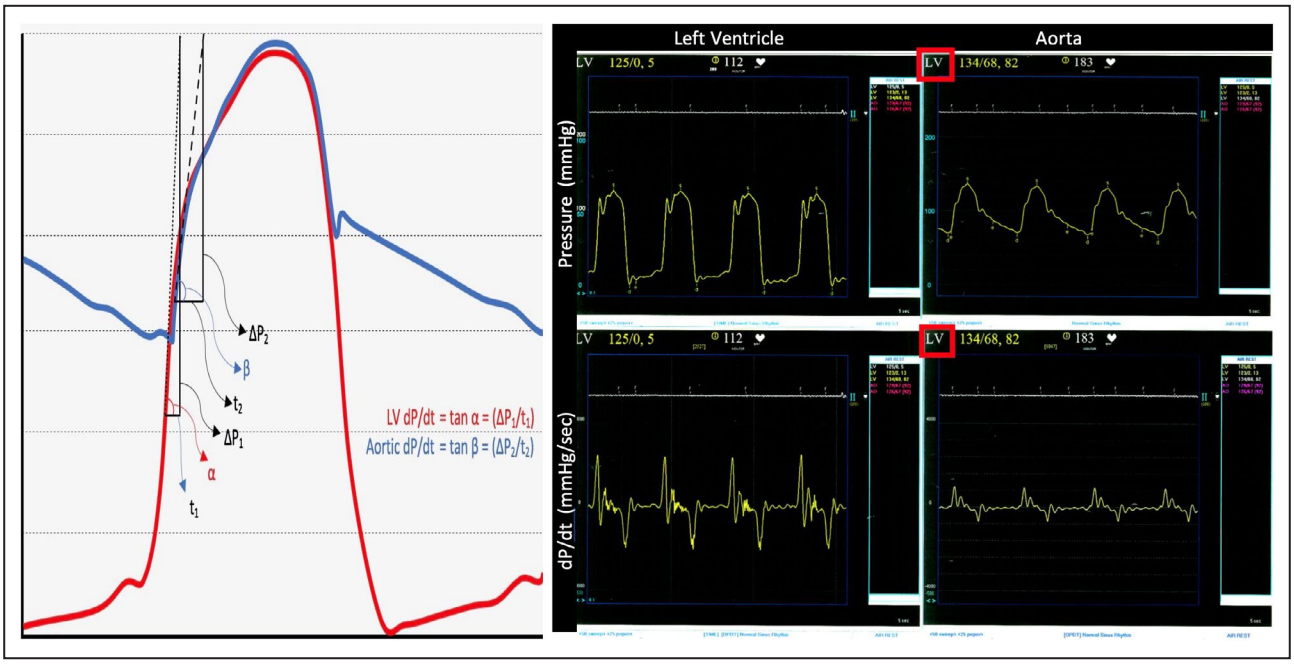

Figure 1. Calculation of LV and aortic dP/dt values.
LV and aortic peak dP/dt values were calculated by introducing all pressure waveform data to the main hemodynamic console as LV pressure, which allowed automatic calculation of dP/dt by the software using standard formula. LV indicates left ventricular.

At the second stage of the study, 20 patients with a permanent dual-chamber pacemaker implanted due to sick sinus syndrome who had ventricular pacing rate <10% in the last 6 months were studied (second cohort). Initial blood samples were collected at baseline condition when patients with a permanent pacemaker were in sinus rhythm. Subsequently, AVDs were adjusted to 60 ms shorter than the patients' native PR interval in order to ensure a constant wide QRS rhythm during follow-up. Then, patients were followed while they were on wide QRS rhythm for 3 weeks, and peripheral blood samples were recollected at the end of this follow-up period. All blood samples were stored at −80°C and MMP-9 concentrations were measured using the enzyme-linked immunosorbent assay method (ELISA kit code: ELH-MMP-9, RayBiotech Inc, Peachtree Corners, GA,). Both baseline and follow-up serum MMP-9 levels were measured blindly twice by 2 different kits and their mean values were used for the comparisons. The coefficients of variation and standard deviations were 23.08% and 32.90, respectively, for the baseline measurements and 36.98% and 32.27, respectively, for the follow-up measurements.

Methods used in this study are summarized in Figure 2.

Statistical Analysis

All statistical tests were performed with SPSS software, version 21. Continuous variables were expressed as mean±SD. Relationships between all continuous variables were examined by using Pearson correlation analysis. At the first stage of the trial we studied Groups I and II separately. We compared the mean values of the analyzed parameters (aortic and LV peak dP/dt or pressure values) measured at each pacing step individually with their baseline (prepacing) average values with the use of paired sample *t* test. MMP-9 levels measured during sinus rhythm and after 3 weeks of wide QRS rhythm were also compared using the paired sample *t* test. A $P<0.05$ was considered statistically significant.

RESULTS

Patient Demographics

In a total of 34 patients, the mean age was 52.8±12.6 years; 32% of the patients were hypertensive and 15% of them were diabetic. The mean ejection fraction was 65.6±9.5%, average heart rate was 80.9±13.2/min, mean PR interval was 141.2±18.6 ms, and mean QRS width was 86.0±9.1 ms. None of the patients included in the first cohort was on β-blocker or non-dihydropyridine calcium channel blocker treatment beforehand. In the second cohort (n=20), mean age was 57.3±14.5. Five percent of the patients were diabetic and 40% of them were hypertensive. In this group, the mean ejection fraction was 65.3±6.5%, mean PR interval was 180.3±29.9 ms, and mean QRS width was 84.50±5.4 ms (Table 1).

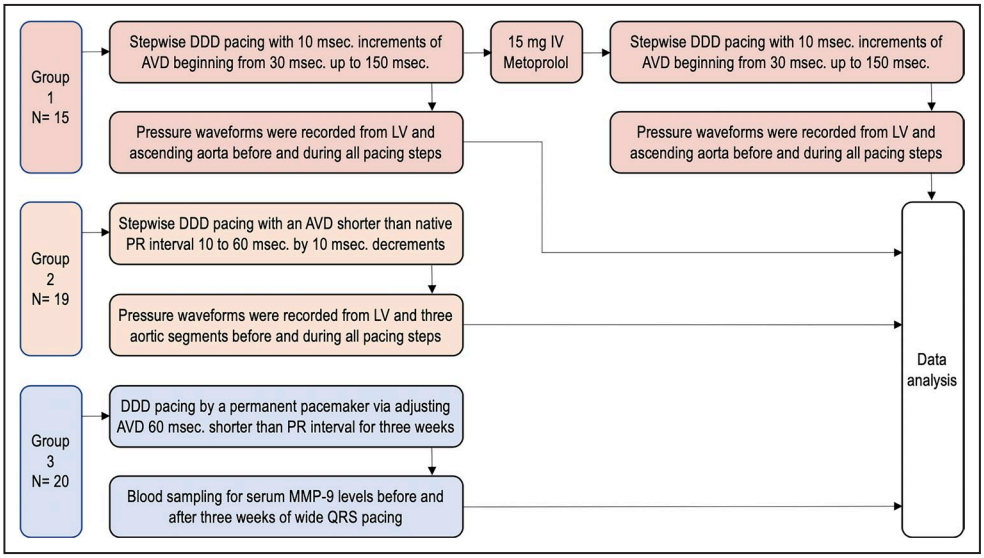

Figure 2. **Summary of the methodology used in the study groups.**

Changes in QRS Duration in Response to Gradually Changed AVD

Both in Groups I and II, stepwise incremental shortening of the AVD resulted in a concordant and stepwise increase in QRS durations (Figure 3).

