PROCEEDINGS

OF THE DEPARTMENT OF CARDIOLOGY AT THE UNIVERSITY OF TARTU

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TARTU 1994

Tartu Ülikooli Kirjastuse trükikoda
Tiigi 78, EE2400 Tartu
Tellimus nr. 81, 1995.

Department of cardiology

Rein Teesalu

Department of cardiology is one of the 18 clinical departments of the University of Tartu. It has 3 equally important and mutually related functions: 1) clinical work, 2) teaching and 3) research work.

Clinical work is carried out in three divisions — cardiological (80 beds), myocardial infarction (36 beds, including 7 beds in CCU) and cardiosurgical (40 beds, including 6 beds in postoperative ward). The staff of the department is also involved in outpatients' service, working in the outpatients' clinic of the University of Tartu as consultants in cardiology.

Teaching is an important part of our activities as the only medical faculty in Estonia is at the University of Tartu. The number of medical undergraduate students has shrunk in the near past and is now (in 1994) 1200. On the other hand, more attention is now payd to postgraduate students, though the system of postgraduate teaching is still in state of rearrangements.Postgraduate students are interns (2-year study period), residents (3-year study period) and doctorants (4 years to obtain Ph.D.). Teaching is carried out in three chairs: 1) cardiology, 2) cardiosurgery and 3) internal medicine propedeutics. In addition, a subunit for more profound teaching of nurses (headed by associate professor Mare Lind) was lately founded.

Research work has become more effective in comparison with what it was a few years ago. We took part in the biggest multicentral study in cardiology ISIS-4. At the present time our colleagues are taking part in several international projects: 1) "Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety/Tolerability of Miroton® forte for Heart Failure". Clinical project manager: Prof. Dr. Axel Brattström, Knoll Deutchland GMBH. Investigator: Prof. Rein Teesalu, University of Tartu. 2) "Blinded Comparison of d-Sotalol and Amiodarone in the Treatment of Life-Threatening Ventricular Arrhythmias". Study Director Kathleen Moulton. Bristol-Myers Squibb Pharmaceutical Research Institute. 3) "Efficacy and Safety of Dofetilide in the Acute Conversion of Paroxysmal Supraventricular Tachycardia to Sinus Rhythm- a Randomised Comparison with Verapamil and Placebo". Study Director Peter Aurup. Pfizer Ltd. We were represented (jointly with the department of biochemistry) by an oral report on the Joint XIIth World Congress of Cardiology and XVIth Congress of the European Society of Cardiology (T. Parik, K. Allikmets, K. Zilmer, T. Vihalemm, T. Kullisaar, R. Teesalu, M. Zilmer "Evidence for oxidative stress in essential hypertension: perspective for antioxidant therapy). Two of our colleagues — Margus Viigimaa and Rein Kolk — have obtained Ph.D.

in 1994: 1) Margus Viigimaa "Primary Haemostasis, Antiaggregative and Anticoagulant Treatment of Acute Myocardial Infarction". Tartu, 1994. 2) Rein Kolk "Atrial versus Ventricular Pacing in Patients with Sick Sinus Syndrome". Tartu, 1994.

Board of the department of cardiology.

1) Rein Teesalu, M.D., Ph.D., prof. of cardiology, head of the department
2) Lembit Roostar, M.D., Ph.D., prof. of cardiosurgery
3) Kaljo Valgma, M.D., Ph.D., extraordinary prof. of cardiology
4) Maido Uusküla, M.D., Ph.D., associate prof. of cardiology
5) Margus Viigimaa, M.D., Ph.D., senior research worker
6) Kai Saks, M.D., Ph.D., associate prof. of propedeutics of internal medicine
7) Enno Kõiv, M.D., Ph.D., head of the division of cardiology
8) Üllar Soopõld, M.D., Ph.D., head of the division of myocardial infarction
9) Kadri Siim, M.D., senior doctor of the division of cardiology
10) Mati Ress, M.D., head of the division of cardiosurgery
11) Marju Meus, chief nurse of the division of myocardial infarction
12) Svetlana Rääbis, chief nurse of he division of cardiology
13) Anita Priks, chief nurse of the division of cardiosurgery
14) Ulvi Sooru, nurse of the division of cardiology

Chair of cardiology

Rein Teesalu

Teaching staff:

1) Prof. Rein Teesalu, head
2) Extraordinary prof. Kaljo Valgma
3) Associate prof. Mare Lind
4) Associate prof. Eevi Maiste
5) Associate prof. Maido Uusküla
6) Assistent prof. Külliki Karu
7) Laboratory assistent Sille Tamme (on maternity leave)

Teaching:

1) Full course on cardiology for 4th year medical students
   a) 24 lectures each 2 academic hours (prof. R. Teesalu)
   b) practical training (80 hours, whole staff)
2) Seminars and practical training for 6th year students (75 hours, whole staff)

Optional courses for students:

1. Diseases of myocardium. Prof. K. Valgma
2. Fundamentals of clinical echocardiography. Associate prof. E. Maiste
3. Atherosclerosis. Diagnostics, prevention, treatment. Epidemiology of ischemic heart disease. Assistent prof. M. Zemtsovski
4. On diagnostic mistakes in heart patients. Associate prof. M. Lind
5. Acute coronary insufficiency. Unstable angina, myocardial infarction. Associate prof. M. Uusküla

Courses for physicians:

1. Arrhythmias. Diagnosis. Treatment. Prof. R. Teesalu
2. Acute coronary insufficiency. Unstable angina. Myocardial infarction. Associate prof. M. Uusküla
3. Electrocardiography. Assistent prof. K. Karu
4. Clinical physiology and functional diagnostics of circulation. Associate prof. E. Maiste
5. Actual problems of cardiology. Extraordiary prof. K. Valgma
6. Selected problems of diagnostics and treatment of heart diseases. Associate prof. M. Lind
7. Intensive course on electrocardiography. Assistent prof. K. Karu
8. Electrocardiogrphy. Associate prof. I. Liiv
9. Selected problems of cardiology. Associate prof. I. Liiv

Research:

I Doctorants and their topics of research:

1) Kristina Allikmets (supervisor prof. R. Teesalu): "Renin Profiling in Arterial Hypertension: Association with Metabolic Cardiovascular Risk Factors".
2) Triin Parik (supervisor prof. R. Teesalu): "Oxidative Stress and Metabolic Disturbances in Essential Hypertension".
3) Tiina Ristimäe (supervisor prof. R. Teesalu): "Silent Myocardial Ischemia in Patients with Congestive Heart Failure".

II Main research fields of the clinical physiology research group (Dr. Margus Viigimaa, PhD; Dr. Y. Saareoja, Dr. Maie Ojamaa, researcher Tiiu Jõudu):

1) Blood coagulation, antiaggregative, anticoagulant and thrombolytic treatment in cacdiac patients.
2) Nuclear medicine methods in cardiology.

Current collaboration:

1) Low molecular weight heparin in the treatment of coronary heart disease (Uppsala University, Dept. of Cardiology, Prof. L. Wallentin).
2) Activated protein C resistence in young patients suffering from myocardial infarction (Lund University, Prof. B. Dahlbäck).

Boarb of the department of cardiology. **Sitting (from the left)**: Marju Meus, Anita Priks, Kadri Siim, Rein Teesalu, Lembit Roostar, Ulvi Sooru, Kai Saks, Svetlana Rääbis. **Standing (from the left)**: Enno Kõiv, Mati Ress, Maido Uusküla, Margus Viigimaa, Üllar Soopõld, Kaljo Valgma.

Chair of cardiology. Sitting (From the left): Kaljo Valgma, Eevi Maiste, Rein Teesalu, Mare Lind, Maido Uusküla. **Standing (from the left)**: Triin Parik, Külliki Karu, Kristin Lamp, Margus Viigimaa, Rein Kolk, Silvia Noodla, Tiina Ristimäe, Kristina Allikmets.

Chair of internal medicine propedeutics. Sitting (from the left): Riste Ridala, Tiit Pokk, Jaan Riiv, Elmut Laane, Regiina Kaskmets. **Standing (from the left)**: Mari Lööper, Ilme Nadel, Kai Saks, Andres Mesila, Mihhail Zemtsovski.

Chair of cardiothoracic surgery. Sitting (from the left): Vootele Laisaar, Helju Luts, Lembit Roostar, Terje Arak, Mati Ress. **Standing (from the left)**: Toomas Aro, Indrek Roose, Tõnu Loog, Hannes Kuiv, Heino Leesik.

Personell of the division of myocardial infraction Sitting (from the left): Silvi Otsalt, Külli Teesalu, Üllar Soopõld, Rein Teesalu, Marju Meus, Malle Põllusaar, Meeli Arst. **Standing (from the left)**: Aleksandra Golubtsova, Kima Tuvik, Kaja Uibo, Sirje Tikk, Ago Kõrgvee, Mare Õim, Mart Kalder, Marge Laving, Merle Vaher, Ene Ranne.

Retired lecturers (from the left): prof. em. Jaan Riiv, associate prof. Regina Kaskmets, prof. em. Elmut Laane.

Division of cardiac surgery Sitting (from the left): Mae Randala, M.D., Iivi Kõbas, M.D., Assoc. Prof. Jüri Samarütel, M.D., Ph.D., Mati Ress, M.D. (Head of Division) Prof. Lembit Roostar, M.D., D.Sc., Elvi Liiv, M.D., Ass. Prof. Tähti Saar, M.D. **Standing (from the left)**: Peeter Tähepõld, M.D., Toomas Hermlin, M.D., Ürjo Ploom, M.D., Toomas Aro, M.D., Arvo Klaar, M.D., Liidia Litvinova, M.D., Indrek Roose, M.D., Mehis Mikkel, M.D., Tõnu Loog, M.D., Hannes Kuiv, M.D., Jüri Väli, M.D. **Not on photo:** Eve Int, M.D., Sirje Kõvask, M.D.

Personnel of the outpatients' consultation room. Sitting (from the leht): Ljubov Keis, cardiologist; Enno Kõiv, head of the devision of cardiology; Koidu Tauk, nurse.Standing **(from the left)**: Urve Angerjärv, nurse; Helgi Kärner, nurse.

Personnel of the devision of cardiology. Sitting (from the left): Silvia Noodla, Ljubov Keis, Svetlana Rääbis, Enno Kõiv, Kadri Siim, Ülvi Sooru, Ülo Lepp, Mare Lind, Mihhail Zemtsovski. **II row**: Anita Kändra, Margarita Kink, Kristin Lamp, Sirje Hansen, Külliki Karu, Regina Kaskmets, Eevi Maiste, Helma Tõnno, Arma Allik, Ilona Kasperg, Natalia Nikitenko, Nadezda Rundan, Elsa Palgi. **III row**: Malle Sander, Kaljo Valgma, Tiit Pokk, Ingrid Siigur, Reet Välkman, Margus Viigimaa, Rein Kolk. **IV row**: Ilmar Särg, Malle Talur, Valentina Korrovits, Vaike Kiis, Natalia Jermolajeva, Kadi Oras, Külli Kangur, Karmen Barhov, Maido Uusküla.

3) Preclinical studies of recombinant hirudin and transcutaneous prostaglandin E1 (Hannover Medical School, Dept. of Clinical Pharmacology, Prof. J. Frölich).
4) Nuclear medicine methods in cardiology (Oulu University, Dept. of Nuclear Medicine, Dr. A. Ahonen).

III Research work of the clinical cardiology research gpoup (Maido Uusküla, Kristin Lamp, Silvia Noodla):

During many years the group has studied the immune response in acute myocardial infarction. Two original methods were elaborated by this group: the test for detection lymphocytes, specifically sensitized to myocardial antigen-active rosette formation inhibition test (Laboratornoje Delo, 1985, No 1, pp. 38–40) and the test of spontaneous and specific adherence and spreading of phagocytes in presence of myocardial antigen (Immunologija, 1989, No 9, pp. 50–52). The present topic of research is the role of immunological and clinical data in the diagnosis, clinical course and prognosis of myocarditis, dilated cardiomyopathy and bacterial endocarditis. Also, the study on cardiac morphometry and body composition is carried out to investigate their role as risk factors in borderline hypertension in young age.

Grants of the Estonian Scientific Foundation.

1. Estimation of the antithrombotic efficacy of low molecular weight heparin in patients with acute myocardial infarction.
2. Influence of different antihypertensive drugs on arterial hypertension as risk factor of coronary artery disease.

Chair of Cardiothoracic Surgery

Lembit Roostar

The Department of Cardiothoracic Surgery is part of the University Heart and Lung Hospitals, situated at the Maarjamõisa Hospital Complex. This is a training center for university students in cardiac and thoracic surgery, disaster medicine and military surgery. The Department is also responsible for postgraduate and continued education studies. The Department has designed programs for three year courses of cardiac and thoracic surgery. The Department is in charge of both lecture courses and practical supervised training (2500 hours per year). Students are required to work in hospital under the guidance of experienced doctors.

The programs the Department offers are:

* cardiac surgery aimed at fourth-year students, 30 hours of work: lectures — 10 h, practical training — 18 h, seminars — 2 hours;
* thoracic surgery for fourth-year students, 30 hours of work: lectures — 10 h, practical training — 18 h, seminars — 2 hours;

* disaster medicine and military surgery for sixth-year students, 85 hours of work: lectures — 25 h, practical training — 54 h, seminars — 6 hours;
* cardiothoracic surgery for residents of general surgery, 180 hours of work;
* cardiac surgery for residents of heart surgery lasting three years (lectures — 54 hours, seminars — 86 hours, clinical and research work);
* thoracic surgery for residents of chest surgery lasting three years (lectures — 60 hours, seminars — 80 hours, clinical and research work);
* for students in doctorate studies lasting four years in cardiothoracic surgery, disaster medicine and military surgery.

Clinical training is conducted in the following study and therapeutic centers:

* Cardiosurgery Division (40 beds) including invasive procedure center and operating theaters:
* Thoracic Surgery Division (25 beds):
* Intensive Care Unit of the Anaesthesiology and Intensive CareHospital and the Traumatology and Orthopedics Hospital and General Surgery Division of the Surgery Hospital.

The Cardiosurgery Division takes care of all the patients in Estonia with congential and acquired heart defects and rhythmic disdurbances and for 50 *per cent* of the patients with coronary artery disease. The relevant statistics for the 1994 are: 141 open heart operations with the help of heart-lung machine, 71 closed operations and 250 pacemaker implantations.

The Division of Thoracic Surgery takes care of 30 *per cent* of the patients in Estonia. About 200 operations are performed in a year. The research work concerns:

* epidemiology of heart surgical diseases,
* Estonian heart disease building registers,
* diagnosis and surgery of infective endocarditis,
* diagnosis and surgery of multiple valve diseases,
* reoperations of the heart,
* emergency cardiac surgery on newborns and infants,
* use of biological materials,
* intraoperative cardiac function measurements,
* operative techniques in coronary bypass grafting,
* prevention and surgery in pleural empyema,
* combined lung tumors treatment,
* thoracic traumata,
* polytraumata,
* gunshot injuries in peacetime.

The basic lines of research for 5–10 years are:

* congential heart defects,
* acquired heart defects,
* coronary disease,
* heart rhythmic disturbances,
* heart transplantation,
* invasive endovascular surgery,
* by-pass circulation, anaesthesia and intensive care in cardiac surgery,
* new materials and techniques in thoracoscopy,
* reconstructive thoracic operations,
* lung transplantation,
* analysis of disasters from their medical point of view,
* organisation of first-aid institution for disasters of multiple casualities,
* combined and multiple injuries,
* gunshot injuries.

At present the staff of the Chair of Cardiothoracic Surgery includes:
Professor L. Roostar — head of the Chair,
T. Arak — assistent, part-time 0,25
T. Aro — assistent, part-time 0,25
H. Kuiv — assistent, part-time 0,25
V. Laisaar — assistent, part-time 0,5
E. Leesik — assistent, part-time 0,5
T. Loog — assistent, part-time 0,25
B. Malikov — assistent, part-time 0,5
M. Murruste — assistent, part-time 0,5
M. Ress — assistent, part-time 0,25
I. Roose — assistent, part-time 0,25.
There are four students of the doctorate study. The subjects of their research are:
M. Murruste: "Therapy strategy by combined injuries of the intraabdominal organs"
T. Loog: "Long-term prognosis of surgical treatment of acquired heart defects"
T. Arak: "Preventive measures to avoid wound complications"
T. Laisaar: "Therapy strategy by pleural empyema"

The members of the Department have published over the past five years 111 papers (monographts, papers, abstracts) and participated in international conferences abroad and at home.

Chair of internal medicine propedeutics

Kai Saks

Teaching staff:

Kai Saks, M.D., Ph.D., Associate Professor, Head of the Chair
Elmut Laane, M.D., Ph.D., Professor Emeritus
Michail Zemtsovsky, M.D., Ph.D., assistant
Riste Ridala, M.D., assistant
Tiit Pokk, M.D., assistant
Andres Mesila, M.D., doctorial student

Research work:

Myocardial reserve, heart failure.

Physical rehabilitation of cardiac patients (mineral water baths, curative mud baths, sauna procedures, regulation of respiratory rhythm, etc.).

Blood lipids and lipoproteins in coronary heart disease patients.

Teaching courses:

1. Propedeutics of internal medicine
Subject supervisor: Associate Professor Kai Saks
For:
1) students of the department of medicine, 6. semester, 80 hours
2) students of the department of stomatology, 5. semester, 32 hours

At the end of this course the student should be able to elicit, organize, record and present a full medical history, to have the skills required to conduct a full physical examination, to interpret the meaning of information obtained by such examination, to present (orally and in writing) the results of the examination, and to establish the most common syndromes in internal medicine.

2. Cardiology
Subject supervisor: Associate Professor Kai Saks
For:
1) students of the department of stomatology, 6. semester, 48 hours
2) students of the department of nursing, 2. semester, 24 hours

At the end of this course the student should be able to performe examination of the cardiovascular system, to establish serious disorders of the cardiovascular function, to know the epidemiology and risk factors of cardiovascular diseases, main principles of diagnostics and management of cardiac patients, and be able to give first aid to acute cardiac patient.

3. Nursing
Subject supervisor: Assistant Tiit Pokk
For:
students of the department of medicine and stomatology, 1. semester, 32 hours.

At the end of this course students should know the main principles of the functioning of the medical establishment, be able to perform the physical examination of vital functions, to be familiar with the main principles of nursing, be able to perform certain medical procedures.

Optional courses:

1. Research work in a doctor's work. Professor Emeritus Elmut Laane
2. The sauna and health. Professor Emeritus Elmut Laane
3. Geriatric cardiology. Associate Professor Kai Saks
4. Diagnostics, prevention and treatment of atherosclerosis. Epidemiolgy of ischemic heart disease. Assistant Michail Zemtsovski

Courses for physicians:

1. Principles of physical rehabilitation for coronary heart disease patients and hypertonic patients. Professor Emeritus Elmut Laane
2. Electrocardiography. Professor Emeritus Elmut Laane
3. Age-dependant cardiology. Associate Professor Kai Saks

The unit of nursing science

Mare Lind

The unit was opened in 1991. The study period is 3 years. The first 20 students graduated in June 1994 and in September 1994 the magistry study was established in this discipline. The teaching staff of practically all clinics of the Medical Faculty and several other faculties is involved in the teaching process. The head of the department is associated professor M.Lind. Valuable help in organizing teaching process and practice has been delivered by the Estonian Nurses Association and Tartu Medical School.

Why has the necessity for medical nurses with higher education come up?

In 1977 the 30-th World Health Assembly adopted two important resolutions: "Health for all by the year 2000" and the resolution recognizing the importance of nursing and midwifery personnel in primary health care. Estonia belongs to the European Region of the WHO, that is why those resolutions serve as guidelines for our activities also. The global strategy of WHO pays special attention to the training of health personnel. In addition, the European Region has formulated its own four main areas of concearn: lifestyles and health,

risk factors affecting health and environment; the reorientation of the health care system; preventing disease; treatment and nursing. The member states share their experiences in professional training of nursing and midwifery personnel. Estonia has closest relations with the Scandinavian regional organizations. For example, we have very useful contacts with Ersta Diakonisallskaps Sjeksköterskehög Skola and Ersta Vārdetiska Institut. Nursing practice should focus on promoting and maintaining health as well as preventing diseases in whole population, especially in risk groups. The nursing and the nurses are part of the process of change today. These changes involve also our medical school.

After graduating from the medical school and practising as a nurse for 2 years, nurses can start their higher education programme at the unit of nursing science. Candidates for nursing training should go through intelligence test and write an essay.

Why is higher education of medical nurses reasonable within the University and not in a medical school?

The subjects include preclinical and clinical disciplines, nursing, medical deontology, psychology, pedagogics, philosophy, languages, economy, book-keeping and basis for leadership. The teaching process is not limited with medical disciplines only but requires involvement of the staff of other faculties. In practical training special attention is paid to intensive care, administrative work and pedagogics. The first graduates had the possibility to go through practice in Sweden and Finland. For this we are very thankful to the Estonian Nurses Association and similar national organizations in Sweden and Finland. We are looking forward to continue this kind of work.

Final exams include pedagogics, intensive care and health care. The graduates get the qualification to act as a leader of nursing care team and help nurses and other staff to acquire new knowledge and skills.

Division of cardiology

Maido Uusküla, Enno Kõiv

The division of cardiology with 80 beds began to work in April, 1976 and is one of teaching units of Maarjamõisa Hospital. The personell is made up of 1 head of division and 10 cardiologists, working in the wards and giving emergency treatment as doctors in charge; 19 nurses, 11 assistant-nurses and 8 technical workers. All of the physicians have high or first degree of qualification in cardiology. In 1993 *ca* 7000 ambulatory patients were seen by cardiologists in our outpatient department.

Everyday clinical and teaching activities are connected with other units of clinic, as laboratory, sonography, X ray, cardiosurgery, radionuclear image etc. There is a good cooperation with CCU in the division of myocardial infarction. Among cardiologists there are two who are specialized in echocardiography, two — in rhythmology. Regarding cardiac arrhythmias, all the major fields are covered both by research and everyday clinical work. The following procedures and operations are available: electrophysiologic studies, noninvasive and invasive; antiarrhythmic treatment testing; Holter and ambulatory blood pressure monitoring; cardiac pacing, temporary and permanent, single, dual chamber and rate responsive. Besides, radiofrequency catheter ablation is about to be started.

There are supervisors-consultants from the teaching staff of the university who are responsible for everyday clinical and research work in the division: prof. K. Valgma, ass. prof. M. Uusküla.

Main statistical data about the 5-year period are as follows:

	Mean data of last 5 years per year
No of beds	80
No of patients	2159
No of bed-days	31542
Turnover of bed per year	27,6
Mean lenght of hospitalization	14,6
No of deaths	24
In-hospital mortality	1,1%

The mean number of more frequent diseases, treated in the division of cardiology were as follows:

Diseases of myocardium viral or infectious myocarditis, dilated or hypertrophic cardiomyopathy	622	27%
Coronary heart disease	481	21%
Hypertension	268	12%
Rhythm and conduction disorders	355	15%

35% of patients treated in the division of cardiology were urgent: acute heart failure, uncontrolled hypertension, rhythm and conduction disturbances.

Division of myocardial infarction

Üllar Soopõld

The division of myocardial infarction, was founded in 1976. The Coronary Care Unit started working as an ingredient part of this department in 1980. The following seven physicians are working there at present: Üllar Soopõld Ph.D, head of department, Ago Kõrgvee deputy head, Külli Teesalu, Mare Õim, Mart Kalder, Sirje Tikk, Heli Pallo. Everyone has high-degree cardiological qualifications and has been specially trained for intensive care. Rein Teesalu is the consulting professor.

The medical staff consists of 28 people (nurses, hospital attendants, technical workers and students). We have 36 beds and 7 ones in CCU. About 800 patients are hospitalized per year. The majority of patients suffer from coronary heart disease. Approximately 250 patients are hospitalized with myocardial infarction. A large number of patients with angina pectoris, rhythm disturbances and heart failure need stationary treatment. Frequently patients with hypertonia and arterialhypertension, infectious myocarditis are examined. On an average, a patient stays in our department for 13.5 days. Hospital mortality rate of myocardial infarction was 15.5% in 1993. Successful cardiopulmonary resuscitations were performed in 14 cases last year.

CCU plays a great part in emergency cardiology. In 1993 53% of patients who needed examination and treatment in the department passed through the CCU. They are patients with acute myocardial infarction, lifethreatening rhythm distrubances, expressive heart failure, hypertonic crisis, pulmonary artery embolism and with other cardiological emergencies.

In CCU there are medicinal facilities for ECG and hemodynamic monitoring, noninvasive or transvenous cardiac stimulation. In 1993 we used electric cardioversion in 56 cases to restore regular sinus rhythm.

In the management of myocardial infarction we try to use thrombolytic therapy as early as possible. As a rule, we give intravenous infusion of 1,5 million units of streptokinase. In 1993 about 20% of patients with myocardial infarction were treated by thrombolysis. In post-thrombolytic period we continue prohylaxic treatment with aspirin and Fragmin to avoid reocclusion.

The information about our clinical experiences is of interest for research workers of Tartu University and others. In 1992–1993 the personnel of the department participated in the international cooperative study ISIS-4.

Division of Cardiac Surgery

Mati Ress

The Division of Cardiac Surgery dates back to the sixties and has developed over a period of more than 30 years. The first closed mitral commissurotomy was performed in 1958. Open heart surgery started in 1966 when the first atrial septal defect was closed. Up to now 1755 open heart and 1463 closed operations have been carried out. Over 2600 cardiac pacemaker operations have been performed.

The division includes 40 beds and a 8-bed ICU. Preoperative diagnostics, surgery and postoperative care are performed in the division. This is the only center for congenital and heart valve surgery in Estonia. About 600 patients are admitted and 250 of those are operated upon.

Congenital heart defects are operated on from the very first days of life. These operations include arterial switch, palliative shunts, coarctation of aorta, closure of DAP in premature babies etc. Altogether some 40–60 open heart and 40–50 closed operations are carried out for congenital heart defects annually.

Over 120 patients with acquired heart valve disease are operated upon per year. Of those 70–80 are open heart operations. Patients with single or multiple valve disease, but without complications, present very low operative mortality. However, more complex cases (e.g. extensive valve calcinosis, intracavitary thrombosis, reoperations, high grade CHF) account for 60–70% of our case load. Patients with infective endocarditis of native cardiac valves often present various complications, however the results of operative treatment are highly rewarding. Operative mortality of the consecutive 112 cases was 11.6%. Operative treatment of ascending aortic aneurysms or dissections has been introduced. The results so far are promising. Smaller amount of our patients include combined cases of heart valve and coronary artery disease and patients with heart tumors.

The overall number of operations on cardiac pacemakers exceeds 2600, including over 1600 primary implants. Total heart block and sick sinus syndrome are the main indications. Intermittent heart block and atrial fibrillation account for implants as well. Transvenous approach is used exclusively, both atrial and ventricular leads are being implanted. We perform single and dual chamber pacing as well as rate responsive pacing.

MAGNESIUM STATUS IN PATIENTS WITH ESSENTIAL HYPERTENSION: RELATIONSHIP WITH PLASMA RENIN ACTIVITY

Kristina Allikmets, Triin Parik, Rein Teesalu

Abstract

Objectives. This study was designed to investigate the relationship between magnesium metabolism and renin-angiotensin system activity in patients with essential hypertension

Subjects and design. Patients with uncomplicated essential hypertension (n=32) with diastolic blood pressure 95–115 mmHg were studied. Assessment of plasma renin activity (PRA) related to urinary sodium excretion was used to define subgroups with high (n=7), medium (n=16) and low renin profile (n=9). Serum magnesium and calcium concentration, also urinary magnesium and calcium excretion (in 24-h urine sample) were assessed photometrically. Normotensive age- and sex-matched persons (n=19) served as controls.

