Cardiovascular Engineering: An International Journal, Vol. 5, No. 4, December 2005 (© 2005)
DOI: 10.1007/s10558-005-9071-0

Myocardial Hemodynamics During Exercise Treadmill Test By a Computer-Aided Clinical Decision System

JOHN KABAL* and BRUCE K. LAGERMAN*,†

Objective: By applying a clinical decision system, the Noninvasive Hemodynamic Analyzer (NHA), demonstrates its capability to compute the Myocardial Hemodynamic status of exercising patients. *Design:* Retrospective study to use the average vital signs and anthropological data of a large clinical trial of Exercise Treadmill Test. The NHA system computes Stroke Volume and various hemodynamic parameters. With the assistance of the NHA computer-aided clinical decision system; the Epicardial and Endocardial Blood Pressure/Blood Flow relationships, as well as components or determinants of Myocardial Oxygen Supply during exercise treadmill test were calculated. *Patients:* Four groups of the clinical study (1) Healthy, (2) Hypertensive, (3) Angina Pectoris, and (4) Post-Myocardial Infarction and Angina Pectoris were used in this study which comprised the average data of several hundred patients. Each group had three subgroups according to the Exercise Treadmill Test, upright and two exercise periods. *Validity:* We previously conducted a comparative study of Stroke Volume computed by the NHA with the Thermodilution technique which proved to be clinically acceptable concerning Bias, Accuracy, and Precision. In this particular study, the statistical evaluation was not available because the average values did not allow for such computation. Instead, we have chosen to compute the Myocardial Hemodynamic Parameters parallel with their Ideal values. Altogether 18 hemodynamic parameters were included and the normal values were expressed in ±20%. *Conclusion:* The NHA clinical decision system can differentiate among the reported clinical conditions of the "Seattle Heart Watch" report. We were able to comparatively evaluate physiological and pathophysiological principles, such as, coronary flow reserve, endocardial autoregulation, and remodeling. Further medical trials will reveal the practical clinical importance and applicability of our NHA system.

Key words: myocardial hemodynamics; endocardial auto regulatory response; myocardial oxygen demand; computer aided clinical decision system; noninvasive hemodynamic analyzer; treadmill exercise test.

INTRODUCTION

Myocardial vascular research has paramount importance in clinical cardiology. Every effort to understand this aspect of physiology and pathophysiology is justified by the large numbers of morbidity and/or mortality of coronary artery disease (CAD), heart failure (CHF), left ventricular hypertrophy (LVH), cardiomyopathies, and one of the major cause of these diseases—hypertension. Myocardial ischemia, in particular, subendocardial ischemia could lead to microvascular alterations which is one of the hallmarks of these common diseases (Chilian, 1997; Fuster *et al*., 1992; Hoffman and Sclafani, 2000).

Our understanding of coronary circulation and myocardial pathophysiology, in particular, metabolic and pharmacologic control, epi- and endocardia! hemodynamic status, has grown rapidly as a result of a variety of different methods applied for animal and human research (Bianco and Alpert, 1997; Wolters-Geldof *et al*., 1997). The applications of the accumulated information about the myocardial circulation have opened new diagnostic, therapeutic, and prognostic avenues in clinical cardiology. However, the use of these techniques for evaluating patients in everyday practice is limited in specificity and sensitivity including the applicability to ambulatory patients.

The primary noninvasive test for coronary artery disease is still the Electrocardiographic Treadmill Test (ETT) (Bruce and Hornstein, 1979; Froelicher *et al*., 1999). In

*Reston Noninvasive Hemodynamic Center, Reston, Virginia.
†To whom correspondence should be addressed at Reston Noninvasive Hemodynamic Center, 1712 Clubhouse Road, Suite 103, Reston, Virginia 20190. E-mail: lagerman@attglobal.net

several situations of CAD, exercise assessment combined with Radionuclide Angiography or Echocardiography is used. In certain groups of patient, pharmacologic stress testing is preferred. Coronary angiography, although an invasive test, remains the "gold standard" for assessment of CAD and severity.

Other important methods to directly evaluate myocardial hemodyanamics are complicated, difficult to make comparisons, and require prohibitively expensive techniques for follow-up. Above all, most of them still remain institutional clinical and/or research approaches, e.g. Doppler Coronary Flow Velocity studies, Fast Magnetic Resonance Imaging or Positron Emission Tomography (PET). All of them have their special merit as well as limitations in the methodological hierarchy.

In this paper we describe a novel noninvasive approach to indirectly evaluate coronary hemodynamic responses of ambulatory patients by a computerized clinical decision system during Exercise Treadmill Test.

METHODS

The databank of a large clinical trial from the cardiovascular literature was selected to compute the hemodynamic profile of the clinical groups of an original ETT study. The "Seattle Heart Watch" clinical trial (Bruce *et al*., 1974) organized a network of 15 exercise testing facilities in four teaching hospitals and other clinics. During an eighteen month period more than 2000 adult men were tested. The summary of the Seattle Heart Watch clinical trial is shown in Table 1.

In this trial a multistage, symptom-limited, submaximal exercise protocol was applied for different groups of cardiac conditions. For compilation purposes only, the average data of each particular group, composed of several hundreds participants, were utilized. Patients were placed into four different clinical groups according to the EGG results of ETT and clinical symptoms.

This clinical trial did not include hemodynamic data except the average vital sign changes were presented with the corresponding anthropological information which was utilized in this retrospective study.

The computerized clinical decision system (NHA) is able to utilize this databank independently of the EGG results and by computing myocardial hemodynamic parameters allow it to reach the same conclusions as the clinical trial (Kabal and Lagerman, 2004a,b, Kabal and Lagerman, 2005). Considering that the results of this study could not be compared to any available actual counterparts of the obtained myocardial hemodynamic parameters, but only to our calculated ideal values, the real purpose of this research was to find applicability of the NHA to evaluate and differentiate among the reported clinical conditions with scientific objectivity during treadmill stress testing.

A flowchart of the NHA clinical decision system computing myocardial hemodynamic parameters is presented in Fig. 1.

The NHA software algorithm is programmed to calculate essential hemodynamic values and, in this presentation, those myocardial parameters (with ideal and actual values), which are needed to evaluate coronary circulation as follows:

1. Mean arterial pressure (MAP) (mmHg):

$$\mathrm{MAP} = ((\mathrm{SBP} - \mathrm{DBP})/3) + \mathrm{DBP}$$

   It is calculated as the geometric mean of systolic and diastolic blood pressure. It represents the "opening" BP, which is maintained steady in a healthy person. MAP is equivalent to the EPICARDIAL BLOOD PRESSURE.
2. Endocardial blood pressure (EBP) is calculated as

$$\text{Diastolic blood pressure} - \mathrm{LVEDP}$$

   where LVEDP is the left ventricular end diastolic pressure.
3. Cardiac output (CO) (L/min): This most important oxygen transport related parameter describes the perfusion capability of the left ventricle. The NHA computes first the STROKE VOLUME as follows:

$$\sqrt{3.14 \times B \times C \times L} \times ((A/3.14) \times 2) \times (D/1000)$$

   where A is the actual pulse pressure ratio (PPR), PPR = actual pulse pressure/(60/actual HR); B is the actual heart rate ratio (HRR), HRR = (60/Actual HR); C is the floating factor, i.e. ((100 – actual %HR) × $(E + F)$, E and F are the correction factors; and D is the actual HR.
4. Acceleration index (ACI) (s^{-2}): It represents myocardial contractility (inotropy): the peak acceleration of blood after opening of the aortic valve:

$$\mathrm{ACI} = \sqrt{((\text{actual PPR} \times 20)/\mathrm{HRR})/1000} \times \text{factor}$$

