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## **Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing**

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Short title: Age-effects of NTG in routine tilt testing

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## ABSTRACT

Nitroglycerine (NTG) is used in routine tilt testing to elicit a vasovagal response. We hypothesized that with increasing age NTG triggers a more gradual blood pressure decline due to a diminished baroreflex buffering capacity. The purpose was to examine the effect of NTG on baroreflex control of blood pressure in patients with distinct age-related vasovagal collapse patterns.

The study groups consisted of 29 patients (16-71 yrs, 17 females) with clinically suspected VVS and a positive tilt test. Mean finger arterial pressure (MAP) was monitored continuously (Finapres). Left ventricular stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were computed from the pressure pulsations (Modelflow). Spontaneous baroreflex control of heart rate (BRS) was estimated in the time domain.

In the first 3 minutes after NTG, blood pressure was well maintained in all patients. This implies an adequate arterial resistance response to compensate for steeper reductions in SV and CO with increasing age. Heart rate (HR) increased and the BRS decreased after NTG. The rate of MAP-fall leading to presyncope was inversely related to age ( $r = 0.51$ ,  $p = 0.005$ ). Accordingly, patients with a MAP-fall  $> 1.44$  mmHg/s (median) were generally younger compared to patients with a slower MAP-fall ( $30 \pm 10$  yrs vs.  $51 \pm 17$  yrs;  $p = 0.001$ ). The main determinant of the rate blood pressure drop on approach of presyncope was the rate of fall in HR ( $r = 0.75$ ,  $p < 0.001$ ).

It is concluded that, in the older patients, sublingual NTG provokes a more gradual blood pressure decline compared to the younger. This gradual decline cannot be ascribed to failure of the baroreflex buffering capacity with increasing age. Age-related differences in the laboratory presentation of a vasovagal episode depend on the magnitude of the underlying bradycardic response.

## INTRODUCTION

Vasovagal syncope (VVS) is a common clinical problem that afflicts patients of all ages [1]. Although the sequence of hemodynamic events associated with VVS should be investigated during spontaneous episodes, this request makes adequate hemodynamic study practically impossible, for obvious reasons. Therefore, head-up tilting has become a widespread diagnostic test to document a tendency toward VVS [2]. In order to increase the diagnostic yield of head-up tilting, sublingual nitroglycerine (NTG) is commonly administered [3-5], because as potent venodilators [6], nitrates might facilitate VVS by enhancing venous pooling in the upright posture [7]. The yield of positive tilt testing has been reported to increase substantially more after NTG provocation in older compared to younger patients [8-10]. A marked reduction in the capacity of the arterial baroreflex to buffer blood pressure responses to vasoactive drugs with physiological aging has been reported [11]. With this information as a background, we hypothesized that presyncope induced by NTG in older patients is brought on by baroreflex failure to maintain arterial blood pressure, which, rather than presenting as a sudden vasovagal reflex, is accompanied by a more gradual blood pressure decline compared to younger patients. The purpose of this study was to test the hypothetical baroreflex involvement by investigating the hemodynamic mechanisms underlying the direct effect of NTG, in routine tilt tests. For this we studied patients with suspected VVS, applying pulse wave analysis to the continuously measured Finapres blood pressure signal.

## **METHODS**

### **Study population**

This is a retrospective study. The study group consists of patients with suspected VVS who had shown a positive response to head-up tilt testing with NTG provocation at the Syncope Unit of the Academic Medical Center. A positive response was defined as a progressive fall in blood pressure and impending vasovagal syncope. The patient's medical history included at least one syncopal episode of unknown origin in the last year, in the presence of (prolonged) orthostatic stress, pain, or an unusually strong emotional trigger. Excluded were patients with a history of cardiovascular disease, carotid sinus syndrome, or any disease that might affect the autonomic nervous system, as well as patients using medication that might affect the circulation or circulatory control. In addition, we excluded patients who had experienced a vasovagal episode before administration of NTG ( $n = 4$ ). A total of 29 otherwise healthy patients with a positive tilt test response (12 men and 17 women) and history of VVS were included in this study. The mean age was  $41 \pm 18$  years (range 16 – 71, median 39 years).

### **Tilt-test protocol and measurements**

Tests were performed between 9:00 AM and 1:00 PM in a temperature-controlled room ( $23^{\circ}\text{C}$ ). A manually operated tilt table with a footboard was used. The tilt test started with 5 min of supine rest, followed by 20 min head-up tilt ( $60^{\circ}$ ). If no vasovagal reaction developed, NTG was administered sublingually (0.4 mg) for an additional 15-min tilt duration. An impending vasovagal response was aborted by means of tilt-back, or by counter-maneuvers such as legs crossing to prevent loss of consciousness [12]. The term tilt-back is further used to indicate the moment an impending vasovagal syncope was aborted. Blood pressure was measured continuously and non-invasively using the Finapres Model 5 (TNO Biomedical Instrumentation, Amsterdam, the Netherlands). The hand was held at right atrium level and kept in place using an arm sling. The study was carried out in accordance with the Declaration of Helsinki (2000) and has been approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam, the Netherlands.

