Performing a mental task has effects on the cardiovascular system. The magnitude of these cardiovascular changes are related to task difficulty. To quantify these changes, heart rate and blood pressure are measured during rest and task conditions. Mean values as well as the variability of heart rate and blood pressure (determined by means of spectral analysis) are calculated for the conditions of a number of experiments. To explain the results, an approach will be used that combines experimental and simulated data. The simulations are performed with a model of the short-term blood pressure regulation.
1.1 Applying mental tasks

Performing a mental task usually requires attention, information processing and a certain amount of effort of someone. Physiological effects of mental task are increases in heart rate and blood pressure compared to rest conditions. The cardiovascular responses are related to the task demands: if more mental effort is needed to perform the task, the responses will be larger. So, the cardiovascular response can be used to evaluate the mental load of a task. However, the actual effort depends on internal (e.g. skills, training) and external (e.g. distractions) factors, and the initial state (e.g. fatigue) of the subject (Mulder, G, 1985b). In psychophysiology, these three influences have been studied (Aasman, 1987; Mulder, L, 1987; Carter, 1989; Damos, 1991; Schleifer, 1990; Veldman, 1992; Jorna, 1993; Sirevaag, 1993; Braby, 1993).

In medicine, the cardiovascular effects of mental load have been studied to find out more about cardiovascular disease. A large increase in blood pressure and heart rate (large reactivity) accompanying the performance of a mental task is believed to be a risk factor for essential hypertension or coronary disease (Mulder, G, 1985b; Manuck, 1985; Steptoe, 1985a). In practice, these tests are integrated in a series of tests including physical exercise, cold-pressor stress and orthostatic load (Steptoe, 1985a; Fahrenberg, 1985; Hatch, 1986; Mormino, 1993). These tests have various effects on the autonomic nervous system.

A variety of mental tasks are used in psychophysiology (Mulder, G, 1985b; Carter, 1989; Damos, 1991; Grossman, 1991; Veldman, 1985, 1992) and in medicine (Steptoe, 1985a; Schulte, 1985; Rüddel, 1985; Tulen, 1991). Mental arithmetic\(^1\) tasks are most common in medicine (Rüddel, 1985; Hatch, 1986; Pagani, 1991). Examples of reaction time tasks are the Stroop\(^2\) test (Tulen, 1991), and the Bondet\(^3\) (Langewitz, 1987; Mulder, L, 1993). Memory search\(^4\) tasks are used in our laboratory in various designs (Aasman, 1987; Veldman, 1985, 1992; Mulder, L, 1993). It depends on the research questions which tasks are, or should be (Steptoe, 1985a), selected. In medicine, a task should increase blood pressure to establish blood pressure reactivity. In psychophysiology, the mental processes that have to be studied determine the choice of

---

\(^1\) Adding or subtracting numbers for several minutes.

\(^2\) Stimuli are coloured words like ‘blue’ with red letters.

\(^3\) Stimuli are coloured squares, presented on different locations a screen, one at a time. The subject have to press the push button with the same colour as the presented square.

\(^4\) Stimuli are letters. The subject has to memorize a small letter set. If the presented letters are part of this set, the subject responds with ‘yes’, and with ‘no’ if not.
Another application of mental tasks is to study the effects of treatment. The tasks are used in experiments with pre- and post-treatment measurements. The differences in cardiovascular responses before and after treatment are compared in order to measure the mental load effect of the treatment. Examples are experiments to measure the effect of everyday work (Mulder, L, 1987), or to measure the effect of stress-management programs (Albright, 1991).

The cardiovascular effects of mental load are caused by changes in the autonomic nervous system. Both sympathetic and vagal part of the autonomic nervous system are involved in the response.

The cardiovascular effects of mental task performance are similar to the defence reaction (Mulder, G, 1980; Jordan, 1990; Berntson, 1991). This cardiovascular reaction can be evoked by stimulating the defence area in the hypothalamus and results in a decrease in vagal tone and an increase in sympathetic tone. This increases heart rate and blood pressure and decreases variability of the heart rate. Suppression of the vagal tone will also diminish the strength of the relation between blood pressure variations and inter-beat interval changes, expressed as the baroreflex sensitivity. However, several of these effects are reported to be different for different mental tasks and subject groups.

