

# A Theoretical Model for the Dependency of Heart Rate on Gradual Vagal Blockade by Atropine

E Pyetan, O Zoran, E Toledo, S Akselrod

Tel Aviv University, Tel Aviv, Israel

## Abstract

*A mathematical model for the dependence of heart rate (HR) on atropine (AT) dose was devised based on the IPFM process as well as on other physiological and pharmacological assumptions. The model leads to two equations, which predict, as a function of AT dose, exact values for mean HR and for the power of HR fluctuations at respiratory frequency ( $HF_p$ ).*

*ECG data from an experimental procedure was used to test the validity of our model. A remarkable agreement between theory and experiment was observed. Moreover, the computed values of the pharmacodynamic parameters, which were defined by the model, displayed a surprisingly small variance among the different subjects. These findings suggest that these parameters might be a basis for a quantitative classification method for cardiovascular control, expressing specific heart or brain diseases.*

## 1. Introduction

Parasympathetic (vagal) control is responsible for the slowing of Heart Rate (HR) in response to physiological and environmental changes. Its neurotransmitter, acetylcholine (ACh), binds to the  $M_2$ -receptors of the SA-node, and exerts an inhibitory effect, causing a decrease in HR. Atropine (AT) modifies vagal input by antagonizing the action of this ACh, thus inducing a marked, dose-dependent tachycardia at sufficiently high doses of AT.

In this study we present a theoretical model, which quantifies the relationship between atropine dose, administered to a patient, and the resulting change in his heart rate signal. The idea for the work originated from a set of experiments performed in our laboratory in 1988 [2], in which eight male adults were injected with cumulative doses of atropine while their ECG signal and respiration were recorded. Our goal was the derivation of an independent theoretical model, based entirely on

physiological and pharmacological assumptions, which would predict mean heart rate as well as the power of the heart rate fluctuations at the breathing frequency, for any given dose of atropine.

The experimental data, which was obtained from the original experiments, was used as a test for the accuracy of our theoretical predictions.

## 2. Theoretical model

In this section the assumptions of the model as well as the resulting equations are presented and discussed.

### 2.1. Assumptions

The assumptions, relied upon in the development of the present model, originate from basic physiology and pharmacology as well as from the IPFM approach.

The concentrations of ACh and NE (norepinephrine), which are, respectively, the neurotransmitters released in the SA node by the parasympathetic and sympathetic systems, are assumed to possess a DC level as well as a time dependent AC value. The AC component is composed of a sum of sine waves with frequencies reflecting various control mechanisms as well as noise sources. The most clearly defined and usually highest of these frequencies is the breathing frequency, which is apparent only in the AC component of the fast responding ACh concentration [1].

We assume that under the specific physiological conditions dictated by the protocol of the experiment, the AC and DC amplitudes of ACh and NE concentrations in the SA node remain constant. In other words, we assume that administration of AT does not evoke a significant feedback response from the body. Obviously, this assumption may be true only as a first approximation.

The binding of ACh to the  $M_2$ -cholinoceptors at the SA-node, in the presence of AT, is assumed to obey the following pharmacodynamic formula, which is commonly applied for the quantitative description of competitive antagonist action [6]:

$$M_{2,\text{bound}} = \frac{M_2 \cdot [\text{ACh}]}{[\text{ACh}] + K_{\text{ACh}} \left( 1 + \frac{[\text{AT}]}{K_{\text{AT}}} \right)}$$

In this equation,  $M_{2,\text{bound}}$  is the total number of receptors to which ACh is bound,  $M_2$  is the total number of the relevant receptors in the SA-node,  $[\text{ACh}]$  and  $[\text{AT}]$  are the concentrations of ACh and AT at the SA-node,  $K_{\text{ACh}}$  and  $K_{\text{AT}}$  are their respective dissociation constants.

The mediation between the neural input to the heart and the resulting firing events of the cardiac pacemaker cells in the SA-node has been repeatedly described by the IPFM (Integral Pulse Frequency Modulation) process [5]. This mathematical device integrates an input signal until reaching a predefined threshold, at which point the device sends out a pulse, resets the integrator to zero and starts the integration anew. This is well described by:

$$I = \int_{t_k}^{t_{k+1}} m(t) dt$$

in which  $I$  is the given integration threshold,  $m(t)$  the input signal, and  $\{t_k\}$  the resulting time sequence of pulses.

In the present case the input signal,  $m(t)$ , corresponds to the overall effect of both vagal and sympathetic influences on the SA-node as well as to intrinsic SA-node pacemaker activity. The resulting pulse train is the sequence of firing events and, therefore, may produce the HR sequence.

