Non-linear regularity of arterial blood pressure variability in patient with Atrial Fibrillation in tilt-test procedure.

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Abstract

Aims Dynamics of cardiovascular series may be explored with non-linear techniques. It is unknown if the arterial pressure irregularity commonly observed in patients with AF might be further increased by a sympathetic stimulus such as orthostatic tilt.

Methods Twenty patients (62±14 years, 15 men) were recruited for the study. Continuous beat-to-beat non-invasive arterial pressure was acquired at rest and during a passive orthostatic stimulus ("tilt test"). Systolic (SAP) and diastolic (DAP) arterial pressure series of 300-samples were analyzed in both conditions. Approximate (ApEn) and sample entropy (SampEn) were computed, as irregularity measures. Equivalent metrics ($ApEn_{AR}$ and $SampEn_{AR}$) derived from an autoregressive model of the series were also obtained through numerical simulations, to further elucidate the nonlinear mechanisms present in the series.

Results In 11 patients (group A), SAP significantly increased during tilt (from 103±13 to 114±17 mmHg, $p<0.001$ rest vs. tilt), whereas in 9 patients (group B) SAP remained almost unchanged (SAP: 110±18 vs. 106±19 mmHg, rest vs. tilt). No clinical differences were found between group A and B. When analyzing group A, all irregularity measures significantly increased in SAP (ApEn: 1.75±0.20 vs. 1.88±0.16, $p<0.05$; SampEn: 1.71±0.30 vs. 1.88±0.27, $p<0.05$; $ApEn_{AR}$: 1.87±0.20 vs. 1.96±0.18, $p<0.05$; $SampEn_{AR}$: 1.94±0.27 vs. 2.06±0.18, $p<0.05$; rest vs. tilt), whereas no differences were found in DAP series. No significant differences were found in group B for either SAP or DAP.

Conclusion The alterations of SAP during tilt in AF patients are not uniform and seem associated with different regularity patterns. The pressor response to sympathetic stimulation was also associated with an increase of SAP series irregularity.

1 Introduction

Atrial fibrillation (AF) is a common arrhythmia characterized by an irregular ventricular rhythm. It is almost unknown whether this irregularity of ventricular response might directly affect arterial pressure variability. Pitzalis *et al.* (1) observed a respiratory related high-frequency component of systolic arterial pressure (SAP) variability during AF, in absence of a respiratory sinus arrhythmia. More recently, we observed a low frequency component of arterial pressure variability during AF, independently from the presence of a corresponding component in RR variability (2) and, very recently, we reported that the low frequency component of SAP variability in patients with AF increases its amplitude after tilt test (3). These results were interpreted as an indirect evidence for a possible instrumental role of oscillatory components of sympathetic discharge in determining the low frequency oscillations of SAP and diastolic arterial pressure (DAP).

The above-mentioned results were obtained by analyzing arterial pressure variability with traditional linear methods, thus with a limited capability of collecting information on the dynamic patterns used by the cardiovascular regulation systems to adjust heart rate and blood pressure. Nonlinear methods of signal analysis can be useful when characterizing complex dynamics. Nonlinear analysis of heart rate has been largely applied during sinus rhythm (4–6) and to some extent during AF (7,8), providing information related to the irregularity of the series, in terms *i.e*. of pattern repetition and their dynamics. On the contrary, very few studies have analyzed irregularity of blood pressure variability in patients during normal sinus rhythm (9,10) or AF (11). Aim of the present study was to assess the effects of sympathetic activation induced by tilt on the patterns of blood pressure irregularity in patients with AF: *i.e.*, in a physiological model in which the coupling between cardiac cycle duration and pulse pressure is regulated independently of functioning baroreflex control mechanisms for the lack of regularity of RR intervals. In addition,

we verified if the effects of sympathetic stimulation acting on blood pressure control could also be observed in patients with AF.

2 Methods

2.1 Patients

We analyzed 20 consecutive patients (62 ± 14 years, 75% male gender) admitted to the hospital for programmed electrical cardioversion for persistent AF according to international guideline indication (*i.e.* an AF episode lasting longer than 7 days and requiring termination by electrical cardioversion,) (12). The mean duration of arrhythmia was 3±4 months (2-9 range). Patient characteristics are reported in Table 1.

