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Intravenous instrumentation alters the autonomic state in humans

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Abstract Intravascular instrumentation may induce syncope or presyncope. It is not known whether asymptomatic subjects also have autonomic reactions, albeit concealed. We addressed this issue by studying 44 healthy young male subjects of various levels of fitness, ranging from inactivity to athletic (mean maximal oxygen uptake was 49.1 (SD 10.7) ml·kg⁻¹·min⁻¹, range 28.7-71.9 ml·kg⁻¹·min⁻¹). The autonomic response to venous cannulation was quantified by measuring heart rate before cannulation (HR₁), after cannulation (HR₂), and after complete pharmacological autonomic blockade (HR₃). The sympato-vagal balance before and after cannulation was computed as HR₁/HR₀ and HR₃/HR₀, respectively. The group means of heart rate and sympato-vagal balance decreased significantly (paired Student's t-test P < 0.01) from 62.5 to 59.9 beats·min⁻¹, and from 0.71 to 0.68, respectively. The maximal decrease in heart rate was 8.8 beats·min⁻¹, and in the sympato-vagal balance was 0.11. Our study demonstrated that the asymptomatic subjects responded to intravenous instrumentation with a concealed autonomic reaction. Thus, from our findings it would seem that intravenous instrumentation interferes with measurements relating to autonomic nervous system activity.

Key words Heart rate · Autonomic nervous system · Intravenous injections · Metoprolol · Atropine

Introduction

It is common clinical experience that intravascular instrumentation may cause syncope and presyncope. In overt syncope, the autonomic state of a subject obviously changes dramatically. In presyncope, however, such changes are less pronounced, and it may well be that mild autonomic reactions to intravascular instrumentation are not perceived at all. The existence of such a concealed autonomic response seems likely considering the reported increased incidence of vasovagal symptoms due to orthostatic stress in association with intravascular instrumentation (Imholz et al. 1991; McIntosh et al. 1994; Stevens 1966; Tuinenburg et al. 1992). It is possible that a concealed autonomic response to intravenous instrumentation would make the subjects more prone to a vasovagal response to orthostatic stress.

Intravascular instrumentation is inherent in studies and diagnostic procedures that involve the intravascular administration of drugs, arterial or venous blood sampling, or invasive blood pressure measurement. It is conceivable that a concealed autonomic response to the instrumentation could flaw the interpretation of such measurements. However, no studies investigating the existence of a concealed autonomic reaction to intravascular instrumentation have yet been reported.

One way to quantify a concealed autonomic response to intravenous instrumentation is the measurement of the heart rate before and after instrumentation, and after complete pharmacological autonomic blockade. According to the classical Rosenblueth-Simeone model (Rosenblueth and Simeone 1934), heart rate (HR) can be expressed as the product of a sympathetic factor, m, a vagal factor, n, and the intrinsic heart rate, HR₀:

$$ HR = m \cdot n \cdot HR_0 \quad (m \geq 1; n \leq 1) $$

The factors m and n represent the simultaneous sympathetic acceleration and vagal deceleration of sinus node firing. In the absence of sympathetic and/or vagal tone, m and/or n equal 1. When the sympathetic tone increases, m increases, and when the vagal tone
increases, \( n \) decreases. The sympathovagal balance has been expressed by the product \( m \cdot n \) (Bootsma et al. 1994; Smith et al. 1989). This product is greater or less than 1 in states of sympathetic or vagal predominance, respectively. It has been reported that the values of \( m \cdot n \) and \( H R_0 \) can be determined by complete pharmacological blocking of the adrenergic and cholinergic influences on the heart (Katona et al. 1982; Smith et al. 1989). Thus, when \( H R \) before and after intravenous instrumentation is divided by \( H R_0 \), the sympathovagal balance before and after instrumentation is known.

The current study explores, using the method described above, the autonomic effects of inserting a needle into a vein of the left underarm of healthy young male subjects.

