Development of a Closed-Loop Pacemaker Controller Regulating Mixed Venous Oxygen Saturation Level

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Abstract—The cardiovascular (CV) plant dynamics must be known in order to develop a closed-loop pacemaker controller. A simplified model of the CV system is developed where the heart rate (HR) is the controlled input variable, the mixed venous oxygen saturation level (SO_2) is the model output, and the work loads are the disturbances. The model relates the SO_2 level to the HR and the work through linear relationships, gains and first-order time constants, and nonlinear relationships, the most important being the nonlinear relation between cardiac output (CO) and heart rate due to the "optimal" heart rate phenomenon.

The critical gain is calculated and is shown to be a function of the CO due to the shortening of circulation time delay with increased CO—a stabilizing phenomenon. The step response of the system in open and closed-loop modes to various loads are simulated in the time domain.

A proportional-plus-derivative controller is described which in the simulation increases SO_2 from 36 percent with a 100 W load at constant HR to 57 percent. This is achieved at a cost of increasing HR from 62 to 96 bpm.

The "optimal" heart-rate problem, which proves to be the major destabilizing factor in the system, is dealt with by an optimal mode that is included in the controller and tested in the simulation. According to this procedure the HR is perturbed by 10 beats per min every minute and the SO_2 response is recorded. According to preselected bounds the HR is then maintained at the new level, brought back to its preperturbation level or is reduced by 10 bpm. An optimal SO_2 response to HR drive can thus be achieved in addition to overcoming the "optimal" HR problem. The performance of the controller, in its different modes of operation, with varying loading conditions and varying "optimal" HR values is demonstrated through its computer simulation. Preliminary results from patient experiments demonstrate the range of usefulness of such systems and exhibit their *in vivo* performance.

I. Introduction

ALL PHYSIOLOGICAL systems operate in closed-loop mode to maintain hemiostasis, i.e., maintain its performance in the face of changing loading conditions and changes in the parameters of the physiological system itself. These closed-loop systems can be of the servo-regulated type [1], [2] or of the more complicated nonlinear adaptive and optimal type [2], [3]. The normal cardiovascular system is no exception to the above [4] and the regulation of heart rate (HR) is no exception to the cardiovascular system. Attempts have been made to improve the performance of implanted pacemakers by trying to regulate their pacing rate in accordance with a measured physiological parameter which is exercise dependent. To facilitate comparison between different pacemakers (PM) the following is observed. Physiological responsive PM's regulate HR in accordance with a measured physiological parameter which is related to the applied metabolic load. Closed-loop PM's are those systems in which HR regulates the measured physiological parameter which in turn is fed back to the PM controller to regulate HR. An SO_2 closed-loop PM controller system is shown in Fig. 1. Closed-loop systems have certain properties missing in open-loop systems. A valuable property is the decrease in the system's sensitivity to variations in changes of its internal parameters. This reduction in sensitivity is a function of the loop transmission gain which in physiological systems is not very high compared with man-made systems. Sensitivity analysis of the present design is carried out in the Appendix. Closed-loop systems can however become unstable and oscillate with certain conditions of gain and phase.

In an open-loop system, a metabolically related variable, which is HR independent, is measured to control the HR. The system then operates with only a feedforward branch. The reference in Fig. 1 is then replaced by an input signal and the feedback loop is opened. The best example of an open-loop PM is the activity controlled PM [5]–[7]. In these PM's, the reference input signal is related to the body acceleration; however, the HR neither controls body acceleration nor the amount of desired activity. It is clear that the physiological responsive PM's can be either closed or open-loop systems.

In a recent paper [8], trends in pacemakers which are physiologically rate responsive were analyzed according to the physiological variable which regulates the PM. Some of these PM are closed-loop and some are open-loop. In addition to the activity PM's, the respiratory rate control PM is the most notable additional example of an open-loop PM since HR does not control respiration [9].

The most natural closed-loop control mode of HR is the atrial triggered pacing. Atrial driven PM's are not dealt with here except as the most natural example of a closed-loop HR control, although they do suffer from practical

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problems [8]. Other parameters have been used to drive HR in a closed-loop mode. The most notable are the QT interval [10], [11] and temperature [12]–[14]. Experiments are currently being carried out on sensing stroke volume (SV) [15], [16] and venous oxygen saturation (SO_2) [17], [18]. All these PM's, commercial and experimental systems, suffer from two basic problems, in addition to problems that are PM type specific. They do not deal with the problem of "optimal" pacing frequency, (HROP), i.e., the frequency of HR above which an increase in HR decreases CO. This is a severe problem in closed-loop PM's because it can cause instability and overpacing as described later—or "just" futile overpacing in the open-loop systems. It is known that the HROP can hardly be reached by normal human subjects; however, in patients, especially those with myocardial disease, the HROP can be as low as 110 bpm and lower. It is clearly not beneficial to the patient to be paced above this frequency [19]. In addition, none of the PM's on the market or in the experimental stage optimize the rate that maximizes CO for a given work load, i.e., it is known that as the SO_2 level goes down, oxygen transfer to the tissues becomes less for the same CO. SO_2 cannot decrease below a minimum of roughly 20 percent. The nonlinear relationship between SO_2 level and oxygen transfer can yield an optimal CO at a given level of work load.

In the present paper, a closed-loop PM controller is described which alleviates some of the problems stated above. To design a controller, the plant gain and dynamics must be known. Since no model exists that relates SO_2 to HR and work load, this model is first being developed based on existing data from the literature and from experiments using the SO_2 sensor [20]. A conventional proportional controller is then developed which with a loop gain of about five guarantees stability and marked improvement in SO_2 level and in the system insensitivity to parameter variations. An optimal controller is then developed to circumvent the HROP problem and to optimize pacing. Finally, preliminary clinical results are presented for the conventional controller.

II. The Simplified Model

The cardiovascular system is a very complicated multicompartmental multi-input–output distributive system. To obtain a workable model with which a pacemaker controller can be studied, a highly simplified model must be developed. Such a model is developed for the special case of HR as the input controlled variable and SO_2 as the output variable Fig. 1. Furthermore, it is assumed that only external work provides the loading disturbances to the system.

The following are the transfer characteristics of the individual subcomponents from which the total model is developed.

A. Oxygen Supply (OXS)

The oxygen supplied by the heart is the simple product of cardiac output (CO) times the oxygen saturation level in the arterial blood (K_{SO_2}) leaving the heart.

