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Short-term cardiovascular effects of mental tasks

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

1998

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Roon, A. M. V. (1998). *Short-term cardiovascular effects of mental tasks: physiology, experiments and computer simulations*. s.n.

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In our study, the underlying psychophysiological explanation for the commonly observed cardiovascular effects during mental task performance is the defence reaction. However, the defence reaction as underlying mechanism for the short-term cardiovascular effects of mental load is not enough. There is evidence from experiments (LIV, no modulus change in some cases, autonomic blockade experiments) and simulations (G_v and G_s do not explain all experimental changes) that there is another mechanism that increases heart rate and blood pressure as an effect of mental load. This NTS by-pass reaction changes the autonomic activations directly, and not by inhibition of the NTS. The defence reaction is related to the mental effort that is required for the task performance, while we think that the NTS by-pass is more related to stressors like additional noise and preparation of the subject. About the same division has been made in the emotional motor system, where the lateral part is involved in the defence reaction, and the medial part is a level setting system (which influences the RVLM directly).

The autonomic blockade experiment showed that the vagal system is mainly involved in task effects on IBI and modulus in the mid frequency band, while the β -sympathetic system is more important for the blood pressure task effects. Both systems play an important role in establishing heart rate and blood pressure variability effects.

We could improve the simulation of the vagal blockade by an additional effect on systemic vascular resistance. We think that this effect can be an explanation for the different effects on heart rate with low and high doses of atropine.

Future applications of the model are, for example, simulation of evoked heart rate and blood pressure responses or simulation of other medications. Simulation of the experimental data of one single subject is an important factor for a number of applications. This requires, however, a major change in the estimation procedure and/or the experimental design.

We conclude that in the research on the effects of mental load, the study of the mechanisms involved is the most important. The situation is similar to the study of mechanisms involved in pharmacological interventions (for example, administration of atropine, β -blockers or imipramine), where several mechanisms can be involved. The model simulations of mean and spectral measures of heart rate and blood pressure can help to unravel the mechanisms that are involved.

Chapter 7: General discussion

7.1 Psychophysiological effects of mental task performance

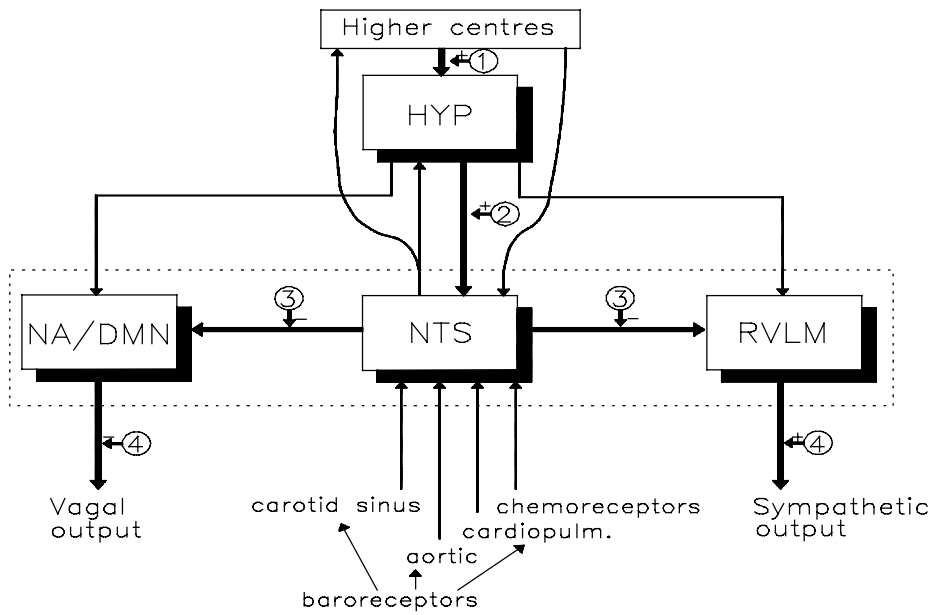
7.1.1 Mechanisms of cardiovascular control

In our study, the underlying psychophysiological explanation for the commonly observed cardiovascular effects during mental task performance is the defence reaction. This reaction causes an increase in heart rate and blood pressure and a decrease in heart rate variability and baroreflex sensitivity (BRS). In many cases, this mechanism is sufficient to explain and to simulate the observed cardiovascular effects. However, in cases that do not show a BRS decrease in response to mental load, but do show the increase in heart rate and blood pressure and a decrease in variability (HRV and BPV), the defence reaction cannot be the (full) explanation.

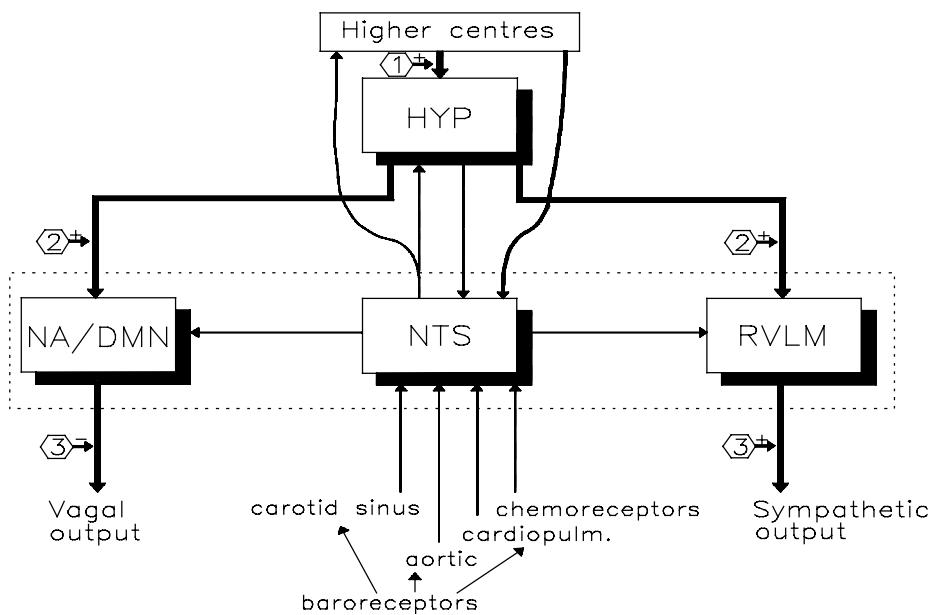
Firstly, we will show the sequence of a defence reaction and the involvement of the cardiovascular control centre. In this reaction, the Nucleus Tractus Solitarii (NTS) plays a central role. Then, we will summarize the evidence from experimental and simulated data that the defence reaction is not always sufficient to explain the results. Therefore, a possible second mechanism is presented, which affects autonomic activation without involving the NTS. This mechanism is called the NTS by-pass.