**Methods**

**Subjects**

The study protocol was approved by the Leiden University Hospital Medical Ethics Committee on November 3, 1993. The subjects were recruited by advertisement in the local university press. After informed consent, and prior to inclusion, the subjects had a physical examination, a 12-lead electrocardiogram (ECG), and a medical history was taken. Also, the maximal oxygen uptake (\( VO_{2\text{max}} \)) was determined by a cycle exercise test [initial load 40 W, increment 20 W \( \cdot \text{min}^{-1} \); after the principle of Bruce et al. (1963)].

**Protocol**

Measurements were done between 8.30 and 11 a.m., after a light breakfast, in a quiet, comfortable room (temperature 22°C). The subjects were instructed to abstain from any caffeine containing beverages and alcohol after 8 p.m. the preceding evening. Smoking was not allowed on the morning of the study.

During the sessions, a 2-lead ECG and a single lead respiration signal (thoracic impedance) were recorded on a Marquette Holter recorder (Marquette Electronics Inc., Milwaukee, Wis, USA). The ECG was also monitored visually. Arterial blood pressure was noninvasively measured from the left upper arm (Accutor 3, Datascope Corp., Montvale, N.J., USA). To prevent undue mental stress or falling asleep, the subjects were entertained with a video tape (wildlife, arts). The subjects breathed freely, and did not speak during the session. All measurements were made in the supine position.

First, the subjects were supine for 20 min. After this stabilization period, HR was measured in three 6-min episodes (called episodes 1, 2, 3). Episode 1 immediately followed the 20-min stabilization period. For the administration of the autonomic blocking agents, a cannula (Venflon 2.0 1.2 mm, length 4.5 mm, BOC Ohmeda AB, Helsingborg, Sweden) was placed in a vein of the left underarm, and, after 4 min of re-stabilization, HR was again measured (episode 2). Prior to episode 3, adrenergic and cholinergic blockade was accomplished by four equal doses of atropine (4.0.01 mg \( \cdot \text{kg}^{-1} \)), given 3 min apart, and by four equal doses of metoprolol tartrate (4.0.05 mg \( \cdot \text{kg}^{-1} \)), given 3 min apart (Katona et al. 1982). The subjects thus received total doses of 0.20 mg \( \cdot \text{kg}^{-1} \) metoprolol and 0.04 mg \( \cdot \text{kg}^{-1} \) atropine, which have been reported to block completely the sympathetic and parasympathetic influences on the sinus node for about 20 min (Jose 1966).

After the session, the ECG was analysed with a Marquette Series 8000 Holter Analyser. Data were then downloaded to a personal computer. First, the HR in episodes 1, 2 and 3 (\( HR_1, HR_2, \) and \( HR_3 \)) were computed, and, subsequently, the sympathovagal balances in episodes 1 and 2 (\( m_1 \cdot n_1 \) and \( m_2 \cdot n_2 \)) were computed by dividing \( HR_1 \) and \( HR_2 \) by \( HR_0 \). Finally, we computed the change in HR, \( \Delta HR = HR_2 - HR_1 \), and the change in sympathovagal balance, \( \Delta m \cdot n = m_2 \cdot n_2 - m_1 \cdot n_1 \). To investigate the relationships between fitness level, \( HR_1, m_1 \cdot n_1 \), \( HR_0 \), and \( \Delta m \cdot n \), we made linear regressions of \( HR_0 \) on \( VO_{2\text{max}} \), \( HR_1 \) on \( VO_{2\text{max}} \), \( m_1 \cdot n_1 \) on \( VO_{2\text{max}} \), \( \Delta HR \) on \( VO_{2\text{max}} \), \( \Delta m \cdot n \) on \( m_1 \cdot n_1 \).

**Results**

Originally, 50 subjects participated in the study. Of these, 6 subjects were excluded from further analysis because of technical failure (bad ECG, 1 subject), episodes of nonsinus rhythm (3 subjects), and overt vasovagal syncope shortly after venous cannulation (2 subjects). The remaining 44 subjects (see Table 1 for subject characteristics) did not show any overt sign or symptom of a vasovagal reaction during the session.