Results. Serum magnesium concentration in the patient group (n=32) was significantly lower, than in the controls ($p<0.01$), so was the urinary excretion of magnesium ($p<0.05$). Serum total calcium concentration was similar in the patients and in the control group, so was the urinary excretion of calcium. Patients with high PRA had lower levels of serum magnesium and lower urinary magnesium excretion, than the low PRA group ($p<0.05$). Serum calcium concentration was higher in patients with high PRA, when compared to the low PRA group ($p<0.05$). Urinary calcium excretion was also higher in the high PRA group, but this difference was statistically not significant.

Conclusions. Our results indicate, that patients with essential hypertension display lower serum magnesium concentrations when compared with the normotensive controls, and that this magnesium deficiency is more pronounced in the high PRA group of patients.

Introduction

Hypertensive disease in known to be associated with abnormalities of magnesium metabolism (Altura 1990). Magnesium, in close cooperation with calcium, is an important regulator of vascular tone and peripheral vascular reactivity (Altura 1984). It has been suggested that magnesium can regulate calcium flux across the vascular smooth muscle cell membranes as well as its release from intracellular storage sites, thus facilitating muscle contraction and relaxation (Sjogren 1989). Magnesium depletion could therefore induce vasoconstriction, resul-

ting in elevated blood pressure (Zhang 1993). Several studies have demonstrated the presence of hypomagnesemia in serum and/or in tissues in arterial hypertension (Touyz 1987, McCarron 1983).

While the deviations of calcium metabolism in essential hypertension have been studied extensively and shown to be closely linked with the renin-angiotensin-aldosterone system activity (Resnick 1983), the relation between magnesium metabolism and blood pressure is still incompletely understood (Altura 1993). Despite the above mentioned hypomagnesaemia, not all hypertensive patients benefit from magnesium supplementation, suggesting an underlying heterogenity of magnesium metabolism in essential hypertension (Ferrara 1992, Cappuccio 1985).

Therefore, this study was designed to investigate the relationship between magnesium metabolism and renin-angiotensin system activity in patients with essential hypertension.

Materials and Methods

Study subjects. Thirty two patients with mild to moderate essential hypertension were studied (diastolic blood pressure 95–115 mmHg; mean age 30.7 yr., range 20–44 yr.). Blood pressure was determined with mercury sphygmomanometer, with the subject seated for 10 min before the pressure was measured. The diastolic blood pressure (DBP) was recorded at the disappearance of Korotkoff sounds (phase 5). The mean of three measurements was used. None of the subjects had evidence of coronary heart disease according to history, ECG, exercise test and echocardiography. Secondary forms of arterial hypertension were excluded on the basis of clinical and laboratory investigation (incl. renography). Body mass index (BMI) was calculated as weight (kg) divided by height squared (in meters). Subjects did not use any drugs for at least 4 weeks prior to the study. Normotensive, healthy, age and sex-matched persons (n=19) served as controls. Informed consent was obtained from all study subjects.

Methods. Venous blood samples were drawn at 8–9 a.m. after an overnight fast. Blood for the determination of plasma renin activity (PRA) was collected into K3 EDTA Vacutainers and centrifuged at 2000 g for 10 min. Samples were not chilled during processing to avoid cryoactivation of prorenin, that could result in artificially high PRA values (Sealey 1991). Plasma was stored immediately at –20°C and analysed later by radioimmunoassay (kits by Medgenix, Belgium). Assessment of PRA related to concurrent 24-h sodium excretion was used to define patients with low, medium and high renin profiles according to the method of Laragh and co-workers (Brunner 1972). Magnesium concentrations in serum and in 24-h urine were determined photometrically (FB-901, Labsystems, Finland) by xylidyl-blue

methods ("Mercotest", by Merck, Germany). Serum total calcium concentration and urinary calcium excretion (in 24-h urine sample) were assessed photometrically with cresolphtalein complexon (by "Biolabo", France).

Statistical methods. Results were expressed as mean ± standard deviation. Statistical differences between groups were determined by Student's t-test, $p<0.05$ was considered as significant.

The study protocol was approved by the Ethical Committee of the Medical Faculty, University of Tartu.

Results

Baseline characteristics of the study subjects according to their renin profile are presented in Table 1. The groups did not differ significantly with regard to age, gender or BMI. Blood pressure values were also similar in the three PRA groups.

Table 1

Baseline characteristics of patients with essential hypertension, according to renin profile and of normotensive controls

Characteristic	High PRA (n=7)	Medium PRA (n=16)	Low PRA (n=9)	Controls (n=19)
Gender (M/F)	5/2	10/6	6/3	13/6
Age (years)	27.2(20–38)	30.1(17–44)	30.4(19–41)	30.2(20–44)
BMI (kg/m2)	27.9±5.7	29.1±4.8	28.5±5.2	25.2±3.4
SBP (mmHg)	161±5	156±6	155±8	117±6*
DBP (mmHg)	101±4	102±3	100±3	74±4*

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure;
*$p<0.05$ vs. all the three PRA groups

Serum magnesium concentration in the patient group (n=32) was significantly lower, than in the controls ($p<0.01$, Table 2). The same applies to the urinary excretion of magnesium ($p<0.05$, Table 2). Serum total calcium concentration was similar in the patients and in the control group, so was the urinary excretion of calcium (Table 2).

Magnesium and calcium concentrations (in serum and in 24-h urine) in patients according to their PRA group are presented in Table 3. Patients with high PRA had lower levels of serum magnesium and lower urinary magnesium excretion, than the low PRA group ($p<0.05$). Serum calcium concentration was higher in patients with high PRA, when compared to the low PRA group ($p<0.05$). Urinary calcium excretion was also higher in the high PRA group, but this difference was statistically not significant. In the medium PRA group,

Table 2

Serum levels and urinary excretion of magnesium and calcium in patients with essential hypertension and in normotensive controls

Characteristic	Patients (n=32)	Controls (n=19)
Serum magnesium (mmol/l)	0.86±0.10*	0.93±0.02
Serum calcium (mmol/l)	2.35±0.26	2.41±0.16
Urinary magnesium (mmol/l)	3.29±0.25*	3.62±0.06
Urinary calcium (mmol/24 h)	4.85±1.84	4.69±3.04

Mean values ± SD are given;
* $p<0.05$ compared to the control group

the serum and urinary concentrations of magnesium and calcium did not differ significantly neither from the high PRA group nor from the low PRA group (Table 3).

Table 3

Serum levels and urinary excretion of magnesium and calcium in patients with essential hypetension, according to renin profile

Characteristic	High PRA (n=12)	Medium PRA (n=16)	Low PRA (n=8)
Serum Mg (mmol/l)	0.84±0.08*	0.89±0.11*	0.92±0.08
Serum Ca (mmol/)	2.43±0.08*	2.3±0.28	2.25±0.17
Urinary Mg(mmol/l)	3.04±1.3*	3.38±1.63*	3.96±1.65
Urinary Ca (mmol/24 h)	5.6±2.23*	4.87±1.65	4.31±2.08
PRA (ng/ml h)	7.4±3.34*	1.75±0.96	0.64±0.33
Urinary Na (mmol/24 h)	157.4±51.8*	149.0±32.5	123.8±22.6
ALDO (ng/ml)	118.6±43.1	158.8±39.9	181.8±54.9

Means ±SD are given; Mg, magnesium; Ca, calcium; Na, sodium; ALDO, serum aldosterone;
* $p<0.05$ vs. the low renin group

Urinary sodium excretion was significantly higher in the high PRA group, than in the low PRA group ($p<0.05$). This is in concordance with the lower serum aldosterone levels detected in the high PRA group. In the medium PRA group, the values for urinary sodium excretion were in between the values the high and low PRA groups, but these differences were not statistically significant.

Discussion

Our results indicate, that patients with essential hypertension display lower serum magnesium concentrations when compared with the

normotensive controls, and that this magnesium deficiency is more pronounced in the high PRA group of patients.

Contradictory data have been presented concearning the serum magnesium level of the hypertensive patients. Early studies reported that hypertension was associated with elevations of serum magnesium levels (Walker 1936). However, others found lower levels of serum magnesium in hypertensive patients (McCarron 1983; Touyz 1987; Tillmann 1988), and some detected no difference in this respect in comparison to normotensive controls (Fisher 1993; Kjeldsen 1990; Resnick 1983).

Our results are in concordance with the hypothesis that essential hypertension is associated with hypomagnesaemia. Up to the present there are at least 28 independent studies to confirm this (see Altura 1990, for references). In addition, one recent study demonstrates clearly that subjects with a positive family history of hypertension have concommitant lower levels of serum magnesium (Shibutani 1990). Magnesium deficiency has been implicated in the pathogenesis of hypertension, because at the cellular level magnesium acts as a gate for entry and exit of calcium at the vascular smooth muscle cell membrane (Altura 1993). Therefore, magnesium deficiency promotes excess calcium uptake and induces elevation of the peripheral resistance (Altura 1986). Also, it has been shown that magnesium depletion inhibits the release of endothelial-derived relaxant factors (Ku 1987), and potentiates the action of a variety of neurohumoral constriction agents, including angiotensins, serotonin and adrenergic amines (Turlapaty 1982; Goldstein 1978). Overall, these findings suggest that magnesium deficiency is, at least partially, responsible for a rise in blood pressure and that a genetic predisposition to hypertension is probably closely related to magnesium metabolism.

We analysed the measurements of magnesium concentrations with respect to the concurrent plasma renin activity. It appeared, that the magnesium deficiency was most pronounced in the high PRA group. Admittedly, serum magnesium level is an insensitive measure of total body magnesium stores, but 24-hour urinary magnesium excretion is considered to be a reliable index of magnesium status, provided that fluid balance and renal function are normal (Altura 1986). We detected significant differences ($p<0.05$) in the urinary magnesium excretion between the PRA groups, thus confirming, that each renin group had a distinctive magnesium profile.

Considering the close association between magnesium and calcium at the cellular level, we evaluated the indices of calcium metabolism in hypertensive patients and detected differences between the PRA groups, that were opposite to those observed in magnesium concentration. Thus, high-renin hypertension is a condition characterized by lower levels of serum magnesium and higher levels of serum calcium.

Conversely, hypertensives with low plasma renin activity have higher levels of serum magnesium and lower serum calcium levels. When all the hypertensives were analysed together, no deviations in calcium metabolism were observed in comparison to normotensive controls.

Conclusions

In conclusion, magnesium deficiency is a characteristic feature for essential hypertension, especially for the high PRA group. These findings raise the possibility that the pathophysiologic mechanism that causes either suppression or stimulation of renin secretion is also involved in the deviations of magnesium metabolism in patients with essential hypertension. However, the precise mechanism of this association needs to be futher defined.

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Kokkuvõte

Essentsiaalne hüpertensioon on seotud heterogeensete muutustega magneesiumi metabolismis. Käesoleva töö eesmärgiks oli uurida magneesiumi metabolismi ning reniin-angiotensiin-aldosterooni süsteemi aktiivsuse vahelisi seoseid essentsiaalse hüpertoonia korral. Uuritud 32 patsienti tüsistumata essentsialse hüpertensiooni diagnoosiga (diastoolne vererõhk 95–115 mm Hg). Uuritavad jagatud kolme reniini aktiivsuse gruppi vastavalt plasma reniini aktiivsuse (PRA) ja 24-tunni uriinis erituva naatriumi hulga suhtele nomogrammi alusel. Kontrollgruppi kuulus 19 tervet, normaalse vererõhuga isikut. Fotomeetriliselt määratud magneesiumi ja kaltsiumi sisaldus seerumis

ning 24-tunni uriinis. Tulemustest selgus, et haigetel oli seerumi magneesiumi sisaldus märgatavalt madalam, kui kontrollgrupis ($p<0.001$), seerumi kaltsiumi sisalduse osas erinevust ei olnud. Kõrge PRA-ga haigete grupis ($n=7$) oli seerumi magneesiumi sisaldus madalam ning, vastupidi, seerumi kaltsiumi sisaldus kõrgem ($p<0.05$), kui madala PRA grupis ($n=9$). Ööpäevas erituva magneesiumi hulk oli väiksem kõrge PRA grupis, võrreldes madala PRA grupiga ($p<0.05$), erituva kaltsiumi hulga osas oluline erinevus puudus. Kokkuvõttes selgus, et essentsiaalse hüpertensiooni korral esineb magneesiumi defitsiit seerumis normotensiivse kontrollgrupiga võrreldes ning et see defitsiit on enim väljendunud kõrge PRA-ga haigete grupis.

DYNAMIC INVESTIGATION OF POSTINFARCTION PERIOD BY STATISTICAL DATA PROCESSING METHODS

Külliki Karu, Liina Mai Tooding

Abstract

The authors present a possibility for the complex evaluation of the functional status of the cardiovascular system by the hemodynamic response to low-level exercise 2–3 weeks after acute myocardial infarction and in the posthospital phase by modelling the dynamics of the postinfarction period. The multidimensional analysis in combination with the development of integrated parameters was employed. For every observation moment factor analysis was used.

Introduction

The choice of management strategies and the optimal level of physical activity for patients with recent myocardial infarction (MI), as well as solving the problems of return to work, assume evaluation the degree of rehabilitation. The time needed for the improvement of functional status of the cardiovascular system greatly differs in individual patients. In this connection, predicting of the course of the postinfarction period becomes particularly important.

The authors present a possibility for the complex evaluation of the functional status of the cardiovascular system by the hemodynamic response to low-level exercise before hospital discharge (2–3 weeks after acute MI) and in the posthospital phase by modelling the dynamics of the postinfarction period.

Material and Methods

Initial data for processing constituted about 1500 variables: clinical characteristics, data of selective coronarography and left ventriculography, as well as parameters measured during exercise in 62 patients with acute transmural MI without clinical evidence of congestive heart failure aged from 31 to 60 years (mean 49,6 ± 0,9 years). At rest (in the supine and sitting position), during and after moderate upright exercise on bicycle ergometer (maximal load up to 1 $W.kg^{-1}$ in most patients) in about 8–10 moments of time the ECG, FCG, central pulse tracings and impedance cardiograms by W. C. Kubicek (1966) were recorded. The patients were studied three times in the course of a 6-month follow-up period.

Although the number of parameters was reduced to 270 by means of exploratory analysis, the essential complexity of data set makes the traditional statistical approach inefficient. To overcome methodical difficulties the multidimensional analysis in combination with the development of integrated parameters was employed. For every observation moment factor analysis was used to get complex indicators which were added to the initial data.

Results and Discussion

30 most informative parameters forming the basis for the factor models included the age, arrhythmias, previous MI, previous arterial hypertension, the duration of the coronary artery disease, the type of asynergy and the number of impaired segments, the ejection fraction, maximal work load, "double product", PEP/LVET at rest and at the maximal work load, changes in stroke index, systolic ejection rate and total peripheral vascular resistance, as well as in heart rate-corrected systolic and diastolic time intervals during exercise.

This initial information was expressed by 6 synthetic factors (V1,...,V6), describing 65% of the total dispersion of the initial data. The content of the factors was interpretated as follows: V1 — factor of age and central hemodynamics; V2 — orthostatic factor; V3 — factor of asynergy; V4 — factor of anamnesis and physical working capacity; V5 — factor of time interval changes; V6 — preejection period factor.

Individual factoral coefficients for every patient were calculated while the direction of the favourable effect was connected with the positive area and the adverse effect with the negative area of the scale. General estimates of the functional status of the cardiovascular system of the patients were derived by summarizing the values of individual factoral coefficients. On the basis of general estimates, using the expert method, patients were grouped as belonging to the good, satisfactory and poor functional condition level, respectively 12, 38 and 12 patients. Moreover, it was possible to judge which of these factors was the most important in determining the functional status of a concrete patient.

On the basis of these data regression models were found to prognosticate the functional state F_t of patient in moment t by F_s while $s<t$. Physical working capacity, stroke volume index (SVI), cardiac index, duration of systolic time intervals and other central indicators have obtained statistical significant prognosis by hospital leave state for F_3 (3 months later) and F6. The corresponding regression equation for predicting individual values for SVI at rest (in the sitting position) 3 months later was:

$$Y_1 = 26,6 + 5,8V1 - 2,9V2 - 1,4V3 + 3,2V4 - 0,3V5 - 0,9V6,$$

where Y_1 — prognosis for SVI at rest, V1–V6 — factor coefficients. The coefficient of multiple correlation $R = 0,62$ ($p<0,001$) was obtained.

SVI at exercise 3 months later might be expressed as:

$$Y_2 = 33,6 + 5,9V1 - 3,6V2 - 1,0V3 + 1,0V4 + 0,9V5 + 0,2V6,$$

where Y_2 — prognosis for SVI at exercise ($R = 0,56$; $p<0,01$).

Conclusions

Predicted values of central indicators were compared with really measured values of these parameters to evaluate treatment and physical rehabilitation efficiency. Such analysis allowed to distinguish the patients whose functional status in the posthos pital phase strongly differed from the predicted one.

At the present time we are continuing our studies to find out the prognostical significance of echocardiographically gained data for predicting development of heart failure after acute MI.

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Kokkuvõte

Autorid on uurinud ägeda müokardi infarkti kulu prognoosimise võimalusi haiglajärgses perioodis, lähtudes hemodünaamika muutustest varajasel veloergomeetrilisel koormustestil. Mitmemõõtmelise faktoranalüüsi meetodil on välja töötatud regressioonivõrrandid hemodünaamika parameetrite (löögiindeks, südameindeks, väljutusfraktsioon) prognoosimiseks ning võrreldud haigetel 3 ja 6 kuud peale ägeda infarkti põdemist reaalselt mõõdetud näitajaid prognoositutega. Leiti, et tetrapolaarne reograafia kombinatsioonis varajase veloergomeetrilise testiga võimaldab usaldusväärselt prognoosida müokardi kontraktiilse funktsiooni dünaamikat infarktijärgses perioodis.

ATRIAL VERSUS VENTRICULAR PACING IN PATIENTS WITH SICK SINUS SYNDROME

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Abstract

The present study was undertaken (a) to evaluate comparative acute hemodynamic effects of atrial pacing (AP) versus ventricular pacing (VP), and VP in the presence versus absence of retrograde ventriculoatrial (VA) conduction in symptomatic sick sinus syndrome (SSS) patients, and (b) to study their long-term survival, development of permanent atrial fibrillation (AF), systemic embolism and atrioventricular (AV) conduction defects. Cardiac index (CI) was assessed by thermodilution technique in 22 patients undergoing pacemaker (PM) implantation. Altogether 30 atrial and 58 ventricular paced patients were followed up for an average of 3.6 and 7.2 years, respectively. Noninvasive electrophysiologic study was performed preoperatively and at follow-up.

Conclusions: AP produced an average of 19% higher CI than VP. VA conduction was the crucial hemodynamic determinant during VP: CI was higher in patients without VA conduction than in those with intact VA conduction, and could decrease below prepacing values in the latter subgroup. Atrial paced patients exhibited better long-term survival than ventricular paced ones and no incidence of permanent AF or systemic embolism. AP reduced the incidence of paroxysmal AF. Development of high degree AV block during AP was uncommon. Moderately impaired AV conduction ("Wenckebach point" 100–120 pulses per minute (ppm)) does not exclude the use of AP.

Key words: arrhythmia; cardiac pacing, artificial; cardiac output; follow-up studies; hemodynamics; pacemaker, artificial; sick sinus syndrome.

Introduction

Permanent cardiac pacing has become the treatment of choice for SSS. Its main aim is symptom relief. Long-term follow-up studies suggest that cardiac dysfunction and the rate of systemic complications can be reduced by physiologic rather than VP (Sasaki *et al.* 1991). Although this concept is widely accepted, supporting evidence is not fully conclusive. On the other hand, SSS is reported to have comparatively benign natural course (Rasmussen 1981) and the overall survival rate is not much different from that of normal population

(Shaw *et al.* 1980). So far there is no evidence of better survival in paced patients compared to those not paced.

A variety of single and dual chamber (DDD) PMs is available for clinical use. It has been postulated that AP is the most physiological mode for patients with SSS as it provides both AV synchrony and a normal ventricular activation pattern (Rosenqvist 1990). DDD pacing can be chosen if the risk for developing high-degree AV block is considered significant. However, it is an expensive and sophisticated method of treatment with a greater potential for complications (Hayes, Furman 1983). Therefore, it should be reserved for only a well-defined subgroup of PM recipients.

Ventricular inhibited (VVI) pacing was the first pacing mode used to treat patients with symptomatic SSS. Unfortunately, in contrast to AP, it does not offer the above-mentioned hemodynamic advantages. Furthermore, preserved VA conduction is supposed to be an additional contributor to the impaired hemodynamics during VP. In the most pronounced cases these factors may lead to pacemaker syndrome, referred to by Ausubel and Furman as "a complex of clinical signs and symptoms related to the adverse hemodynamic and electrophysiologic consequences of VP in the absence of other causes" (Ausubel, Furman 1985). Unfortunately, it does not coincide with everyday practice: according to the last published World Survey of Cardiac Pacing in most cases of SSS conventional VVI pacing was still employed (Feruglio *et al* 1987). It seems that the hemodynamic superiority of AP is sacrified to the convenience of handling the ventricular lead.

This study was performed to: 1. To evaluate the comparative acute hemodynamic effects of (a) AP *versus* VP (b) VP in the presence versus absence of VA conduction in symptomatic patients with SSS. 2. To study their long-term survival, development of permanent AF, systemic embolism and AV conduction defects. 3. To define these subgroups of PM recipients with SSS who are to benefit from AP and those who will do satisfactory with VP.

Material and methods

Hemodynamic study. Twenty-two consecutive patients (8 males and 16 females) with symptomatic SSS undergoing permanent atrial inhibited (AAI) pacing were studied. Clinical details of the patients are listed in Table 1. The mean age was 64±9 years (M±SD). The average New York Heart Association (NYHA) functional class was 2.5±0.7. The patient population was divided into two groups according to the presence (Group 1; 12 patients) or absence (Group 2; 10 patients) of VA conduction. The two groups did not differ statistically significantly from each another by the variables listed in Table 1.

Table 1

Patient data

No	Age and sex	Underlying heart disease	ECG findings	NYHA class	Prepacing symptoms
			Group 1		
1	70 M	None	AV escape rhythm	II	Dizziness
2	80 F	CAD	Sinus bradycardia	IV	Syncope
3	61 F	CAD	Sinus arrest	III	Syncope
4	59 M	None	SA Block II	II	Dizziness
5	63 F	None	AV escape rhythm	II	Syncope
6	62 F	CAD+SH	BTS	II	Syncope
7	58 M	HC	Sinus bradycardia	II	Syncope
8	78 F	CAD	Sinus bradycardia	III	Syncope
9	77 M	CAD	Sinus bradycardia	III	Dizziness
10	64 F	CAD	BTS	IV	Syncope
11	76 F	CAD	Sinus bradycardia	III	Syncope
12	54 F	None	Sinus bradycardia	II	Syncope
			Group 2		
13	66 F	None	Sinus bradycardia	III	Syncope
14	64 F	None	BTS	III	Dizziness
15	55 M	CAD	BTS	II	Dizziness
16	57 F	CAD	Sinus bradycardia	II	Syncope
17	51 F	None	Sinus bradycardia	II	Syncope
18	75 F	SH	AV escape rhythm	II	Syncope
19	58 F	CAD+SH	AV escape rhythm	II	Syncope
20	70 M	CAD	Sinus bradycardia	III	Dizziness
21	63 F	None	Sinus bradycardia	III	Dizziness
22	48 F	None	Sinus bradycardia	II	Syncope

CAD = coronary artery disease;
HC = hypertrophic cardiomyopathy;
SA = sinoatrial;
SH = systemic hypertension.

Studies were carried out in the angiocardiographic laboratory. In all cases antiarrhythmic treatment had been stopped 2–4 weeks earlier. Transesophageal electrophysiologic testing was performed to assess sinus node automaticity and AV conduction defects. Corrected sinus node recovery time and AV conduction "Wenckebach point" were determined. Quantitative assessment of hemodynamic changes was carried out by standard thermodilution technique (Ganz, Swan 1972). Transesophageal ECG lead was used to determine the presence of VA conduction during VP.

Through left external jugular or left cephalic vein monopolar screw-in PM lead was positioned in right ventricle. Asynchronous VP was performed at two rates: 70 and 90 ppm. Thereafter the PM lead was removed from the ventricle and positioned in right atrium

from where asynchronous pacing at the same rates was carried out. Cardiac output measurements were performed in triplicate after stable hemodynamics were obtained, but not earlier than 5 minutes after each adjustment of PM settings. Later the mean was calculated and cardiac hemodynamics were expressed as CI.

Follow-up study. Thirty out of 41 consecutive AAI paced symptomatic SSS patients (7 males and 23 females) aged 64±9 years were followed up for an average of 38±10 months (ranging 20 to 80 months). Four patients operated during the study period were interviewed only and the remaining 7 were lost for follow-up. In 16 cases (53%) the underlying heart disease was coronary artery disease, in 3 cases (10%) systemic hypertension, in 2 cases (7%) their combination, in 2 cases (7%) rheumatic heart disease and in 1 case (3%) hypertrophic cardiomyopathy. Six subjects (20%) were without morphologic heart disease. Among ECG findings sinus bradycardia was prevailing (17 cases). Sinoatrial block was diagnosed in 7 cases and sinus arrest in 1 case. Bradycardia-tachycardia syndrome (BTS) was present in 5 cases. The average preoperative NYHA functional class was 2.6±0.7. The leading indications for PM implantation were syncopal attacks, dizziness, fatigue and cardiac failure.

Transesophageal electrophysiologic investigation was carried out both preoperatively and at follow-up. The same protocol was employed as in previous hemodynamic study. Besides, basic heart rhythm and rate were recorded when reprogramming the pacing rate of the implanted PM below the spontaneous heart rate.

Fifty-eight ventricular paced patients, 38 females (66%) and 20 males aged 60±11 years were followed up for a mean of 75±40 months (6.2 years). In the majority of cases an underlying heart disease such as coronary artery disease, systemic hypertension or cardiomyopathy was diagnosed. The remaining 25% of cases were classified as idiopathic. The leading indication for PM insertion were syncopal attacks in 81% of patients. In 39 patients transesophageal electrophysiologic study was carried out according to the above-mentioned protocol. Besides, the presence of VA conduction was tested.

All data are presented as the group mean (M) and standard deviation (SD). Comparisons of means for continuous variables were made by Student's paired and unpaired t-test. Probability levels with p value of <0.05 were regarded as significant.

Results

Hemodynamic study. Prolonged (>525 ms) corrected sinus node recovery time was demonstrated in 13 patients (68%). First degree AV block with prolonged P–R interval was present in 2 cases. Another

6 patients developed "Wenckebach point" during incremental left AP at rates below 120 ppm. So, in 8 cases (42%) some kind of AV conduction defect was revealed. No His bundle branch block or intraventricular conduction defect was present.

In all cases basic rhythm was either sinus or AV escape rhythm with the mean rate of 49±7 beats per minute (bpm) and no significant difference between the groups at baseline (50±5 bpm in Group 1 and 49±8 bpm in Group 2). CI was roughly on the same level with baseline during VP in the overall patient population. In Group 1 at pacing rate of 70 ppm it was even 11% lower than during basic rhythm ($p<0.05$). AP resulted in 16–20% higher CI from baseline in both groups. Figure 1 compares CI during AP and VP. In Group 1 the former pacing mode offered higher CI than the latter ($p<0.01$). In Group 2 the corresponding difference was nonsignificant.

