The influence of beta-blockade on cardiac output in a maximum exercise test

Fikenzer S[1], Drechsler K[4], Falz R[1], Tegtbur U[3], Thomas M[2], Schulze A[1], Bressau K[1], Hoppe S[1], Busse M[1]

1 Institute of Sports Medicine, University of Leipzig (Director: Prof. M. Busse, MD)
2 Orthopedic Clinic & Polyclinic, University of Leipzig (Director: Prof. Dr. med. G. Von Salis-Soglio)
3 Center of Sports Medicine, Hannover Medical School (Leader: PD Dr med. U. Tegtbur)
4 Clinic of Cardiology, Heart-Center-Leipzig (Director: Prof. Dr. med. G. Schuler)

Abstract

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Objective:
This study examines the changes in cardiac output (Q) during and after effort and assesses the extent to which β-blockade influences the development of cardiac output during effort. This was examined during and after a maximal anaerobic test.

Methods:
Five male students of the University of Leipzig (average age – 25.4 yrs, average BMI – 23.98 kg/m^2, average RR – 141.2/80.8) with hypertension and pre-hypertension participated in a maximal anaerobic test. After four days' rest, they began a three-day course of 5 mg/d of bisoprolol and, on the last day of this, they participated in a repeat test. We used the bioimpedance device Physio Flow™ to analyze Q. Variables were examined between 0% and 100% of maximum effort at 10% increments and in the rest periods after the first, third and fifth minutes.

Results:
- β-blockade does not influence Q during effort;
- β-blockade does not influence maximum effort;
- β-blockade does not influence maximum oxygen uptake.

Conclusion:
It was possible to demonstrate that cardioselective β-blockers do not affect cardiac haemodynamics under maximum effort, or do they restrict cardiac performance regarding VO_2max, V_E and Watts.

Key words:
arterial hypertension, cardiac output, stroke volume, heart rate, exercise test, beta blocker, students

Introduction:

More and more frequently, young people in the second decade of life have blood pressure readings at the level of Stage 1 hypertension, ≥140/90 mm Hg, which means that treatment with drugs to lower blood pressure has to be considered (7th Report of the Joint National Committee, 2003 in Falz, 2007). Hypertension is "repeatedly elevated blood pressure in the arterial system" and "is directly or indirectly responsible for a range of damage to organs and blood vessels" (Reuter, 2007, p.835).

Treating hypertension using drugs has, therefore, the aim of lowering blood pressure. In the case of young people, the treatment of choice is mainly monotherapy with a beta-blocker. The "first-line beta-blockade…is at least as efficacious as first-line ACE-inhibition in reducing the morbidity/mortality of moderate/severe heart failure" (Cruickshank, 2007, p.11). When treating hypertension with beta-blockers, the latter's negative inotropic effect plays a crucial role, as "blood pressure is created solely by contraction of the heart" (Bartels & Bartels, 2004, p.167). The question arises as to how far beta-blockers influence the performance ability of these young, mainly athletic, active people. Statements made in the literature regarding this are somewhat contradictory.

Methods

Study Group:
The test group consisted of five young adult men with pre-hypertension or Stage 1 hypertension (see 7th Report of the Joint National Committee, 2003). These subjects were in the age range 23-30 (average = 25.4 ± 2.8). Their average weight was 82.4 ± 13.3 kg. Their average height was 185 ± 10.5 cm. All subjects took part in sport (> 4 hr/wk) and, apart from elevated blood pressure at rest, had no other acute or chronic illnesses. The test

group could be described as specifically accomplished at sport, as all subjects had already completed cycle ergometer tests for diagnostic purposes on many occasions. Tables 1 and 2 contain detailed information on the test group and the inclusion and exclusion criteria. Tests took place under the following average conditions, which were held at an approximately constant level by an air conditioning system:

- Temperature: 20.4° C (± 0.75)
- Air pressure: 982.2 hPa (± 0.7)
- Humidity: 63.05% (± 3.75)

At the time of the tests the subjects were free from inflammatory diseases and none of them had a medical contraindication. The commonly used criteria for maximal anaerobic tests were taken as the basis for these tests (Löllgen, 1995).

