Clinical Investigations

Effects of Isosorbide Dinitrate on Electrocardiography, Hemodynamics, and Ventilation in Patients with Exercise-Induced Elevation of Pulmonary Artery Wedge Pressure

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Summary

Background: The mechanisms underlying exertional hyperpnea in patients with coronary artery disease and transient left ventricular dysfunction are still not fully understood.

Hypothesis: The study was undertaken to investigate whether the ventilatory response to exercise reflects the effects of acute medical treatment of exercise-induced left ventricular dysfunction, and to evaluate mechanisms relevant to excessive exertional ventilation.

Methods: In 11 male patients, aged 65.2 ± 6.0 years, all with pulmonary artery wedge pressure (PAWP) > 25 mmHg and ST depression > 2 mm during moderate supine exercise, ventilation ($\dot{V}$), oxygen uptake ($\dot{V}_{O_2}$), hemodynamics, electrocardiogram (ECG), and arterial and mixed venous blood gases were examined during supine rest and exercise, before and at hourly intervals after peroral intake of 30 mg isosorbide dinitrate (ISDN). Six similar patients were examined with the same protocol without ISDN administration and comprised a control group.

Results: Before administration of ISDN, exercise PAWP was 35.3 ± 5.9 mmHg, ECG showed 2.77 ± 1.06 mm ST depression, and $\dot{V}/\dot{V}_{O_2}$ was 31.8 ± 4.8 l/l. One h after ISDN administration, exercise mean PAWP was 11.0 ± 2.5 mmHg ($p < 0.001$), ST depression 0.59 ± 0.8 mm ($p < 0.001$), whereas $\dot{V}/\dot{V}_{O_2}$ was unchanged, 30.1 ± 5.3 l/l. Two h later, PAWP remained reduced and there were only minor ST depressions, while $\dot{V}/\dot{V}_{O_2}$ remained high. Exercise cardiac index (CI) and mixed venous oxygen tension (PvO_2), initially 4.7 ± 0.67

l/min/m² and 3.54 ± 0.35 kPa, respectively, remained at the same low level throughout the study. In the six nontreated patients, there were no significant changes in ST depression, exercise PAWP, or exertional ventilation.

Conclusion: Isosorbide dinitrate treatment markedly improved exercise-induced left heart dysfunction, whereas excessive ventilatory response was unaffected, even after 3 h. Thus, measurements of the exercise hyperpnea did not properly reflect effective reduction of myocardial ischemia.

Key words: electrocardiography, exertional hyperpnea, invasive hemodynamics, blood gases, left heart failure, isosorbide dinitrate

Introduction

Electrocardiographic (ECG) changes,^{1,2} rise in pulmonary artery wedge pressure (PAWP),^{3,4} and hyperpnea^{5,6} are regularly observed during exercise in patients with ischemic heart disease. Acute anti-ischemic treatment reduces ECG changes^{7,8} and the rise in PAWP.^{9,10} There is, however, no unequivocal evidence that acute reduction of ischemia and improvement in cardiac function contribute to normalize the ventilatory response.^{11–13} Excessive exertional ventilation in patients with ischemic heart disease has been ascribed to a multitude of changes induced by the hemodynamic failure, involving pulmonary congestion and disturbed gas exchange, deranged muscular circulation and metabolism, and altered central command of circulation and ventilation.^{14–20} However, the underlying mechanisms are not fully understood.

The purpose of this study was to investigate the ventilatory response to exercise in patients with transient exercise-induced left ventricular dysfunction and to establish whether or not measurements of ventilation can be used to assess the improvement in left ventricular function in such patients. Furthermore, the aim was to evaluate some mechanisms relevant to the excessive exertional ventilation, with emphasis on the relationship between hyperpnea and low cardiac output response and reduced mixed venous oxygen tension (PvO_2).

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With a view to this, ventilation (V), ECG, invasive hemodynamics, and arterial and mixed venous blood gases were studied at supine rest and exercise in patients with exertional left ventricular dysfunction due to myocardial ischemia but without evidence of congestive heart failure (CHF). They were examined before and for several h after administration of isosorbide dinitrate (ISDN).

