Quantitative optimisation of atrioventricular delay of biventricular pacemakers

Short title: “Parabola-and-plateau” optimisation

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Abstract

Background

Optimisation of atrioventricular (AV) delay of biventricular pacemakers by fitting a parabola to the systolic blood pressure (SBP) data over the whole range of AV delays, might be biased if the true dependence of SBP is not parabolic at large AV delays.

In this study, we tested a new algorithm, which we call the 'question-mark algorithm', in which the range of AV delays is automatically restricted to the parabolic zone prior to fitting the parabola.

We tested whether the AV delay by the question-mark algorithm produces better acute hemodynamic response than the AV delay predicted by the parabolic algorithm.

Methods and results

In 93 patients with biventricular pacemakers, whilst pacing at an elevated heart rate, the AV delay was adjusted and the beat-to-beat systolic blood pressure (SBP) was simultaneously measured non-invasively. We then compared the selected AV delays using both the parabolic and the question-mark algorithms.

For 10 patients, the question-mark algorithm detected that the pattern was not parabolic for the larger AV delays used. For these patients, we re-measured the SBP according to the two different AV delays. The optimal AV delay predicted by the question-mark algorithm increased SBP by on average 1.26 mmHg above that predicted by the parabolic algorithm (95% confidence interval: 0.60 mmHg to 1.92 mmHg, p-value = 0.002).

Conclusion

Identifying the optimal AV delay by automatically eliminating the range of AV delays in which the pattern is not parabolic before finding the maximum of the best-fit parabola has potential to improve acute hemodynamics.

Introduction

In chronic heart failure patients with dyssynchrony, biventricular pacemakers improve the efficiency of cardiac function by adjusting the atrioventricular (AV) and interventricular (VV) delays; this treatment is also known as Cardiac Resynchronization Therapy (CRT). The hemodynamic benefit of biventricular pacing is immediately apparent when the device is switched on [1—5] and its long-term benefits have also been demonstrated in randomised clinical trials [6, 7]. The acute improvement in hemodynamics can be further maximised by optimising the AV and VV delay settings of the pacemaker [8—12].

In practice, most optimisation involves assessing cardiac function using non-invasive approaches. Echocardiography using Doppler is often used to acquire the blood velocity, from which the velocity—time integral is derived as a surrogate for stroke volume. This approach is time-consuming, requires experienced operators, and has limited reproducibility [13, 14]. An alternative technique consists of using non-invasive measurement of systolic blood pressure (SBP), which has been demonstrated to be highly reproducible [15, 16]. This approach does not require experienced operators but may be time-consuming depending on the number of measurements acquired. For AV delays near the optimum, a graph of SBP against AV delay is known to fit closely to a parabola, with R^2 values greater than 0.95 [17]. The algorithm predicts that the optimal AV delay is the one corresponding to the peak of the parabola, and in this paper we refer to this as the 'parabolic' algorithm.

However, for long AV delays, ventricular contraction can occur due to intrinsic conduction. This phenomenon should be apparent as a plateau region appears in the graph of SBP against AV delay at high values of the AV delay. If this part of the data were included in the parabolic algorithm, then the predicted optimal AV delay would be too large. Currently, in order to avoid this, a human operator is required to identify the parabolic region visually and eliminate it from the curve fitting. This human element leads to non-reproducibility, uncertainty and subjectivity of the analysis.

In this study we developed a new 'question mark' algorithm that automatically removes the plateau region from the curve fitting process, and we tested its performance against that of the parabolic algorithm.

Methods

Subjects

All patients included in this study are participants in the ongoing British randomised controlled trial of AV and VV optimisation (BRAVO) study (NLM Identifier: NCT01258829). Patients gave informed written consent for BRAVO, which was approved by the United Kingdom Research Ethics Committee.

Anonymised data from 93 patients (75 male, 18 female, 40—88 years old, mean 68 years old) were used; the patients underwent AV optimisation by non-invasive pressure measurement between April 2013 and July 2013. The causes of heart failure were ischemic (49), idiopathic dilated (19), valvular (7), other reasons (6) and unknown (12). At the time of the BRAVO study, 8 were New York Heart Association (NYHA) class 3, 79 were NYHA class 2, 1 was NYHA class 1 and the NYHA was unknown for 5.