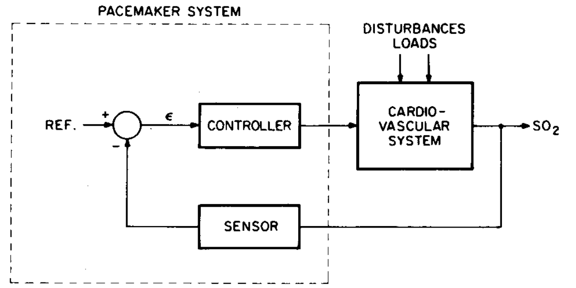

Fig. 1. A closed-loop pacemaker system regulating SO_2. Ref.—the reference signal, which can be constant or it can be modified according to some optimizing criteria. ϵ—the error which is the difference between the desired SO_2 level—Ref—and the measured level. ϵ is the signal that drives the PM.

$$\text{OXS} = \text{CO} \times K_{SO_2} \tag{1}$$

where $K_{SO_2} = 0.2$ (liter O_2/liter blood) is assumed throughout the present work to be constant.

B. CO = f (HR, work)

CO in liter per minute of blood is assumed to be a function of two variables, the HR and the external mechanical work load of power (P) performed by the patient, i.e.

$$\text{CO} = f(\text{HR}, P). \tag{2}$$

The relationships expressed by (2) are simple to understand for certain regions of HR, i.e., as the HR goes up it is expected that CO will go up with it. The above is complicated by the Starling phenomenon, the pumping force being a function of the end diastolic ventricular volume (preload), and the residual blood left unpumped. Both of these factors are influenced by and related in a linear and nonlinear way to the HR and skeletal muscular pumping generated by the mechanical work as explained below.

From published results [21] of experiments carried out on a large and diversed population of men and women of different ages, the following average functions are obtained.

For young subjects

$$\text{CO} = 5.87 + \frac{\text{HR} - 68}{7.5} \tag{3}$$

CO in liter blood/min and HR in beats per min (bpm).

For the group of older subjects

$$\text{CO} = 5.47 + \frac{\text{HR} - 62}{6.2}. \tag{4}$$

From another study, [22], the following relationship is obtained

$$\text{CO} = 6.4 + \frac{\text{HR} - 64}{7.14}. \tag{5}$$

C. Optimal Pacing Frequency (HROP)

Optimal HR frequency is known as the HR for which an increase in HR fails to further increase CO or may even decrease it [20], [23]. This rate is a function of the state of the heart and it varies widely, especially between patients who are candidates for pacemaker implant. In healthy subjects, this frequency is not exceeded under normal loading conditions. For normal hearts HROP > 160 bpm. For patients with heart problems it is not uncommon to have HROP in the range of 80–110 bpm, [19].

The "optimal HR" poses a major problem in the design of a closed-loop pacemaker controller since a positive feedback situation occurs when this frequency is exceeded. In the present simulation studies K_2, the negative slope of the CO versus HR gain characteristic above HROP was assumed to be half of its positive values K_1 as shown in the appropriate block of Fig. 2, i.e.,

$$\mathrm{CO} = K_1 \times \mathrm{HR} \text{ for HR} \leq \mathrm{HROP} \tag{6}$$

$$\mathrm{CO} = K_2 \times \mathrm{HR} \text{ for HR} > \mathrm{HROP} \tag{7}$$

$$K_2 = -1/2K_1. \tag{8}$$

The optimal pacing frequency itself could be varied to test for instability phenomena.

D. CO Dependency on SV

A simple relationship exists between CO and SV, i.e.,

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR}. \tag{9}$$

The problem with (9) is the SV dependency on HR which is neither constant nor linear. Equation (9) has not been used in the present study since SV is currently not available as a separate measured variable. The SV, when available [7], can be used to a greater advantage in coping with the optimal frequency problem and in optimizing the pacing rate.

E. CO Dependency on Power

Due to the venous return and the Starling phenomenon, CO increases with work even with fixed HR. This increase is a major factor in regulating CO with work load, and can account for up to 50 percent of load compensation. This phenomenon is clearly demonstrated in patients with fixed pacing rate [20]. In an experiment performed on ten patients with implanted pacemakers, CO was measured at a low-level of bicycle work. For a 25 W power of work load (P), the average results can be fitted to the following equation:

$$\Delta\mathrm{CO} = \frac{P}{14}. \tag{10}$$

The additional cardiac output (ΔCO) in liter/min and power in W.

The above process builds up with an average time constant of $\tau_1 = 10$ s [24]. The dynamic relationship between work and CO is

$$\Delta\mathrm{CO} = \frac{P}{14(1 + s\tau_1)} \tag{11}$$

where s is the Laplace variable.

The influence of work on CO is bounded by the increase in venous tone and the backpumping of the muscles both of which increase venous return. The heart properties, especially its ability to increase its force of contraction, have the same effect. This is incorporated as a saturation nonlinearity in the model (Fig. 2), but the saturation level is never reached with power loads simulating patients' loading conditions. For simplicity, tractability, and lack of their precise relationships, CO is asumed to be an additive function of both HR and work. When SV measurements are available the model can be improved by changing SV with P directly.

F. Oxygen Consumption—OXC = f_1 (Power)

The function f_1 describes the oxygen consumption (OXC) as a function of the power (P). In a very large study of young men, the following relationship was found between OXC and power [25]:

$$\mathrm{OXC} = 0.269 + 2.10^{-4} \times P \text{ (in Nm/min)} \tag{12}$$

where OXC is in liters per minute and power in Nm/minute, or in W

$$\mathrm{OXC} = 0.269 + 1.25 \times 10^{-2} \times P \text{ (in W)}. \tag{13}$$

Similar results have likewise been obtained in other studies [22], [26]. The deviations from the mean values used in (12) and (13) are taken into account in the sensitivity analysis. The response of OXC to work has a time constant τ_3 of approximately 30 s under light loading conditions [24]. The work, above OXC at rest, must therefore be multiplied by $1/1 + s\tau_3$. Under heavy loading conditions, SO_2 does not reach a steady state level due to lack of capacity in the oxidative processes and in the ability of the cardiovascular system to apply the demand [24]. For patients with implanted pacemakers, only a relatively light load is assumed. This does not affect the closed-loop part of the model, but only the way the load is applied to it. Work is taken here as the only load affecting the system since physical work can increase cardiac demand by as much as 700 percent of the rest values versus 30 percent for eating and 50–100 percent during anxiety and excitement [22].

G. Oxygen Saturation Level in the Venous Return—SO_2

The oxygen saturation level in the venous return (SO_2) is the difference between oxygen supplied by the heart (OXS) and oxygen consumed by the body (OXS), divided by the venous return (VR). Since the cardiovascular system is a closed system the same volume of blood leaving the left ventricle enters the right ventricle, i.e.,

$$\mathrm{VR} = \mathrm{CO}. \tag{14}$$

This is strictly true only under steady state conditions but is used here even for dynamic calculations. The equality VR = CO is true only in the absence of valvular regurgitation and septal defects.