Material and Methods

The study comprised two patient groups referred to the laboratory for investigation because of suspicion of ischemic heart disease manifested by fatigue, dyspnea, or vague chest pain. None had characteristic angina pectoris or pulmonary disease. Included in the first group were 11 male patients, aged 65.2 ± 6.0 years. During an incremental ergometercycle exercise test in the sitting position,²¹ all patients developed ST depression of at least 1.00 mm (on average 2.81 ± 1.1 mm) in the precordial leads and were referred for diagnostic right heart catheterization,²² which took place several days later. Patients with PAWP > 25 mmHg and ST depression > 2 mm during moderate supine exercise were eligible for the supplementary ISDN study that took place in direct conjunction with the preceding measurements.

The other study group that included 6 male patients, aged 60.5 ± 10.7 years, also with definite ST depression and marked rise in PAWP during moderate supine exercise, served as a control group.

Of the 17 patients, 13 were referred for coronary angiography, and significant coronary artery disease was found in all.

Right heart catheterization began at 8 A.M., after a light morning meal. A Swan-Ganz catheter was introduced through the cubital vein and led into the pulmonary artery. It allowed measurements of right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), PAWP, and sampling of central, mixed venous blood. A cannula in the right cubital artery was used for measurement of mean arterial pressure (MAP) and sampling of arterial blood.

The patients remained in supine position throughout the study to obtain valid hemodynamic comparisons during the resting and exercise registrations and between registrations. Both at rest and during exercise, all recordings were performed with the legs slightly elevated and fixed to the pedals.

Fifteen min after instrumentation, with the patients in a steady resting state, the initial registrations were performed. Half an hour later, the patients performed a bicycle exercise at a constant load, mean 238 ± 33.1 kpm/min (200–300 kpm/min) for 7 min, with measurements beginning 3 min after start of exercise. In accordance with previous experience, the supine exercise load, which had to be tolerable for 7 min, was set to 40% of the maximal load for each individual patient sustained in the previously performed sitting exercise test.

Fifteen min after the first exercise test, the patients included in the first study group received 30 mg ISDN (Sorbangil®, Kabi Pharmacia, Uppsala, Sweden) orally. The patients in the control group received no medication. Then new sets of mea-

surements were performed at rest and during exercise after 1 and 2 h in both groups and a third h after drug consumption for the group treated.

To avoid anxiety and to minimize a possible influence from habituation to the procedure during the repeated exercise tests, emphasis was put on careful instruction of the patients about the steps of the procedure, both before and continuously during the catheterization.

Cardiac output was determined according to the direct Fick principle, while the ST depression was based on measurements 60 ms after the J point in at least three consecutive QRS complexes in the precordial leads. $\dot{V}$ and oxygen uptake ($\dot{V}O_2$) were measured during the last 3 min of respiratory steady state with a modification of the method of Bjerknes and Scholander.²³ The ventilatory data were compared with observations in normal male patients of the same age and size, previously examined with the same technique and at the same level of exercise. Blood was sampled anaerobically in heparinized glass syringes, cooled in ice water, and analyzed for blood gases and pH, using an OSM 3 Hemoxymeter (Radiometer, Copenhagen, Denmark) and an IL pH/blood gas analyzer (Instrumentation Laboratories, Lexington, Mass., USA).

Repeated studies with the present procedure several days apart have documented a high degree of reproducibility of the measurements.²⁴

The Regional Ethical Committee approved the protocol. The patients gave their written, informed consent to participate in the study.

Statistics

The observations are given as means $\pm$ standard deviation. Repeated measures analysis of variance and Student's *t*-test were used for intra- and intergroup comparisons. A *p* value of 0.05 was considered significant.

Results

Table I shows hemodynamic and ECG data, while Table II gives ventilatory and blood gas observations, respectively, all at rest and during exercise, before and with ISDN, in the 11 patients who received treatment.