Table 1. **Demographic, Clinical, and Electrocardiographic Characteristics**

	Cohort I (n=34)		Cohort II (n=20)
	Group I (n=15)	Group II (n=19)	
Age, y	52.8±12.6		57.3±14.5
	57.1±8.3	49.4±14.5	
Sex, male (%) n	(50) 17		(55) 11
	(60) 9	(42) 8	
Smoking, (%) n	(44) 15		(15) 3
	(47) 7	(42) 8	
Hypertension, (%) n	(32) 11		(40) 8
	(27) 4	(37) 7	
Diabetes mellitus, (%) n	(15) 5		(5) 1
	(0) 0	(26) 5	
Ejection fraction, %	65.6±9.5		65.3±6.5
	71.3±8.6	61.0±7.6	
Heart rate, per min	80.9±13.2		70.6±9.5
	77.2±8.5	83.8±15.7	
PR interval, ms	141.2±18.6		180.3±29.9
	144.7±18.8	138.5±15.7	
QRS duration, ms	86.0±9.1		84.5±5.4
	87.3±8.8	84.9±9.4	

Effect of Short AVD Dual-Chamber Pacing on Aortic Pressure

Dual-chamber pacing with AVD between 30 and 90 ms caused a significant reduction in systolic aortic pressure when compared with baseline value (144±15 mm Hg). (At 30 ms: 138±17 mm Hg, [P=0.0001], at 40 ms: 138±17 mm Hg, [P=0.001], at 50 ms: 139±17 mm Hg [P=0.0001], at 60 ms: 140±17 mm Hg, [P=0.002], at 70 ms: 141±16 mm Hg, [P=0.001], at 80 ms: 141±16 mm Hg, [P=0.005], and at 90 ms: 143±16 mm Hg, [P=0.035]). In the subsequent steps of pacing (AVD >90 ms), aortic systolic pressure did not change significantly. In other words, at the stages when patients were paced with AVD longer than 90 ms, magnitude of QRS lengthening seemed to be not enough to modulate LV contractility and, therefore, aortic systolic and mean pressures came closer back to their initial values. Whereas systolic and mean aortic pressures constantly decreased in response to gradually decreased LV and aortic dP/dt, diastolic pressure did not change in any pacing steps, when compared to baseline value (Table 2, Figure 4).

The Relationship Between Left Ventricular and Aortic Peak dP/dt

At baseline situation, LV dP/dt did not correlate with aortic dP/dt (r=0.231, P=0.407). However, there was a robust association (r=0.980, P<0.001) between peak aortic dP/dt values changed in response to gradually changed peak LV dP/dt via incremental lengthening of AVD by DDD pacing with (r=0.916, P<0.001) or without background β-blocker (r=0.978, P<0.001) administration (Figure 5). Although the slopes appear different

in Figure 5, ratios of aortic to LV dP/dt with and without baseline β-blocker administration were similar (*P*=0.911). This could be related to the current sample size with which statistical analysis did not indicate significance. Correlation between aortic and LV dP/dt remained highly significant both in males (*r*=0.978, *P*<0.001) and females (*r*=0.981, *P*<0.001). Furthermore, aortic peak dP/dt values in ascending (*r*=0.825, *P*=0.02), descending (*r*=0.893, *P*=0.007), and abdominal (*r*=0.964, *P*<0.001) segments showed excellent correlations with LV peak dP/dt values (Figure 6A). Progressively reduced LV peak dP/dt values by means of gradual widening of the QRS complex led to a gradual and concordant reduction in the peak dP/dt values measured in all 3 aortic segments (Figure 6B).

Effect of Short AVD Dual-Chamber Pacing on Left Ventricular Peak dP/dt

LV dP/dt changed in accordance with incremental lengthening of the AVD with dual-chamber pacing beginning from 30 ms. In the absence of background β-blocker administration, when compared with baseline value, pacing between AVD of 30 to 70 ms were associated with statistically significant declines in LV dP/dt values at each pacing step. Pacing with AVD longer than 70 ms did not induce statistically significant changes in LV dP/dt values as compared to baseline (prepacing) LV dP/dt value (Figure 7, Table 3).

β-blocker administration, compared with the baseline value, resulted in a significant reduction in LV dP/dt (1.531±265 versus 1.302±166, *P*=0.002). Moreover, short AVD pacing between 30 and 80 ms on top of the background β-blocker administration, was associated with a significant reduction in LV dP/dt at each step compared with LV dP/dt value measured after β-blocker administration but before pacing. This additive benefit of pacing on top of the β-blocker treatment lost at the further stages of pacing with AVD >80 ms (Figure 7, Table 3). Additionally, stepwise QRS prolongation by means of shortening of AVD was also shown to be associated with a progressive reduction in LV dP/dt. QRS width was indeed robustly correlated with LV dP/dt in the presence (*r*=0.930) or absence (*r*=0.935) of background β-blocker therapy (Figure 8A).

Effect of Short AVD Dual-Chamber Pacing on Aortic Peak dP/dt

Like LV dP/dt, aortic peak dP/dt changed in accordance with incremental lengthening of the AVD with DDD pacing beginning from 30 ms. In the absence of background β-blocker administration, when compared

