Prediction of vasovagal syncope from heart rate and blood pressure trend and variability: Experience in 1,155 patients

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BACKGROUND Vasovagal syncope (VVS) is a complex fainting disorder commonly triggered by orthostatic stress.

OBJECTIVE We developed an algorithm for VVS prediction based on the joint assessment of RR interval (RR) and systolic blood pressure (SBP).

METHODS Simultaneous analysis of RR and SBP trends during head-up tilt as well as their variability represented by low-frequency power (LFRR and LFSBP) generated a cumulative risk that was compared with a predetermined VVS risk threshold. When cumulative risk exceeded the threshold, an alert was generated. Prediction time was the duration between the first alert and syncope. In the first 180 sec of head-up tilt, baseline values were established, following which VVS prediction was possible. An analysis was performed using 1,155 patients who had undergone head-up tilt for syncope: 759 tilt-positive and 396 tilt-negative patients. In the tilt-test protocol, at syncope or after 35 min, the patient was returned to supine.

RESULTS In tilt-positive patients, VVS was predicted in 719 of 759 patients (sensitivity 95%), whereas 29 false alarms were generated in 396 tilt-negative patients (specificity 93%). Prediction times varied from 0 to 30 min but were longer than 1 min in 49% of patients.

CONCLUSION Predicting impending syncope requires use of simultaneous blood pressure and heart rate, which may shorten diagnostic testing time, free patients from experiencing syncope during a diagnostic tilt-test, and have application in risk-guided tilt training and in an implanted device–to–trigger pacing intervention. The prospects for relieving patient discomfort are encouraging.

KEYWORDS Autonomic nervous system; Blood pressure; Heart rate variability; Tilt-test; Vasovagal syncope

(Heart Rhythm 2007;4:1375–1382)

Vasovagal syncope (VVS) is a form of neurally mediated reflex syncope that is marked by a sudden decrease in blood pressure with an associated decrease in heart rate often resulting in syncope.[1] It is a common condition that may be severe enough to have an important reduction in the patient's quality of life.[2] Furthermore, VVS is potentially dangerous in those with high-risk occupations and in older patients who lack warning symptoms because fainting may lead to falls and injury.

The diagnosis of VVS may be made from the patient's history when typical circumstances exist,[1,3] but a historical diagnosis is not always possible. Therefore, tilt testing is commonly used to gather information about VVS using electrocardiography (ECG) and blood pressure monitoring with medical observation. Tilt testing makes a diagnosis of VVS in approximately 35% of patients,[1] and another 35% are diagnosed from the history.[1] Patients find tilt testing unpleasant, and some older patients find the upright posture difficult to sustain.[4]

The study objective was to develop and test an algorithm, using ECG and blood pressure, to provide advance warning of an impending episode of VVS. Clinical application of such prediction could reduce the duration required for tilt testing and avoid the necessity to impose a full syncopal event on a patient, which may result in quicker patient recovery and therefore in a reduction in the time the patient spends in the syncope clinic.

Similarly, it might reduce the duration required for tilt training while maintaining efficacy. This technology could possibly be incorporated into an implanted device to trigger a patient alarm, drug delivery, or pacing therapy.

Methods

Patients and protocol

Data from routine clinical tilt tests of 1,380 consecutive patients at a tertiary referral syncope clinic were analyzed retrospectively and anonymously. All presented with a his-

Supported by grants from the Swiss Governmental Commission of Innovative Technologies (CTI) and Medtronic, Inc. Virag, PhD, Erickson, BS, and Markowitz, BS, are full-time Medtronic Inc. employees. Drs. Vetter and Sutton have acted as consultants for Medtronic Inc. **Address reprint requests and correspondence:** Dr. Nathalie Virag, Medtronic Europe Sàrl, Route du Molliau, CH-1131 Tolochenaz, Switzerland. E-mail address: nathalie.virag@medtronic.com. (Received April 30, 2007; accepted July 12, 2007.)

  doi:10.1016/j.hrthm.2007.07.018

tory of syncope that was suspected to be neurally mediated. Patients fasted for at least 3 hours. Head-up tilt testing, for which patients gave oral consent, was performed applying a 2-stage protocol.[5,6] After 5 min supine rest, each subject was tilted to a 60° head-up position. If symptoms did not develop after 20 min of tilt sublingual glyceryl trinitrate (GTN), 400 μg was administered and the patient remained upright for a further 15 min. The patient was returned to supine as soon as syncope developed or after a total of 35 min of tilt. The investigation conforms with the principles outlined in the Declaration of Helsinki.[7]

During head-up tilt, digital photoplethysmographic blood pressure was recorded noninvasively with a Portapress (TNO, Amsterdam, the Netherlands) at 100 samples/sec, which has been shown to follow faithfully blood pressure changes during tilt testing,[8] together with surface ECG. Simultaneously, patient symptoms were monitored and recorded in an event file. We extracted beat-to-beat RR interval and systolic blood pressure (SBP)[9] for the design of a prediction algorithm.

