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A NEW PACEMAKER CONCEPT FOR RATE-RESPONSIVE PACING BASED ON THE ATRIO-VENTRICULAR CONDUCTION TIME.

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Abstract: The atrio-ventricular conduction time (AVCT), a time interval which can be obtained from an electrocardiogram, was used for rate-responsive pacing in chronotropically incompetent patients. A control loop is always established as AVCT is sensitive to both the level of exertion and the pacing frequency. Based on experiments a set of plant models was derived for each patient. The controller design was governed by the necessity to attenuate the disturbances acting on AVCT which are correlated with the respiratory cycle. In an ongoing experimental study individual controllers are realized for each patient, but with the same closed-loop bandwidth. *Copyright © 2002 IFAC*

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1. INTRODUCTION

People suffering from the sick-sinus syndrome are mostly chronotropically incompetent, meaning that their heart is unable to increase the beating frequency during physical activity. In this case a "rate-responsive pacemaker" is implanted, in order to guarantee the excitation of the heart at a rate which is sufficient to meet the circulatory and metabolic requirements. In these pacemakers a sensor system is included which provides some kind of information about the strain on the body. This information is used by an algorithm in order to adjust heart rate. Up to now many sensor systems have been tested, but only a few are in clinical use. These are sensors for measuring body movements (accelerometers), minute ventilation (trans-thoracic impedance), StimT-interval (a distinct time interval in the intra-cardial electrogram) or the ventricular inotropic parameter VIP, a signal derived from the intra-cardial impedance which correlates with the right ventricular volume (overview: Sutton, *et al.,* 1999).

The concept described here is based on the well-known dromotropic effect (Guyton, 1986). The sensitive signal used is the conduction time between the right atrium and the ventricles (atrio-ventricular conduction time, AVCT). AVCT can be measured by means of the intra-cardial electrogram (IECG) There it is defined as the time interval starting with the right-atrial stimulus and ending with the following right-ventricular depolarisation. The most important feature of the AVCT-signal is that it is directly influenced by the autonomic nervous system, as the atrio-ventricular node (av-node), the site where AVCT is generated, is innervated by both sympathetic and parasympathetic fibres of the autonomic nervous system. Hence, by using AVCT for heart rate control in an implanted pacemaker it can be assumed that the original physiological control loop can be restored to a great extent. However some care must be taken during the design process as AVCT is also sensitive to the heart rate. By this mechanism a closed loop will always be installed by a pacemaker which uses AVCT as a sensor.

2. EXPERIMENTAL SETUP

Throughout this study experiments were conducted on patients with an implanted pacemaker. All patients suffered from chronotropic incompetence, but had an intact atrio-ventricular conduction. During the experiments the implanted pacemaker was set into the so-called AAT-mode by means of the external pacemaker programmer. In this mode stimulation impulses, which initiate a new heart cycle, are applied only to the right atrium. Stimulation takes place if the built-in sensing amplifier measures an event which is above a programmable threshold, regardless of the event's origin. Therefore a stimulation impulse may be initiated either by a natural depolarisation of the atrium or by an external electrical event which penetrates the heart. The latter effect was used in the experiments to manipulate pacing frequency or heart rate respectively, by applying low-energy trigger impulses (<18 V, <2ms) on the body surface via two spot electrodes. The repetition time of these impulses could be controlled by a computer. As all pacemakers have built-in safety mechanisms, the effective heart rate is limited in order to prevent any serious health risk. The experiments were approved by the local ethic committee.

AVCT was measured by means of a surface electrogram (ECG) sampled with 12bit/5kHz. AVCT was defined as that time interval between an atrial stimulation impulse and the consecutive depolarisation of the ventricles (R-wave). Further measurements which were undertaken comprised the analysis of the ventilatory gases and the respiratory frequency. The latter was obtained by measuring the pressure in an inflated cuff fixed onto the patient's chest.

