Blood pressure analysis on time scales from seconds to days
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Chapter 5

Variations in cardiac oxygen supply and demand in hypertensive subjects after rising

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The increased risk of sudden cardiac death soon after awakening suggests mechanisms that are particularly likely to occur during this time. Specifically, the increase in heart rate and blood pressure early in the morning increases cardiac oxygen demand and has been associated with morning excess of acute myocardial infarction (1–3). We hypothesized that in hypertensive subjects this early morning increase in heart rate and blood pressure also affects the oxygen supply potential, further compromising the relationship between cardiac oxygen supply and demand. To test our hypothesis we analyzed a group of hypertensive patients; a group of normotensive volunteers served as reference.

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Pulse wave analysis was performed to determine parameters which were shown to correlate to cardiac oxygen supply potential, cardiac oxygen demand, and the supply-demand ratio. The effects of diurnal variations in blood pressure and heart rate on indices estimating cardiac oxygen supply potential and cardiac oxygen demand were studied. We used previously recorded 24-hour continuous intra-arterial and finger arterial blood pressure measurements in 14 hypertensive patients and 8 healthy normotensive volunteers (4). Reconstructed aortic pressure was used for all calculations.

**Methods**

**Subjects**
For a detailed description we refer to our original report (4). In short, 14 hypertensive patients, aged 20–60 years, and 8 normotensive volunteers, aged 19–32 years, were studied. In the hypertensive group 11 patients were male, in the normotensives group all participants were male. The hypertensives had discontinued their medication two weeks prior to the measurements. All subjects gave written informed consent and the respective review committees approved the protocol (4).

**Measurements**
Brachial Artery Pressure (BAP) was measured intra-arterially at the non-dominant arm with the Oxford Medilog Mark II system and ambulatory finger arterial pressure was obtained from the dominant arm using the Portapres device (4). Measurements were performed from 1 PM until 1 PM the next day. Apart from free in-hospital activities, all subjects performed the following activities at preset times: siesta (2:00 – 3:30 PM), cycling at 50 W (4:45 – 5:15 PM), sleep (10 PM – 6 AM), and two walks outside the hospital (10:00 – 10:30 AM, 11:00 – 11:30 AM).

**Data analysis**
Blood pressure was A/D converted with a sampling rate of 100 Hz. Beat to beat values of systolic, mean and diastolic BAP (corrected for zero drift) and Heart Rate (HR) were calculated. Episodes with artifacts were rejected. Aortic pressure waves were reconstructed from invasive brachial and noninvasive finger artery pressures using a generalized transfer function (5–14). The transfer function compensates for the physiological wave transformation of pressure waves traveling towards the periphery.
Diastolic Time Fraction (DTF, the ratio of duration of diastole and heart period) was
calculated to assess the oxygen supply potential, since a decrease in DTF is directly
related to coronary blood flow if the vasodilatory reserve is exhausted (15,16). Rate-
Pressure Product (RPP, systolic pressure times heart rate), was calculated to assess
cardiac oxygen demand (17,18). The supply - demand ratio (19–22) was assessed by the
ratio of the diastolic area (A_{dia}, in mmHg·s) and systolic area (A_{sys}, in mmHg·s) under the
pressure curve.

Statistics
Thirty-minute averages were calculated for all parameters. The effect of rising was
evaluated by comparing equal periods before (01:00 – 06:00, night) and after rising
(08:00 – 13:00, morning). Results were expressed as mean ± SD in tables and as mean ±
SEM in figures. Night vs. morning values and hypertensives vs. normotensives were
compared by paired t-tests. Linear regression analysis was performed over the 48 half-
hour averages to analyze the relationship between parameters and HR.

Figure 1

Left, Normotensives, right, Hypertensives. Systolic, mean and diastolic aortic pressure in top panel, Heart Rate
(HR) in second panel. Dotted vertical lines demarcate Night and Morning periods; bars over the time scale
indicate the activities listed in the Methods section (siesta, cycling, sleeping and two walks). The change in
blood pressure and heart in the morning is slower in the hypertensives.
Results

Diurnal variations in blood pressure and heart rate are depicted in Figure 1. In the hypertensive subjects, systolic, mean and diastolic blood pressure and heart rate were higher during the night (Table 1, right panel), with oxygen supply parameter DTF as well as supply – demand ratio (A_{dia} / A_{sys}) lower and with demand parameter RPP higher. In the morning, blood pressure and HR increased (Table 1, lower panel, Figure 1) in both groups. Pressures were higher in hypertensives but HR was comparable. DTF decreased as did the supply - demand ratio while RPP increased (Table 1, Figure 2). Supply potential and the supply - demand became equivalent for normotensive and hypertensive subjects. RPP remained higher in the hypertensive group.