Figure 1 shows the consequences of venous cannulation on the instantaneous HR of subject no. 42. During supine stabilization, HR decreased. Inserting the needle caused a transient period of a lower HR with relatively few sinus arrhythmia. Then, HR variability resumed, but at a decreased rate. This pattern differed from subject to subject as to the immediate reaction to inserting the needle, and to the later HR decrease. Some

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.7</td>
<td>3.6</td>
<td>20.2</td>
<td>33.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182.7</td>
<td>7.3</td>
<td>166</td>
<td>201</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>75.8</td>
<td>8.9</td>
<td>61.0</td>
<td>101.0</td>
</tr>
<tr>
<td>Maximal ( O_2 ) uptake (ml ( \cdot \text{kg}^{-1} \cdot \text{min}^{-1} ))</td>
<td>49.1</td>
<td>10.7</td>
<td>28.7</td>
<td>71.9</td>
</tr>
</tbody>
</table>

![Fig. 1 Cardiogram of subject no. 42. The averaged heart rate (HR) of this subject was 63.8 beats \( \cdot \text{min}^{-1} \) in episode 1, and 56.9 in episode 2.](image)
Tabic 2 Heart rate and sympathovagal balance before and after cannulation (n = 44). HR0, Intrinsic heart rate HR1, initial heart rate, HR2, heart rate after cannulation, ΔHR change in heart rate due to cannulation, m1, n1, sympathovagal balance before cannulation, m2, n2, sympathovagal balance after cannulation Δm·n change in sympathovagal balance due to cannulation

<table>
<thead>
<tr>
<th></th>
<th>Mean (beats·min⁻¹)</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR0</td>
<td>88.3</td>
<td>9.1</td>
<td>73.3</td>
<td>107.1</td>
</tr>
<tr>
<td>HR1</td>
<td>62.5</td>
<td>9.8</td>
<td>45.9</td>
<td>95.1</td>
</tr>
<tr>
<td>HR2</td>
<td>59.9</td>
<td>9.5</td>
<td>43.9</td>
<td>92.9</td>
</tr>
<tr>
<td>ΔHR</td>
<td>-2.6**</td>
<td>3.1</td>
<td>-8.8</td>
<td>+3.0</td>
</tr>
</tbody>
</table>

m1 · n1: 0.71 0.08 0.50 0.89
m2 · n2: 0.68 0.09 0.49 0.91
Δm·n: 0.03** 0.04 -0.11 +0.04

Paired Student's t-test, P < 0.01

subjects even tended to assume a HR after insertion of the needle that was slightly higher than the control value. Table 2 lists mean, SD and ranges of the intrinsic HR, and of the HR and m·n before and after cannulation. Cannulation entailed a significant decrease in both HR and m·n. There were no differences between the responses of smokers and nonsmokers.

Table 3 lists the regression constants and correlations between fitness level, HR1, m1, n1, HR0, and ΔHR or Δm·n due to venous cannulation. The decreases in HR and in m·n seemed to become smaller with increasing fitness level, and to become larger with increasing HR1 or m1·n1. However, the correlation coefficients did not reach statistical significance. Significant correlations were found for HR0 and HR1 versus VO2max.

Figures 2 and 3 show the scatterplots of the relationship between VO2max and ΔHR, and between HR1 and ΔHR. Obviously, there is no influence of the fitness level on ΔHR (Fig. 2). Also, there is no relationship between HR1 and ΔHR (Fig. 3). Figures 2 and 3 show also that the fitness levels and HR1 were evenly distributed over the entire ranges.

**Discussion**

We studied a group of 50 apparently healthy men, from which 4 subjects were excluded for technical reasons.

Table 3 Regression constants and correlations between fitness level (maximal oxygen uptake, VO2max) and initial resting heart rate (HR0), initial sympathovagal balance (m1·n1), intrinsic heart rate (HR1), and the change in the sympathovagal balance due to venous cannulation (Δm·n) and change in heart rate due to cannulation (ΔHR)