Procedure:

All subjects were fully informed of the content and procedure of the voluntary study. The study was approved by the University of Leipzig's Ethics Committee. Before taking part in the study, all subjects had to undergo a medical check, including a survey of anthropometric data, routine lab tests, cardiac ultrasound, ECG at rest and bioimpedance analysis.

After the subjects had been included in the study, a schedule was established for the maximal aerobic tests. The schedule was drawn up in such a way that, on the one hand, there was enough recovery time for the patients between the tests and, on the other hand, there was no possibility that training effects could influence the results. That meant the post-test took place after seven days.

On the first test day the subjects underwent the preliminary examination described above. After being included in the test group, the first incremental exercise test followed on the second day. The intervention with the cardioselective β_1-receptor blocker bisoprolol hemifumarate began two days before the repeat test. This involved the patients taking one 5mg tablet of bisoprolol every day, two hours before their respective test times. A further incremental exercise test followed on the third day of the intervention. The cycle ergometer maximal aerobic test was carried out during the period from 10.00 to 15.00. During this, it was ensured that each individual patient's test took place at exactly the same time of day, in order to prevent fluctuations in performance due to time of day. The test was performed using a semi-recumbent ergometer in a laboratory designed for exercise ECG testing. The advantage of using a semi-recumbent rather than an upright ergometer is that the upper body position is considerably more restful and, therefore, there is considerably less artefact sensitivity. Furthermore, this position ensures a better tolerance in the subjects in respect of access to peripheral veins, as the arm unit does not need to be used for support.

The angle of the semi-recumbent ergometer was set at 35° and the saddle height and pedal pressure point could be adjusted to suit the body's proportions.

The feet were fixed firmly to the ergometer pedals with Velcro fastenings, so the subjects had to concentrate solely on pedalling. A cadence of between 75-85 rpm was set and a firm lower limit was specified, at which point the test would be terminated.

All subjects were examined in the semi-recumbent position. The load was raised by 10 Watts/min from a starting point of 30 Watts, until the subject was exhausted or until the objective criteria were reached for terminating the test (Fig. 1). Assessments were made of the following, beginning with the value at rest before exercise, at the end of every third minute of exercise and at the point of maximum effort (Test, Fig. 1): heart rate (HR), cardiac output (Q), lactate (Lac), respiratory minute volume (V_E), oxygen uptake (VO_2) and the catecholamines adrenaline (A) and noradrenaline (NA). Subsequently, subjects rode for five minutes at 25% of maximum effort achieved. Data was collected in the rest period at the end of the first, third and fifth minutes (Rest, Fig. 1).

Table 1: Inclusion and Exclusion Criteria for Taking Part in the Study.

Inclusion Criteria	*Exclusion Criteria*
• Healthy • Pre-hypertension, Stage 1 Hypertension • No known cardiac ailment • No orthopaedic ailment • Aged between 20-35 • Cardiac ultrasound (with no pathological findings)	• Coronary heart disease (CHD) • Cardiac insufficiency • Cardiac conduction disorders • Any cardiac arrhythmia • Resting bradycardia (under 50 bpm) • Bronchial asthma • Hypotension (under 110 mmHg systolic) • Angina pectoris • Evidence of orthopaedic and traumatological pathology • Acute viral/bacterial infections

Table 2: Socio-Demographic Data.

Group	Number of subjects	N = 5
	Age	Average = 25.4 ± 2.8 years
	Height	Average = 184.8 cm ± 10.5 cm
	Weight	Average = 82.4 kg ± 13.3 kg
	Blood pressure	Average = 141 (± 9)/81 (± 8)
	Sex	Male

Measuring cardiac output with Physio Flow™:

Manatec Biomedical developed the Physio Flow™ device in the 1990s. Only six gel electrodes are needed to measure cardiac output, two to measure heart rate and four to record the impedance signal. A calibration stage of 30 cardiac cycles was carried out entirely under rest conditions, after previously inputting external patient parameters such as blood pressure, height and weight. This permitted exact measurements of cardiac output to be taken.