Figure 2

Same layout as Figure 1. Parameter of cardiac oxygen supply potential, Diastolic Time Fraction (DTF) in the top panel, in the middle panel the supply - demand ratio A_{dia} / A_{sys}, and the parameter of cardiac oxygen demand, Rate Pressure Product (RPP), in the bottom panel. The change in the parameters in the morning is slower in the hypertensives.
DTF and $A_{\text{dia}} / A_{\text{syst}}$ decreased with HR, RPP increased (Table 2). The early morning increase in HR (BPM) in the hypertensive subjects (from $67 \pm 3$ to $89 \pm 5$ BPM; 33%) was smaller than in the normotensives (from $53 \pm 2$ to $82 \pm 11$ BPM; 55%). The smaller HR increase limited the untoward changes in cardiac oxygen parameters.

The results based on non-invasive finger arterial pressure and those of brachial intra-arterial pressure, both reconstructed to aortic pressure, lead to the same outcomes of the tests given in Table 1.

### Table 1
Hemodynamic parameters and cardiac oxygen indices.

<table>
<thead>
<tr>
<th>Night</th>
<th>Normotensives</th>
<th>Hypertensives</th>
<th>$P_{HT vs. NT}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{sys}}$</td>
<td>96 2</td>
<td>124 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$P_{\text{dia}}$</td>
<td>61 2</td>
<td>79 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$P_{\text{mean}}$</td>
<td>77 2</td>
<td>99 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR</td>
<td>53 2</td>
<td>67 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DTF</td>
<td>67.5 0.9</td>
<td>64.0 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$A_{\text{dia}} / A_{\text{syst}}$</td>
<td>1.79 0.07</td>
<td>1.52 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RPP</td>
<td>5100 260</td>
<td>8400 410</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morning</th>
<th>Normotensives</th>
<th>Hypertensives</th>
<th>$P_{morning \ vs. \ night}$</th>
<th>$P_{morning \ vs. \ night}$</th>
<th>$P_{HT vs. NT}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{sys}}$</td>
<td>115 4</td>
<td>136 3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$P_{\text{dia}}$</td>
<td>76 4</td>
<td>92 3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$P_{\text{mean}}$</td>
<td>94 4</td>
<td>112 2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR</td>
<td>82 11</td>
<td>89 5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.054</td>
</tr>
<tr>
<td>DTF</td>
<td>58.9 3.6</td>
<td>58.3 1.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.613</td>
</tr>
<tr>
<td>$A_{\text{dia}} / A_{\text{syst}}$</td>
<td>1.27 0.22</td>
<td>1.20 0.06</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.303</td>
</tr>
<tr>
<td>RPP</td>
<td>9200 1300</td>
<td>11900 930</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Night averages (top) and morning averages (bottom) for normotensives (left) and hypertensives (right). In the right column, Hypertensives (HT) are tested versus Normotensives (NT). In the lower half of the Table the morning averages are tested versus night. $P_{\text{sys}}$, $P_{\text{dia}}$ and $P_{\text{mean}}$ are systolic, diastolic and mean aortic pressure (mmHg), HR is heart rate in beats per minute (BPM), DTF is diastolic time fraction (%), RPP is Rate Pressure Product (mmHg·BPM), $A_{\text{dia}} / A_{\text{syst}}$ is the ratio of diastolic and systolic areas (mmHg·s), respectively, under the aortic pressure curve.
Discussion

We studied diurnal variations in blood pressure, heart rate, and of parameters estimating cardiac oxygen supply potential and oxygen demand, in both hypertensive and normotensive subjects. The new findings of this study are that in hypertensive subjects the diurnal variation in cardiac oxygen supply parameters and in the supply - demand ratio is smaller, and that soon after awakening an increase in cardiac oxygen demand is accompanied by a concomitant reduction in supply potential.

Table 2
Linear regressions on Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Normotensives</th>
<th>Hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>R^2</td>
<td>Regression</td>
</tr>
<tr>
<td>DTF</td>
<td>−0.30 x HR + 84 0.97</td>
<td>−0.23 x HR + 79 0.94</td>
</tr>
<tr>
<td>A_{sys}/A_{sys}</td>
<td>−0.018 x HR + 2.77 0.96</td>
<td>−0.013 x HR + 2.38 0.91</td>
</tr>
<tr>
<td>RPP</td>
<td>130 x HR − 1730 0.97</td>
<td>150 x HR − 1300 0.85</td>
</tr>
</tbody>
</table>

Regressions of parameters for cardiac oxygen supply potential and cardiac oxygen demand on Heart Rate (HR). For explanation of the quantities refer to Table 1.

