Effects of ventricular pacing-induced tachycardia on aortic mechanics in man

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Abstract

Objective: Effects of pacing-induced tachycardia on left ventricular function have been studied extensively. However, little attention has been focused on aortic elastic properties during heart rate increments. The aim was to determine the effects of right ventricular pacing on the aortic elastic properties. Methods: We studied 14 normal subjects (baseline blood pressure, 129/84±10/6 mmHg; aortic diameter, 23.5±21.3±2.4/1.9 mm) at rest, during rapid right ventricular pacing (at five stepwise heart rate increases of 20 bpm every 2 min) and after 5 min recovery. Shifts as well as changes in the slope and the stiffness constant of the pressure diameter (p±d) relation, derived from simultaneous tip-micromanometer aortic pressure recordings and high-fidelity ultrasonic intravascular aortic diameter recordings, were used as indices of aortic stiffness. Wave reflection was also studied. Results: Aortic pulse pressure and strain significantly decreased after pacing-induced tachycardia (p<0.0001 and <0.05, respectively). During pacing, the slope of the linear p±d relation as well as the stiffness constant were decreased, followed by increases at recovery (p<0.0001). The augmentation index and the aortoventricular coupling ratio were significantly decreased (p<0.0001). Conclusions: Pacing-induced increases in pulse frequency may result in improved aortic distensibility and aortoventricular coupling. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Pacing; Aorta; Distensibility; Pressure–diameter relationship

1. Introduction

Previous investigators have described hemodynamic alterations associated with pacing-induced tachycardia in patients and in normal subjects [1,2]. Patients who are stressed by ventricular-paced tachycardia generally demonstrate changes in cardiac output, mean arterial pressure and systemic vascular resistance. Left ventricular end-diastolic and end-systolic volumes fall during pacing tachycardia with a decrease in stroke volume [3].

No previous study has analyzed aortic pressure–diameter relationships during pacing-induced tachycardia in humans. The present study was undertaken to determine the effect of rapid right ventricular pacing on the elastic properties of the aorta in normal subjects by using pressure–diameter analysis.

2. Methods

2.1. Study population

We investigated 14 patients with no angiographic evidence of significant coronary artery stenosis who underwent coronary angiography for evaluation of symptoms that were compatible with angina pectoris. All of the patients had an indeterminate exercise treadmill test. In addition, all patients had a normal transesophageal echocardiography of the descending aorta. Patients with...
previous myocardial infarction, valvular heart disease or evidence of left ventricular dysfunction were excluded. In all patients, medications were discontinued five half-lives before the study. The protocol was approved by our institutional Ethics Committee and all patients gave informed consent before participating.

2.2. Measurement of diameter and pressure

Pulsatile movement of the wall of the proximal descending aorta was invasively measured by a Y-shaped intravascular catheter employing an ultrasonic displacement meter that was developed in our institution [4–6]. The body and each arm of the catheter consist of a 0.014\textsuperscript{\textregistered} stainless steel wire. At each arm of the catheter, a piezoelectric crystal (5 MHz in frequency, 1 mm; Crystal Biotech, Hopkinton, MA, USA) is attached. The ultrasonic crystal is secured in the tips of the catheter with epoxy glue. The crystals oppose each other at any angle of the Y tips. The arms are spring-loaded and always achieve the open position. The length of each arm is 6 cm and the angle at the expanded unstrained configuration is 40°. The wire of the main body and each arm of the catheter is placed inside a smooth polyurethane protective sheath [4–6].

The principles of the ultrasonic crystals are as follows: The transit time of the acoustic impulses traveling at the sonic velocity is approximately 1.5×10\textsuperscript{6} mm/s. Thus, the distance from the piezoelectric crystal to the oppositely positioned receiver crystal can be measured with a high degree of accuracy. A voltage proportional to the transit time and, thus, the instantaneous dimension of the aorta, can be recorded continuously. Crystal alignment after fabrication of the catheter is verified using an oscilloscope (Model 2120, B and K Precision, Chicago, IL, USA) displaying the received ultrasonic signal. Similarly, continuous verification is also obtained during the procedure [4].