Charloux et al (2000) proved in their study on impedance cardiography that this is a reliable, non-invasive method. In it, measurements taken with Physio Flow™ were compared with a simultaneous data collection using the Fick method. Cholley & Payen (2005), Kööbi et al. (1997) and others also carried out comparative studies on the Fick method, whereas, for example, Cotter et al. (2004), Scherhag et al. (2005), Van de Water et al. (2003) and Woltjer et al. (1996a) made comparisons with the thermodilution method. In all studies the accuracy of the bioimpedance analysis measurement could be proved and confirmed.

Evaluation:

One part of the evaluation was obtained from the relative effort (% of maximum effort). In order to be able to specify the same percentage rates for all subjects, the data sets were interpolated. The statistical comparison took place on the basis of the relative effort.

The results are specified as Average (Av) and Standard Deviation (SD). Significant differences were calculated by means of a variance analysis for repeat measurements. Significance levels: $p<0.05$: *, $p<0.01$: **, $p<0.005$: ***, $p<0.001$: ****.

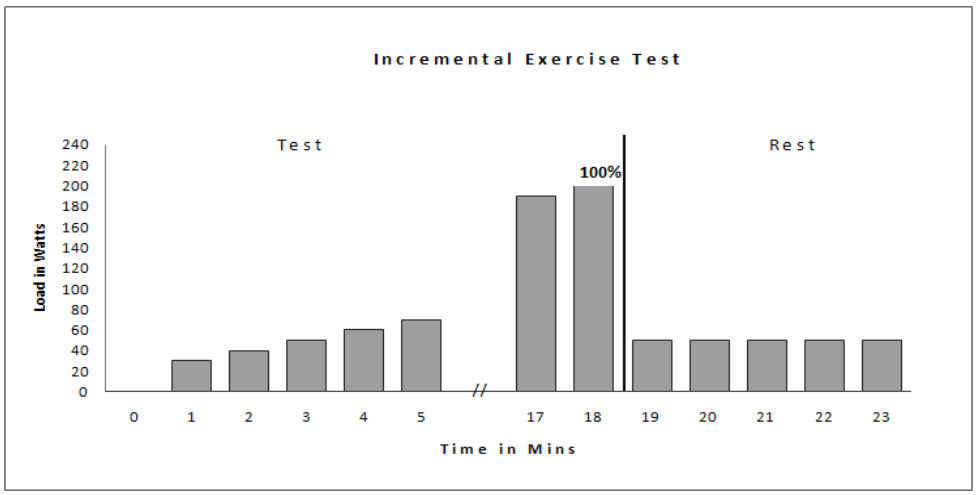

Figure 1: Test Procedure

Results

Table 3 summarizes the results of the incremental exercise tests with and without β- blockade. From this it can be seen that the β-blockade had no influence on maximum effort. All haemodynamic variables and the spirometric parameters remained unaffected. There was a tendency for heart rate, diastolic blood pressure at rest and diastolic blood pressure five minutes after effort to be affected. Heart rate at maximum effort and systolic blood pressure, both at rest and five minutes after effort, were significantly lower. Figure 2 presents the data for HR, stroke volume (SV), Watts and Q at maximum effort with and without β-blockade. Figure 3 shows how heart rate changed during the course of the incremental test. It should be recognized that resting heart rate tended to be lower and that heart rate was significant lower at maximum effort by, on average, 25 bpm.

Table 2: Overall results summary.