Algorithm

We developed an algorithm to predict VVS during head-up tilt testing. The algorithm is based on concurrent analysis of several signals, each with a potential predictive value. The algorithm (Figure 1) is based on the continuous evaluation of: (1) a normalized trend of RR intervals, (2) a normalized trend of SBP, and (3) an indicator of autonomic modulation. Beat-to-beat RR and SBP are extracted from raw data. To obtain trends of heart rate and blood pressure, RR and SBP were low-pass filtered at 0.01 Hz. Preprocessing was performed to remove ectopic beats.

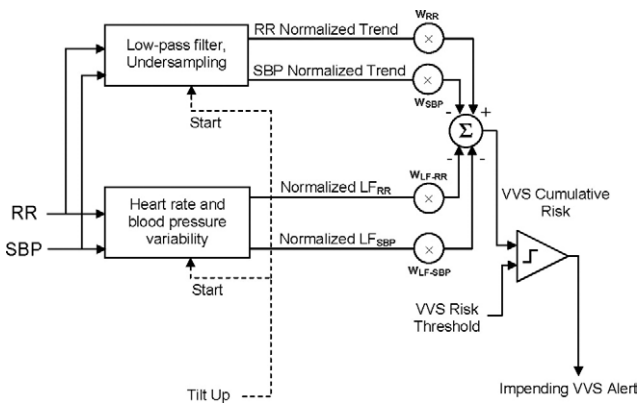

Figure 1 Proposed algorithm for prediction of vasovagal syncope (VVS) using RR intervals (RR) and systolic blood pressure (SBP). Signals are represented by lines and processes within a box. In our case the indicator of autonomic modulation is obtained by computing heart rate and blood pressure variabilities (HRV and BPV), and LF represents the low-frequency power. Circles with a cross inside represent multiplication by the indicated weighting factor (wRR, wSBP, wLF-RR, wLF-SBP). The circle with the sigma sign Σ represents the addition/subtraction of the 4 parameters with the sign of their contribution as indicated. The triangle box represents the comparator between VVS cumulative risk and VVS risk threshold. This whole process of VVS risk computation is triggered by the tilt up (dotted line).

Several methods are available to derive noninvasive measures of autonomic modulation from RR and/or SBP. We used classic heart rate variability (HRV) and blood pressure variability (BPV), which have been used in several clinical applications as a physiological marker of cardiac autonomic control.[9] An autoregressive frequency spectrum was evaluated in sliding windows of 360 sec, shifted in 10-sec increments.[9] Low-frequency (LF) oscillations from 0.04 to 0.15 Hz are primarily an indicator of sympathetic modulation,[9] although the relative contribution of the sympathetic and parasympathetic systems to LF components remains controversial. Their predictive value for syncope has been investigated.[10–12] We selected LF power of RR intervals (LFRR) and systolic blood pressure (LFSBP) to provide information regarding the patient's autonomic modulation. In the development of the algorithm, high-frequency parameters (vagal effects) were also investigated and were found to offer no significant benefit.

RR trend, SBP trend, LFRR, and LFSBP have different ranges, so the values were normalized with respect to baseline to bring them to comparable levels. HRV and BPV baseline values (mean and standard deviation) were established during the 300 sec before tilt because stable signals are needed. Baseline values for the trends were established during the first 180 sec of head-up tilt, after which VVS prediction is enabled. Orthostatic stress initiates variations in RR and SBP that reach a new steady state after approximately 180 sec. Meanwhile, observed variations are characteristic of patient response to cardiovascular changes. Therefore, this period was used to establish a mean and standard deviation for RR and SBP baseline.

RR trend, SBP trend, LFRR, and LFSBP were normalized by performing the following computation: a subtraction of their respective baseline mean and a division by their baseline standard deviation, followed by truncation. Values less than -1 were represented as -1. Values greater than 1 were represented as 1. Resulting normalized values are in the range -1 to 1, -1 meaning a strong decrease, 0 no change, and 1 a strong increase with respect to baseline.