As mentioned before, the binding of ACh to  $M_2$ -cholinoceptors at the SA-node has an inhibitory effect on pacemaker activity. Hence, we assumed the following function as the input signal to the IPFM:

$$m(t) = C - \lambda \cdot M_{2,\text{bound}}$$

$C$  represents the contribution of the intrinsic cardiac pacemaker activity as well as including the sympathetic contribution (which is assumed constant, as mentioned above), and  $\lambda$  is simply a proportion constant.

## 2.2. Artifact influences

Low doses of AT were observed to result in a slight unexpected bradycardia, usually termed "the paradoxical low dose effect of AT" [2,6]. The most accepted explanation of this phenomenon is associated with peripheral binding of AT to  $M_1$ -cholinoceptors [6]. AT is not a cardioselective antagonist and it binds to all five types of M-cholinoceptors, causing a variety of effects. The binding of AT to peripheral  $M_1$ -cholinoceptors was

shown to enhance vagal activity at the SA-node and is, therefore, responsible for the paradoxical decrease in HR. Hence, contrary to a previous assumption, vagal activity is not constant during the entire experimental procedure and a small change in the AC and DC levels of  $[\text{ACh}]$  does occur. However, saturation of these  $M_1$ -cholinoceptors is achieved by a small AT dose. Thus, a modification of our mentioned assumption will state that no other change in AC and DC levels of  $[\text{ACh}]$  is expected by an increase in AT, once the  $M_1$ -cholinoceptors are saturated. A sufficient dose of AT,  $[\text{AT}]_i$ , restores the HR to its initial baseline value, therefore compensating for the paradoxical low dose effect of AT.

Since no other evidence proved our assumptions to be wrong, we proceeded in the derivation of the theoretical model, based on these assumptions, for AT doses which are  $\geq [\text{AT}]_i$ .

Another artifact, which is relevant in our case, is the mechanical contribution to the HR signal due to lung volume oscillation [4]. The power of HR fluctuations at the breathing frequency ( $HF_p$ ) is mainly determined by vagal activity if normal conditions are maintained [1]. The mechanical contribution is relatively small under such conditions, however, under high levels of vagal blockade its effect cannot be ignored. Hence, in the derivation of  $HF_p$  as a function of AT, this contribution was taken into account.

## 2.3. Resulting equations

With the help of the above assumptions, a time-dependent expression for the input signal,  $m(t)$ , was derived for any given dose of  $[\text{AT}]$ , which satisfy  $[\text{AT}] \geq [\text{AT}]_i$ . Inserting this expression into the IPFM model produced a prediction of the heart beats, which in turn can be used to generate a time- and AT dose-dependent HR signal.

For any given dose of AT, satisfying  $[\text{AT}] \geq [\text{AT}]_i$ , the following equation for Mean HR ( $MHR$ ) is predicted:

$$MHR([\text{AT}]) = HR_\infty - \frac{1}{a + b \cdot ([\text{AT}] - [\text{AT}]_i)} \quad (1)$$

where  $HR_\infty$  is HR at total vagal blockade,  $a$  and  $b$  are positive coefficients, inversely dependent on DC level of  $[\text{ACh}]$ .

The power of HR fluctuations at the breathing frequency, obtained from the Fourier transform of the HR signal, is given by:

$$HF_p([\text{AT}]) = \frac{1}{4} \cdot \left( (cq - dq^2)^2 h^2 - L(cq - dq^2)h + E \right) \quad (2)$$

The positive constants  $L$  and  $E$  are related to the mechanical contribution to the HR fluctuations at the breathing frequency ( $L = 2\varepsilon \cdot \cos(\varphi)$  and  $E = \varepsilon^2$  with  $\varepsilon$  representing the amplitude of the mechanical contribution and  $\varphi$  representing the phase between mechanical and neural contributions). The coefficients  $c$  and  $d$  are positive constants, which are proportional to the AC level of [ACh] and inversely dependent on its DC level. The fraction  $c/d$  reflects the maximal change in HR due to parasympathetic activity alone.

The components  $q$  and  $h$ , which are AT-dose dependent, are given by:

$$q([\text{AT}]) = \frac{1}{a + b \cdot ([\text{AT}] - [\text{AT}]_i)} \quad (3)$$

and

$$h(q) = 1 - \frac{\omega_b^2}{24(HR_\infty - q)^2} \quad (4)$$

where  $\omega_b$  is the breathing angular frequency and  $a$  and  $b$  are the same constants, defined earlier for the  $MHR$  equation.