The technical characteristics of the device include: (1) resolution for assessment of changes in diameter of 10 \( \mu \)m (2) flat (±5%) frequency response in testing, up to 40 Hz, (3) no measurable phase lag between forced oscillations of the device and the signal in the frequency response range and (4) minimal loading on the aortic wall (0.45 g per arm when the distance between the arms is 1 cm) [4].

Aortic pressure was simultaneously measured by a catheter-tip micromanometer (Model SPC-330, Millar Instruments).

2.3. Study protocol

The subjects were studied during a day’s hospitalization. Studies were performed at 9 a.m. under a controlled room temperature of 20 ± 1°C. Before insertion of the diameter device and the pressure micromanometer, all of the patients received an intravenous bolus injection of heparin (100 U/kg) and, during the procedure, a continuous infusion of heparin, to maintain an activated clotting time of >300 s.

For insertion of the diameter device, a long (50 cm) 8F guiding sheath was introduced through a 9F introducer that was placed in the right femoral artery and positioned to the level of the proximal descending aorta under fluoroscopic guidance. The catheter (with the wires collapsed) was then advanced into the guiding sheath. Once the catheter-tip was in position, the guiding sheath was withdrawn to expose completely the Y-shaped end of the catheter, which allowed the arms to spread apart until they touched the aortic wall and freely followed its movements during the cardiac cycle (Fig. 1). The catheter position was frequently checked by fluoroscopy throughout the study, to document its stability.

The catheter-tip micromanometer (3F) was inserted through a 5F introductory sheath punctured into the left femoral artery and advanced slightly below the exact level of the pair of crystals. A 6F bipolar pacing catheter was positioned at the right ventricle.

Baseline measurements were obtained 30 min after the last infusion of contrast medium. Right ventricular pacing was initiated at a rate of 80 beats/min and was increased in a stepwise manner by 20 beats/min every 2 min. Data were recorded during sinus rhythm, during right ventricu-
lar pacing, for the last 30 s of each pacing interval, and after a 5-min recovery period.

2.4. Data acquisition

Throughout the study, ECG, aortic diameter and aortic pressure signals, collected with a VF-1 mainframe fitted with appropriate modules for acquisition of data, were simultaneously displayed in real time mode on a PC (Pentium 100) using a multichannel 12-bit analog-to-digital converter (Data Translation Inc.) and commercially available data acquisition software (Dataflow, Crystal Biotech). The digitized data were stored and later processed using commercially available software (Microsoft Excel 97 for Windows). Signals were digitized every 5 ms. For aortic pressure and diameter values and for subsequent calculations of derivative parameters, analyses were performed on ten consecutive cycles and the results were averaged.

2.5. Estimation of aortic elastic properties

2.5.1. Aortic strain and distensibility

Aortic strain was calculated as the ratio: Aortic strain = (systolic–diastolic aortic diameter)/diastolic aortic diameter. Cross-sectional distensibility of the aorta was calculated with the following formula: Aortic distensibility = 2 × strain/aortic pulse pressure [7–10].

2.5.2. Aortic pressure–diameter relation

The aortic pressure–diameter relationship was obtained by plotting the pressure versus diameter of digitized data by means of a commercially available computer software package (Excel 97 for Windows). To characterize the pressure–diameter relationship and to determine the aortic loop orientation, the slope and the intercept of the linear regression line of pressure versus diameter were calculated [4].