This normalization of the 4 variables allows a direct comparison of their effect on the global risk of VVS. As shown in Figure 1, the VVS cumulative risk is the combination of the normalized trends of RR, SBP, LFRR, and LFSBP, each of them preliminarily multiplied by a weighting factor wRR, wSBP, wLF-RR, and wLF-SBP, respectively representing the relative contribution of each component to the cumulative risk. This may be expressed as:

$$\begin{aligned}\text{VVS cumulative risk} = {} & \text{wRR} \times \text{normalizedRR} \\ - {} & \text{wSBP} \times \text{normalized SBP} \\ - {} & \text{wLF-RR} \times \text{normalizedLFRR} \\ - {} & \text{wLF-SBP} \times \text{normalizedLFSBP}\end{aligned}$$

In this computation, the sign is positive for the normalized RR because an RR increase (corresponding to a heart rate decrease) has a positive contribution to the global risk. On the other hand, the sign for normalized SBP, LFRR, and

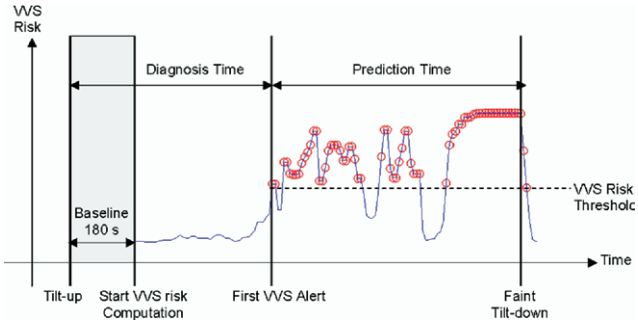

Figure 2 Diagram showing how prediction time and diagnosis time are computed on the vasovagal syncope (VVS) risk. VVS alerts (indicated by unfilled circles) occur when the VVS risk is higher than the VVS risk threshold. Diagnosis time is computed between tilt up and the first VVS alert. Prediction time is computed between the first alert and VVS. During the baseline computation (indicated in gray), no VVS risk is computed.

LFSBP is negative because an increase in these values decreases global risk.

The VVS cumulative risk (VVS risk) reflects the probability that patients will experience VVS. It is compared with an empirically determined risk threshold. When the threshold is exceeded, the algorithm predicts an imminent VVS episode and an alert is generated (Figure 2).

Algorithm tuning

The database contained 1,380 patients. The RR and SBP recordings were inspected visually. Patient recordings with poor signals, artifacts, or signal loss were discarded (125, 9%) leaving 1,255. Of these, 100 were used to optimize the algorithm parameters and the remaining 1,155 for algorithm validation.

The VVS prediction algorithm has 5 parameters to be optimized: the 4 weighting factors wRR, wSBP, wLF-RR, and wLF-SBP and the VVS risk threshold. Algorithm tuning was done with a set of data composed of 50 tilt-positive and 50 tilt-negative patients chosen at random. Receiver operating characteristics (ROC), representing true prediction as a function of false prediction, were used to optimize algorithm sensitivity and specificity. VVS risk threshold was varied from 0 to 1 to obtain 1 ROC curve. A family of ROC curves was then developed by varying the relative importance of normalized trends. Table 1 shows the different combination of parameters tested during algorithm tuning and the resulting sensitivity and specificity. Based on this optimization, the following parameters were chosen: wRR = 2/9, wSBP = 5/9, wLF-RR = 1/9, wLF-SBP = 1/9, and VVS risk threshold = 0.42.

Our aim was to determine parameters leading to the highest positive predictive accuracy, not timing of prediction. However, longer prediction times could be achieved with reduced specificity.

Algorithm validation

Algorithm validation was performed on 1,155 patients. Of these, 759 tilt-positive patients showed symptoms that the patients identified as those experienced at syncope. Seven hundred thirty-eight patients showed the classic decrease in blood pressure with or without decrease in heart rate that is expected in VVS. The other 21 patients showed no change in heart rate or blood pressure but lost consciousness, and were therefore retained in the test database. The remaining 396 tilt-negative patients were asymptomatic after 35 min of tilt per protocol.[5,6]

Prediction time was the duration between first alert and syncope (Figure 2). This value informs us about how long before the event a VVS can be predicted independent of the duration of the tilt. The diagnosis time is the duration between the start of tilt and the first alert (Figure 2). This indicates how long we should wait during the tilt until a diagnosis can be made. Results are expressed as mean ± standard deviation and median, where appropriate.