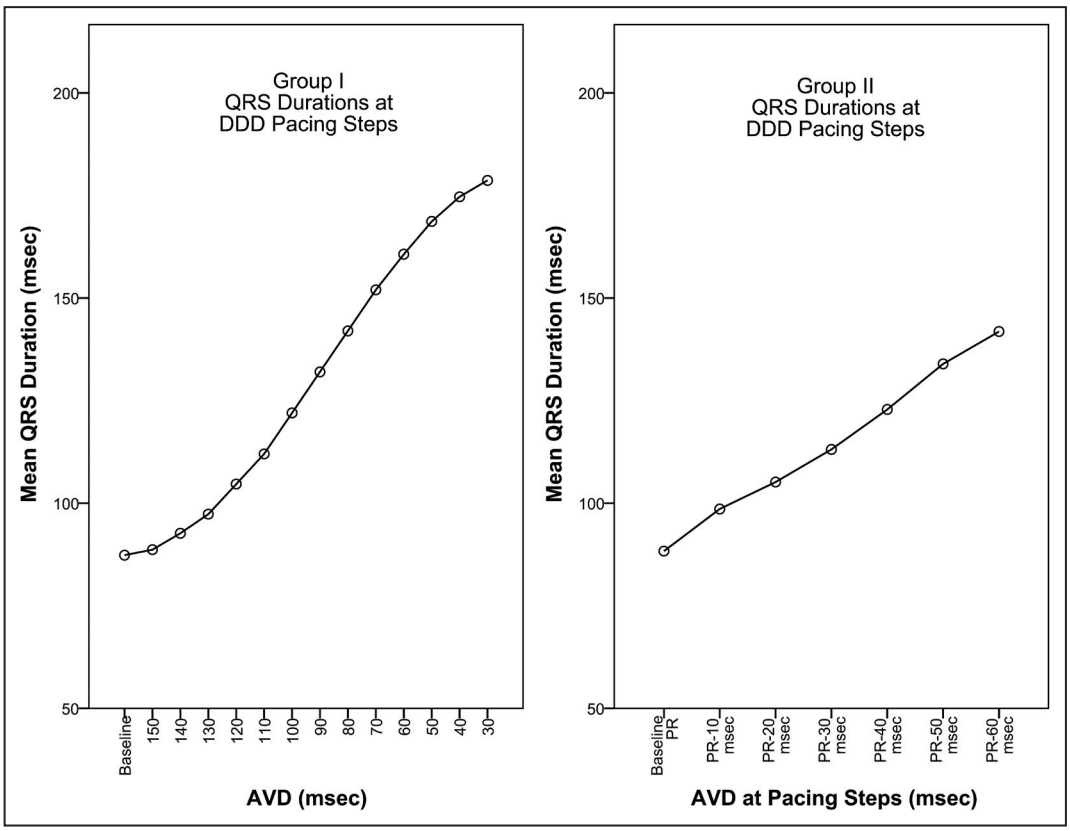

Figure 3. Changes in QRS durations in response to incrementally shortened AVD (atrioventricular delay) by dual-chamber pacing.

to baseline value, pacing between AVD of 30 to 70 ms was associated with constant and statistically significant declines in aortic peak dP/dt values at each pacing step. Pacing with AVD longer than 70 ms, when compared to the baseline value, did not induce statistically significant changes in aortic peak dP/dt values (Figure 9, Table 2).

β-blocker administration, as compared with the baseline value, resulted in a significant reduction in aortic peak dP/dt (600±109 versus 521±104, $P<0.001$). Additively, short AVD pacing on top of the β-blocker administration was associated with further reduction of aortic peak dP/dt. In the presence of background β-blocker therapy, dual-chamber pacing with AVD between 30 and 80 ms resulted in significant and constant reductions in aortic peak dP/dt values at each pacing step. However, significance of this additive effect of pacing in reducing aortic peak dP/dt lost at the further stages of pacing with AVD ≥80 ms (Figure 9, Table 2). Similar to the hemodynamic response observed in LV peak dP/dt, stepwise QRS prolongation via shortening of AVD resulted in a constant decrease in aortic peak dP/dt. Likewise, QRS width was robustly associated with aortic dP/dt in the presence ($r=-0.927$, $P<0.001$) or absence ($r=-0.891$, $P<0.001$) of background β-blocker therapy (Figure 8B). Moreover, stepwise QRS prolongation was accompanied by corresponded reductions in peak dP/dt values in ascending ($r=0.920$, $P=0.003$), descending ($r=0.979$, $P<0.001$), and abdominal ($r=0.994$, $P<0.001$) aortic segments. Notably, peak dP/dt values at each pacing steps, when compared with other segments, were significantly higher ($P<0.001$) in abdominal aorta (Figure 6A and 6B).

Effect of Short AVD Pacing on Serum MMP-9 Levels

In patients with permanent pacemakers, in whom the effect of the wide QRS rhythm provided by short AVD pacing was evaluated, the mean baseline heart rate was 70.7±9.5 per minute and mean paced heart rate was 70.0±10.8 per minute. DDD pacing with AVD 60 ms shorter than patients' individual PR interval resulted in a significant prolongation in QRS (from 84.5±5.4 to 147.5±14.8, $P<0.001$). Overall, this prolonged QRS duration corresponded to a significant reduction in average MMP-9 levels from baseline value of 142.6±32.9 pg/mL, which was measured while patients were on sinus rhythm, to 87.5±32.3 pg/mL measured after 3 weeks of wide QRS rhythm by short AVD pacing ($P<0.001$, Figure 10). As compared with baseline values, both systolic (129.3±14.6 mm Hg versus 127.0±15.3 mm Hg, $P=0.58$) and diastolic blood pressures (77.0±10.2 mm Hg versus 75.8±10.0 mm Hg, $P=0.438$) did not change significantly during 3 weeks of wide QRS pacing.

Table 2. Comparisons of the Aortic Peak dP/dt and Aortic Systolic Pressure Values (Mean±SD) Under Dual-Chamber Pacing (DDD) With Incremental Lengthening in Atrioventricular Delay (AVD) Measured at Baseline Condition and After Intravenous β-Blocker (βB) Administration

	DDD Pacing With Incremental Lengthening in AVD (ms)													
	Baseline	30	40	50	60	70	80	90	100	110	120	130	140	150
Aortic peak dP/dt	600±109	546±98	552±109	569±106	574±112	572±115	587±118	598±122	599±125	600±122	608±117	608±117	608±119	614±119
P		<0.000*	<0.000*	0.003*	0.017*	0.006*	0.254	0.828	0.892	0.983	0.533	0.567	0.612	0.372
Ao. systolic pressure	144±15	138±17	138±17	139±17	140±17	141±16	141±16	143±16	144±15	144±15	145±15	145±15	145±15	146±15
P		0.0001*	0.0001*	0.0001*	0.002*	0.001*	0.005*	0.035*	0.263	1.000	0.296	0.257	0.195	0.142
	βB+DDD Pacing With Incremental Lengthening in AVD (ms)													
	Baseline, After βB	30	40	50	60	70	80	90	100	110	120	130	140	150
Aortic peak dP/dt	521±104	462±86	464±94	473±96	482±103	484±97	497±101	509±107	512±98	517±94	525*±102	528±93	537±97	546±100
P		0.0001*	0.0001*	0.001*	0.007*	0.002*	0.037*	0.381	0.386	0.685	0.654	0.337	0.011*	0.002*
Ao. systolic pressure	134±12	127±13	126±13	128±13	129±13	130±12	130±12	129±14	133±12	134±12	135±11	133±11	135±11	136±11
P		0.0001*	0.0001*	0.0001*	0.0001*	0.001*	0.002*	0.084	0.448	0.887	0.280	0.802	0.090	0.031

Aortic peak dP/dt and systolic pressure values measured at each pacing steps were compared each time with their baseline values.
*Indicates comparisons which were significant.