		Rest			Max			5 min after effort		
		without β-blocker	with β-blocker	p	without β-blocker	with β-blocker	P	without β-blocker	with β-blocker	p
P_{max}	Watts	0	0	ns	284.0 (±55.5)	284.0 (±55.5)	ns	69.0 (±13.4)	69.0 (±13.4)	ns
HR	bpm	75.4 (±12.1)	58.8 (±10.5)	p= 0.056	183.4 (±12.1)	158.0 (±11.7)	*	131.1 (±14.3)	106.4 (±13.1)	p= 0.056
RRsys	mmHg	141.2 (±9.5)	117.6 (±6.3)	**	225.4 (±21.6)	202.4 (±19.1)	ns	164.4 (±19.7)	137.8 (±9.7)	*
RRdia	mmHg	80.8 (±8.2)	70.2 (±9.8)	p= 0.095	80.0 (±16.1)	73.8 (±14.9)	ns	69.01 (±7.7)	60.2 (±13.0)	p= 0.095
Q	L/min	8.9 (±2.5)	7.6 (±2.0)	ns	31.3 (±6.3)	29.0 (±6.1)	ns	20.6 (±6.0)	18.1 (±4.3)	ns
SV	ml	118.0 (±25.4)	129.6 (±20.0)	ns	171.1 (±35.6)	183.0 (±33.2)	ns	158.1 (±46.3)	170.1 (±33.9)	ns
Ef	%	57.2 (±6.1)	58.8 (±3.8)	ns	84.3 (±4.1)	82.2 (±2.9)	ns	72.9 (±10.5)	72.7 (±7.2)	ns
V_E	L/min	13.8 (±2.8)	14.7 (±5.6)	ns	125.4 (±21.8)	133.4 (±31.3)	ns	52.3 (±6.6)	53.3 (±7.4)	ns
VO_2	ml/min	273 (±31.5)	260 (±15.1)	ns	3320 (±527.9)	3114 (±545.0)	ns	1536 (±281.0)	1453 (±354.2)	ns

Figure 4 shows how cardiac output changed during the course of the incremental exercise test. As effort increased during the test, Q rose, both with and without β-blockers, and immediately fell when effort ceased. In the test with β-blockade, the lowering that can be seen on the graph cannot be statistically proved, due to the small number of subjects and the relatively large standard deviation.

So, at the present time, it is not possible to determine any influence of the β-blockade on cardiac output. The same result was determined for stroke volume (Fig. 5). As effort increased, stroke volume rose and then fell again immediately effort ceases. It is also not possible to prove statistically the higher SV values in the test with β-blockade that can be seen on the chart. Based on the results, this means that it is not possible to infer that the β-blockade had an influence on stroke volume.

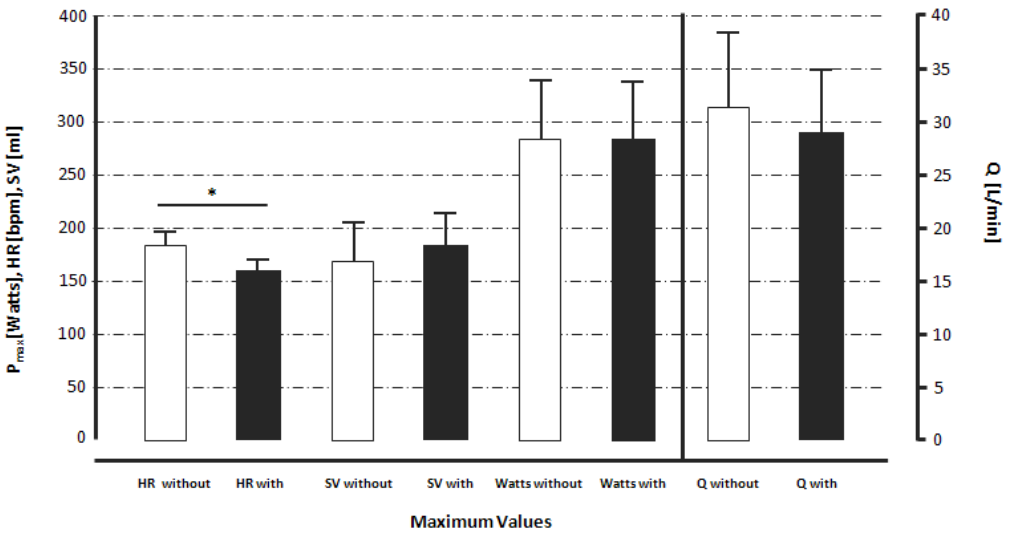

Figure 2: Maximum values in incremental exercise test (Av ± SD)

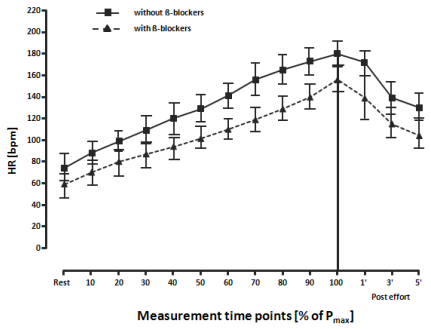

Figure 3: Heart rate in incremental exercise test (Av ± SD)