We use the term false prediction instead of the scientifically correct term false positive occurring on a tilt-negative patient so as to avoid confusion between the outcome of tilt

Table 1 Tuning of the optimal parameters of the VVS prediction algorithm on 50 tilt-positive and 50 tilt-negative patients

w_{RR}	w_{SBP}	$w_{LF\text{-}RR}$	$w_{LF\text{-}SBP}$	VVS risk threshold	Specificity (Spe)	Sensitivity (Sen)	Product Spe × Sen
2/9	**5/9**	**1/9**	**1/9**	**0.419**	**96**	**92**	**8,832**
1/4	1/4	1/4	1/4	0.441	94	90	8,460
1/3	1/3	1/3	0	0.402	96	90	8,640
1/3	1/3	0	1/3	0.378	96	88	8,448
1/8	4/8	1/8	2/8	0.363	96	88	8,448
1/8	4/8	2/8	1/8	0.258	98	84	8,232
2/9	4/9	1/9	2/9	0.396	94	90	8,460
0	4/5	1/5	0	0.627	92	90	8,280
1	0	0	0	0.339	94	86	8,084
0	0	1/2	1/2	0.258	94	84	7,896
0	1	0	0	0.412	96	88	8,448
0	0	1	0	0.258	94	84	7,896
0	0	0	1	0.369	92	92	8,464

Different combinations of RR intervals (RR), systolic blood pressure (SBP), and heart and blood pressure variability (represented by the low-frequency components LFRR and LFSBP) were tested by changing their relative importance, WRR, WSBP, WLF-RR, WLF-SBP, in the VVS cumulative risk computation. The optimal combination leading to the highest sensitivity/specificity was obtained with VVS risk = 2/9 RR − 5/9 SBP − 1/9 LFRR − 1/9 LFSBP (in bold).

and prediction. For the same reason, we use failed prediction instead of false negative.

Results

In the validation database of 1,155 patients, 932 were male and 223 were female, ranging in age from 5 to 94 years (51.2 ± 21.1, median 53 years). For the 759 tilt-positive patients, VVS occurred at a mean of 25 ± 6.8 min (range 4.1 to 35 min, median 25.5 min) of tilt. VVS was predicted in 719 patients (sensitivity 95%), whereas VVS occurred but was not predicted in 40 patients. For the 396 tilt-negative tests, the algorithm generated 29 false predictions (7%, specificity 93%).

Distribution of prediction time for the 719 patients is shown in Figure 3. Figure 3A shows the wide range, from 0 to 1,813 sec, before VVS (mean 128 ± 216 sec, median 59 sec). Figure 3B shows that for 352 tilt tests (49%), prediction time was longer than 60 sec. Figure 3C displays the portion of patients having a given prediction time. Median diagnostic time was 23.6 min.

Figure 4 shows 4 examples of the evolution of RR and SBP together with computed LFRR, LFSBP, and VVS cumulative risk. Periods when the patient's VVS cumulative risk was above threshold are indicated by unfilled circles. Figure 4A shows that dysfunction in autonomic regulation can be assessed at an early stage well before heart rate and blood pressure decrease. The bottom panel shows the VVS cumulative risk oscillating for as much as 12 min before syncope. Among the correctly predicted 719 tilt-positive patients, 144 (20%) showed a similar pattern with oscillations in VVS risk occurring well before VVS (more than 5 min). The remaining 575 (80%) correctly predicted tilt-positive patients represented by the example shown in Figure 4B: the VVS risk does not show oscillations and stays high once an alarm has been produced until fainting occurs. In these cases, prediction time is generally shorter and the algorithm reacts only when heart rate and/or blood pressure decrease.

For patients in whom VVS was not predicted, 13 of the 40 failed predictions (32.5%) resemble the pattern of Figure 4C with no decrease in blood pressure preceding VVS. The example of Figure 4C illustrates an immediate decrease in blood pressure on tilt up with hypotension persisting until syncope. In addition, 2 patients (5%) also showed an immediate decrease in SBP followed by a gradual decline until syncope. The algorithm failed to predict because the majority of the blood pressure decrease took place in the first 180 sec during baseline computation. Of the remaining failed predictions, 4 (10%) showed a slight SBP decrease before VVS, and in 10 (25%) cases strong artifacts were observed in the RR and SBP signals. In the remaining 11 cases (27.5%), no explanation for lack of prediction was obvious.

Figure 4D shows a patient with no significant decrease in blood pressure or heart rate and in whom syncope did not occur (negative test). We further analyzed the tilt-negative patients in whom VVS was predicted (29 false predictions). In 24 patients (83%), this incorrect positive detection is clearly caused by artifacts (eg, patient movement) and noise present in ECG and/or blood pressure channels. The remaining 5 showed less noise and in post hoc analysis could be reinterpreted as 3 with postural orthostatic tachycardia syndrome and 2 with vasovagal presyncope.

Optimal performance of the algorithm requires a compromise between sensitivity and specificity with the customary tradeoff of high specificity for lower sensitivity. Prediction times presented above could be increased from a median of 59 sec to a median of 118 sec if a lower specificity was tolerated (decreased from 93% to 70%). This decrease in specificity was achieved by lowering the VVS risk threshold lower than the optimal value of 0.42, as summarized in Table 2. Similarly, diagnostic time could be decreased from 23.6 to 22 min.