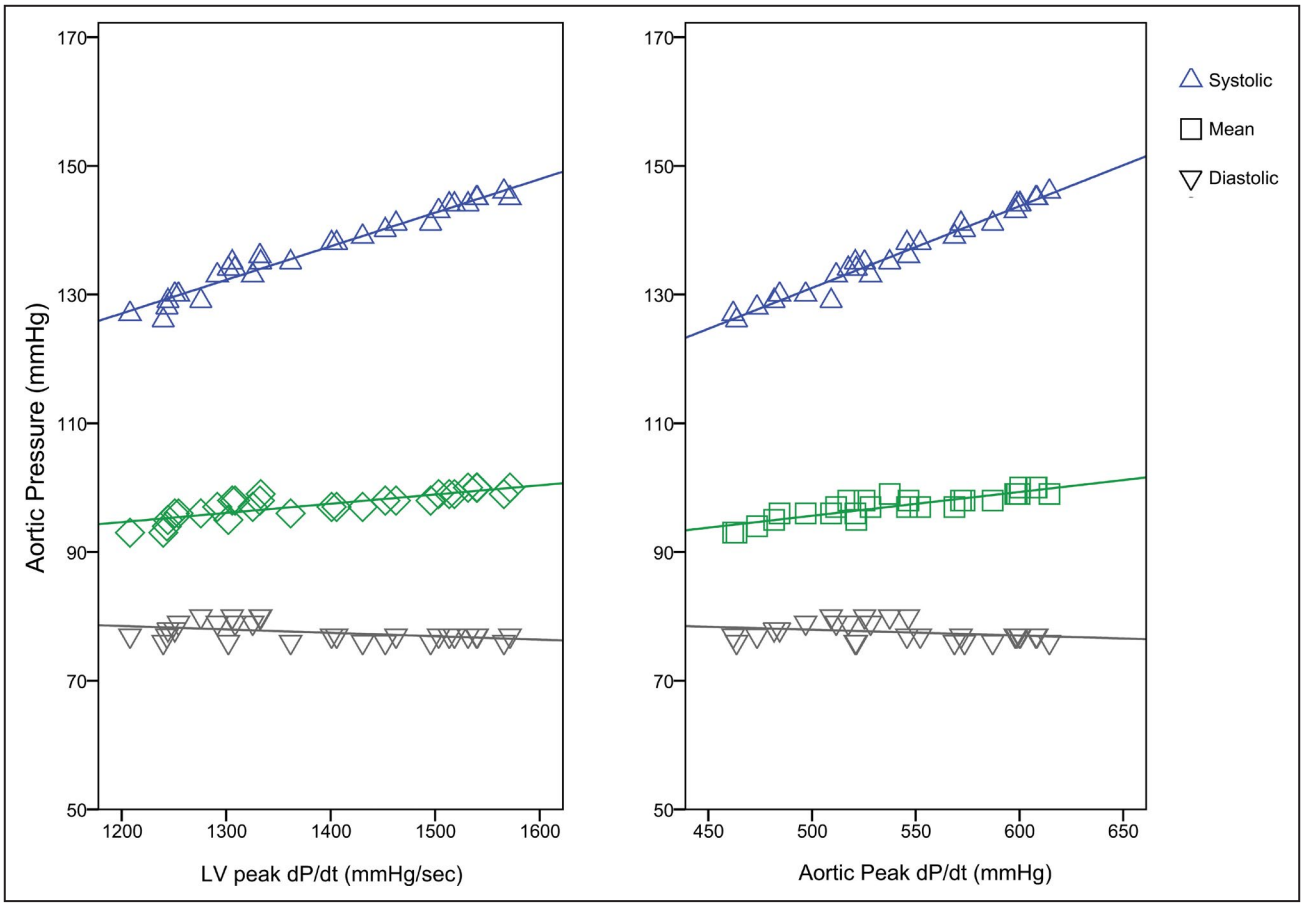

Figure 4. Changes in aortic pressures in response to changes in LV and aortic peak dP/dt.
LV indicates left ventricular.

DISCUSSION

The results of the present study are 4-fold. First, there is a causal relationship between maximum values of the acceleration rate of pressure increase (peak dP/dt) in the left ventricle and aorta. Second, this causal relationship between LV and aortic peak dP/dt persisted in all 3 aortic segments. Progressively reduced LV peak dP/dt values by means of gradual widening of the QRS complex, led to concordant reductions in the peak dP/dt values in all aortic segments. Third, contribution of modulation of ventricular contractility by short AVD dual-chamber pacing in reducing aortic peak dP/dt values was additive to the effect of β-blocker administration. Fourth, in patients with permanent pacemaker in whom wide QRS rhythm ensured by short AVD pacing resulted in a significant reduction in the serum level of a vascular extracellular matrix degradation marker, MMP-9, at the end of 3 weeks follow-up. Taken together, our findings indicate that, as well as with β-blocker therapy, both magnitude and peak acceleration rate of aortic pressure can be significantly reduced in a controlled manner in all aortic levels by short AVD pacing, which, may in turn, lead to restrain mechanical stress induced expression of extravascular matrix degradation markers.

Although it enables circulation, increased arterial pressure is also regarded as an important risk and an exacerbating factor for acute and chronic arterial diseases. In this regard, extent of the pressure-related vascular damage is known to be associated with the magnitude and duration of the pressure exerted on vascular structures as well as individual susceptibility.[16,17] Besides these factors, the acceleration rate of pressure increase can also be considered as one of the parameters that determine the risk for pressure-related vascular pathologies.

Should the pressure increase rate be a risk factor and a variable in pressure-related vascular diseases, obviously, its maximum value (peak dP/dt) would primarily be responsible for the damage it caused. Indeed, the principal mechanism of action underpinning the use of β-blockers in the management of aortic aneurysm and dissection is through the reduction of the LV peak dP/dt and shear stress in the aorta.[18]