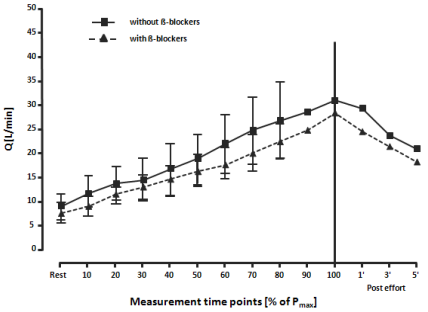

Figure 4: Cardiac output in incremental exercise test (Av ± SD)

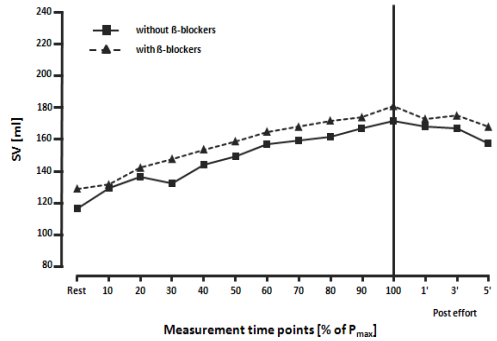

Figure 5: Stroke volume in incremental exercise test (Av ± SD)

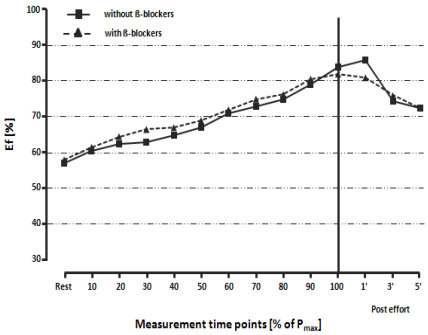

Figure 6: Ejection fraction in incremental exercise test (Av ± SD)

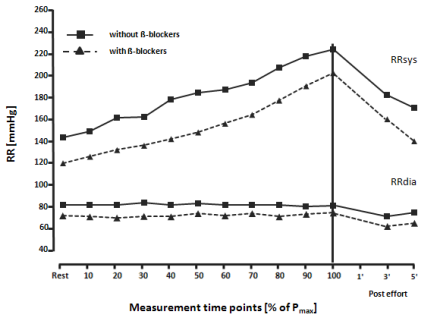

Figure 7: Blood pressure in incremental test (Av ± SD)

Figure 6 shows how the ejection fraction progressed over the course of the incremental exercise test. As effort increased, the Ef rose from 57% to 84% in the test without β-blockade and from 59% to 82% in the test with β-blockade. There was no measurable statistical difference between test conditions. After the effort was terminated, the Ef remained at the termination level and it was only from three minutes after effort that Ef started to decrease. Figure 7 shows blood pressure (systolic and diastolic) in the incremental exercise test. The initial lower systolic values in the test with β-blockade remained unchanged over time. The trend in blood pressure values was the same in both series of tests.

Discussion

Maximum effort leads to a significant rise in the Q parameter and its components HR, SV and Ef, together with RRsys and the respiratory parameters V_E and VO_2. These results confirm the findings of other scientists, such as Jilka et al. (1983) and Wilmore et al. (1985). During effort, the sympathetic nervous system is activated. There is increased sympathetic tone, but reduced vagal activity. The release of additional NA and A causes increased myocardial contractility, as a result of which HR and RRsys are raised. When the body moves, in particular its extremities, the muscle pump increases venous return, which raises end-diastolic volume (EDV). The rise in contractility and EDV lead to an increase in SV (Frank-Starling mechanism) and Ef. As HR also rises, Q increases. In the maximal aerobic test, the beta-blocker bisoprolol leads to a significant reduction in HR and RRsys. All other parameters, Q, SV, Ef, VO_2, RRdia and V_E show no significant changes through the use of bisoprolol. Testing for a correlation or a possible interaction between maximum effort and beta-blockers is