As the prepacing values of CI varied noticeably from one patient to another the change from baseline at each PM setting was calculated (Table 2). Figure 2 compares these variables from the point of view of presence or absence of VA conduction. There was a significant difference in the change in CI from baseline between the two groups during VP: in Group 1 towards increase and in Group 2 towards decrease ($p<0.05$). Nonsignificant increase in CI was gained from raising the pacing rate from 70 to 90 ppm at either pacing modes.

Table 2

The change in cardiac index from baseline (l/min/m^2) during pacing

	Overall n=22	Group 1 n=12	Group 2 n=10
VP 70 ppm	-0.10±0.33	-0.31±0.23	+0.17±0.24
VP 90 ppm	-0.01±0.41	-0.19±0.20	+0.23±0.50
AP 70 ppm	+0.43±0.40**	+0.37±0.43*	+0.51±0.36**
AP 90 ppm	+0.53±0.39**	+0.48±0.42**	+0.58±0.37**

*$p < 0.05$; **$p < 0.01$; vs baseline

Follow-up study. Ninety-seven per cent of AAI paced SSS patients were alive after an average follow-up period of 3.2 years. One patient died of congestive heart failure at the age of 84 sixty months after PM insertion. During follow-up no sudden deaths occurred. AP offered excellent symptom relief in all cases. Dizziness and syncopal attacks were abolished completely. In all 5 patients with systemic hypertension the tendency towards lowering both systolic and diastolic blood pressure was noticed, and only one of them remained on antihypertensive medication at follow-up. In 3 out of 5 subjects with BTS the episodes of atrial tachycardia were prevented by AP alone. In the remaining the incidence of paroxysmal AF was markedly diminished by combining AP and antiarrhythmic medication. No onset

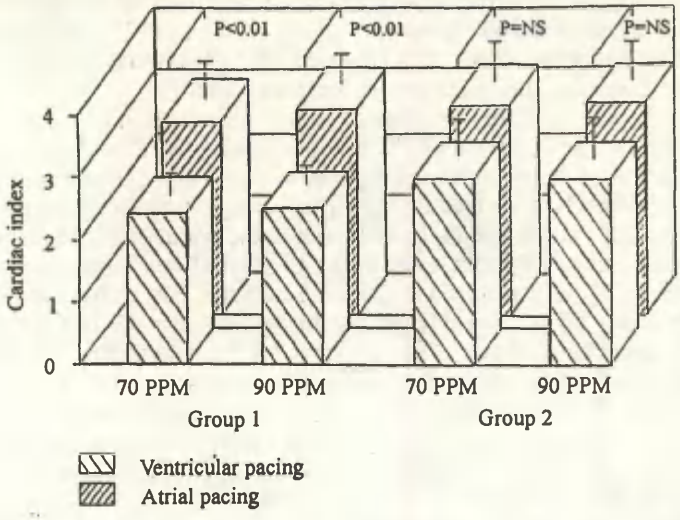

Figure 1.

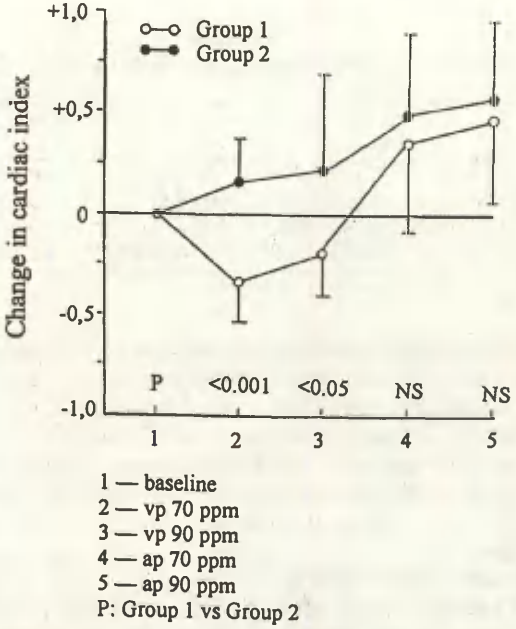

Figure 2.

of permanent AF was documented, neither were thromboembolic events present. The average NYHA functional class changed from the prepacing value of 2.6±0.7 to 1.4±0.4 at follow-up ($p<0.01$).

At follow-up the underlying heart rhythm was sinus bradycardia in 24 cases and AV escape rhythm in 6 cases. The average preoperative basic heart rate was 51±7 bpm and decreased nonsignificantly to 50±9 bpm at follow-up. The corresponding figures for "Wenckebach point" were 138±22 ppm and 136±18 ppm (p=NS), respectively. Two patients having first degree AV block showed the same degree of AV conduction defect at follow-up. No development of second or third degree AV block was present. All 12 patients (40%) with impaired AV conduction ("Wenckebach point" <130 ppm) showed 1:1 AV conduction at pacing rate of 100 ppm at follow-up.

Eighty-one per cent of ventricular paced patients survived more than 3.6 years and 78% were alive by the end of an average of 6.2-year follow-up period. Thirteen patients aged 68±9 years had died. Fatal stroke was present at least in 3 cases. However, the cause of death was not known for all patients. No patient had had syncopal attacks after PM insertion in either subgroup. Not surprisingly, a few among ventricular paced ones, particularly those having intact retrograde VA conduction, complained on mild dizziness and hypotension, that may be attributed to pacemaker syndrome.

All ventricular paced patients were either in sinus rhythm or AV escape rhythm at implantation. Sinus rhythm persisted only in 49% and AV escape rhythm was present in another 10% of ventricular paced patients at follow-up. In 36% and 5% of ventricular paced patients permanent AF or high-grade AV block had developed, respectively. Basic heart rate and AV conduction "Wenckebach point" were 58±16 bpm and 124±21 ppm, respectively, in ventricular paced subjects at follow-up. In this subgroup 46% of patients showed 1:1 VA conduction during VP at 70 ppm. Among these 7 patients had normal AV conduction and a suggestion was made to change their pacing mode to AAI.

Discussion

The average 19% increase in CI in the overall patient population from VP to AP in our study is similar to other studies using invasive techniques (Samet *et al.* 1966, Mukharji *et al.* 1990). Substantial differences in cardiac hemodynamics were revealed when the overall patient population was divided into two groups according to the presence of VA conduction. So, in group 1 the average increase in CI from VP to AP was 27% opposed to 10% in group 2 patients who showed no evidence of VA conduction. AP offered equal improvement in cardiac output from basic rhythm in both groups. The average augmentation

was 16–20% and is comparable to studies of Samet *et al.* 1966 and Wirtzfeld *et al.* 1987.

There was no significant change in CI from baseline in the overall population during VP. Nevertheless, changes of different direction and magnitude were demonstrated in patients of the two groups during that particular pacing mode. Our study shows clearly, that VA conduction is the critical determinant of cardiac performance during VP. In case there is no VA conduction, VP develops AV dissociation and atrial systole is of very little benefit to left ventricular performance. In case retrograde conduction is intact, excitation from the paced ventricles reaches atria during ventricular ejection period when AV valves are closed. The atria will empty in the retrograde direction into the pulmonary and systemic veins, causing a marked increase in the mean right atrial and pulmonary wedge pressures (Ausubel, Furman 1985). This might be called a "negative atrial kick" resulting in further deterioration of cardiac output. However, this can happen intermittently in exceptional cases in the absence of VA conduction during bad timing of atrial and ventricular contraction.

DiCarlo *et al.* 1987 measured cardiac hemodynamics at AV intervals of 130, 0 and –130 ms during VP in patients with normal and diminished left ventricular ejection fraction. Significant decrease in CI appeared in both groups when AV interval was changed from 130 to 0 ms. No further decrease in cardiac hemodynamics occurred in either group when AV interval was changed from 0 to –130 ms. With some limitations the latter condition can be extrapolated as VA conduction during VP. This finding is in contrast with our study and may partly be due to considerable variance in the magnitude of hemodynamic changes in DiCarlo's study, so that the average changes didn't reach statistical significance.

Special considerations when pacing patients with SSS include improving the overall prognosis, prevention of atrial tachyarrhythmias, overcoming an increased risk for systemic embolism, the state of AV and VA conduction. There are few data on overall mortality in this disorder and these available have described a survival rate similar to a matched control population (Shaw *et al.* 1980). Whether cardiac pacing per se affects longevity in patients with SSS deserves further investigation. Although no prospective randomized studies exist comparing AP with VP, a considerable amount of data has accumulated over the last decade indicating the beneficial long-term effects of AP. It has to be pointed out that in none of these studies a bias in favour of preoperative selecting the sickest patients with the worst prognosis for VVI pacing cannot be excluded.

In larger patient series Hesselson *et al.* 1992, Santini *et al.* 1990 and Rosenqvist *et al.* 1988 have reported on better survival in AAI paced compared to VVI paced subgroups. In our series, too, patients with an

atrial PM showed better overall survival than those with a ventricular PM. However, the average follow-up time of VP was significantly longer than of AP (7.2 years *versus* 3.6 years). AP became available at the University Hospital of Tartu in 1987. The majority of ventricular PM implants were performed prior to 1987 that excludes the bias favoring one or another pacing mode in these patients.

There is no doubt about that cardiac pacing offers significant symptom relief in most of SSS patients. Syncopal attacks are usually prevented by either pacing mode. Randomized double-blind studies have proven that all other symptoms are better controlled and general well-being provided by physiologic pacing compared to VVI pacing (Rediker *et al.* 1988). An interesting study was performed by Sulke *et al.* 1992, who upgraded symptom free patients with a ventricular PM to a dual chamber device. Seventy-five per cent of patients preferred DDD pacing and it was concluded that this is the incidence of "subclinical" pacemaker syndrome. The prevalence of "clinical" pacemaker syndrome is supposed to be 7–20% of VVI patients (Travill, Sutton 1992).

A number of follow-up studies comparing the incidence of atrial tachyarrhythmias, the onset of permanent AF, in particular, have proven AP to be more favorable in SSS patients. The development of chronic AF will render atrial PM ineffective, but many patients will have an adequate ventricular response rate, and the need for the change in pacing mode to VVI is rather limited. Lamas *et al.* 1992 have reviewed published data concerning the likelihood of permanent AF in paced SSS patients and reported on an average reduction of the incidence of AF from 34% in VVI to 9% in AAI or DDD pacing over an average 51-month follow-up. The 36% incidence of permanent AF in ventricular paced patients in our series is in line with these data, but still impressive. We agree that AP has somewhat protective effect on the onset of atrial tachyarrhythmias. This is of clinical relevance for patients with BTS. As shown, in some cases AP alone may be sufficient to avoid paroxysmal AF.

The risk of systemic embolism is closely linked with the development of AF. Thus, it is not surprising that the incidence of stroke is lower when a PM with an incorporated atrial lead is chosen. Camm and Katritsis (Camm, Katritsis 1990) have pooled the data of published studies and calculated the thromboembolic incidence for the first year of VP of 12%.

We found only one study comparing AP and VP where the ventricular paced group was further subdivided according to the presence of VA conduction. Ebagosti *et al.* 1988 in a 3-year follow-up of 45 VVI patients, noted atrial arrhythmias and deaths only in cases with demonstrated VA conduction and they proposed it as an independent prognostic factor in patients treated with VP.

The main reason why AP is not widely used is probably the fear of impending high-degree AV block. This is based on the observation that associated conduction disturbances in the AV node and the His-Purkinje system frequently coexist (Vallin, Edhag 1981). In addition, some of the patients with normal conduction at the time of implant may develop impairment of AV conduction in time. Thus far it may be concluded that the risk of development of clinically important AV conduction disturbances in atrial paced subjects is low. Rosenqvist and Obel (1989) surveyed published reports and found 28 studies. The median prevalence of development of significant AV block was 2.1% during the median follow-up period of 3 years, the annual incidence was 0.6%. This is contradictory to the survey of Sutton and Kenny (1986) who reported on an estimated annual incidence of significant AV conduction dysfunction of 3%. Such high incidence might reflect the fact that their definition of significant AV dysfunction included first degree AV block, complete bundle branch block, HV prolongation in His bundle electrogram and "Wenckebach point" at left atrial incremental pacing below 120 ppm. Rosenqvist and Obel restricted their definition to second and third degree AV block.

Patient selection criteria for AP have direct influence on the outcome. The key question to be answered is to what extent AV conduction may be defective to provide still safe AP. One method to establish eligibility for AP has been to assess "Wenckebach point". An unfortunate finding of the survey of Rosenqvist and Obel was that there was no correlation between the "Wenckebach point" used and the prevalence of AV block. In our series no significant change in AV conduction "Wenckebach point" was observed during an average of 3.2 years of AP. Even in these cases when it was as low as 100–120 ppm the outcome was satisfactory. No second or third degree AV block developed and no changing of pacing mode to VVI or DDD was needed. Therefore, we agree with van Mechelin *et al.* 1984, who suggest that the deterioration of antegrade AV conduction is possibly more often related to the use of antiarrhythmic drugs rather than degeneration of the AV conduction system itself.

In several published guidelines for PM prescription in symptomatic bradycardia AP is considered an appropriate pacing mode for SSS (Dreifus *et al.* 1991, The British... 1991), and one has to agree with it. In our opinion there is a limited but defined subgroup of SSS patients without VA conduction, who do not necessarily require a DDD unit when concomitant AV conduction defect is present, but will do with VP. These are most likely elderly people with limited physical activity suffering from clinical symptoms associated with episodes of severe bradycardia or temporary cardiac arrest. Although VP offers only a little increase in cardiac output, the attacks of syncope and dizziness are prevented this way. Besides, rate hysteresis function has proven

to be helpful for these patients: it enables to keep the PM inhibited most of the time and pacing is performed only as the attack of severe bradycardia develops (Stangl *et al.* 1988).

Conclusions

1. AP produced higher cardiac output than VP and, therefore, should be preferred in symptomatic SSS patients with normal AV conduction.

2. VA conduction was the crucial hemodynamic determinant during VP: CI was higher in patients without VA conduction than in those with intact VA conduction, and could decrease below prepacing values in the latter subgroup.

3. Atrial paced SSS patients exhibited better long-term survival than ventricular paced ones and no incidence of permanent AF or systemic embolism.

4. AP reduced the incidence of paroxysmal atrial tachycardias in patients with BTS.

5. Development of clinically significant AV conduction defects during AP was uncommon. Moderately impaired AV conduction ("Wenckebach point" 100–120 ppm) does not exclude the use of AP, however, more frequent pacemaker follow-up (once in 3 months) is mandatory to check the status of AV conduction.

6. As suggested both by hemodynamic and follow-up studies AP should be chosen for SSS unless contraindicated. VVI can be considered for controlling symptoms associated with attacks of severe bradycardia or temporary cardiac arrest in selected patients without VA conduction, when clinically significant AV conduction defect coexists.

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T-CELLULAR IMMUNITY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AFTER THROMBOLYTIC TREATMENT

Kristin Lamp, Maido Uusküla

Abstract

Cellular immunity (the number of T- and functionally active T-lymphocytes, the level of sensibilization of T-cells to myocardial antigen) was investigated in 150 patients with acute myocardial infarction (AMI). 35 of them received intravenous thrombolytic therapy (TT) with 1,5 million units of Streptokinase. TT caused a short-term decrease of the number of lymphocytes in peripheral blood that was accompanied by decreased numbers of T- and functionally active T-lymphocytes. In patients with TT sensibilization to myocardial antigen appeared later and was on lower level as compared with patients without TT. This lower level of sensibilization is favourable to the course and prognosis of AMI.

Introduction

There is a general agreement, that coronary thrombosis is the precise pathological event in the majority of transmural myocardial infarctions. Although this view was postulated in 1912 already it remained a contraversial issue until the end of the 1970-s when substantial pathological, anatomic and angiographic data had been accumulated. It was the time when thrombolytic therapy became an important part of complex treatment of patients with acute myocardial infarction (AMI) and many of the trials showed a significant reduction of mortality in patients treated with thrombolytics when compared with untreated controls (Stampfer M. J. *et al.* 1982, Heikkilä J. *et al.* 1988).

The effect of several drugs used in treatment of patients with ischaemic heart disease (verapamil, nifedipine, dipyridamol, pindolol, propranolol, heparin) on the function of lymphocytes has been determined (Molinoff P. B., Aarons R. D. 1984, Derenne F. *et al.* 1987, Bruserud Q. 1987) . The influence of thrombolytic therapy on the function of macrophages and phagocytes has been investigated quite thoroughly but the results of different investigators have been contradictory. It is found that essential activation of phagocytes takes place after thrombolysis and these activated cells are recognized as mediators of reperfusion injury (Engler R. L. 1989, Ranjadayalan K. *et al.* 1991). Danish researchers (Obel N. *et al.* 1993) have shown that streptokinase treatment did not modulate neutrophil function. The

opinion of T. W. Stief (1991) is that activated phagocytes participate in physiologic fibrinolysis. There is very few data about the effect of thrombolysis on lymphocytes, the other part of immune system. The aim of our study was to investigate cellular immunity, that plays certain role in healing processes, in patients with AMI in connection with administration of thrombolytic therapy.

Subjects and methods

150 patients with AMI in age of 31–70 years (mean age 53±0, 8 years) were investigated. In 35 of them intravenous thrombolytic therapy with 1,5 million units of streptokinase was carried out. Thrombolysis was started 1–8 hours (3 h 25 min±18 min) after onset of anginal pain, in case of firm electrocardiographical signs of AMI. All 35 patients received prednisolone (90 mg) as premedication. Streptokinase was infused intravenously for 30–60 min: 250.000 units in 20 ml saline given rapidly in 5–10 min, followed by 1,25 million units in 150 ml saline at a slower infusion rate. Thrombolytic treatment was combined with anticoagulant-therapy with heparin for 3–5 days (20.000 units per day s/c → 10.000 units per day). All patients received oral or intravenous nitrates and acetylsalicylic acid (125 mg dayly); antiarrhythmic drugs or other supportive treatment were given, if necessary.

Early coronary reperfusion was clinically indicated in 72% of streptokinase treated patients (rapid relief of chest pain, resolution of ST-T wave changes, ventricular arrhythmias, early enzyme peak). These indirect data were supported by data of coronary angiography , carried out 2–5 weeks after the onset of AMI.

Electrocardiographically 80% of streptokinase-treated patients developed transmural infarctions. In 6 cases subendocardial and in 1 case microinfarction was diagnosed.

Lymphocytes were separated from whole blood by density gradient centrifugation over Ficoll-Verographin (Boyum A. 1974). After washing lymphocytes were resuspended in Eagle medium to final concentration of 1,5×10 cells/ml. The number of T- and functionally active T-lymphocytes was determined by E-rosette formation methods. The level of sensibilization of T-cells to myocardial antigen (MA) was determined by a method, worked out by us, the method of inhibition of active E-rosette formation under the influence of myocardial antigen (Reisenbuk V. *et al.* 1985). Briefly: 1,0 ml of lymphocyte-suspension was incubated for 2 hours in 37°C with 30 μl of MA (concentration of protein 0,25 mg/ml, i.e. 5 ng per 1,0 million cells). After that the number of active T-cells was determined in lymphocyte-suspension, incubated with MA and in control suspension. The inhibition % of active E-rosette formation showing the quantity of sensibilizated cells, that have receptors to MA was calculated as follows:

$$\text{Inhibition\%(I\%)} = \frac{\%\text{AE-RFC}_C - \%\text{AE-RFC}_{MA}}{\%\text{AE-RFC}_C}$$

$\%AE\text{-}RFC_C$ — % of active E-rosette forming cells (active T-lymphocytes) in control suspension

$\%AE\text{-}RFC_{MA}$ — % of active E-rosette forming cells in lymphocyte suspension incubated with MA

The absolute number of sensibilizated T-lymphocytes per mm^3 was also figured out.

Results

In patients with AMI next day after thrombolytic therapy the number of lymphocytes in peripherial blood was considerably lower than in patients, who were not treated with streptokinase. The normal quantity of lymphocytes was restored by the end of the first week of illness (Table 1), in some patients even on the second or the third day after thrombolysis. The number of T-lymphocytes (Table 2) as well as functionally active T-lymphocytes (Table 3) was decreased during the first week after thrombolysis and also normalized on the second week after the onset of AMI.

Table 1

The effect of thrombolytic therapy on the number of lymphocytes

Days	Pts with thrombolysis n=35 cells/mm^3	Pts without thrombolysis n=115 cells/mm^3	p
1.	1214±111	2030±96	<0.02
7.	1928±121	2156±106	ns
14.	2192±123	2164±104	ns
21.	2236±104	2307±98	ns
28.	2164±108	2172±98	ns

Table 2

The effect of thrombolytic therapy on the number of T-lymphocytes

Days	Pts with thrombolysis n=35 cells/mm^3	Pts without thrombolysis n=115 cells/mm^3	p
1.	569±54	1115±46	<0.001
7.	838±58	1133±51	<0.05
14.	989±63	1165±43	ns
21.	1147±73	1225±49	ns
28.	1196±101	1241±54	ns

Table 3

The effect of thrombolytic therapy on the number of active T-lymphocytes

Days	Pts with thrombolysis n=35 cells/mm^3	Pts without thrombolysis n=115 cells/mm^3	p
1.	320±41	617±34	<0.001
7.	509±39	722±42	<0.05
14.	645±66	753±39	ns
21.	725±70	849±39	ns
28.	802±81	823±39	ns

Sensibilization to myocardial antigen in patients with primary infarction appeared by the end of the second week of illness. In case of reinfarction sensibilizated cells were present on the first day already. After thrombolytic treatment sensibilization in patients with primary infarction developed by the end of the third week and the number of sensibilizated cells was considerably lower than in patients, not receiving thrombolytic therapy, so was the level of sensibilization in patients with reinfarction (Figure 1).

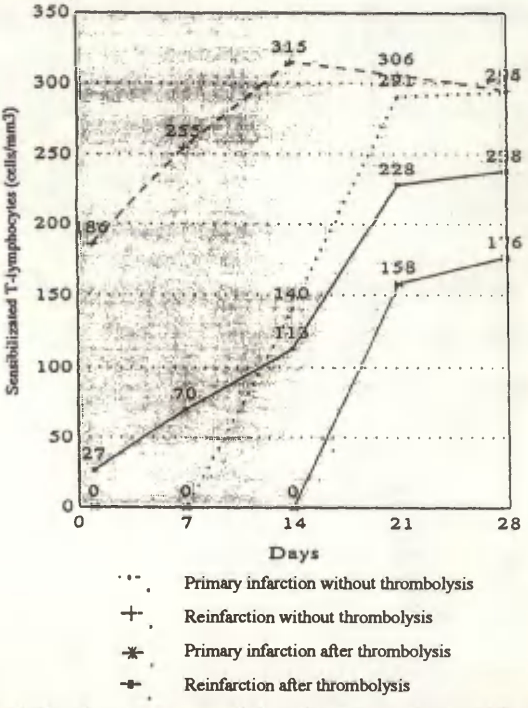


Figure 1. Sensibilization to myocardial antigen in patients with myocardial infarction.

In our previous works we have shown that in patients with constantly decreased activity of cellular immunity myocardial infarction often (in 70–80%) is accompanied by inflammatory processis. From 35 thrombolized patients 4 had pneumonias and in one patient exacerbation of chronic pancreatitis was diagnosed (14%). Patients with long-lasting immunodepression often have healing disturbances, that may lead to forming of left ventricular aneurysm and progression of heart failure. In thrombolized patients no left ventricular aneurysm was diagnosed and chronic cardiac failure progressed considerably more rarely as compared with patients not receiving thrombolysis and having constantly low number of active T-lymphocytes.

Thrombolized patients, as compared with patients with high level of sensibilization, had considerably better left ventricular function (Figure 2), although most of them had transmural infarction. They had seldom anginal pain and rhythm disorders in subacute phase of infarction. No Dressler's syndrome, nor exitus letalis was met among them (Table 4).

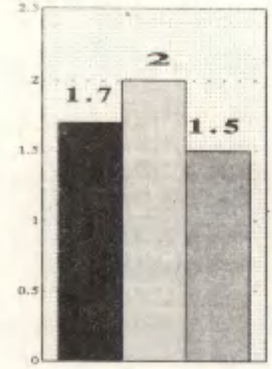
Table 4

Some clinical data of patients with myocardial infarction with different level of sensibilization to myocardial antigen

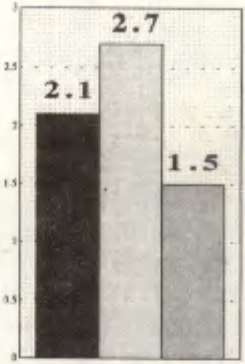
	Low sensibilization I%<40 n=43	High sensibilization I%>40 n=35	p
Stenocardia			
acute phase	82%	84%	ns
subacute phase	16%	80%	<0.001
Rhythm disorders			
acute phase	42%	56%	ns
subacute phase	13%	44%	<0.01
Congestive heart failure	15%	76%	<0.001
Aneurysm	9%	32%	<0.05
Dressler's syndroma	0%	20%	<0.001
Mortality	0%	24%	<0.001

Discussion and conclusions

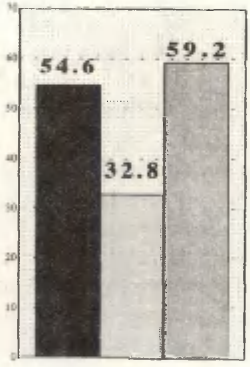
Thrombolytic therapy causes a short-term decrease of the number of lymphocytes in peripheral blood. It can most likely be explained by displacement of these cells from circulation into depot organs. In some patients we can even notice enlargement of peripheral lymph nodes. As organism tries to keep its homeostase, the constant relationship between various populations of blood cells, a decrease of one population (thrombocytes) may bring about the leaving of another



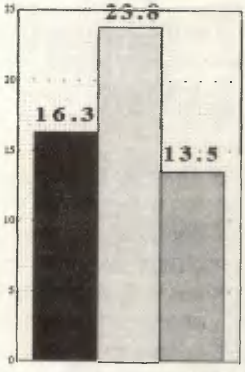
Stenosis >75% (number of arteries)



Number of a- and dyskinetic segments



Ejection fraction (%)



End diastolic pressure (mmHg)

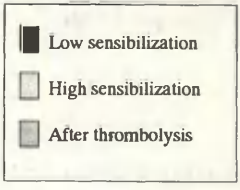


Figure 2. Angiographic and ventriculographic data of patients with myocardial infarction with different level of sensibilization to myocardial antigen.

population (lymphocytes) from circulation. As a rule younger and more active cells depart from circulation.

Decrease of the number of lymphocytes is accompanied by a temporary diminishing of the quantity of T- and functionally active T-lymphocytes, that lasts for a certain extent longer. Although, usually this kind of diminishing of the number of immunocompetent cells in peripheral blood of thrombolized patients is not long lasting, we should take into consideration the possible complications (inflammatory processes, healing disturbances) that may occur in case of long duration of immunosupression, particularly in patients, who have had trouble with their immune system before.

Releasing from the area of necrosis myocardial antigen calls forth the answer of the immune system: formation of sensibilizated to MA T-lymphocytes and production of antimyocardial antibodies. This reaction is a physiological one. But in some cases the answer of immune system is inadequate, an increased sensibilization to MA develops. It has been shown in experiments (Terechova-Uvarova N. A. 1982 Guthrie M. *et al.* 1984), that sensibilizated to MA lymphocytes are able to damage the function and structure of myocytes. Histamine, releasing from these damaged cells can irritate receptors of the nervous system and induce pain. Mediators, produced by activated T-lymphocytes are able to modify the inotropic and chronotropic answer of the tissue of myocardium and cause rhythm disorders (De Bracco M. M. E. *et al.* 1985).