### **Hemodynamic analysis**

The arterial pressure signal was analog to digital converted at 100 Hz and stored on a hard-disk. Beat-to-beat systolic and diastolic pressures were derived from the arterial pressure waveform. Mean arterial pressure (MAP) was the true integral of the arterial pressure wave over one beat divided by the corresponding beat interval. Heart rate (HR) was computed as the inverse of the inter-beat interval (IBI), and expressed as beats per minute. Beat-to-beat changes in stroke volume (SV) were estimated by modeling flow from the finger arterial pressure waveform (Modelflow, TNO Biomedical Instrumentation) [13-15]. The patient's gender, age, height and weight were inserted in the model to determine Modelflow parameters using previously established equations [16]. Cardiac output (CO) was computed by the product of SV and HR. Systemic vascular resistance (SVR) was obtained through a self-adapting process in which an initial value is assumed for the first beat. The ratio of MAP to CO for this first beat defines a new resistance value which is used in the model for the next beat. Within 5 beats from the start, the model resistance stabilizes to actual SVR and further allows close tracking of changes in real SVR [17]. Due to this self-adapting process to estimate SVR, the tracking precision of the model is unaffected by administration of vasoactive drugs like NTG [17]. Stroke volume, CO and SVR were set at 100% (baseline) in the upright posture, 3 min before NTG, and variations were expressed as percentages (%) of this baseline. Beat-to-beat hemodynamic values were averaged per 30-s periods; slopes were calculated over the initial 3-min time frame starting at NTG administration to assess hemodynamic trends after NTG in all patients.

### **Rate of arterial pressure fall in the presyncopal episode**

The rate of arterial pressure fall (mmHg/s) in the presyncopal episode was computed in each individual patient by calculating the first derivative of a 6<sup>th</sup> order Givens polynomial approximation of MAP in the hypotensive 30-s episode prior to tilt-back (Figure 1). The same procedure was adopted to calculate the rate of IBI-increase (bradycardic response) during the presyncopal episode (ms/s).

### **Baroreflex sensitivity (BRS)**

Time domain analysis of spontaneous BRS was performed using the cross-correlation method [18]. The SAP and IBI time series were resampled at 1 Hz. In a 10-s window, the

correlation and regression slope between SAP and IBI were computed. Delays of 0- to 5-s increments in IBI were computed, and the delay with the highest positive coefficient of correlation was selected. The slope between SAP and IBI was recorded as a BRS estimate if the correlation was significant at  $p = 0.01$ .

### **Statistical analysis**

Statistical analysis was performed with SPSS version 11.5 for windows (Scientific Packages for Social Sciences, Inc., Chicago, IL, USA). Variables were tested for normality using the Kolmogorov-Smirnov test and expressed as the mean value  $\pm$  SD, unless stated otherwise. The BRS was transformed by calculating its natural logarithm to achieve a normal distribution. Pearson's correlation coefficient ( $r$ ) was computed to evaluate the relationship between age and the rate of arterial pressure fall at presyncope. Differences between patients with distinct blood pressure patterns at presyncope were analyzed using the Student t-test or by analysis of variance with statistical correction for age as a continuous covariable.

## RESULTS

### Study population

In all 29 patients, prodromal symptoms and signs such as pallor, diaphoresis, lightheadedness and/or impending loss of consciousness were present within 4 to 11 minutes after NTG provocation. All patients recovered by counter-maneuvers or on return to the supine position. Figures 1A and 1B show blood pressure tracings during 3-min periods (180 s) prior to tilt-back in two representative patients, aged 31 (upper panel) and 69 years (lower panel). In both patients there is a reduction in blood pressure during the vasovagal episode. However, the rate of blood pressure fall was much more rapid in the younger compared to the older patient (3.5 versus 0.7 mmHg/s). When tested in all patients, the rate of blood pressure fall in the presyncopal episode was shown to be inversely related to age ( $r = 0.51$ ,  $p = 0.005$ ) (Figure 2). The median rate of arterial pressure fall was 1.44 mmHg/s. Patients with a steeper blood pressure fall ( $> 1.44$  mmHg/s) were regarded as Type A responders. Patients with a more gradual blood pressure decline ( $\leq 1.44$  mmHg/s) were regarded as Type B responders. The time from NTG administration to tilt-back was not different in patients with a Type A ( $426 \pm 165$  s) or Type B ( $379 \pm 129$  s) blood pressure response ( $p = \text{NS}$ ). This implies that blood pressure started to fall earlier after NTG administration in those patients with a Type B blood pressure response ( $257 \pm 127$  vs.  $361 \pm 166$  s,  $p = 0.047$ ).