From the above assumption

$$SO_2 = \frac{\mathrm{OXS} - \mathrm{OXC}}{\mathrm{CO}} \tag{15}$$

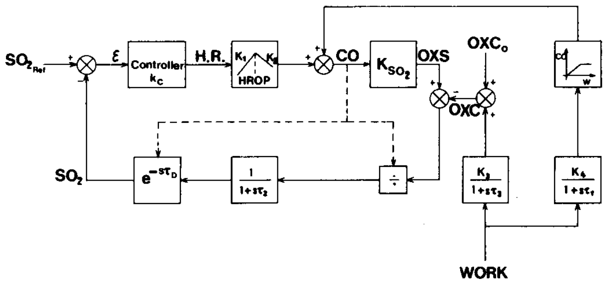

Fig. 2. Block diagram of the complete model in its closed-loop form. Notation according to text.

OXS and OXC in liter O_2/min, CO in liter blood/min and, therefore, SO_2 in liter O_2/liter blood.

Changes in oxygen supply and demand due to work, take time to reach the right ventricle which is the sensing location of SO_2. The average circulation time and the effect of mixing of blood from various parts of the body can be incorporated into the model by adding a time delay (τ_D), and a time constant (τ_2). In the present model, the average time delay at rest is assumed to be $\tau_D = 15$ s and the average time constant $\tau_2 = 15$ s. In addition, it was assumed that the time delay is a function of cardiac output. Since the volume of blood that exists in the system is constant, an increase in CO shortens the circulation time and with it the time delay. This dependence of τ_D in seconds on the CO is described by

$$\tau_D = \frac{82.5}{\mathrm{CO}} \tag{16}$$

which gives for a CO of 5.5 l a delay of 15 s. Equation (16) is a manifestation of *a stabilizing mechanism* which is inherent to the cardiovascular system. Most probably a similar effect exists for the time constant τ_2. Since no exact knowledge of its behavior is known, and most probably τ_2 is shortened with an increase in CO—a stabilizing effect—only the influence on τ_D is incorporated into the model.

The Complete Model

The complete model which consists of the subcomponents developed above is shown in Fig. 2. All the blocks in the above diagram have been explained in the preceding section. $SO_{2\mathrm{Ref}}$ is the reference SO_2 level to be introduced in the design considerations of the controller and ϵ is the error, the difference between the measured and reference SO_2 levels. ϵ is the signal which drives the controller. (./.) is a division operation of (15). K_3 and K_4 are the coefficients of (11) and (12), and K_c is the controller gain. Although all the model parameters are assumed constant, they are clearly a function of CO, SO_2, HR, and work loads P. The sensor used in the present study has been described elsewhere [27].

III. Conventional Controller Design

First, the open-loop characteristics of the model must be analyzed. The critical gain K_{CR}, which is the maximum gain value before oscillations takes place in the closed-loop system, was calculated to be $K_{cr} = 380$ bpm · liter blood/literO_2. It should be noted that an increase in HR increases CO and shortens τ_D. The calculated K_{cr} is for a fixed τ_D. As a result, the system is more stable than indicated by the use of a fixed τ_D of 15 s at CO of 5.5 liter/min. Calculations show that

For CO = 13 l/min

$$K_{cr} = 1750 \text{ bpm} \cdot \text{liter blood/liter } O_2$$

For CO = 20 l/min

$$K_{cr} = 3935 \text{ bpm} \cdot \text{liter blood/liter } O_2.$$

The system open-loop response in the time domain is shown in Fig. 3(a) for work loads of up to 100 W. In this figure the simulation program must stabilize before work disturbances are introduced. The CO is seen to go up in the open-loop mode due to the Starling phenomenon which is included in the model. The oxygen saturation level goes down from 0.15 (75 percent) at rest to as low as 36 percent or 0.072 (liter O_2/liter blood) for a 100 W load. It should be noted that there is an initial rise in SO_2 after the application of the disturbance, not seen so well in the figure itself, which is due to $\tau_1 < \tau_3$, i.e., CO is increased before OXC starts to rise.

The Controller

The purpose of the controller is to maintain a desired tolerable SO_2 level in the mixed venous return with minimum demands from HR and CO which could guarantee this SO_2 level. At rest, the level of oxygen saturation in the venous return is about 0.15 liter O_2 in a liter of blood, i.e., about 75 percent. The controller is designed to work as a regulator about the 75 percent SO_2 level.

The difference between the 75 percent level and the oxygen saturation level measured is defined as the error in literO_2/liter blood

$$\epsilon_2 = 0.15 - SO_2. \tag{17}$$

A simple nonlinear element is introduced in the controller to limit the HR from falling below HR minimum and from exceeding a predetermined level of HR maximum. The HR_{min} is selected to be 62 bpm and the maximum permissible stimulation rate is set at $HR_{max} = 150$ bpm for the present simulation studies. However, it may be desirable in the future, to use a lower HR_{min} of approximately 50 bpm as these rates do certainly occur in healthy individuals at rest. HR_{max} can of course be adjusted to the individual patient's need.

Gain calculations: The controller gain is selected in accordance with stability considerations, and the required level of SO_2 at a given level of work load. From the following equations, the relationship between work load, steady state SO_2 error, ϵ_2, and the controller gain can be derived:

$$SO_2 = \frac{\mathrm{OXS} - \mathrm{OXC}}{\mathrm{CO}} \tag{18}$$

$$HR = (0.15 - SO_2):K \triangleq \epsilon \cdot K \tag{19}$$

$$CO = 5.47 + \frac{HR - 62}{6.2} = 5.47 + \frac{K \cdot \epsilon - 62}{6.2} \tag{20}$$

$$OXC = 0.267 + 0.0125 \times \text{power (in watts)}. \tag{21}$$

Equation (20) is the same (4) from the development of the model, (21) is (13) there, and (18) here is (15), all with the same notations.

From the above equations, the following relationship is obtained:

$$\epsilon^2 K + \epsilon(K \cdot 0.05 - 4.53) - (1.1185 + \text{power} \times 0.0125) = 0. \tag{22}$$

Thus, the gain necessary to achieve a desired SO_2 level with a given load can be determined.

For the present study it has been decided to require a 60 percent SO_2 level at 100 W work load. This is a rather high SO_2 level, and in reality a lower one is sufficient or rather more realistic. The above requirement yields relatively high-controller gain and a relatively stiff system which is interesting to study for its stability performance. A lower SO_2 level at 100 W load requires a lower controller gain but also maintains a lower SO_2 level. For each patient, the controller gain ought to be determined in accordance with his particular cardiovascular system performance and well being.