In figure 7.1.1a, the sequence of effects of the defence reaction is shown and is indicated by circles with numbers. The signs indicate whether there is an increase (+) or decrease (-) in activity. The higher centres start the sequence by an increase in activation at ①. The hypothalamus influences the NTS via ② and this changes the vagal and sympathetic system ③ in such a way that blood pressure increases. This occurs by means of an increase in heart rate, mainly via a decrease in vagal activation ④ and/or by means of an increase in systemic resistance via an increase in sympathetic activation ④ (Mulder, 1980; Spyer, 1990).

The hypothalamic output ② inhibits NTS outputs ③. This results in a decrease in baroreflex gain (Manning, 1977; Mulder, 1980; Jordan, 1990; Spyer, 1981, 1990; Berntson, 1991, 1993). The gain decrease in response to mental task performance at the level of the NTS is the basic assumption about the origin of cardiovascular effects of mental load in this study. This gain decrease is measured as a reduction of BRS (modulus in the mid frequency band).



a)



b)

Figure 7.1.1: Two scenarios (mechanisms) for the influence of mental task performance on the cardiovascular control centre: a) the defence reaction b) the NTS by-pass reaction. Numbers indicate the effect sequence, signs the direction of change in activity. DMN= Dorsal Motor Nucleus, HYP= Hypothalamus, NA= Nucleus Ambiguus, NTS= Nucleus Tractus Solitarii, RVLM= Rostral Ventrolateral Medulla.

We estimated the gain decrease by means of model simulations of the cardiovascular system. We estimated the vagal (G_v) and sympathetic (G_s) gain changes for the mental load effects in six experiments. In general, simulations of the defence reaction show most experimentally observed effects. Therefore, most experimental effects can be simulated simply by a change in baroreflex gain. However, there is evidence that mechanisms other than the defence reaction are involved. Summarizing:

- Experimental task effects appear without modulus change (Exp. 2, 3, 6), whereas the simulated modulus decreases when task effects are simulated by a gain decrease in the model. This means that another mechanism has to be involved in task effects.
- The Law of Initial Values is true for the (transformed) modulus in the mid frequency band (section 5.3.4). This means that there is a limited decrease in the modulus as a result of mental load. A cardiovascular reaction to mental tasks at low modulus values (for example Exp. 3) requires another mechanism.
- The findings of the blockade study show remarkable results that require another mechanism to explain task effects. Task effects on HRV, and BPV remain the same after vagal blockade without a modulus effect. Secondly, task effects on blood pressure, HRV, and BPV are changed by β -sympathetic blockade but the effects on the modulus were the same before and after blockade.

We conclude from these findings that other mechanisms are involved. A possible scenario is indicated in figure 7.1.1b, by means of numbers in hexagons. The Nucleus Ambiguus and the Rostral Ventral Medulla are now directly influenced by the hypothalamus (2). We will call this the NTS by-pass reaction. These pathways are also described in the literature (see figure 2.3.4) and an extreme example is the frontocortical-brainstem pathway of Skinner (1985, 1988). This is a direct influence of the frontal cortex on sympathetic activation to the heart.

The direction of the effect on vagal and sympathetic output (3) is the same as during a defence reaction, but now the gain decrease is not present. In the cardiovascular control centre, another path from the hypothalamus, the NTS by-pass, is supposed to be involved in the required changes. A major question to investigate is whether this NTS by-pass is active at all times but overshadowed normally by the defence reaction, or only becomes active when the defence reaction is no longer effective.

From the model point-of-view, the NTS by-pass reaction is a change in the basic level of autonomic activation ($D_{F,vag}$ and $D_{F,sym}$ in figure 3.3.3). From the differences in the effects of vagal gain and basic level changes (section 4.3.2), we know that complex relations can be expected. Therefore, a further detailed analysis of gain and basic level changes in the vagal and sympathetic systems is required to understand the implication for the cardiovascular effects of such a manipulation.

Reducing the gains, G_v and G_s , is a more effective way to establish a blood pressure increase than adaptation of the basic levels. The changes in the basic level $D_{F,vag}$ must be larger than the changes in gain G_v for the same effect on blood pressure. For instance, the blood pressure increase induced by a vagal gain decrease of 40% can only be obtained by a 80% decrease in vagal basic level (see figure 4.3.7a). This shows that the defence reaction, and thus an autonomic gain decrease, is an effective way of increasing blood pressure.

However, the defence reaction can become hazardous if the gain is reduced below a certain level. A lower limit for the modulus can then be a protection for the regulation. A very small modulus means poor regulation. For instance, patients with impaired autonomic function (and thus very low modulus, see section 6.3), are known to suffer from orthostatic hypotension (Man in 't Veld, 1988; Low, 1993; Schondorf, 1993; Tulen, 1996). Fortunately, the mental load in our studies cannot lead to such a situation.

7.1.2 Relation with psychophysiological concepts

The two mechanisms of changes in cardiovascular control can be of importance for understanding psychophysiological concepts as 'effort' (Mulder, G, 1986) and 'modes of autonomic control' (Berntson, 1991).