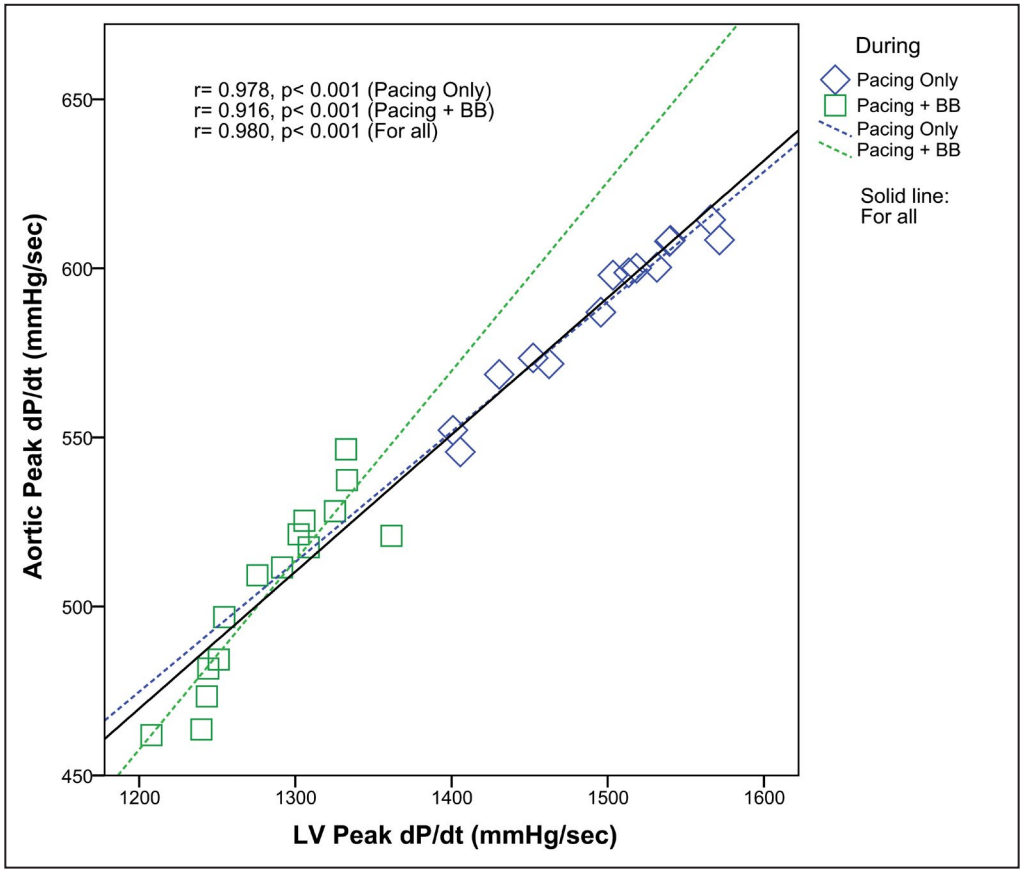

Figure 5. Relationship between corresponding peak LV and aortic dP/dt values during DDD pacing with incremental lengthening of AVD (beginning from 30 ms) with and without background beta-blocker.

Each symbol represents average peak dP/dt values obtained from 15 subjects. DDD indicates pacing mode of dual pacing, dual sensing and dual response to sensing; AVD, atrioventricular delay; and LV, left ventricular.

Nevertheless, in general, vascular (aortic) peak dP/dt is not taken into account when the vascular risk factors are counted. This is not due to its irrelevance but rather to lack of epidemiological data because of the difficulties originated from its measurement. Indeed, indirect data implying its potential clinical relevance also exist. For instance, high pulse pressure, which is associated with accelerated rate of pressure increase, is known to be an important risk factor that is independent from systolic and diastolic pressures.[19]

In this context, undoubtedly, one of the most important clinical pathology, which is highly susceptible to magnitude and characteristics of the pressure rise, is aortic aneurysms. Nevertheless, in patients with aortic aneurysm, medical treatment options are quite limited and mainly directed to comorbidities that do not meet established criteria for repair. Lifestyle changes, conventional pharmacological agents aiming to reduce blood pressure, and LV contractility and statins may help to control expansion rate of aortic aneurysms.[17] Despite taking all known conventional measures to control its expansion rate, patients with progressively increasing aortic diameter are generally followed medically within recommended limits due to inherent risk of the surgical or interventional operations.[17] This watchful waiting approach entails preacceptance of an ≈1% risk for dissection/rupture during follow-up period,[20,21] which underscores the necessity of the new and effective treatment modalities in reducing or preventing growth of aortic aneurysm. In the present study, short AVD pacing provided an additive reduction in aortic peak dP/dt values on top of the effect observed after β-blocker administration. In this regard, short AVD pacing might be beneficial in limiting the propagation rate of aortic aneurysms via reducing acceleration rate of pressure rise in aorta (aortic dP/dt) and consequently shear stress in the aneurysmatic segments. Moreover, besides enhancing their potency, background short AVD pacing can make it possible to use β-blockers in this critical situation in the presence of absolute contraindications such as atrioventricular/intraventricular conduction defects or deep bradycardia.

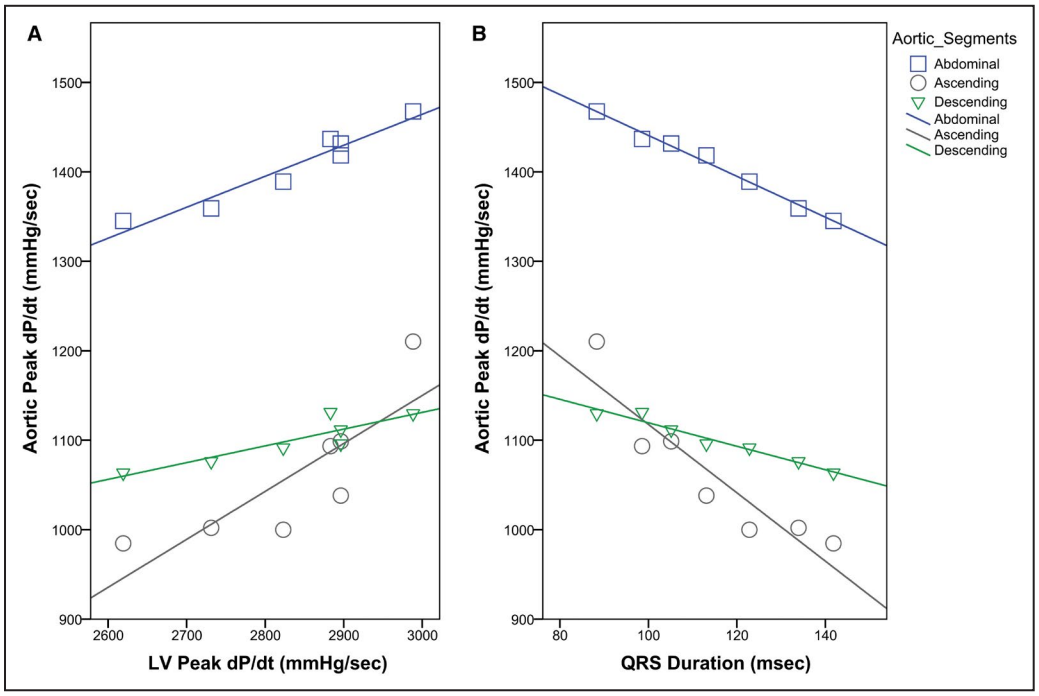

Figure 6. Changes in aortic peak dP/dt values at ascending, descending, and abdominal aortic segments in response to progressively reduced LV peak dP/dt values (A) by means of stepwise widening of the QRS complex (B) by incremental shortening of AVD by DDD pacing.
Each dot represents average aortic peak dP/dt values obtained from 19 subjects. Note that peak dP/dt values, when compared with other segments, were significantly higher in the abdominal aorta at each step. DDD indicates pacing mode of dual pacing, dual sensing, and dual response to sensing; AVD, atrioventricular delay; and LV, left ventricular.