### Distribution of age and gender

Figure 3 shows the age-distribution in patients with a Type A or Type B vasovagal response. Patients with a Type A response were younger compared to Type B responders ( $30 \pm 10$  vs.  $51 \pm 17$  years;  $p < 0.001$ ). All patients with a Type A response ( $n = 14$ ) were below 50 years old. Of those patients with a Type B response ( $n = 15$ ), 67 % ( $n = 10$ ) were older than 50 years. Accordingly, the analysis of possible age-effects on the baroreflex response to NTG is further presented in terms of Type A or Type B blood pressure patterns in the presyncopal episode. The distribution of gender was not different between patients with a Type A (5 men and 9 women) or Type B (7 men and 8 women) vasovagal response.



### Circulatory response to NTG

Cardiovascular trends in patients who experienced a Type A or Type B vasovagal response are shown in Figure 4. Before NTG, all patients were asymptomatic, and the average HR was 86 beats/min (range 61 to 134 beats/min; no difference between Type A and Type B). Mean blood pressure tended to be higher in Type B patients; however, this difference was not significant ( $91 \pm 7$  vs.  $85 \pm 11$  mmHg,  $p = 0.11$ ). The cardiac BRS was reduced with age ( $r = -0.51$ ,  $p = 0.003$ ). Accordingly, Type B patients had a lower BRS compared to Type A ( $5 \pm 2$  vs.  $8 \pm 3$  ms/mmHg,  $p = 0.001$ ). Stroke volume, CO and SVR were stable before NTG in both groups of patients (Figure 4).

Hemodynamic trends after NTG were analyzed by calculation of the slope during the first 3 minutes after NTG provocation (Figure 4). Type B patients had a steeper drop in SV compared with Type A ( $-11.8 \pm 2.1$  vs.  $-7.6 \pm 1.5$ ,  $p = 0.023$ ). Because the concomitant rise in HR was similar in both groups, Type B patients had a larger drop in CO ( $-6.3 \pm 1.4$  vs.  $-2.0 \pm 1.4$ ,  $p = 0.046$ ). This was adequately compensated by a greater rise in SVR compared to Type A ( $6.2 \pm 2.7$  vs.  $1.0 \pm 1.7$ ,  $p = 0.045$ ). In both groups, MAP was well maintained during the first 3 min after NTG in all patients (Figure 4). There was a similar reduction in BRS after the hemodynamic changes induced by NTG. After introduction of age as a covariate, no significant differences were observed in the hemodynamic slopes following NTG provocation.

### Vasovagal episode

There was marked hypotension, both in patients with a Type A and a Type B vasovagal response (Figure 4). During the last 15 s before tilt-back, MAP averaged respectively 49 mmHg (range 25 to 87 mmHg) and 55 mmHg (range 45 to 68 mmHg) ( $p = \text{NS}$ ). Heart rate dropped below 60 beats/min in 9 Type A patients (64%) compared to only 4 Type B patients (27%). Consequently, during the last 15 s before tilt-back, HR was lower on average in patients with a Type A vasovagal response ( $62 \pm 21$  vs.  $82 \pm 17$  beats/min,  $p = 0.041$ ) (Figure 5). The slope of the bradycardic response in the last 30 seconds before tilt-back was related to the rate of fall in blood pressure within the same time period ( $r = -0.75$ ,  $p < 0.001$ ) (Figure 6). In all patients, the last 30 seconds before tilt-back were characterized by a marked reduction in CO, which was not compensated for by a further increase in SVR (Figure 4, shaded area). The drop in CO was mediated by significant

reductions in both SV and HR, while, in 24 of the 29 patients, SVR was increased compared with baseline.

## DISCUSSION

This study describes the impact of age on hemodynamic patterns induced by sublingual NTG during routine tilt testing in patients with suspected VVS.

1. Analysis of blood pressure patterns during the presyncopal episode shows age-related differences. We observed a gradient in the rate of arterial pressure fall from the younger to the older patients, with the younger patients being more likely to have a more rapid blood pressure fall compared to the older (Figure 2). The main determinant of the rate blood pressure drop on approach of presyncope appears to be the rate of fall in heart rate (Figure 6).
2. The first 3 min after NTG, arterial blood pressure was well maintained, both in patients with a rapid (Type A) and more gradual (Type B) blood pressure fall prior to tilt-back (Figure 4). Cardiac output decreased more in Type B patients. This implies an (initially) adequate arterial vasoconstrictor response in the older patients to NTG-induced venous pooling.

The present findings support our hypothesis that, in the older patients, sublingual NTG provokes a more gradual blood pressure decline compared to the younger patients. However, this gradual fall in arterial pressure cannot be attributed to the hypothesized failure of the arterial baroreflex buffering capacity with increasing age. Age-related differences in the rate of fall in arterial pressure appear to depend on the bradycardic response in the presyncopal episode.