Measurements

Data acquisition

SBP was measured non-invasively using a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands); an inflatable cuff was placed around the finger with a built-in photoelectric plethysmograph and a volume-clamp circuit, resulting in a continuous pressure waveform [18]. This technique is highly reliable at quantifying beat-to-beat changes in SBP [19, 20].

In order to minimize hemodynamic variations due to heart rate fluctuations, baseline atrial pacing at 45 bpm above the resting hear rate was applied [12], and an electrocardiography (ECG) signal was recorded simultaneously, acquired with an analogue-to-digital card (National Instruments, Austin, Texas, USA) using a custom software [21] and analysed with further custom software [22—26], produced using Matlab (MathWorks).

Measurement of relative change in blood pressure across different AV delays

To obtain the hemodynamic response curve, the AV delay was adjusted in 40 ms increments, starting from an AV delay of 40 ms. For each AV delay considered, the heart was first paced with the reference AV delay of 120 ms

before suddenly switching to the AV delay in question (120 ms was chosen because it is attainable by all participants, unlike atrial pacing only (AAI) that requires intact atrioventricular conduction). The VV delay was kept at 0 ms (or as close as possible). The relative change in blood pressure, SBP_{rel}, was set to be the difference between the mean pressure over the 8 beats immediately before the switch and that over the 8 beats immediately after the switch [15], and at least 6 replicate measurements for each AV delay were obtained. Note that, since 120 ms was used as the reference value, the response curve passes through a SBP_{rel} of 0 mmHg for this AV delay.

To compare the difference in SBP between the parabolic and the question-mark optima, we used as reference the optimum found by the parabolic algorithm and alternated between that AV delay and the one found by the question-mark algorithm. For each patient, we used the mean SBP_{rel} over the multiple replicates as measure of the difference in SBP between the two optimum types.

Automated determination of presence of non-parabolic segment

If the patient's tissue is intact so that intrinsic conduction can occur, then, when the programmed AV delay is longer than the patient's PR interval, ventricular conduction would be initiated by this natural mechanism. Consequently, the pacemaker would adjust by not delivering a pacing stimulus. The result is that for these AV delays, further lengthening of the delay has no effect on the SBP. See for example Figure 2, which corresponds to a patient whose PR interval was determined from the ECG to be about 200 ms, and for whom the red squares (representing the average values of SBP_{rel} for each given AV delay) lie approximately on a horizontal line for AV delays longer than 200 ms.