Before Isosorbide Dinitrate

Except for MAP, which was clearly elevated, all observations were within the normal range at rest. However, PAWP was close to the upper limit of the normal range, whereas cardiac index (CI) was in the lower part, suggesting subnormal left ventricular function. During exercise PAWP and MPAP rose markedly to distinctly pathologic levels, RAP showed a moderate rise, while MAP was further elevated. Cardiac index showed a subnormal rise. All patients developed definite ST depression ($2\text{--}8$ mm) (Table I). The levels of exercise and heart rate (HR) necessary to induce the same individual ST depression (2.73 ± 0.65 mm) during a routine incremental sitting

TABLE I Hemodynamic and electrocardiographic data at rest and during supine bicycle exercise before and after 1–3 h influence of 30 mg isosorbide dinitrate (ISDN) in patients with exercise-induced left ventricular dysfunction

	Before ISDN		With ISDN		p Value	
	0 h	1 h	2 h	3 h	0–1 h	0–3 h
RAP (mmHg)						
Rest	6.7 ± 1.74	4.1 ± 1.35	4.5 ± 1.51	5.0 ± 1.65	***	***
Exercise	11.9 ± 1.84	5.8 ± 1.32	6.7 ± 1.72	6.8 ± 1.67	***	***
PAWP (mmHg)						
Rest	12.0 ± 2.16	6.0 ± 1.48	6.7 ± 1.72	7.6 ± 2.22	***	***
Exercise	35.3 ± 5.86	11.0 ± 2.52	14.4 ± 2.57	15.0 ± 3.06	***	***
MAP (mmHg)						
Rest	118 ± 21.8	82 ± 13.9	91 ± 16.2	91 ± 17.3	***	***
Exercise	141 ± 29.5	112 ± 19.3	110 ± 21.6	110 ± 19.8	***	***
HR (beats/min)						
Rest	67 ± 12.4	71 ± 18.5	68 ± 13.7	67 ± 14.9	NS	NS
Exercise	101 ± 13.8	96 ± 11.4	95 ± 11.5	96 ± 10.7	*	NS
CI (l/min/m ²)						
Rest	2.9 ± 0.78	2.2 ± 0.61	2.2 ± 0.40	2.3 ± 0.48	***	**
Exercise	4.8 ± 0.67	4.5 ± 0.67	4.4 ± 0.53	4.6 ± 0.58	NS	NS
ST depression (mm)						
Rest	0.09 ± 0.30	0.07 ± 0.16	0.11 ± 0.30	0.09 ± 0.30	NS	NS
Exercise	2.77 ± 1.06	0.59 ± 0.83	0.68 ± 0.87	0.86 ± 0.74	***	***

Data given as means ± standard deviation.

*** = $p < 0.001$.

** = $p < 0.01$.

* = $p < 0.05$.

Abbreviations: RAP = right atrial pressure, PAWP = pulmonary artery wedge pressure, MAP = mean arterial pressure, HR = heart rate, CI = cardiac index, NS = not significant.

exercise test several days before catheterization were considerable higher; they were 536 ± 92 kpm/min and 118 ± 11 beats/min, respectively ($p < 0.001$). $\dot{V}/\dot{V}_{O_2}$ was clearly higher than in normals, 122% of predicted ($p < 0.05$). Except for Pv_{O_2} , which was definitely lower than expected (4 kPa), the blood gas observations were normal (Table II).

With Isosorbide Dinitrate

Apart from HR which remained unchanged, all hemodynamic parameters were reduced at rest, in particular CI (Table I). Initially, alveolar CO_2 (P_{aCO_2}) showed a fall and pH_a a rise, while Pv_{O_2} was markedly reduced (Table II). During exercise there was markedly less rise in pressures than before ISDN, in particular PAWP. Heart rate showed a slight decline, while CI remained at the same subnormal level. Thus, the PAWP–CI relationship reflected a distinct improvement in left ventricular function. In six patients ST depression disappeared completely, while in five it was markedly reduced (Table I). $\dot{V}$ was slightly lower, while $\dot{V}/\dot{V}_{O_2}$ was unchanged (Table II). P_{aCO_2} remained the same, whereas P_{aO_2} showed a tendency to rise, suggesting some improvement of the alveolar-arterial gas exchange.