3. THE PLANT MODEL

The plant is the cardiac conduction system. Based on earlier experiments (Meine, *et al.,* 1999a,b) where only the steady-state behaviour of the atrio-ventricular conduction time *(avct)* had been of concern the following linear relationships were formulated:

$$avct = avct_{BIAS} + k_P \cdot pf - k_{AND} \cdot and + n \qquad (1)$$

Input signals are the pacing frequency *(pf)* a zero mean noise signal *(n)* and the <u>a</u>uto<u>n</u>omic <u>d</u>rive *(and)*, a dimensionless variable relating the actual exercise rate *(ex)* to the individual peak exercise rate *(ex_{max})*. The particular expression "*and*" was chosen to emphasize the inherent coupling between the exercise rate and the activation of the autonomic nervous system.

$$and = \frac{ex}{ex_{\max}} \qquad (2)$$

k_P is a gain factor which expresses the steady-state sensitivity of *avct* to the pacing frequency *pf.* This gain depends on the particular patient. k_{AND} is another gain factor relating the steady-state sensitivity of *avct* to the exercise intensity (*and*). Finally $avct_{BIAS}$ is a constant bias term. Both $avct_{BIAS}$ and k_{AND} depend on some steady-state parameters of the particular patient:

$$avct_{BIAS} = avct_0 - k_P \cdot ihf_0 \qquad (3)$$

$$k_{AND} = (avct_0 - avct_1) + k_P \cdot (ihf_1 - ihf_0) \qquad (4)$$

$avct_0$, $avct_1$, ihf_0 and ihf_1 are the atrio-ventricular conduction time and the intrinsic heart frequency during rest (index 0) and at the individual peak exercise rate (index 1) if the heart beats with his own rhythm.

On the macroscopic level the plant appears as an inherently sampled system because the most important variables have a discrete nature. Both the pacing frequency (*pf)* and the atrio-ventricular conduction time *(avct)*, can be measured/updated only at distinct time instants: *avct* can be measured only once within a heart cycle, as it is defined as the time interval between an atrial stimulus and the following ventricular depolarisation, and *pf* can be updated only once in a heart cycle, as this variable controls the heart cycle. The discrete plant model which is used here is based on (1):

$$\begin{aligned} AVCT(z^{-1}) = AVCT_{BIAS}(z^{-1}) + \\ G_P(z^{-1}) \cdot PF(z^{-1}) + \\ G_{AND}(z^{-1}) \cdot AND(z^{-1}) + \\ N(z^{-1}) \end{aligned} \qquad (5)$$

AVCT (z^{-1}), *PF* (z^{-1}), *AND* (z^{-1}), $N(z^{-1})$ and $AVCT_{BIAS}$ (z^{-1}) are the original discrete-time signals now in the complex z-domain.

$G_P(z^{-1})$ is a discrete transfer function with gain k_P, which represents the relationship between *AVCT* and *PF.* This transfer function again depends on the particular patient and, additionally, to the pacing frequency and the level of exercise.

$G_{AND}(z^{-1})$ is another discrete transfer function with gain k_{AND} considering the dynamics of *AVCT* due to changes of the exercise intensity *AND* (patient-dependent).

4. SYSTEM IDENTIFICATION

4.1 Experiments

Knowledge about all decisive plant parameters, transfer functions and the disturbances had been obtained during a series of experiments.

Experiment 1: In the first experiment the patient had to work on a bicycle-ergometer. Exercise was changed incrementally. In this experiment the rate adaptation of the pacemaker was switched off by means of the pacemaker programmer so that the patients worked with their intrinsic heart rhythm. The experiment was terminated at the patients maximum capacity or by their request. Linear correlations between the exercise related oxygen consumption both to the intrinsic heart frequency and the atrio-ventricular conduction time could be observed. The decisive parameters of this type of experiment were the intrinsic heart frequency and the corresponding atrio- ventricular conduction time at rest and during peak exercise ($avct_0$, $avct_1$, ihf_0, and ihf_1).