Effort

Mulder, G. (1986) defines two types of effort: one related to the difficulty of the task and the other related to maintaining a certain psychophysiological state. The effort related to task difficulty is, for instance, influenced by memory set size, inter-stimulus interval etc. (most task elements in table 5.3.1). The second type of effort is more related to stress factors like additional noise during task performance or sleep deprivation. Incentives like rewards for better performance can also produce different states prior to or during the task. We assumed that the first type of effort evokes a defence reaction and the corresponding cardiovascular responses by NTS inhibition. It would be of interest to know whether the second type of effort is effected either via the NTS or via the NTS by-pass. The emotional motor system (EMS), as introduced by Holstege (1992, 1996, 1997) can be decisive here. The EMS is divided into a lateral and a medial part. The lateral part is involved in specific emotional behaviour and includes the periaqueductal gray matter (PAG) and NTS. The PAG is involved in mediating the defence responses (Nosaka, 1993; Holstege, 1997). The medial part is mainly "a level-setting system which regulates the excitability of the midbrain defence area" (from Holstege, 1996, chapter 18). This part consist of raphe nuclei that influence the RVLN directly, rather than through the NTS (Holstege, 1997). If we connect the first type of effort with the lateral

EMS and the second type with the medial EMS, the second type of effort is more likely to result in cardiovascular effects via the NTS by-pass. Experiments especially designed for this research question could possibly resolve this question if combined with simulations. Study 2 is in fact such an experiment, containing additional noise conditions and probably another kind of preparation by the subject for long-lasting tasks compared to the normal five minutes tasks). New simulations with level parameter estimates besides the gains can be used to test this hypothesis. We expect further that the level parameters must be changed also to simulate the baseline measurements, because of the different preparation of the subjects for long lasting experiments compared to shorter ones (This also applies to experiment 4).

Mode of autonomic control

Since the publication of an extensive review of the different modes of autonomic control (Berntson, 1991), the question has been raised by several investigators: "Are these modes of autonomic control also present in the model?". Of course, they have to be, but this may require some explanation. Additionally, the question is whether the two mechanisms, defence reaction and NTS by-pass, differ in their mode of autonomic control or not.

The control of heart rate is subdivided into a sympathetic and vagal (parasympathetic) part. The activation of these two parts is combined in the sinoatrial node and results in a certain heart rate. An increase in vagal activation decreases heart rate, an increase in sympathetic activation increases heart rate. These relations are present in the model, and that is basically sufficient to model the different modes of control.

The control of heart rate is effected by changes in these activations. The modes of autonomic control reflect these changes, while there is no direct relation with the structure of the autonomic system. Berntson (1991) distinguishes nine modes of control (table 7.1.1). The usual mode for heart rate control is the reciprocal mode and this mode has resulted in the general view on the sympathetic and vagal system as two antagonistic systems. However, essentially different modes of control are related to different points of impact of the changes in the cardiovascular system. We will discuss some examples now.

Blood pressure variations change the levels of autonomic activation continuously via the baroreflex. Baroreceptor output changes result in reciprocal modes of control. For *Table 7.1.1: Modes of autonomic control (Berntson, 1991)*

		Vagal response	
		Increase	Decrease
Sympathetic	Increase	No change	Decrease

response

Increase	Coactivation	Uncoupled sympathetic activation	Reciprocal sympathetic activation
No Change	Uncoupled vagal activation	Baseline	Uncoupled vagal withdrawal
Decrease	Reciprocal vagal activation	Uncoupled sympathetic withdrawal	Coinhibition

instance, a blood pressure increase results in reciprocal vagal activation, since a rise in blood pressure results in decreased sympathetic activation and increased vagal activation. Both systems work together in order to decrease blood pressure.

However, a decrease in vagal influence on the heart caused by a pharmacological intervention results in a heart rate increase and consequently in a small blood pressure increase. The blood pressure increase is reduced by a regulatory action of the sympathetic system. Effectively, this action is a decrease in sympathetic activation and therefore the mode of control is coinhibition.

The frontocortical-brainstem pathway of Skinner (1988) can change the sympathetic activation to the heart directly. If this pathway becomes active alone or dominates a response, it will result in an increase in heart rate and stroke volume (by an elastance decrease). The increased blood pressure will be reduced by a regulatory action that will increase vagal activation. Therefore, the mode of control is coactivation. This is in good agreement with Skinner’s ideas about cardiovascular vulnerability of dual autonomic control (Skinner, 1985; see section 1.1).

Another example is the decrease in baroreflex gain, as found in the defence reaction, which causes a reciprocal mode of control (reciprocal sympathetic activation),

Table 7.1.2: Occurrence of modes of autonomic control of the heart with intact baroreflex (for mode name, see table 7.1.1)

	Vagal response		
Sympathetic response	Increase	No change	Decrease

Increase	Inside one of the branches Skinner,1985	Never	Outside the branches BP decrease
No Change	Never	Baseline	Never
Decrease	Outside the branches BP increase	Never	Inside one of the branches Autonomic block.

resulting in an increased blood pressure. Here lies the solution for Anderson's observation* (Anderson, 1991; section 1.3). Phenylephrine injection increases blood pressure by an increase in systemic resistance. The baroreflex reacts with reciprocal vagal activation. Mental load results in reciprocal sympathetic activation (see 7.1.1). In these examples, the points of impact (the origin of the blood pressure increase) and sympathetic changes are different and this results in different modes of control.

The mode of autonomic control of heart rate can easily be determined from the following rules for a given change in the system (see table 7.1.2):

- Within the heart rate effector (vagal or sympathetic): coactivation or coinhibition.
- Outside the heart rate effector: reciprocal activation.
- In a fully intact baroreflex, uncoupled modes will never occur.

Therefore, it is possible that the same mode of control is present with a different cause (point of impact). The case of G_v or C_v change are examples: They do not differ in mode of control, since F_{vag} and F_{sym} change in the same way (see figure 4.3.5). A G_v or C_v decrease results in coinhibition. These kinds of changes cannot be distinguished by this approach of Berntson (1991), but they do have distinct effects on spectral measures!

In the case of a mental load effect, we have to deal with two changes in stead of one: both vagal and sympathetic systems are changed. We have argued above that the mode of control during a defence reaction is reciprocal sympathetic activation. Since the NTS by-pass will result in the same blood pressure and heart rate effects, we must assume that the mode of control is the same, but only when both vagal and sympathetic NTS by-pass appear at the same time or in combination with a defence reaction. We conclude,

*Anderson's observation:"...However, although mental stress increases blood pressure, it also increases MSNA..." (MSNA=Muscle Sympathetic Nerve Activity), and "...In contrast, increases in arterial pressure caused by phenylephrine can reduce MSNA..."

therefore, that the two mechanisms do not differ in their mode of control.