### 3. Experimental procedures

This section investigates the agreement between the theoretical predictions of the previous section and the experimental data from an atropine study, performed in our laboratory [2].

#### 3.1. Methods

Eight subjects participated in the study (age:  $29 \pm 1.5$  years, body weight:  $77.4 \pm 8.8$  kg). None of the volunteers took any medication on a regular basis or any other drug (including alcohol and caffeine) for at least 24 hours before the study.

The subjects were placed in supine position with a 30-degree upright tilt, connected to an ECG monitor and a respiratory inductive plethysmograph. After the subjects rested for 30 [min] to allow for stabilization, the ECG and respiration signals were recorded on analog tape during 15 minutes for baseline.

AT (distribution half life = 1 [min]; elimination half life = 140 [min]) was injected with nine consecutive intravenous bolus doses at 10 minutes intervals. Five small bolus doses of 0.1 [mg] were administered during the first 50 [min] and four larger bolus doses of 0.3 and 0.5 [mg] were administered during the next 40 [min]. ECG and respiration were continuously recorded for 7 [min], starting 3 [min] after each new AT bolus. During the recording sessions the volunteers breathed

spontaneously and were instructed to lie quietly without any movement.

The original tapes were digitally resampled, by a Biopac system, at a rate of 1000 [Hz]. The respiration signal was digitally resampled at 10 [Hz]

HR signals were obtained from the ECG traces, using the algorithm presented in [3]. Mean HR value and the power spectrum density (using the Welch periodogram with a Hanning window of 51.2 [sec] and 25.6 [sec] overlapping) were computed for each of the 7-minutes HR traces of each subject. The power of HR fluctuations at the breathing frequency ( $HF_p$ ) was obtained for each AT dose of each subject, by an integral of the HR periodogram over the HF band (respiration peak).

### 3.2. Results and discussion

#### 3.2.1. Mean HR

For all subjects, we observed that the  $[\text{AT}]_i$  dose, which is responsible for the restoration of baseline HR, lay between 0.4 and 0.5 [mg]. Since the manner of AT administration was not continuous in this study, the dose corresponding to  $[\text{AT}]_i$  was determined as 0.4 or 0.5[mg], depending on the subject.

A graph of mean HR, as a function of AT dose, was plotted for each of the subjects for doses higher than  $[\text{AT}]_i$ . The data was fitted to the predicted equation of  $MHR$  (see (1)), and optimal values were obtained for the three parameters,  $a, b$  and  $HR_\infty$ , using the least squares method. A representative plot (Fig. 1) shows a tight agreement between the fitted curve and the experimental data (the percentage of explained variance was  $R = 0.9978$ ). The optimal values of the three parameters, averaged for 8 subjects, are:  $a = 0.016 \pm 0.004$  [1/BPM],  $b = 0.020 \pm 0.006$  [mg/BPM] and  $HR_\infty = 126 \pm 16$  [BPM].

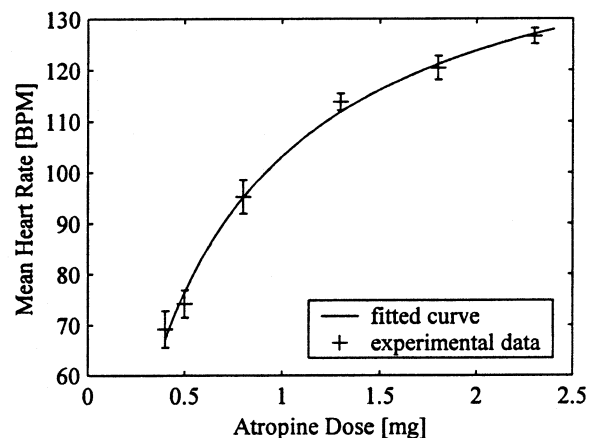


Figure 1. Fit to  $MHR$  graph of one subject, based on the equations of the theoretical model.

### 3.2.2. HR fluctuations with respiration

As indicated above the power of the HR fluctuation at the breathing frequency,  $HF_P$ , was computed for every AT dose of every subject. However, similarly to the  $MHR$  analysis, only power values for AT doses  $\geq [AT]_i$  were used in the analysis.

A quantitative investigation of the theoretical model was performed on the  $HF_P$  of four subjects out of the eight. The other four cases were excluded since one (or more) of the subtraces had a low quality HR signal, good enough for the analysis of  $MHR$ , but causing major artifacts in their power spectrum.