Experiment 2,3,4: In the second type of experiment the patient had to work at three distinct levels: rest, 1/3 and 2/3 of the individual peak exercise rate. Each experiment started with a time interval (phase 1) where the pacing frequency was kept constant *(pf_{MEAN})*. This frequency was chosen to be that which a comparable subject would have at that particular exercise rate. Thereafter (phase 2) the pacing frequency was changed pseudo-randomly *($pf_{MEAN}\pm 10bpm$)*. Finally (phase 3) pacing frequency was increased incrementally starting from the intrinsic rhythm and ending at that pacing frequency at which a conduction block occurred (Wenckebach point).

4.2 Identification results

Steady-state gain k_P. This parameter was obtained during phase 3 of experiments 2,3,4. It could be seen, that this gain depends on the particular patient and, additionally, on the pacing frequency and the level of exercise. However, if only a narrow range around that exercise dependent pacing frequency is regarded, which a comparable healthy subject would have, it can be assumed that k_P is insensitive to the pacing frequency and the exercise level. Under these conditions the individual k_P ranges between 0.2 and 1.0 ms/bpm (bpm=beats per minute).

Bias term $avct_{BIAS}$,, steady state gain k_{AND}: These parameters were calculated for each individual according to (3) and (4), using that k_P obtained from the resting condition.

Disturbances $N(z^{-1})$. Phase 1 of the experiments served to evaluate the disturbances acting on the *avct*-signal. An example is given in fig 1. Beside some low-frequency fluctuations which may be due to a changing tone of the autonomic nervous system an oscillation coupled to the respiration was always present. This coupling could be noticed both in the signal traces and in the power spectra of the *avct*-signal and the respiratory related cuff pressure (fig. 2). There the respiratory peak always coincided with a peak in the AVCT-spectrum.

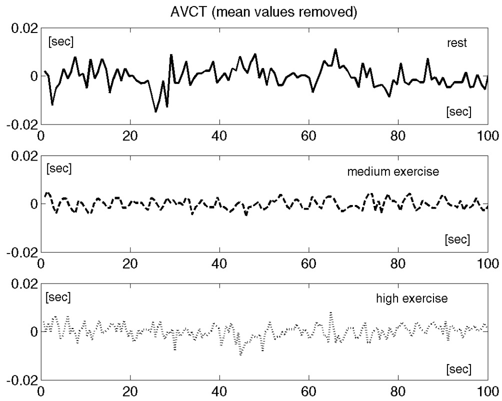

Fig. 1. The avct-signal of a sample patient at three different exercise levels (mean values removed)

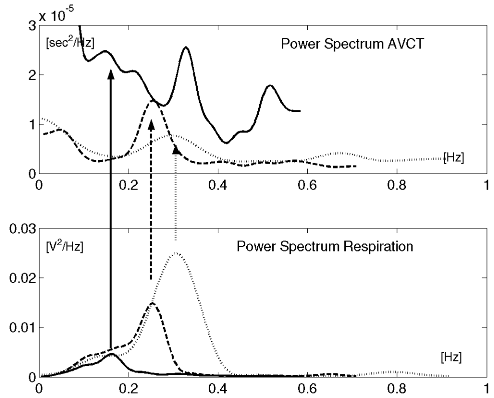

Fig. 2. The power spectra of the *avct*-signal and the respiratory related cuff pressure (output voltage of the pressure transducer) for three different levels of exercise (rest: solid, medium exercise level: dashed; high exercise level: dotted). The arrows indicate the coincidence.

This observation can be explained by the close coupling between cardiovascular and respiratory control in the autonomic nervous system. In some patients these oscillations were as high as ±6 ms at rest, while lower during exercise. With regard to the mean activity-induced span of *avct* (20..30ms) these oscillations imply a rather poor signal-to-noise ratio.