The modes of control have limited use for evaluating changes in the cardiovascular system. Many changes in the cardiovascular system result in the same mode while the mechanism that caused the changes may be very different. Spectral measures of heart rate and blood pressure, combined with simulations, give a much better insight into the changes within the cardiovascular system than do the modes of control.

7.2 Spectral analysis

In this section, we will discuss three topics concerning psychophysiological research and spectral measures:

- Is the mid frequency band of heart rate (0.1 Hz component) an adequate measure of mental effort?
- Is the high frequency band of heart rate, or RSA, a good vagal index?
- Is the ratio of mid and high frequency power of heart rate a good sympathetic index?

The power in the mid frequency band of heart rate is often used as an index of mental effort: A larger decrease in power compared to the baseline indicates greater effort (see 1.2). The power in the mid frequency band of heart rate also shows a decrease when the vagal and/or sympathetic gains are reduced to simulate the effects of mental load in the model (see figure 4.3.2). A larger decrease in gain results in a larger decrease in power. A vagal as well as a sympathetic gain decrease results in a decrease of the 0.1 Hz component; we think that this finding is a reason for the 0.1 Hz component to decrease in so many cases. However, we have shown in section 7.1 that the gain change cannot be the only explanation for the cardiovascular effects of mental task performance and that the two types of effort have different effects on the cardiovascular system. The 0.1 Hz component of heart rate is thus not enough to measure the effects of mental load in every situation, since gain and basic level changes have opposite effects on this component. The simulations, presented in figure 4.3.7, showed that this differential effect does not appear in the high frequency band of heart rate. Then, RSA, or the power in the high frequency band of heart rate could be a better index, but it is insensitive to sympathetic gain changes. However, if RSA is used as an index of mental effort, respiration should not be affected by mental task performance. Unfortunately, in all experiments except one, respiratory frequency did change. Neither respiratory amplitude nor pattern has yet been evaluated, but they may also be changed. Therefore, the autonomic effects of mental load can be mixed up with respiratory effects. If respiration is unchanged, the high frequency band of heart rate, or RSA, is a good index of vagal activation.

A method described in literature (Pagani, 1986; 1991) to construct an index of sympathetic activation using spectral measures, is the ratio of the power in the mid frequency band and high frequency band of heart rate (see section 4.4.3). The idea is that the mid frequency band is effected by both vagal and sympathetic systems and the high frequency band only by the vagal system. Using the ratio, the mid frequency band is supposed to be compensated for vagal influences. However, simulations show that the power ratio is sensitive to differences in mechanism of vagal changes. In figure 7.2.1a, the sympathetic activation is shown for changes in gain (G_v) and basic level (C_v), see also figure 4.3.5b. The power ratio for these simulations is shown in figure 7.2.1b. The effects of C_v and G_v on the sympathetic activation are the same. The ratio is changed by C_v changes, but hardly affected by G_v changes.

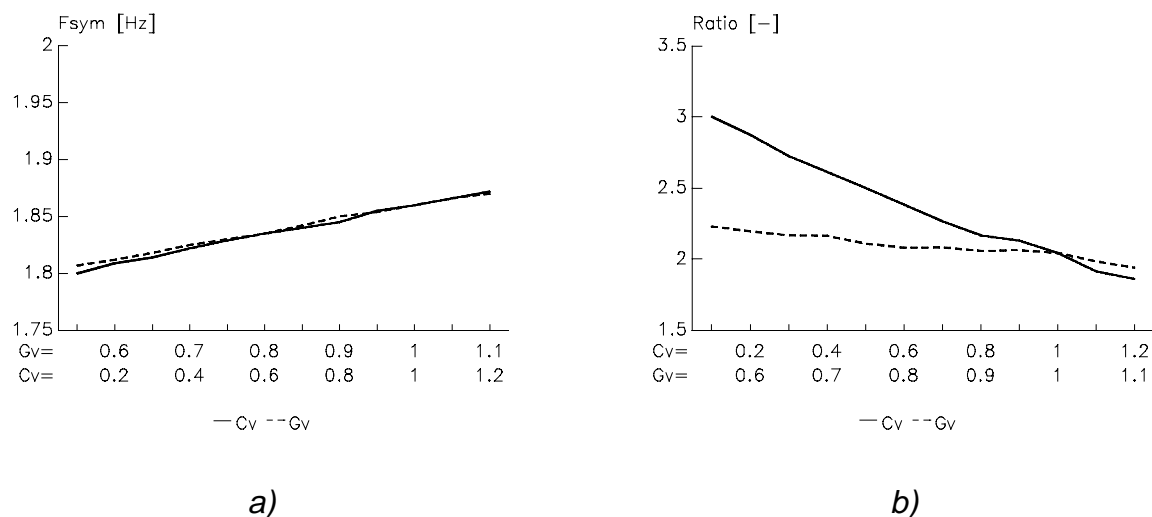


Figure 7.2.1: Effect of changes in C_v or G_v for a) Sympathetic firing rate and b) Heart rate power ratio (power mid frequency band/power high frequency band).

For measuring effects of mental load, assuming a defence reaction, the mid frequency band itself is more sensitive than the power ratio. By dividing the power of the mid frequency band by the power of the high frequency band, the ratio depends on respiratory changes, which is not desirable.

We conclude that a defence reaction can be supposed to be the underlying mechanism if

- heart rate and blood pressure increase
- the mid as well as high frequency band of heart rate decrease and
- the modulus in the mid frequency band decreases
- while respiration is hardly changed.

In that case, the amount of the decrease will be related to the intensity of the reaction and thus of the mental load. In other cases, the use of spectral measures in combination

with simulations can help to resolve the meaning of the measured changes.

7.3 Blockade of the autonomic nervous system

An experiment was performed to evaluate the contributions of vagal and β -sympathetic parts of the autonomic system to mental load effects in heart rate and blood pressure. This was investigated by pharmacological blockade of one of these parts with an intravenously administered blocking agent. The effects of the blockades on cardiovascular baseline values were also studied, but we will start with the changes on the effects of mental load caused by vagal or β -sympathetic blockade.