For the 60 percent SO_2 level at 100 W work load, the controller gain, as calculated from (22), using $\epsilon = 0.15 - 0.12 = 0.03$ is

$$K = 1043.$$

This gain is larger than the critical gain K_{cr} for a CO = 5.47 l/min as obtained before; however, it does not cause instabilities due to the reduction in τ_D. For the present simulation study, the gain has been selected to be

$$K = 1000 \text{ bpm} \cdot \text{liter blood/liter } O_2.$$

In order to improve the response time of the system, an additional derivative term has been added. This term, only 10 percent of the proportional term, is not critical and is visible only when the SO_2 falls rapidly. No integral term is used since it tends to bring SO_2 to the 75 percent rest level even under load, at the cost of almost always pushing the HR towards and above its 150 bpm limit. In the clinical experiments outlined later, the gain was selected to stay under the calculated critical value of $K \leq K_{cr} = 380$.

The closed-loop system response to step loads of up to 100 W, with the parameters at their nominal value, is shown in Fig. 3(b).

The regulating feature of the system is shown in Fig. 3 in comparing the closed and open-loop results of the SO_2 level after the application of the load. Note that for the first few tens of seconds—depending on the load—the CO is increased due to the Starling law, without an increase in HR—which does go up only after a drop in SO_2 is sensed by the controller.

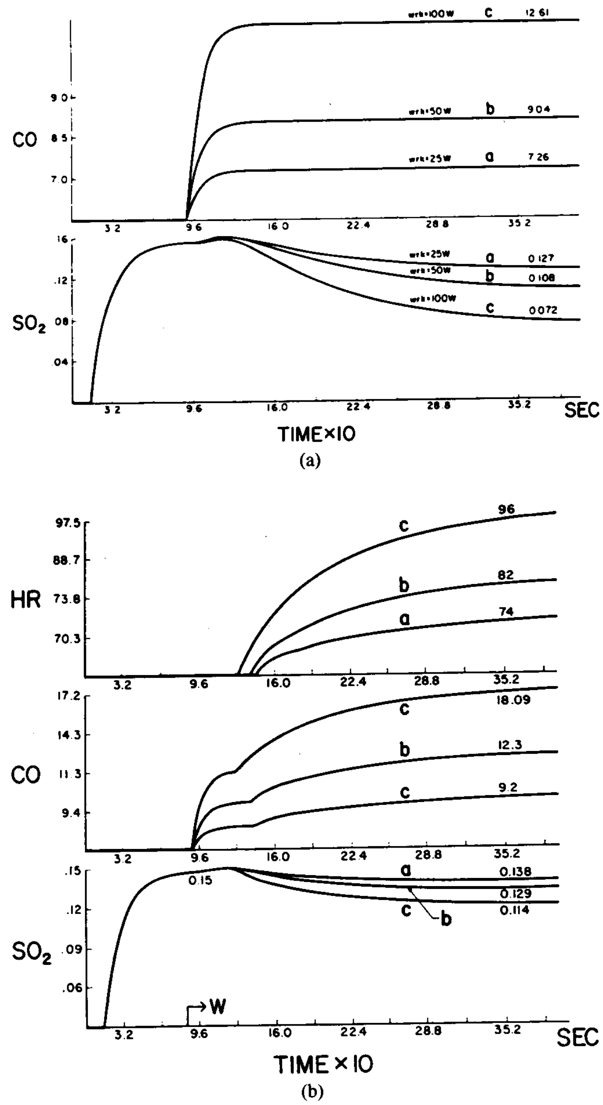

Fig. 3. Model system response to a step in work load: (a) open-loop mode, (b) closed-loop mode. Computer program stabilizes in less than 100 s. Work load applied 90 s from start of simulation time. HR in OL is 62 bpm throughout. The controller gain in the closed-loop mode is set to $K_c = 1000$ and $\tau_D = 5.5$ s. a = 25 W, b = 50 W, c = 100 W.

The reading from the sensor tends to fluctuate with body motion and catheter motion. In addition, instantaneous SO_2 regulation is prohibitive due to intracycle in addition to intercycle fluctuations. As a result, the sensor's readings are phase locked to the lowest value during a cardiac cycle and then averaged over a few cycles. Running averaging is equivalent to low-pass filtering and it therefore introduces an extra pole to loop transfer function. The result of this pole is a critical gain $K_{cr} = 275$, instead of $K_{cr} = 380$, for the rest case of CO = 5.47 l/min (and $K_{cr} = 2283$ instead of $K_{cr} = 3935$ for the CO = 20 l/min case).

To improve the stability, a lag-lead network has been introduced. While it increases the stability margins, it also slows down the response of the system which, as seen

TABLE I
STEADY STATE VALUES IN OPEN AND CLOSED-LOOP MODES FOR THREE LEVELS OF WORK LOAD

Work Load	HR bpm	CO liter/min	SO_2	Type of Control
25 W	62	7.26	63 percent	Open-Loop
25 W	74	9.2	69 percent	Closed-Loop
50 W	62	9.04	54 percent	Open-Loop
50 W	82	12.3	65 percent	Closed-Loop
100 W	62	12.61	36 percent	Open-Loop
100 W	96	18.09	57 percent	Closed-Loop