In the tilt-test protocol, patients who did not develop VVS symptoms after 20 min were administered sublingual GTN. We tested our algorithm on tilt-positive patients without and with sublingual GTN, and we observed no significant difference in sensitivity and median diagnostic time for these 2 groups.

After having assessed the performance of the optimal combination of parameters (wRR = 2/9, wSBP = 5/9, wLF-RR =

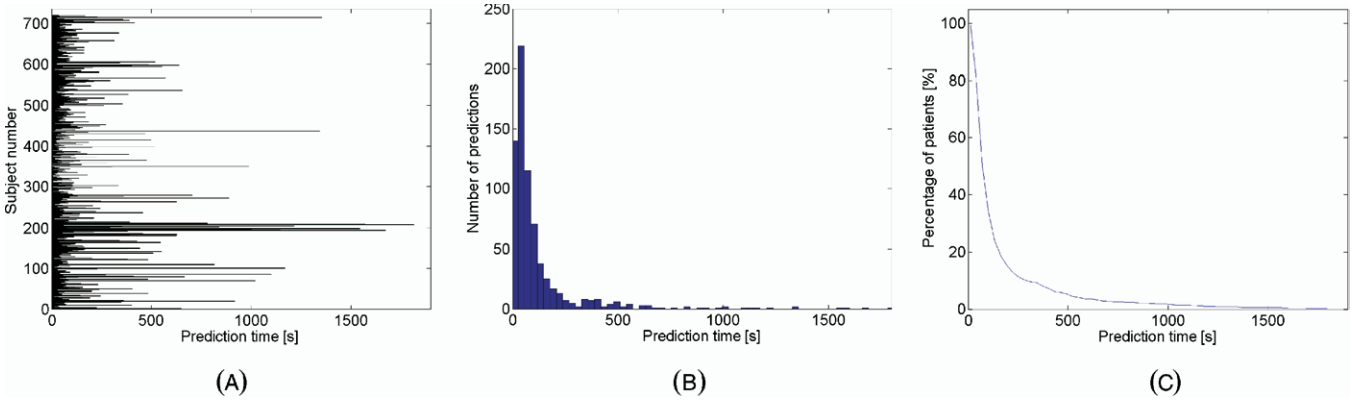

Figure 3 Prediction times for the 719 of 759 tilt-positive patients for which VVS was predicted: **(A)** prediction times for all patients showing the great variability, **(B)** histogram of prediction times, **(C)** percentage of patients for a given prediction time.