The fitted curves to the  $MHR$  data produced specific optimal values for  $a$  and  $b$  for each subject. With the help of equation (3) and these individual parameters, a  $q([AT])$  array of values (corresponding to the array of AT doses) may be computed for every subject. The breathing frequency,  $\omega_b/2\pi$ , was detected for every subtrace by locating the maximum of the HF peak of the subtrace's power spectrum density. No significant change in breathing frequency within subject was observed. Hence,  $h(q)$  may be predicted for each subject by inserting the average  $\omega_b$  as well as the individual  $HR_\infty$  to equation (4).

$HF_P$  was plotted versus  $q$  for each of the four subjects. The data was individually fitted according to the predicted equation (see (2)) and optimal values for the four parameters,  $c, d, L$  and  $E$ , were obtained by the least squares method. The graph in Fig. 2, which shows the experimental data as well as the predicted curve for one of the subjects, again demonstrates the tight agreement between theory and experimental data ( $R = 0.9986$ ). The optimal values of the four parameters, averaged over 4 subject, are:  $c = 0.031 \pm 0.008$ ,  $d = 0.00085 \pm 0.0003$  [1/BPM],  $L = 1.0 \pm 0.6$  [BPM],  $E = 0.4 \pm 0.3$  [BPM<sup>2</sup>].

According to the paragraph following equation (2), the portion  $L/(2\sqrt{E})$  is equal to  $\cos(\varphi)$ , with  $\varphi$  being the phase between mechanical and neural contributions. The

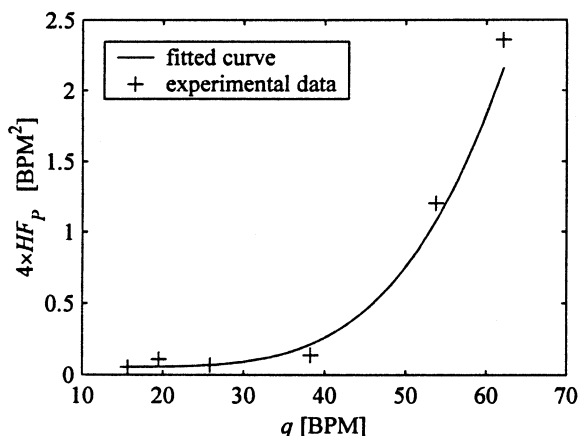


Figure 2. Fit to  $HF_P$  graph of one subject, based on the equations of the theoretical model.

computed values of this portion of the 4 subjects were: 0.46, 0.886, 0.81, 1.26. In three out of the four cases the computed value lies between  $-1$  and  $1$ , and may therefore represent a cosine value. The last value deviates within an acceptable range from the cosine restriction.

## 4. Conclusions

In the present study, a theoretical IPFM based model was derived to describe the dependence of HR on AT concentration in the SA-node. An experimental procedure, in which consecutive AT doses were administered to eight subjects, was used to test the model's validity. The experimental results displayed a tight agreement between theory and experiment. Moreover, the computed values for parameters  $a, b, c$  and  $d$  display a surprisingly small variance among the subjects. This observation suggests that these parameters may contain important clinical information.

In summary, the developed model seems to faithfully describe the dose dependence of HR and its fluctuations on the level of vagal blockade.

## Acknowledgements

This work was partially supported by grant no. 447-98 of the Israeli Science Foundation and by the Abramson Foundation.

## References

- [1] Akselrod S, Gordon D et al. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213:220-222.
- [2] Alcalay M, Izraeli S, Akselrod S et al. Pharmacological modulation of vagal cardiac control measured by heart rate power spectrum: A possible Bioequivalent Probe. *Neurosci. Biobehav. Rev.* 1991;15:51-55.
- [3] Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans. Biomed. Eng* 1986 ;33:900-904.
- [4] Bernardi L, Salvucci F et al. Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise? *Cardiovasc. Res* 1990;24:969-981.
- [5] Hyndman BW, Mohn RK. A model of the cardiac pacemaker and its use in decoding the information content of cardiac intervals. *Automedica* 1975;1:239-252.
- [6] Wellstein A, Pitschner HF. Complex dose-response curves of atropine in man explained by different functions of  $M_1$ - and  $M_2$ -cholinoceptors. *Naunyn Schmiedebergs Arch. Pharmacol.* 1988 ;338:19-27.

Address for correspondence:

Akselrod Solange.  
Tel Aviv University.  
Abramson Center of Medical Physics  
Ramat Aviv 61390, Israel.  
E-mail: solange@post.tau.ac.il