

12. Gstaader Treffen der Schweizerischen Herzstiftung, 26.–29. 01. 2006

Sudden cardiac death in hypertrophic cardiomyopathy

*PD Dr. Xavier Jeanrenaud, Lausanne /
Dr. Dagmar Keller, Basel*

Hypertrophic cardiomyopathy (HCM) is a complex monogenic disorder inherited as autosomal dominant trait with a prevalence of 0.2% in the young adults. HCM is characterised by left and/or right ventricular hypertrophy predominantly involving the interventricular septum and is associated with a high SCD risk as first manifestation, mostly in young and asymptomatic patients. A hallmark finding is diastolic dysfunction which can progress to end-stage cardiac disease resulting in cardiac transplantation. Mutations in thirteen genes have been identified so far in the pure form of HCM, which, except one, encode sarcomeric proteins indicating wide genetic heterogeneity. A minority of families shows complex genotypes with homozygous, double heterozygous and compound heterozygous mutations, which can influence the phenotype dramatically.

The most challenging issue in HCM is to identify individuals at high risk for SCD. Major and minor clinical factors for the SCD risk have been suggested by the ACC/ESC consensus report in 2003. Major SCD risk factors include cardiac arrest, spontaneous sustained VT, nonsustained VT, family history of SCD, septum thickness >30 mm, unexplained syncope and abnormal blood pressure response during exercise. Minor SCD risk factors are myocardial ischaemia, atrial fibrillation, LVOT obstruction, intensive physical exertion and also a genetic defect. Thus it is strongly recommended to risk stratify all patients for SCD, even if asymptomatic. Risk stratification can take place with non-invasive tests in a first line, including TTE, Holter-ECG and an exercise-stress test. ICD implantation is the only tool to prevent HCM patients from SCD in terms of primary and secondary prevention. It is a class I indication for HCM patients who survived SCD. If 2 or more major risk factors

are present ICD implantation should be considered, if one major risk factor is present ICD implantation should be discussed individually. If no risk factor is present at the initial assessment, the patient can be reassured. But risk stratification should be repeated every 3–5 years with non-invasive tests as in some patients the HCM phenotype develops later in life and SCD can occur at any time. Additionally genotyping should be offered to all patients and their families.

Sudden cardiac death in coronary artery disease

Prof. Dr. Martin Fromer, Lausanne

Sudden cardiac death (SCD) remains a challenge in contemporary medicine. Enormous progress in the understanding of the mechanism involved in SCD, in the prevention of SCD, in the identification of patients at risk and in the treatment of cardiac arrest has been undertaken and achieved during the last years.

The identification of patients at risk and their management involves the cardiologist at referral centre and the referring cardiologist but also the physician in a gatekeeper role.

Strategies for prevention of SCD include

1. Identification of the patient subgroups at high risk
2. Modification of risk factors (life style, drug therapy, myocardial ischaemia, electrolytes disbalance, cardiac function)
3. Specific and unspecific treatment (cardiac pacing, ICD therapy, percutaneous coronary interventions, AC inhibitors, beta-blocker, aldosterone antagonists, therapy with statins)

Identification of subgroups at risk

In addition to the cardiac arrest survivor, increased risk is present in chronic post myocardial infarction patients and ejection fraction

(EF) <35%, especially if they present non sustained ventricular tachycardia. It is also present in patients with ejection fraction <25% and haemodynamic well tolerated slow VT, in patients with bad revascularisation status and in patients during antiarrhythmic drug therapy and QT prolonging drugs.

Modification of risk factors

Large scale trials have shown that AC-inhibitors, beta-blockers and aldosterone antagonists reduce SCD rate. This has not been shown for statins yet.

Specific treatments

Secondary ICD therapy to terminate VT or VF has been shown to be highly effective and represents after exclusion of reversible causes a class I indication.

Prophylactic indication has been studied in the MADIT and MADIT II trial, in the SCD-HEFT trial, in DINAMIT and Amiovirt and many other trials. On top of medical therapy, the ICD provides in general further benefits regarding mortality in these patients. Subgroup analysis show conflicting results on the role of EF and NYHA function class, but in general patients with NYHA class II–III and EF ranging from 25–35% profit most.

Sudden cardiac death in sport. What about the public?

Dr. Eugène Katz, Lausanne

Sudden cardiac death (SCD) is actually defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness *within one hour of the onset of acute symptoms*; pre-existing heart disease may have been known to be present, but the time and mode of death are *unexpected* [1]. In Europe the incidence of SCD is estimated to be of 1 per 1000 persons per year between 20 and 75 years [2]. The estimated number of SCD varies from 184 000 up to 450 000 per year in the USA [3]. There is actually no collected data on incidence of SCD in Switzerland. One of the estimations is that of 8000–10 000 of SCD per year [4].