Three orthogonal leads, a periodic reference arterial pressure measurement, continuous beat-to-beat non-invasive recordings of arterial pressure and the respiratory signal were obtained with a Task Force Monitor (CNSystem; Austria) recording system. Surface ECG and blood pressure signals were acquired at rest, and during a passive orthostatic stimulus (head-up tilt test, 75° tilting). Both phases lasted about ten minutes. The sampling frequency was 1 kHz for the ECG signal and 100 Hz for continuous arterial pressure recording. Raw data were exported as ASCII text files for off-line analysis.

The study conforms to the Declaration of Helsinki, and was approved by the Ethics Committee of San Paolo Hospital in Milan (Italy). All patients gave their written informed consent for the procedures related to the study.

2.2. Blood pressure series extraction

During normal sinus rhythm, the beat-to-beat systolic pressure series is commonly obtained by searching for a local maximum in the blood pressure signal following each R-wave. This approach has been shown to be inappropriate during AF (2). In fact, R waves may not be coupled with an

adequate left ventricular output (*i.e.* the left ventricle can be only partially filled when an atrial impulse propagates through the AV node triggering the contraction) to generate regular pulses in arterial pressure. Thus the QRS complexes are not necessarily followed by an arterial pressure pulse of regular amplitude, see Figure 1. For this reason, when measuring beat-to-beat pressure systolic values, we applied a method that coarsely localizes arterial pressure systolic peaks and then refines their positions, thus obtaining the systolic values not relying on the information about QRS location, see (2) for details. An interactive graphic interface allowed the operator to visually identify and correct misdetected arterial pressure pulse events. We also extracted and analyzed DAP series, whose values were defined as the local minimum preceding all systolic values.

As series length influences the following analyses, we considered 300-samples series for all patients and all phases, being 300 the length of the shortest available series of sufficient quality during tilt (which is slightly more than 3 minutes). In particular, we selected the last 300 points of rest, while we discarded the first 25 points on tilt, to avoid the initial drift, and then selected 300 points thereafter.

2.3 Entropy

Approximate and sample entropy

Approximate entropy (ApEn) (13) is a regularity statistic quantifying the unpredictability of fluctuations in a time series. Intuitively, the presence of repetitive patterns of fluctuation makes it more predictable than a time series in which such patterns are absent. ApEn reflects the likelihood that similar patterns will not be followed by additional similar observations (13). A time series containing many repetitive patterns, *i.e*. a regular and predictable series, has a relatively small ApEn, while a less predictable, *i.e.* more complex process, has a higher ApEn. The computation of ApEn for any series of length (N) starts with the choice of two parameters: the length of patterns to be compared, m, and the tolerance of mismatch, r, between the corresponding elements. ApEn(m,

r, N) quantifies the number of similar patterns which will remain similar when a new sample is added (*i.e.* when the length of the pattern increase from *m* to *m*+1).

Sample entropy (SampEn) (14) is an improved version of ApEn, which does not consider self matches of patterns, an inclusion that makes ApEn a biased estimator. SampEn has the advantage to converge more rapidly than ApEn and thus it can be safely computed on shorter series.

To compute SampEn we used the classical parameters *m*=2 and *r*=0.2×SD. For ApEn, given the fact that it usually requires longer series to converge, we employed *m*=1.

Synthetic approximate and sample entropy

A time series can be modeled as the output of an autoregressive (AR) model of order *P*, by the linear combination of *P* previous samples weighted by the models' coefficients, plus white Gaussian noise. The coefficients define the model which has generated the series, and thus the coefficients themselves contain all the information on the signal dynamics, including its entropy. We can therefore use the AR model to generate synthetic signals, compute SampEn on them and get an idea of the Entropy values generated by a purely linear process (*i.e.* the AR model).