In the control group, the initial PAWP and ST depression were 27.2 ± 5.89 mmHg and 1.5 ± 0.71 mm, respectively,

while $\dot{V}$ and $\dot{V}/\dot{V}_{O_2}$ were 26.3 ± 3.07 l/min and 32.5 ± 6.29 l/l, respectively. Repeated exercises 1 and 2 h later led to no changes in these parameters: PAWP was 24.9 ± 4.68 mmHg, ST depression 2.1 ± 0.73 mm, $\dot{V}$ 27.0 ± 3.2 l/min, and $\dot{V}/\dot{V}_{O_2}$ 34.1 ± 7.68 l/l during the last test (NS).

Discussion

In the present study, in patients without definite evidence of left ventricular dysfunction at rest but marked elevation of PAWP during exercise, ISDN significantly reduced exercise-induced ST depression and also effectively prevented pathologic rise in PAWP during exercise for at least 3 h. However, ISDN had no effect on exertional ventilation. The data support previous observations in patients with transient exercise-induced left ventricular dysfunction, in whom successful acute treatment with improvement of left ventricular function was not paralleled by changes in the exertional ventilatory response.^{11–13} This suggests that patients who have near normal hemodynamics at rest but with exertional left ventricular dysfunction develop slowly reversible changes in the pulmonary structures and mechanisms governing the ventilatory response to exercise.^{14–20} The data are furthermore in line with observations in patients with CHF, in whom exertional hyper-

TABLE II Arterial and mixed venous blood gases and ventilatory data during supine rest and exercise, before and after 1–3 h influence of 30 mg isosorbide dinitrate (ISDN) in patients with exercise-induced left ventricular dysfunction

	Before ISDN		With ISDN		p Value	
	0 h	1 h	2 h	3 h	0–1 h	0–3 h
PaCO_2 (kPa)						
Rest	5.17 ± 0.307	4.90 ± 0.293	5.00 ± 0.342	5.04 ± 0.339	*	NS
Exercise	5.14 ± 0.434	5.19 ± 0.391	5.20 ± 0.390	5.16 ± 0.344	NS	NS
pHa						
Rest	7.414 ± 0.0193	7.424 ± 0.0172	7.411 ± 0.0228	7.411 ± 0.0313	*	NS
Exercise	7.399 ± 0.0238	7.403 ± 0.0173	7.397 ± 0.0244	7.404 ± 0.0233	NS	NS
PAO_2 (kPa)						
Rest	10.58 ± 0.859	10.64 ± 1.690	10.95 ± 1.185	10.75 ± 1.266	NS	NS
Exercise	11.21 ± 1.474	11.65 ± 1.377	11.84 ± 1.662	11.52 ± 1.524	NS	NS
PVCO_2 (kPa)						
Rest	5.70 ± 0.324	5.46 ± 0.190	5.58 ± 0.307	5.64 ± 0.287	*	NS
Exercise	6.54 ± 0.514	6.55 ± 0.395	6.54 ± 0.462	6.51 ± 0.378	NS	NS
pHv						
Rest	7.389 ± 0.0178	7.394 ± 0.0154	7.389 ± 0.0215	7.383 ± 0.0254	NS	NS
Exercise	7.349 ± 0.0294	7.341 ± 0.0221	7.349 ± 0.0257	7.349 ± 0.0192	NS	NS
$\text{PV}\dot{\text{O}}_2$ (kPa)						
Rest	5.05 ± 0.336	4.39 ± 0.421	4.54 ± 0.364	4.61 ± 0.327	***	***
Exercise	3.54 ± 0.350	3.49 ± 0.396	3.49 ± 0.339	3.52 ± 0.328	NS	NS
$\dot{V}$ (l/min)						
Rest	7.16 ± 0.634	7.29 ± 1.059	7.53 ± 0.902	7.50 ± 1.162	NS	NS
Exercise	26.24 ± 4.36	24.39 ± 3.54	24.70 ± 3.98	24.38 ± 3.26	*	*
$\dot{V}/\dot{V}_{\text{O}_2}$ (l/l)						
Rest	32.2 ± 6.90	33.2 ± 8.29	34.5 ± 6.99	34.0 ± 6.75	NS	NS
Exercise	31.8 ± 4.84	30.1 ± 5.29	30.8 ± 5.29	30.4 ± 4.14	NS	NS

Data given as means $\pm$ standard deviation.