### **The initial circulatory response to NTG (first 3 minutes)**

The circulatory response to NTG was characterized by a rapid drop in SV, and despite a rise in HR, CO was diminished. Furthermore, BRS was decreased in the early period after NTG, which, together with the rise in HR and SVR suggests sympathetic activation. Interestingly, sublingual NTG provoked a steeper drop in SV in the first three minutes after application in the older patients with a Type B vasovagal response (Figure 4). This steeper drop in SV in Type B patients may be surprising because, in the older patients, reduced venous compliance is reported to account for a diminished peripheral fluid shift, which attenuates the reduction in SV during the hypovolemic stress of lower-body negative pressure [19]. Two factors may be involved. First, pooling in the splanchnic area

of the upright human body seems more important than previously reported in studies using simulated orthostasis by applying lower-body negative pressure [20]. Thus, increased splanchnic pooling may be hypothesized in patients with a Type B vasovagal response. On the other hand, in the older subjects, increased myocardial stiffness and impaired diastolic relaxation make the heart more dependent on cardiac preload to adequately fill the left ventricle [21]. This age effect becomes particularly important if heart rate is increased and thus diastolic filling time is shortened [22;23]. Therefore, age-related impairments in diastolic left ventricular filling may account for the greater SV reduction induced by sublingual NTG in our patients with a Type B blood pressure pattern in the presyncopal episode (Figure 4).

Unlike the reduction in SV, the concomitant rise in HR after NTG provocation was similar in Type A and Type B patients (Figure 4). Thus, in patients with a Type B vasovagal response, a steeper drop in SV after NTG is not accompanied by a larger baroreflex-mediated rise in HR. This can be ascribed to a diminished HR regulation with increasing age [24], which is further supported in this study by a lower spontaneous cardiac baroreflex sensitivity (BRS) in the patients with a Type B vasovagal response. The steeper fall in CO compared to Type A patients is adequately compensated by a greater rise in SVR, supporting the concept that orthostatic blood pressure control essentially relies on sympathetic vasomotor responses [24-26].

The precise sequence of events leading to the hypotensive, presyncopal episode is still matter of debate. Certain data suggest that orthostatic hypotension results from inadequate compensatory responses of the venous system [27-29]; other data point more to an underlying arterial vascular resistance deficit [30-32]. In agreement with Gisolf et al. [7], the present data signify that the NTG-triggered vasovagal response is CO-mediated and is not preceded by a decrease in SVR (Figure 4). The reduction in CO relies on the bradycardic response within the last 30 seconds prior to tilt-back; the rate of fall in HR is clearly associated with the rate of arterial pressure fall in the presyncopal episode (Figure 6). Within the last 15 seconds before tilt-back, average HR was lower in patients with a Type A versus Type B vasovagal response (Figure 5). Therefore, the main determinant of age-related differences in the laboratory presentation of a NTG-triggered vasovagal response appears to be the rate of fall in HR.

### **The final vasovagal response**

The more gradual development of a vasovagal response with increasing age was formerly labeled as a dysautonomic response [33], suggesting that vasomotor failure might be involved. In the new Vasovagal Syncope International Study (VASIS) classification of tilt-induced VVS [34], patients with a decrease in HR of less than 10% are labeled as 'vasodepressor' responders, further pointing to sympathetic vasomotor failure with a decrease in SVR as the underlying mechanism. In this study, we found that SVR did not decrease in the presyncopal episode, but remained above baseline (100%) in all Type B patients. This, together with the adequate steady-state arterial vasoconstrictor response to NTG-induced venous pooling, shows that the previous assumption of sympathetic vasomotor failure in the older patients is rather unlikely. Instead, the NTG-triggered vasovagal response appears to be CO-mediated and is not preceded by a decrease in SVR [7].

Previous studies associated tilt-table testing in younger patients with an increased incidence of severe vagal-cardiac inhibition [10;35;36]. A much stronger vagal-cardiac neural outflow in younger subjects may be involved here [37;38]. The decrease in vagal cardiac outflow with aging is reflected in the present study by a lower cardiac BRS in patients with a Type B vasovagal response (Figure 4). Although the occurrence of a bradycardic response during tilt testing seems predominant in younger patients, the use of an implantable loop recorder (ILR) has learned that, during spontaneous vasovagal events, asystolic syncope is a very frequent observation in older adult and elderly patients [39;40]. At present, these contradictory findings are hard to explain. The fact that HR usually starts to fall after the onset of hypotension may be involved [41]. Only in those patients with fully developed vasovagal faints does a marked heart rate decrement occur, without exception [42]. Thus, the timing to abort oncoming syncope, by tilt-back, may affect the extent of reflex bradycardia. The more rapid vasovagal symptoms develop, the more likely this will be associated with severe bradycardia in routine tilt testing. Alternatively, the spontaneous asystolic events observed during ILR could result from other than vasovagal mechanisms, e.g. early stage of sick sinus syndrome and/or Adam-Stokes syndrome in the older patients.