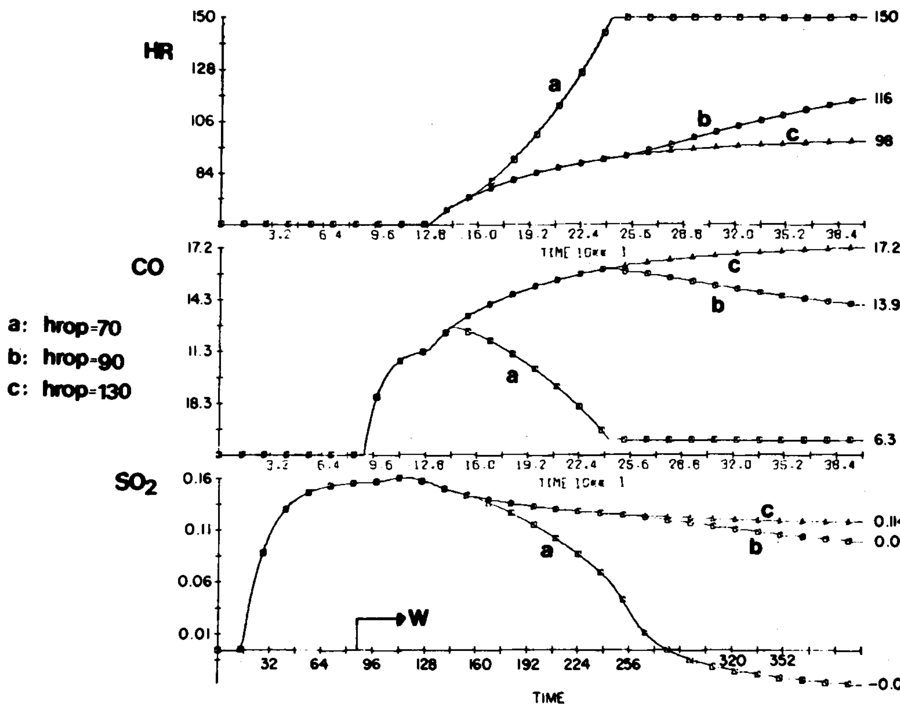

Fig. 4. The closed-loop system response to the application of a 100 W work load with HROP as a parameter. (a) HROP = 70 bpm, (b) HROP = 90 bpm, and (c) HROP = 130 bpm. Nominal value of the model parameters.

later in Fig. 6, is still faster than normal body response time.

In Table I, the steady state values of the SO_2 level, CO, and HR are listed in open and closed-loop modes for three levels of loading conditions. Sensitivity analysis of the present system is carried out in the Appendix. The system was simulated with 100 W ramp loads at 0.5, 1.0 and 2.0 W/s increase rate. It is well behaved under these conditions and HR, CO and SO_2 converge to the same steady state levels as with the 100 W step load. A sinusoidal loading at 0.0064 Hz give similar good results.

IV. The "Optimal" HR Problem

As explained in the introduction the CO is not a monotonic function of HR and above a certain frequency, HROP, an increase in HR causes a decrease in CO. When the system is required to reach higher HR than HROP the closed loop system will diverge to high HR and low CO. To demonstrate the above phenomenon the CO to HR gain above HROP has been selected to be half the negative value of this gain below HROP, i.e., $K_2 = -\frac{1}{2} K_1$, as is also shown in Fig. 2. In Fig. 4, the HROP is a parameter taking three values; HROP = 70, 90, or 130 bpm and the system response to a 100 W load is simulated. For HROP = 70 bpm, the HR goes rapidly up to its saturation level of 150 bpm and the SO_2 level goes to nonphysiological negative values. For HROP = 90 bpm, the general phenomenon is the same; however, it takes place at lower rates. For HROP = 130 bpm, the optimal frequency is not reached and the response is identical to the one shown in Fig. 3.

The HROP phenomenon is a destabilizing phenomenon which is difficult to overcome as HROP is not a stable frequency for an individual, changing with time and the patient's state of health. Even a fixed HROP is difficult to handle since a decrease in SO_2 as HR is increased can be the result of either an increase in work load or the result of HR > HROP. When no other parameter in the cardiovascular system is accessible for measurement—the SV being an ideal candidate—the only solution for the HROP problem is to examine SO_2 and HR behavior about this frequency. This is done in the following section.

Optimization

A method to overcome the problems generated by the HROP phenomenon, *and to improve system performance despite variations in the HR to CO gain characteristics is* outlined below. The method is based on continuous small HR perturbations while the SO_2 response is being monitored. For an increase of HR the normalized SO_2 response is measured. If the SO_2 exceeds a predetermined level it is interpreted that the heart is not working to its full capacity and a higher HR is "optimal." If the SO_2 response is below the preset level the HR is brought back to its original value and then a negative HR perturbation is applied, i.e., the HR is reduced by a preset level. If the SO_2 response, i.e., the amount of SO_2 decrease, is below a preset level, it is interpreted that the heart is being overpaced for the amount of improvement it generates in SO_2 and therefore a lower HR is "optimal." If the SO_2 reduction exceeds the preset level it is interpreted that the higher HR is desirable. This "optimization procedure" continuously monitors the above responses and the perturbations being applied every τ_{sec} regardless of the outcome. It should be clear that between perturbations the system operates with its conventional controller. The "optimization procedure" is turned on if the SO_2 fluctuations during a sampling interval τ_{sec} are smaller than a preset level. The amount of perturbation in HR has been selected to be ± 10 bpm, which is well within the normal HR fluctuations.

To implement the above optimization algorithm the following parameters are defined:

$$\text{(a) } A_2 = \frac{F}{\text{HR}} \times (SO_{2\max} - SO_{2\min}) \tag{23}$$

where F is a parameter to be selected for the individual patient.

For the present study $SO_{2\max} = 80$ percent or 0.16 l O_2/liter blood, $SO_{2\min} = 20$ percent or 0.04 l O_2/liter blood is the minimum SO_2 level which a patient can reach. These parameters can be fitted to each patient by monitoring SO_2 at rest and under a heavy load.

For $F = 4$ and HR = 60

$$A_2 = \frac{4}{60}(0.16 - 0.04) = 0.008 \text{ l } O_2/\text{liter bl}$$

i.e., 4 percent of the oxygen saturation level. This is the threshold for activating the optimization procedure.

$$\text{(b) } BS_1 = \frac{SO_{2\max} - SO_2}{SO_{2\max} - SO_{2\min}} \tag{24}$$

where BS_1 is a normalized value of the running ΔSO_2 reading.

$$BS_2 = BS_1(\tau_n) - BS_1(\tau_{n-1}) \tag{25}$$

BS_2 is ΔBS_1 in the nth interval.

(c) The sampling time τ can be selected as a function of the heart rate, being shorter at higher HR.

$$\tau = \sum_{i=1}^{k} \frac{1}{\text{HR}_i} \qquad i = 1 \cdots m - 1$$

and m is a parameter. For the present simulations τ has been selected to be 60 s and constant.

Operation

1) If the normalized SO_2 reading BS_2 in a time interval τ is smaller than A_2, then the "optimization procedure" is activated. This allows the system to reach a steady state before attempting to optimize.

2) If $A_2 > |BS_2|$ then the slope in HR, DHR is measured. If DHR > 0 a 10 bpm is added and BS_1 is measured after τ seconds. If $BS_2 > A_2$ the interpretation is that the increase in SO_2 is significant and the process is repeated up to three times. IF $BS_2 < A_2$ the interpretation is that the cost of increase in HR is too high compared with the improvement in SO_2 and the HR is brought back to its previous level.

3) If $A_2 > |BS_2|$ and DHR < 0 the process is repeated as in case 2 above but in the negative direction.