To this aim, the AR coefficients are estimated for each series using the Levinson Durbin algorithm and model order is identified by Akaike Information Criteria (15), such that the residuals pass the Anderson whiteness test. Then, 1000 synthetic series of 300 samples (*i.e.*, the same length of the real series) are obtained by feeding the estimated AR model by different realizations of white Gaussian noise of the same variance. SampEn(*m*,*r*,N) is computed on each synthetic signal and the average value over the 1000 realization will be referred in the following as *synthetic* Sample Entropy ($SampEn_{AR}$). SampEn computed on each series is then compared with the values computed on synthetic signals: if SampEn of the series is outside the 95% standard range of the synthetic values, then nonlinear, non-stationary or non-Gaussian components are present in the

data and its dynamic cannot be described by a purely linear AR process. Conversely, if the SampEn of the series is within the 95% standard range, then an agreement with the synthetic sample entropy is observed and a linear model is likely to fully describe the signal's dynamics. In this paper, we quantified the number of subjects for whom the agreement between data and synthetic SampEn was present and we defined "probability of agreement" the ratio between this value and the size of the population. The same procedure is performed also using ApEn and generating a *synthetic* approximate entropy ($ApEn_{AR}$) and its probability of agreement.

2.4. Statistical Analysis

The data are given as mean values ± SD. A paired t-test or the Wilcoxon signed rank test was used to evaluate the differences between parameters during rest and tilt. An unpaired t-test or Wilcoxon-Mann-Whitney was used to evaluate the differences between patient groups. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Entire population

Table 2 shows the mean and the standard deviation for RR and blood pressure series. Mean RR significantly decreased during tilt, as well as RR standard deviation. The mean of SAP slightly increased during tilt, whereas a much larger increase was observed in the mean of DAP series. The standard deviation of both SAP and DAP series remained almost unchanged, even if there was a trend towards larger values in tilt.

Both ApEn and SampEn were significantly higher during tilt for SAP (ApEn: 1.73 ± 0.22 vs. 1.81 ± 0.20, $p < 0.05$, rest vs. tilt; SampEn: 1.68 ± 0.31 vs. 1.84 ± 0.30, $p < 0.05$, rest vs. tilt). On the contrary, no difference was observed in entropy values when comparing rest vs. tilt for DAP series. The series were fitted with AR models of orders in the range 8-15 (85% of the models had order 8). No significant changes were observed when comparing $ApEn_{AR}$ and $SampEn_{AR}$ during rest and tilt

phases ($ApEn_{AR}$: SAP: 1.85 ± 0.21 vs. 1.89 ± 0.18, ns; DAP: 1.99 ± 0.06 vs. 1.98 ± 0.13, ns; rest vs. tilt. $SampEn_{AR}$: SAP: 1.91 ± 0.26 vs. 1.97 ± 0.24, ns; DAP: 2.07 ± 0.10 vs. 2.04 ± 0.17, ns; rest vs. tilt.). The probabilities of agreement between ApEn and SampEn computed on surrogate data showed almost no changes when moving from rest to tilt.

3.2. Arterial pressure response to tilt

We observed two different patterns of SAP alteration due to tilt. A first group (group A, 11 patients) was composed of patients whose systolic pressure increased more than 5 mmHg during tilt. In these patients the systolic pressure increased on average 12 ± 7 mmHg (range 5-26 mmHg), see Table 2. In the remaining 9 patients (group B) the average value of SAP remained almost unchanged or it even decreased (110 ± 18 vs. 107 ± 19 mmHg, ns). Therefore, we further analyzed the two groups A and B, separately. A summary of the parameters obtained on both groups is reported in Table 2, where it can be noted that patients of group A had also an increased standard deviation of SAP and DAP series during tilt, whereas no differences were found in patients of group B.

Figure 2 shows the results of entropy values for SAP series in the two subgroups (no difference were found in DAP series, thus data are not shown). In group A we observed a significant increase in SampEn and ApEn of SAP series during tilt, together with an augmented $ApEn_{AR}$ and $SampEn_{AR}$. On the contrary, no significant differences were found in group B, neither for ApEn and SampEn, nor for $ApEn_{AR}$ or $SampEn_{AR}$.

Table 3 shows the percentage of agreement of ApEn and SampEn. Group A did not display an evident change during tilt and in half of the cases the observed dynamics were consistent with a purely linear process. On the contrary, group B showed a definite increase in agreement, thus suggesting that the series dynamics were well described by a linear process.