5. Total body oxygen consumption ($VO_{2,max}$) (mL/kg/min): A valuable index of total body

Table 1. Summary of the "Seattle Heart Watch" Clinical Trial

Parameters	Healthy group			Hypertensive group			Angina pectoris group			Post-myocardial infarction & AP group		
Number of participant	1275			193			306			228		
Age (years)	44.5 ± 7.4			49.3 ± 8.7			51.2 ± 8.4			51.9 ± 8.0		
Sex												
Height (cm)	178.3 ± 6.8			178.7 ± 6.0			176.3 ± 7.3			176.1 ± 6.9		
Weight (kg)	80.8 ± 9.8			84.4 ± 12.6			80.8 ± 12.1			77.5 ± 9.9		
	U	E-1	E-2	U	E-1	E-2	U	E-1	E-2	U	E-1	E-2
Systolic blood pressure	123 ± 13	155 ± 21	185 ± 22	141 ± 16	173 ± 25	197 ± 28	125 ± 17	151 ± 25	164 ± 30	120 ± 16	142 ± 25	150 ± 27
Diastolic blood pressure	77 ± 10	76 ± 11	71 ± 17	90 ± 10	90 ± 11	88 ± 15	80 ± 10	82 ± 12	82 ± 16	77 ± 10	81 ± 12	82 ± 12
Heartrate	72 ± 11	108 ± 14	168 ± 15	77 ± 15	115 ± 18	167 ± 17	75 ± 12	116 ± 18	144 ± 21	78 ± 13	120 ± 19	142 ± 23
EST.VO_2max	35.3 ± 5.2			30.2 ± 8.0			21.3 ± 9.1			18.8 ± 8.8		
Clinical classification of heart disease	0%			8%			27%			73%		

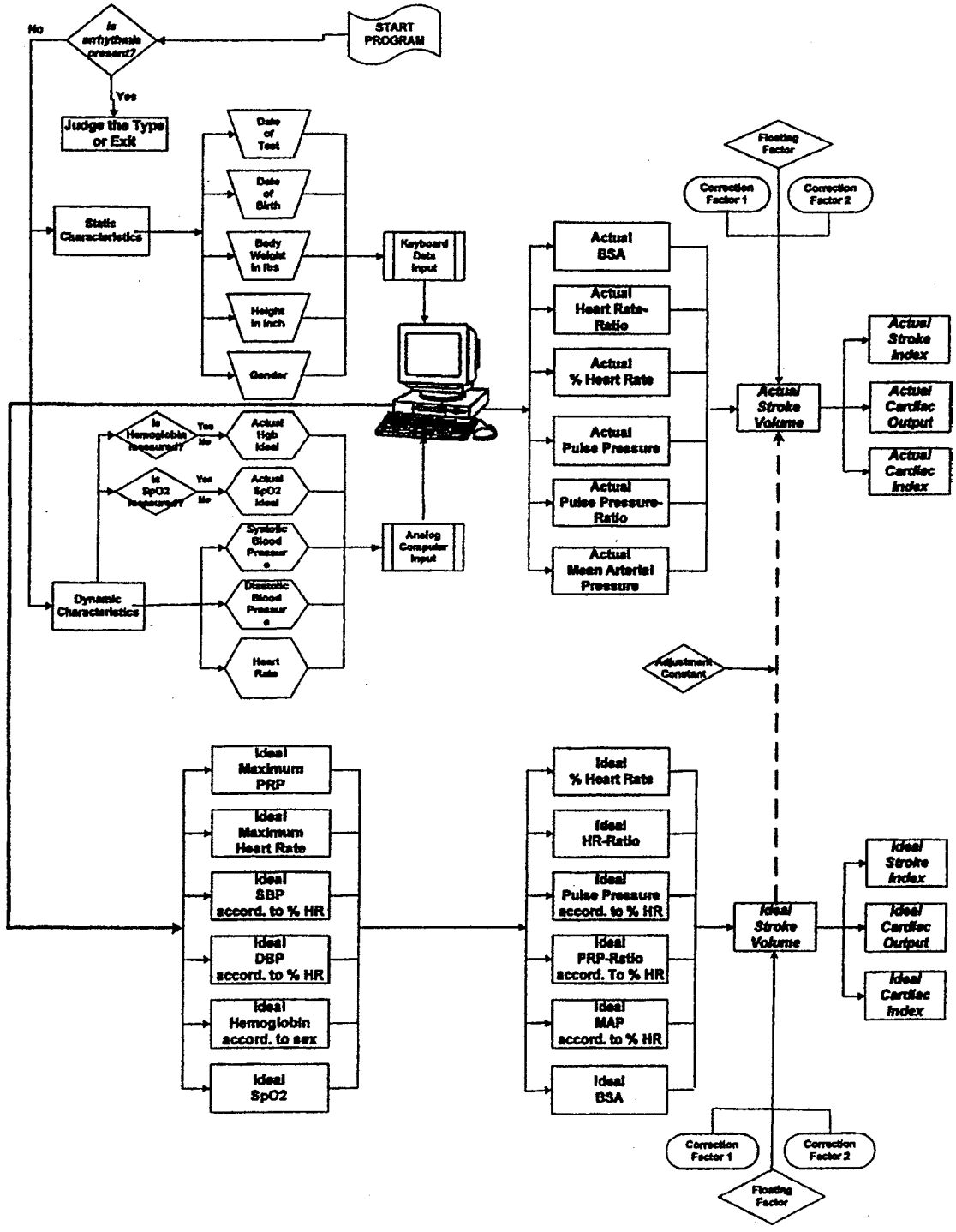

Figure 1. Flowchart of the noninvasive hemodynamic analyzer (NHA).

fitness at maximal exercise:

$$VO_{2,max} = \frac{(1.5/60) \times (60 - (100 - \%HR) + 4) \times CO \times 10}{LBW}$$

where LBW is the lean body weight.

6. Coronary oxygen perfusion (COP) (mL/min/100 g):

$$COP = \frac{(VO_{2,max} \times \text{diastolic time interval})}{\text{cardiac cycle (RR)}}$$

7. Coronary blood flow (CBF) (mL/min/100 g): It was calculated in the following way: (a) the human adult heart averages approximately 325 ± 75 g in men and 275 ± 75 g in women (Edwards, 1987; Gutgesell and Rembold, 1990); (b) the weight of the heart is correlated to the body surface area (BSA). For adult normal men, the heart weight is changing between 250 and 400 g by 1.48–2.48 m^2 BSA scale and for women between 200 and 350 g by the scale of 1.26–2.36 m^2, respectively.
8. Endocardial blood flow (EBF) (mL/min/100 g):

$$EBF = \frac{(CBF \times \text{diastolic time interval})}{\text{cardiac cycle (RR)}}$$

9. Left ventricular end diastolic pressure (LVEDP) (mmHg) was obtained by the following exponential equation as its components were also obtained noninvasively bytheNHA:

$$LVEDP = (I - LCWI/A - LCWI) - (10^{0.4342944819} \times LVEDI)$$

where I-LVCWI is the ideal left cardiac work index, A-LVCWI is the actual left cardiac work index, and LVEDI is the left ventricular end diastolic index.

At present, the invasive Swan–Ganz catheter is used directly to measure the Pulmonary End-Capillary Pressure (PECP) or Wedge Pressure. Normally, the extramural pressure (pericardial and mediastinal pressure) is negative, thus the calculated PECP values could accurately represent the true LVEDP in most of the cases.