Vagal blockade resulted in a significant change of the task effects on IBI, the low frequency band of blood pressure, and the mid frequency band of the modulus. Effects on IBI and modulus disappeared. Effects on heart rate variability were smaller while effects on blood pressure variability increased. Blood pressure effects were slightly smaller. The results suggest that the vagal system does not solely determine the task effects on variability measures, but that the sympathetic system is involved as well. The sympathetic system is able to influence the changes in blood pressure without large modulus and IBI changes. The simulations show that the change of the sympathetic gain is somewhat smaller after blockade than before ($G_s=0.74$ after vs. $G_s=0.78$ before). However, the effect on blood pressure of task performance is not significantly different in this experiment, meaning that the blood pressure can be changed more easily in the blocked state (a smaller sympathetic gain reduction is required). This is in agreement with the 'loss of control' that occurs during the vagal blockade. Under normal circumstances, this 'loss of control' is partly achieved by a reduction in baroreflex gain in the vagal part, as measured by the modulus reduction.

The β -sympathetic blockade resulted in a decreased effect of mental load on blood pressure. The effect on modulus as well as that on IBI was not changed. This is in agreement with our expectations and with the vagal blockade experiment. The simulations show a smaller effect on sympathetic gain after blockade compared to that before blockade ($G_s=0.86$ and $G_s=0.78$ respectively), while vagal gain remains approximately the same ($G_v=0.70$ and $G_v=0.68$ respectively). This shows that the β -sympathetic system is an important factor in establishing the task effect on blood pressure (the effect is significantly smaller after blockade).

In conclusion: Both experimental data and simulations show that the vagal system is mainly involved in the effects of a task on IBI and modulus of the mid frequency band, while the β -sympathetic system is mainly involved in the effects of a task on blood pressure. Both systems however are involved in effects on heart rate and blood pressure

variability in the mid frequency band. Looking at the mid frequency band of heart rate, both systems change this band in the same direction, resulting in usually clear results of mental load in this band.

The effects of vagal blockade on the baseline values are very dramatic: The variability in heart rate almost disappears, modulus in the mid and high frequency bands are close to zero, and heart rate is almost doubled. Simulations in section 6.6.1 have shown that the results can be better explained if a small effect on systemic vascular resistance is included. The findings of Bruning (1994a,b) made us believe that such an effect is more than likely. The small increase in systemic vascular resistance enhances the blood pressure effect and reduces the effect on the mid frequency band of blood pressure. To verify this explanation, an experiment with selective cholinergic (muscarinic) blockers should be performed. These blockers affect cardiac cholinergic receptors (M2) or vascular cholinergic receptors (M3) only. If M3-blockers are used, no significant change in task effects are expected, since the contribution of cholinergic control of systemic resistance, if it exists, is small under normal circumstances (Von Scheidt, 1992). The effect of M2-blockade will be about the same as with atropine, but with a smaller effect on baseline blood pressure and increase in power in the mid frequency band of blood pressure. Task effects should remain the same as with atropine.

There are remarkable differences in the cardiovascular effects of low and high doses of atropine (Weise, 1989; Alcalay, 1992). The cardiovascular effects of the atropine paradox include an increase in IBI and HRV with low doses and a decrease in IBI and HRV with high doses. Bruning (1994a,b) found the effects on vascular resistance with very low doses atropine (0.6-60 ng/kg/min). Our suggestion is that the low dose effects of atropine (section 6.4; Weise, 1989; Alcalay, 1992) might be the effect of atropine on M3-receptors. We do not have experimental evidence for this hypothesis, but we can (and have) simulated the case that only $D_{0,Rsys}$ is changed. This simulation includes only an effect on systemic vascular resistance (see figure 3.3.7) and is related to an M3-blockade. The results can be compared with the results of the simulation in which both G_v and C_v were changed (cardiac effects by an M2-blockade only). Table 7.3.1 shows the parameter changes of G_v , C_v , and $D_{0,Rsys}$ for the two simulations and, to be complete, the parameter changes for the simulation of the effect of atropine. Results of both simulations are shown in figure 7.3.1. These simulations indeed show opposite effects on heart rate, power in the high frequency band, and modulus. Experimental support of this hypothesis, using M2- and M3-blockades, would be of great importance for understanding the atropine paradox.

Another way to explain this paradox is on the basis of central (brain) effects of atropine

(Brown, 1990). However, mental effects are usually found with high doses (above approximately 60 $\mu\text{g}/\text{kg}$, Brown, 1990). It may be possible that the affected centres can influence RVLM or that the RVLM is directly affected (even with doses below 5 $\mu\text{g}/\text{kg}$; Julu, 1992). According to Julu (1992), a low dose of atropine may increase sympathetic activation to the vasculature but a central vagal effect is not likely. More experimental data and simulation research are necessary to evaluate these possibilities.

Table 7.3.1: Model changes for M2-, M3-, and atropine blockades. Last line gives references to the figures that show the simulation results.

parameter	baseline value	M2 blockade	M3 blockade	M2+M3 =atropine
G_v	1.00	0.02		0.02
C_v	1.00	0.00		0.00
$D_{0,Rsys}$	1.55		1.90	1.90
Figure		6.6.1 7.3.1	7.3.1	6.6.2

β -Sympathetic blockade affects only baseline IBI significantly. The changes due to task effects are now found in blood pressure effects. A low heart rate and an apparently normal blood pressure does not mean a normally functioning cardiovascular system. It shows that a mental task can be helpful to determine the capability of the cardiovascular system to control blood pressure. This situation also occurs with some types of medication affecting parts of the cardiovascular system as side effect (for example imipramine, (Tulen, 1996) or lorazepam (Tulen, 1991)) and autonomic neuropathies (see 7.1.1).