Transfer function $G_P(z^{-1})$. Models with two inputs and one output had been identified for each patient and each exercise level from the data obtained during phase 2 of experiments 2,3,4 by means of MATLAB® (Identification Toolbox). The first input was the pacing frequency and the second one the respiratory related cuff pressure. The only output had been the measured *AVCT*-signal. In all cases Box-Jenkins models were appropriate. First or second order models $G_P(z^{-1})$ were sufficient to describe the dependency of the *AVCT* on the pacing frequency (*PF*) whereas higher order models had to be used in the case of the *AVCT* dependency on the respiration (cuff-pressure) and the noise. In all cases the poles and zeroes of $G_P(z^{-1})$ were inside the unit disc and a time delay of one sampling period was present.

Transfer function $G_{AND}(z^{-1})$. In the case of $G_{AND}(z^{-1})$ the procedure was different (lack of patient fitness, age>60). Hence the time course of *avct* after a single step change of exercise (rest to 20W) and constant pacing frequency was used to get a rough estimate of the dynamics G_{AND} of the sensor signal. The step response was approximated by a first order system with an additional dead time. Based on this procedure a time constant T=9.1s and a dead time of T_D=5.2 s can be assumed.

5. THE CONTROL LOOP

Heart rate control should be performed in a beat-to-beat mode. That means that whenever a new *AVCT* is valid, the pacing frequency *PF* is updated according to the implemented control algorithm. Figure 3 depicts a block diagram of such a pacing-system. The model of the plant is derived on the basis of (5). The block "limiter 1" accounts for the mentioned limitation in the case that an intrinsic heart frequency *IHF* is generated which is higher than the stimulation frequency *PF* delivered by the pacemaker. This limit is not constant, but influenced by the autonomic nervous system. The controller which is currently under test consists of a constant reference value $AVCT_{REF}$ and a transfer function $G_C(z^{-1})$ with steady-state gain k_C but without integral behaviour. A second limitation ("limiter 2") is present, as all pacemakers have rate limits which are usually programmed by the physician.

5.1 The stimulation law

In contrast to many other control-applications, the behaviour of the measured/controlled variable (*AVCT*) with respect to disturbances and set-point changes is of minor interest here. The main focus is on the behaviour of the control variable *PF*. Based on the control loop the "stimulation-law" can be calculated for the case that no limitation occurs (argument z^{-1} omitted)

$$PF = \frac{G_C}{1+G_C \cdot G_P} \cdot \left[AVCT_{REF} - AVCT_{BIAS} + k_{AND} \cdot G_{AND} \cdot AND - N\right] \qquad (6)$$

whereby the closed loop transfer function $G_{CL}(z^{-1})$ can be defined as:

$$G_{CL}(z^{-1}) = \frac{G_C(z^{-1})}{1+G_P(z^{-1}) \cdot G_C(z^{-1})} = \frac{C(z^{-1})}{D(z^{-1})} \qquad (7)$$

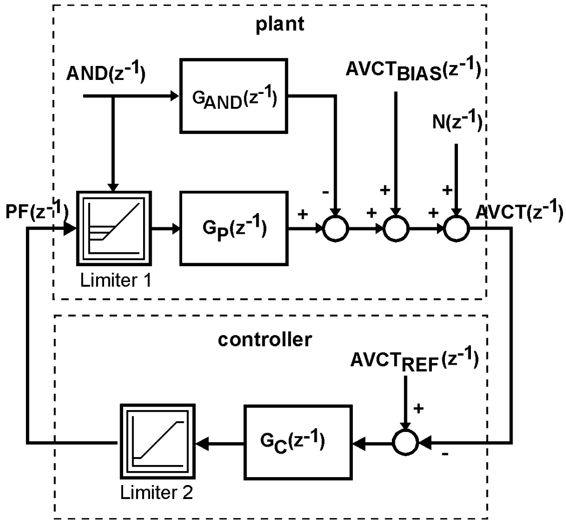

Fig. 3. The control loop. Steady state gains of $G_P(z^{-1})$ and $G_{AND}(z^{-1})$ are k_P and k_{AND} respectively.