*** = $p < 0.001$.

* = $p < 0.05$.

See text for abbreviations.

pnea also remains unchanged during acute treatment of heart failure²⁵ and is gradually reduced only after prolonged medication.^{14, 26–28} Three h observation did not yield differences from the immediate effects observed after ISDN intake. Thus, also in patients with only transient left ventricular dysfunction, exertional hyperpnea probably will only disappear after prolonged treatment.

Observations in a cohort of patients not treated with ISDN revealed that there was no spontaneous improvement in ST depression, left ventricular filling pressures, or exertional hyperpnea during 2 h observation, which differs from what can be obtained in patients with severe CHF.^{29, 30} This, together with previous experience with nitrate effects under similar conditions strongly indicate that the marked improvement in PAWP and ST depression in the patients treated with ISDN was not due to habituation to the procedure or placebo effects, and thus valid conclusions could be made without the use of a placebo group.

The persistence of excessive exertional ventilation after effective improvement in central hemodynamics has been attributed to chronic, congestion-induced changes in the lungs

and increased dead-space ventilation, necessitating rise in ventilation to preserve normal PaCO_2 ,^{15, 16, 26} to chronic changes in skeletal muscles, leading to increased ventilatory stimuli from muscular metaboreceptors,^{14, 15, 17, 27} and to changes in the central ventilatory command.^{15–20}

Since the exercise PaCO_2 – PaO_2 relationship remained normal after ISDN, there was no evidence that the persistence of exertional hyperpnea was due to disturbances of the alveolo-arterial gas exchange and compliance or to acute changes induced by the initial exercise. The data are in line with previous observations that there is no direct connection between high PAWP and pulmonary congestive changes.³⁶

The constancy of exercise PaCO_2 throughout the study may fit in with the CO_2 homeostasis hypothesis. However, the data are at variance with a previous, corresponding study, where glycerol trinitrate led to distinct decline in PaCO_2 .¹³ The hypothesis is further challenged by the fact that in both studies the nitrates at rest led to slightly reduced PaCO_2 and slightly increased ventilation. This reflects ventilation in excess of metabolic needs and a ventilatory regulation unrelated to the level of PaCO_2 .^{13, 15}

The exercise PvO_2 and CI were distinctly reduced and remained unaltered throughout the study after normalization of PAWP. This may fit in with previous data suggesting that the excessive exercise ventilation is linked to failing cardiac output.^{36, 37} The fact that exercise PvO_2 , CI, and $\dot{V}$ remained unaltered may indicate that both a low CI and an excessive ventilation are due to a common mechanism, the central command.^{18, 19, 38} Under the assumption that exercise PvO_2 fairly well reflects the state of oxygenation in exercising muscles, the data are also compatible with the hypothesis that the persisting exertional hyperpnea is related to stimuli from hypoxia-induced metabolic changes in the muscles.^{14, 17, 27}

This study revealed that the exercise loads needed to induce the same ST depression were considerably lower during supine than during sitting exercise, indicating that the volume load on the heart of a given amount of exercise in the supine position is greater and more provocative to induce ST depression and left ventricular dysfunction.^{39–43} Thus, ventilatory changes directly related to stimuli from pathologic changes in central circulation and pulmonary gas exchanging tissues are probably more easily demonstrated during supine exercise, whereas changes related to stimuli from alterations in peripheral circulation and skeletal muscle metabolism may more readily be observed during upright exercise. Thus, the observed pattern and changes in exercise hyperpnea, ECG, and PAWP might be different in the sitting position.