### **Study limitations**

Results were obtained in subjects with no cardiovascular or neurological disease and no medication. The older patients therefore represent a very healthy part of the total of older patients referred for unexplained syncope (selection bias). Included were only those patients who did not have a vasovagal episode before NTG, thus excluding the most outspoken cases. Whether the present findings also account for spontaneous vasovagal events should be addressed in future studies.

### **Conclusion**

It is concluded that, in the older patients, sublingual NTG generally provokes a more gradual blood pressure decline compared to the younger. This gradual decline cannot be attributed to failure of the baroreflex buffering capacity with increasing age. Age-related differences in the rate of development of vasovagal symptoms depend on the bradycardic response in the hypotensive, presyncopal episode.

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**Figure legends:**

**Figure 1:** Blood pressure tracings during 3-min periods (180 s) preceding tilt-back in two patients, aged 31 (A) and 69 (B) years old. The rate of arterial pressure fall in the hypotensive presyncopal episode is computed by calculating the first derivative of a 6<sup>th</sup> order Givens polynomial approximation during 30-s periods prior to tilt-back or counter-maneuver. The blood pressure fall was more rapid in the younger (A) compared to the older (B) patient (3.5 versus 0.7 mmHg/s).

**Figure 2:** Relationship between age and the rate of arterial pressure fall in the presyncopal episode ( $r = 0.51$ ,  $p = 0.005$ ). The median rate of arterial pressure fall was 1.44 mmHg/s. Patients with a steeper blood pressure fall ( $> 1.44$  mmHg/s) were regarded as Type A responders. Patients with a more gradual blood pressure attenuation ( $\leq 1.44$  mmHg/s) were regarded as Type B responders.

**Figure 3:** Distribution of age in patients with a rapid (Type A) and more gradual (Type B) arterial blood pressure fall in the presyncopal episode. Note that all patients with a Type A blood pressure response were younger than 50 yrs.

**Figure 4:** Hemodynamic response to NTG during 60° tilt table testing. Data are presented as 30-s averages and SEM and cover 3-min time periods before and after NTG administration. In addition, data from the last 4 min before tilt-back are presented. Note the discontinuity in the X-axis. Shaded areas correspond to the final minute before tilt-back. Closed circles = Type A, open circles = Type B. MAP = mean arterial pressure, HR = heart rate, BRS = baroreflex sensitivity, SV = stroke volume, CO = cardiac output, SVR = systemic vascular resistance.

**Figure 5:** Distribution of mean heart rate (HR) during the last 15 seconds before tilt-back in patients with a Type A and Type B vasovagal blood pressure response.

**Figure 6:** Relationship between the rate of blood pressure fall and the bradycardic response (rate of IBI-enlargement) during the last 30 seconds prior to tilt-back or counter-maneuver ( $r = -0.75$ ,  $p < 0.001$ ).