After thrombolytic therapy sensibilization to myocardial antigen develops later and is on a moderate level. Reasons for that may be: 1) lack of lymphocytes in circulation during the period of releasing of antigen from necrotic myocardium, 2) immunosupressive effect of streptokinase, 3) immunosupressive quality of heparin, thrombolysis was combined with. As it was shown by Q. Bruserud and K. Ludin (1987) heparin inhibited antigen, but not mitogen induced DNA synthesis.

However, the lower level of sensibilization to MA noticed in patients after thrombolysis is in every respect favourable to the course and prognosis of acute myocardial infarction.

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Kokkuvõte

150-l südamelihase infarkti põdenud haigel uuriti rakulist immuunsust. Määrati T-lümfotsüütide ja funktsionaalselt aktiivsete T-lümfotsüütide hulk ning T-rakkude sensibilisatsiooni tase müokardi antigeenile. 35-l haigel 150-st viidi läbi intravenoosne trombolüüs 1,5 miljoni ühiku streptokinaasiga. Trombolüüsi järgselt esines haigetel lühiaegne (kuni 1 nädal) statistiliselt tõepärane nii lümfotsüütide koguhulga kui T- ja funktsionaalselt aktiivsete T-rakkude hulga langus perifeerses veres. Sensibilisatsioon müokardi antigeenile kujunes neil välja hiljem ning oli oluliselt madalam kui ilma trombolüütilise ravita haigeil. Taoline madal sensibilisatsiooni tase mõjub soodsalt haiguse kliinilisele kulule ja prognoosile.

EFFECT OF ADAPTATION ON THE MODERATE VELOERGOMETRIC STRESS IN YOUNG SUBJECTS WITH EARLY MILD HYPERTENSION

Eevi Maiste

Abstract

Adaptationprocessions of cardiorespiratory system on the bicycle stress test (of 1 W/kg body weight) were studied in young subjects (in 19...30 years) with early mild hypertension, and in normotensive vegetolabile and unvegetolabile healthy persons. Hemodynamic parameters were recorded by impedance cardiography. Significant difference of adaptional process of hemodynamic were evaluated between subjects with hypertensive heart disease in early stage and normotensive persons. Special attention should be paid the parameters, which characterize the systolic dysfunction (initial velocity of elevation of left ventricular pressure and mean velocity of stroke volume ejection velocity) as marker of hypertensive heart disease in nonhypertrophic left ventricle.

Introduction

Hypertension plays an important role in the factors for heart disease and heart mortality (Levy *et al.* 1990, Koren *et al.* 1991). In young people the progression of hypertension in early stage is often asymptomatic and difficult to discover by ordinary screening methods (Iriarte *et al.* 1993). Quite recently diastolic dysfunction accompanied by an increase in left ventricular wall thickness has been recognized as an early marker of hypertensive heart disease (Cohn *et al.* 1986, Dianzumba et al. 1986, Frohlich *et al.* 1992). Systolic function in the early stages is often preserved (Hartford *et al.* 1985). But animal models of pressure overload (Dubeus *et al.* 1993) have shown that modification of the shortening velocity of hypertensive heart can be detected very early.

Subjects and Methods

One hundred and thirthy eight persons in 19...30 (mean 25.6+1.16) years were included in study (73 females and 65 men). Mild essential hypertension was diagnosed in 47 subjects, of them borderline hypertension (0) in 16, the first stage (I) in 17, the second stage (II) in 14 persons. The history of hypertension was not more than 3 years.

For the comparision 50 normotensive vegetolabile and 41 normotensive unvegetolabile healthy persons were studied. The vegetolabile

were deleted into 2 subgroups — without complaints (A) and with complaints (B). All subjects had normal weight. In all groups the relative quantity of adipose tissue was equal. Nobody of them didn't have got a high degree physicaltrainingstage.

All patients underwent echocardiographic examination following the recommendations of the American Society of Echocardiography (Sahn *et al.* 1978). A physical exercise capacity was established by bicycle exercise testing. For examination of adaptationprocession of cardiorespiratory system was used the load of 1 W/kg body weight until 5 minutes. That intensity of exercise is used as the basisload for the value of the adaptationprocesses (Schwalb *et al.* 1981). Hemodynamic parameters were recorded by impedance cardiography in rest, during the exercise and in the 8 minutes recovery time. We continuously monitored the oxygen consumption during the some time and recorded the dynamics of the blood gases by Micro-Adstrup in the capillare blood before and after the test.

Results and Discussion

By echocardiography only in hypertensive II stage in part of the patients hypertrophy of left ventricle was found. In the other groups the wall thickness of the left ventricle didn't exceed the wellknown standards. The left ventricle wall thickness in vegetolabile subjects was significantly thinner ($p<0.05$) then in the other groups. The parameters of hemodynamics and oxygen consumption didn't differ between the groups in the rest (Table 1). The exercise tolerance was significavithy less ($p<0.05$) compared with hypertensive subject. The cause to stop the exercise test in the majority of cases was complain of dyspnea.

As shown in Table 2 by exercise with load of 1 W/kg body weight dynamics of storke volume index, heart index and increasing of the oxygen consumption didn't differ between the groups. We found significant decrease of the adaption velocity of oxygen consumption in early stage of arterial hypertension. In patients with the first stage arterial hypertension the disturbances were also registered in the initial stage of recovery period. In approximately one half of the subjects with vegetolabile disturbances there was no onset of steady state plateau.

Initial velocity (Table 3) of elevation of left ventricular pressure on onset of exercise increased by 23.6±1.65%, during the exercise did not change and increases by approximately 30% during the first minute of recovery time and reaches preexercise values to the end of 3 minutes recovery period in all cases. In 50% of vegetolabile patients, who had complaints Vi velocity decreases during exercise in relation to lengthening of isovolumetric contraction stage.

Table 1

Main characteristics of groups in rest

PARAMETER	HEALTHY	VEGETOLABILE		HYPERTENSIVE		
		A	B	0	I	II
Heart rate	72.60±1.96	76.20± 3.20	87.40±2.30	86.60±3.10	84.80±4.3	81.30±3.20
Average SBP (mmHg)	110.90±1.79	107.60±2.57	112.20±2.38	128.50±3.50	131.30±3.43	140.20±4.30*
Average DBP (mmHg)	72.20±1.26	76.53± 1.48	73.15±1.64	80.12±2.90	84.80±4.50*	95.00±2.20*
Mean BP (mmHg)	85.10±1.20	86.90±1.50	86.20±1.70	96.20±2.40*	100.20±3.20*	110.10± 2.70*
Stroke volume index	40.00±1.20	36.90± 2.40	33.60±1.81	34.00±2.75	35.90±2.70	30.10±2.48
Heart index	2.78±0.91	2.80±0.12	2.85±0.12	2.88±0.25	2.91±0.26	2.40±1.40
Initial velocity of left ventri-cularpressure increment (Vi)	2639.30±64.8	2772.80±79.0	2913.9±98.1	3284.28±12.5	3387.70±139.0	3744.10±13.90*
oxygen con-sumption ml/kg	5.59±1.30	5.90± 0.39	5.75±0.23	5.44±0.32	6.54±0.45	5.68± 0.31
exercise capacity (W)	200.40±8.20	137.60±10.70*	124.90±7.50*	169.40±9.20*	165.40±13.20*	144.00±11.00*

*$p<0.05$ compared with healthy group

Table 2

The mean values of hemodynamic and oxygen consumption parameters in exercise of1 W/kg

PARAMETER	GROUPS					
	HEALTHY	VEGETOLABILE		HYPERTENSIVE		
		A	B	0	I	II
	X±m	X±m	X±m	X±m	X±m	X±m
Maximale Heart Rate (m-l)	116.90±3.20	136.20±5.20	145.00±3.90*	140.80±5.40*	126.30±5.40	124.70±4.90
Maximale SBP (mmHg)	146.10±2.30	140.90±3.90	147.60±2.80	174.90±2.90*	172.90±5.30*	185.30±5.70*
Mean BP (mmHg)	70.80±2.10	76.60±4.20	77.80±1.87	84.60±4.60*	89.10±4.10*	98.80±2.90*
Stroke volume index	96.20±1.48	100.84±3.70	103.10±1.90	113.00±2.90*	119.28±3.67	129.20±3.00*
Heart index	5.48±0.22	6.14±0.42	5.84±0.27	6.10±0.45	5.45±0.59	4.84±0.27
Increasing of oxygen consumption (METS)	3.42±0.08	3.48±0.17	3.62±0.09	3.55±0.16	3.11±0.15	3.19±0.31
Velocity of adaptation (min)	1.43±0.06	1.60±0.10	1.50±0.08	1.45±0.08	1.64±0.13*	1.59±0.11*
Time of stadystate (min)	1.39±0.06	1.68±0.10	2.17±0.30*	1.73±0.18	2.20±0.72*	2.30±0.43*
Recovery phase I	0.75±0.04	0.70±0.08	0.75±0.06	0.79±0.01	0.89±0.01*	0.75±0.03
phase II	4.27±0.52	3.20±0.40	2.64±0.03	3.70±0.61	3.67±0.53	3.20±0.60

*$p<0.05$ compared with healthy group

Table 3

Dynamics of the initial velocity of left ventricular pressure increment (Vi) at steady exercise 1 W/kg

	Vi velocity (mm Hg/sec)					
TIME	HEALTHY	VEGETOLABILE		HYPERTENSITIVE		
		A	B	0	I	II
rest (sitting)	2639.3±64.8	2772.8±79.0	2913.9±98.1	3284.2±12.5	3387.7±21.8	3744.1±139.0
exercise						
3'	3027.0±133.6	3534.8±21.2	3534.8±21.2	4105.8±143.7	4032.3±112.1	4565.6±176.8
5'	3108.0±118.3	3586.3±123.7	2990.7±252.0	3956.9±254.4	4083.9±107.5	4994.3±128.0
recovery						
1'	2740.4±100.9	2990.7±152.0	3210.6±174.0	2600.3±240.8	3693.0±106.7	4260.1±180.0
3'	2820.2±69.9	2802.3±98.0	3112.8±91.6	3523.6±145.0	3649.6±116.0	3132.8±142.5

In hypertensive subjects the Vi velocity is significantly higher ($p<0.05$) than in normotensive subjects. In the borderline hypertension during exercise the excessive increase of Vi velocity at first is diminished and absolute values in most of cases do not differ from those of healthy subjects. In I stage hypertension no decrease of Vi velocity does occur and in II stage hypertension the Vi velocity shows tendency to increase exceeding significantly ($p<0.05$) the normal values.

Mean velocity of stroke volume ejection velocity (VQS) in normal subjects increases during exercise by 48...60% as compared to rest values and during the exercise has tendency to accelerate. In subjects with borderline and stage I hypertension VQS is shortening during exercise ($p<0.05$). The values of VQS and Vi at rest and during exercise are in correlation with the left ventricular mass and volume ($r=0.495$).

The increase of the heart rate during exercise in vegetolabile subjects were both in absolute values and as calculated per 1 W intensity of the exercise, significantly higher ($p<0.05$) than in other groups (Figure 1). The increase of the heart rate during exercise with intensity of 1 W/kg is in correlation with mass of skeletal muscles ($r=0.560$), proportional index ($r=0.528$) and left ventricular mass ($r=0.368$).

Absolute values of systolic blood pressure (SBP) were in hypertensive subjects regardless of the stage during exercise significantly higher ($p<0.05$) than in normotensive subjects. The increase of SBP per 1 W/kg (Figure 2) was in correlation with skeletal muscle mass ($r=0.501$) and with relation of the interventricular septum and left ventricular volume ($r=0.340$). SBP increment per 1 W/kg did not differ between the groups.

The values of diastolic blood pressure (DBP) were in hypertensive subjects significantly higher than in other groups. In stage II hypertension we found continuos increase of DBP during exercise. Characteristic of hypertensive subjects is a short time decrease of DBP during the first minute of recovery time after the DBP rises and by the 8 minute of recovery exceeds preexercise values in a number of cases.

Conclusion

In young hypertensive subjects the disease of adaptational process on the stress test can be evaluated already in the early stage of mild hypertension.

Special attention should be paid to the parameters, which characterize the systolic dysfunction (Vi and VQS dynamics) as marker of hypertensive heart disease in nonhypertrophic left ventricle.

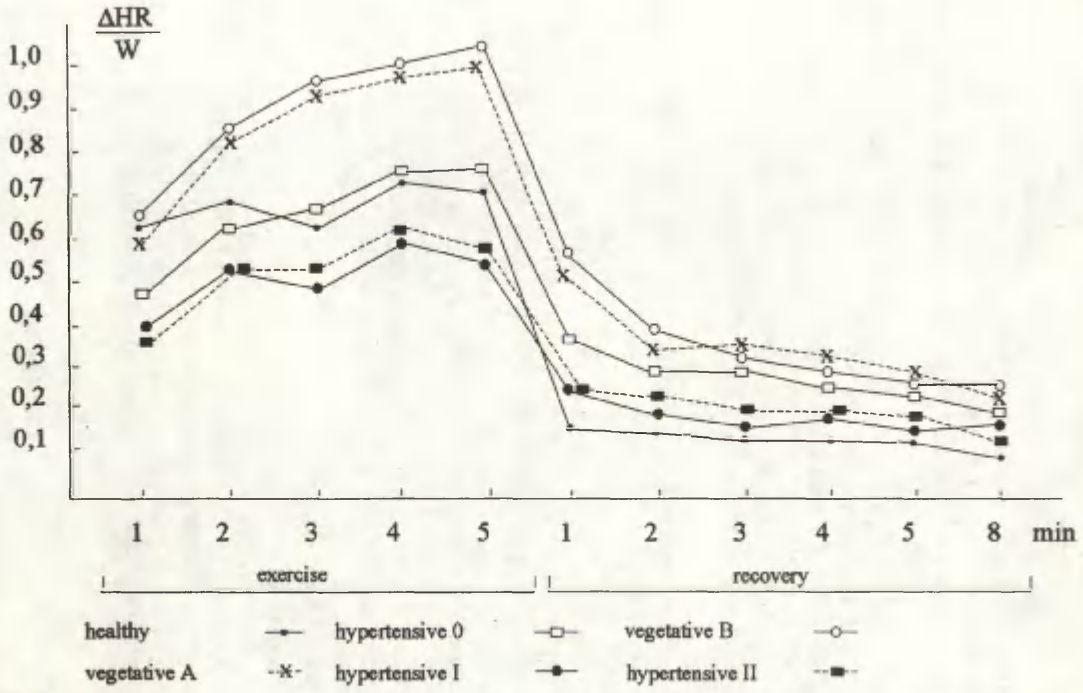

Figure 1. Dynamic increasing of heart rate of 1 W/kg during exercise and recovery time.

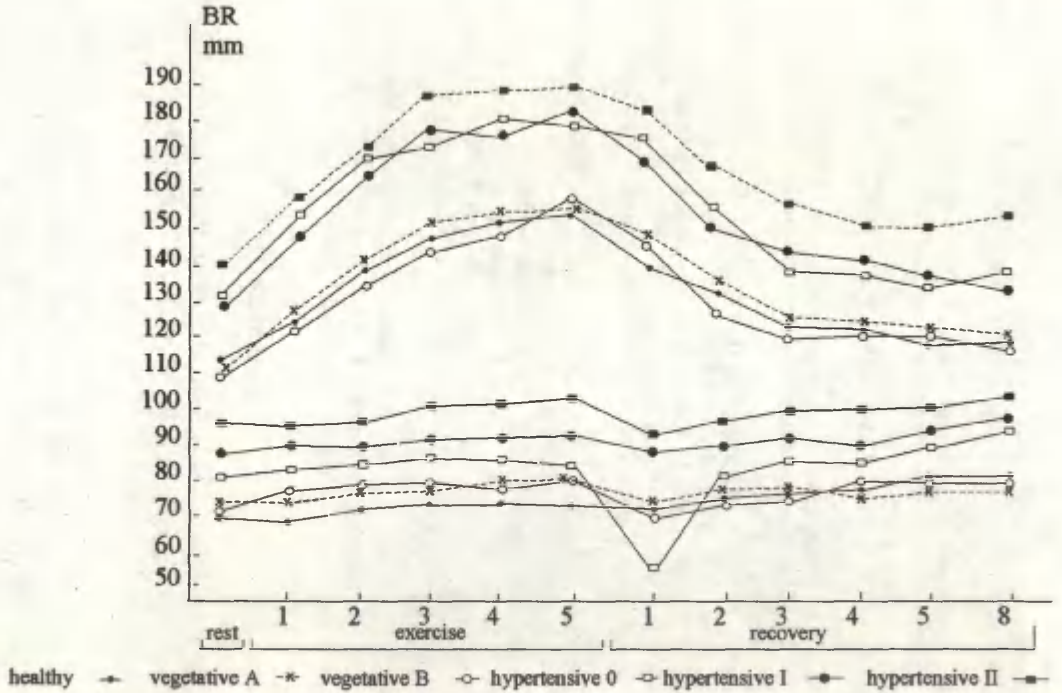

Figure 2. Dynamic SPB and DPB during exercise and recovery.

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Kokkuvõte

Uuriti hemodünaamika ja respiratoorse süsteemi adaptatsioonireaktsioone veloergomeetrilisele koormusele 1 W/kg hüpertooniatõve varases staadiumis ning tervetel vegetolabiilsetel ja mittevegetolabiilsetel isikutel.

Juba hüpertooniatõve labiilses ja I staadiumis ilmnesid kardiorespiratoorse süsteemi olulised adaptatsioonihäired koormusele. Vasaku vatsakese süstoolset funktsiooni peegeldavaid parameetreid (rõhutõusu algkiirus vasakus vatsakeses ja löögimahu keskmine väljutuskiirus) võib pidada üheks olulisemaks varaseks differentsiaaldiagnostiliseks markeriks hüpertrofeerumata vasaku vatsakesega isikutel.

REACTION OF MACROPHAGAL PHAGOCYTIC SYSTEM ON THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Silvia Noodla, Maido Uusküla

Abstract

The aim of this study was to investigate the influence of thrombolytic therapy on functional activity of macrophagal-phagocytic system in pts with acute myocardial infarction (AMI), to compare the connection of functional activity of phagocytes with the size of the necrotic zone and the left ventricle function in pts with myocardial infarction with and without thrombolytic therapy.Intravenous thrombolytic therapy with streptokinase in the first hours of AMI increases the spontaneous adherence of phagocytes and causes normalization of phagocytic reaction to myocardial antigen. The increased spontaneous adherence of phagocytes is not connected with the size of necrotic zone, the functional state of the left ventricle and the occurrence of some complications. Normal phagocytic reaction to myocardial antigen accompanies the formation of smaller necrotic zone and the development of fewer left ventricular dyskinetic segments.

Introduction

Myocardial necrosis induces the activation of phagocytes and their migration to the zone of necrosis, where they participate in the formation of necrotic zone and in healing processes (Chatelain *et al.*, 1987). Achievement of reperfusion with thrombolytic agents reduces myocardial infarction size, improves infarct healing and reduces its complications (Ritchie *et al.*, 1988).

Reperfusion after thrombolysis may cause several metabolic and functional changes in ischaemic myocardium, such as the production of a large amount of oxygen-derived free radicals, which can induce an irreversible oxidative damage in the myocardium and thus decrease the benefit from reperfusion (Giardino *et al.*, 1993). One source for oxidative metabolites in the damaged myocardium is activated leucocytes. It has been established that reperfusion increases the amount and the functional activity of leucocytes in the necrotic zone and that antiinflammatory pretreatment before ischaemia and after reperfusion reduces infarct size and leucocyte infiltration. (Klein *et al.*, 1988).

The aim of this study was to investigate the influence of thrombolytic therapy on functional activity of macrophagal-phagocytic sys-

tem (FAP) in patients (pts) with acute myocardial infarction (AMI) and to compare the connection of FAP with the size of the necrotic zone and the left ventricle function in pts with AMI with and without thrombolytic therapy.

Material and Methods

We examined 51 pts with AMI (mean age 55 years), who received intravenous thrombolytic therapy with streptokinase (Celiase) in the first hours of AMI (group I) and 52 pts with AMI (mean age 51 years), who received conventional therapy without thrombolysis (control group).

Spontaneous adherence of phagocytes and the adherence with myocardial antigen (MA) were measured by the modified K. Donaldson macrophage adherence and spreading assay on the first to second and fifth to seventh days of AMI. The infarct size was assessed on the basis of maximum numbers of ECG leads with Q/QS. The left ventricle ejection fraction (EF) and the number of dyskinetic segments were assessed on the basis of ventriculography and echocardiography.

Results and Discussion

Spontaneous adherence of phagocytes (SAP) on the first days of AMI was normal in 14% of pts in group I (7 from 51 pts).It increased above 80% in all pts by the end of the first week of disease. In the control group SAP was normal in 48% of pts (16f from 33 pts, $p<0.05$) on the first days of AMI. By the end of the first week of AMI SAP was increased in group I in 86% of pts (44 from 51 pts), which was significantly higher than in the control group (in 10 pts from 60, $p<0.01$)

By the end of the first week a more extensive necrotic zone was found in pts without thrombolytic treatment with increased SAP than in pts with normal SAP, despite the lack of differences in degree of coronary stenosis. But in pts with thrombolytic therapy regardless of the increased adherence of phagocytes statistically fewer ECG leads with Q/QS (2.3 ± 1.5) was found and the EF was higher (51.6 ± 13.9) than in pts with increased SAP in the control group (ECG leads with Q/QS were 4.8 ± 3.1, $p<0.05$ and EF was 32.9 ± 16.6, $p<0.01$).

The occurrence of some complications in pts with thrombolysis with increased SAP was smaller than in respective pts in the control group, for example, in group I there were no pts with acute heart insufficiency, whereas in the control group there were 2 cases from 10 pts ($p<0.05$); in group I chronic heart insufficiency was noted in 9 pts from 43, but in the control group in 8 pts from 10 ($p<0.05$). The occurrence of rhythm disturbances in the two groups did not differ.

The adherence with MA (FFA-MA) on the first to second days of AMI treatment with thrombolysis was increased in 6 from 51 pts (12%), was normal in 35 from 51 pts (69%) and decreased in 10 from 51 pts (19%). In the control group the appropriate data were 15 from 52 pts (29%), 29 from 52 pts (56%) and 8 from 52 pts (15%).

In the control group in pts with normal FFA-MA on the first days of AMI significantly fewer dyskinetic segments, higher EF and fewer occluded coronary arteries were found than in pts with increased FFA-MA. But in pts with thrombolysis and with normal FFA-MA significantly fewer leads with Q/QS and fewer dyskinetic segments were established as compared with the respective pts in the control group; no differences in EF and the number of occluded coronary arteries were found (Table 1). The occurrence of complications on the first and second weeks of AMI did not differ in the 2 groups.

These data indicate that in case of thrombolytic therapy there were significantly more pts with normal FFA-MA, the necrotic zone and the number of dyskinetic segments were smaller than in pts with conventional therapy, which indicates the opportune effect of thrombolysis on the formation of necrotic zone and healing processes.

Table 1

Data of necrotic zone size and left ventricle function in pts with AMI with and without thrombolytic therapy and with normal FFA-MA on the first days of AMI (M±SD)

	FFA-MA -8.5 ÷ 51.5		
	control group n = 29	pts with thrombolytic therapy	p
No of ECG leads with Q/QS	3.7 ± 2.3	2.5 ± 1.5, n = 33	< 0.05
No of dyskinetic segments	0.4 ± 0.8	0.04 ± 0.2, n = 23	< 0.05
EF%	53.3 ± 13.4	50.9 ± 13.5, n = 23	> 0.05
No of occluded coronary arteries	0.4 ± 0.5	0.9 ± 0.9, n = 14	> 0.05

The increased spontaneous adherence in pts with thrombolytic therapy is not connected with the size of the necrotic zone, but evidently it is due to immediate activating effect of thrombolytic drug on phagocytes, because streptokinase is foreign protein with antigenic properties (Bremm *et al.*, 1987). The frequent occurrence of rhythm disturbances in pts with thrombolytic therapy indicates microcirculatory disturbances in the ischaemic zone. Reperfusion increases the accumulation of leucocytes in the necrotic zone, which can induce plugging of white blood cells in capillaries, and thus increase microcirculatory disturbances.

Conclusions

1. Intravenous thrombolytic therapy with streptokinase (Celiase) in the first hours of AMI increases the spontaneous adherence of phagocytes. The increased spontaneous adherence of phagocytes is not connected with the size of the necrotic zone, the functional state of the left ventricle and the occurrence of some complications of AMI.

2. Intravenous thrombolytic therapy causes normalization of phagocytic reaction to MA, which accompanies the formation of the smaller necrotic zone and the development of fewer left ventricular dyskinetic segments.

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Kokkuvõte

Müokardiinfarkti puhul fagotsüüdid võtavad osa infarktitsooni formeerimisest ja paranemisprotsessist. Töö eesmärgiks oli uurida trombolüüsi mõju makrofagaal-fagotsütaarsüsteemi funktsionaalsele aktiivsusele akuutse müokardiinfarktiga (AMI) haigetel ja võrrelda trombolüüsitud haigete ja ilma trombolüüsita ravitud haigete fagotsütaarsüsteemi aktiivsust ja selle seost nekroosikolde suurusega ja vasema vatsakese funktsionaalse seisundiga. Uuriti 51 AMI haiget, kes said intravenoosset streptokinaas-ravi AMI esimestel tundidel ja 52 AMI haiget, kes ei saanud trombolüütilist ravi.

Trombolüütiline ravi AMI haigetel provotseeris kõrgenenud spontaanse fagotsüütide kleepuvuse 86%-l haigetest (kontrollgrupis — 17%-l). Trombolüüsitud haigetel kõrgenenud fagotsüütide

spontaanse kleepuvusega ei kaasnenud ulatuslikum nekroosikolle, madalamad vasema vatsakese funktsiooni näitajad ja sagedasem tüsistuste esinemine, nagu seda leiti kontrollgrupi vastavatel haigetel. Seega võib arvata, et kõrgenenud fagotsüütide spontaanne kleepuvus on tingitud trombolüütikumi otsesest aktiveerivast mõjust fagotsüütidele. Fagotsüütide kleepuvus müokardi antigeeni (MA) toimel trombolüüsitud haigetel näitas normaliseerumise tendentsi: trombolüüsitud haigete grupis oli fagotsüütide kleepuvus MA toimel kõrgenenud 12%-l ja normaalne 69%-l haigetest, kontrollgrupis olid vastavad näitajad 29% ja 56%. Trombolüüsitud haigetel, kellel oli normaalne fagotsüütide kleepuvus MA toimel, esines väiksem nekroosikolle ja vasemal vatsakesel täheldati vähem düskineetilisi segmente kui kontrollgrupi vastavatel haigetel, mis näitab trombolüüsi soodsat mõju infarktikolde formeerumisele ja paranemisele.

LUNG PERFUSION SCANNING AS A SCREENING METHOD IN DIAGNOSTICS OF PULMONARY EMBOLISM IN CARDIOLOGY DEPARTMENT

M. Ojamaa, K. Uist, M. Viigimaa

Abstract

Diagnosis of the patient with pulmonary embolism remains avexing clinical problem. Radionucleide methods offers the only non-invasive technique with an accetable sensitivity. We studied 40 patients with suspicion of pulmonary emboli. 16 of them had a pulmonary emboli, witch was seen also in the perfusion-ventilation studies. We suggest that radionucleide perfusion-ventilation study is always needed when there is a suspicion of pulmonary emboli and pulmonary angiography is needed only occasionally.