Conclusion

Patients with high PAWP and ST depression during exercise only develop distinct exertional hyperpnea that persists beyond acute improvement of left ventricular function, and thus, measurements of exercise ventilation cannot be used to assess the degree of success of acute medical treatment for myocardial ischemia. However, long-term, effective, anti-ischemic therapy may give different results.

References

- Weiner DA, McCabe C, Hueter DC, Ryan TJ, Hood WB Jr: The predictive value of anginal chest pain as an indicator of coronary disease during exercise testing. *Am Heart J* 1978;96:458–462
- Detrano R, Gianrossi R, Mulvihill D, Lehmann K, Dubach P, Colombo A, Froelicher V: Exercise-induced ST segment depression in the diagnosis of multivessel coronary disease: A meta analysis. *J Am Coll Cardiol* 1989;14:1501–1508
- Müller O, Rørvik K: Hemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitro-glycerin. *Br Heart J* 1958;20:302–310
- Wortman A, Bachmann K, Meinhold M: Circadian investigation of interval therapy with isosorbide dinitrate in coronary heart disease. *Eur Heart J* 1988;9(suppl A):119–124
- Hagman M, Wilhelmsen L: Relationship between dyspnea and chest pain in ischaemic heart disease. *Acta Med Scand* 1981; 644(suppl):16–18
- Cook DG, Shaper AG: Breathlessness, angina pectoris and coronary artery disease. *Am J Cardiol* 1989;63:921–924
- Froelicher VF: *Exercise and the Heart*. 3rd ed. Chicago: Mosby - Year Book, Inc., 1987
- Ellestad MH: *Stress Testing. Principles and Practice*. 3rd ed. Philadelphia: F.A. Davis, 1993
- Malmborg RO: A clinical and hemodynamic analysis of facts limiting the cardiac performance in patients with coronary heart disease. *Acta Med Scand* 1964;426(suppl):1–177
- Parker JO, di Giorgi S, West RO: A hemodynamic study of acute coronary insufficiency precipitated by exercise, with observations on the effects of nitroglycerin. *Am J Cardiol* 1989;63:921–924
- Sullivan M, Myers J, Buchanan N, Froelicher V: Effects of nitroglycerin on the gas exchange response to exercise in stable angina pectoris. *Am J Cardiol* 1993;72:767–769
- Meyer K, Samek A, Pinchas A, Baier M, Betz P, Roskamm H: Relationship between ventilatory threshold and onset of ischemia in ECG during stress testing. *Eur Heart J* 1995;16:623–630
- Jørgensen LH, Thaulow E, Refsum HE: Relationship between exercise hyperpnea, hemodynamics and blood gases before and during glyceryl trinitrate infusion in patients with exercise-induced elevation of pulmonary artery wedge pressure. *Clin Cardiol* 1997; 20:773–777
- Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P, Coats AJS: Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure. Effects of physical training. *Circulation* 1996; 93:940–952
- Clark AL, Coats AJS: Mechanisms of exercise intolerance in cardiac failure: Abnormalities of skeletal muscle and pulmonary function. *Curr Opin Cardiol* 1994;9:305–314
- Mancini DM: Pulmonary factors limiting exercise capacities in patients with heart failure. *Progr Cardiovasc Dis* 1995;37:347–370
- Sullivan MJ, Hawthorne MH: Exercise intolerance in patients with chronic heart failure. *Progr Cardiovasc Dis* 1995;38:1–22
- Chua TP, Clark AL, Coats AJS: Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1996;27:650–657
- Andreas S, Morguet AJ, Werner GS, Kreuzer H: Ventilatory response to exercise and to carbon dioxide in patients with heart failure. *Eur Heart J* 1996;17:750–755
- Harrington D, Coats AJS: Mechanisms of exercise intolerance in congestive heart failure. *Curr Opin Cardiol* 1997;12:224–232
- Nordenfeldt J, Adolfson L, Nilsson JE, Olsson S: Reference values for exercise tests with continuous increase in load. *Clin Physiol* 1985;5:161–172
- Jørgensen LH, Thaulow E, Refsum HE: Hemodynamic time course of acute and chronic isosorbide dinitrate treatment at rest and during exercise in patients with stable ischemic heart disease. *Clin Cardiol* 1996;19:718–724
- Bjerknes W, Scholander PF: Method for continual air-breathing in a closed circuit system. *Skand Arch Physiol* 1938;79:164–168
- Jørgensen LH, Refsum HE, Thaulow E: Influence of glyceryl trinitrate on venous and arterial effects of chronic, asymmetrical isosorbide dinitrate treatment in patients with ischemic heart disease. *Clin Cardiol* 1994;17:65–70
- Fink LJ, Wilson JR, Ferraro N: Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. *Am J Cardiol* 1986;57:249–253
- Sullivan MJ, Higginbotham MB, Cobb FR: Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation* 1989;79:324–329
- Coats AJS, Adamopoulos S, Radacelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway JC, Sleight P: Controlled trial of physical training in chronic heart failure. *Circulation* 1992;85:2119–2131
- Cowley AJ, Rowley JM, Staner K, Hampton JR: The effect of angiotensin converting enzyme inhibitor, enalapril on exercise tolerance and abnormalities of limb blood flow and respiratory function in patients with severe heart failure. *Eur Heart J* 1993;14:964–968