It is important to know how these cardiovascular effects are produced by the autonomic nervous system. Specific changes in the autonomic nervous system can be associated with health risks. Heightened sympathetic nervous tone may be important in the initiation of the hypertensive process (Steptoe, 1985a; Obrist, 1985; Scher, 1989c; Ciriello, 1991; Esler, 1991; Julius, 1992; Miller, 1991, 1994). A high dual (vagal and sympathetic) tone at rest seems to exist during states of enhanced sensitivity to cardiac arrhythmia (Shepherd, 1985; Skinner, 1985, 1988) and facilitates ventricular fibrillation. Sudden cardiac death is associated with a low vagal tone (Algra, 1990; Julius, 1992).

1.2 Spectral analysis of heart rate and blood pressure

The effects of performing a mental task on the autonomic system can be diverse, as stated in section 1.1. To determine the changes in the vagal and sympathetic system due to mental load, mean heart rate and blood pressure values are not sufficient. For instance, dual autonomic tone changes result only in minimal changes of heart rate (Skinner, 1985, 1988; Berntson, 1991). The idea that measures of variability derived from the beat-to-beat heart rate and blood pressure can provide more information about vagal and sympathetic activation is based on the differences in dynamic properties of both parts of the autonomic nervous system. Indeed, spectral measures have been used for

At least four techniques are used to calculate spectral densities of cardiovascular variables. The frequency bands defined by several groups over the years are even more diverse, as well as the derived indices. However, there is enough evidence that the differences in analytical methods are not the main cause of differences between studies (Mulder, G, 1980; Mulder, L, 1988a; Grossman, 1990; Ten Voorde, 1992; Di Rienzo, 1993; Task Force, 1996). Therefore, we will not focus on the methodological differences, but instead try to use spectral data of a number of (psycho)physiological studies in an attempt to improve our understanding of the regulation of blood pressure by the autonomic nervous system.

Two frequency components of heart rate variations have been studied very extensively: The 0.1 Hz component, and the Respiratory Sinus Arrhythmia (RSA). The 0.1 Hz component is associated with the regulatory properties of the short-term blood pressure control system. Resonance in the vasomotor system (‘Vascular resistance’ in figure 1.3.1) is probably the origin of this frequency peak (Wesseling, 1985; Mulder, G, 1985a; DeBoer, 1985a, 1987; Mulder, L, 1988a; Yambe, 1993). RSA is the variability in heart rate that is related to respiratory activity, usually around 0.25 Hz (Angelone, 1964; Grossman, 1983, 1993; Porges, 1982, 1992; Kollai, 1990). There is an increase in heart rate during inspiration, and a decrease during expiration.

A third frequency component of importance is associated with slow regulatory processes. Adaptation to new cardiovascular demands, general homeostatic processes and body temperature regulation are examples of these slow processes (Kitney, 1974, 1980; Kunitake, 1992; Lossius, 1994).

Since 1985, three frequency bands have been defined and used in our laboratory (Mulder, G, 1985a,b) that include these three frequency components. They are summarized in table 1.2.1.
Table 1.2.1: Definition of the frequency bands.

<table>
<thead>
<tr>
<th>Band</th>
<th>Frequency range [Hz]</th>
<th>Origin of variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.02-0.06</td>
<td>body temperature, homeostatic processes</td>
</tr>
<tr>
<td>Mid*</td>
<td>0.07-0.14</td>
<td>resonance of vasomotor system</td>
</tr>
<tr>
<td>High**</td>
<td>0.15-0.50</td>
<td>respiration, task repetition rate</td>
</tr>
</tbody>
</table>

*Also called the 0.1 Hz component; ** Can be used as measure for RSA

Not only heart rate variability can be calculated in these bands, but also blood pressure variability. We will express the power in a frequency band relative to the squared mean of the signal (Akselrod, 1985; Mulder, L, 1988a), for example squared mean heart rate for heart rate). The power values become dimensionless and we will use the unit mMl² for power values expressed in this way. MI is the abbreviation of modulation index, while the power values are multiplied by 1000², explaining the milli-prefix. A value of 10000 mMl² corresponds with 10% variation of a signal around its mean value.

Several studies have shown that mental load decreases both the mid and high frequency bands of heart rate (Mulder, G, 1980, 1985a,b; Vicente, 1987; Mulder, L, 1987, 1988a; Kramer, 1991; Veldman, 1985, 1992; Porges, 1992; Jorna, 1992, 1993). To understand the changes in blood pressure regulation better, we would like to distinguish the vagal and sympathetic effects. We hope to do this by means of these frequency bands, but there are some problems which we will summarize here.