In the second part of the study, wide QRS rhythm over 3 weeks ensured by short AVD pacing resulted in a significant reduction in the serum levels of MMP-9, which is a well-known vascular extracellular matrix degradation marker.[7,22] Based on the aforementioned initial findings, this outcome most likely occurred as a

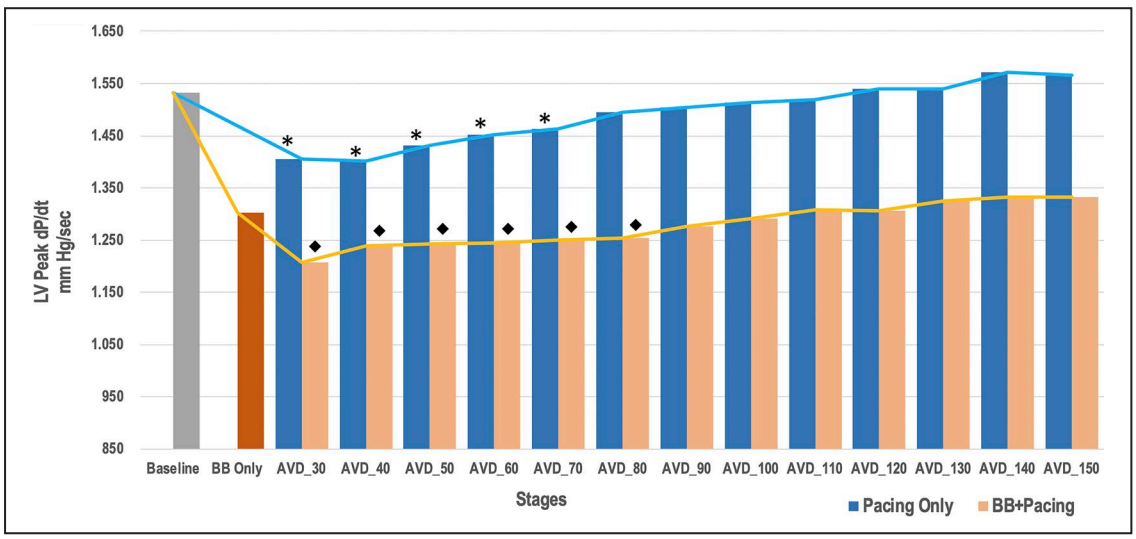

Figure 7. Changes in LV dP/dt values in response to incremental lengthening of AVD by DDD pacing without (blue bars) or with (orange bars) background beta-blocker (β-blocker).
In the absence of background β-blocker administration, significant reduction in LV dP/dt, compared to baseline, has begun from the step when left ventricle paced with AVD ≤70 ms (*). In the presence of background β-blocker administration, this transition occurred at the stage when AVD ≤80 ms (◆). Symbols ([◆] with and [*] without background β-blocker) represent the steps when the differences between LV dP/dt values measured at pacing steps and baseline LV dP/dt became significant. Corresponding *P* values at each step are found in Table 3. DDD indicates pacing mode of dual pacing, dual sensing, and dual response to sensing; AVD, atrioventricular delay; and LV, left ventricular.

Table 3. Comparisons of the Left Ventricular (LV) Peak dP/dt and LV Systolic Pressure Values (Mean±SD) Under Dual-Chamber Pacing (DDD) With Incremental Lengthening in Atrioventricular Delay (AVD) Measured at Baseline Condition and After Intravenous β-Blocker (βB) Administration

	DDD Pacing With Incremental Lengthening in AVD (ms)												
	Baseline	30	40	50	60	70	80	90	100	110	120	130	140	150
LV peak dP/dt	1531±265	1406±278	1401±263	1431±278	1452±278	1462±272	1496±266	1503±264	1513±287	1518±270	1540±270	1540±264	1572±267	1566±269
P		<0.001*	<0.001*	<0.001*	0.001*	0.005*	0.101	0.208	0.404	0.574	0.708	0.728	0.082	0.127
LV sys. pressure	144±16	138±17	138±17	139±17	140±17	141±16	141±16	143±16	144±15	144±15	145±15	145±14	145±15	146±15
P		0.0001*	0.0001*	0.0001*	0.002*	0.001*	0.005*	0.035*	0.263	1	0.296	0.257	0.195	0.142
	βB+DDD Pacing With Incremental Lengthening in AVD (ms)													
	Baseline, After βB	30	40	50	60	70	80	90	100	110	120	130	140	150
LV peak dP/dt	1302±166	1208±180	1240±176	1243±179	1244±179	1251±184	1254±176	1276±187	1291±194	1309±192	1306±195	1325±190	1333±190	1332±190
P		0.0001*	0.0001*	0.001*	0.0001*	0.002*	0.002*	0.186	0.604	0.744	0.830	0.158	0.063	0.056
LV sys. pressure	134±12	127±13	127±14	129±13	129±13	131±12	131±12	129±14	133±12	134±12	135±11	135±12	136±11	136±12
P		0.0001*	0.0001*	0.0001*	0.0001*	0.008*	0.006*	0.076	0.580	0.883	0.253	0.215	0.049*	0.060

LV peak dP/dt and LV systolic pressure values measured at each pacing steps were compared each time with their baseline values.
*Indicate the comparisons which were statistically significant.

result of corresponded reduction of the rate of aortic pressure rise (aortic peak dP/dt) in response to wide QRS rhythm. MMP-9 participates in extracellular matrix degradation in aortic wall where its excessive production might lead to a progressive aortic remodeling and dilatation. In a recent study conducted by Li et al, serum MMP-9 levels predicted thoracic aortic aneurysm with 70% sensitivity and 91% specificity, abdominal aortic aneurysm with 50% sensitivity and 88% specificity.[7] As serum MMP-9 shows a high specificity for both thoracic aortic aneurysm and abdominal aortic aneurysm, it may be a feasible biomarker of diagnostic and clinically predictive value. The matrix proteins in normal aortic wall, that is without aneurysms or dissection, also possess a turnover activity. Hence, in healthy individuals, the enzymes that catalyze matrix proteins can be detected at a certain level in the blood. These levels may increase or decrease depending on the speed of the turnover. Reduction of serum MMP-9 levels using this mode of application suggests that matrix protein degradation can also be reduced in cases of vascular damage or increased tissue sensitivity. Mechanical stretch of the aorta, which is cyclical due to pulsatile flow, seems to regulate MMPs and in turn affects the matrix metabolism and remodeling in vascular tissue.[7,23] Consistently, recent publications indicated that MMPs are activated in the vessel wall in response to cyclic mechanical stresses either circumferential or longitudinal.[13,24,25] In the current trial, putting patients on a wide QRS rhythm for 3 weeks may have decreased the increased rate of tensile stress on the wall of the aorta presumably by means of decreasing aortic peak dP/dt during that period, which may have consequently reduced mechanical stress–induced MMP-9 gene expression and serum MMP-9 concentration.