10. Left ventricular end systolic volume (LVESV):

$$LVEDV = SV/\text{ejection fraction (EF)}$$

where EF is calculated by a two-step process wherein in the first step an Ideal EF is calculated and adjusted to HR according to

$$I - EF = ((\text{actual } \%HR - 40) \times 0.1) + 57$$

where actual %HR = (HR × 100)/max HR, 57 is the theoretical average EF, in the second step the actual EF is calculated according to

$$A - EF = \sqrt{\frac{A - PP \times A - HR}{I - PP \times I - HR}} \times I - EF$$

LVESV = LVEDV – SV.

11. Left ventricular end systolic wall tension (WTJ) was computed in the following way (Edwards, 1987; Gutgesell and Rembold, 1990; Smith, 1992):

$$LVESV = r^3 \times 1,887,902$$

$$r = \sqrt[3]{\frac{LVESV}{4.1887902}}$$

$$WT = \frac{P \times r}{2}$$

12. Systolic and diastolic time intervals were calculated by the following equations:

$$\text{cardiac cycle (RR, ms)} = 60,000/\text{heart rate}$$

Electromechanical systole is designated as QS_2: $QS_2 = 546 - 2.1HR$ (males) and $QS_2 = 549 - 2.0HR$ (females); systolic time intervals (STI) = RR – DTI; diastolic time intervals (DTI) = RR – QS_2.

The data of the "Seattle Heart Watch" clinical trial were computed in three sequences (one in standing and two during treadmill stress testing) and the above listed hemodynamic parameters were calculated for each sequence. For each actual hemodynamic parameter, the corresponding ideal hemodynamic parameters and percent differences were computed with the same heart rate. The differences from the ideal values were considered normal within ±20%.

VALIDITY AND LIMITATION OF THE NHA CLINICAL DECISION SYSTEM

The bias, precision, and accuracy of cardiac output measurements were compared to the Thermodilution technique and applied to more than 200 ICU patients with six different cardiac conditions (Kabal and Lagerman,

2004a,b). The results of this retrospective study demonstrated that the NHA system performs well over a wide range of CO values and within statistically accepted clinical accuracy.

The clinical application of this method is limited to adult humans of both sexes over 18 years old, provided that the input data are reliable and no significant arrhythmia is present.

RESULTS AND DISCUSSION

The Noninvasive Hemodynamic Analyzer system belongs to the field of a composite scientific area, comprising mathematics, applied computer sciences, and statistics to develop models of complex problems. The application of this science is only recently being applied to clinical medicine. The NHA is essentially a clinical decision system which computes SV/CO and other related hemodynamic parameters (derivatives). It may receive typed-in data for computation and, therefore, can be used for multiple purposes, such as, prospective or retrospective studies and "what if . . ." research studies. Where data was unavailable, such as, hemoglobin, arterial oxygen saturation, the parameters were computed with the average sex-dependent values.

In this presentation we performed a retrospective study utilizing the data of a large clinical trial. Despite the fact that we were able to use only the average vital sign values and average anthropological data of this clinical trial, our purpose was satisfied when the results of the NHA system fell into the same diagnostic groups as the clinical trial had presented.

Eighteen actual parameters and their ideal counterparts per subgroups (upright-rest, exercise-1, and exercise-2) are presented in each Tables 2–5. Although the original study did not contain the calculated hemodynamic parameters, instead the ETT evaluation clearly designated four groups of cardiac conditions, namely (1) Healthy (H), (2) Hypertensive (HT), (3) Angina Pectoris (AP), and (4) Post-Myocardial Infarction and Angina Pectoris (PMI & AP).

With the assistance of the NHA computer-aided clinical decision system, the Epicardial-, and Endocardial Blood Pressure/Blood Flow relationships as well as components or determinants of Myocardial Oxygen Supply during exercise treadmill test were calculated and tabulated.

From the tables of Myocardial Hemodynamic Analysis, representative graphics are composed to view hemodynamic changes during ETT. All graphics show the ideal and actual values. The ideal parameters were calculated with the same heart rate as the actual parameters in each subgroup.

The Myocardial Blood Flow calculation is based on previous observations that its participation in the CO is steady in rest and/or exercise at 4% (Abboud and Smid, 1976; Di Giantomasso *et al*., 2002; Falls, 1968). The mechanism of CO is complex and not entirely understood. These observations are corroborated by the fact that coronary blood flow increases four or five times (Gosse and Clementy, 1995), similarly to CO during exercise over the resting level (Upton *et al*., 1980). It is important to note that even the infarcted heart, there was a close correlation between CO/CI and mean regional myocardial blood flow (Hoffman and Sclafani, 2000).

The coronary circulation is biphasic and contrary to other vital organs, where the greatest flow occurs in systole, the myocardial blood flow occurs predominantly during diastole. During systole, because of compression of the coronary vessels by the contracting myocardium and during diastole, the intramyocardial pressure is primarily determined by the magnitude of the intraventricular pressure (Hoffman and Buckberg, 1976). Therefore, systolic blood flow is preferentially distributed to the epicardial layers and diastolic blood flow to the endocardial layers.

The regulation of coronary blood flow and vascular resistance are not distributed sharply between the epicardial large conduit vessels and the endocardial resistance vessels. Nevertheless, there are major differences in the level of autoregulatory control between epi- and endocardial regions due to metabolic factors, endothelial modulation, and myogenic control or transmural variations. The segmental distribution of regulation integrated with a variety of mechanisms are still exploratory.

The physiology of the myocardial blood flow, or more precisely of myocardial oxygen supply, is different from that in any other organs. First, the myocardium cannot compromise its oxygen supply and it normally uses almost maximal oxygen uptake at rest. With this limited margin of safety, the increased coronary oxygen in exercise can be met mainly by an increase of coronary vasodilation (Schremmer and Dhainaut, 1998). In a normal heart, there is excess capacity on supply side (adequate CO), so that ischemia does not occur even with very rigorous exercise.

The increment of coronary blood flow above its basal value during peak exercise is called the coronary flow reserve (Bourdarias, 1955; Nitenberg and Antony, 1995; Strauer, 1990), which indicates the flow added to the basal flow for a given coronary perfusion pressure when the coronary vascular bed is maximally dilated.

Table 2. Myocardial Hemodynamic Analysis of Exercise Performance in the Healthy Group