The mid and high frequency bands are affected by changes in vagal activation, but are also influenced by ‘disturbing’ factors. RSA is dominated by vagal control, but changes in respiratory frequency and amplitude, can attenuate or amplify the effect of mental load. The 0.1 Hz component (the mid frequency band) is influenced by both the vagal and sympathetic systems. In this band, changes in the sympathetic system can attenuate or amplify the vagal effects. Since different kinds of mental tasks can affect respiration and sympathetic activity differently, an independent measure of vagal activity is difficult to obtain without additional information. Blood pressure variability and information about changes in baroreflex sensitivity can supply this information.

To find a measure of sympathetic activity is even more difficult. The sympathetic system hardly affects the high frequency bands, but the low and mid frequency bands are affected by both the vagal and sympathetic system. The low frequency band of the blood pressure is probably the most sympathetically dominated band (Wesseling, 1985; Veldman, 1992; Siché, 1992), but vagal influences and trends of unknown origin (non-stationarities) cannot always be excluded (Veldman, 1992; Siché, 1992).
In conclusion, independent measures of vagal and sympathetic activation are not yet defined in terms of spectral measures. At least we know that heart rate variability measures are not enough to determine the mental load effects in terms of vagal and sympathetic activation changes. Blood pressure spectra and baroreflex sensitivity can give more information about the autonomic changes.

To calculate spectra of blood pressure, it is necessary to measure blood pressure beat-to-beat. In medicine, intra-arterial blood pressure measurements are commonly available, but outside the hospital they cannot be obtained easily. For psychophysiology, the development of a non-invasive technique for blood pressure measurement on a beat-to-beat basis was therefore of vital importance. The FIN.A.PRES or Finapres is such a measurement device (Settels, 1985; Wesseling, 1991) and it has been used in many psychological laboratories and is now commercially available as the Ohmeda 2300. It has been shown that the difference between intra-arterial measurements and Finapres measurements are usually small (Settels, 1985; Parati, 1989; Imholz, 1988, 1990; Curio, 1991; Mulder, L, 1991; Van Roon, 1991).

A spin-off of spectral analysis of heart rate and blood pressure is the possibility of estimating baroreflex sensitivity in a non-invasive way (Robbe, 1987; Mulder, L, 1988a; Pagani, 1991). This gain between variations in blood pressure and inter-beat interval is an important measure for the control properties of autonomic regulation. In agreement with the dynamic properties of the vagal and sympathetic systems, the baroreflex gain is different at different frequencies. Spectral analysis provides the modulus (the strength of the relation between blood pressure and inter-beat interval changes and is expressed in ms/mmHg), the phase shift (or time relationship) between blood pressure and inter-beat interval changes (expressed in radians), and the coherence between these signals (dimensionless value that is 1 if the relation is linear).

1.3 Blood pressure regulation

Mental load leads to changes in heart rate and blood pressure. The nervous system has many ways of influencing the heart and blood vessels, the main components of the circulatory system. A large and complex regulation system (Guyton, 1980) keeps the blood pressure between narrow limits. To achieve a rise or fall of blood pressure, a major change in the control is required. The total control system consists of many subsystems that have different functions within the overall regulation.

The cardiovascular control centre gets information about the state of the system by means of several receptors. These include information about the arterial blood pressure from baroreceptors in the aorta and carotid sinus, about pressures in the atria and
pulmonary vessels and about blood gases from chemoreceptors. This information, processed in a control centre in the medulla, is used to control blood pressure by means of a number of effector systems, such as heart rate and heart muscle contraction force, arterial and venous calibre, volume of body fluids (urine excretion by the kidneys), etc. The information is sent to these subsystems directly by the autonomic nervous system and indirectly by hormones.

Blood pressure, receptors, control centre, effectors and circulation form a closed loop control system (see figure 1.3.1). In a closed loop system, especially with parallel loops, it is difficult to understand what happens when disturbances impinge on the system. Clearly, the blood pressure control system is such a closed loop system with parallel loops: Baroreceptors measure blood pressure, the information is processed, and sent to parallel working effectors (heart rate, contraction force, vascular resistance, venous volume) to change blood pressure. For example, in this closed loop system, a change in heart rate may result indirectly in a change in vascular resistance. The complexity can lead to paradoxal results, as shown by the following quotation from Anderson (1991): "...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...". This example shows that an increase in blood pressure can be accompanied by increased as well as decreased sympathetic activation.