In addition, short AVD pacing led to a constant reduction in aortic systolic and mean pressures but not in diastolic pressure. These findings also suggested that short AVD pacing might also be beneficial in patients with refractory hypertension as an adjunct to antihypertensive therapy. Moreover, because the peak dP/dt value is also reduced in conjunction with systolic and mean aortic pressures with short AVD pacing and because the magnitude of circumferential stress in the vascular wall is mainly determined by the blood pressure, a considerable benefit can be expected from this mode of intervention in patients with pressure-sensitive aortic pathologies.

Although the aortic dP/dt is one of the factors that play role in the development of pressure-sensitive aortic pathologies such as aneurysms, lowering this parameter alone may not be enough to show clinical benefit. Because, aortic pathologies are also affected by parameters other than LV contractility such as preload, stroke volume, structural properties of the aortic wall, compliance, and vascular resistance. Lowered LV and

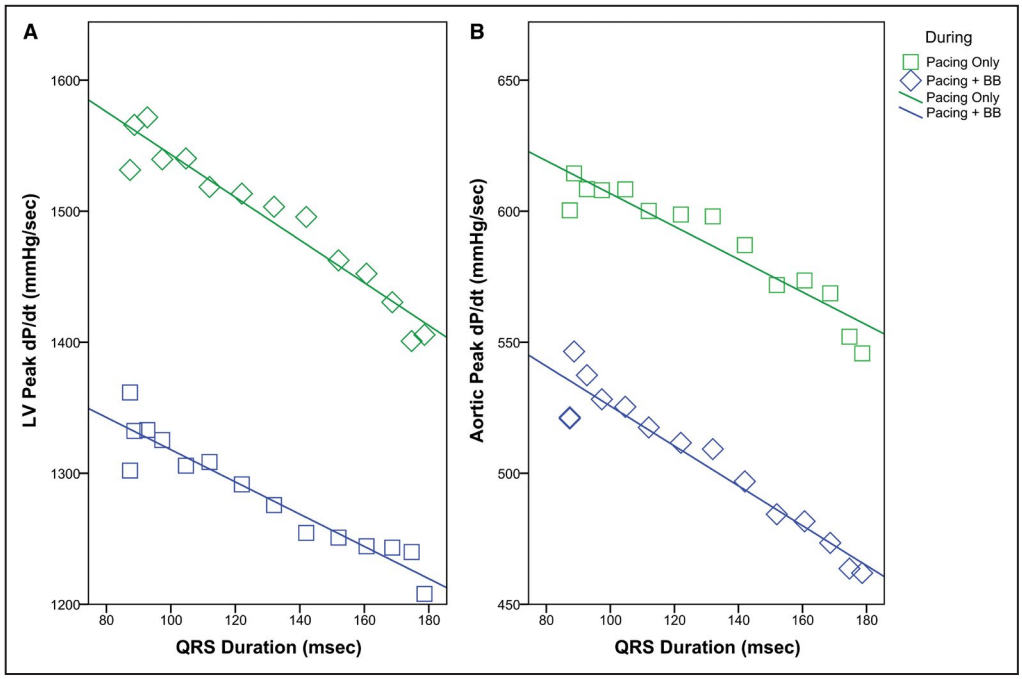

Figure 8. A, The relationship between QRS duration and LV dP/dt with and without background beta-blocker (β-blocker) administration.
Each dot represents the average of the data obtained from 15 subjects. **B**, The relationship between QRS duration and aortic dP/dt with and without background β-blocker administration. Each dot represents the average of the data obtained from 15 subjects. LV indicates left ventricular.

aortic peak dP/dt values using PM (pacemaker) and the decrease in blood levels of an enzyme, MMP-9, used as an indicator of aortic matrix proteins, after 3 weeks appears promising. However, this finding alone cannot be considered sufficient to indicate necessity of pacemaker implantation in patients with aortic aneurysm.

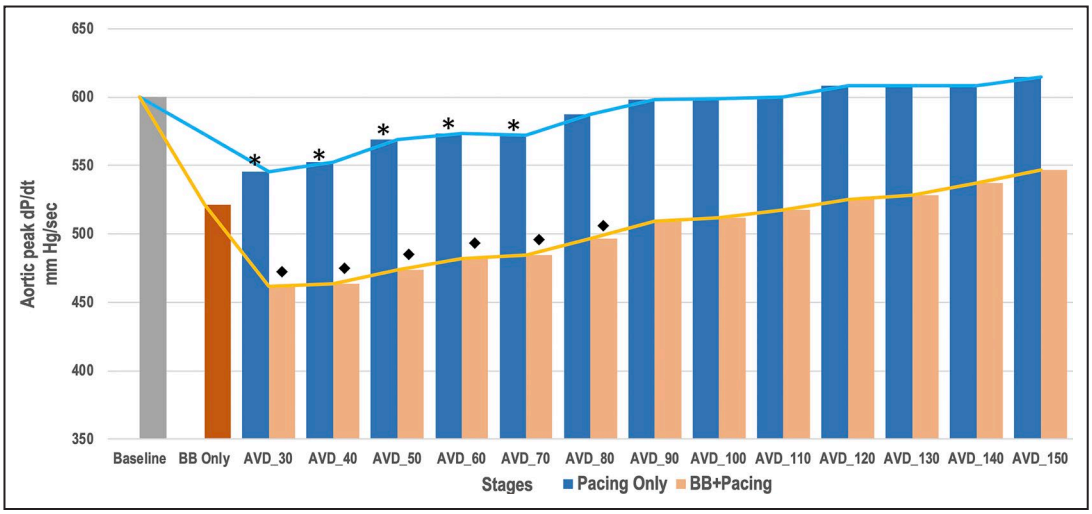

Figure 9. Changes in aortic peak dP/dt values in response to incremental lengthening of AVD by DDD pacing with or without background beta-blocker (β-blocker).
In the absence of background β-blocker administration (*), significant reduction in aortic peak dP/dt, compared with baseline, is seen to begin at the step when left ventricle paced with AVD ≤70 ms (blue line). In the presence of background β-blocker administration (◆), this transition has begun at the stage of AVD ≤80 ms (yellow line). Symbols ([◆] with and [*] without background β-blocker) represent the steps when the differences between aortic dP/dt values measured at pacing steps and baseline aortic dP/dt became significant. Corresponding *P* values at each step are found in Table 2. DDD indicates pacing mode of dual pacing, dual sensing, and dual response to sensing. AVD indicates atrioventricular delay.