Healthy group	Upright			Exercise-1			Exercise-2		
	Ideal	% difference	Actual	Ideal	% difference	Actual	Ideal	% difference	Actual
Myocardial blood flow (mL/min/100 g)	90.0		78.2	258.6		214.1	541.1		472.5
Total coronary blood flow (mL/min/100 g)		−13.1			−17.2			−12.7	
Myocardial oxygen supply (mL/min/100 g)	17.5		15.2	50.4		41.7	105.4		92.0
Coronary oxygen perfusion (mL/min/100 g)		−13.1			−17.2			−12.7	
Epicardial blood pressure (mmHg)	97		92	97		102	97		109
Epicardial perfusion BP (mmHg)		−4.7			5.7			12.5	
Endocardial blood pressure (mmHg)	71		70	42		56	5		24
Endocardial perfusion BP (mmHg)		−1.3			32.8			337.4	
Epicardial blood flow (mL/min/100 g)	42.6		37.0	148.6		123.0	270.8		236.5
Epicardial perfusion BP (mL/min/100 g)		−13.1			−17.2			−12.7	
Epicardial blood flow (mL/min/100 g)	47.6		41.1	110.0		91.1	270.3		236.0
Epicardial perfusion BP (mL/min/100 g)		−13.1			−17.2			−12.7	
Epicardial resistance (dyn s cm^{-5}/100 g)	181		199	52		66	29		37
		9.8			27.6			28.9	
Endocardial resistance (dyn s cm^{-5}/100 g)	120		137	31		49	2		8
		13.6			60.3			400.9	
Endocardial oxygen supply (mL/min/100 g)	9.2		8.0	21.4		17.7	52.6		46.0
Endocardial oxygen perfusion (mL/min/100 g)		−13.1			−17.2			−12.7	
Epicardial blood pressue (mmHg/ms)	0.245		0.234	0.303		0.321	0.584		0.657
EPI – dP/dT (mmHg/ms)		−4.7			5.7			12.5	
Endocardial blood pressue (mmHg/ms)	0.163		0.161	0.178		0.237	0.033		0.145
ENDO – dP/dT (mmHg/ms)		−1.3			32.8			337.4	
Epicardial blood flow (mL/ms/100 g)	0.108		0.094	0.465		0.385	1.632		1.425
EPI – dV/dT (mL/ms/100 g)		−13.1			−17.2			−12.7	
Endocardial blood flow (mL/ms/100 g)	0.108		0.094	0.465		0.385	1.632		1.425
ENDO – dV/dT (mL/ms/100 g)		−13.1			−17.2			−12.7	
Systolic wall tension[a]	172		161	253		246	295		300
		−6.7			−2.7			1.6	
Myocardial contractility acceleration index (s^{-2})	1.1		1.0	2.2		2.0	4.3		4.0
Inotropy (s^{-2})		−6.5			−9.0			−6.6	
Endocardial blood flow/cycle (mL/cycle/100 g)	0.66		0.57	1.02		0.84	1.49		1.30
Endocardial perfusion/min (mL/cycle/100 g)		−13.1			−17.2			−12.7	
Endocardial O_2 supply (mL/cycle/100 g)	0.13		0.11	0.20		0.16	0.29		0.25
Endocardial O_2 perfusion (mL/cycle/100 g)		−13.1			−17.2			−12.7	
Endocardial resistance per cycle (dyn s cm^{-5}/100 g)	63		72	13		21	1		4
		13.6			60.3			400.9	

[a]Systolic wall tension of the LV end systolic volume (wall tension=$(P \times r)/2$).

Table 3. Myocardial Hemodynamic Analysis of Exercise Performance in the Hypertensive Group

	Upright			Exercise-1			Exercise-2		
Healthy group	Ideal	% difference	Actual	Ideal	% difference	Actual	Ideal	% difference	Actual
Myocardial blood flow (mL/min/100 g)	108.4		89.6	291.8		227.2	496.3		406.0
Total coronary blood flow (mL/min/100 g)		−17.3			−22.1			−18.2	
Myocardial oxygen supply (mL/min/100 g)	21.1		17.5	56.8		44.2	96.7		79.1
Coronary oxygen perfusion (mL/min/100 g)		−17.3			−22.1			−18.2	
Epicardial blood pressure (mmHg)	100		107	100		118	100		124
Epicardial perfusion BP (mmHg)		7.5			18.2			24.9	
Endocardial blood pressure (mmHg)	67		81	38		66	11		43
Endocardial perfusion BP (mmHg)		20.8			74.0			297.4	
Epicardial blood flow (mL/min/100 g)	53.5		44.2	170.3		132.6	261.4		213.9
Epicardial perfusion BP (mL/min/100 g)		−17.3			−22.1			−18.2	
Epicardial blood flow (mL/min/100 g)	54.9		45.4	121.5		94.6	234.8		192.1
Epicardial perfusion BP (mL/min/100 g)		−17.3			−22.1			−18.2	
Epicardial resistance (dyn s cm^{-5}/100 g)	149		193	47		71	30		46
		30.0			51.8			52.6	
Endocardial resistance (dyn s cm^{-5}/100 g)	98		143	25		56	4		18
		46.1			123.5			385.7	
Endocardial oxygen supply (mL/min/100 g)	10.7		8.8	23.7		18.4	45.7		37.4
Endocardial oxygen perfusion (mL/min/100 g)		−17.3			−22.1			−18.2	
Epicardial blood pressue (mmHg/ms)	0.259		0.278	0.327		0.386	0.545		0.681
EPI – dP/dT (mmHg/ms)		7.5			18.2			24.9	
Endocardial blood pressue (mmHg/ms)	0.171		0.206	0.174		0.304	0.065		0.260
ENDO – dP/dT (mmHg/ms)		20.8			74.0			297.4	
Epicardial blood flow (mL/ms/100 g)	0.139		0.115	0.559		0.435	1.431		1.171
EPI – dV/dT (mL/ms/100 g)		−17.3			−22.1			−18.2	
Endocardial blood flow (mL/ms/100 g)	0.139		0.115	0.559		0.435	1.431		1.171
ENDO – dV/dT (mL/ms/100 g)		−17.3			−22.1			−18.2	
Systolic wall tension[a]	197		199	274		281	301		320
		1.2			2.5			6.3	
Myocardial contractility acceleration index (s^{-2})	1.3		1.1	2.5		2.2	4.1		3.8
Inotropy (s^{-2})		−13.0			−11.8			−9.5	
Endocardial blood flow/cycle (mL/cycle/100 g)	0.71		0.59	1.06		0.82	1.36		1.11
Endocardial perfusion/min (mL/cycle/100 g)		−17.3			−22.1			−18.2	
Endocardial O_2 supply (mL/cycle/100 g)	0.14		0.11	0.21		0.16	0.26		0.22
Endocardial O_2 perfusion (mL/cycle/100 g)		−17.3			−22.1			-18.2	
Endocardial resistance per cycle (dyn s cm^{-5}/100 g)	50		73	10		23	2		8
		46.1			123.5			385.7	

[a]Systolic wall tension of the LV end systolic volume (wall tension=$(P \times r)/2$).

Table 4. Myocardial Hemodynamic Analysis of Exercise Performance in the Angina Pectoris Group