4 Discussion and Conclusions

Head-up tilt is one of the most employed experimental protocol for the assessment of the homeostatic response to a cardiovascular stressor challenge (16–19). The caudal shift of blood, and the consequent reduction of the venous return, triggers a compensatory baroreflex-mediated increase of heart rate and peripheral vascular resistance aiming at maintaining arterial pressure into a physiological range (20). Systolic and diastolic pressures have been shown to increase during head-up tilt in normal subjects (18,21).

The first finding of our study is that not all patients with AF experienced a similar increase of systolic pressure during tilt: 9 out of 20 patients had blood pressure values that remained almost unchanged or it even sharply decreased. Therefore, we divided the study population into two groups, depending on the increase (group A)/invariance (group B) of the systolic pressure during tilt. No substantial clinical difference could be found between the two groups. Nevertheless, some consistent tendencies were observed: patients of group A were on average younger (59 ± 14 vs. 65 ± 14, ns; group A vs. group B) than those of group B, they had a slightly lower ejection fraction (54 ± 10 vs. 60 ± 5%, ns; group A vs. group B) and smaller mean RR at rest and tilt (rest: 749 ± 140 vs. 800 ± 176 ms, ns; tilt 683 ± 126 vs. 726 ± 149 ms, ns; group A vs. group B).

When assessing autonomic response of heart rate and blood pressure to head-up tilt test, frequency domain analysis is the most commonly used technique (5,16,17,22–24). However, nonlinear dynamics of cardiovascular response can also be assessed in order to evaluate regularity and synchronisation among cardiovascular beat-to-beat variability signals during the sympathetic activation induced by head-up tilt.

The second finding of our study, is that both measures of irregularity (ApEn and SampEn) were significantly higher during tilt for SAP series, especially when the two subgroups were separately considered. It can be hypothesized that in Group A patients the vascular regulatory mechanisms was still efficient (*i.e.* the response to the autonomic stimulus was similar to what observed in

subjects in normal sinus rhythm), in spite of the presence of persistent AF. On the contrary, patients of group B seemed to have lost their vascular capability of a physiological response to sympathetic stimulation.

Many studies assessed nonlinear regularity of heart rate in response to head-up tilt, all showing a decrease in complexity of RR series due to sympathetic stimulation (6,25). A very few studies have analyzed irregularity and/or dynamics of blood pressure (10,11,26). In a small group of healthy subjects undergoing a head-up tilt test, Porta *et al.* found that the sympathetic activation did not modify SAP regularity. This was explained by the high degree of co-ordination among SAP regulatory mechanisms: it was hypothesised that the several control mechanisms are simultaneously acting to regulate SAP, thus keeping the SAP complexity low (26). Kuusela *et al.* (10) assessed changes in heart rate and blood pressure in healthy subjects at rest by means of nonlinear metrics. They showed that RR interval and systolic arterial pressure subsystems are mutually connected but may have different dynamic properties especially when the strength of the baroreflex feedback loop was modified by terbutaline, a selective beta2-adrenoceptor agonist, RR interval and systolic blood pressure lost mutual synchrony, and the entropy of blood pressure series decreased significantly. Corino *et al.* (11) using a symbolic distance showed that the short-term dynamics of systolic arterial pressure seem to significantly change when comparing rest and tilt phases, while RR dynamics remain unchanged.

It may be hypothesized that during normal sinus rhythm the feedback from blood pressure to RR is predominant in defining the low complexity of SAP series. The baroreflex pathway plays a role in determining the dynamics of SAP series which have been observed to be much simpler when baroreflex strength was reduced by drug infusion. During AF, the traditional baroreflex control mechanisms are almost ineffective and blood pressure control is mainly demanded to pressure-to-pressure loops. Opposite to the case of selective beta2-adrenoceptor agonist infusion (10) where

physiological control mechanisms are activated, in patients with AF, RR intervals are erratic and have a much larger variability: as a result blood pressure regulation is no longer under control of baroreflex mechanisms and is mainly based on the interaction between sympathetic control mechanisms and arterial vasomotion. The most evident result is a marked increase in arterial pressure variability and pulse pressure irregularity. In our study, these patterns were more evident in patients who presented a pressor response to tilt, thus suggesting their capability of a physiological response to a sympathetic stimulation.