only significant in the case of HR, i.e. the way HR progresses during effort is influenced by both effort and bisoprolol. In addition, bisoprolol has an enhanced effect at maximum effort. It is to be expected that HR and RRsys will be lowered, as this is a primary purpose of beta-blockers, and this confirms the results of other studies such as, for example, those of Franz et al. (1982), Jilka et al. (1983) and Nutall et al. (2003). It is apparent from the significantly reduced values for HR and RRsys, that an effective beta-receptor blockade is also achieved with a lower dose of 5 mg/d. In all studies examined, no change in RRdia was observed under beta-receptor blockade, which also confirms the present results. According to Anderson et al. (1985), an increase in SV results from prolonged ventricular diastolic filling due to lowered HR, through an increase in EDV and from a larger myocardial contraction, as per the Frank-Starling law. Bruce et al. (1979) and Cohn (1985) established significant reductions in RRsys, Q and HR. The increase in SV can be considered as a compensation mechanism for this and possibly arises from the same myocardial contractility (as Ef). Yet V_E and VO_2 do not behave any differently under cardioselective beta-blockade than without (Cogliati et al., 2004; Franz et al., 1982; Sheehan et al., 1983) and this was actually established by Sklar et al. (1982) in tests with non-selective and cardioselective beta-blockers. Stoschitzky et al. (2004) tested solely the change in plasma concentrations of NA and A under beta-receptor blockade with bisoprolol (5 mg) and established that this increases during effort in the case of both transmitters. They also discovered that, during effort, bisoprolol was released from the receptors and discharged into the plasma. Therefore the effect of the beta-blockers would have to decline and the effect of the catecholamines on the heart would have to increase. This could explain the concurrent haemodynamics of the heart under effort. Unfortunately there is a lack of additional studies that confirm this connection.

Summary

It was possible to demonstrate that cardioselective β-blockers do not affect cardiac haemodynamics under maximum effort, or do they restrict cardiac performance regarding VO_2max, V_E and Watts.

References

1. **Bartels, R. & Bartels, H., (2004).** *Physiologie. Lehrbuch der Funktionen des menschlichen Körpers* (7th edition). Munich: Elsevier GmbH.
2. **Bruce, R.A., Hossack, K.F., Kusami, F. & Clarke, L. J., (1979).** Acute effects of oral Propanolol on hemodynamic responses to upright exercise. *The American Journal of Cardiology,* 132-140.
3. **Charloux, A., Lonsdorfer-Wolf, E., Richard, R., Lampert, E., Oswald-Mammosser, M., Mettauer, B., Geny, B. & Lonsdorfer, J., (2000).** A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *European Journal of Applied Physiology,* **82**, 313-320.
4. **Cholley, B. & Payen, D., (2005).** Noninvasive techniques for measurements of cardiac output. *Current Opinion in Critical Care,* **11**, 424-429.
5. **Cogliati, C., Colombo, S., Russcone, T.G., Gruosso, D., Porta, A., Montano, N., Malliani, A. & Furlan, R., (2004).** Acute β-Blockade increases muscle sympathetic activity and modifies its frequency distribution. *Circulation,* **110**, 2786-2791.
6. **Cohn, J.N., (1985).** Clinical implications of the hemodynamic effects of beta blockade. *The American Journal of Cardiology,* **55**, 125D-128D.
7. **Cotter, G., Moshkovitz, Y., Kaluski, E., Cohen, A.J., Miller, H., Goor, D. & Vered, Z., (2004).** Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. *Chest,* **125**, 1431-1440.
8. **Cruickshank, J.M., (2007).** Review – Are we misunderstanding beta-blockers. *International Journal of Cardiology,* IJCA-09503.
9. **Falz, R., (2007).** *Hypertonieprävalenz und Einfluss von anthropometrischen Parametern und der Lebensweise auf den Blutdruck bei Studenten.* Veröffentlichte Diplomarbeit, Universität Leipzig.
10. **Franz, I.-W., Lohmann, F.W. & Koch, G., (1982).** Effects of chronic antihypertensive treatment with Acebutolol and Pindolol on blood pressures, plasma catecholamines and oxygen uptake at rest and during submaximal and maximal exercise. *Journal of Cardiovascular Pharmacology,* **4**, 180-186.
11. **Jilka, S.M., Joyner, M.J., Nittolo, J.M., Kalis, J.K., Taylor, J.A., Lohman, T.G. & Wilmore, J.H., (1983).** Maximal exercise responses to acute and chronic beta-adrenergic blockade in healthy male subjects. *Medicine and science in sports and exercise,* **20**, 570-573.
12. **Manatec Biomedical (eds.), (2006).** *Physioflow – Non invasive hemodynamic cardiac output* [cited 5 August 2007]. Available from: http://www.physioflow.com.
13. **Nuttall, S.L., Routledge, H.C. & Kendall, M.J., (2003).** A comparison of the β1-selectivity of three β1-selective β-blockers. *Journal of Clinical Pharmacy and Therapeutics,* **28**, 179-186.
14. **Pschyrembel, W., (2004).** *Pschyrembel. Klinisches Wörterbuch* (260., new edition). Berlin: Walter de Gruyter GmbH & Co. KG.
15. **Reuter, D.A. & Goetz, A.E., (2005).** Messung des Herzzeitvolumens. *Der Anaesthesist,* **54**, 1135-1153.