Angina pectoris group	Upright			Exercise-1			Exercise-2		
	Ideal	% difference	Actual	Ideal	% difference	Actual	Ideal	% difference	Actual
Myocardial blood flow (mL/min/100 g)	103.8		73.9	292.7		183.5	400.8		262.9
Total coronary blood flow (mL/min/100 g)		−28.8			−37.3			−34.4	
Myocardial oxygen supply (mL/min/100 g)	19.8		14.1	55.9		35.0	76.5		50.2
Coronary oxygen perfusion (mL/min/100 g)		−28.8			−37.3			−34.4	
Epicardial blood pressure (mmHg)	101		95	101		105	101		109
Epicardial perfusion BP (mmHg)		−5.6			4.3			8.6	
Endocardial blood pressure (mmHg)	69		74	38		65	23		56
Endocardial perfusion BP (mmHg)		7.4			72.4			146.7	
Epicardial blood flow (mL/min/100 g)	50.4		35.9	171.1		107.3	234.3		153.7
Epicardial perfusion BP (mL/min/100 g)		−28.8			−37.3			−34.4	
Epicardial blood flow (mL/min/100 g)	53.4		38.0	122.6		76.2	166.5		109.2
Epicardial perfusion BP (mL/min/100 g)		−28.8			−37.3			−34.4	
Epicardial resistance (dyn s cm^{-5}/100 g)	160		212	47		79	34		57
		32.6			66.3			65.5	
Endocardial resistance (dyn s cm^{-5}/100 g)	103		155	25		68	11		41
		50.9			175.0			276.1	
Endocardial oxygen supply (mL/min/100 g)	10.2		7.3	23.2		14.6	31.8		20.9
Endocardial oxygen perfusion (mL/min/100 g)		−28.8			−37.3			−34.4	
Epicardial blood pressue (mmHg/ms)	0.259		0.245	0.333		0.347	0.413		0.449
EPI – dP/dT (mmHg/ms)		−5.6			4.3			9.6	
Endocardial blood pressue (mmHg/ms)	0.167		0.179	0.175		0.301	0.132		0.325
ENDO – dP/dT (mmHg/ms)		7.4			72.4			146.7	
Epicardial blood flow (mL/ms/100 g)	0.130		0.092	0.566		0.355	0.962		0.631
EPI – dV/dT (mL/ms/100 g)		−28.8			−37.3			−34.4	
Endocardial blood flow (mL/ms/100 g)	0.130		0.092	0.566		0.355	0.962		0.631
ENDO – dV/dT (mL/ms/100 g)		−28.8			−37.3			−34.4	
Systolic wall tension[a]	197		174	277		244	296		269
		−11.7			−12.1			−9.2	
Myocardial contractility acceleration index (s^{-2})	1.3		1.0	2.5		2.0	3.3		2.7
Inotropy (s^{-2})		−18.7			−20.8			−19.0	
Endocardial blood flow/cycle (mL/cycle/100 g)	0.71		0.51	1.05		0.66	1.16		0.76
Endocardial perfusion/min (mL/cycle/100 g)		−28.8			−37.3			−34.4	
Endocardial O_2 supply (mL/cycle/100 g)	0.14		0.10	0.20		0.13	0.22		0.14
Endocardial O_2 perfusion (mL/cycle/100 g)		−28.8			−37.3			−34.4	
Endocardial resistance per cycle (dyn s cm^{-5}/100 g)	53		80	10		28	5		17
		50.9			175			276.1	

[a]Systolic wall tension of the LV end systolic volume (wall tension=$(P \times r)/2$).

Table 5. Myocardial Hemodynamic Analysis of Exercise Performance in the Post-Myocardial Infarction & Angina Pectoris Group

Post-myocardial infarction and angina pectoris group	Upright			Exercise-1			Exercise-2		
	Ideal	% difference	Actual	Ideal	% difference	Actual	Ideal	% difference	Actual
Myocardial blood flow (mL/min/100 g)	112.6		74.9	311.6		167.9	394.4		214.9
Total coronary blood flow (mL/min/100 g)		−33.5			−46.1			−45.5	
Myocardial oxygen supply (mL/min/100 g)	21.9		14.6	60.7		32.7	76.8		41.8
Coronary oxygen perfusion (mL/min/100 g)		−33.5			−46.1			−45.5	
Epicardial blood pressure (mmHg)	101		91	101		101	101		105
Epicardial perfusion BP (mmHg)		-9.7			0.2			3.5	
Endocardial blood pressure (mmHg)	67		71	35		66	24		62
Endocardial perfusion BP (mmHg)		6.3			86.9			159.7	
Epicardial blood flow (mL/min/100 g)	56.0		37.2	183.2		98.7	231.3		126.0
Epicardial perfusion BP (mL/min/100 g)		−33.5			−46.1			−45.5	
Epicardial blood flow (mL/min/100 g)	56.7		37.7	128.4		69.2	163.1		88.9
Epicardial perfusion BP (mL/min/100 g)		−33.5			−46.1			−45.5	
Epicardial resistance (dyn s cm^{-5}/100 g)	144		196	44		82	35		66
		35.8			85.9			90.0	
Endocardial resistance (dyn s cm^{-5}/100 g)	94		150	22		76	12		56
		59.8			246.7			376.7	
Endocardial oxygen supply (mL/min/100 g)	11.0		7.3	25.0		13.5	31.8		17.3
Endocardial oxygen perfusion (mL/min/100 g)		−33.5			−46.1			−45.5	
Epicardial blood pressue (mmHg/ms)	0.265		0.239	0.344		0.345	0.408		0.422
EPI – dP/dT (mmHg/ms)		−9.7			0.2			3.5	
Endocardial blood pressue (mmHg/ms)	0.172		0.183	0.171		0.319	0.136		0.354
ENDO – dP/dT (mmHg/ms)		6.3			86.9			159.7	
Epicardial blood flow (mL/ms/100 g)	0.146		0.097	0.623		0.336	0.933		0.508
EPI – dV/dT (mL/ms/100 g)		−33.5			−46.1			−45.5	
Endocardial blood flow (mL/ms/100 g)	0.146		0.097	0.623		0.336	0.933		0.508
ENDO – dV/dT (mL/ms/100 g)		−33.5			−46.1			−45.5	
Systolic wall tension[a]	202		169	281		228	295		243
		-16.3			−18.8			−17.4	
Myocardial contractility acceleration index (s^{-2})	1.4		1.1	2.7		1.9	3.3		2.4
Inotropy (s^{-2})		−23.1			−26.6			−26.2	
Endocardial blood flow/cycle (mL/cycle/100 g)	0.73		0.48	1.07		0.58	1.15		0.63
Endocardial perfusion/min (mL/cycle/100 g)		−33.5			−46.1			−45.5	
Endocardial O_2 supply (mL/cycle/100 g)	0.14		0.09	0.21		0.11	0.22		0.12
Endocardial O_2 perfusion (mL/cycle/100 g)		−33.5			−46.1			−45.5	
Endocardial resistance per cycle (dyn s cm^{-5}/100 g)	47		76	9		31	5		23
		59.8			246.7			376.7	

[a]Systolic wall tension of the LV end systolic volume (wall tension=$(P \times r)/2$).

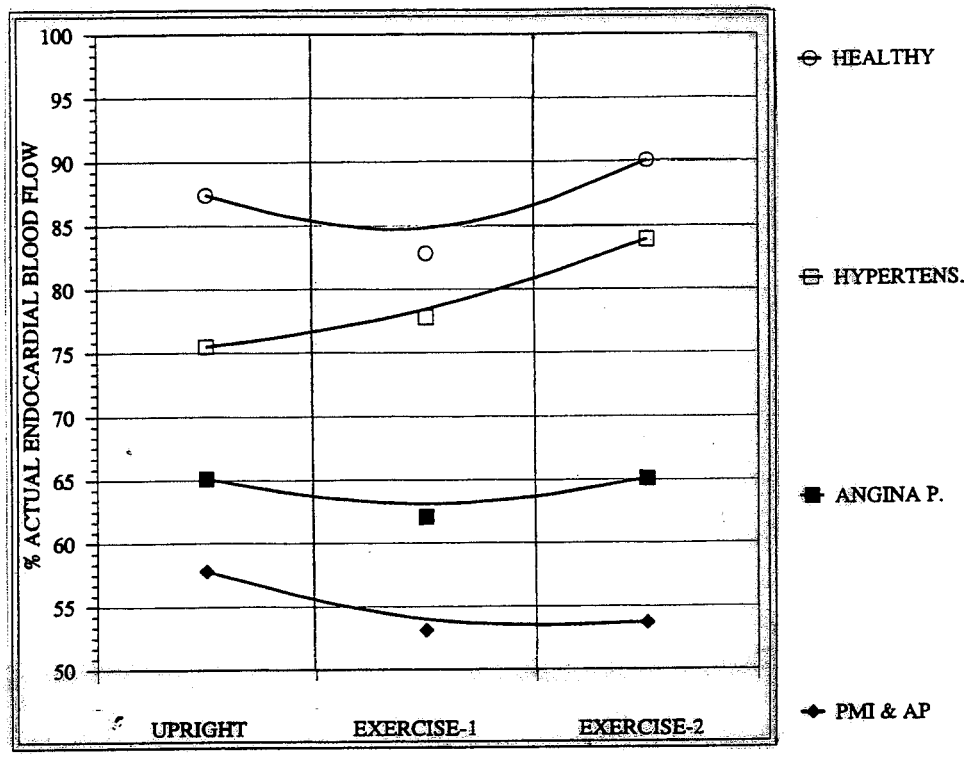

Figure 2. Changes of actual endocardial blood flow (mL/min/100 g) of the four cardiac condition in the Seattle Heart Watch Trial during Exercise Treadmill Test. Values are calculated as percentage of the corresponding meal values.