A possible limtation is the small number of patients. However, even in this small cohort, we observed that all the patients with an increase of SAP during tilt, also displayed an increased irregularity. This observation was very-consistent in our data and thus the result does not seem to be occasional, and it is likely it might be replicated with a larger population of patients.

Conflict of interest: none declared.

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Table 1: Demographic characteristics and cardiovascular history in the study population and in the two subgroups (group A: patients whose systolic arterial pressure increased during tilt, group B: patients whose systolic arterial pressure did not increase during tilt).

Variable	All patients	Group A	Group B
Number	20	11	9
Gender (male/female)	15/5	8/3	7/2
Age (years)	62 ± 14	59 ± 14	65 ± 14
AF duration (months)	3±4 (range 2-9)	3±4 (range 2-9)	3±4 (range 2-9)
Previous AF	11	5	6
Left atrium diameter (mm)	46 ± 7	47 ± 5	45 ± 8
Ejection fraction (%)	57 ± 8	54 ± 10	60 ± 5
Diabetes	2	0	2
Hypertension	12	5	7
Beta-blockers	11	7	4
Flecainide	3	1	2
Cordarone	5	3	2
ACE-inhibitor	13	6	7
Ca-antagonist	3	2	1

Table 2: Cardiovascular variables during rest and tilt in the study population and in the two subgroups (group A: patients whose systolic arterial pressure increased during tilt, group B: patients whose systolic arterial pressure did not increase during tilt). ns: not significant.

		REST	TILT	p-value
All patients				
RR (ms)	mean	772 ± 155	702 ± 135	<0.001
	SD	163 ± 42	146 ± 30	<0.05
SAP (mm Hg)	mean	106 ± 16	110 ± 18	0.05
	SD	4.90 ± 1.56	5.59 ± 1.86	0.06
DAP (mm Hg)	mean	77 ± 12	85 ± 15	<0.001
	SD	4.42 ± 1.05	4.83 ± 1.33	0.07
Group A				
RR (ms)	mean	749 ± 140	683 ± 126	<0.001
	SD	167 ± 38	152 ± 26	0.04
SAP (mm Hg)	mean	103 ± 13	114 ± 17	<0.001
	SD	4.54 ± 1.22	5.63 ± 1.93	0.02
DAP (mm Hg)	mean	77 ± 10	90 ± 12	<0.001
	SD	4.31 ± 1.03	4.76 ± 0.91	0.04
Group B				
RR (ms)	mean	800 ± 176	726 ± 149	<0.05
	SD	158 ± 48	140 ± 35	<0.05
SAP (mm Hg)	mean	110 ± 18	106 ± 19	ns
	SD	4.90 ± 1.56	5.59 ± 1.86	ns
DAP (mm Hg)	mean	78 ± 16	79 ± 16	ns
	SD	4.57 ± 1.13	4.92 ± 1.78	ns

Table 3: Percentage of agreement between real and synthetic values of ApEn and SampEn for the two subgroups (group A: patients whose systolic arterial pressure increased during tilt, group B: patients whose systolic arterial pressure did not increase during tilt).

	Group A		**Group B**	
	Rest	**Tilt**	**Rest**	**Tilt**
ApEn	55%	64%	56%	100%
SampEn	64%	55%	78%	89%

Figures caption

Figure 1: (a) ECG signal and (b) blood pressure signal of a patient during AF. The circles in (a) correspond to the detected QRS, being the filled circle a beat which is not followed by a pressure pulse. (c) The systolic arterial pressure series obtained without preprocessing: the filled circle identifies a drop in systolic value due to an insufficient pressure pulse.