Introduction

Pulmonary embolism (PE) is the third most common cardiovascular disease, after acute ischaemic syndroms and stroke. PE continues to be a major contributing factor for in-hospital mortality in patients and is responsible for approximately 10% of deaths in hospital (Sandler 1989). The mortality in patients with PE is 31%, but if patients are treated the mortality is only 8%. 11% of patients will die within the first hours from the onset of PE, in 29% of patients the PE is diagnosed and the treatment is started, the rate of underdiagnose is 64% (Benotti 1983). PE is known clinically as the "great masquerader", the most common features that suggest this diagnosis are chest pain, profound dyspnea, tachypnea, hemoptysis, cyanosis with distended neck veins. The EKG tends to show characteristic abnormalitis, traditional manifestation of acute cor pulmonale, only in patients with massive PE. The chest X-ray may demonstrate an oligaemic segment of the lung if the embolus is large or a small basal effusion with a linear atelectasis with smaller emboli. It is generally accepted that pulmonary angiography, as the "gold standard" (Alderson 1987) is the definitive examination for excluding or confirming the presence of PE. But in patients with pulmonary hypertension and/or elevated right ventricular and diastolic pressure risk of mortality in this examination is very high (Perlmutt 1987). Therefore the non-invasive ventilation/perfusion lung scanning with its acceptable sensitivity is the screening test for the PE (Gray 1990, Kohn 1990, Cooper 1991, Juni 1991, Berg 1993, Gottschalk 1993). In the perfusion scan the

radiotracer is distributing in the lungs proportionally with blood flow, and an area of reduced perfusion will visualise as an area of decreased activity. In the case of PE the ventilation in the reduced perfusion area remains unchanged and combining these two scans together will increase the accuracy of the diagnose.

The aim of this study was to evaluate the lung perfusion scanning as a screening method in diagnostics of PE.

Matherial and Methods

During the period from January 1993 to October 1994, 40 patients with suspected PE from the Department of Cardiology of Tartu University Hospital were submitted to lung perfusion scanning to Nuclear Medicine Department of TUH. The patients were 22–82 years old (mean age 51 years); 17 of them were men and 23 were women. Prior to the perfusion study the chest X-ray was performed to exclude the other possible causes of the perfusion defects in lung scans. Two patients with perfusion defects underwent lung ventilation scanning. Perfusion lung scans were performed after an intravenous injection of 100–140 MBq (3–5 mCi) of Tc-labelled human albumin macroaggregates. Four views (anterior, posterior, left lateral and right lateral) were done with the use of the planar gamma camera PHO GAMMA IV equipped with the low energy and high resolution, diverging collimator. Each view was acquired for 400 000 counts. Ventilation lung scan was performed using a nebulizer filled with 100 MBq (3 mCi) 99mTc-DTPA in 4 ml, and inhalation was performed through the mouth using the nasal clip for 8 min of forced ventilation with 8–10 l/min oxygen flowing trough the nebulizer. Scan images were obtained in the same way as the perfusion images.

To evaluate the lung scan images we used modified Biello criteria (Biello 1987):

1. Normal:

— no perfusion defects present

2. Low probability of PE:

— subsegmental perfusion defect without ventilation study
— segmental or larger perfusion defect with ventilation matching
— any perfusion defect with a substantially larger chest X-ray abnormality

3. Intermediate probability of PE:

— subsegmental perfusion defect with mismatching ventilation study
— segmental or larger perfusion defect without ventilation study

4. High probability for PE:

— segmental or larger perfusion defects mismatching ventilation study.

Results and Discussion

Using the above described criteria our patients divided into groups:

I group: 22 patients
II group: 2 patients
III group: 7 patients
IV group: 9 patients

PE diagnose was excluded in 24 cases: 22 patients from group I with normal lung perfusion scan and 2 patients from group II whose perfusion defects size and location was matching with the chest X-ray film lesions. The remained 16 patients demonstrated variable size and location perfusion defects on lung perfusion scan. In all those patients the lung perfusion scan was performed 2 to 7 days after the onset of clinical symptoms, and 9 of them had already been submitted to anticoagulation and/or thrombolytic therapy. However in lung scan there were still visible some perfusion defects in variable sizes. Perfusion defect size was quite well correlated with clinical symptoms and PE was diagnosed in all of 16 patients. 9 patients had large multiple segmental perfusion defects, 5 patients had over two subsegmental perfusion defects, 2 patients had lobar defects. In 2 patients we performed the lung ventilation scan and the mismatching defects confirmed the PE diagnose. 5 patients underwent the pulmoangiography and there was no significant differense between the size and localisation with defects found in perfusion scan.

In conclusion the present study showed that radionucleide imaging of lung is a valuable test for the diagnosis of PE. It is easy to perform, noninvasive and safe for the patient. The test has also sufficient sensitivity. Low probability lung scan makes PE unlikely and high probability lung scan usually indicates the presence of PE. By using the radionucleide scanning as the first choice diagnostic modality, we could in most cases avoid performing an invasive and relatively high risk pulmonary angiography.

We suggest that radionucleide lung scanning is always needed when there is a suspicion of PE and pulmonary angiography is needed only in some cases, mostly in patients from the group of intermediate PE probability.

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Kokkuvõte

Kopsuarteri trombemboolia diagnoosimine ja õigeaegne ravi alustamine on haiguse prognoosi seisukohalt väga oluline. Tänapäeval kasutatakse kopsuarteri trombemboolia diagnoosimiseks kogu maailmas üha enam kopsude perfusiooni-ventilatsiooni uuringut radionukleiididega. Uuring on piisava tundlikkusega, mitteinvasiivne ja haigele kergesti talutav. Tartu Maarjamõisa Haigla isotoopdiagnostika osakonnas on tehtud 40 kopsude perfusiooni uuringut kopsuarteri trombemboolia kahtlusel. Perfusioonidefektid esinesid 16-l patsiendil ja neil diagnoositi ka kopsuarteri trombembooliat. Kopsude ventilatsiooniuuringuid on osakonnas võimalik teha alates 1994 a. jaanuarist ning seda on tehtud patsientidel, kellel perfusiooniuuringul esinesid defektid. Need on rutiinuuringud kopsuarteri trombemboolia diagnostikas ja nende uuringutega on võimalik välja selekteerida ka need patsiendid, kes vajavad diagnoosi täpsustamiseks kopsude angiograafiat.

METABOLIC DISTURBANCES AS CHARACTERISTIC FEATURES OF ESSENTIAL HYPERTENSION

Triin Parik, Kristina Allikmets, Rein Teesalu

Abstract

Objective: To evaluate metabolic cardiovascular risk factors in young (<40 yr) untreated patients with uncomplicated essential hypertension (EH) compared to normotensive controls.

Metods: Plasma glucose and insulin responses during oral glucose (75 g) tolerance test (GTT) were measured along with plasma lipid profile in 32 patients with mild-to-moderate EH and in 26 matched normotensive controls. Insulin sensitivity index (ISI) and fasting glucose-insulin ratio were calculated. Metabolic parameters were compared in normo- and hyperinsulinaemic (fasting plasma insulin >1 SD than the mean of all subjects) patient subgroups.

Results: Plasma insulin response during GTT was significantly ($p<0.01$) greater and fasting glucose-insulin ratio lower in EH patients, despite normal glucose tolerance. ISI was decreased ($p<0.01$) in EH patients. The hyperinsulinaemic patients (25%) had elevated plasma levels of triglycerides, total and LDL-cholesterol compared to normoinsulinaemic subgroup.This pattern of dyslipidaemia was also found in the entire EH group, when compared to controls.

Conclusions: The results show that young untreated patients with uncomplicated EH are characterized by multiple disturbances in glucose and lipid metabolism. Therefore, appropriate therapeutic approaches should be considered already in the early phases of the disease.

Introduction

The impact of antihypertensive treatment on coronary artery disease (CAD) endpoints has been disappointing (Hansson 1992), indicating that factors beyond high blood pressure (BP) contribute to the development of atherosclerosis in hypertensive patients. Recently, increased attention has been focused on the association of essential hypertension with metabolic abnormalities, particularly hyperinsulinaemia and/or insulin resistance (Laws 1993). These disturbances, in addition to the widely accepted risk factors like hypercholesterolaemia and dyslipidaemia have been implicated in the development of atherosclerosis (Standley 1993). Plasma glucose concentration has also been related to the incidence of atherosclerotic lesions, and this relation extends into the nondiabetic range of glycaemia (Drexel 1994).

Novel therapeutic strategies highlighten the need to consider interventions already in the developing phases of hypertensive vascular disease. Therefore, the present study was performed to evaluate metabolic risk factors in young (<40 years) untreated patients with uncomplicated essential hypertension.

Subjects and methods

Study subjects. Thirty-two untreated patients with mild-to-moderate essential hypertension (diastolic BP 95–114 mmHg), aged 20–40 years (mean 32.4) were studied. The diagnosis of hypertension based upon measurements of diastolic BP (Korotkoff phase V, mercury sphygmomanometer) of 95 mmHg or above and systolic BP of 140 mmHg or above in the seated position on three separate occasions at least 1 week apart. The average known duration of hypertension was 6.8 years (range 0.5–12). None of the patients had any evidence suggestive of CAD, based on a negative history, ECG, exercise test and echocardiography. Other systemic diseases and secondary hypertension were excluded on the basis of clinical and laboratory investigations.

The control group consisted of 26 healthy age-, sex- and body mass index-matched volunteers, in whom physical and biochemical examinations did not reveal any abnormalities and systolic BP and diastolic BP were lower than 140 and 85 mmHg, respectively.

No dietary restrictions were imposed, and none of the participants used any drugs, including antihypertensives at least 4 weeks prior to the study. Informed consent was obtained from all subjects and the study protocol was approved by the Ethical Committee of the Medical Faculty, University of Tartu.

Measurements. After an 12 h overnight fast an oral glucose (75 g) tolerance test (GTT) was performed. Blood samples were drawn at fast, after 60 and 120 minutes to determine plasma glucose levels (by the glucose oxidase method) and plasma insulin levels by radioimmunoassay kits (Medgenix, Belgium). In the fasting samples total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured by standard enzymatic methods. Body mass index (BMI) was calculated by weight (kg) divided by height (m) squared.

Data analyses. Hyperinsulinaemia was defined as fasting plasma insulin level >1 standard deviation (SD) higher than the mean of all study subjects. Insulin sensitivity index (ISI) was calculated according to Cederholm *et al.* (Cederholm 1990), expressed as the relation between the glucose uptake rate and the mean plasma insulin concentration at 0 and 120 minutes during GTT. Fasting glucose-insulin ratio was calculated according to Caro *et al.* (Caro 1991), after expressing plasma glucose levels in mg/dl.

Results are presented as mean ± standard deviation. Statistical differences between the groups were tested by Student's t-test. Linear regression analysis was used to show correlations between variables. $P<0.05$ was considered statistically significant.

Results

Fasting plasma glucose concentrations were similar in hypertensives and in controls, but significantly ($p<0.05$) higher fasting insulin level was found in the patient group (Table 1). Also, insulin response during oral GTT was significantly ($p<0.01$) greater in EH patients, despite similar plasma glucose responses in both groups. In addition, hypertensives were characterized by significantly ($p<0.01$) lower fasting glucose-insulin ratio and lower insulin sensitivity index compared to controls. Despite the significant overall differences, a considerable overlap of plasma insulin values was observed between the two groups.

Table 1

Characteristics of glucose metabolism according to responses during oral glucose tolerance test in patients with essential hypertension and in the control group

	Essential hypertension (n=32)	Control (n=26)	p
F-insulin (mU/l)	13.3±7.1	6.7±1.9	<0.0I
Insulin 1h (mU/l)	68.0±33.7	31.3±18.2	<0.0I
Insulin 2h (mU/l)	27.5±11.5	13.3±9.2	<0.0I
F-glucose (mmol/l)	4.9±0.7	4.5±0.6	NS
Glucose 1h (mmol/l)	6.5±1.7	6.2±1.7	NS
Glucose 2h (mmol/l)	4.4±0.9	4.2±0.8	NS
F-glucose/insulin	1.7±0.5	3.6±2.2	<0.01
ISI	51.9±17.8	72.3±14.2	<0.01

F-insulin, plasma insulin level at fast;
F-glucose, plasma glucose level at fast;
F-glucose/insulin, fasting glucose (mg/dl) insulin (mU/l) ratio;
ISI, insulin sensitivity index.
Values are expressed as mean ± SD.
NS, not significant.

Eight patients had abnormally high fasting insulin values (>1 SD than the mean of all subjects), leading to a 25% prevalence of hyperinsulinaemia in the hypertensive group. A similar prevalence was found while using postglucose-load insulin values. Metabolic characteristics of hyper- and normoinsulinaemic hypertensives are presented in Table 2.

Hyper- and normoinsulinaemic patients did not differ significantly in respect of age, BMI, and blood pressure values Plasma gluco-

Table 2

Metabolic characteristics of hyper- and normoinsuli- naemic hypertensive patients

	Hyperinsulinaemic patients	Normoinsulinaemic patients	p
F-insulin (mU/l)	22.6±5.7	10.3±4.3	<0.01
F-glucose (mmol/l)	5.0±1.1	4.8±0.6	NS
Cholesterol (mmol/l)	6.4±1.5	5.9±1.5	NS
Triglycerides(mmol/l)	1.9±1.2	1.6±1.0	NS
LDL (mmol/l)	4.4±1.2	3.9±1.3	NS
HDL (mmol/l)	1.2±0.1	1.2±0.2	NS

Values are expressed as mean ± SD. NS, not significant.

se concentrations were similar in both subgroups of hypertensive patients. Plasma levels of total cholesterol, triglyceride and LDL-cholesterol were higher in the hyperinsulinaemic subgroup, but this difference was not statistically significant.

The comparison of plasma lipid profile between hypertensive patients and controls is shown in Table 3. Total cholesterol, triglyceride and LDL-cholesterol levels were significantly ($p<0.05$) elevated in the patient group. Plasma HDL-cholesterol concentration was lower in EH patients, but this change was not statistically significant.

Table 3

Plasma lipid profile in patients with essential hypertension and in the control group

	Essential hypertension (n=32)	Control (n=26)	p
Cholesterol (mmol/l)	5.99±1.02	4.98±0.8	<0.05
TG (mmol/l)	1.66±0.97	1.08±0.35	<0.05
LDL (mmol/l)	4.06±1.30	3.28±0.97	<0.05
HDL (mmol/l)	1.17±0.20	1.21±0.19	NS

TG, triglycerides;
LDL, low-density lipoprotein cholesterol;
HDL, high density lipoprotein cholesterol.
Values are shown as mean±SD.
NS, not significant.

Discussion

The results demonstrate that young untreated patients with essential hypertension are characterized by multiple metabolic disturbances compared to matched normotensive controls. Plasma insulin levels

were significantly elevated both at fast and after glucose load in hypertensives compared to controls, despite normal fasting glucose levels and normal glucose tolerance in both groups. The lower fasting glucose-insulin ratio detected in the patient group indicates that higher plasma insulin concentrations are needed to maintain normoglycaemia in young hypertensive patients. This finding is clinically meaningful, since hyperinsulinaemia generally precedes and provokes insulin resistance as a result of downregulation of insulin receptors (Rizza 1985). Besides, raised plasma glucose levels are recognized as independent risk factors for CAD and even in the nondiabetic range of glycaemia (Drexel 1994).

There are several ways of assessing insulin sensitivity, the hyperinsulinaemic euglycaemic clamp technique being the "gold" standard (Berger 1994). However, some simple and noninvasive methods, including the calculated insulin sensitivity index (ISI) have shown a high correlation to the insulin sensitivity measured by the clamp technique (Cederholm 1990). In our patients, ISI was significantly lower compared to controls. Evidently, ISI cannot differentiate between various reasons for insulin resistance, but a low peripheral glucose disposal in skeletal muscle is the most probable cause (Lindhal 1993). To define the optimal cutoff point for hyperinsulinaemia with respect to plasma insulin levels, we used a value above the 75th percentile of the mean of all study subjects. Using this approach, eight patients out of 32 were hyperinsulinaemic, leading to the 25% prevalence of hyperinsulinaemia in the hypertensive group. This result is in accordance with other studies (Pollare 1990, Pool 1993), although even higher (up to 50%) prevalence has been reported previously (Zavaroni 1992). Such data have recently been challenged due to inadequately defined criteria of hyperinsulinaemia (Berger 1994). Our results support the view that hyperinsulinaemia, although a characteristic feature of hypertensive patients, is not an invariable finding in essential hypertension.

Hyperinsulinaemia may directly promote atherosclerosis by enhancing LDL-cholesterol accumulation, vascular smooth muscle migration and proliferation, and by augmenting connective tissue synthesis in the vessel wall (Sowers 1993). The adverse impact of insulin resistance on the activity of the fibrinolytic system has likewise been emphasized (Swan 1994). In the hyperinsulinaemic patients the traditional lipid risk factors were all changed in an "atherogenic" direction compared to the normoinsulinaemic patients, except for HDL-cholesterol. However, these differences did not reach the level of statistical significance. This finding is consistent with previous observations that abnormalities in lipid profile tend to cluster together with disturbances in carbohydrate metabolism (Laws 1993, Pool 1993). Positive correlations between plasma insulin and triglycerides and inverse correl tions with HDL-cholesterol have been shown in hypertensive patient

(Laws 1992). In this context, insulin is assumed to enhance the activity of lipoprotein lipase, which stimulates triglyceride synthesis in the liver (Jackson 1990). Besides, high plasma insulin levels may downregulate both HDL-cholesterol binding and LDL-cholesterol efflux from the vasculature (Pool 1993). More recently, it has become apparent that small, dense LDL particles, which are thought to be highly atherogenic (Sowers 1993), are also related to hyperinsulinaemia (Laws 1992). A decrease in HDL-cholesterol and increase in LDL-cholesterol are well-established risk factors for CAD. Although less commonly appreciated, hypertriglyceridaemia, particularly at lower plasma cholesterol levels, was reported to be an independent risk factor according to a metaanalysis of 15 prospective studies (Criqui 1994). Collectively, the pattern of dyslipidaemia observed in the hyperinsulinaemic patients may be considered highly atherogenic.

The "atherogenic" pattern of plasma lipids was characteristic also for the entire group of hypertensive patients, suggesting that hypertension is only one part of a complex risk factor syndrome. While the search for the basis of metabolic risk factor clustering with essential hypertension continues, the patological significance of this relation is evident (Williams 1992).

In conclusion, the detected association between hypertension, hyperinsulinaemia and dyslipidaemia emphasizes that many young hypertensive patients have an important metabolic component to their disease. Therefore, the presence of metabolic risk factors should be seeked for actively, and appropriate nonpharmacological and treatment approaches considered already in the early phases of hypertensive disease. One further aspect to take into account is the metabolic profile of the antihypertensive drug itself (Pool 1993, Williams 1994).

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Kokkuvõte

Antihüpertensiivse raviga pole saavutatud hüpertensiooni peamise tüsistuse — südame isheemiatõve riski oodatud vähenemist, mille üheks põhjuseks võib olla essentsiaalse hüpertoonia (EH) kombineerumine metaboolsete häiretega. Seetõttu uurisime metaboolseid riskifaktoreid noortel (<40 a) tüsistumata EH haigetel ja kontrollgrupil.

Teostatud glükoosi (75 g) tolerantsustesti (GTT) alusel selgus, et plasma insuliini väärtused, samuti veresuhkru-insuliini suhe enne GTT-d olid EH haigetel oluliselt ($p<0.01$) kõrgenenud, vaatamata normaalsele glükoosi tolerantsusele. Haigetel oli insuliintundlikkuse indeks vähenenud. Hüperinsulineemiaga haigetel (25%) olid plasma triglütseriidide, samuti üld- ja LDL-kolesterooli sisaldus oluliselt kõrgenenud võrreldes normoinsulineemiliste haigetega. Düslipideemia oli iseloomulik ka kogu haigete grupile võrreldes kontrollrühmaga.

Antud tulemused näitavad, et noortel kliiniliselt tüsistumata essentsiaalse hüpertooniaga haigetel esinevad väljendunud häired süsivesikute ja lipiidide metabolismis, mida tuleks ka antihüpertensiivses ravis arvestada.

CARDIAC OUTPUT AND FOREARM BLOOD FLOW CHANGES DURING UPRIGHT EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE

Tiit Pokk

Reflex adjustements of the cardiovascular system to the initiation and continuation of muscular exercise include a redistribution of of cardiac output (CO) by limiting blood flow to the skin, kidneys, splanchnic vessels and nonexercising muscles and at the same time delivering more blood to working skeletal muscle.

We have previously reported using impedance cardiography for measurements of stroke volume (SV) and CO as well as forearm stroke volume (FSV) and forearm blood flow (FBF) changes during leg exercise in healthy subjects (1989). We have also described abnormal FBF recordings during exercise test (ET) in patients with various types of heart disease.

The aim of our present study was to evaluate to what extent abnormalities in FBF changes correlate with altered parameters of central hemodynamics during ET in patients with coronary artery disease (CAD).

Methods

19 male patients with CAD (NYHA I–II, age 31–61 years) and 18 healthy men (age 29–60 years performed upright ET on a cycle ergometer. The initial load was set at 0.5 W/kg and the load was increased by 0.5 W/kg increments. Each load lasted for 3 minutes. Cardiac output was measured by impedance cardiography. The technique depends upon the conversion of changes in thoracic impedance during each cardiac cycle into information about blood flow.

Pairs of voltage sensing electrodes are placed at the root of neck and at the level of the xiphisternum. Of the current injecting electrodes one is placed around the forehead and the other 10 cm below the thoracic sensing electrode.

Thus an alternating current of low amplitude and high frequency is introduced and simultaneously sensed. Stroke volume is calculated in ml according to an empirical formula described by Kubicek.

FBF was also measured by rheography and calculated using the same equation. For this purpose two sets of electrodes are placed around the right forearm with a distance of 10 cm between the two inner electrodes.

All the recordings were done before the exercise test, at the end of each 3-minute stage, immediately after exercise, and at 3 minutes of recovery. The ECG was continously monitored during the test and recorded at the same time intervals.

Results

Absolute values of SV and CO were in the CAD patients statistically lower as before ET so at all workloads and at 3 minute recovery time. At the same time the values of FSV and FBF differed significantly from those of healthy men only at workloads 0.5 W/kg and 1.5 W/kg ($p<0.05$).

In the CAD group a strong positive relationship could be demonstrated between rest values of SV and FSV ($p<0.006$) and between CO and FBF ($p<0.05$). In contrast, no such correlation existed in the control group between the same parameters.

Pre-exercise values of FBF as % CO were in CAD patients approximately same and even exceeded those of healthy men being statistically different at maximal workload and at the end of 3 minute recovery time ($p<0.05$).

In CAD patients the reduction of FBF as % of CO occurred mainly in response to the initiation of ET, with little changes on greater workloads and the values returned to pre-exercise levels in 3 minute recovery time ($p<0.05$). In healthy subjects we registered a progressive reduction in FBF as % of CO with increasing intensity of exercise and the values failed to return to rest values in 3 minute recovery time ($p<0.05$).

In CAD group we found a negative correlation between CO and FBF as % of CO (from the first workload onward) and between SV and FBF as % of CO (from the second workload onward) and those correlations were present in 3 minute recovery time. In control group we found analogous correlations only at maximal workloads.

Conclusions

The results of present study confirm assumptions that inadequate redistribution of blood flow away from nonactive regions to activate skeletal muscles in CAD patients may in part be responsible for their decreased work performance.

SEQUENTIAL CHANGES IN CARDIAC INDEX IN 35 MALE-PATIENTS WITH FIRST MYOCARDIAL INFRACTION

T. Ristimae, M. Viigimaa, R. Teesalu

Abstract

In 35 men (mean age 54,9 years) with first myocardial infarction cardiac index was serially assessed on the day 1, 2, 6, 14 and 21 during in-hospital stay by the method of integral rheography. 19 patients submitted the hospital with anterior infarction; a total of 12 patients presented complicated course of disease during hospitalization. For the whole study group, bi-directional curve of cardiac index during convalescence was observed, with significant decline in cardiac performance by the day 14 (3,53±1,00 on the day 1 *vs* 2,72±0,46 l/min/m^2), and subsequent moderate increase at the final measurement on the day 21 (2,80±0,67 l/min/m^2). However, in the whole study-population as well as in either subgroups admission levels of cardiac index were not obtained at discharge-point. In terms of individual differences during hospitalization, dynamic and mostly unpredictable bi-directional changes were found for all patients. Altogether, in the current study, complicated patients, those who received digoxin at discharge, and those who submitted the hospital with anterior myocardial infarction, presented lower values of cardiac index when compared to the remaining subjects.

Introduction

It is now recognized that among a number of factors determining both short-term and long-term survival after acute myocardial infarction (AMI) the most important is the state of left ventricular performance (Beller *et al.*, 1986, Cannon *et al.*, 1976, Thanavaro *et al.*, 1980, Madsen *et al.*, 1984). As a consequence, left ventricular function during in-hospital stay as well as alterations several months or years later have been extensively studied (De Feyter *et al.*, 1982, Gibson *et al.*, 1989, Sanz *et al.*, 1982, Gimple *et al.*,1989, Brown *et al.*,1990).

In earlier years, predominantly measurements of cardiac output/cardiac index have been a widely used time-honoured method of assessing cardiac performance and therapeutic interventions in the patients with AMI (Gammill *et al.*, 1955, Thomas *et al.*, 1965, Broch *et al.*, 1959, Hamosh *et al.*,1971, Ramo *et al.*, 1970, Forrester *et al.*, 1976), whereas in past two decades investigators have highlighted evaluation of left ventricular ejection fraction as a powerful indicator of prognosis (Rigo *et al.*, 1974, Schelbert *et al.*, 1976, Shah *et al.*, 1980, Pilate *et al.*,

1989). Altogether, however, there have been few hemodynamic studies that examined the sequential changes in ventricular performance during in- hospital period (Schillingford *et al.*, 1967, Rigo *et al.*, 1974, Kupper *et al.*, 1977, Nemerovski *et al.*, 1982, Kan *et al.*, 1984, Traina et al., 1993). More detailed analysis of the natural history of ventricular function following AMI might provide valuable information that may not be available from assessment of cardiac pumping ability during the first few days after admission or later on discharge alone. These serial data can be important in understanding clinical presentations and determining reasonable therapy in patients with AMI. Furthermore, regarding cardiac output and cardiac index (CI), the range of values and overlap encountered in uncomplicated patients as well as those in heart failure and cardiogenic shock (Freis *et al.*, 1959, Gunnar et al., 1966, Ramo *et al.*, 1970, Ratshin *et al.*, 1971) restrict the interpretation of a single measurement of these variables. Considering the lack of comprehensive measurements of CI over the entire period of hospitalization, the current study was performed to define the sequential changes in CI that occur during the hospital course in patients with first AMI treated with conventional therapy.