The first row of the tables (Tables 2–5). represent the coronary reserve (maximum/minimum flow) of the four groups. The ideal and actual values are presented and their differences were expressed in percentage. The four groups show a characteristic distribution of coronary flow reserve at peak exercise. However, it is apparent that the numerical designation of individual coronary reserves could not explain the real changes without comparing the actual values to the corresponding ideal values, obtained during exercise.

The relative changes of actual endocardial blood flow differences are represented by Fig. 2. The percent changes (of the corresponding ideal values) of the actual endocardial blood flow (mL/min/100 g) of the four cardiac conditions are illustrated during ETT. It became clear, that it is more meaningful, to calculate the % changes between ideal and actual values during ETT. In this manner more distinguishable differences of the myocardial hemodynamic state can be demonstrated amongst the different cardiac conditions. This graph also shows a progressively decreasing endocardial blood flow level in the groups of H, HT, AP, PMI & AP during ETT and culminating in almost 50% decrease of the actual values (compared to the corresponding ideal values) in the groups of AP and PMI & AP, respectively.

The concept of Coronary Flow Reserve (CFR) stems from the description of Coronary Autoregulation by Mosher *et al.* (1964). The autoregulation of coronary circulation in the endocardium maintains the blood flow independent from changes of perfusion pressure (in physiological ranges) and protects the myocardium from pressure-induced changes in oxygen consumption (Bai *et al.*, 1994).

The endocardial perfusion pressure is the vector of diastolic blood pressure minus the left ventricular end diastolic pressure. The extravascular compressive forces become the principal determinant of the transmural distribution of blood flow and may significantly influence the balance of supply and demand of oxygen in the subendocardium. The subendocardium is especially susceptible to ischemia (Pagliaro *et al.*, 2003) because this region is most vulnerable to hyperperfusion and the oxygen demands are greatest in the subendocardium owing to the greater systolic tension development in this region.

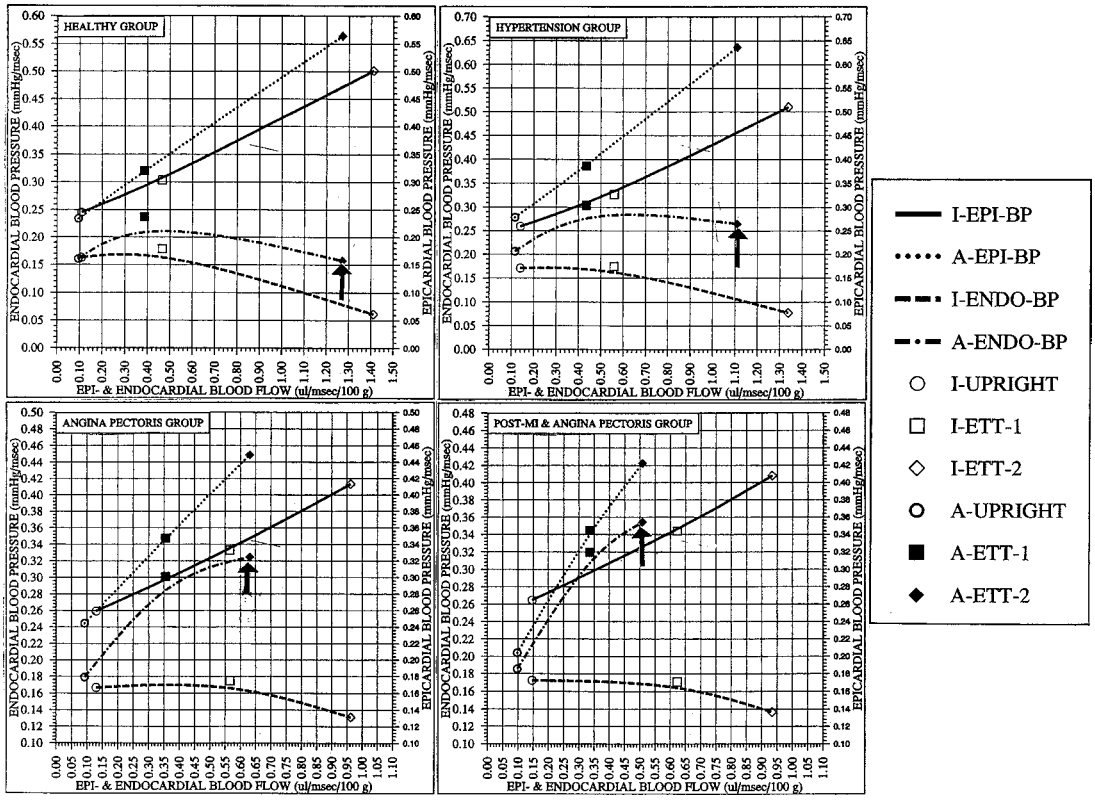

Figure 3. Regional coronary blood pressure and regional coronary blood flow changes during exercise (*dP*/*dT*/*dV*/*dT*).

During exercise the left ventricular intracavitary pressure (LVEDP) is increasing according to the heart rate or workload and the particular cardiac condition (Andersen *et al*., 1990). Thus the resulting endocardial perfusion pressure (DBP-LVEDP) is continuously decreasing normally. There are indications that in young athletes, the endocardial perfusion pressure can go down to "negative" pressure for a short period of time at peak workload. We found similar results with Olympic champion athletes.

If the *P*/*F* relationship is expressed as *dP*/*dT* per *dV*/*dT*, or their values calculated in the epicardial and/or endocardial time interval unit, these parameters become the "true function of time". This type of graph normally shows a linear relationship for epicardial *P*/*F* and an autoregulatory process of endocardial *P*/*F* (Fig. 3).

Although the endocardial autoregulatory responses are still well preserved in the mild HT-group, the endocardialperfusion pressure responses appeared at a higher level, inducing increased endocardial resistance during exercise. This process could be the first signs of "remodeling process" (Britten *et al*., 2003; Mundhenke *et al*., 1997; Weber *et al*., 1992) toward ischemia and/or hypertrophy in this mildly hypertensive middle-aged group.

There are indications that in left ventricular hypertrophy, therapeutic agents could reverse the remodeling process not only by altering the local myocardial hemodynamic condition but also by some other presently unknown mechanism(s). The autoregulatory adjustments maintain the subendocardial resistance normally much lower than the subepicardial. However, according to the two time-dependent parameters of epi- and endocardial pressures (expressed as *dP*/*dT*), both layers must receive equal volumes of blood per unit time.

Iriarte *et al*. (1995) described, that in hypertension, hypertrophy of the left ventricle might enhance the risk of ischemia because of an augmented oxygen demand and insufficient oxygen supply. Myocardial ischemia may also be associated with cardiac hypertrophy even in the absence of atheromatous coronary disease.