2.5.3. Aortic stiffness constant

Aortic pressure–diameter data obtained during the ventricular ejection, which corresponds to the ascending limb of the loop, were used for the calculation of the aortic stiffness constant. The rate of aortic blood pressure changes (dP/dt) was instantaneously calculated and simultaneously recorded with the high-fidelity pressure. Pressure and diameter data during the ascending limb of the loop, starting at the time when the dP/dt curve reached zero baseline (at the beginning of the ascending limb of the loop) and ending at peak +dP/dt, were fitted to the exponential function: \( P = b \times e^{a \times D} \), where \( P \) is the instantaneous aortic pressure and \( D \) is the aortic diameter. The least-squares method was used for calculation of \( a \) and \( b \), where \( a \) is the elastic aortic stiffness constant (mm\(^{-1}\)), which determines the slope of the exponential curve, and \( b \) is the elastic constant (mmHg) [6].

Fig. 2. Aortic pressure and diameter curves versus time at baseline and at 80, 100, 120, 140 and 160 bpm and 5 min after recovery, from a single subject. It is obvious that, during ventricular pacing, pulse pressure is decreased and both systolic and diastolic diameters are also diminished. A divergence of the curves is manifested, which is due mainly to an increase in the aortic diameter immediately after the dicrotic notch. This could represent hysteresis of the aortic wall.
2.5.4. Wave reflections and aortoventricular coupling

Wave reflections were evaluated by measuring the augmentation index, defined as the ratio: (Pressure from inflection point to late systolic peak)/(pulse pressure) [11]. The beginning of pressure wave upstroke, the inflection point (P, i.e. the point at the beginning of reflected wave) and the late systolic peak (P, end) were defined by using the fourth derivative of pressure. When plotted against pressure derivatives, the timing of the P, was indicated by a local minimum in the first derivative. To simplify the detection of this point, higher order derivatives were used to identify the zero-crossing point equivalent to the local minimum of the first derivative. The first zero crossing of the fourth derivative (in a direction from above to below the zero line) corresponded to the beginning of the pressure wave upstroke. The second zero crossing in the same direction corresponded to the P, [12]. Scatter in each primary pressure derivative was smoothed by applying a moving average curve (Microsoft Excel 97 for Windows). This resulted in phase shifts that depended on the interval parameters during the study. For comparisons of serial changes in aortic pressures, repeated-measures ANOVA was performed to examine heart rate differences and interactions. Values of peak response to pacing tachycardia were compared with baseline and with recovery using the paired t-test (Table 1). Serial changes in aortic diameters with heart rate as an independent variable and the use of 13 “dummy variables”, to adjust for intersubject variation,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group (n=14)</th>
<th>Baseline</th>
<th>160 bpm (Δ%)</th>
<th>5 min Recovery (Δ%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>55±2</td>
<td>109.0±8.2* (−15)</td>
<td>126.2±9.4* (16)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/7</td>
<td>89.4±6.7* (6)</td>
<td>82.3±10.2* (~8)</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.85±0.18</td>
<td>19.6±5.4* (~56)</td>
<td>43.9±12.1* (~124)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67±2</td>
<td>95.9±6.7 (~3)</td>
<td>96.9±8.2 (~1)</td>
<td></td>
</tr>
</tbody>
</table>

**Aortic pressures (mmHg)**

- Systolic: 128.6±10.0
- Diastolic: 84.3±6.2
- Pulse pressure: 44.3±12.2
- Mean pressure: 99.1±5.1

**Aortic diameters (mm)**

- Systolic: 23.5±2.4
- Diastolic: 21.3±1.9
- Strain (%): 10.3±2.9
- Distensibility (mmHg⁻¹ 10⁻³): 0.64±0.03
- Slope (mmHg/mm): 20.62±2.23
- Stiffness constant (mm⁻¹): 0.29±0.03
- Augmentation index (%): 3.7±0.5

- RR (s): 0.859±0.000
- LVET (s): 0.286±0.000
- ΔT, (s): 0.124±0.003
- RR/ΔT, (s): 6.96±0.14
- LVET/ΔT, (s): 2.32±0.05

ΔT,=time from the foot of the pressure wave to the foot of the late systolic peak; RR=sinus rhythm cycle length; LVET=left ventricular ejection time.