Methods

Patient population. The study group comprised 35 patients admitted to the Coronary Care Unit at Tartu University Hospital with the diagnosis of first AMI. The diagnosis was assigned to the patient if two of the following three criteria were present: 1) compatible clinical history with characteristic pain in the precordium or associated areas; 2) raised serum creatine phosphokinase, glutamic oxaloacetic transaminase (GOT), and lactic dehydrogenase (LDH) activity in samples from at least two different days; 3) development of pathologic Q waves ($\geq$40 msec duration) in at least two ECG leads, or of evidence of non-Q-wave myocardial infarction. The diagnosis of nontransmural AMI was established when serial electrocardiogram revealed ST-depression $\geq$1 mm, or T-wave inversion $\geq$3 mm in $\geq$2 adjacent leads leads (lasting $\geq$7 days). No previous myocardial infarction (MI) according to vital history and preadmission ECG was required. The location of AMI was characterized according to established ECG criteria (Prineas *et al.*, 1982). For purposes of analysis, the location of infarction was categorized into either anterior or inferior groups. Anterior infarction was considered to include anteroseptal and anterolateral leads, and inferior infarction included inferolateral and inferoposterior locations. Patients with intermediate infarct locations (e.g., presence of left bundle branch block) were excluded from analysis. Main characteristics for the patient population are given in Table 1. All patients were categorized as to their clinical status on

admission according to the criteria of Killip and Kimball (Killip & Kimball, 1967).

Table 1

Patients' characteristics

Number of patients	35
Men (n)	35
Age (years: mean and range)	54,9 (29-69)
Previous infarction	None
Q-wave AMI (n)	31
Admission Killip class:	
class I	23
class II	11
class III	0
class IV	1
Anterior AMI (inferior AMI)	19 (16)
Beta-blockers at discharge	11
Digoxin at discharge	11
Complicated course of AMI	12
Mean hospital stay (days)	17+11

AMI=acute myocardial infarction

During the period of our study, the patients received the following cardioactive drugs: nitrates (29–82,3%), aspirin 125 mg per day (33–94,3%), beta-blockers (11–31,4%), calcium channel blockers (9–25,7%), dopamine (3–8,6%), digoxin (11–31,4%), lidocaine (4–11,4%), and diuretics (9–25,7%). Four patients were treated with streptokinase (1,5 millions IU). Any therapy was not standarized and was at the discretion of the attending physician.

Reproducibility of the method of measuring CI was concurrently assessed in 10 patients with AMI who were studied twice on the same day (with a 30 minute interval) by two different observers. The mean absolute difference in CI between the paired observations was 0,29+0,17 with a range of 0,10 to 0,33. Therefore, changes in CI of less than 0,7 were recognized as spontaneous variability, or the limited reproducibility of the method.

Statistical methods

Data are expressed as means ± standard deviation (SD). Analysis among groups was made by Pearson's chi square test, or Fisher's exact test, as appropriate. Correlation coefficients were obtained using standard linear regression equations. Probability (p value) of less than 0,05 was considered significant. In measurements of CI the method of integral rheography was used (Tischenko, 1973, Tischenko *et al.*, 1973).

Results

CI values (l/min/sq m) for both the whole group and subsets of patients during hospitalization on the days 1, 2, 6, 14 and 21 are summarized in Table 2. For the whole study group, bi-directional curve of CI during in- hospital stay was observed. Important decline in cardiac performance evaluated on the day 6 (2,76 + 0,73, $p<0,05$) resulted in peak reduction of CI on the day 14 (2,72 + 0,46, $p<0,05$). Subsequent increase of CI was less pronounced (2,80 + 0,66, NS), failing to attain admission- level (3,53 + 1,00).

Table 2

Serial changes of cardiac index during hospitalization

	Day 1	Day 2	Day 6	Day 14	Day 21
Total population (n=35)	3,53±1,00	3,46±0,73	2,76±0,73	2,72±0,46	2,80±0,67
Anterior AMI (n=19)	3,47±1,00	3,34±0,75	2,53±0,62	2,69±0,33	2,74±0,75
Inferior AMI (n=16)	3,61±1,00 NS	3,59±0,78 NS	3,03±0,78 NS	2,75±0,59 NS	2,95±0,38 NS
Complicated AMI (n=12)	3,59±0,93	3,29±0,70	2,89±0,82	2,68±0,30	2,35±0,53
Uncomplicated AMI (n=23)	3,50±1,06 NS	3,55±0,74 NS	2,69±0,69 NS	2,74±0,53 NS	3,07±0,60 *
Beta-blockers (n=11)	4,18±0,97	3,77±0,79	3,00±0,71	3,01±0,53	3,41±0,17
Digoxin (n=11)	3,19±0,11 *	3,29±0,74 NS	2,64±0,75 NS	2,52±0,40 *	2,36±0,42 *

Relation to AMI location. Mean age of the anterior group was insignificantly lower (52,5 + 8 years), compared with inferior subset (55,5 + 8,5 years). Mean hospital stay was significantly longer in patients with anterior wall damage (22 + 9 *vs* 16 + 7 days). Therefore, CI on the day 21 was assessed in 15 patients with anterior AMI and in 6 patients presented with inferior AMI. There were no significant differences in treatment and in- hospital course of AMI between patients. Figure 2. depicts the serial changes in the mean CI for anterior and inferior AMI subsets over the entire course of the study. In terms of differences between subsets, patients with anterior infarctions as a group had lower mean CI than those with inferior wall damage at all points of the study. However, these differences failed to obtain statistical power. With respect to peak reduction values of CI, occurred on the day 6 in the anterior subset (2,53 + 0,62, $p<0,001$) and on the day 14 in the patients with inferior AMI (2,75 + 0,59, $p<0,002$), there were not significant difference between groups.

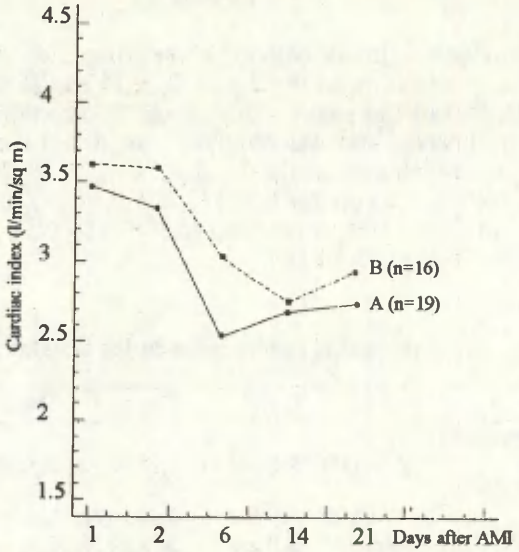

Figure 1. Changes in the mean CI for the patients with anterior (A) and inferior AMI (B).

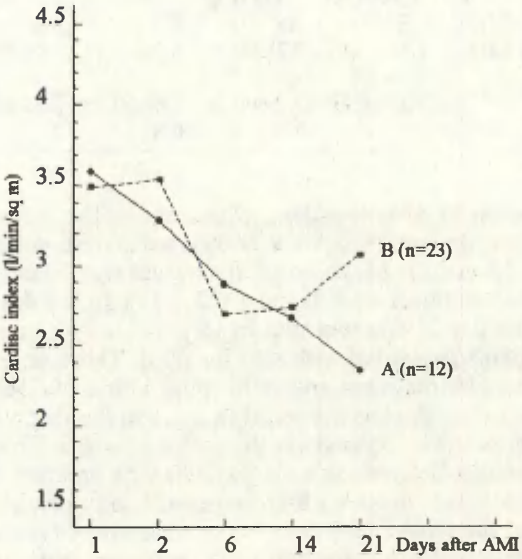

Figure 2. Sequential changes in CI for the patients with complications (A) and the patients presenting uncomplicated course of AMI (B) during hospitalization.

In-hospital course of AMI. A total of 12 patients presented a complicated course of AMI during 10 days after onset of symptoms as follows: infarct extension (2), ventricular tachycardia (2), ventricular fibrillation (2), advanced atrioventricular block (2), paroxysmal atrial fibrillation (1), cardiogenic shock (1), heart failure NYHA III–IV (2). Infarct extension or reinfarction was diagnosed if a new period of ischemic pain accompanied by development of re-elevation of the ST-segment, occurred in conjunction with a new rise in CK activity. Recurrent episodes of chest pain (4) and non-cardiac complications after AMI (acute pneumonia — 4) were not referred as complicated course of AMI in the current study. There were no significant difference in relevant demographic data (mean age, site of AMI) between two groups. Five patients with anterior AMI and seven patients with inferior infarction presented the complicated course of AMI during hospitalization. Only, the time for mean hospital stay was longer in complication-group (20+11 and 16 + 9 days, respectively).

Concerning serial changes of CI, the permanent worsening of cardiac performance in complication-group opposites the bi-directional curve of CI in uncomplicated patients (with the "break-point" on the day 6, Figure 3). However, no admission-values were obtained in either subset. Significantly lower CI in complicated patients was exhibited on the day 21 only, when compared with the remaining study subjects (2,34 + 0,53 *vs* 3,08 + 0,60, $p<0,05$).

Treatment regimen implications. Special attention in the current series was given to CI changes in patients' subsets receiving either beta-blockers (11 patients — 31,4%, group I), or digoxin (11 patients — 31,4%, group II). All patients taking any of these two drugs at discharge and at least 4 consecutive days before leaving the hospital, were included the analysis (Table 2.). Sequential changes of CI in hospital period are depicted for all subsets of patients in accordance to different treatment regimens (Figure 4). The remaining 13 patients (37,1%, group III, Figure 4.) constituted the group receiving neither digoxin nor beta-blocking agents on discharge, and admitting the hospital predominantly with anterior infarction (9 *vs* 4 patients, $p<0,05$). When compared to digoxin-group, the values of CI were observed during entire period in this subset. Nevertheless, no statistical significance was shown for any point of the series. Contrawise, in comparison with patients taking beta- blockers, depressed values of CI were demonstrated throughout the hospitalization in group III. Differences between subsets were found to obtain statistical power on the day 1 (3,28 + 0,70 *vs* 4,18 + 0,97) and on the day 21 (2,85 + 0,82 *vs* 3,40 + 0,17), whereas others were insignificant.

Individual changes of CI. In order to uncover any relationships or trends that might have been masked by analysis of mean data, CI database was additionally analyzed with respect to changes in CI

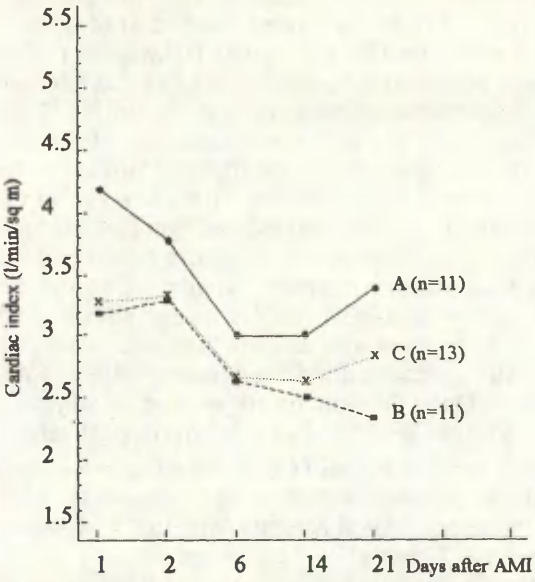

Figure 3. Dynamical changes of the mean CIs for the different treatment regimens: beta-blockers (A), dgoxin (B), the remaining patients (C).

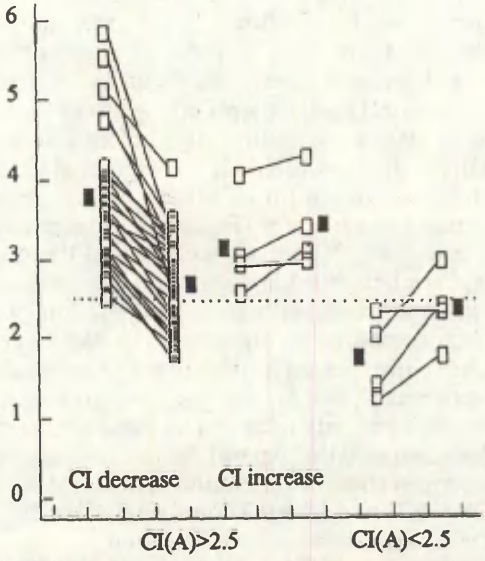

Figure 4. Individual changes on admission and discharge in patients submitted the hospital with normal values of CI (left and medium boxes), and those with abnormally low values of CI on admission (right box).

between admission and discharge levels for each individual patient. In 14 patients (40%) leaving the hospital before the day 21, CI values from the ultimate existing study point were assigned to the discharge-database. On the basis of CI values assessed on admission (day 1), the study population was splitted into two subdivisions: those with a normal CI (>2,5 l/min/sq m) and those with an abnormal CI (<2,5 l/min/sq m). The profile of patients according to hemodynamical changes is given (Figure 5).

Summarizing bidirectional changes of CI between admission and discharge assessments for individual patients, 17 of them demonstrated decrease of CI ($p<0,05$) and 3 had a significant improvement of CI. The remaining 15 patients, presenting predominantly depressed values of CI on discharge (10 patients), exhibited increase/decrease trends what did not attain statistical power. For this reason, those patients might be related as patients with no change between index- and final- points in the current study.

For patients with uncomplicated course of AMI (Figure 5) as well as for those with cardiac complications during hospitalization individual changes throughout the study are shown (Figure 6). CI fluctuations were revealed in both groups at sequential meas- urements. 18 patients (51,4%) demonstrated abnormally low values of CI during study period, and 13 of them showed it on discharge. Unexpectedly, 9 patients without complications presented abnormal variables for cardiac performance, and 6 of them (3 with anterior AMI) left the hospital with remarkably depressed CIs. One patient (with inferior non-Q AMI and acute bilateral pneumonia) in this setting demonstrated abnormally low CI on admission as well as at discharge, whereas in others important depression developed during hospitalization. Thus, among 6 patients discharged the hospital with abnormal levels of CI, in 3 patients (one with anterior AMI and two with inferior AMI, all Q-wave infarction) recurrent chest pain was registered on the day 2–5, without concomitant increase of serum levels of specific enzymes. Also, one patient in this subset had pneumonia dextra with pleuritis.

In complication-group, 9 patients from 12 (75%) showed abnormal levels of CI during in-hospial stay. 7 of them left the hospital with abnormally low CIs.

However, 3 patients in this group revealed no abnormal CIs at any measurement. All of them admitted the hospital with transmural inferior AMI; one patient suffered ventricular fibrillation on the day 2, in one advanced atrioventricular block developed, and one presented heart failure NYHA III at measurements on the day 6.

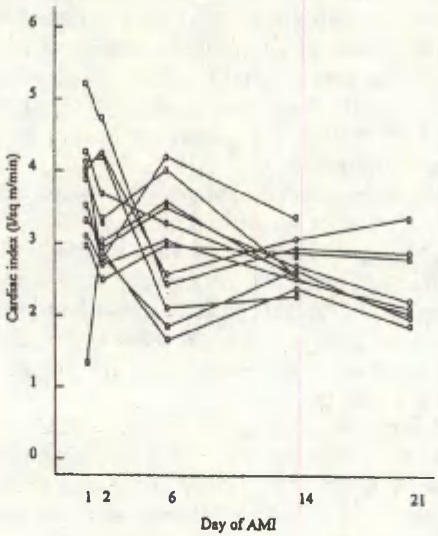

Figure 5. Sequential individual changes of CI for patients presenting complicated course of AMI.

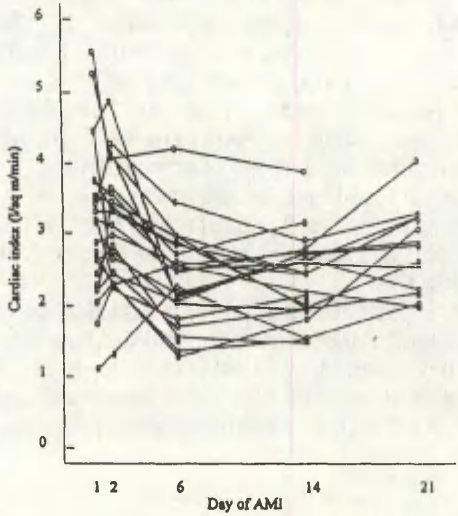

Figure 6. Serial changes of CI in uncomplicated patients.

Discussion

The current study was performed to evaluate sequential changes of CI during hospitalization in male-patients with first AMI.

First of all, a wide degree of variability in ventricular performance at the time of hospitalization was demonstrated with CI range from 1,30–5,15 l/min/m. This finding is in accordance with previous data (Forrester, 1976, Freis, 1952, Gilbert, 1954, Hamosh & Cohn, 1971, Thomas, 1965).

Most patients in our study (31–88,6%) presented normal CIs (i.e. $\geq$2,5 l/min/sq m) on admission. Surprisingly, no signifficant differences on admission were revealed between subset presented complications and those with more benign course of AMI. In previous studies, the level of cardiac performance at the time of hospitalization was shown to bear a direct relation to in-hospital mortality (Forrester, 1976), and patients with severely depressed cardiac pump performance have shown to demonstrate more malign course of AMI (Freis, 1952, Gilbert, 1954, Brock, 1959).

However, besides an overall variability of CI, a range within clinical subsets and overlap of hemodynamic profiles between patients with different clinical manifestations were exhibited also (Ramo, 1970, Forrester, 1976, Ratshin, 1972). Despite differences in mean baseline values for CIs in nonsurvivors and those who survived hospitalization measurements in two groups overlapped enough to preclude considerations of CI as a prognostic indicator (Ratshin, 1972). Also, significant differences in mean values of CI in complicated patients with circulatory failure were revealed in studies. Thus, in 9 patients with AMI and shock studied by Cohn and co-workers (Cohn, 1967), the average CI was 3,2 l/min/m, while in other study (Weil, 1968) mean CI of 1,3 l/min/m was found in patients complicated with cardiogenic shock after AMI.

In our study, among four patients presenting abnormally low CIs on admission (<2,5 l/min/m), one patient was hospitalized in cardiogenic shock, and three remaining patients belonged to Killip class II. In the subset of initially normal CI, the majority of patients demonstrated no clinical deterioration (Killip class I — 23) and 8 patients admitted in Killip class II by initial evaluation.

The most interesting finding in our study was bi-directional curve of CI during convalescence, with its highest value on the day 1 and peak reduction on the day 14.

Up to now, limited data concerning serial assessment of CI after AMI (Schillingford, 1967, Broder & Cohn, 1972) have shown some augmentation of ventricular performance during in-hospital stay. Over the first several weeks following AMI, CI has been demonstrated to increase, particulary in patients who had only mild hemodynamic

impairment during the acute phase of infarction (Thomas, 1965, Kupper, 1977, Rahimtoola, 1972, Broder, 1972). However, in the first study (Thomas, 1965) the number of subjects seems to be too small to draw any substantial conclusions. Also, in other investigation (Rahimtoola, 1972) it was indicated that clinical improvement after AMI is not usually associated with the normalization of the impaired left ventricular curve relating left ventricular filling pressure to stroke volume, allowing the authors to interprete gained data as the sign for unchanged ventricular function during covered period or consider them not to be a reliable index of ventricular performance in this setting.

Altogether, in the current study, complicated patients, those who received digoxin at discharge, and those who submitted the hospital with anterior AMI, presented lower values of CI when compared to the remaining subjects.

Small increases in CI and stroke volume, as well as reduction in left ventricular end-diastolic pressure (LVEDP), have been observed after digitalization in patients with left ventricular failure following AMI (Ratshin, 1972), the finding that seems at first sight to be somewhat conflicting with our results. However, the preliminary observations have also suggested receipt of digoxin at the time of hospital discharge to be the number one multivariate predictor of 1 year mortality (Bigger, 1985). Previous experience suggests that myocardial infarction is less well tolerated in older patients because of preexisting heart failure, a decline in myocardial reserve, a higher incidence of multivariate disease, age-related hypertrophy of the left ventricle, reduced ventricular compliance and other causes (Robinson, 1988, Wilcox, 1980). In the current study, patients receiving digoxin at discharge were elder ($57 + 5{,}0$ *vs* $51 + 9{,}4$, $p<0{,}05$) and tended to have more complicated course of AMI when compared with the beta-subset (5 *vs* 2, respectively). So, we postulate that in our study patients receiving digoxin at discharge comprised the group with more advanced hemodynamic deterioration and obviously in higher postinfarction risk.

Patients receiving nonselective beta-adrenergic blockers without intrinsic sympathomometic activity (propranolol, metoprolol) demonstrated higher mean values of CI throughout the study. In the current study, patients receiving beta-blockers comprised the AMI-subset with apparent hyperkinetic status of ventricular function, tended to be younger and less complicated when compared to other population. Our finding indirectly supports previous data revealing secondary cardioprotective properties of beta-adrenoblocking drugs in patients with AMI (ISIS-1 Collaborative Group, 1986). Also, life-saving benefit has also been shown to be particulary noticable in postinfarction patients with coexisting heart failure (Chadda, 1986).The latter could be of importance in some our patients as well. Also, the positive effect

of beta-blockers on myocardial metabolism (Chierchia, 1993) might explain the overall hemodynamic recovery in AMI-patients receiving this mode of therapy. However, concerning the differences between patients receiving beta- blockers or digoxin, it must be pointed out that dynamic and apparently unpredicatable changes in left ventricular function during hospitalization could hinder the validity of valuating the effects of therapeutic interventions by comparing posttherapy values of CI to mean data on previous study points.

Hemodynamic differences in anterior and inferior wall AMI subgroups were in consistence with previous experience confirming the importance of the site of ischemic damage. In the current study, the greater functional impairment with anterior wall infarction was followed during whole hospitalization, with significantly lower discharge value for CI on the day 21.

Surprisingly, no initial mean value of CI for enrolled population was attained in our study by discharge point (Table 2). Transient sympathetic stimulation could possibly explain this finding, resulting in an improved performance during the earliest measurements on the day 1 (and on the day 2), predominantly through improved function in noninfarcted zones. Acute compensatory mechanisms including the Frank-Starling mechanism and increased levels of plasma catecholamines account for this hyperkinesis (McAlpine, 1981, Rigo, 1974). An increased motion of the noninfarcted region has shown to subside within 2 weeks after AMI (Serruys, 1986). So, in our study , the significant fall for CIs was demonstrated by the day 14. Over time, as sympathetic stimulation decreases, left ventricular function also may decrease, resulting in apparent deterioration in performance.

Also, there appears to be a limit to the adaptive nature of increasing ventricular volume as evidenced by studies that have shown that survival is inversely correlated with ventricular volumes after myocardial infarction (Norris, 1984, White, 1987). Dependance on Starling mechanism has been shown to be even more evident in patients with signs of manifest left left ventricular dysfunction (Rigo, 1974). While the increase in left ventricular end-diastolic volume maintains CI in these patients, it also increases left ventricular wall tension, myocardial oxygen demand (Rigo, 1974) and therefore possibly infarct size and number of complications. Thus, the compensatory mechanisms that promote ventricular dilatation (McKay, 1986) and initially preserved stroke volume (and decreased left ventricular filling pressure) may later contribute to deterioration of ventricular function. So, in our study, unexpectedly for the authors at first sight, higher initial values of CI were demonstrated in patients who later presented more manign course of AMI with pronounced fall in cardiac performance.

In the current study, analysis of individual changes revealed significant decrease of CI in 17 patients, whereas the remaining 18 patients

demonstrated no change (15 patients) or increse (3 patients) in CIs. However, all enrolled patients survived the disease and left hospital with clinical improvement. Symptomatic improvement in patients with AMI that can occur without much change or augmentation in the cardiac output, or even despite a fall in CI has been demonstrated formerly (Thomas, 1965); thus there may be factors quite apart from the circulatory disturbance that contribute to the patient's clinical condition. Also, in evaluation CIs and clinical outcome, it it has to be pointed out that all subjects in our study had their first AMI, and presumably well-preserved left ventricular function and less mechanical dysfunction than patients with previous myocardial infarction (Moss, 1990).

During in-hospital stay, bidirectional fluctuations for all patients were found in our study, whereas the changes in values of CI were more pronounced between the days 2 and 6, i.e. by the end of the first postinfarction week. Formerly it has been demonstrated that in 56% of patients with AMI spontaneous changes in left ventricular ejection fraction took place during the 24 hours after onset of disease (Wackers, 1982). Therefore, changes in CIs that could not be related to complications as well-recognized directly deteriorating factor of ventricular performance might be regarded as spontaneous variability (for example, as a result of changes in loading conditions, in neurohhormonal activity, or due to the recovery of ischemic myocardium).

However, using CI for assessing the pumping ability of the heart, one always has to keep in mind that the wide range of CI (between 2,5 and 4,2 l/min/sq m) makes this variable relatively insensitive in the evaluation of cardiac function (Braunwald, 1992). CI is considered to be quite incomplite and an occasion misleading due to variations in left ventricular compliance (Rigo *et al.* 1974). In previous studies, CI has been found to correlated poorly with the ejection fraction, and was often normal in the presence of the reduced ejection fraction (Schelbert, 1976).

Also, CI is critically dependent on preload and afterload in addition to myocardial contractility (Braunwald, 1974). Changes in left ventricular preload and afterload would have gone undetected in the present study because left ventricular volumes were not assessed. No measurements of ventricular filling pressure were made in the current study.

Because of the limited number of basic hemodynamic variables in our study, direct comparisons of patients based on CI values only might be avoided. As it is shown formerly, caution must be taken in interpretation of changes of CI alone as approach for cardiac function (Rigo et al., 1974, Forrester et al., 1976, Rahimtoola *et al.*, 1972, Rackley & Russell, 1972,).

Conclusions

As hemodynamics varies widely among patients with AMI with similar clinical presentations, measurements of pertinent hemodynamic variables may be of great value in this setting suffering circulatory disturbances of different extent. Method of integral rheography is free of discomfort, and most important, it is suitable for repeated application at intervals in the same patient. As it was demonstrated in the current study, although the most pronounced differences of CI between AMI-subsets were measured on the discharge point, individual changes during the hospitalization carry useful information about current hemodynamic status and might effectively used as guidlines for interventional therapy.

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Kokkuvõte

Käesolevas uurimuses vaadeldi südameindeksi (l/min/m^2) dünaamikat haiglaperioodil 35-l meeshaigel esmase müokardi infarktiga. Mõõtmistel 1., 2., 6., 14. ja 21. infarktijärgsel päeval kasutati integraalse reograafia meetodit Tischenko järgi. Haigete keskmine vanus oli 54,9 aastat, eesseina infarktiga hospitaliseeriti 19 patsienti; 12-l haigel ilmnesid haiglaperioodil kardiaalsed komplikatsioonid. Tulemuste töötlemisel eristati täiendavalt 3 ravimrühma: patsiendid, kes tarvitasid haiglast lahkumisel digoksiini (11) või beeta-adrenoblokaatorit (11), ning ülejäänud haiged, kes ei tarvitanud hospitaliseerimise lõpul kumbagi nimetatud ravimit (12).

Uuritud gruppi iseloomustas 2-suunaline südameindeksi kõver: vähenemisele 1.–14. päevani (3,53±1,00 kuni 2,72±0.46 l/min/m^2) järgnes tõus 21. infarktijärgsel päeval (2,80±0,67 l/min/m^2,). Üllatuslikult ei saavutatud hospitaliseerimise lõpuks (21. päev) üheski vaadeldud alagrupis südameindeksi lähteväärtusi (1. päev). Vaadeldud populatsioonis mõõdeti madalamaid südameindeksi väärtusi eakamatel haigetel, neil, kes haiglast lahkumisel tarvitasid digoksiini (*vs* beeta-blokaatorit) ning eesseina infarktiga alarühmas. Siiski täheldati südameindeksi ulatuslikku individuaalset ja rühmasisest varieeruvust, mis polnud üheselt seostatav kardiaalset jõudlust deprimeerivate lisafaktoritega ning mis eriti ilmekalt esines esimestel mõõtmispäevadel. Summeerides individuaalseid muutusi haiglaperioodi 1. ja 21. päeva vahel leiti, et 17-l haigel esines märkimisväärne südameindeksi langus, 3-l patsiendil oluline paranemine ning 15-l haigel esinenud muutused kvalifitseeriti ebaolulistena.