Figure 1A

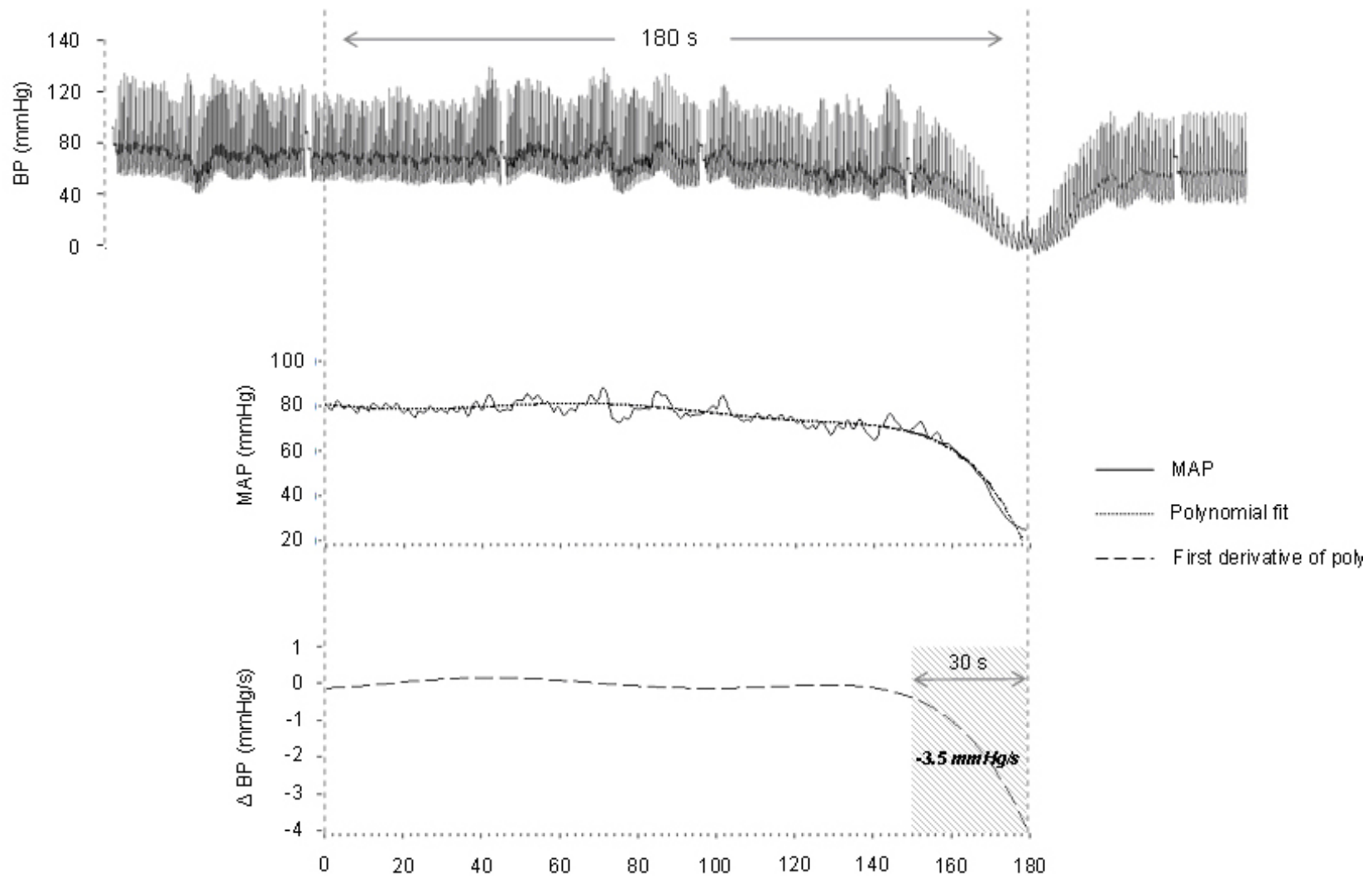


Figure 1B

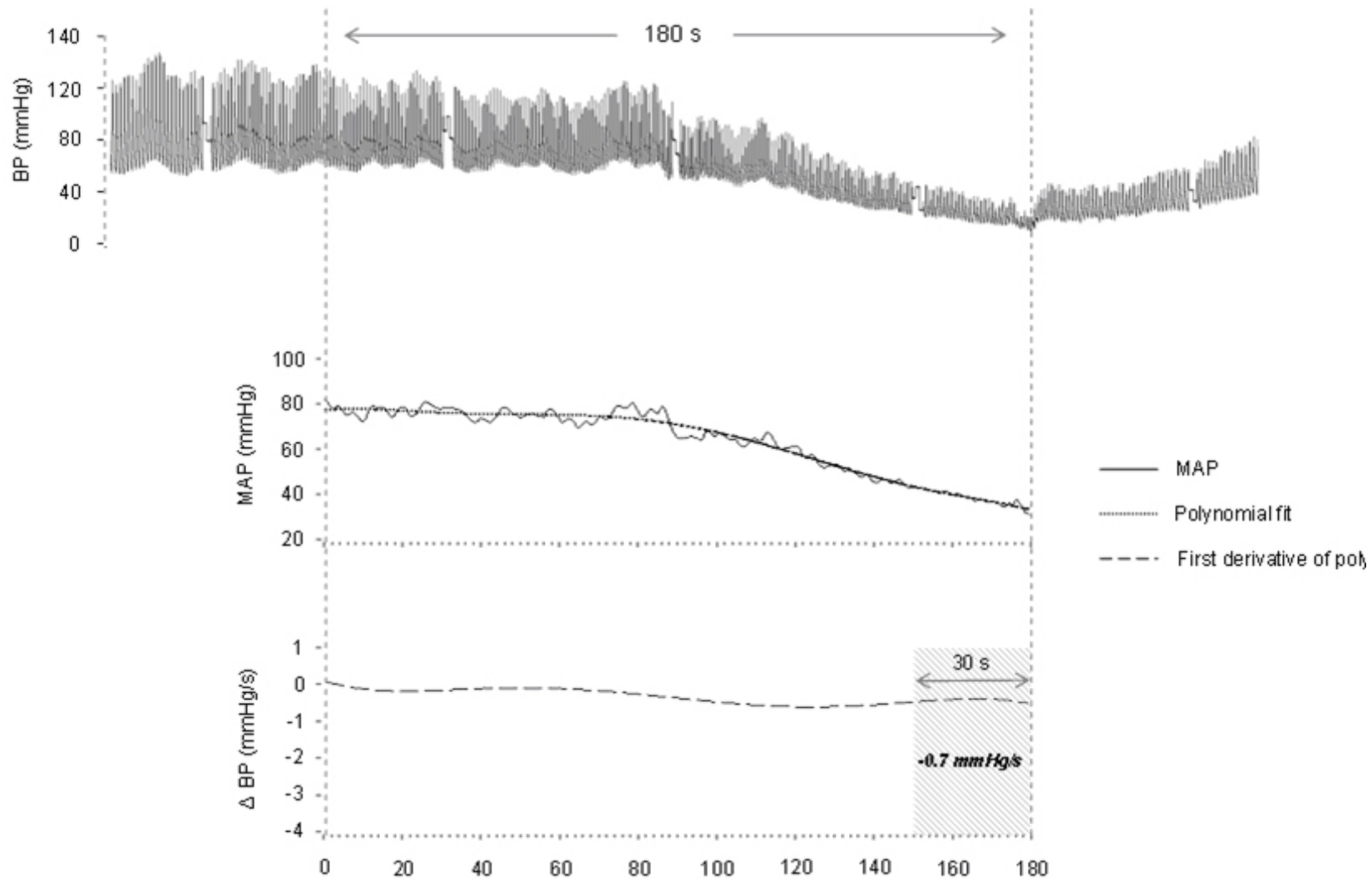