The subsystems as well as the pathways of information transmission to the effectors have different time characteristics (Guyton, 1980). The urine excretion is slow (hours), while heart rate can change instantaneously. The information transmission in the vagal part of the autonomic system is very fast, while transport by hormones is much slower. In general, it will take some time to activate an effector after a blood pressure change; this is the time delay. After the start of the activation, it will take time before the effector is maximally activated; this can be expressed in a time constant. The time delays and time constants in the sympathetic system are about five to ten times longer than in the vagal system.

Since the subsystems have different dynamic properties, the influences on variability of heart rate and blood pressure will also be different. A good understanding of the
subsystems involved in generating cardiovascular effects of mental task performance is necessary to be able to interpret the spectral measures of heart rate and blood pressure in relation to vagal and sympathetic changes. Therefore, a (simulation) model of the regulation is very useful in combination with spectral measures. This is the reason that this research has been initiated by the Mulders in Groningen in 1985.

It will be clear that performing a short-lasting mental task of about five minutes will not affect all subsystems. A selection from these subsystems can be made to describe, or model, the short-term blood pressure effects. The baroreflex model of Wesseling and Settels (Wesseling, 1983, 1985, 1993; Settels, 1990) contains these subsystems and has been chosen as starting point for the model study.

1.4 Objectives of the model study

- To adapt the model of Wesseling to our constraints. Although most elements are modelled by Wesseling, two major extensions have to be made. We want to include sympathetic control, besides vagal control, of heart rate and respiratory effects on the cardiovascular system.
- To develop an estimation procedure for baseline parameters and task effects. We want to compare experimental data with simulated data and to determine which simulation of a set of simulations is the best fitting one.
- To apply the model and procedures to mental load studies to determine the effects on blood pressure regulation. We selected six mental load studies with comparable tasks for this purpose.
- To unravel a part of the sequence ‘mental load - defence reaction - autonomic activation - spectral measures’. To study this sequence, we will use the results of the mental load studies and the results of an study in which we performed partial autonomic blockades.

1.5 Outline of this thesis

Chapter 2 is a physiological description of the short-term blood pressure regulation. The physiology as described there is the basis of the model that is described in chapter 3. The sections that describe the physiology are in the same order as the sections that describe the model (e.g. section 2.4.2 describes the physiology of respiratory influences on the cardiovascular system, and section 3.4.2 describes the model of respiratory
Chapter 4 shows the basic properties of the model. The effects of changes in baroreflex gain in the model are shown, as well as those of vagal blockade. Most important are the effects of these manipulations on spectral measures. From these findings, a method is developed to estimate model parameters that define baseline variability from experimental results. With these baseline values, the effects of mental load during the experiment can be estimated using the same procedure, but, of course, using other parameters. If we want to perform a statistical test on the estimation outcome, the variables included in the estimation procedure have to be normally distributed. Since we know that most variables are not normally distributed, transformations for the variables are selected on the basis of theoretical considerations.

Chapter 5 consists of three parts. The first part deals with findings in the literature concerning the relation of spectral measures, autonomic activation and mental load. Then, results of a number of mental load studies are summarized. Special attention is given to the distribution of the variables, because the estimation procedure requires normally distributed variables. The effects of the transformations are shown for data from a group of 73 subjects. A related issue, the Law of initial value, is discussed at the end of this part. The third part of chapter 5 contains simulation results using the model, procedures, and transformations as described in chapter 4.

In chapter 6, a study is presented in which an autonomic blockade is applied in human subjects. The study was performed to answer two questions: How are spectral measures related to autonomic activation, and which role do vagal and sympathetic systems play in the effects of mental load. In the first part, the experimental results are shown, and the second part presents the experimental model simulations. The estimation procedure as described in chapter 4 can be used to estimate the autonomic blockade parameters in the model.

Chapter 7 is a general discussion. Issues as the model, spectral analysis and mental the estimation method are discussed. The conclusions about the objectives finishes this chapter.

Appendix A is a schematic overview of the model. The model overview can be unfolded. Appendix B contains the details of the simulation procedures, while appendix C contains the experimental procedures. The last appendix D explains the theoretical model that is used to evaluate transformation of variables in relation to the Law of Initial values.