Käesoleva uuringu põhjal võib infarktihaigetel kui ilmeka individuaalse variaabelsusega ebastabiilse hemodünaamikaga populatsioonis otstarbekaks pidada tsirkulatsioonihäirete ja ravi efektiivsuse hindamiseks südameindeksi korduvat registreerimist.

EFFECT OE RECOMBINANT HIRUDIN AND HEPARIN ON PLATELET AGGREGATION IN CORONARY ARTERY DISEASE PATIENTS

Yelena Saareoja, Tiiu Jõudu, Margus Viigimaa

Abstract

Hirudin is the most potent and specific known inhibitor of thrombin. The present study was aimed to compare the effect of recombinant hirudin and heparin on platelet aggregation in coronary artery disease (CAD) patients. Platelet aggregation measurements were made in 16 patients (mean age 56.8 years) with chronic CAD. Control group consisted of 14 healthy volunteers (HV; mean age 34.2 years). Platelet aggregation was determined according to method of Born and by a new method based on the statistical analysis of platelet rich plasma light transmission fluctuations. Results of our study showed that spontaneous platelet aggregation, measured by both methods was significantly higher in heparinized than in r-hirudinized blood both in CAD patients and HV groups. ADP-induced platelet aggregation, measured by method of Born was more pronounced in heparinized blood than in r-hirudinized in both groups studied. The differences between aggregation in r-hirudinized and heparinized blood were more pronounced when adrenaline was used to induce aggregation. In conclusion, no activation of platelets by r-hirudin was observed in CAD patients when compared to heparin. This finding supports the opinion that r-hirudin has clinically important advantages compared to heparin in the treatment of CAD patients.

Introduction

The formation of a thrombus in a stenosed coronary artery has a causative role in the pathogenesis of acute form of CAD. Many thrombolytic and anticoagulant drugs have been used in clinical practice, but to date, without complete or consistent benefit (Topol, 1989). Developments in contemporary scientific methods have contributed significantly to provide some such drugs.

The first description of the anticoagulant action of a water-soluble, heat-resistant substance derived from the salivary glands of leeches (Hirudo medicinales) dates back to 1884. This substance was called hirudin in 1904, but scientific research regarding this compound was studied in 1960's. More recently, after production of hirudin or fractions by recombinant techniques and by synthetic methods, there has been a fast growing interest in the clinical use of this most potent and

specific inhibitor of thrombin (Buller, 1993). Direct thrombin inhibitors have several potential advantages compared to heparin: they can inhibit thrombin bound to clots or extracellular matrices, which are relatively resistant to heparin.Also, their effect does not depend on antithrombin III as a cofactor, which may lead to a more predictable dose response. Furthemore, they are not inhibited by activated platelets, which release platelet factor 4 and other molecules that neutralize heparin (Johnson, 1994). Moreover, heparin may increase platelet aggregation and thrombocytopenia has been reported in some patients.

The aim of the present study was to compare the effect of recombinant hirudin and heparin on platelet aggregation in CAD patients.

Material and Methods

Platelet aggregation measurements were made in 16 patients (mean age 56.8 years) with chronic CAD. All patients did not use neither r-hirudin nor heparin. Control group consisted of 14 HV (mean age 34.2 years). Blood was taken from the antecubital vein into 2 plastic test-tubes with either r-hirudin (Behring) or heparin (Rotexmedica GMBH) as an anticoagulant, and mixed immediately. Blood was centrifuged 10 min for at 160 g, room temperature. The upper layer of platelet-rich plasma (PRP) was separated. The remaining blood specimens were centrifuged for 20 min at 1400 g, room temperature to prepare platelet-poor plasma (PPP). Platelet aggregation was determined according to method of Born and by a new method based on the statistical analysis of PRP light transmission fluctuations (LTF) on 2-channel aggregometer (Biola, Russia) by continuously stirring the plasma (1000 rpm) at 37°. Using this new method relative dispersion of such fluctuations is proportional to the mean aggregate size, and it is applicable if aggregates are small and the aggregation can not be detected by turbidometric method (Gabbazov, 1989). Platelet aggregation was induced by 1.0 μM ADP (Reanal) solution and 0.5 μM adrenaline (Sigma) solution. All studies were carried out within 90–180 min after blood obtainment.

Data are presented as mean ± SD. Statistical analysis was performed using STATISTICA for Windows program. A P value <0.05 was considered significant.

Results and Discussion

Results of our study showed that spontaneous platelet aggregation, measured by Born or LTF methods was significantly higher in heparinized than in r-hirudinized blood both in CAD patients and HV

groups (Table 1). But no significant differences in platelet aggregation were detected between CAD patients and HV group either in r-hirudinized or heparinized blood.

Table 1

Spontaneous platelet aggregation in r-hirudinized and heparinized plasma in CAD patients and HV group

		CAD	HV
Platelet aggregation (light transmission), %	Hirudin	1.5±0.9***	2.0±1.1***
	Heparin	4.6±2.0	7.1±7.2
Platelet aggregation (aggregate size), relative unit	Hirudin	1.3±0.9*	1.1±0.1***
	Heparin	1.7±0.4	1.9±1.0

*p<0.05 when compared corresponding results hirudin versus heparin
***p<0.001 when compared corresponding results hirudin versus heparin

ADP-induced platelet aggregation, measured turbidometrically was more pronounced in heparinized blood than in r-hirudinized in both groups studied. Data are presented in Table 2. However, these results are not consistent with results obtained by LTF method. Thus, in both CAD patients and HV group ADP-induced platelet aggregation in heparinized blood is more pronounced, but the average radius of aggregates is significantly lower than in r-hirudinized blood. CAD patients and HV group did not differ significantly in respect of platelet aggregation in r-hirudinized blood. ADP-induced platelet aggregation in heparinized blood was more pronounced in HV group when compared with CAD patients.

Table 2

1.0 μM ADP- induced platelet aggregation in r-hirudinized and heparinized plasma in CAD patients and HV

		CAD	HV
Platelet aggregation (light transmission), %	Hirudin	19.61±11.44***	19.9±16.15***
	Heparin	33.77±15.15	56.25±25.33
Platelet aggregation (aggregate size), relative unit	Hirudin	12.80±4.38***	13.90±5.93***
	Heparin	4.58±1.57	5.40±1.26

***p<0.001 when compared corresponding results hirudin versus heparin

Extent of aggregation induced by adrenaline was significantly lower compared to ADP (Table 3). The differences between aggregation in r-hirudinized and heparinized blood were more pronounced when adrenaline was used to induce aggregation. Also, no significant differences in platelet aggregation were found between CAD patients and HV group in r-hirudinized blood, but in heparinized blood adrenaline-induced aggregation was significantly higher in HV group when com-

Table 3

0.5 μM adrenaline-induced platelet aggregation in r-hirudinized and heparinized plasma in CAD patients and HV

		CAD	HV
Platelet aggregation	Hirudin	4.1±3.4***	2.2±1.6***
(light transmission), %	Heparin	18.2±11.2	35.3±28.5
Platelet aggregation	Hirudin	2.4±1.0*	2.1±0.8***
(aggregate size), relative unit	Heparin	2.9±0.7	3.9±1.4

*$p<0.05$ when compared corresponding results hirudin versus heparin
***$p<0.001$ when compared corresponding results hirudin versus heparin

pared to CAD patients. This finding demonstrates that heparin increases platelet aggregation in HV group more than in CAD patients.

Our data concerning platelet aggregation in r-hirudinized and heparinized plasma are similar with some previous reports. The result of spontaneous platelet aggregation and aggregation induced by adrenaline are in good agreement with results of Glusa (Glusa, 1990; 1991). However, in both of these studies ADP-induced platelet aggregation was reported to be similar in differently coagulated plasma samples. Basic-Micic and co-workers showed that spontaneous platelet aggregation was rarely observed in hirudinized PRP compared to citrate PRP. In addition, hirudin reduced the maximal response to adrenaline, but had no influence on the maximal response to ADP (Basic-Micic, 1991). Also Chen et al (1991) showed that hirudin did not stimulate platelet aggregation in contrast to heparin and low molecular weight heparin.

Conclusion

No activation of platelets by r-hirudin was observed in CAD patients when compared to heparin. This finding supports the opinion that r-hirudin has clinically important advantages compared to heparin in the treatment of CAD patients.

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Kokkuvõte

Hirudiin on spetsiifiline ja tugevaim teadaolev trombiini inhibiitor. Käesoleva töö eesmärgiks oli võrrelda rekombinantse hirudiini (r-hirudiini) ja hepariini toimet kroonilise südameisheemiatõve (KSIT) haigete trombotsüütide agregatsioonile. Uuriti 16 KSIT haiget (keskmine vanus 56,8 a.). Kontrollgrupis oli 14 tervet vabatahtlikku (TV) keskmise vanusega 34,2 a. Trombotsüütide aggregatsioon määrati Borni meetodil ja uuel meetodil, mis põhineb plasma valgusläbilaskvuse fluktuatsiooni analüüsil. Uurimistulemused näitasid, et trombotsüütide spontaanne agregatsioon oli hepariniseeritud veres kõrgem kui r-hirudiniseeritud veres nii KSIT haigetel kui ka kontrollgrupis. ADP-ga indutseeritud trombotsüütide agregatsioon (määratud Borni meetodil) oli hepariniseeritud veres enam väljendunud kui r-hirudiniseeritud veres mõlemas grupis. Suuremad erinevused trombotsüütide agregatsioonis r-hirudiniseeritud ja hepariniseeritud veres olid siis kui agregatsioon kutsuti esile adrenaliiniga. KSIT haigetel ei täheldatud trombotsüütide aktivatsiooni r-hirudiini toimel. Need tulemused näitavad, et hepariiniga võrreldes omab r-hirudiin eelist KSIT haigete ravis.

THE DYNAMICS OF STROKE VOLUME DURING EXERCISE: HOW TO INTERPRET?

Kai Saks, Elmut Laane, Ruth Kullus, Tiit Pokk

Abstract

100 healthy persons (40 women and 60 men) and 136 cardiac patients were examined to determine the dynamics of the stroke volume index (SVI) during an upright bicycle ergometer stress test. SVI was measured by means of impedance cardiography before exercise and after each minute of load (the initial workload of 0.5 W/kg was increased by the same amount after each minute). SVI did increase in all the healthy persons during the exercise but did not increase in 17 (12.5%) cardiac patients. The maximal SVI was 167%±45% (mean±SD) in healthy individuals when compared to rest value and it was achieved at the load of 1.7±0.7 W/kg. Criteria for assessing normal dynamics of SVI for young and middle-aged men and women were determined. Lack of increase of SVI during upright stress test might be considered as failure of myocardial reserve.

Introduction

It is generally recognized that during upright physical exercise the stroke volume (SV) increases in healthy individuals. Different studies report various mean SV increases during load, from 12 to 100 *per cent* (Wyns W. *et al.*, Higginbotham M. B. *et al.*, Scruggs K. D. *et al.*). There are many factors that might account for these differences: age and sex of subjects, level of physical training, different exercise schemes and positions during exercise, differences in variance analysis (Blomqvist C. G. *et al.*, Hindman M. C. *et al.*, Ehsani A. A. *et al.*, Mizutani Y. *et al.*, Grandi A. M. *et al*, Ray C. A. *et al.*). A prospective study was undertaken to examine the dynamics of SV during the upright bicycle ergometer stress test in healthy men and women of different ages and in various groups of cardiac patients.

Methods

Subjects. Healthy population. A hundred healthy individuals (60 men and 40 women, 17...64 years, mean age 42±9 years, mean±SD) volunteered to participate in the study; none had a history of heart disease, hypertension or diabetes mellitus, no cardiac abnormalities were found on physical examination or stress electrocardiogram. They all were physically moderately active (1...3 hours a week) but

none was an active athlete. The line between young and middle-aged persons was drawn at 40 years of age.

Patients population. Twenty-five male patients had angiographically documented significant coronary artery disease (CAD) and were on medical treatment (mean age 49±7 years, NYHA functional class 2.3±1.5); fifty male patients with CAD had had a coronary artery bypass operation 52±26 months before our investigation (mean age 54±7 years, NYHA functional class 1.4±0.7); twenty male patients with evidences of myocardial ischemia had no significant stenoses in coronary arteries and were considered having syndrome X (mean age 47±8 years, NYHA functional class 1.3±0.4); fourty one female patients (mean age 39±9 years) had light or moderate myocarditis.

Exercise protocol. Exercise on the bicycle ergometer (Monark ergometer) was performed in the upright position at the constant pedalling rate of 60 rpm. After baseline measurements at rest were obtained in subjects sitting on the bicycle, exercise at the workload of 0.5 W/kg was begun, each minute the workload was increased by the same amount. After each minute of load the exercise was stopped for 10...15 seconds to have a good quality impedance cardiogram. The exercise was continued until it had to be stopped because of fatigue, shortness of breath or anginal pain (at least 5 points on Borg's scale) or by changes in electrocardiogram.

Electrical impedance data were obtained by means of an impedance cardiograph (RPG 2-02, Russia) with four disposable strip electrodes as described by Kubicek *et al.* The outer electrodes provided an electrical field from a constant current oscillator generating a constant sinusoidal current of 2 mA r.m.s. with a frequency of 40 KHz. The first derivative of the impedance change wave form was recorded on an 8 channel inkjet recorder (Nihon Kohden) simultaneously with ECG and phonocardiogram at the paper speed of 50 mm per second. SV was calculated after the equation of Kubicek et al. An impedance cardiogram was recorded by normal breathing during 10...15 seconds after every step of the load, waveforms were manually determined.

Data analysis. The SV standardized index i.e. the stroke volume index (SVI) was used to analyse absolute SV changes during the stress test. A relative SVI change (SVI%) during the exercise was expressed in *per cent* of the rest value (rest value±100%). The maximal value of SVI (SVI_{max}) and SVI% ($SVI\%_{max}$) during the exercise were recorded for each individual, as well as the step of the work load at which SVI_{max} was registered ($SVI_{max}L$); thus the mean maximal values for each index were calculated from the individual maximal values. The individual peak SVI was marked as SVI_{end}, a relative SVI change at the peak exercise as $SVI\%_{end}$. A SVI change was considered significant if it differed from the previous one by at least 5 *per cent*.

The variables between the groups of subjects at rest and during exercise were compared with unpaired t-tests, the difference was considered significant at a p value of <0.05

Results

Healthy population. Load tolerance. The mean load tolerance of all healthy subjects was 2.9±0.5 W/kg (1.5...4.0 W/kg),peak heart rate 161±16 bpm (111...189 bpm). Load tolerance was higher and peak heart rate (HR) slower in men compared to women. Load tolerance was not influenced by age, while peak HR was higher in young subjects (Table 1).

Dynamics of the absolute values of the stroke volume index.

The resting SVI of young female subjects was higher than that of other healthy persons (however the difference between young men and young women was not significant). SVI increased during exercise in all the healthy subjects. The maximal SVI during bicycle stress test did not differ in young men, young women and middle-aged women,but in middle-aged men it was significantly lower (Table 1). At peak exercise SVI was lower than the maximal SVI values in all the groups. The SVI_{end} of the middle-aged male subjects was significantly lower than in the other groups.

Relative dynamics of the stroke volume index.

The mean maximal SVI as compared to its rest value was 167±45% (106...355%). The $SVI\%_{max}$ did not differ in young women, middle-aged women and middle-aged men (156...168%) but in young men $SVI\%_{max}$ was higher (191%). The mean decrease of SVI% from its maximal to the peak load value ranged from 15 to 30% but the differences were statistically not significant. The mean $SVI\%_{end}$ of all healthy persons was 142±46% (77...310%).

Exercise rate at the maximal SVI

The maximal SVI was measured at the load of 1.7±0.7 W/kg in the whole group of healthy subjects. The load of the maximal SVI was bigger in men than in women but the age did not have any influence on SVI_{maxL} (Table 1, Figure).

We could not find any significant correlation between the work tolerance and the relative SVI increase or the load at which the maximal SVI was achieved.

Patients population. The stroke volume index did not increase during exercise in 6 medical CAD patients, 2 surgical CAD patients, 4 patients with syndrome X and 5 patients with myocarditis. That means that in 17 (12.5%) of 136 cardiac patients SVI failed to increase during upright physical exercise. In all the patient groups the mean SVI increase was smaller than in the age- and sex-matched healthy persons (Table 2) although the difference was statistically not

Table 1

Hemodynamic variables of healthy persons depending on age and sex ($\bar{X}\pm SD$)

	Women<40 (n=17) 1	Women>40 (n=23) 2	Men<40 (n=13) 3	Men>40 (n=47) 4	P_{1-2}	P_{1-3}	P_{2-4}	P_{3-4}
Age (yrs)	31±7	45±4	31±5	47±6	.001	N.S.	N.S.	.001
HR_{max} (bpm)	172±10	162±12	166±12	155±17	.01	N.S.	N.S.	.05
Peak load (W/kg)	2.7±0.5	2.5±0.4	3.0±0.3	3.2±0.4	N.S.	.05	.001	.05
SVI (ml/m^2)	60±22	47±16	47±15	41±12	.05	N.S.	N.S.	N.S.
SVI_{max} (ml/m^2)	90±28	77±17	86±22	63±17	N.S.	N.S.	.01	.001
$SVI\%_{max}$ (%)	157±34	168±59	191±45	162±46	N.S.	.05	N.S.	.05
SVI_{maxL} (W/kg)	1.2±0.7	1.5±0.6	1.9±0.6	1.9±0.8	N.S.	.01	.05	N.S.
SVI_{end} (ml/m^2)	76±22	66±16	72±18	52±14	N.S.	N.S.	.05	.001
$SVI\%_{end}$ (%)	135±40	153±50	161±47	134±44	N.S.	N.S.	N.S.	N.S.

HR_{max} — heart rate at peak load; SVI — stroke volume index (rest value);
SVI_{max} — maximal value of SVI during exercise;
$SVI\%_{max}$ — percentage of SVI_{max} from SVI;
SVI_{maxL} — load step when SVI_{max} was registered;
SVI_{end} — SVI at the peak load;
$SVI\%_{end}$ — percentage of SVI_{end} from SVI

Table 2

Dynamics of stroke volume index in cardiac patients

	Medical CAD (n=25)	Surgical CAD (n=50)	Syndrome X (n=20)	Myocarditis (n=42)
SVI_{max} (ml/m^2)	43±12***	55±15*	39±11***	57±25*
$SVI\%_{max}$ (%)	133±40*	148±29	131±19***	147±45
SVI_{maxL} (W/kg)	0.82±0.75***	1.38±0.64***	0.92±0.63***	0.85±0.54*

* — P<0.05; ** — P<0.01; *** — P<0.001

The three first groups are compared with the results for middle-aged healthy men; patients with myocarditis to middle-aged healthy women (Table 1).

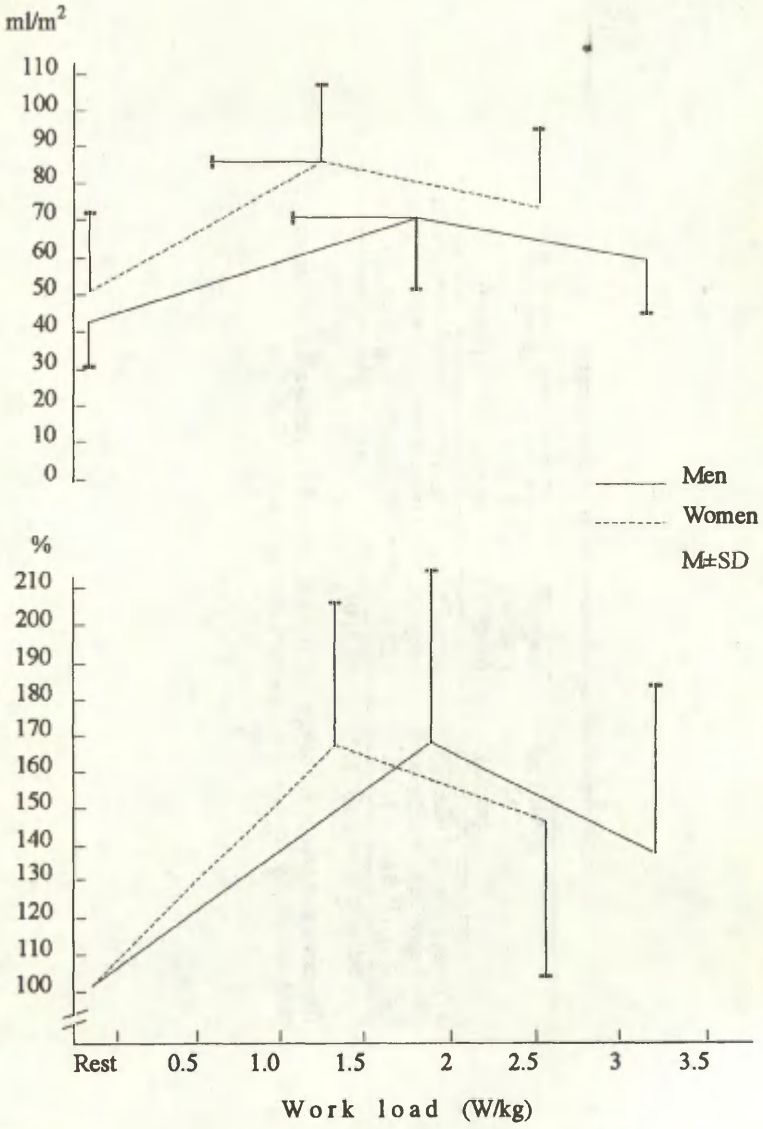

Figure. Dynamics of stroke volume index and its relative values during exercise in healthy men and women.

significant for the surgical CAD patients and patients with myocarditis. The maximal SVI was achieved at lower loads in cardiac patients compared to healthy individuals. There were no correlations between the work tolerance and the relative SVI increase or the work load at which SVI_{max} was registered in the cardiac patients. No correlations could be established between the NYHA functional class and the dynamics of SVI.

Discussion

We used impedance cardiography to estimate the dynamics of the stroke volume index during exercise. The question is: how reliable is this method? Our aim was not a comparative study of the results of impedance cardiography and those of invasive measurements as there are many reports confirming a good correlation between the SV values of impedance cardiography and those of invasive methods (Aust P. E. et al., Eisenberg B. M. *et al.*, Spinale F. G. *et al.* White S. W. *et al.*) Therefore, the absolute SVI values in our study should be treated with some caution. For instance the SVI was higher in women compared to men in our investigation. These results are opposite to the generally approved ones (Geigi...) but in accordance with the results of another study where impedance cardiography was used (Gundarov I. A. *et al.*). Different conduction qualities of the skin in men and women might be responsible for the finding. However, the correlations have been good for both sexes in impedance cardiography SV measurements compared to invasive methods at rest and during exercise (Fujinami R. M. *et al.*) and therefore relative SV changes were not dependant on a systematic error of the method.

Our results confirm that in healthy young and middle-aged males and females SVI increases during upright bicycle exercise. These data agree well with the results of other investigations (Wyns W. *et al.*, Higginbotham M. B. et al., Scruggs K. D. *et al.*, Hindman M. C. *et al.*, Fujinami T. *et al.*, Steingart R. M. *et al.*, Miyamoto Y. *et al.*, Ohlsson O. *et al.*). However the expected SV increase during exercise was not observed in 17 (12.5%) cardiac patients.

We could not find correlations between SVI dynamics and work tolerance in healthy individuals and functional status in cardiac patients. Is this a conflicting result? We do not think so as our healthy group was rather homogeneous in their physical activity status and work tolerance capacity and most of our cardiac patients belonged to the first or second NYHA functional class. Many studies have pointed out that the NYHA classification based on the information gained through the patient's interview fails to reveal good correlations with the objective parameters of the left ventricular function (Dunselman P. H. M. J. *et al.*, Remes J. *et al.*, Dougherty A. H. *et al.*, Davidoff R. *et al.*). Vent-

ricular dysfunction may exist without evident heart failure; likewise heart failure is not always connected with persistent left ventricular dysfunction (Dougherty A. H. et al., Ross J. *et al.*). Lack of increase of stroke volume during upright exercise characterizes failure of myocardial reserve that should be taken as a sign of myocardial damage but not necessarily of heart failure. D. W. Kitzman *et al.* have found that exercise intolerance in patients with heart failure and normal resting and peak ejection fraction correlated well with the depressed increase of left ventricular end diastolic volume and stroke volume during exercise. The findings of M. A. Konstam *et al.* indicate that symptoms of heart failure are linked to left ventricular responsiveness during diastole rather than during systole.

The relative SVI increase varied much among the healthy persons (SVI%max 106...355%). In medicine (as well as in biology) the question of normal and abnormal reaction is a very difficult problem. One of the possibilities often used in the evaluation of variable normal limits is the determination of the area as a mean value ±1.5 standard deviation of the mean. In this way about 80% of those investigated would be included. The consideration of everybody in the group of healthy persons (100%) will increase the sensitivity but diminish the specifity of the study. We could not apply the method (mean ±1.5 SD) because if we regard the SVI increase as an index of the myocardial systolic reserve then a SVI increase can never be considered excessive, i.e., myocardial systolic reserve does not have an upper limit. Our approach to evaluating a normal SVI increase during physical stress is based on the following assumption: 80% of healthy people can be expected to have a good myocardial reserve. The criteria for normal SVI increase were calculated with the help of distribution tables in different age and sex groups. An increase of SVI by at least 30% and up to the load of 1.0 W/kg or more were considered normal reaction in young and middle-aged women. The increase of SVI by 50% or more and up to the load of 1.5 W/kg or more was considered normal reaction in young men. In middle-aged men the dynamics of SVI was considered normal when the SVI increased by at least 30% and up to the load of 1.5 W/kg or more.

The mean increase of SVI in healthy individuals was 67% in our study. The data presented by other investigators vary on a large scale. Fujinami *et al.* reported a 30% increase of SV during upright bicycle stress test in healthy young and middle-aged men measured by impedance cardiography. Miamoto *et al.*, using the same method, registered a SV increase by 18% in four young healthy men. Higginbotham *et al.* reported a 20–30% increase of SV in normal men and women (31...68 years) without a significant difference between the sexes, measured by radionuclide ventriculography and expired-gas analysis. Steingart *et al.* used radionuclide ventriculography during graded

upright exercise and described a 73% increase of SV in normal subjects. Analysing these data it is evident that the results do not depend on the method used of SV estimation. Further analysis reveals that one of the reasons for the results being different may be the differences in the exercise scheme. Fujinami *et al.* and Higginbotham *et al.* used the same exercise scheme (increase of load by 25 W, duration of each load 3 minutes) and got similar results. Steingart *et al.* used the same exercise scheme but the SV was measured after the first minute of exercise at a given work load. Miyamoto *et al.* tested the effect of two separate loads (50 W and 100 W) of 8 minutes each with a period of rest between them. The SV was monitored during loading and the data suggest a rapid SV increase immediately after the initiation of exercise and a possible decrease after some minutes of exercising at a constant load.

Our exercise scheme differed from all the above-mentioned ones. It is more or less like the scheme used by Steingart *et al.* (Steingart R. M. *et al*). We measured SVI values after each minute of loading and then the load was increased. Our data do not differ from the results obtained by Steingart.

In healthy persons the SVI values did not become stabilized after the initial rapid increase at low loads but, in most cases, they decreased slightly at high loads. The same SVI dynamics have been recorded by other investigators (Higginbotham M. B. *et al.*, Fujinami T. *et al.*, Miyamoto Y. *et al.*) but there are also data about a gradual SV increase up to the submaximal exercise (Steingart R. M. *et al*). These different findings are not easy to explain but one of the explanations may be in the differences of physical activity of the subjects.