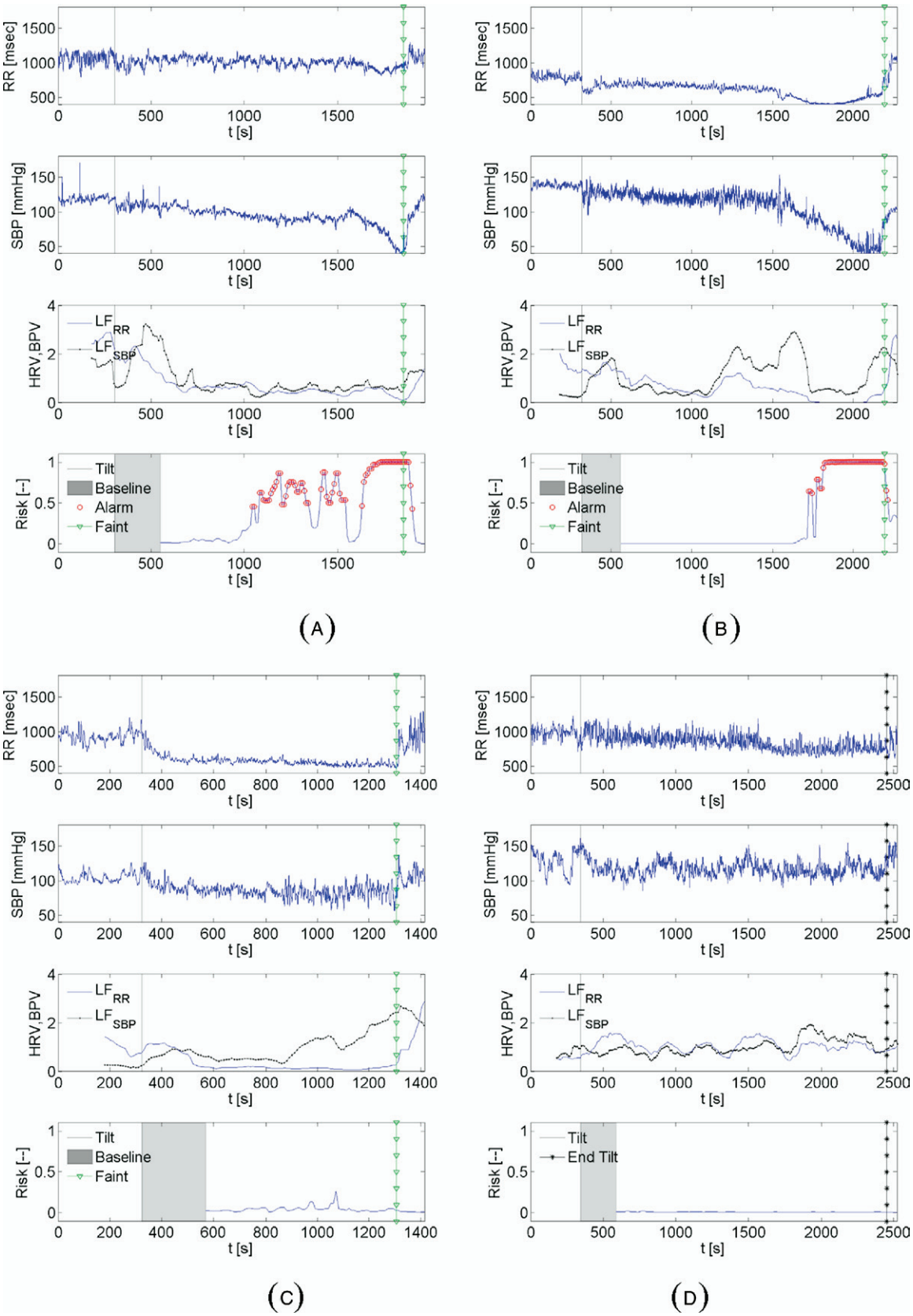

Figure 4 Examples of VVS prediction: **(A)** Example with long prediction time, **(B)** example with short prediction time, **(C)** example with no decrease in blood pressure, **(D)** example of tilt-negative case. Each panel shows the following signals: RR intervals (RR), systolic blood pressure (SBP), heart rate and blood pressure variability (HRV and BVP represented by the low-frequency power, LFRR and LFSBP), and risk of VVS. The time of tilt and syncope (faint) are indicated as vertical bars. The time during which baseline computation is performed and no VVS risk is computed in indicated in gray. The amplitudes of LFRR and LFSBP have been scaled so that they can be represented on the same graph. VVS alarms are represented by unfilled circles on the VVS risk signal.

Table 2 Prediction and diagnostic times for the 759 tilt-positive tests

VVS risk threshold	0.42	0.34	0.25	0.19
Specificity (%)	93	90	80	70
Sensitivity (%)	95	96	98	98
Mean prediction time (sec)	128 ± 216	147 ± 240	210 ± 319	313 ± 423
Median prediction time (sec)	59	65	85	118
Number of patients with prediction time more than 60 sec (%)	49	53	63	70
Median diagnostic time (min)	23.6	23.3	22.8	22.0

Prediction and diagnostic times for the 759 tilt-positive tests for various sensitivities and specificities of the algorithm for the an optimal combination of RR intervals (RR), systolic blood pressure (SBP), and heart and blood pressure variability (represented by the low-frequency components LFRR and LFSBP): VVS risk = 2/9 RR − 5/9 SBP − 1/9 LFRR − 1/9 LFSBP. The different sets of sensitivity/specificity presented are obtained by varying the VVS risk threshold as indicated.

1/9, wLF-SBP = 1/9), we determined the predictive value of RR alone (wRR = 1, wSBP = 0, wLF-RR = 0, wLF-SBP = 0), SBP alone (wRR = 0, wSBP = 1, wLF-RR = 0, wLF-SBP = 0), and HRV and BPV alone (wRR = 0, wSBP = 0, wLF-RR = 1/2, wLF-SBP = 1/2). Results are summarized in Table 3. SBP is best and is significantly better than RR alone or HRV and BPV. Blood pressure taken alone results in prediction and diagnostic times comparable with our chosen combination of parameters. Use of RR alone leads to a shorter prediction time of about 20 sec. HRV yields a longer prediction time of about 10 sec but with a loss of specificity represented in Table 3.