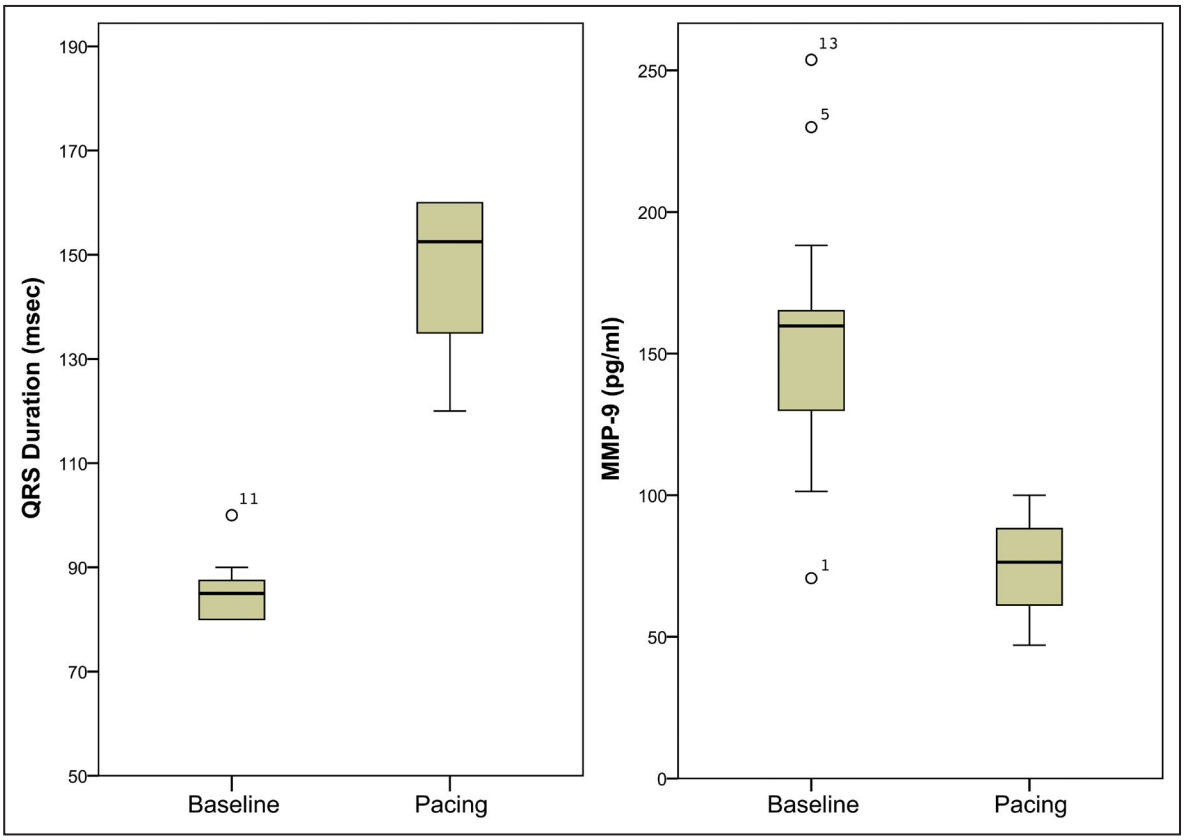

Figure 10. Effect of widening of QRS complex by dual-chamber pacing with atrioventricular delay 60 ms shorter than the patients' individual P-R interval on QRS duration and serum matrix metalloproteinase-9 levels (*P*<0.001 for all).

Even so, the study can be considered incentivizing for pilot studies performed on high-risk volunteers who have aortic aneurysm that cannot be controlled with medical treatment and can benefit from this mode of intervention. Notably, this technique may be helpful in patients with aortic aneurysm and poor medication compliance, particularly in those on complicated medical regimen. Moreover, this method may enable administration of higher dosages of β-blockers, which is the only widely accepted medication in use, and may also potentiate its effect. Considering this augmented effect of combined use of β-blocker and pacing, combined usage may result in more profound decrease in serum MMP-9 level than β-blocker alone. This method, therefore, may be a unique option for patients with poor medical compliance and patients with contraindication for β-blockers.

Several limitations of the present study should be noted. First, this mode of intervention cannot be applicable in patients with LV systolic dysfunction since short AVD pacing may further decrease LV contractility. Nevertheless, LV and aortic peak dP/dt values were already low in this group of patient. Second, the source of circulating MMP-9 cannot be clearly identified in our patient population. Third, in this paper, 2 sequential cohorts were used to test the hypothesis. In the first step, temporary pacing was appropriate and necessary to test the primary hypothesis. However, effect of 3 weeks continuous short AVD pacing on serum biomarker levels (secondary hypothesis) can only be tested in another group of patients with permanent pacemaker. Moreover, second stage of the trial could be designed iteratively only on the basis of the initial findings of the first experiments. Fourth, negative hemodynamic effect of the method that potentially leads to a lower stroke volume need to be considered. Even if only patients with sufficient systolic reserve were selected for the implementation; de novo events/pathologies developed in the long run would decrease patients' tolerance to a wide QRS rhythm during follow-up. Symptoms and signs of heart failure should be monitored and QRS width should be renarrowed by prolonging AVD when needed. In addition, due to lack of sufficient sample size and short follow-up period (3 weeks of wide QRS pacing), we could not provide long-term data regarding safety and patient tolerance. Therefore, it should also be kept in mind that potential beneficial effects of this mode of therapy that can be translated into the patients with aortic aneurysm were derived from short-term data. Last, we mainly aimed to show at

which pacing step the statistically meaningful transition would occur in the measured parameters (peak dP/dt or pressure) as compared with their initial baseline values. Therefore, because we did not compare interstep differences and we did not study multiple groups, we did not account for multiplicity and we did not made any further adjustments. Even if we had applied Bonferroni correction for comparison of 13 pairs and used P=0.0038 as the criteria, significance would have been changed at only 1 step for aortic dP/dt (at 80 ms) and aortic pressure (at 90 ms, Table 3).

In conclusion, gradually reduced LV peak dP/dt values by means of widening of the QRS complex via adjustment of the AVD resulted in a concordant decrease in the peak dP/dt values in all aortic segments, which in turn led to a significant reduction in circulating levels of an extracellular matrix degradation marker, MMP-9. On the basis of these assessments, findings of this study suggest that this mode of mechanobiological intervention may open a new therapeutic avenue in the management of pressure-related aortic pathologies such as aortic aneurisms. Therapeutic potential and clinical reflections of this mode of intervention should be explored in further longitudinal trials in patients with aortic aneurysm.

ARTICLE INFORMATION

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Disclosures

None.

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