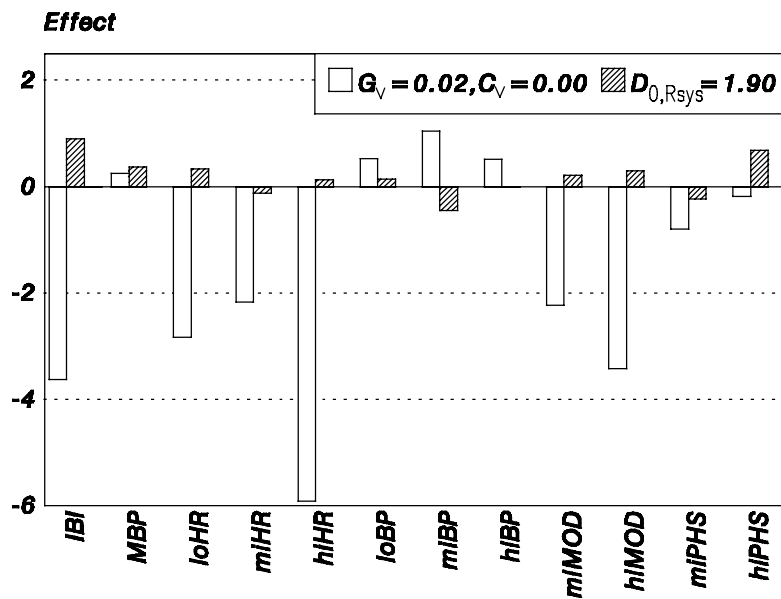


Figure 7.3.1: Simulation results of M2-blockade ($G_v=0.02$ and $C_v=0.00$) and M3-blockade ($D_{0,R_{sys}}=1.90$). Scales: IBI effect of 1 corresponds with 100 ms, MBP effect of 1 corresponds with 10 mmHg, power and modulus differences after log transformation.

7.4 Future application of the model

The simulation model can be used to investigate the origin of the effects of medication affecting the short-term blood pressure regulation. Examples are described in chapter 6. We found that atropine is most likely to have two effects: Suppression of vagal influence on the heart and an increase in systemic resistance. We needed both assumptions to simulate the effects of heart rate, blood pressure, and the variability measures well. This kind of research can easily be extended to other medication, like lorazepam or imipramine (experimental data sets of Tulen (1991, 1996) are good examples). One can verify by simulation whether these ideas regarding the points of impact on the cardiovascular control could be correct, too simple or too complicated.

Some other applications require extensions of the model. The effects of tilting a subject, or changing body posture from the sitting to the standing position, can also be investigated. For that purpose, however, the circulation needs to be divided into a intra- and extra-thoracic part (Neus, 1984; Akkerman, 1991). For simulation of physical exercise, cerebral blood flow effects, temperature effects etc., the circulation has to be divided into different parts for the relevant organs (kidney, coronary circulation, brain, skin, muscles, see Masuzawa, 1992 and Melchior, 1992). One of the major problems will be finding model parameters for the nervous control of the vasculature of these organs.

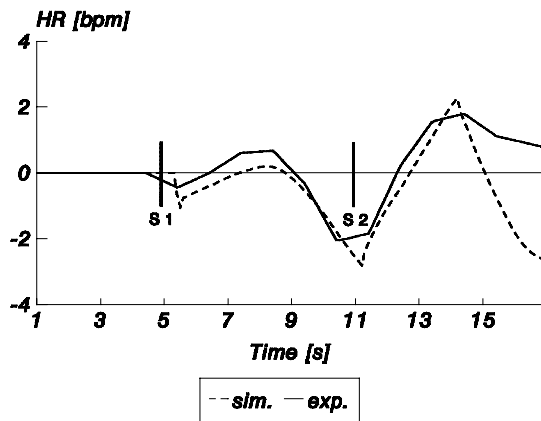
Evoked heart rate and blood pressure responses

Another way to analyze heart rate and blood pressure time series is by means of

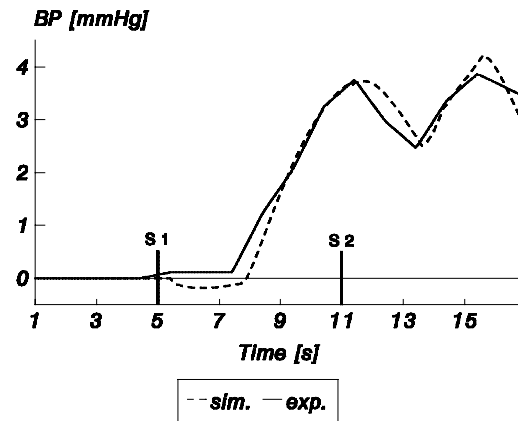
averaging responses to certain stimuli (Wölk, 1991; Elbert, 1992; Birbaumer, 1992; Otten, 1995; Van der Veen, 1996). For the averaging process, an equidistant time series is required. One way to acquire such a series is by weighting each beat according to the proportion of the new interval it occupies (Graham, 1978; Wölk, 1991; Birbaumer, 1992). This is an approximation of a reversed IPFM-model (DeBoer, 1985a; for the IPFM-model see section 3.5). This heart rate signal that is averaged is therefore the input signal of the IPFM-model. Now remember that the output of the simulation is also input for the IPFM-model, which means that simulation and experimental averages can be compared directly.

An example of simulation of evoked responses is shown in figure 7.4.3. The experimental data are from Wölk (1991). The task that the 20 subjects performed was a signalled reaction task. Each stimulus is preceded by a warning signal at S1 (see figure 7.4.3). The imperative stimulus itself was presented at S2. In figure 7.4.3, the averaged responses of heart rate and blood pressure are shown as solid lines. The simulated responses, broken lines in figures 7.4.3a and 7.4.3b, were obtained by a specific pattern of gain changes (G_v and G_s), as shown in figure 7.4.3c. Directly after S1 and S2, changes in vagal and sympathetic gain were induced, with different durations. Strength and duration were used to fit the experimental responses by trial and error. The result is shown as the broken lines in figure 7.4.3a and 7.4.3.b. The correspondence between simulated and experimental responses is very good.