The simulation of the "optimization procedure" is shown in Fig. 5 for a 100 W load, $F = 4$ and HROP = 90. Below the level reached without optimization, the conventional controller pushes the HR to 134 bpm at 12.46 l/min and $SO_2 = 39$ percent. With the optimization the HR fluctuates between 93 ÷ 88 bpm at CO = 15.7 ÷ 14.9 l/min and $SO_2 = 51.5 \div 49$ percent an almost equal performance of the system with HROP = 150, i.e., without reaching the negative gain slope. Without the optimization and with HROP = 150, the system settles on CO = 18.09 l/min, HR = 96, and $SO_2 = 58$ percent, as outlined before.

V. Preliminary Clinical Tests

The system has been constructed using an Intel 80C39 microprocessor and tested in two ways.

1) Initially, experiments were carried out on young healthy volunteers in whom the SO_2 electrode was temporarily introduced via an arm vein. The SO_2, HR, temperature, and other parameters were measured while the subjects performed controlled work. The SO_2 measured was fed into the pacemaker controller which was run open-loop to compare its simulation frequency, driven by the SO_2, with the measured normal HR response of the subjects. Fig. 6 shows the results from such a test. The controller was tested, in all cases without the "optimization" routine. The tests showed very good "agreement" between the normal HR and the pacer frequency. A few features of the measurements should be noted: 1) The PMF

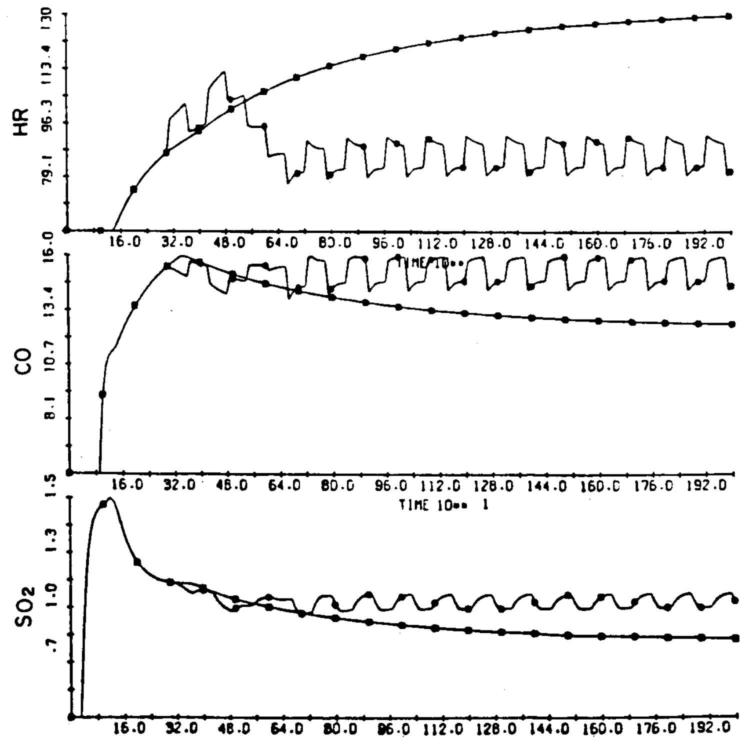

Fig. 5. Closed-loop system response with and without the "optimization procedure" to a 100 W step work load, HROP = 90 bpm and $F = 4.0$.

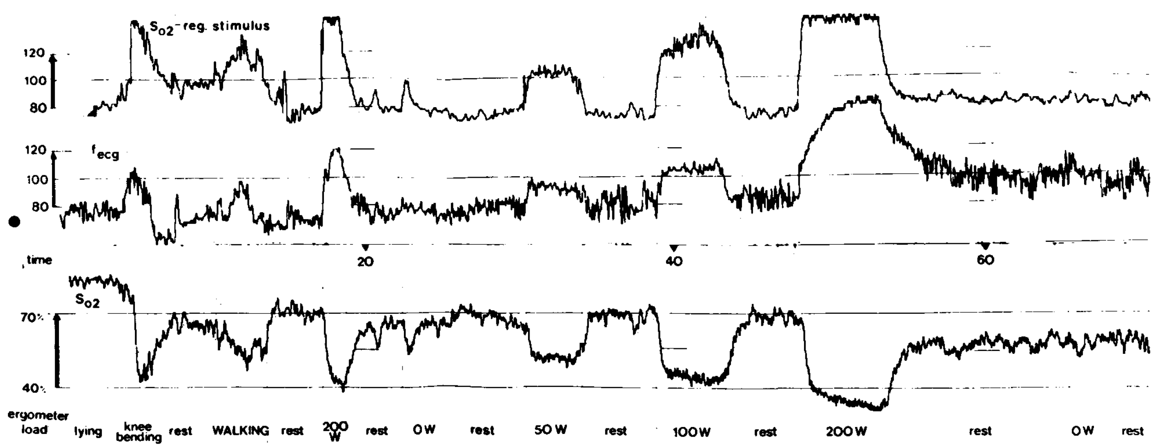

Fig. 6. Comparison between measured HR regulation in a normal subject (fecg) and the PM controller HR (SO_2 regular stimulus) driven by the measured SO_2.

(pacemaker frequency) rise time is faster than normal HR rise time in response to high loads. If clinically undesirable, this could be easily corrected by a leg-lead network in the feedforward path of the controller (a simple high pass). 2) The PMF fall-time is shorter than normal HR. A similar correction can be added. In both cases, the system response will slow down. 3) The PMF is saturated with 200 W loads. The PMF steady state response at all levels indicates a high controller gain which can easily be reduced. 4) The initial 200 W load is used to calibrate the system for maximal load performance where SO_2 is defined as having its minimum value. 5) Normal subjects show a decrease in HR with a fall in SO_2 after a long working period—for example, here at the end of the walking period and the period of 50 W load. This cannot be performed by the controller which increases the HR with a decrease in SO_2 level regardless of other factors. 6) The controller gain in this and the next experiment was always below the $K_{cr} = 380$ value obtained in the simulations of the model.

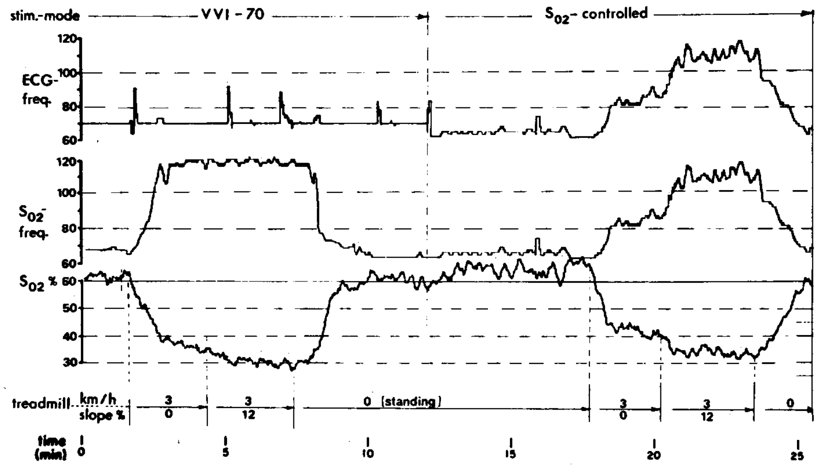

Fig. 7. Comparison between a patient's open-loop VVI response and his response with the new closed-loop controller without the optimization procedure.