Δ% = percentage difference between baseline and 160 bpm and between 160 bpm and recovery.

Comparisons were made between baseline and 160 bpm and between 160 bpm and recovery.

*p<0.0001, *p<0.05, *p<0.005, **p<0.001.
were correlated with multilinear regression analysis (SPSS, 7.0 version, for Windows). Stepwise multiple regression analysis was performed to study any age dependency of augmentation index. A value of $p<0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Fourteen subjects (age range 51–58 years, seven males and seven females) were studied (Table 1). All patients were in normal sinus rhythm with a heart rate lower than 80 bpm. Thus, ventricular pacing eliminated competitive rhythms. Aortic hemodynamics and aortic function indexes were within the normal range.

3.2. Changes during ventricular pacing and after recovery (Table 1)

All patients manifested peak responses to all measured parameters at a 160 bpm pacing rate. All parameters returned towards baseline within 5 min after cessation of pacing (Fig. 3 Fig. 4). All patients remained asymptomatic both during right ventricular pacing and at the recovery time.

3.2.1. Aortic pressures and diameters

Systolic and diastolic aortic pressures and diameters as well as pulse pressures and strain, before, during and after pacing, are shown in Fig. 3. Pacing was associated with decreases in the systolic aortic pressures (ANOVA: $p<0.0001$) and increases in the diastolic aortic pressures (ANOVA: $p<0.01$). The pulse pressures significantly decreased (ANOVA: $p<0.0001$), while the mean blood pressure remained unchanged [ANOVA: $p=$ not significant (NS)]. Systolic and diastolic diameters show significant decreases during the study (Multilinear regression analysis: $p<0.0005$ and $<0.05$, respectively). Strain decreased significantly (ANOVA: $p<0.05$, Fig. 3).

Fig. 2 shows changes in the time–diameter and time–pressure curves during pacing.

3.2.2. Aortic pressure–diameter relationship

Aortic pressure–diameter loops were obtained in all patients before, during and after pacing-induced tachycardia. Representative examples of aortic pressure–diameter loops are shown in Fig. 5. Pacing-induced tachycardia resulted in a leftward and downward shift of the pressure–diameter loop (Fig. 5) and a decrease in the pressure–diameter slope ($p<0.0001$, Fig. 5) Thus, pacing-induced tachycardia increased aortic distensibility. The pressure–diameter loop returned towards the baseline position and became steeper 5 min after the termination of pacing.

3.2.3. Aortic distensibility and stiffness

Aortic distensibility was gradually increased ($p<0.0001$) during pacing and returned to the basic value during recovery (Table 1). In contrast, the aortic stiffness constant gradually decreased ($p<0.0001$) during increases in heart rate and returned to the initial value after cessation of pacing (Table 1). The mean aortic distensibility and the mean aortic stiffness constant are shown in Fig. 4.

3.2.4. Wave reflections

The augmentation index decreased ($p<0.0001$) to nega-
Fig. 4. Changes in distensibility, slope of the pressure–diameter relation and the aortic stiffness constant in 14 subjects at baseline (bas) and at 80, 100, 120, 140, and 160 bpm, as well as at 5 min recovery. $P$ values refer to the ANOVA (left). Changes in the augmentation index, RR/Δt and LVET/Δt in 14 subjects at baseline (bas) and at 80, 100, 120, 140, and 160 bpm, as well as at 5 min recovery. $P$ values refer to the ANOVA (right).

4. Discussion

This study demonstrates that ventricular pacing-induced tachycardia produces an acute increase in aortic distensibility in humans. The effect of pacing was completely eliminated 5 min after a return to baseline heart rate.

Hutcheson and Griffith [14] demonstrated frequency-dependent vasodilatation in isolated perfused aortas in vitro. They found that relaxation of the aorta depended on the frequency of flow. In contrast, increases in pulse pressure amplitude augmented constriction of the aorta. They concluded that flow-induced release of endothelium-derived relaxing factors (EDRFs) is frequency encoded and that the release of EDRFs is inversely related to pulse pressure.