Discussion

This study presents an algorithm using RR interval and SBP as well as their variability to predict the occurrence of VVS a substantial time before the event. The data have been gathered from a large population, 1,155 patients, undergoing routine tilt testing for clinical indications, of which 759 were positive and 396 were negative. Correct prediction of VVS was achieved with sensitivity of 95% and specificity of 93%. The average prediction time was 128 ± 216 sec, median 59 sec. The median diagnostic time was 23.6 min. We believe this is a clinically valuable period permitting the tilt to be considered positive without imposing severe symptoms or syncope on the patient. Secondly, tilt tests may be shortened not only by stopping earlier but also avoiding a recovery period. This implies more efficient use of resources and a less traumatic experience for the patient. Prospective studies are justified and might lead to inclusion of this technology in a patient alarm or an implanted therapeutic device.

Table 3 Separate predictive value of parameters

	Specificity (%)	Sensitivity (%)	Median prediction time (sec)	Median diagnostic time (min)
Optimal combination	93	95	59	23.6
RR	86	90	41	24.9
SBP	91	92	58	23.6
HRV and BPV	88	94	70	23.1

Separate predictive value of the following parameters: RR intervals (RR), systolic blood pressure (SBP), heart rate and blood pressure variability (HRV and BPV). Performance is compared with the optimal combination of these parameters with VVS risk = 2/9 RR − 5/9 SBP − 1/9 LFRR − 1/9 LFSBP.

The mechanism of VVS is complex and incompletely understood. It is clearly a disturbance of the autonomic nervous system. An initial increase in neuroendocrine sympathetic activity is followed by an increase in vagally mediated parasympathetic activity with a concurrent withdrawal of the sympathetic activity.[13–17] Previous studies have shown that patients with VVS have a dysfunctional baroreflex regulation during orthostatic stress, abnormal sensitivity of pressure receptors in the heart and the arterial system, abnormalities of gain in central nervous system processing, and failure of normal pressure regulatory mechanism.[18–21] Most of these changes in pathophysiology of the neuroendocrine system and hemodynamics may be detected before symptoms appear.[22,23] This offers the opportunity to develop systems that predict VVS. Approaches using HRV[10–12] or blood pressure[23] alone have limited predictive value. Mallat et al[24] reported excellent positive and negative accuracy using heart rate alone; however, we have been unable to reproduce these results. Because vasovagal patients present more than one and perhaps several patterns of neuroendocrine abnormality before collapse,[12] underlining the likelihood that a single measured parameter would fail to address all circumstances, we therefore chose to study simultaneous heart rate (RR interval), systolic blood pressure (SBP), and an indicator of autonomic modulation represented by heart rate and blood pressure variability (HRV and BPV).

Algorithm development

Blood pressure is an important regulated variable in the cardiovascular system; under normal conditions, a decrease in pressure is followed by an increase in sympathetic activity leading to an increase in heart rate to restore and maintain blood flow to the vital organs. As stated above, VVS is characterized by a paradoxical withdrawal of sympathetic activity leading to a decrease in blood pressure and, sometimes, a significant decrease in heart rate. Our algorithm design was based on knowledge of normal cardiovascular regulation and alterations occurring in VVS. Trends of RR interval, SBP, and HRV and BPV are each weighted in the

determination of VVS cumulative risk. These trends reflect variations in cardiovascular control that indicate successive alterations away and toward homeostasis (for example a slight decrease in SBP followed by an increase in sympathetic tone and/or heart rate to restore it). To model this behavior in our algorithm, we used the weighted sum of the 4 parameters to describe their physiological interactions. Different values for the relative weighting of each normalized trend have been tested. The best predictive accuracy was obtained when SBP was 2.5 times as important as RR, HRV, and BPV (wRR = 2/9, wSBP = 5/9, wLF-RR = 1/9, wLF-SBP = 1/9), emphasizing again the importance of blood pressure.

This study highlights the separate predictive value of blood pressure, heart rate, and HRV and BPV derived from these variables. The best sensitivity and specificity performance is obtained by the combination of these parameters. If these variables are taken alone, blood pressure yields the highest specificity. In situations in which a low specificity can be tolerated, the use of HRV and BPV yields a slightly longer prediction time. The addition of blood pressure results in higher specificity, if needed. Heart rate alone provides significantly reduced prediction time, sensitivity, and specificity compared with single or multiple parameters discussed above.

In this algorithm, information about autonomic modulation was taken into account using classic HRV and BPV. Any method developed to provide an indicator of autonomic modulation could be used. A multidimensional approach using RR and blood pressure overcomes some limitations of HRV, such as the need to determine specific frequency bands.[25,26]

The algorithm has been implemented on a personal computer and calculates VVS risk in real time using RR intervals and SBP measured from a Portapress as inputs. The output on the screen is similar to graphs presented in Figure 4. When the risk is above the arbitrarily determined VVS risk threshold, an alarm is indicated in red. It is therefore easy to use in a clinical setting. Alternate noninvasive measures of pressure could be used as input. Moreover, it should be noted that this algorithm does not require measures of the absolute value of pressure, but only its variations with respect to a baseline value determined during the 180 sec after the posture change. In this study we used tilt-up to start the computation. In real-life situations, the algorithm could be triggered by a posture change detector such as an accelerometer.