At least 90% of sudden deaths are of cardiac origin, according to autopsy studies, and the single most important cause of SCD is coronary artery disease [5]. The causes of SCD differs before and after 35 years. In young athletes (before 35 years) the commonest cause is hypertrophic cardiomyopathy, fol-

lowed by coronary artery anomalies, right ventricular arrhythmogenic dysplasia, Brugada syndrome and aortic rupture in those with Marfan syndrome. After 35 years coronary artery disease is the first cause of SCD. Near 80% of SCD are due to malignant arrhythmias: ventricular tachycardia (VT) or ventricular fibrillation (VF) – and only 20% – to pulseless electrical activity (PEA) or asystole. The incidence of SCD increases with age because of higher prevalence of the coronary artery disease in older age groups. For nearly 50% of victims sudden death is the first manifestation of coronary artery disease. 15–20% of SCD occur in public places (street, airport, casino, shopping mall, stadium), but most of them (70–80%) happen at home. Only one half of SCD are witnessed [6]. Most of the currently reported survival rates are poor (near 5%).

Risk factors for SCD are the same as those for coronary artery disease. Some studies addressed initiating events (triggers) of myocardial infarction and SCD. Anger, mental stress, cocaine and marijuana use, heavy exertion and, exceptionally, sexual activity were described as such triggers [7]. It was suggested that the emotional intensity of sporting events and other behaviours associated with spectating such as smoking, binge drinking and overeating could trigger myocardial infarction and SCD. Soccer has often been the focus of such studies since the intensity of football games is arguably unmatched by few other sporting events. Studies in the Netherlands and Great Britain have shown the significant increase in cardio-vascular mortality on the day of important matches [8, 9]. Our group also confirmed increase of sudden cardiac deaths in Switzerland during major football tournaments [10].

The survival in SCD is dependent on a series of critical interventions described as *“the chain of survival”*.

Recently efforts were made to develop automated external defibrillator (AED) for laymen use and to change strategies of AED deployment including its placement in public places, apartment buildings and private homes. AED are lightweight machines, easy to use even by 9–10-year-old children or old age people after minimal training [11, 12]. Public access defibrillation (PAD) initiatives promote basic life support and defibrillation by laymen with an AED. The survival doubled in the locations where AED were deployed in the recent PAD trial and even tripled in Piacenza, Italy, where public initiative was limited to defibrillation *without* BLS [13, 14].

Two recent studies from Germany and Spain confirmed the interest of early defibrillation programs on football stadiums [15]. Football spectators suffering from myocardial infarction or sudden death were treated early – this resulted in impressive survival rates (62% of victims discharged alive without neurological disabilities in Germany).

We also advise general practitioners to inform their patients and their families before major sporting events about the risks of medical non-compliance, decreased physical activity and increased alcohol and tobacco consumption. More information has to be provided for the general public by physicians and the media about practical measures to adopt in case of chest pain or sudden death. Information about how to reach the local emergency medical service and how to perform cardiopulmonary resuscitation has to be more broadly advertised before major sporting events. The reinforcement of the emergency cardiac care systems (increased number of physicians and paramedics on call, changes in automated defibrillator deployment strategies) and development of public access defibrillation should be proposed in order to reduce the burden of sudden cardiac death during major sporting events.

References

- 1 Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. New York: WB Saunders Publishing Co; 2005. pp. 865–908.
- 2 de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, Dalstra J, van Ree JW, Wellens HJJ. Out-of-hospital cardiac arrest in the 1990s a population-based study in the Maastricht area on incidence, characteristics and survival. *J Am Coll Cardiol* 1997;30:1500–5.
- 3 Zheng ZJ, Croft JB, Giles WH, Menash GA. Sudden cardiac death in the United States, 1989–1998. *Circulation* 2001; 104:2158–63.
- 4 Wietlisbach M, Schupfer G. Resuscitation. *Schweiz Rundsch Med Prax* 1997;86:182–8.
- 5 Leach IH, Blundell JW, Rowley JM, Turner DR. Acute ischaemic lesions in death due to ischaemic heart disease. An autopsy study of 333 cases of out-of-hospital death. *Eur Heart J* 1995;16:1181–5.
- 6 Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital “sudden” cardiac arrest. *Resuscitation* 2002;52:235–45.
- 7 Mittelman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset study investigators. *Circulation* 1995;92:1720–5.
- 8 Witte DR, et al. Cardiovascular mortality in Dutch men during 1996 European football championship: longitudinal population study. *BMJ* 2000;321:1552–4.
- 9 Carroll D, et al. Admissions for myocardial infarction and World Cup football: database survey. *BMJ* 2002;325: 1439–42.
- 10 Katz E, Metzger JT, Kappenberger L, et al. Increase of out-of-hospital cardiac arrests in male population of the French speaking provinces of Switzerland during 1998 FIFA World Cup. *Heart* 2005;91:1096–7.