4.1. Pacing-tachycardia and aortic elastic properties

In the present study, we found that aortic diameters were decreased during pacing despite a rise in diastolic pressure, reflecting a leftward shift of the pressure–diameter loop. This finding must reflect some altered (adversely so) aortic
mechanics, despite the decreased local slope, as the heart rate increases. Furthermore, the vasodilatory effect [14] of tachycardia on the aortic wall and the increased compliance, as shown in our study, were overcome by the reduced stroke volume during ventricular pacing. Thus, a composite effect occurred, which decreased the aortic diameter. This may be an example of a compensatory mechanism where humoral factors counterbalanced hemodynamics.

As the heart rate was increased step-by-step, systolic and diastolic aortic pressures were changed so that pulse pressure gradually declined. Systolic blood pressure decreased due to the decreased diastolic period, resulting in decreased left ventricular filling. The first finding of the increased distensibility of the aorta is a decrease in pulse pressure [15]. Rapid ventricular pacing induced acute hemodynamic changes, with the pulse pressure undergoing the greater alteration. The other parameter that determines aortic distensibility is aortic strain [7–10]. A decrease in aortic strain during ventricular pacing may be the result of reduced stroke volume. However, aortic distensibility (strain/pulse pressure ratio) increased because the percentage decrease in pulse pressure (56%) was larger than the percentage decrease in strain (29%).

The physiologic consequence of having a compliant aorta during ventricular pacing, or even ventricular tachycardia, may be the decreased left ventricular afterload in a situation of emergency, as it is defined by the increased heart rate. The parallel increase in aortic distensibility with the stepwise increase in the heart rate suggests that the underlying mechanisms are sensitive enough to changes in pulsatility. These mechanisms may be either hemodynamic or metabolic [16].

An interesting finding of this study was the displacement of the aortic pressure–diameter loop, indicating changes in aortic function. [5]. Pressure–diameter loops lie on the same hypothetical curve that is determined by the intrinsic elastic properties of the aortic wall. Therefore, it is expected that aortic pressure–diameter loops will remain on that curve, although at different segments, despite blood pressure and diameter changes, if the intrinsic elastic properties of the aorta remain unchanged (passive mechanism). Any displacement of the pressure–diameter loops along a different hypothetical curve would indicate an active alteration of the elastic properties of the aorta (active mechanism). Thus, the changes in aortic pressure–diameter loops observed in the present study are the result of an active and not a passive mechanism.

In addition to a decrease in the slope and in the stiffness constant, indicating improved aortic distensibility, there was a leftward shift of the pressure–diameter relationship, leading to a lower aortic diameter at increased heart rate for a given aortic pressure. This could be explained by the fact that absolute aortic diameter is determined not only by the distending pressure and the aortic distensibility but by other factors as well, such as peripheral vascular resistance and aortoventricular coupling. Aortic distensibility is a dynamic property of the aortic wall and reflects changes in aortic strain in relation to pulse pressure. The decrease in local stiffness that we observe may simply reflect that the aorta is operating on a flatter portion of its hypothetical curve of elasticity.

The slope of the pressure–diameter relationship represents the orientation of the loop, whereas the stiffness constant is a more specific index of aortic elasticity [6]. The aortic stiffness constant takes into account data from the ejection period only. Both indexes supported our hypothesis that ventricular pacing increases aortic distensibility.