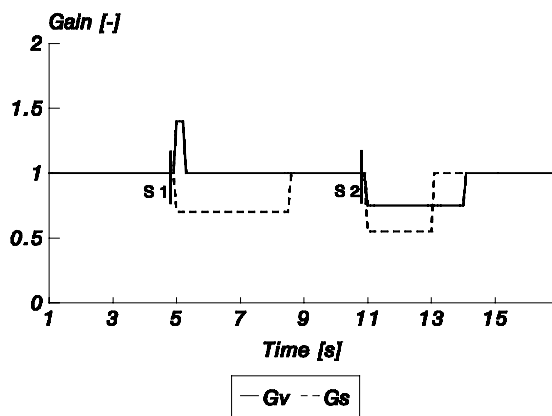
Possibly the approach is too simple in two respects. Firstly, we applied the pattern only once in the cardiovascular model. A different result is likely if the pattern is repeated for several minutes. The reason for the differences is that the time constants in the cardiovascular control system are longer than the task repetition interval. This concerns especially the sympathetic system. In such a setup, the simulated time series can be used to calculate the averages from stimulus responses in the same way as for the experimental data. Secondly, respiratory influences are not included, assuming that they are also absent in the experimental average. However, one can imagine that a respiratory pattern does occur in the task rhythm. Then, the individual respiratory patterns (S_{resp} in figure 3.4.3) should be included, together with the repeated gain patterns.



a)



b)



c)

Figure 7.4.3: Simulation of evoked responses found by Wölk (1991). S1 is the moment of a warning signal, S2 of the stimulus.

a) Heart rate responses

b) Blood pressure responses

c) Gain changes used for the simulations

Temperature regulation

Temperature sometimes plays a role in psychophysiological research (Surwit, 1982; Larsen, 1986; Shusterman, 1995). The environmental temperature influences performance of mental tasks (Åstrand, 1986), and the cold pressor test is sometimes part of studies of autonomic function and hypertension (Obrist, 1985; Low, 1993). Although we did not pay much attention to thermoregulatory influences, we will have to do so in the near future for the reasons mentioned in section 5.6.

A substantial part of thermoregulation coincides with cardiovascular regulation. Firstly, the route from the anterior hypothalamus* (Larsen, 1986) down to the skin vessels is a part of the systemic resistance control. Secondly, the control of metabolism by general sympathetic activation will also affect the cardiovascular system. The skin vessels are

*The anterior hypothalamus is also known as the depressor area.

not only affected by central control but also by a local mechanism (sweating results in local vasodilatation, Houdas, 1982; Berne, 1992) and the spinal reflex by cold receptors (Houdas, 1982; Berne, 1992). This mixture of effects will have consequences for the cardiovascular system as well.

7.5 Towards estimation of parameters in individual subjects

We developed a procedure for estimating the model parameters in experimental data from a group of subjects. In order to decide which set of parameters is the best, the multivariate distance measure, d^2 , was used. It is defined as:

$$d^2 = N(\bar{\mathbf{S}} - \bar{\mathbf{E}})' \mathbf{C}^{-1} (\bar{\mathbf{S}} - \bar{\mathbf{E}}) \quad [4.4.2]$$

where \mathbf{E} contains the experimental values, \mathbf{S} the simulated values, \mathbf{C} is the covariance matrix of the experimental values and N the number of subjects. The distance can be used to find the best set of model parameters using M measured variables. The set with the smallest distance is the best fitting set.

When the variables included are normally distributed, the distance, d^2 , follows an F distribution. We found that all the cardiovascular measures were normally distributed after appropriate transformation. Therefore, we could test whether the estimation is good enough ($p < 0.95$) or not ($p > 0.95$). In the latter case the means of the experimental data differ significantly from the best fitting simulated means.

A partial distance can be calculated for each variable included in the multivariate distance. This partial distance is used to determine which variable contributes the main part of the total distance. The largest partial distance variable (LPDV) can be used to evaluate the estimation results in more detail, which is especially important for those cases where the estimation is not good enough.

The graphs of the relationship between multivariate distance and gain parameters show that there is usually only one clear minimum (see figures 5.5.1-5.5.3). It makes the estimations of the parameters uncomplicated. Other, more sophisticated, estimation procedures which do not require a large table with simulations of all parameter combinations can then be used. The resolution can be improved with less simulations.

So far, we have applied the estimation method on group data. However, besides estimates for groups, we would like to make estimates for single subjects for several reasons:

- Only with these estimates we can determine individual differences in mental load effects. Especially for the groups with a small number of subjects, group means can be

deceptive. In field experiments outside the laboratory, the differences between subjects and circumstances may also require an individual approach.

- An interesting research question is whether the means of individually estimated parameters is equal to the parameters estimated for those of the group. We simply hypothesised this until now for our group estimates, but it can be shown by using individual estimates.
- As stated in section 5.6, respiration can be a cause for changes in power outside the high frequency band. This could be caused by changes in the amplitude of respiration. To investigate this in the model, the changes in amplitude have to be included in the model. This can be done only by using the measured respiratory signal as S_{Resp} (see figure 3.4.3) which includes amplitude changes. Of course, this requires separate simulations for each subject.

Four approaches for a single-subject estimate will be discussed now. The order in which they are discussed is also the order of preference.

(1) Another way to obtain a covariance matrix for one subject is by means of repeated measurements. The values of each measurement are used instead of the values of each subject. The vector $\bar{\mathbf{E}}$ contains the means of the measurements.

The measurements can be obtained in two ways: a) by repeating baseline measurements on several occasions, like every morning for five successive working days, or b) by splitting a baseline measurement into smaller parts, for instance, a ten minute baseline measurement into six 100 second periods. The number of measurements, N , should exceed the number of variables, M , in the estimate. Since M must be at least 4 in order to estimate the baseline variability of heart rate and blood pressure, N should be at least 5. The whole procedure can be adapted easily to this approach (just replace 'subjects' by 'measurements' in the procedure, and the same statistics can be used).

(2) We consider the subject as an individual member of the group of subjects. Therefore, the estimated covariance matrix, \mathbf{C} , for the group is now used as a given covariance matrix for this subject. The vector, $\bar{\mathbf{E}}$, should now contain the values of the variables for this specific subject, instead of the group means. In this case, since the covariance matrix is considered to be known, the multivariate distance measure d^2 has a Chi-squared distribution.