At present, it is already well established that both chronic and acute hypertension produce numerous abnormalities of coronary flow regulation (Harrison *et al*., 1991; Maruyama *et al*., 1997). They include impairments of autoregulation as observed in the groups of HT, AP, and PMI & AP changes in vascular responsiveness and alterations of endothelial cell functions. One of the consequences of

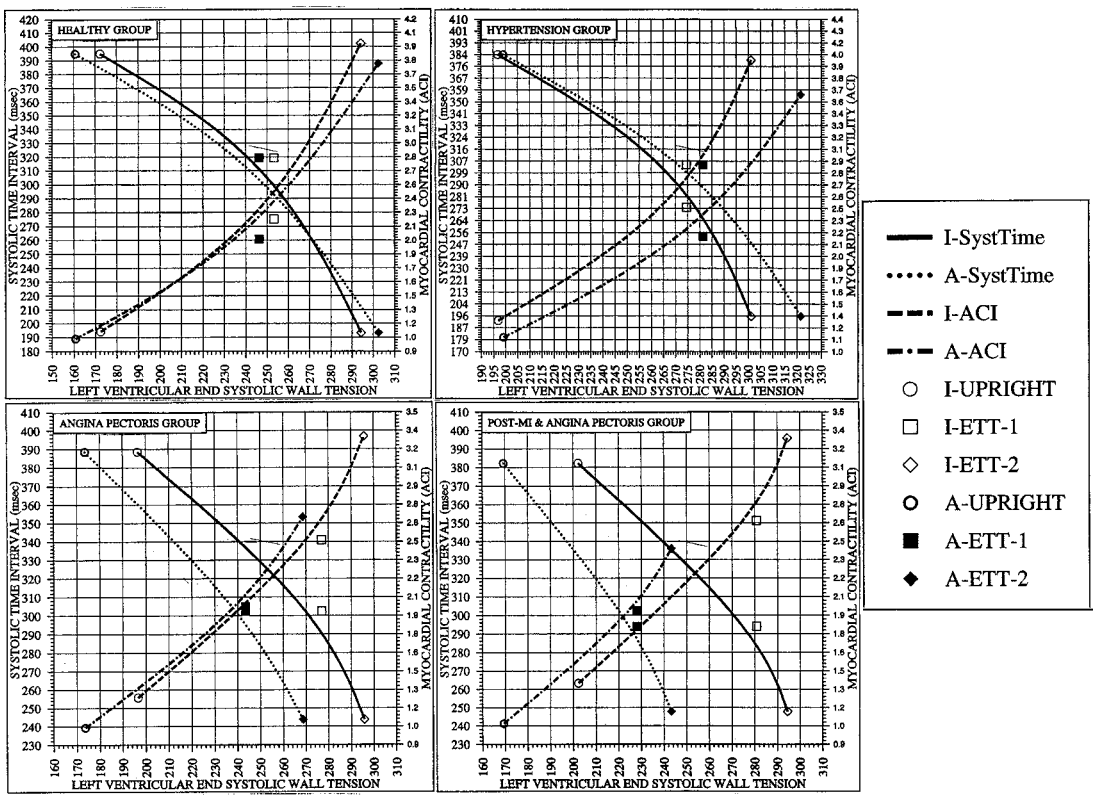

Figure 4. Determinants of myocardial oxygen demand: (a) systolic wall tension, (b) systolic time interval, and (c) myocardial contractility during exercise.

hypertension could be the onset of left ventricular hypertrophy when the coronary vasodilator reserve is impaired (Schaefer *et al*., 2002; Wallbridge and Cobbe, 1996).

The increased vulnerability of the endocardium to ischemia results from both structural and functional abnormalities in the hypertrophied heart. Kannel (1991) and Deedwania (1995) have indicated that left ventricular hypertrophy is now well recognized as a common and important risk factor for cardiac morbidity and/or mortality.

The endocardial autoregulation curve in ischemic state gradually becomes linear due to maximum vasodilatation (hyperemia). In this condition, coronary blood flow is no longer autoregulated and varies linearly with perfusion pressure. Indeed, the AP and PMI & AP curves demonstrate that no more autoregulation exists in these groups during exercise. This missing autoregulatory process with the elevated resistance may indicate the presence of progressive endocardial microcirculatory disease. These altered functions could lead to ischemic remodeling due to the already increased oxygen demand (DeFily and Chilian, 1995).

Essentially, the coronary blood flow in rest and exercise depends on the magnitude of the following determinants of myocardial oxygen demands (Factor and Bache, 1994):

(a) left ventricular end systolic wall tension,
(b) systolic time interval, and
(c) myocardial contractility.

In normal aerobic situation these determinants of oxygen demands and myocardial blood flow could clearly represent the balance of oxygen supply and demands. However, these "mechanical factors" will lose their role when ischemic remodeling is developing.

The H group showed negligible changes to the corresponding ideal group. However, in the mild hypertension group, the already increased oxygen demand might accelerate ischemic remodeling. The oxygen demand becomes expressed in the groups of AP and AP & PMI in which groups the endocardial vasodilatation as well as endocardial blood flows are markedly diminished (Fig. 4).

These changes may worsen the clinical consequences of ischemic microvascular disease either by producing

structural alterations of the coronary vasculature or, equally importantly, by altering coronary vascular responsiveness to either mechanical or neurohumoral stimuli. Although we do not know all the factors in the "remodeling process," these changes are now well accepted pathophysiological facts (De Boer *et al*., 2003;Willenheimer, 2000).

Finally, we can state that in this retrospective study of hypertensive and coronary artery disease, it was possible to reproduce several physiological/pathophysiological patterns of the endocardial circulation, such as, coronary flow reserve, autoregulation, and remodeling. We hope that further studies prove the usefulness of this noninvasive NHA system as a screening process of the myocardial.

SUMMARY

The purpose of this retrospective study was to use the NHA system to apply the summarized result of the "Seattle Heart Study" clinical trial to calculate myocardial hemodynarnic parameters. This large clinical trial used conventional ETT to identify CAD and published the average data of the different groups with healthy, hypertensive, angina pectoris, and post-myocardial infarction participants. We harvested these data and computed the hemodynamic profile of each groups. This presentation deals only with the application of the NHA system to select/identify the reported groups according to their hemodynamic parameters and not by the application of the usual statistical evaluation.

We are aware of two insurmountable facts that (1) published data are scant to directly compare one technique with another in the same set of patients and (2) misinterpretation and/or imprecision could cause incorrect deduction of certain pathophysiological events. Nevertheless, in this data-set of four distinguishable cardiac groups, we were able to recalculate and reaffirm previously established physiological and/or pathophysiological myocardial hemodynamic principles, such as, coronary flow reserve, endocardial autoregulation, and remodeling. Further medical trials will reveal the practical clinical importance and applicability of the NHA system.

According to this presentation, the NHA computer-aided clinical decision system may find its place in the instrumental hierarchy as an early screening method for CAD. The results of this retrospective study proved that the hemodynamic computation of the NHA system is a valid approach to evaluate ETT. We conclude that the NHA clinical decision system deserves further studies to fully understand its potential.

REFERENCES

Abboud FM, and Smid PG. Regulation of peripheral and coronary circulation. In Levine HJ, Ed, *Clinical Cardiovascular Physiology*. New York: Grune & Stratton, 1976, pp. 143–205.

Andersen FR, llebekk A, and Kill F. Variations in left ventricular volume after myocardial oxygen consumption more at low then at high inotropy. *Acta Physiol Scand* 193(1): 95–102, 1990.