5.2 Controller design

From the stimulation-law (6), the steady-state value of the pacing frequency pf_{STAT} for a distinct exertion (*and)* can be calculated. Assuming that the noise signal $N(z^{-1})$ has zero mean and that $G_{CL}(z^{-1})$ is stable with a steady state gain of $k_{CL}= G_{CL}(1)$, it holds:

$$pf_{STAT} = \left[k_{CL} \cdot (avct_{REF} - avct_{BIAS})\right] + \left[k_{CL} \cdot k_{AND}\right] \cdot and \qquad (8)$$

The first bracket represents a basal stimulation frequency pf_0 which acts on the heart if there is no activity (*and=0*) whereas the second bracket represents a gain factor k_{PF} , often called "slope" in pacemaker technology, by which a certain level of activity (*0#and#1*) is transformed in to an increase of the pacing frequency. In order to guarantee physiological stimulation frequencies at any level of activity both parameters pf_0 and k_{PF} must be tailored to the patient by means of the controller parameters k_C and $avct_{REF}$:

$$k_{CL} = \frac{k_{PF}}{k_{AND}} \qquad avct_{REF} = \frac{pf_0}{k_{CL}} + avct_{BIAS} \qquad (9\ a,b)$$

From equation (6) it can be seen that both the exercise induced variation $k_{AND} \cdot G_{AND}(z^{-1}) \cdot AND(z^{-1})$ and the disturbances $N(z^{-1})$ are acting via the same closed-loop transfer function $G_{CL}(z^{-1})$ (7) on the pacing frequency $PF(z^{-1})$. A major design goal must be the attenuation of the oscillation which coincides with the respiration. Hence $G_{CL}(z^{-1})$ must be chosen with a gain according to (9a) and an appropriate cut-off frequency $f_{g,CL}$. The choice of $f_{g,CL,}$ is governed by the need to maintain the natural sensor dynamics and to guarantee an effective damping of the oscillations.

In a straightforward calculation (7) can be solved for the controller dynamics:

$$G_C(z^{-1}) = \frac{S(z^{-1})}{R(z^{-1})} = \frac{G_{CL}(z^{-1})}{1 - G_{CL}(z^{-1}) G_P(z^{-1})} \qquad (10)$$

With the plant transfer function

$$G_P(z^{-1}) = \frac{B(z^{-1})}{A(z^{-1})} \cdot z^{-d} \;;\; d >= 1 \;;\; A(z^{-1})\ monic \qquad (11)$$

it follows that:

$$G_C(z^{-1}) = \frac{S(z^{-1})}{R(z^{-1})} = \frac{C(z^{-1})A(z^{-1})}{D(z^{-1})A(z^{-1}) - C(z^{-1})B(z^{-1})z^{-d}} \qquad (12)$$

As $D(z^{-1})$ can always be chosen to be monic the controller is always realizable. The characteristic polynomial of the control loop

$$A(z^{-1})^2 \cdot D(z^{-1}) = 0 \qquad (13)$$

implies that the plant must be stable, which is always the case here. However (13) only holds true for that plant model for which the controller was designed. If an other plant model

$$G'_P(z^{-1}) = \frac{B'(z^{-1})}{A'(z^{-1})} \cdot z^{-d'} \qquad (14)$$

is valid because of an other operating (exercise) condition, the characteristic polynomial changes to:

$$\begin{aligned} &C(z^{-1}) \cdot A(z^{-1}) \cdot B'(z^{-1}) \cdot z^{-d'} + \\ &D(z^{-1}) \cdot A(z^{-1}) \cdot A'(z^{-1}) - \\ &C(z^{-1}) \cdot A'(z^{-1}) \cdot B(z^{-1}) z^{-d} = 0 \end{aligned} \qquad (15)$$