- 11 Lawson L, March J. Automated external defibrillation by very young, untrained children. *Prehosp Emerg Care* 2002; 6:295–8.
- 12 Meischke HW, Rea T, Eisenberg MS, Schaeffer SM, Kudenchuk P. Training seniors in the operation of an automated external defibrillator: a randomized trial comparing two training methods. *Ann Emerg Med* 2001;38:216–22.
- 13 Capucci A, Aschieri D, Piepoli MF, Bardy GH, Iconomu E, Arvedi M. Tripling survival from sudden cardiac arrest via early defibrillation without traditional education in cardiopulmonary resuscitation. *Circulation* 2002;106:1065–70.
- 14 Public-access defibrillation and survival after out-of-hospital cardiac arrest. The public-access defibrillation trial investigators. *N Engl J Med* 2004;351:637–46.
- 15 Luiz T, et al. Management des Kreislaufstillstands in einer Fussballarena. *Der Anaesthetist* 2005;54:914–22.

Global risk assessment

Prof. Dr. Roger Darioli, Lausanne

A basic principle of prevention is that the intensity of risk-reduction should be adjusted to a person's absolute risk. Atherosclerosis (ATS) is a progressive disease associated with cardiovascular complications such as coronary heart disease (CHD), stroke and peripheral arterial disease. ATS may, however, remain asymptomatic for many years, with sudden death being its first clinical manifestation. Primary prevention of cardiovascular diseases (CVD) offers the greatest opportunity for reducing the burden of CVD. The selection of patients for clinical intervention for prevention of CVD is done through identification of high-risk conditions and risk factors (RF) for CVD. Three categories of RF that contribute to CVD risk include underlying RF, major RF and emerging RF. Assessment of absolute risk gives priority to the major RF alone. The usual method for estimating absolute risk is to determine ten-year risk for hard CHD events (myocardial infarction + coronary death) or cardiovascular mortality. Absolute risk for total CVD events (acute coronary syndromes, coronary death, coronary procedures, and stroke) typically is about twice that estimated for hard CHD events. Categories of ten-year risk warranting clinical intervention vary according to national health policy. A ten-year risk for CHD of >20% is commonly classified as a high risk status. ATP-III and IAS guidelines further identify a ten-year risk of 10–20% as intermediate risk status and a ten-year risk for CHD <10% as low risk status. ESC guidelines stratify patients in high risk category for fatal CVD events $\geq 5\%$ over the next ten years and in low risk category for fatal CVD events <5%. Several risk-assessment algorithms have been developed for estimating the absolute risk

for CVD. In Switzerland, IAS-modified for Switzerland or ESC guidelines are recommended for daily use in clinical practice.

Inflammation and coronary syndrome

Prof. Dr. François Mach, Geneva

It is now generally recognised that atherosclerosis is a chronic inflammatory disease, characterised by over-recruitment of leukocytes (monocytes and T cells) to the site of inflammation. Vascular injury in response to cardiovascular risk factors promotes endothelial dysfunction, resulting in enhanced adhesion molecule expression and secretion of pro-inflammatory cytokines and chemokines. This, in turn, leads to adherence, migration and accumulation of leukocytes within atherosclerotic lesions. The recent findings on inflammatory processes involved in atherosclerosis development provide important links between risk factors and the mechanisms of atherogenesis. Thus, research interest has increasingly focused on inflammatory biomarkers as means of predicting the risk of future clinical events. Indeed, elevated plasma levels of molecules such as soluble intercellular adhesion molecule 1, interleukin-6 or C-reactive protein (CRP) have been shown to represent inflammatory markers of future cardiovascular risk. Among these, CRP has emerged as the most powerful and accessible for clinical use. Besides its predictive role in determining cardiovascular risk, C-reactive protein (CRP) may exert direct pro-atherogenic effects through pro-inflammatory properties. CRP is mainly produced by hepatocytes in response to interleukin-6 and is then released into the systemic circulation. 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors, or statins, significantly reduce cardiovascular events and mortality in patients with or without coronary artery disease and reduce plasma CRP levels in humans. However, the mechanism by which statins reduce plasma CRP levels remains unknown. Recently, we reported that statins limit both protein and RNA levels of IL-6-induced CRP in human hepatocytes. These effects were reversed by L-mevalonate and mimicked by an inhibitor of the geranylgeranyltransferase. We also provided evidence that this effect was mediated through a reduction of IL-6-induced phosphorylation of the nuclear factor STAT3. These results demonstrate that statins reduce CRP