Figure 2

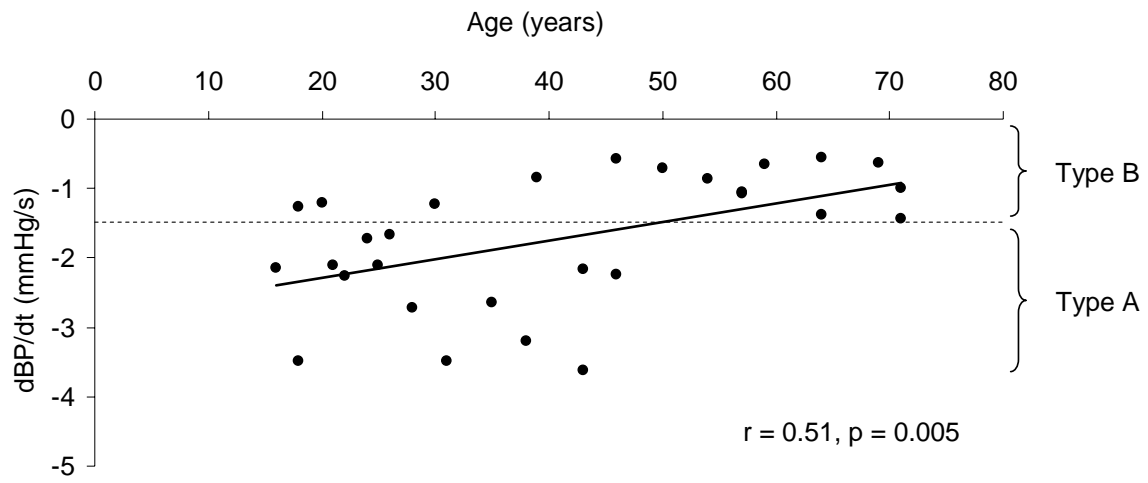


Figure 3

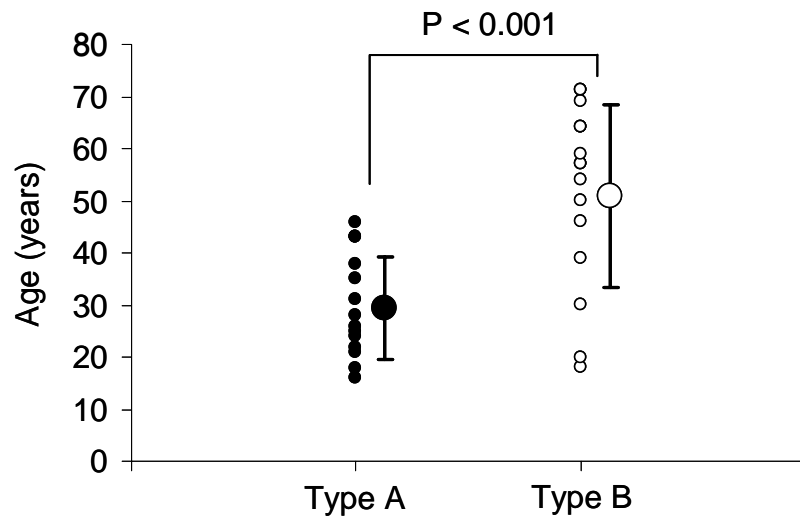


Figure 4