16. **Scherhag, A., Kaden, J.J., Kentschke, E., Sueselbeck, T. & Borggrefe, M., (2005).** Comparison of impedance cardiography and thermodilution-derived measurements of stroke volume and cardiac output at rest and during exercise testing. *Cardiovascular Drugs and Therapy,* **19**, 141-147.
17. **Sheehan, M.W., Brammell, H.L., Sable, D.L., Nies, A.S. & Horwitz, L.D., (1983).** Effect of beta-adrenergic blockade on circulating catecholamines and dopamine-beta-hydroxylase activity during exercise in normal subjects. *American Heart Journal,* **105**, 777-782.
18. **Sklar, J., Johnston, G.D., Overlie, P., Gerber, J.G., Brammell, H.L., Gal, J. & Nies, A.S., (1982).** The effects of a cardioselective (Metoprolol) and a nonselective (Propranolol) beta-adrenergic blocker on the response to dynamic exercise in normal men. *Circulation,* **65**, 894-899.
19. **Stoschitzky, K., Stoschitzky, G., Klein, W., Müller, F., Bühring, K., Lamprecht, G. & Lindner, W., (2004).** Different effects of exercise on plasma concentrations of Nebivolol, Bisoprolol and Carvedilol. *Cardiovascular Drugs and Therapy,* **18**, 135-138.
20. **Van de Water, J.M., Miller, T.W., Vogel, R.L., Mount, E.B. & Dalton, M.L., (2003).** Impedance cardiography. The next vital sign technology? *Chest,* **123**, 2028-2033.
21. **Wilmore, J.H., Freund, B.J., Joyner, M.J., Hetrick, G.A., Hartzell, A.A., Strother, R.T., Ewy, G.A. & Faris, W.E., (1985a).** Acute response to submaximal and maximal exercise consequent to beta-adrenergic blockade: implications for the prescription of exercise. *The American Journal of Cardiology,* **55**, 135D-141D.
22. **Wilmore, J.H., Ewy, G.A., Freund, B.J., Hartzell, A.A., Jilka, S.M., Joyner, M.J., Todd, C.A., Kinzer, S.M. & Pepin, E.B., (1985b).** Cardiorespiratory alterations consequent to endurance exercise training during chronic beta-adrenergic blockade with Atenolol and Propranolol. *The American Journal of Cardiology,* **55**, 142D-148D.
23. **Woltjer, H.H., Bogaard, H.J., Scheffer, G.J., van der Spoel, H.I., Huybregts, M.A.J.M. & de Vries, P.M.J.M., (1996a).** Standardization of non-invasive impedance cardiography for assessment of stroke volume: comparison with thermodilution. *British Journal of Anaesthesia,* **77**, 748-752.
24. **Woltjer, H.H., Bogaard, H.J., van der Spoel, H.I. & de Vries, P.M.J.M., (1996b).** The influence of weight on stroke volume determination by means of impedance cardiography in cardiac surgery patients. *Intensive Care Medicine,* **22**, 766-771.

Correspondence:

Dipl. Sportl. S. Fikenzer
University of Leipzig
Institute of Sports Medicine
Marschner Str. 29
04109 Leipzig
Germany

Email: fikenzer@rz.uni-leipzig.de