In this study, the effects of wave reflections were measured by the augmentation index, and the RR/Δtp and LVET/Δtp ratios. The augmentation index displays an effect on aortic pressure, while Δtp represents the travel time of the pulse wave to the peripheral reflecting sites and its return. The augmentation index was significantly decreased to negative values, representing transformation of the pressure waveform of type B to type C and a decrease in peripheral resistance [11]. Type B referred to patients whose peak systolic pressure occurred in the late systole following an inflection point and had a positive augmentation index <12%. Type C referred to patients whose peak systolic pressure preceded the inflection point and had a
negative augmentation index. During pacing, the RR interval as well as the LVET were decreased. Similarly, we expected \( \Delta t_p \) to decrease along RR intervals if there was no alteration in the arterial wave speed. Nevertheless, we observed an increase in \( \Delta t_p \), which was confirmed by the \( \Delta t_i \) changes. We speculate that a reduction in arterial wave speed may have improved arterial distensibility. This could explain the increased diastolic pressure during the short RR intervals observed in our study. The RR/\( \Delta t_p \) and LVET/\( \Delta t_p \) ratios showed aortoventricular coupling [13]. Thus, pacing-tachycardia improved the timing of wave reflections and the aortoventricular coupling. Another mechanism of the improved coupling was the increased left ventricular contractility during pacing tachycardia [17]. As a result, the efficiency of the ventricular systole was probably increased. The LVET/\( \Delta t_p \) became less than one after a heart rate of 140 bpm. This means that after that the heart rate LVET was less than \( \Delta t_p \) and the return of wave reflections happened after the aortic valve closure, leaving left ventricular ejection unaffected by adverse wave reflections.

4.2. Specific comments

In this study, only ventricular pacing was used; thus, the results can be applied only to increases in heart rate of ventricular origin. Similar hemodynamics in other types of tachycardia, however, may similarly affect aortic elastic properties. The small number of subjects studied is not a limitation of the study because changes reached an increased level of significance. We excluded also the possibility of intramural hematoma as a reason for the patients’ chest pain by transesophageal echocardiogram [18]. Consequently, it is unlikely that altered aortic compliance was the result of aortic wall pathology.

Fig. 2 displays aortic pressure and diameter curves versus time. It is obvious that, during ventricular pacing, a divergence of the curves is manifested. This is due mainly to an increase in aortic diameter immediately after the dicrotic notch. This could represent hysteresis of the aortic wall. Moreover, as shown in Fig. 5, the slope of the linear curve fitting seems to be affected by the diastolic portion of the pressure–diameter loop.

Ideally, if the aortic pressure was modified by manipulation of preload using inferior vena cava occlusion, an exponential pressure–diameter curve would have been obtained. Since we maintained the same preload during ventricular pacing in our study, the aortic stiffness constant was used to express the slope of the exponential pressure–diameter curve at the segment representing the initial ejection phase of the left ventricle. We believe that the initial ejection phase expresses the elastic properties of the aortic wall and that it depended mainly on the elastic fibers. In contrast, aortic distensibility takes into account alterations in aortic pressure and diameter only at the peak-systolic and end-diastolic phases. Thus, the aortic stiffness constant represents regional changes in the slope of the exponential pressure–diameter curve, while aortic distensibility may not.

We consider that the elastic stiffness constant represents the intrinsic resistance of the aortic wall and can be considered as the pressure–axis intercept of the exponential curve, while the exact physiological meaning of this parameter has not been thoroughly evaluated.

The effect on pulse wave shape and, thus, on aortoventricular coupling might be underestimated in the present study, since the measurements were performed in the descending aorta. The reflected waves reach the descending aorta before the ascending aorta. The decrease in the augmentation index might therefore occur at lower heart rates when measured in the ascending aorta. There are, unfortunately, no data available from the ascending aorta to calculate this difference.

In addition, not only the timing but also the nature of the reflected waves may be altered during pacing. The geometric and elastic nonuniformity of the aorta results in many different sites of arterial wave reflections. Furthermore, each of the reflection sites reflects some portion of the pulse wave; thus, there are many reflections with different time lags returning to the site of measurements.

4.3. Conclusions

This study shows that pacing-induced tachycardia in normal subjects results in an acute improvement of aortic distensibility and in a change in the timing of wave reflections. These effects may contribute to the beneficial effects on ventricular/vascular coupling and ventricular efficiency.

Acknowledgements

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References