29. Thaulow E, Ihlen H, Kjekshus J, Forfang K, Storstein O: Effects of bed rest and prazosin in congestive heart failure. *Acta Med Scand* 1982;212:131-136
30. Packer M, Medina N, Yusuf S: Hemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterization in patients with chronic heart failure. *Circulation* 1985;71:761-766
31. Wada O, Asanoi H, Miyagi K, Ishizaka S, Kameyama T, Seto H, Sasayama S: Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J* 1992;125:790-798
32. Metra M, Cas LD, Panina G, Visioli O: Exercise hyperventilation in chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am J Cardiol* 1992;70:622-628
33. Myers J, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher VF: Ventilatory mechanisms of exercise intolerance in chronic heart failure. *Am Heart J* 1992;124:710-719
34. Paterson DJ: Potassium and ventilation in exercise. *J Appl Physiol* 1992;72:811-820
35. Barlow CW, Qayyum MS, Davey PP, Conway J, Paterson DJ, Robbins PA: Effect of physical training on exercise-induced hyperkalemia in chronic heart failure. Relation with ventilation and catecholamines. *Circulation* 1994;89:1144-1152
36. Franciosa JA, Leddy CL, Wilen M, Schwartz DE: Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. *Am J Cardiol* 1984;53:127-134
37. Sullivan MJ, Higginbotham MB, Cobb FR: Increased exercise ventilation in patients with chronic heart failure: Intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988;77:552-559
38. de Burg Daly M: Interactions between respiration and circulation. *Handbook of Physiology, Vol II: Control of Breathing* (Eds. Cherniack NS, Widdicombe JG), Section 3, The Respiratory System, p. 595-619. Bethesda, Maryland: American Physiological Society, 1986
39. Bygdeman S, Wahren J: Influence of body position on the anginal threshold during leg exercise. *Eur J Clin Invest* 1974;4:201-206
40. Currie PJ, Kelly MJ, Pitt A: Comparison of supine and erect bicycle exercise electrocardiography in coronary heart disease: Accentuation of exercise-induced ischemic ST depression by supine posture. *Am J Cardiol* 1983;52:1167-1173
41. Wetherbee JN, Bamrah VS, Ptacin MJ, Kalbfleisch JH: Comparison of ST segment depression in upright treadmill and bicycle exercise testing. *J Am Coll Cardiol* 1988;11:330-337
42. Åström H: Effect of posture on circulation and respiration at rest and during exercise in heart disease. *Acta Physiol Scand* 1970; (suppl 347):1-86
43. Cotsamire DL, Sullivan MJ, Bashore TM, Leier CV: Positions as a variable for cardiovascular responses during exercise. *Clin Cardiol* 1987;10:137-142