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>Slope</th>
<th>Intercept</th>
<th>r</th>
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</thead>
<tbody>
<tr>
<td>VO2max</td>
<td>HR0</td>
<td>-0.35</td>
<td>105.6</td>
<td>-0.42**</td>
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<tr>
<td>VO2max</td>
<td>HR1</td>
<td>-0.44</td>
<td>84.2</td>
<td>-0.48**</td>
<td></td>
</tr>
<tr>
<td>VO2max</td>
<td>m1·n1</td>
<td>-0.00</td>
<td>0.81</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>VO2max</td>
<td>ΔHR</td>
<td>+0.024</td>
<td>-3.8</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>VO2max</td>
<td>Δm·n</td>
<td>-0.08</td>
<td>+2.2</td>
<td>-0.25</td>
<td></td>
</tr>
<tr>
<td>HR1</td>
<td>ΔHR</td>
<td>-0.0001</td>
<td>-0.04</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>m1·n1</td>
<td>Δm·n</td>
<td>-0.08</td>
<td>0.02</td>
<td>-0.18</td>
<td></td>
</tr>
</tbody>
</table>

**Significant correlation, P < 0.01**

and for episodes of nonsinus rhythm. A further 2 individuals had to be excluded because of vasovagal syncope; this again underlines the fact that vasovagal reactions to simple invasive procedures like venous cannulation are relatively common, even in the supine position (see also Pavlin et al. 1993). The VO2max values in the remaining 44 subjects covered fitness levels of which the extreme values corresponded to a sedentary and an athletic lifestyle,
respectively (Table 1, Fig. 2). Table 3 shows that there was a weak, statistically insignificant correlation between fitness and \( m \cdot n \). The correlations between fitness and \( H R \), or \( H R_0 \) were significant (Table 3). This illustrates that a higher fitness level was associated with a lower resting \( H R \), due to a lower \( H R_0 \) rather than to a lower \( m \cdot n \). Table 3, and Figs. 2 and 3, show that the change in \( H R \) in response to venous cannulation was neither related to fitness, nor to \( H R_1 \). Moreover, \( \Delta m \cdot n \) was not related to fitness or to \( m \cdot n \). Hence, in clinical practice, the intensity of the autonomic reaction to venous cannulation cannot be predicted from \( H R_1 \), or from the fitness level.

Both \( H R \) and \( m \cdot n \) decreased significantly after cannulation (Table 2). Possible mechanisms include a reflex response to intravenous receptor stimulation. It has been reported that severe visceral pain [from veins in the viscera (Nicoldi et al. 1994)] may lead to vasovagal fainting, induced by simultaneous vagal activation and sympathetic inhibition (Van Lieshout et al. 1991). The autonomic reactions to cannulation in the group we studied, from which subjects with any clinical sign of a vasovagal reaction were excluded, might be a mild, concealed response, mediated by the same reflex.

The mean decrease in \( H R \) was 2.6 beats \( \cdot \min^{-1} \), the mean decrease in \( m \cdot n \) was 0.03; maximal decreases were 8.8 beats \( \cdot \min^{-1} \) and 0.11, respectively. These numbers can be put into physiological perspective by realizing that the difference between supine and standing values of \( m \cdot n \) is approximately 0.25 (Janssen et al. 1993). The average decrease in \( m \cdot n \) of 0.03 is about 10\%, and the maximally observed decrease of 0.11 is about 40\% of that value. Hence, a concealed autonomic response to venous cannulation can assume such intensity that it imposes a methodological problem on invasive autonomic studies.

The duration of the autonomic response to cannulation might be long, as later fainting in tilting experiments has suggested (McIntosh et al. 1994). However, this issue was not addressed by our study, where only short-term effects were measured. Also, our study did not reveal whether a decrease in sympathetic tone, an increase in vagal tone, or a mixed response caused \( m \cdot n \) to decrease (the two-stage pharmacological blocking revealed the sympathetic and vagal tones after, but not before cannulation).

Several clinical and research procedures might be sensitive to the effect of cannulation on the autonomic status. Examples of such procedures are: programmed electrical stimulation (where vagal activation might influence cardiac arrhythmogeneity), dobutamine stress testing (where sometimes atropine has to be administered in order to increase \( H R \) sufficiently; McNeill et al. 1992), and catecholamine sampling (cannulation might cause lower catecholamine concentrations). Our study demonstrated that cannulation, besides the well-known incidental provocation of syncope, also induces a concealed autonomic response. This finding constitutes an extra argument against cannulation in studies which relate to autonomic nervous system activity: autonomic measurements should preferably be noninvasive.

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References