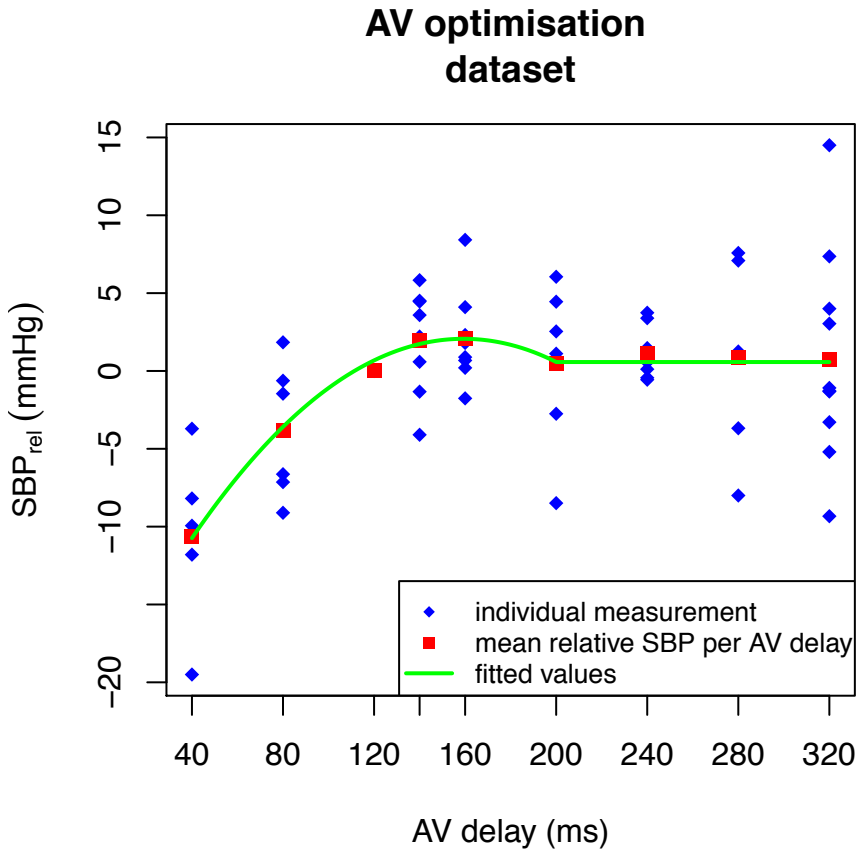

Figure 1. AV optimisation dataset of a patient showing a deviation from the parabolic trend at AV delays longer than 200 ms

The question mark algorithm, which is named after the shape of the fitted curve, finds the AV delay that minimises the sum of the squares of the residual SBP_{rel} of a parabolic fit [15] followed by a flat line (the sum includes the whole range of AV delays, including the flat line).

The optimum AV delay was given as that lying at the peak of the parabola. An annotated version of the algorithm is provided in the Appendix.

Statistics

The difference in SBP between the AV delays determined by the two algorithms was compared using a two-tailed paired t-test, with the null hypothesis that there was no difference in SBP between the two optimum types. A p-value of less than or equal to 5% was considered as significant.

All statistical analyses were performed using the R software for statistical computing version 2.15.1 [27].

Results

The data from all 93 patients could be fitted with a parabola. In 83 of the patients, the SBP curves fitted better to a single parabola rather than a question mark shape, that is the question mark algorithm found that not including a plateau region in the best fit curve was better than including one. However, in the remaining 10 patients, a question mark shape with a plateau was better.

The optimisation datasets of these 10 patients are shown in Figure 3, together with the best-fit curves found by the two algorithms.