The open-loop experiments were performed on ten healthy volunteers with normal cardiac function. The results in Fig. 6 are characteristic of these experiments. These results led us to undertake the closed-loop experiments performed on patients with an implanted pacemaker.

2) A patient with a chronically implanted VVI pacemaker was temporarily provided with a sensing catheter and the pacemaker was controlled either in the fixed frequency mode of the implanted unit or externally through the new sensor controller system. Results from such an experiment, *which is a truly closed-loop exercise responsive pacing experiment*, are shown in Fig. 7. In that figure, SO_2 is shown in response to a two stage treadmill walking experiment, with both a fixed rate stimulation and in the closed-loop SO_2 controlled mode.

In the first part of the experiment, the subject starts walking from a standing position with his VVI system pacing at 70/min. In the upper trace-ECG frequency occasional extrasystoles can be seen. The new pacemaker controller HR, in open-loop (i.e., not operating or rather not influencing the heart rate), is shown in the middle trace where it is seen to saturate already at the 3 km/h zero slope load. At the lower trace the measured level of SO_2 is displayed.

After a resting period in a standing position, the new controller is switched on, as marked in the figure. While the patient continues standing the controller HR stimulation frequency goes down and the SO_2 level rises. The controller frequency drops to 61 bpm before the walking experiment is repeated.

As the SO_2 level goes down with exercise the controller stimulation frequency goes up to about 85 bpm at the zero slope 3 km/h load level. The SO_2 level with the new controller, at this work load, stabilizes at about 40 versus 35 percent and falling SO_2 level in the constant frequency mode. After 2.5 min the load is increased by tilting the treadmill to 12 percent. In the closed-loop mode, the SO_2 level quickly stabilizes at about 34 percent while the HR goes up to about 107 bpm. In the constant frequency stimulation mode, the SO_2 falls below 30 percent.

Four additional patients were stimulated by the pacemaker via the external lead to achieve a truly closed-loop control of the pacing rate. Three patients had AV block III and one was with bradyarrhythmia. The results were reported in [18], [28] and they are summarized below in relation to the system performance and the model predictions.

All three AV block III patients—ages 58, 62, and 67 years—improved their exercise tolerance ability by 35 to 45 W—from 75 to 120 W, from 80 to 125 W, and from 125 W to 160 W, respectively—when using the closed-loop SO_2 pacemaker controller as compared with their constant 70 bpm VVI pacing rate. In the bradyarrhythmia, a female patient age 76 years and poor myocardial function, there was no difference between the two pacing modes and no improvement was detected.

The time delay in the closed-loop system response to load was between 5–8 s and the recovery time 5–15 s depending on load and patients. The time constants for reaching steady state were 15–25 s and not sensitive to load. These numbers are well within the range of the assumed parameters of the model presented.

Discussion

A closed-loop, SO_2 sensing and regulating, pacemaker controller design is presented together with its performance in preliminary clinical experiments. To facilitate the design a simplified first order approximation model is presented in order to relate cardiac output to heart rate and mechanical work performed by the patients. More complex models are needed to better describe the physiological systems; however, they are not needed for the present task.

The model can be used under the above restricted conditions since many of the details of the system are smoothed out in the closed loop system. The highly nonlinear gains involved and the distributed components effects are being averaged out. Stability performance can be studied as long as the linearized assumed gain is higher than the peak nonlinear system gain. The model limitations, however, affect its range of validity. System response to high loads must be avoided since second order time constants and hard gain limits become evident and influence the simulation results.

Patients can expect not to perform very heavy loads, although they may reach saturation gain limitations faster than healthy subjects which will limit the benefit of ther closed loop controller as shown by the bradyarrhythmic patient. It is also clear from (14) that the model represents a good approximation of the system only under steady state conditions or slowly applied loads—valid for patients use.

The controller design was tested on few patients to indicate that it is indeed a viable system to improve the hemodynamic performance of certain patients, especially those that are physically capable and without myocardial disease. It is also evident that access to measurement of another of the cardiovascular variables can considerably improve pacemaker design. Knowledge of cardiac output is essential to better regulate heart rate on demand—the optimization procedure proposed being an interim solution. SO_2 proved to be a viable parameter to sense and to regulate because of its quick response to loads and its high sensitivity at low load levels—the daily loads to be encountered by patients. At high loads, measurements of additional variables, like temperature, may improve controller and system response.

To validate the performance and benefits of the SO_2 regulated pacemaker controller, its use under daily life is required. Such tests are currently being planned with a new implantable version.

Appendix A: Sensitivity Analysis

A pacemaker is supposed to control the HR of a person during prolonged periods of time when his parameters undergo very large variations. The variations are of two kinds. The long term variations, like changes in the general status of the subject, aging, training, etc., and short term variations that take place during the performance of a single task. The long term variations can be compensated for by routine medical check-ups, or by more complex adaptive controllers [3]. Short-term variations must be compensated for by the controller, be it a regulator or an adaptive controller.

To verify that this is indeed the case, that the system is robust and stable under the possible physiological parameter variations, a sensitivity analysis is carried out on the model. Two different types of analysis were carried out:

Simulation: In this method the system is simulated with the nominal parameter values and one parameter at a time is changed, assigned the two most extreme values it could attain according to the published literature. HR, SO_2, and CO were checked under these conditions.

Analytical Analysis: Two transfer functions were defined:

$$1)\ T_1 = \frac{SO_2}{SO_{2\mathrm{ref}}}(S). \tag{A-1}$$

This is the venous oxygen saturation level as compared with its desired level.

$$2)\ T_2 = \frac{SO_2}{OXC}(S). \tag{A-2}$$

This is the venous oxygen saturation level as a function of oxygen consumption.