5.3 Controller parameterisation

After the individual specification of the target range of the stimulation frequency k_{PF}, which is pf_0 (rest) minus pf_1 (peak exercise), by a physician, k_{CL} and $avct_{REF}$ can be calculated according (9a,b). The only universal specification of the controller which is the same for all patients concerns the closed-loop cut-off frequency $f_{g,CL}$ of $G_{CL}(z^{-1})$: Compared to the sensor dynamics with a cut-off frequency of about 0.017 Hz, the respiratory frequency, which is within the range of 12...45 min^{-1} (0.2..0.75 Hz) is always higher. Hence there is a relatively wide margin for the choice of $f_{g,CL,}$ Therefore a discrete first-order lowpass with $f_{g,CL}=0.035\ Hz$ is currently being used for $G_{CL}(z^{-1})$. Sampling frequency is always that frequency which was used as pacing frequency for the particular patient during the identification of the resting condition. The controller is calculated according to (10,12) with that plant transfer function $G_P(z^{-1})$ (11) which was valid for the resting condition. Finally, stability is checked (15) for all plant models which had been identified for the particular patient during the other exercise conditions.

6. EXPERIMENTAL VALIDATION OF THE CONTROLLER

Fig. 4. shows the results of a closed-loop experiment with a chronotropically incompetent patient. On the upper diagram *avct* is shown, whereas on the lower the controlled heart frequency (ventricular frequency) is depicted.

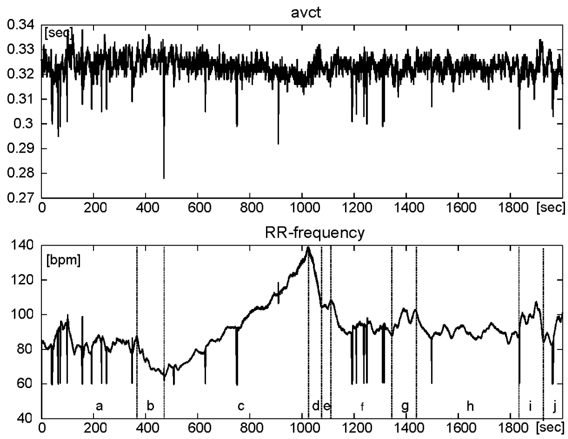

Fig. 4. Closed-loop experiment with the *avct*-signal (upper trace) and the paced heart frequency (lower trace). See text for explanation.

At the beginning of the experiment (a) the patient rested on the ergometer while talking to the laboratory staff. During (b) no conversation was allowed resulting in a decreasing heart frequency. Next the patient had to exercise (c). Exercise intensity was increased incrementally (stair-case). Exercise was zero during (d), while a low level was maintained during (e). Finally the patient was at rest, with lively conversations during (g) and (i).

The spikes in both diagrams are due to some problems concerning the special experimental condition: Not all trigger impulses applied to the body surface had been sensed by the implanted pacemaker with the result that sometimes no stimulation is initiated. If this happens, either an intrinsic heart beat appears or the pacemaker initiates a stimulation a certain time after the last heart beat (lower rate limit of the pacemaker).

The control loop always reacted promptly to any change of the physical exercise level. Furthermore it was observed that an emotional conversation also initiated a prompt increase of the heart rate. This observation is surely due to the direct influence of the autonomic nervous system onto the atrio-ventricular conduction time, which is a clear advantage of this concept as compared to other rate-responsive pacemaker systems. Finally, it could be observed that the noise in the *avct*-signal was effectively damped by the control loop: Notice the span of the *avct*-signal during rest (h) compared to the effective decrease during exercise (c), notice also the smooth heart rate. The peak heart rate (140bpm) which was attained here was higher than in the control experiment (110bpm).

7. SUMMARY

The atrio-ventricular conduction time is a very useful sensor for rate-responsive pacing of chronotropically incompetent patients, because it is directly influenced by the autonomic nervous system. Therefore such a concept has the potential to restore the original physiological control loop. Another striking argument is its rather simple and inexpensive realization (software), as no additional hardware is necessary.

The control concept which is used here is governed by the necessity to attenuate the respiratory related disturbances. A fixed controller was used, which was designed for that plant model valid for the resting condition. Hence, some discrepancy between the specified and the real closed-loop properties is present, as the plant depends on the operating range. The question whether this can be tolerated will be answered after the ongoing study.

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