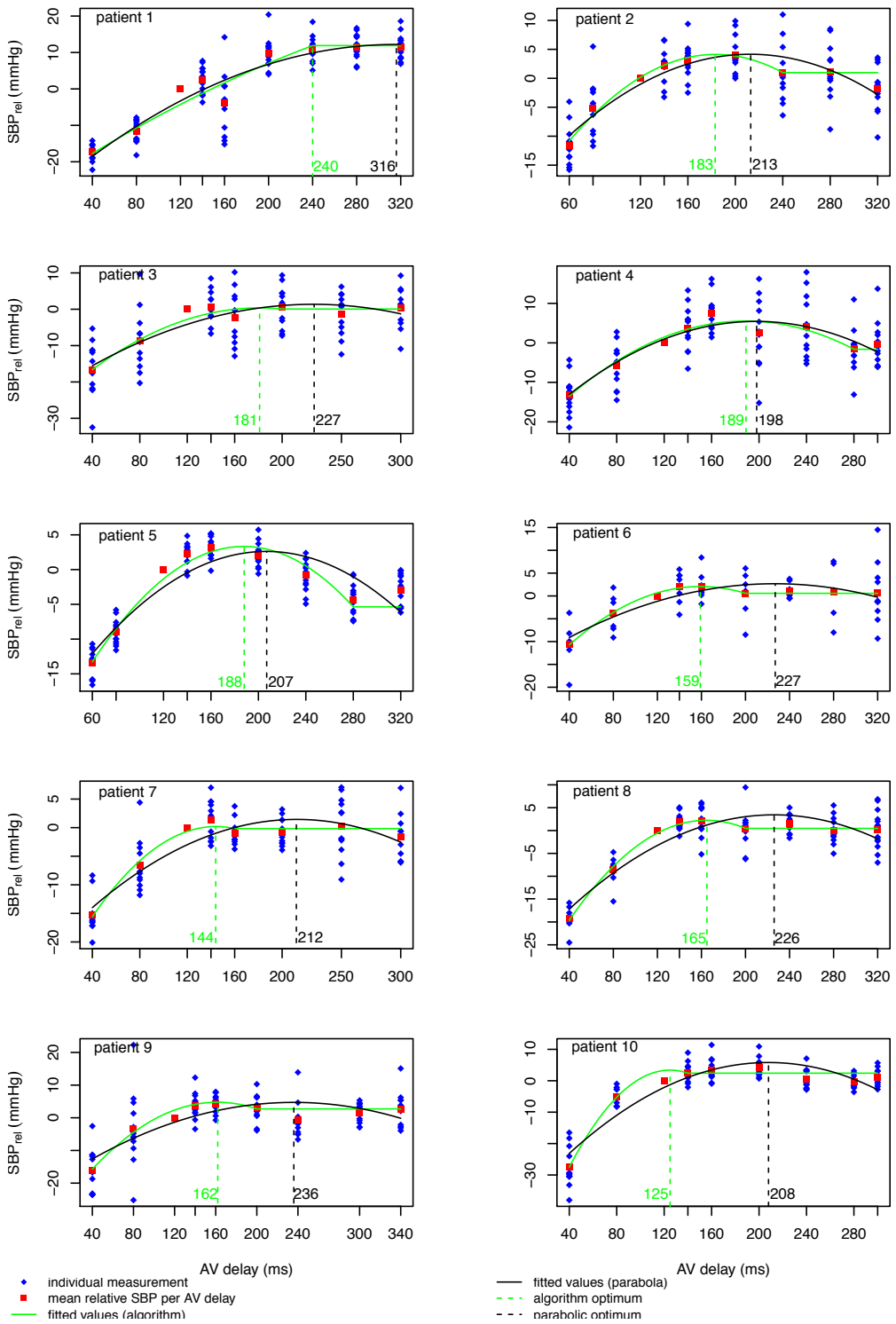

Figure 3. Optimisation datasets of the 10 patients whose data fitted better to a question mark shape (that is, a parabola and a plateau) rather than just a parabola. Fitted question marks and parabolas are also shown.

In Table 1, we report the optimal AV delays predicted by the two algorithms and the corresponding increase in SBP provided by the question mark algorithm optimum compared with the parabolic algorithm optimum. The increase in SBP consists of an average of replicate measurements, whose numbers and standard deviations (SD) are also reported in Table 1.

Table 1. Results of the algorithm for the 10 patients whose data fitted a parabola and plateau better than just a parabola.

Patient	1	2	3	4	5	6	7	8	9	10
Optimum AV delay from question mark algorithm (ms)	240	183	181	189	188	159	144	165	162	125
Optimum AV delay from parabolic algorithm (ms)	316	213	227	198	207	227	212	226	236	208
Increase in SBP from parabolic to question mark algorithm (mmHg)	0.46	0.44	2.14	1.01	2.15	0.24	0.92	2.32	2.55	0.37
# of replicates	16	22	24	16	22	10	22	24	12	20
SD of replicates (ms)	5.60	3.12	5.69	2.73	3.61	4.99	4.87	4.81	3.71	2.49

In these 10 patients the average increase in SBP using the question mark algorithm was 1.26 mmHg (95% confidence interval: 0.60 mmHg to 1.92 mmHg, p-value = 0.002), and thus the null hypothesis that the optimal SPB predicted by the two algorithms are clinically equivalent could be rejected.

Discussion

We have developed a new question mark algorithm that automatically detects the range of AV delays that should not be used when fitting the parabola to the SBP data, and we showed that, for around 11% of CRT patients, this leads to an improvement of on average 1.26 mmHg in SBP. In turn this avoids requiring a human operator to intervene in the parabolic algorithm in a non-reproducible and potentially subjective way.

The new algorithm automatically determines an estimate of the PR interval at which the parabola and straight line are joined, and this works even if, as in most cases, this estimate lies at the top of the range of AV delays considered; in that case the best fit question mark is just the parabola, meaning that the new algorithm gives the same result as the parabolic algorithm.