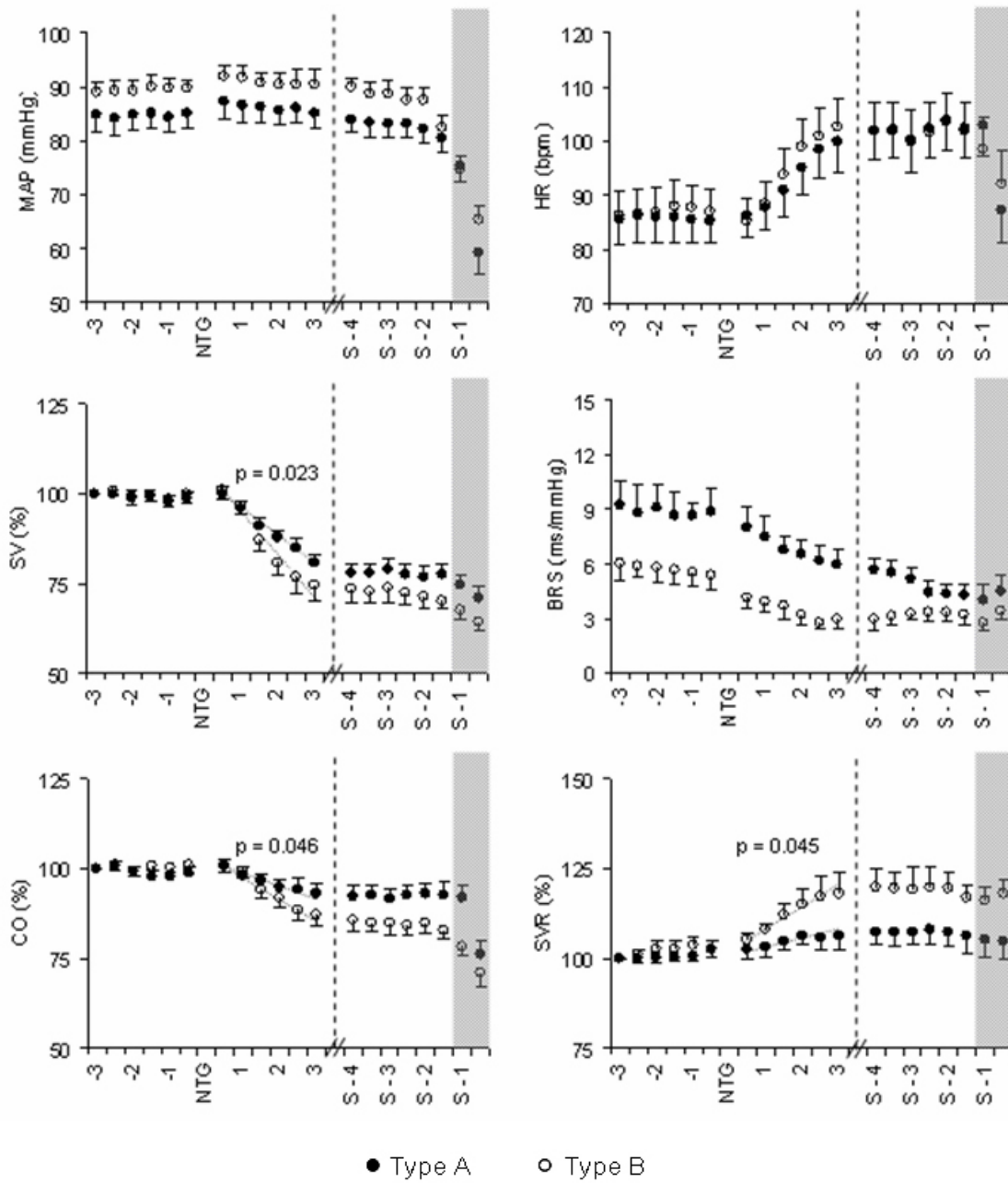


Figure 5

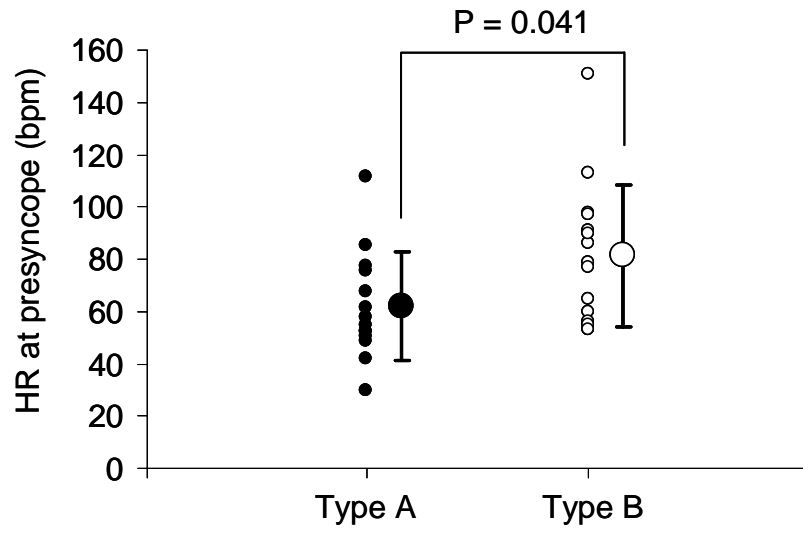


Figure 6