(3) A general covariance matrix can be applied to the single-subject case. This general covariance matrix will be obtained by using measurements of a very large group of subjects. This approach is only a possibility for experimental conditions and subject groups that are well studied, like rest situations (sitting) and may be memory search tasks in young healthy male subjects. For newly explored manipulations or subject

groups, such as vagal blockade or mental tasks performed in the supine position, a general covariance matrix is not available.

(4) The worst case is one measurement in one subject. In that case, we propose a non-parametric approach. To be able to combine variables with different distributions and scales, we will use ranks to find the best estimate. Although the most obvious test is the Chi-squared goodness-of-fit test (Siegel, 1988), this test is not independent of the distribution of the variables included (in fact, their distribution should approach a normal distribution with a variance equal to the mean). We suggest the following method:

- We have a table with M variables of L simulations.
- Calculate the absolute difference between measured value of the subject and simulated value for each simulation and variable in the table.
- Rank these differences for each variable, giving the smallest difference rank 1, the next rank 2, etc. So, a rank R_{ij} ($i=1..M, j=1..L$) is assigned to each simulation.
- Find the simulation with the smallest sum of ranks ($R_j = \sum R_{ij}$, summed over variables), R_{\min} . The corresponding parameter values are the estimation results.

The distribution of R_j can be approximated by a normal distribution, with

$$\text{mean} = M(L+1)/2$$

$$\text{variance} = M(L^2-1)/12$$

if M and L are large enough (Marascuilo, 1977). This distribution is also the basis for the test of the statistic used in the Friedman two-way analysis of variance by ranks (Marascuilo, 1977; Siegel, 1988). Since the tables we use contain at least one or several thousands of simulations, the approximation is good enough. This approximation can be used to decide whether the minimal sum of ranks R_{\min} is small enough. So, to finish the method:

- Calculate the normalized rank, $z = (R_{\min} - \text{mean}) / (\text{stand. deviation})$, and accept the estimation if $z < -1.65$. Then, the chance that this sum of ranks occurred at random is less than 0.05.
- The largest partial distance variable is now the variable with the largest rank $R_{\min,i}$

Note that this test is based on the distribution of the simulation outcomes of the included variables. The statistical test is used to determine whether or not all ranks of the variables included are close enough to 1 (the best fit for each variable). The range and number of simulations should be equal for all related estimations to be comparable between these estimations.

7.6 Conclusions

Model extensions

We adapted the model of Wesseling in such a way that we can simulate the short-term effects of mental load on the cardiovascular system. Two major extensions were necessary: a sympathetic branch in addition to a vagal branch for heart rate control and an effect of respiration on the cardiovascular system. We implemented the description of Rosenbluth (1934) for heart rate control, and used it partly as cardiovascular control centre. Respiratory effects are implemented as inhibition of vagal activation in combination with a decrease in intra-thoracic pressure during inspiration.

We would like to extend the respiratory model with an input from experimental data (like Kitney, 1987). We hope that this extension can improve the simulated task effects in the high frequency band of blood pressure and in part in the low frequency band of both heart rate and blood pressure. These three bands are simulated less well as the others. However, this would require a method for estimating model parameters for individuals (see 7.5) which will be very labour-intensive.

Estimation procedure

We developed an estimation procedure which can include the measured cardiovascular variables and can be used to estimate several model parameters. The procedure determines which simulation has the smallest multivariate distance in a table of simulations. A statistical test of this distance is applied to determine whether the simulated result is not significantly different from the experimental results. The procedure can be used for all experimental conditions that were investigated (baseline, mental load, and blockade), and it can be used to estimate any model parameter(s).

Two conditions must be fulfilled: 1) the number of subjects must be larger than the number of cardiovascular variables included, and 2) for the statistical test the cardiovascular variables should have a normal distribution. The second condition received a great deal of attention, since most of the variables used are not normally distributed (all power and modulus values). After logarithmic transformation of the variables however, this condition is fulfilled. The procedure that is developed is suitable for subject groups, but it is expected to be suitable for estimating model parameters of individual subject as well (see section 7.5).

Mental load- defence reaction- autonomic activations- spectral measures

Spectral measures of heart rate and blood pressure have been used for several purposes: In psychophysiology to estimate mental load, in medicine to estimate autonomic activation. However these purposes are related, and one of the goals of this thesis is to unravel a part of the relation between mental load, autonomic activation and spectral measures.

If mental load evokes a defence reaction, the power of the mid frequency band of heart rate and the modulus of the mid frequency band show a decrease that is related to the

invested mental effort. It is accompanied by a decrease in vagal activation and an increase in sympathetic activation. The decrease in vagal and sympathetic* gains in the NTS are the cause of the cardiovascular changes. This is the basic concept concerning the effects of mental load and we have confirmed these effects by model simulations. The changes in both gains can be estimated by the developed procedure.

However, we found situations where other mechanisms are necessary to explain the changes in the cardiovascular system. In those cases, the gains in the NTS are not changed, but the NTS is assumed to be by-passed and the higher centres and/or hypothalamus influence the vagal and sympathetic outflow levels directly. Examples of these situations are autonomic blockades and mental tasks performed by subjects having a low modulus value during the pre-task baseline.

This NTS by-pass mechanism has other effects on the cardiovascular system, which can (partly) mask the effects of the defence reaction. The vagal NTS by-pass has no effect on the modulus in the mid frequency band and increases the power in the mid frequency band of heart rate (The sympathetic NTS by-pass has not yet been studied in detail, but is more complex since four effectors are involved). The effects on heart rate and blood pressure level are the same, and more importantly now, the effects on autonomic activation levels are also unchanged. However, the change in cardiovascular control is totally different as measured by the modulus and other spectral measures. This is of great importance for the interpretation of the experimental spectral results. We conclude that for the study of mental load, the study of mechanisms involved in the effects of mental task is the most important. Therefore the autonomic activation is less important than the spectral measures. The situation is similar to the study of mechanisms involved in pharmacological interventions (for example, administration of atropine, β -blockers or imipramine), where several mechanisms can be involved. The model simulations of mean and spectral measures of heart rate and blood pressure can help to unravel the mechanisms that are involved.

*A decrease in sympathetic gain results in an increase of sympathetic activation, since the output of the NTS inhibits the RVLM output.