The question mark algorithm was devised because it is a simple extension of the parabolic algorithm based on physiological considerations. In principle a more complicated mathematical function capturing additional physiology could be used to fit the data; however, we believe that the amount of data per patient captured in this study is insufficient to warrant a more complicated algorithm, and, since the collection of this data was anyway time-

consuming for both patient and operator, any new algorithm that requires further data would need to justify the increased time for data collection in terms of a significant additional hemodynamic benefit.

Size of effect

It is important to review the method by which the measurement of the improvement in SBP was made. It was not obtained from the same data used for the parabolic and question mark fitting, because to have done so would have exposed us to positive bias. Instead, the patients in whom the question mark algorithm detected a plateau region were identified, and in each of these, the optima suggested by the two algorithms were documented. The patients then underwent alternations between these two AV delay settings to prospectively quantify the pressure difference between them. It would not have made sense to perform this step in the remaining 83 patients, as the optima predicted by the two algorithms are identical.

Although the predicted increase in SBP with the question mark algorithm is relatively small (it corresponds to about 1% of stroke volume),it is effectively available for free since the device is already in place and it is easy to implement the question mark algorithm. The effect of CRT itself is larger. In the COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure) trial [6], patients randomized to the active CRT arm initially gained approximatively 2 mmHg of SBP compared with the control arm (no confidence interval published), and showed thereafter an 18% relative reduction in the combined endpoint of morbidity and mortality (95% confidence interval: 1% increase to 42% reduction). In the CARE-HF (Cardiac Resynchronization - Heart Failure) trial [7], patients in the treatment arm showed an increase in SBP of 5.8 mmHg compared with controls at three months (95% confidence interval: 3.5 mmHg to 8.2 mmHg) and a subsequent relative mortality reduction of 37% (95% confidence interval: 23% to 49%). However, it should be borne in mind that the advantage we describe from the question mark optimisation is an incremental benefit rather than a replacement for CRT in itself.

Aside from using a more sophisticated algorithm, there are two other potential improvements to the question mark algorithm. Firstly, current protocols tend not to investigate large AV delays because of the greater likelihood that human intervention will be needed to eliminate the non-parabolic region in the graph of SBP. However, if SBPs at higher AV delays were included and the question mark algorithm used, we would be able to use more of the data reliably, potentially leading to improved predictions of AV settings. Secondly, possible future improvements in the accuracy of hemodynamic measurements would significantly enhance our ability to distinguish the non-parabolic behaviour. Another significant reason in favour of adopting the question mark algorithm is that, once it is encoded,

using it does not require extra effort than using the parabolic algorithm, since the computational time required for both algorithms is very small.

Limitations of the study

The patients underwent atrial pacing at raised heart rates in this study, because differences in parameters such as SBP can be seen more clearly in this state. However, optima identified at a high heart rate tend to be different from those identified at resting heart rate with atrial sensing [15]. It is not known which configuration (that is, optimisation at an elevated or at a resting heart rate) would provide better clinical outcomes for the patients in the long term.

We focused on the immediate hemodynamic effects of changing AV delay, rather than the long-term effects. The implications for the long term are unknown, and the predictions of this study might be diluted by the integrated cardiovascular responses to a change in cardiac function [12]. Moreover, it is not clear if the immediate positive hemodynamic effects of optimisation of the AV delay translate into long-term benefits in terms of remodelling, symptoms or prognosis [28]. A recent meta-analysis, including 4,356 heart failure patients with CRT, showed no differences in clinical and echocardiographic outcomes between CRT patients who underwent optimisation of the AV and/or VV delays and CRT patients with pacemakers left at factory settings [29].

Conclusion

This study has focused on improving the precision of CRT optimisation by developing a new question mark algorithm that identifies both a parabolic and a plateau region of SBP response to changes in AV delays.