For the above two transfer functions (TF), the sensitivity to variations of the plant parameters have been calculated. The sensitivity is calculated in steady state with the nominal value of the parameters.

$$\begin{aligned} T_1(S) &= \frac{\dfrac{K_C \cdot K_H \cdot K_{SO_2} \cdot e^{-S\tau_D}}{CO(1+S\tau_2)}}{1+\dfrac{K_C \cdot K_H \cdot K_{SO_2} \cdot e^{-S\tau_D}}{CO(1+S\tau_2)}} \\ &= \frac{K_C \cdot K_H \cdot K_{SO_2} \cdot e^{-S\tau_D}}{CO(1+S\tau_2) + K_C \cdot K_H \cdot K_{SO_2} \cdot e^{-S\tau_D}}. \end{aligned} \tag{A-3}$$

The nominal value of the parameters

$$K_C = 1000\,\frac{\text{bpm}}{\text{liter } O_2/\text{liter bl}} \qquad \tau_D = 15\ \text{s}$$

$$K_H = 0.16\,\frac{\text{liter bl./min}}{\text{bpm}} \qquad \tau_2 = 15\ \text{s}$$

$$K_{SO_2} = 0.2\ \text{liter } O_2/\text{liter bl} \qquad CO = 12.5\ \text{l/min}$$

for a 50 W load for which the sensitivity has been calculated. In a similar way, and after some simple algebraic manipulations, $T_2(S)$ can be brought to the following form:

$$T_2(S) = \frac{e^{-S\tau_D}}{CO(1+S\tau_2) + K_C \cdot K_H \cdot K_{SO_2} \cdot e^{-S\tau_D}}. \tag{A-4}$$

The normalized sensitivity is defined as

$$S_\alpha^T = \frac{dT/T}{d\alpha/\alpha} = \frac{dT}{d\alpha}\cdot\frac{\alpha}{T} \tag{A-5}$$

the sensitivity of the transfer function T to changes in the parameter α, i.e., if X percent change in the parameter α causes X percent change in the transfer function the sensitivity is 1.0.

Parameters Outside the Loop: The sensitivity is clearly always one, independent of the loop gain and the controller design. For example, the transfer function between work and SO_2 can be defined as

$$Y(S) = \frac{SO_2}{\text{work}} \triangleq K \cdot F(s) \tag{A-6}$$

TABLE II
12 HR, CO, AND SO_2 VARIATIONS AND SENSITIVITY TO CHANGES IN THE SYSTEM PARAMETERS

Tested Parameter	Parameter Variations	HR Variations	HR Sensitivity	CO Variations	CO Sensitivity	SO_2 Variations	SO_2 Sensitivity
K_1	0.01035 ÷ 0.0166	78 ÷ 90	0.297	11.6 ÷ 13.6	0.322	0.122 ÷ 0.134	−0.188
K_{14}	1/7 ÷ 1/35	76 ÷ 89	0.057	11.3 ÷ 13.7	−0.054	0.123 ÷ 0.136	−0.036
ΔCO_{sat}	3 ÷ 6	80 ÷ 88	0.147	11.9 ÷ 13.2	0.147	0.124 ÷ 0.132	−0.093
K_H	0.13 ÷ 0.19	81 ÷ 84	−0.069	12 ÷ 12.6	0.14	0.127 ÷ 0.131	0.133
CO_0	4.5 ÷ 6.5	80 ÷ 85	−0.20	11.8 ÷ 12.9	0.259	0.127 ÷ 0.132	0.082
$^*CO_0$	4.5 ÷ 6.5			8.1 ÷ 10.1	0.649	0.093 ÷ 0.114	0.511
K_{SO_2}	0.19 ÷ 0.20	83 ÷ 88	−1.136	12.3 ÷ 13.2	−1.463	0.124 ÷ 0.129	0.775
$^*K_{SO_2}$	0.19 ÷ 0.20					0.094 ÷ 0.104	1.923

*Open Loop

where K is the gain—in the present model it can be K_1 or K_{14}—and $F(S)$ is independent of K.

The sensitivity

$$S_K^Y = \frac{dY}{dK} \cdot \frac{K}{Y} = \frac{F(S) \cdot K}{K \cdot F(S)} \equiv 1. \qquad \text{(A-7)}$$

Despite the above statements concerning the sensitivity of the system to parameters outside the loop and due to the nonlinearities, mainly the division by CO, and dual effects of load on OXC and on CO, changes in K_1, K_{14} and the time constants τ_1 and τ_3 have smaller effects on the overall system performance than expected—a stabilizing effect. Similar desensitizing effects of the closed-loop system have been observed for changes in OXC_0-oxygen consumption at rest—and in the limit imposed on the ΔCO_{sat} as a function of work. The time constant variations in τ_1 and τ_3 did change the transient response of the system but did not affect the stability or the overall regulating characteristics of the system.

Parameters Inside the Closed-Loop: Sensitivity to variations in K_H— the linear cardiac gain relating CO to HR. From (A-3), the sensitivity to K_H is

$$S_{K_H}^{T_1} = \frac{1}{\dfrac{1 + K_H \cdot K_C \cdot K_{SO_2} \cdot e^{-S\tau_D}}{CO(1 + S\tau_2)}} \qquad \text{(A-8)}$$

and in steady state $t \to \infty$ and at 50 W work load

$$S_{K_H}^{T_1} = \frac{CO}{CO + K_H \cdot K_C \cdot K_{SO_2}} = 0.28. \qquad \text{(A-9)}$$

The sensitivity at rest, with CO = 5.5 1/min

$$S_{K_H}^{T_1} = 0.147 \qquad \text{(A-10)}$$

and with 100 W and CO = 18 1/min the sensitivity is 0.36.

The sensitivity of the TF between OXC and SO_2 is from (A-4):

$$S_{K_H}^{T_2} = \frac{1}{1 + \dfrac{CO(1 + S\tau_2)}{K_H \cdot K_C \cdot K_{SO_2} \cdot e^{-S\tau_D}}} \qquad \text{(A-11)}$$

and in steady state it varies between −0.64 ./. −0.85 for work loads ranging from rest, CO = 5.5 1/min, to 100W, CO = 18 1/min.

From the simulations the following results have been obtained in steady state, summarized in Table II.

Except where noted Table II is for the closed-loop case. Sensitivity is defined as the normalized variations in the measured variable divided by the normalized variations of the tested parameter. OXC_{sat}—the saturated level for additional CO from work load. CO_0—CO at rest. The sensitivity to changes in time constant τ_2 and the delay τ_D have been simulated. In steady state they clearly have no effect as long as the system is stable. τ_2 and τ_D were varied independently from 7.5 to 30 s. Steady state solutions have not changed, the system remained stable and transient responses changed slightly.

The foregoing sensitivity analysis demonstrates that a closed-loop controller not only regulates against SO_2 variations with load—a truly exercise responsive pacemaker system—but is more robust and less sensitive to changes in the patient paramters.

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