Clinical considerations

During the 180 sec after the posture change, the patient reaches a new steady state of RR and SBP. During this period the algorithm establishes a baseline for blood pressure and heart rate. VVS is very rare so early in the tilt test. However, it is known that orthostatic hypotension begins within this time, resulting in an inaccurate determination of baseline.[27] The data collected during this baseline period are used to normalize subsequent RR, SBP, HRV, and BPV signals, permitting interpatient comparison, the intrinsic baroreflex sensitivity of each patient.[18]

This analysis optimized the algorithm to achieve the highest specificity. Where low specificity could be tolerated, much longer anticipation time would be conferred, for example, a decrease of 23% in specificity would increase prediction time by 100%.

Analysis of the VVS risk patterns showed that tilt-positive patients could be classified into two groups: one group who has VVS relatively soon after the first alarm has been detected (80% of patients, Figure 4B) and a second group showing prolonged oscillation of VVS risk before syncope (20% of patients, Figure 4A). The second group generally has a longer prediction time.

Analyzing the false predictions in tilt-negative patients, which unfavorably influence specificity, we observed that 24 of the 29 were caused by artifacts present on the input signals. These artifacts could be reduced by appropriate preprocessing of the input signals or a better positioning of the electrodes and Portapress; however, such preprocessing could suppress important information.

Analyzing the failed predictions in tilt-positive patients, which unfavorably influence sensitivity, we observed that 27 of the 40 patients showed low-quality Portapress recordings with low or no decrease in blood pressure before VVS, suggesting malposition or malfunction of the device. Two patients experienced an immediate decrease in blood pressure after tilt up, indicating orthostatic hypotension, which was not detected because it occurred during the 180-sec baseline computation. The remaining 11 failed predictions could not be readily explained. Careful placement of the Portapress and the acceptance that a prediction of orthostatic hypotension is impossible by design with this method would improve sensitivity.

Limitations

This was a retrospective study, the data having been gathered from routine clinical tilt laboratory testing. Patients comprised a large cohort with a broad age range, and may accurately represent current clinical practice. The results must be interpreted rather generally because specific groups were not studied and did not include normal subjects. The retrospective nature of this clinical study allowed us in this large cohort to predict reproduction of symptoms. Tilt-negative patients cannot be considered controls as would normal subjects, but because their symptoms were not reproduced by the test, they allowed effective assessment of algorithm specificity. The algorithm was designed to predict patient symptoms on tilt test, not to test the sensitivity/specificity of the head-up tilt test. Tilt testing sensitivity and specificity are not the same as that of the algorithm because tilt testing is performed to make a diagnosis, whereas the algorithm is designed to predict events.

We suggested 3 applications for the prediction algorithm. The first is to avoid syncope in the tilt laboratory by prediction of imminent syncope and termination of the test before the patient experiences syncope. The second appli-

cation could enable the physician to recognize when the autonomic nervous system is under stress leading toward syncope but allowing adjustment of tilt training rather than pursuing it to full syncope, thus making tilt training both safer and more efficient. Our third application, an alert for a implantable device, will be impacted by the fact that tilt testing recently has been shown to be an imperfect predictor of spontaneous events.[28,29] Therefore, collection of data from spontaneous clinical events including arterial pressure is needed for the design of such a device.

The reproducibility of the algorithm needs testing in the laboratory. Furthermore, algorithm performance should be assessed during cardioinhibitory and vasodepressor collapse patterns.[6]

It is possible that elimination of symptoms during tilt may undermine the benefits of head-up tilt testing, namely to teach the patient about symptoms in a clinical rather than spontaneous setting and to reassure the patient that the physician now understands what has been experienced. These potentially negative aspects require thorough study.

Medications were routine and were not controlled in this retrospective analysis; however, in spite of this, the results show strong predictability. Clearly some patients were using cardiovascular medications at the time of tilt testing, which further underscores the routine clinical cross-section of patients whose data were analyzed.

There are few parallels in medicine for which standard tests are replaced by mechanisms predicting outcomes midway through a laboratory study. This report concerns the first steps in this process.

Conclusion

Predicting impending syncope requires use of simultaneous blood pressure and heart rate, which may shorten diagnostic testing time, free patients from experiencing syncope during a diagnostic tilt test, and have application both in risk-guided tilt training and with an implanted device to trigger pacing intervention. The prospects for relieving patient discomfort are encouraging.

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