Bai XJ, Iwamoto T, William AG, Fan WL, and Downey HFI. Coronary pressure-flow autoregulation protects myocardium from pressure-induced changes in oxygen consumption. *Am J Physiol* 266(6Pt 2): H2359–H2368, 1994.

Bianco JA, and Alpert JS. Physiologic and clinical significance of myocardial blood flow quantitation: What is expected from these measurements in the clinical ward and in the physiology laboratory? *Cardiology* 88(1): 116–126, 1997.

Bourdarias JP. Coronary reserve: Concept and physiological variations. *Eur Heart J* 16(Suppl 1): 2–6, 1955.

Britten MB, Zeiher AN, and Schaechinger V. Effects of cardiovascular risk factors on coronary remodeling in patients with mild atherosclerosis. *Coron Artery Dis* 14(6): 415–422, Sep 2003.

Bruce RA, Gey GO, Cooper MN, Fischer LD, and Peterson DR. Seattle Heart Watch: Initial clinical, circulatory and electrocardiographic responses to maximal exercise. *Am J Cardiol* 33: 459–469, 1974.

Bruce RA and Hornstein TR. Exercise stress testing in evaluation of patients with ischemic heart disease. *Prog Cardiovasc Dis* 11: 371–390, 1979.

Chilian WM. Coronary microcirculation in health and disease: Summary of an NHLBI workshop. *Circulation* 95: 522–528, 1997.

De Boer RA, Pinto YM, and Van Veidhuisen DJ. The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: The role of microvascular growth and abnormalities. *Microcircuiation* 10(2): 113–126, Apr 2003.

Deedwania PC. Hemodynamic variability and myocardial ischemia. *Cardiol Clin* 13(3): 491–500, Nov 1995.

DeFily DV, and Chilian WM. Coronary microcircuiation: autoregulation and metabolic control. *Basic Res Cardiol* 90(2): 112–118, 1995.

Di Giantomasso D, May CN, and Bellomo R. Norepinephrine and vital organ blood flow. *Intensive Care Med* 28(12): 1804–1809, 2002.

Edwards WD. Applied anatomy of the heart. In Brandenburg RO, Fuster V, Giuliani ER, *et al*., Eds, *Cardiology: Fundamentals and Practice*. Chicago Yearbook Medical Publishers, 1987, Vol 47, p. 112.

Factor SM, and Bache RJ. Pathophysiology of myocardial ischemia. Chapter 7. In Schlant RC and Alexander RW, Eds, *Hurst's The Heart, Arteries and Veins*, 8th ed. New York: McGraw-Hill, 1994, pp. 1033–1053.

Falls HB (Ed). The cardiovascular system in exercise. In *Exercise Physiology*, Modified by Anderson KL. New York: Academic Press, 1968.

Froelicher VF, Fearon WF, Ferguson CM, *et al*. Lesson learned from studies of the standard exercise EGG test. *Chest* 116: 1442–1451, 1999.

Fuster V, Badimon L, Badimon JJ, and Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 326: 242–247, 1992.

Gosse P, and Clementy J. Coronary reserve in experimental myocardial hypertrophy. *Eur Heart J* 16(Suppl): 22–25, 1995.

Gutgesell HP, and Rembold CM. Growth of the human heart relative to body surface area. *Am J Cardiol* 65(9): 662–668, 1990.

Harrison DG, Treasure CB, Mugge A, Dellsperger KC, Lamping KG. Hypertension and the coronary circulation. With special attention to endothelial regulation. *Am J Hypertens*, 4(7 Pt 2): 454S-459S, July 19XX .

Hoffman E, and Sclafani R. The coronary circulation and myocardial ischemia. *Ital Heart J* 1(Suppl 2): 7–12, June 2000.

Hoffman JIE, and Buckberg GD. Transmural variations in myocardial perfusion. In: Yu PN, Goodwin JF, Eds, *Progress in Cardiology Philadelphia*, Pennsylvania: Lea & Febiger, 1976, pp 37–38.

Kabal J, and Lagerman BK. A novel approach to measure cardiac output noninvasively. A comparison with the thermodilution method on critical care patients. *J Clin Monit* 18(3): 1–9, 2004a.

Kabal J, and Lagerman BK. Hemodynamic evaluation of Exercise Treadmill Test by a computer aided clinical decision system. *Cardiovasc Eng: Int J* 4(3): 245–259, Sept 2004b.

Kabal J, and Lagerman BK. Computer-aided clinical decision system: Differential diagnosis and treatment of essential hypertension by a novel noninvasive hemodynamic analyzer. *Cardiovasc Eng: Int J* 5(2): 83–96, June 2005.

Kannel WB. Left ventricular hypertrophy as a risk factor: The Framingham experience. *J Hypertens* 9(Suppl 2): S3–S9, 1991.

Maruyama Y, Hory M, and Janicky JS. *Cardiac-vascular remodeling and functional interaction*. Springer Verlag New York 1997.

Mosher P, Ross J, McFate PA, and Shaw RF. Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 14: 250–259, 1964.

Mundhenke M, Schwarzkopff B, and Strauer BE. Structural analysis of arteriolar and myocardial remodeling in the subendocardial region of patients with hypertensive heart disease and hypertrophic cardiomyopathy. *Virchows Arch* 431(4): 265–273, 1997.

Nitenberg A, and Antony I. Coronary vascular reserve in humans: A critical review of methods of evaluation and of interpretation of the results. *Eur Heart J* 16(Suppl 1): 7–21, Aug 1995.

Pagliaro P, Chiribiri A, Mancardi D, Rastaldi R, Gattulo D, and Losano G. Coronary endothelial dysfunction after ischemia and reperfusion and its prevention by ischemic preconditioning. *Ital Heart J* 4(6): 383–394, August 6, 2003.

Schremmer B, and Dhainaut JF. Regulation of myocardial oxygen delivery. *Intensive Care Med* 16(Suppl 2): 157–163, 1990.

Schaefer S, Kelm M, Mingers S, and Strauer BE. Left ventricular remodeling impairs coronary flow reserve in hypertensive patients. *J Hypertens* 20(7): 1431–1437, July 2002.

Smith TW. Heart failure. In Wyngaarden JB, Smith LH, and Bennett JC, Eds, *Cecil Textbook of Medicine*, 19th ed. Philadelphia, PA: Saunders, 1992, p 192.

Strauer BE. The significance of coronary reserve in clinical heart disease. *J Am Coll Cardiol* 15: 775–783, 1990.

Upton MT, Rerich SK, Roeback JR, Newman GE, Douglas JM, Wallace AG, and Jones RH. Effect of brief and prolonged exercise on left ventricular function. *Am J Cardiol* 45: 1154–1160, 1980.

Wallbridge DR, and Cobbe SM. Coronary hemodynamics in left ventricular hypertrophy. *Heart* 75(4): 369–376, 1996.

Weber KT, Anversa P, Armstrong PW, Brilla CG, Burnett JC, Crickshank JM, and Devereux RB. Remodeling and reparation of the cardiovascular system. *J Am Coll Cardiol* 20: 3–16, 1992.

Willenheimer R. Left ventricular remodeling and dysfunction. Can the process be prevented? *Int J Cardiol* 72(2): 143–150, Jan 15, 2000.

Wolters-Geldof MJ, Cats VM, and Bruschke AV. Clinical methods to determine coronary flow and myocardial perfusion. *Int J Card Imaging* 13(2): 79–94; discussion 95–97, 1997.