Figure 2: Errorbar of ApEn (top panel) and SampEn (bottom panel) during rest and tilt phases for the two subgroups of patients. Mean (solid line) ± standard deviation (dashed lines) of $ApEn_{AR}$ and $SampEn_{AR}$ are superimposed. Group A: patients whose systolic arterial pressure increased during tilt, group B: patients whose systolic arterial pressure did not increase during tilt. * $p < 0.05$

Figure 1

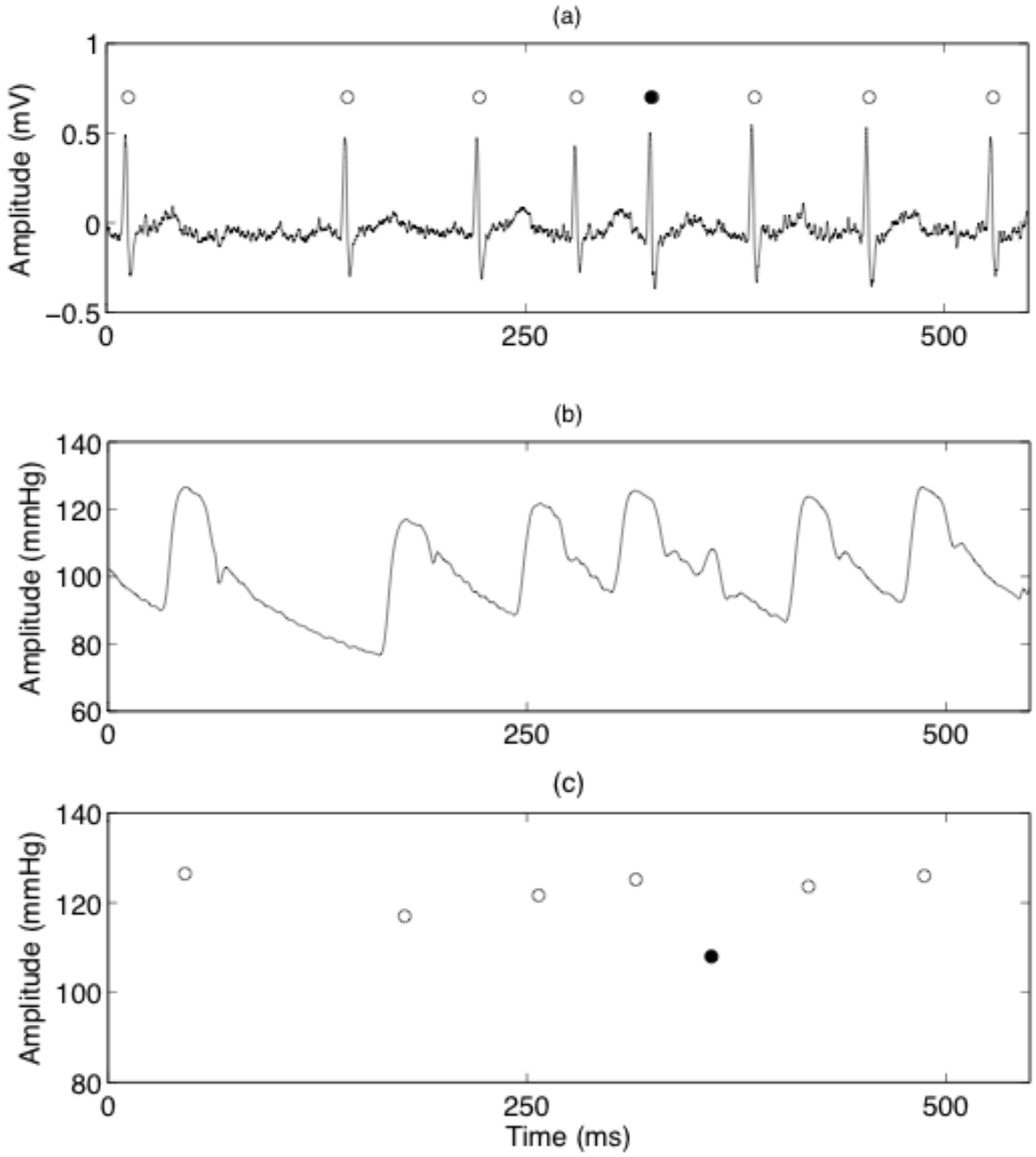
(a)
Amplitude (mV)
1
0.5
0
−0.5
0
250
500
(b)
Amplitude (mmHg)
140
120
100
80
60
0
250
500
(c)
Amplitude (mmHg)
140
120
100
80
0
250
500
Time (ms)

Figure 2