Clinical implications

The dynamics of stroke volume during upright exercise might be an independent diagnostic index of myocardial reserve besides changes in the ejection fraction. In healthy young and middle-aged men and women the stroke volume should increase during upright exercise. Lack of increase of stroke volume indicates failure of myocardial reserve but it is not necessarily a sign of congestive heart failure. The increase of stroke volume is dependent on the exercise scheme. By the upright bicycle stress test with the starting load of 0.5 W/kg with the same amount added after each minute of exercise an increase of the stroke volume by 30% or more in young and middle-aged women and middle-aged men can be considered a normal reaction; in young men the expected increase of the stroke volume is 50% or more.The stroke volume should continue increasing up to the load of 1.0 W/kg or more in women and 1.5 W/kg or more in men. A smaller increase of

the stroke volume may indicate depression of the myocardial reserve or disturbance in the adaptability to physical loading.

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BLOOD LIPIDS AND LIPOPROTEINS IN ACUTE MYOCARDIAL INFARCTION

Mikhail Zemtsovsky, Galina Zemtsovskaya

Abstract

The lipids and lipoproteins spectrum was studied in 197 patients with acute myocardial infarction (AMI). AMI is accompanied by marked changes in plasma lipoproteins. Cholesterol content decreased by 26.7 *per cent* by the 7th day of AMI. The concentration of alpha-cholesterol decreased most — 30.7% of the initial value by the 14th day of AMI. By the third day of AMI the triglyceride content was decreased, 37% of the initial value, but the content started increasing more rapidly than cholesterol and alpha-cholesterol levels. By the fourth-sixth month the content of lipids and lipoproteins had reached the level measured by hospitalization.

There are large changes in the lipoprotein content dynamics in the post-infarction period. The changes usually return to the initial levels by the 4th post-infarction month.

Introduction

The study was aimed at the lipoprotein spectrum analysis by coronary heart disease examined in post-infarction patients. The results show that by myocardial infarction there are distinct changes in the system of lipoproteins, and the type of dislipoproteinemia can be established four — six months after the infarction.

Material and Methods

The lipoprotein spectrum was studied in 197 patients, mean age 52.3 ± 1.4 years, with large myocardial infarction. The diagnosis of infarction was based on the criteria approved by WHO. There were 161 cases of uncomplicated infarction and 36 cases of complicated infarction, i.e. with heart failure, cardiac rhythm disorders in the rehabilitation period, left ventricle aneurysm, early recurrence of angina pectoris, post-infarction syndrome. Cardiospecific ferments returned to the norm in all patients by the seventh-tenth day. The control group was 286 patients mean age 53.2 ± 1.6 with chronic coronary heart disease and angiographically documented atherosclerosis. The lipoproteins were measured on the 1, 2, 3, 7, 14, and 28 days and in 3–6 month after hospitalization.

The apolipoprotein Apo A-1 and apo-B content in blood plasma was measured with the help of a special device produced by "Orion", a Finnish firm.

Results and Discussion

Acute myocardial infarction is accompanied by marked changes in plasma lipoproteins (Table 1). Cholesterol content decreased by 26.7 *per cent* by the seventh day of the disease. The statistical content remained significantly lowered in the first post-infarction month. By the fourth-sixth post-infarction month, the content reached the level measured on the first post-infarction day.

The alpha-cholesterol content reached its lowest level 30.7% of the initial value by the fourteenth post-infarction day and remained lowered all through the first post-infarction month. It remained lower than, even four-six month after the infarction onset.

The largest changes in the plasma of acute infarction patients were noticed in plasma triglycerides. By the third post-infarction day, the triglyceride content was at its lowest, 37% of the initial value, but the content started increasing more rapidly than cholesterol and alpha-cholesterol contents. The beta-cholesterol content was at its lowest on the seventh post-infarction day and remained lowered all through the month. By the fourth-sixth month the content had reached the level measured by hospitalization.

In 18 patients with major infarction the content of apoproteins apo A-1 and apo-B were measured (Table 2). The lowest apo A-1 value was recorded on the seventh post-infarction day (20.1% of initial value). The lowered apo A-1 values are in good correction with the lowered values of alpha-cholesterol, which shows how well alpha-cholesterol changes reflect changes in HDL by myocardial infarction, as apo A-1 is the basic HDL protein. A month after infarction, the statistical level of apo A-1 content was significantly lower than the initial value.

The apo-B content was at its lowest on the third post-infarction day (26.7% of the initial value). The value began coming close to the initial value two weeks after the infarction and reached the initial value by the first post-infarction month. The changes in apo-B content are well correlated with the content changes of triglycerides and cholesterol in beta and prebeta lipoproteins.

Table 1

Lipoprotein spectrum in Myocardial infarction patients (M ± σ mmol/l, n = 197)

	Days of MI						
	1	2	3	7	14	30	4 month
Cholesterol	7.56 ± 1.05	6.67 ± 0.95	6.08 ± 0.87	5.71 ± 0.78	5.87 ± 0.76	6.32 ± 0.73	7.52 ± 1.1 NS
Triglycerides	2.19 ± 0.71	1.55 ± 0.54	1.38 ± 0.44	1.52 ± 0.39	1.67 ± 0.47	1.81 ± 0.51	2.04 ± 0.64
Alpha-cholesterol	1.14 ± 0.16	1.06 ± 0.16	0.99 ± 0.15	0.81 ± 0.15	0.79 ± 0.13	0.91 ± 0.12	1.1 ± 0.14
Beta-cholesterol	5.43 ± 0.96	4.91 ± 0.87	4.46 ± 0.8	4.22 ± 0.71	4.33 ± 0.69	4.60 ± 0.65	5.5 ± 0.99 NS
pre-beta-cholesterol	0.99 ± 0.32	0.7 ± 0.25	0.63 ± 0.2	0.69 ± 0.18	0.76 ± 0.21	0.82 ± 0.25	0.92 ± 0.29
		P_{1-2} P<0.0001-0.001	P_{1-3}	P_{1-7}	P_{1-14}	P_{1-30}	P_{1-120}

Table 2

Apo A-1 and apo-B levels in myocardial infarction patients (M ± σ, n = 18)

	Days of MI					
	1	2	3	7	14	30
Apo A-1 (mg/dl)	140.3 ± 7.4	128.0 ± 8.8	117.5 ± 9.0	112.1 ± 5.0	120.3 ± 12.3	126.4 ± 10.3
Apo B (mg/dl)	189.9 ± 48.8	154.3 ± 32.4	137.5 ± 38.8	159.8 ± 38.8	162.7 ± 42.9	184.1 ± 55.5 NS
		$P_1 - 2$ P<0.001-0.05	$P_1 - 3$	$P_1 - 7$	P_{1-14}	$P_1 - 30$

Conclusions

There are large changes in the lipoprotein content dynamics in the post-infarction period. The changes usually return to the norm by the fourth post-infarction month.

The changes point to an excess of atherogenic lipoproteins in plasma.

As there are large changes in lipoprotein content, the important values are to be measured on the hospitalization day. The alpha-cholesterol content changing most dramatically and recovering slowly recommends the index as the best one for atherosclerosis prevention. The lipoprotein content values are to be measured on the first post-infarction day or in the fourth-sixth month, to administer adequate hypolipidemic and dietic treatment.

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Kokkuvõte

197 akuutse müokardi infarktiga (AMI) haigel määrati lipiidide ja lipoproteiidide spekter perifeerses veres. AMI korral esinesid olulised muutused plasma lipoproteiidide kontsentratsioonis. 7-ndaks AMI järgseks päevaks langes kolesterooli sisaldus 26,7%. Alfa-kolesterooli madalaim tase (30,7% algväärtuses väiksem) esines AMI 14-ndal päeval. Madalaim triglütseriidide kontsentratsioon (37% algväärtusest madalam) määrati 3-ndal infarkti järgsel päeval. Võrreldes kolesterooli ning alfa-kolesterooliga hakkas triglütseriidide sisaldus taastuma oluliselt kiiremini. 4–6 kuu möödudes saavutati sama lipiidide ja lipoproteiidide tase mis oli hospitaliseerimisel.

ECHOCARDIOGRAPHY TODAY AND TOMORROW

Rein Teesalu

(This overview is put together on the basis of the second Canterbury echo symposium "Echocardiography Today & Tomorrow", April 11–15, 1994 at the University of Kent, Canterbury, UK).

The first half of the symposium was "sate of the art" review of current echo topics, including debates on the value of left ventricular function quantification. The second part of the symposium covered new advances, including intracardiac and intracoronary echo and a futuristic introduction into 3-dimensional imaging. Bellow an attemt to overview the ideas and views presented on the symposium has been made.

Contrast echocardiography is an evolving technique. It may be used to get good left ventricular cavity contrast and border delineation, quantification of valvular regurgitation, evaluation of LV function, and detection of intraventricular flow patterns, especially when contrast agent is used during transesophageal echocardiography. More recent development is myocardial contrast echocardiograpfy. This technique may, in the future, provide the means for quantitative assessment of myocardial perfusion. Several contrast agents are used now and others should available in the next years. At the present time the most promising standardized contrast agent seems to be Albunex (R) (Nycomed) — sonicated human serum albumine. The mean size of Albunex bubbles is 4–5 qm. Being iso-osmolar and chemically inert, Alburex microbubbles have no adverse effects on coronary blood flow or LV and systemic hemodynamics. Their intravascular rheology is similar to that of red blood cells, making them ideal blood flow tracers. With the development of albumin microbubbles capable of transpulmonary passage, it may be possible to screen patients for the presence of ischemic heart disease using only a single intravenous injection of ultrasonic contrast material. Contrast echocardiography, performed at the time of coronary angiography, can provide additional information about the anatomical and physiological significance of coronary artery disease. The use of small, sonicated microbubbles to assess myocardial perfusion appears to be safe and efficacious. It is hoped, that myocardial contrast echo can be used to evaluate coronary flow reserve. Albunex microbubbles have the potential to serve as a contrast agent for Doppler sonography in humans. Albunex can be used to enhance the Doppler signal from systemic arteries and the portal vein. Another possible use of Albunex is intraoperative detection of myocardial hypoperfusion to guide the order of graft placement and

to measure regional perfusion during cardioplegia delivery. Both uses might help lessen incidence of perioperative myocardial infarctions.

Three-dimensional echocardiography refers to the technique of visualizing the heart, its structure and flow in three dimensions (either directly or after reconstruction, in static form or in real time) and drawing quantitative information from the three-dimensional data. Dynamic or real-time three- dimensional echocardiography refers to the ability to view the heart in three dimensions as it beats. Because the time factor is added, it is also called four-dimensional echocardiography. Five-dimensional or multidimensional echocardiography are terms occasionally used when viewing both the dynamic anatomy and flow jets. However, it is recommended to use the term three-dimensional echocardiography as general name for all these functions rather than employing a host of confusing and unnecessary names.

Every part of the heart and its pathology, every facet of its function, and every flow jet is three-dimensional in nature. An ability to directly view the heart and its structures in three dimensions rather than attempting to perform mental reconstructions from two-dimensional images could yield a better understanding of the dynamic anatomy, the spatial relationships, intricacies of cardiac pathology and flow disturbances. 3-D echocardiography portrays cardiac anatomy in unique projections not possible by 2-D echo. Recent efforts in three-dimensional echocardiography employing advanced ultrasound instrumentation and computer technology suggest that this approach is almost ready for clinical application. Volume and surface rendered, tissue-depiction three-dimensional reconstructions, performed from sequential tomographic images obtained with computer-controlled movement of the transducer at a predetermined mode and speed, show the best promise in contemporary clinical application. There are several sequential tomographic data acquisition methods using controlled transducer movement: parallel slicing or linear scanning, fan-like scanning in an arc, rotational scanning. Reconstruction of a 3-D image essentially involves realignment of 2-D images according to their relations to each time point in the cardiac cycle and position in space. Interpolation is necessary to fill in gaps. For three-dimensional image display a wire-frame mode and a tissue-depiction mode are used. Wire-frames ("a birdcage") are helpful in assessing geometry and mechanical properties of the left ventricle, chamber volume, and mass. The tissue-depiction mode portrays the cardiac structures better. Using x, y, z coordinates, the image can be rotated and tilted in various orientations and cut in the desired planes. Viewed in a dynamic mode, one could appreciate the motion of walls and the opening and closure of the valves. Images that portray intracardiac structures can be derived simulating intraoperative viewing of surgical anatomy. Basically, any structure can be visualized from any desired

vantage point. Guidelines are currently being formulated to define the clinically useful cut planes for various structures and pathology. Ongoing work in quantitative three-dimensional echocardiography is likely to provide newer indices that describe the cardiac pathology and function that have not been available before. Newer computer algorithms have shortened the image processing time from hours to minutes. Biologic color encoding is another technical advance in the evolution of 3-D echocardiography and is helpful in understanding and teaching 3-D echocardiographic depiction of the cardiac anatomy. Computer capabilities to perform electronic surgery in the reconstructed images has also been demonstrated. A surgical procedure planned for a specific problem could be conceivably simulated in the ultrasound image and the effects and complications of the procedure predicted. This could allow the surgeon to modify the contemplated surgical approach.

A unique truly 3-D display, developed from tomographic ultrasound information is holography. Holographic displays allow such presentations in which the image of the heart could have all the physical depth cues enabling the observer to appreciate the true spatial relations between various parts of the heart.

Use of tomographic transesophageal probes has proven to be safe and easy to perform in patients. 3-D images obtained with this probe depict the valvular structures in a manner that has not been possible before. However, if three-dimensional echocardiography is to be widely employed, one should be able to perform this technique transthoracically as well. Recent work has demonstrated that it is indeed possible to perform 3-D echocardiography with the transducer placed on the chest wall and subcostal regions.

3-D reconstruction methods suffer from the fact that the derived data are collected at different times and are, therefore, not real time. Accordingly, it is difficult to evaluate complex beat to beat changes of the heart because the final data comprise a composite of multiple beats collected over time.

A move towards real-time, three-dimensional appreciation of the heart has been the development of a phased array transducer which has the ability to scan, simultaneously, in two orthogonal planes. Parallel processing of the data corresponding to the two image planes allows, for example, a parasternal long-axis and short-axis view to be displayed simultaneously in real time. An attempt to obtain some perspective within the two-dimensional images can be employed so that, essentially, the two scan planes can be overlapped. However, this is still not true three- dimensional real-time imaging. The latest techniques utilize a matrix-style transducer array, which can collect ultrasound data in real time over a pyramidal volume. This system is still in the early stages of development (J. Kisslo and coworkers,

Duke University, USA). Another unresolved problem is the issue of how best visualize a three-dimensional structure. Region-oriented and lesion-oriented display approaches are under investigation.

Quantitative assessment of left ventricular size and function. Recent developments in digital image acquisition and display allow selection of cardiac cycles from different views followed by side-by-side display of these cycles in a continuous cine loop. This technology enhances the endocardial definition during motion as well as in stand-still frames. Automatic boundary detection is based on quantitative assessment of tissue acoustic properties and permits on-line quantitation of ventricular cavity areas and indexes of function. New computer programs for quantitation of 2-D images are capable of providing measurements of LV volumes, EF, mass and centerline wall motion assessment from tracings of the end-diastolic and end-systolic endocardial contour in the apical views and the end-diastolic outer and endocardial border in the short axis. These programs are becoming part of the newer echocardiographic instruments. Sonographers can therefore be trained to perform these measurements on-line with the physician acting as the experienced observer that integrates the quantitative results with the subjective evaluation. Two 2-D echocardiogrphic methods for determing LV mass have been developed: the area length model and the truncated ellipsoid model.

Application of these methods have been greatly facilitated by the use of computers with digital image acquisition and cine- loop play back. However, the better reproducibility is still to be desired. Factors that will influence reproducibility are multiple and include variability within the patient, differences in image acquisition technique between the two studies and variability between observers in selection of cardiac cycles and performance of the measurements. So, standardization of image acquisition techniques and of measurement methods is as actual as before.

Intravascular ultrasound (IVUS) imaging and intracardiac echocardiography (ICE). IVUS imaging is a newly evolving imaging method that employs miniaturized ultrasound transducers at the tip of catheters to visualize the cross-sectional and longitudinal morphology of small and large arteries. It supplies detailed information on the structure of an atherosclerotic lesion. IVUS imaging has great promise in comparison with angiography and fiberoptic angioscopy. Angiography can depict longitudinal silhouettes of the arterial lumen. It does not delineate the true anatomical severity of an arterial lesion and it does not show morphology of atheromatous lesions or abnormalities of the arterial wall. Fiberoptic angioscopy, another catheter-based technique that offers glimpses of the arterial lumen and inner surface of the wall, is limited by the cumbersome requirement of replacing blood by clear fluid infusion and by its inability

to yield information on the composition of atheroma and the architecture of vessel wall. Intravascular ultrasound has been noted to be quite sensitive in the identification of various pathological components, even in complex lesions. Abnormalities of the arterial wall and lumen are displayed by intravascular ultrasound in great detail, particularly in atherosclerosis. For examining the coronary and peripheral arteries, catheters varying from 3,5 to 9 French in size, carrying 20 to 30 MHz frequency transducers, are used. Higher frequency catheters yield fine-resolution images up to distance of about 5 mm radius. Calibration in the display system allows measurement of the vessel diameter, luminal area, and wall thickness. Currently available intravascular instruments belong to either a mechanical or a phased array category. Repeated viewings of the recorded images are needed to ascertain the spatial relationship of two-dimensional images along the long axis of the vessel and to appreciate the effects of interventions. These problems are overcome by 3-D reconstructions made by image-processing computers from a multitude of two-dimensional images recorded as the ultrasound catheter is pulled back at a constant speed from one location in the vessel to another. At the present time 3-D reconstruction requires a separate off-line image-processing device. However, intravascular ultrasound instrumentation possessing three-dimensional imaging capability in itself is likely to be available in the near future. Intracardiac echocardiography (ICE) is a similar catheter-based ultrasound approach that displays cardiac chambers, valves, and other related structures. ICE catheters can be advanced into various cardiac chambers and the cardiac structures visualized from within the heart. The impetus behind the attempts to develop the modality of ICE is predominantly related to the need for better guidance during various catheter-based therapeutic procedures for treating cardiovascular lesions. Currently 6 to 10 French catheters carrying 10, 12.5, 15, or 20 MHz transducers are used for ICE. For ICE to become a widely applicable clinical technique, the depth of field must be adequate to allow for visualization of the entire heart from the venous circulation. ICE performed with 10 French 10 MHz catheters permits an expanded field of view and represents a significant advance toward the goal of "whole heart imaging". Reduction in catheter size would be desirable to reduce the potential for vascular complications. There are attempts to construct catheters that combine intracardiac imaging and therapy (valvuloplasty, arrhythmia ablation, etc.).

Transesophageal echocardiography (TEE). TEE provides enhanced appreciation of normal cardiac anatomy as well as of a variety of pathological entities in comparison with transthoracic echocardiography. Panoramic transesophageal echocardiography (imaging field can be expanded to a width of 270') allows visualization of the atrium in its entirety, aids a better evaluation of pericardial and paracardiac

abnormalities, presents the aorta and the aortic arch more completely, and helps in recognizing mediastinal pathology. TEE has appeared to be an important diagnostic and monitoring technique after several types of open heart procedures and may reduce the need for repeat cardiac catheterization. TEE should be a complimentary test to transthoracic studies in patients with suspected prosthetic valve dysfunction. Patients suspected of having a prosthetic valve endocarditis should routinely undergo a TEE examination because of its superiority over transthoracic in detection of vegetations, valvular regurgitation and perivalvular abscesses. The role of TEE in detecting intracardiac thrombi, vegetations, and tumors has been well established. In particular, the left atrial appendage is readily apparent, and clots within it can be detected with reliability. Transesophageal echo-Doppler echocardiography is a further refinement of Doppler technique and gives high quality signals of pulmonary venous inflow to help assess function of the left ventricle and left atrium. Transesophageal color Doppler echocardiography is useful in the detection of left-to-right shunts, being more sensitive than oximetry. TEE is very useful in the assessment of aortic dissection, left atrial thrombi and right atrial masses. TEE has emerged as an important adjunct to interventional cardiac catheterization providing crucial information which may not be obtainable by transthoracic echocardiography or angiography. TEE is also a safe and useful diagnostic technique with fairly broad applications in the critical care setting. Technological advances in the design and capability of TEE probes and transducers have been largely responsible for the emergence of TEE as an important clinical tool. Probes with multiplane capability in which an imaging plane is steered through a 180-degree arc have become commercially available. With further refinements in TEE and related technologies, the future of this modality will most likely include clinical application of 3-D reconstruction and acoustic quantification. Eventually, the ultimate diagnostic imaging modality will provide an objective display of cardiac shape and size throughout the cardiac cycle. The availability of objective 3-D images of the heart would greatly improve the diagnostic accuracy in general. In addition to technological problems there is a lot of unresolved medical issues. While one is now better able to identify cardiac pathology by means of TEE, the significance of many of these lesions are not resolved. So, except in certain clearcut scenarios, many of the decisions regarding the use of TEE, and the implications of the TEE findings, will have to be made on an individual basis.

For a long period developments in cardiac surgery and in cardiac catheterization and angiography have occurred to a large extent hand in hand. Rapid growth of noninvasive imaging techniques over the last 10 to 15 years has dramatically changed the situation. These changes

have taken place first of all thanks to diagnostic ultrasound methods, comprising of 2-D echocardiography, Doppler echocardiography, and color flow imaging. These methods have demonstrated the ability to provide detailed anatomic information, generally surpassing that obtained by angiography and hemodynamic information. The methods are noninvasive, nonionizing, and far less costly. As a result, cardiac catheterization and angiography have become almost unnecessary in numerous cardiac conditions. Spectral and color Doppler echocardiographic techniques permit accurate measurement of transvalvular gradient, determination of functional orifice area, evaluation of associated valvular regurgitation, and assessment of pulmonary artery pressures. Doppler echocardiography has been used to assess physiologic changes with exercise in adults with asymptomatic aortic stenosis. Now exercise Doppler echocardiography offers a noninvasive technique to evaluate prosthetic valves. It is reproducible, safe, and less cumbersome than cardiac catheterization. A range of normal exercise hemodynamics has been established for aortic and mitral prostheses. Using these parameters, the diagnosis of early prosthetic dysfunction can be made. It is now possible to assess the severity of the lesion as well as its hemodynamic and functional consequences. The cross sectional imaging provides a far better assessment of the pathologic anatomy than angiographic methods. So, carefully done echocardiographic studies are definitive means of establishing the presence and significance of mitral stenosis and tricuspid stenosis, thereby obviating the need for invasive evaluation in many patients, reducing risk, and potentially decreasing the cost of diagnostic assessment. Doppler echocardiography has also been shown to be useful for documenting the intracardiac flow abnormalities related to constrictive pericarditis and cardiac tamponade. By means of Doppler echocardiography patients with constrictive pericarditis and restrictive cardiomyopathy can be differentiated by comparing respiratory changes in transvalvular flow velocities. It is currently feasible to obtain diagnostic quality echocardiograms in over 90% of the patients and the yield is even higher in a pediatric practice. Since management decisions can and will often made on the basis of echocardiographic findings, a high level of quality control in the administration of present-day echocardiography laboratory is necessary. Echocardiography is highly operator-dependent technique. The more automated it could be in data acquisition and interpretation, the easier it will be to decrease the interoperator variability. Ther are already data which point to the feasibility of this approach.

Two-dimensional and Doppler echocardiography in acute myocardial infarction and in patients with ischemic heart disease in general. Echocardiography, performed in the emergency room, can readily distinguish aortic dissection, pericarditis, pulmonary embolism and

hypertrophic cardiomyopathy from acute myocardial infarction. In the era of thrombolytic therapy it is particularly important to differentiate aortic dissection and pericarditis from acute myocardial infarction. Echocardiography can identify extent of right ventricular involvement. The basis for considering 2-D echocardiography as a tool to evaluate patients with suspected or known coronary artery disease is the clinician's ability to evaluate regional wall motion abnormalities with this examination. Because of the multiple tomographic views that can be obtained with this ultrasonic test, it is possible to evaluate virtually every segment of the heart. Wall motion score index and Doppler-derived ejection parameters serve to help determine the rapidity with which individual patients can be progressed in CCU. Early determination of wall motion score index by 2-D echocardiography has been appeared to be useful for identifying patients for high risk for complications and is especially valuable in the subset of patients who initially seem to be in stable condition as judged from clinical variables. Transthoracic and transesophageal echocardiography can be used to identify complications of acute myocardial infarction. Shortened deceleration time is an independent predictor of heart failure with AMI. 2-D echocardiography is an ideal means for assessing regional ventricular function in the setting of coronary artery disease. The examination is obtained in real-time with excellent spatial and temporal resolution. Ventricular function can be judged with regard to wall thickening as well as wall motion. The examination is painless, avoids any ionizing radiation, and is truly non-invasive not even requiring an intravenous injection. The examination is also less costly than many other sophisticated imaging techniques. The utility of stress echocardiography in the detection of chronic stable coronary syndromes, measured in terms of sensitivity and specificity, is at least comparable to any other noninvasive imaging technique. The introduction of digital recording and display of two- dimensional echocardiograms has enhanced the value of exercise echocardiography for risk stratification following an acute myocardial infarction. The safety of pharmacologic stress echo, and transesophageal paced echo, in the early post-MI period has been established. These modalities (especially dobutamine stress echo) will be increasingly used to diagnose myocardial stunning. Dobutamine stress echocardiography is also used for assessment of cardiac risk before noncardiac surgery. Whereas dipyridamole produces ischemia by coronary steal, dobutamine produces ischemia in a manner similar to exercise. Dobutamine echocardigraphy produces sensitivities and specificities comparable to exercise echocardiography. Pacing the heart is another alternative to exercise. An advantage of pacing is that with echocadiographic monitoring one could compare resting and immediate stress images at the same heart rate, as once the pacing is stopped the heart rate will

revert back to the original rate. Echocardiography can be added to rehabilitation stress test, toward end of hospitalization, to improve both sensitivity and specificity for detecting post-infarct, exercise-induced ischemia. The ability to identify the regions supplied by individual arteries is also as good if not better than with a comparable nuclear approach.

Doppler Tissue Imaging (DTI) is a new echocardiographic imaging technique, which utilizes color Doppler maps designed to optimally image slow-moving but highly echogenic tissue boundaries in preference to blood pool, enabling semi-quantitative assessment of myocardial contraction velocities. It is hoped, that DTI may provide a valuable new method of imaging ischemic myocardium, with greater sensitivity than B mode echocardiography and with the potential to differentiate ischemic but viable myocardium from fibrotic tissue.

Tissue characterization by ultrasound, analyzing integrated backscatter is under investigation. The capability of clearly detecting the structure and composition of tissues (especially myocardial tissue) has come to have major implications in therapy. The clinical utility of this approach is yet to be proven.

So, echocardiography today is what a stethoscope has been to physicians for over a century. It has become an integral part of contemporary cardiology. Though the pace of developments in echocardiography in the last decade has been staggering, ultra- sound technology continues its rapid development. Dr. J. Tajik (The Mayo Clinic, USA) predicted in his Deryck Taylor Lecture during The Second Canterbury Echo Symposium, that by the end of this century invasive hemodynamic techniques would be fully replaced by more informative ultrasound techniques. Clinicians scientists will soon be able to extract the heart from the body electronically for the purpose of anatomic, functional, and histologic analysis without adverse effect on the patient.

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