Out of 93 patients, the algorithm detected 10 patients with significant deviations from the parabolic trend at high AV delays. For these patients, the optimal AV setting from the question mark algorithm generated a SBP that was 1.26 mmHg higher on average than that obtained with the parabolic algorithm (95% confidence interval: 0.60 mmHg to 1.92 mmHg, p-value = 0.002).

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Appendix

```
########## R code to implement to parabola-and-plateau optimisation process ##########

## load dataset and assign names to columns

data <- read.table("XXX.txt")
colnames(data) <- c("delay","deltaBP")


## extract tested delays and calculate mean relative SBP for each tested delay
unique.delay <- unique(data$delay)
means <- rep(NA,length(unique.delay))
for (i in 1:length(unique.delay))
{
means[i] <- mean(subset(data,data$delay==unique.delay[i])$deltaBP)
}


## run a loop to find the parabola and plateau regions for all tested delays
```

```
quadr.coeff <- rep(NA,length(unique.delay)) # empty vector to store the quadratic coeff.
RSS <- rep(NA,length(unique.delay)) # empty vector to store RSS
for (i in (1:length(unique.delay))){
parabola.subset <- subset(data,data$delay<=unique.delay[length(unique.delay)+1-i])
parabola.fit <- lm(deltaBP ~ delay + I(delay^2), data = parabola.subset)
parabola.RSS <- sum(parabola.fit$residuals^2)
plateau.subset <- subset(data,data$delay>unique.delay[length(unique.delay)+1-i])
plateau.constant <- tail(parabola.fit$fitted.values, n=1) #means[length(unique.delay)-1]
plateau.RSS <- sum((plateau.subset$deltaBP - plateau.constant)^2)
RSS[i] <- parabola.RSS + plateau.RSS
quadr.coeff[i] <- parabola.fit$coefficients[3]
}

## create a dataframe with RSS and quadratic coeff. for each tested delay
unique.delay.last.first <- rep(NA,length(unique.delay))
for (i in (1:length(unique.delay))){
unique.delay.last.first[i] <- unique.delay[length(unique.delay)+1-i]
}
RSS.quadr.coeff <- data.frame(quadr.coeff, RSS, unique.delay.last.first)
RSS.quadr.coeff.pos.quadr.coeff <- subset(RSS.quadr.coeff, quadr.coeff <= 0)

## determine which delay minimises the RSS
pos.opt.delay <- which.min(RSS.quadr.coeff.pos.quadr.coeff$RSS)
beg.plateau <- RSS.quadr.coeff.pos.quadr.coeff$unique.delay.last.first[pos.opt.delay]
i <- which (unique.delay.last.first == beg.plateau)
parabola.subset <- subset(data,data$delay<=unique.delay[length(unique.delay)+1-i])

## fit a quadratic curve to the parabolic region of the dataset,
```

```
## perform predictions according to the fit, and calculate the RSS of the
## parabolic region and the plateau region together
parabola.fit <- lm(deltaBP ~ delay + I(delay^2), data = parabola.subset)
parabola.pred.delay <- seq(min(parabola.subset$delay), max(parabola.subset$delay), 1)
parabola.predictions <- predict(parabola.fit,newdata = data.frame(delay = parabola.pred.delay))
plateau.subset <- subset(data, data$delay > unique.delay[length(unique.delay)+1-i])
plateau.constant <- tail(parabola.fit$fitted.values, n=1)
parabola.RSS <- sum(parabola.fit$residuals^2)
plateau.RSS <- sum((plateau.subset$deltaBP - plateau.constant)^2)
RSS.min <- parabola.RSS + plateau.RSS

## plot the data with the fitted values according to the algorithm
plot(x = data$delay, y = data$deltaBP, xlab = "AV delay (ms)",
ylab=expression(SBP[rel]~(mmHg)),
main = "AV optimisation dataset ",
pch = 18, col = "blue", xaxt="n")
axis(1, at=unique.delay)
points(x = unique.delay, y = means, col = "red", pch = 15)
lines(x = c(parabola.pred.delay, plateau.subset$delay),
y = c(parabola.predictions, rep(as.numeric(plateau.constant), length(plateau.subset$delay))),
col = "green", lwd = 2)
```