Methodological considerations

Oxygen supply - demand parameters were calculated from aortic pressure waves reconstructed from invasive brachial artery pressure and non-invasive finger arterial pressure recordings, using transfer functions (11–14). Transfer functions compensate for the physiological wave transformation of pressure waves traveling towards the periphery. The transfer functions mainly correct for the amplification of the systolic pressure (11–14). The use of a transfer function therefore mainly affects calculation of RPP. Generalized waveform filters in the upper limb show little inter-individual variation at low frequencies (7–11), which are of importance for the calculation of mean and diastolic pressure, and thus for calculation of DTF. Therefore, the inaccuracies introduced by the use of a transfer function have no major effect on the estimates of cardiac oxygen supply potential.
The measurements of cardiac oxygen supply potential and oxygen demand in groups of normotensives and hypertensives were indirect. Continuous ambulatory coronary flow measurement to validate the suggested reduction in coronary perfusion in patients with coronary heart disease is as yet not feasible. Simultaneous oxygen supply - demand parameters from continuous blood pressure together with ST-segment depression in patients known with coronary heart disease, might, in part, answer the question whether ischemia correlates best with changes in oxygen supply vs. demand parameters.

**Diurnal hemodynamic variations**

Major changes in parameters occurred after rising, i.e. at the time that the peak in ischaemic events is usually observed (23,24). In healthy subjects subendocardial perfusion is hampered if the $A_{\text{dia}} / A_{\text{sys}}$ ratio falls below 0.4 to 0.6 (22,25). The ratios observed in this study, in which no strenuous exercise was performed, remained well above this limit in all subjects. However, this limit is not fixed but may increase under circumstances where the vasodilatory reserve is exhausted, e.g. in case of coronary artery stenosis. Thus the magnitude of the observed changes in $A_{\text{dia}} / A_{\text{sys}}$ ratio per se does not reflect early morning myocardial ischemia in healthy subjects, but may explain occurrence of coronary ischemia in those subjects who suffer from coronary artery disease. In hypertensives (26) as well as in myocardial hypertrophy (27), coronary flow reserve is less. Therefore, oxygen supply parameters are better indicators of subendocardial ischemia in hypertensives than in normotensives. The diurnal variation in the cardiac oxygen supply potential parameters and in the $A_{\text{dia}} / A_{\text{sys}}$ ratio in the hypertensive subjects was smaller, a phenomenon not described before. Of interest, the finding that oxygen supply - demand parameters as derived from invasive pressure was tracked by a non-invasive arterial pressure determination allows to study these supply and demand parameters in a non-invasive manner.

**Cardiac Oxygen Supply Potential**

As soon as coronary vasodilatory reserve is exhausted, e.g. related to the presence of a stenosis, subendocardial and mid-myocardial perfusion become dependent directly on diastolic pressure and time (15,16,20–22). Usually, reduced supply is associated with coronary vasospasm or atherosclerosis (1). The present study demonstrates that hemodynamic changes may equally affect DTF as parameter of cardiac oxygen supply potential in the morning.
A reduction in DTF can be attributed to an increase in HR primarily by shortening of diastole. In healthy subjects a decrease in perfusion pressure or time is compensated for by coronary vasodilation (22) rendering the decrease in the oxygen supply potential parameter of importance mainly in patients with coronary stenosis. To the best of our knowledge the supply parameter, in contrast to the demand parameters has never been associated with cardiac ischemic events in the morning (24). Pepine (28) mentions the beneficial effects of beta-blockers on cardiac oxygen supply because of the prolongation of diastolic time, but not in relation to circadian rhythms and cardiac oxygen supply.

**Cardiac Oxygen Demand**

Diurnal variations in the balance between cardiac oxygen supply and demand have traditionally been attributed to changes in oxygen demand due to physical activity (1,2,29,30). The close correlation between an increase in HR and subsequent development of coronary ischemia is considered to reflect this increase in oxygen demand (31,32). The observed increase in RPP after rising, which results from an increase in both systolic blood pressure and heart rate, is in agreement with the hypothesis that the morning increase in ischemic events may be caused by an increase in cardiac oxygen demand.

**Hypertensives versus normotensives**

Hypertensive subjects appear to be at risk for ischemic events due to larger oxygen demand (33,34) during night as well as in the morning. During the morning period, the oxygen supply potential of the hypertensives vs. normotensives did not differ, possibly related to a damped HR response to rising. In contrast, during the night oxygen supply potential was lower in hypertensives. This may play a role hitherto overlooked in nocturnal ischemia (35–37)
Conclusion

We observed a decrease in cardiac oxygen supply potential parameters and the ratio $A_{\text{dia}} / A_{\text{sys}}$ after rising in healthy subjects and in hypertensive patients. Traditionally an increased cardiac oxygen demand has been considered as the factor reducing the oxygen supply - demand balance. However, we observed that the supply - demand balance may change detrimentally by a reduction of the oxygen supply potential as well. The smaller increase in HR in our hypertensive group limits a further deterioration of oxygen parameters.
References