production directly in hepatocytes. These findings furnish new evidence for direct anti-inflammatory properties of statins and provide new mechanistic insight into their clinical benefits. A major challenge for future research would be the identification and development of promising novel anti-inflammatory therapies to reduce cardiovascular events.

Le stress et l'hypertension artérielle

Prof. Michel Burnier, Lausanne

Le stress aigu est reconnu comme un élément qui fait augmenter la pression artérielle. Cependant, l'hypothèse selon laquelle un stress psychique soutenu est responsable de l'apparition d'une hypertension artérielle reste très débattue. La réponse cardiovasculaire à un stress mental est en effet un phénomène très complexe qui comprend la perception individuelle du stress, l'activité du système nerveux autonome ainsi que la structure et la fonction du système cardiovasculaire lui-même. A cela, il faut encore ajouter les facteurs génétiques et psychosociaux propres au sujet. Plusieurs études de longue durée ont démontré une association entre la réponse à un stress psychique ou physique et la survenue d'une hypertension artérielle avec le temps. De manière intéressante, ce type d'association a été trouvé essentiellement chez l'homme et moins souvent chez la femme, à moins que celle-ci ne soit ménopausée. Toutefois, même chez l'homme, certains sujets qui répondent beaucoup au stress deviennent hypertendus alors que d'autres ne le deviennent jamais, observation qui renforce une fois encore l'hypothèse du terrain génétique de chaque individu. La problématique est presque la même lorsque l'on parle des thérapies qui visent à diminuer le stress psychosocial des patients. La plupart de ces approches produisent des baisses transitoires de la pression artérielle mais très peu d'entre elles ont un impact soutenu à long terme sur la pression artérielle. Il en va ainsi de certaines thérapies cognitives (méditation, relaxation, training autogène ...) qui ne semblent pas avoir une efficacité soutenue lorsqu'elles sont comparées à des interventions contrôles non-médicamenteuses.

En conclusion, si le stress semble être associé à l'hypertension artérielle, il est aujourd'hui difficile de savoir si l'augmentation de la sensibilité au stress observée chez beaucoup de patients à risque de devenir hyperten-

du est en fait une caractéristique précoce de l'hypertension artérielle, comme par exemple l'effet blouse blanche, ou si la réponse exagérée au stress est un facteur causal responsable de l'hypertension artérielle.

Insuffisance cardiaque et mort subite

Dr Charles Seydoux, Lausanne

La maladie coronaire est l'étiologie la plus fréquente d'insuffisance cardiaque, représentant près de la moitié des cas, suivie par un groupe de pathologies incluant la cardiopathie hypertensive, les maladies valvulaires et la cardiomyopathie dilatative idiopatique. Près de 50% des décès attribuables aux conséquences d'une insuffisance cardiaque l'est sous forme de mort subite, le plus souvent consécutive à des arythmies ventriculaire malignes, plus rarement à des asystolies. Malgré une meilleure compréhension de ces phénomènes et un traitement plus agressif des facteurs de risque, en particulier coronariens, les mécanismes sous-jacents responsables des arythmies fatales chez ces patients restent mal connus. Ceux-ci peuvent être classés en quatre catégories:

1. les anomalies structurales comme la cicatrice d'un infarctus favorisant l'apparition de tachycardies ventriculaires par réentrée, l'hypertrophie myocardique conduisant à l'augmentation du nombre de potentiels tardifs, ou l'ischémie myocardique responsable de perturbation de l'homéostasie régionale comme l'hypoxie ou l'acidose modifiant l'excitabilité cellulaire;
2. les anomalies métaboliques comme l'augmentation de l'activité sympathique chez les patients en insuffisance cardiaque ou les troubles électrolytiques comme l'hypokaliémie souvent favorisée par le traitement diurétique;
3. le traitement médical lui-même par effet direct (comme les anti-arythmiques de classe 1C) ou indirect (comme les troubles électrolytiques sur diurétique, l'inhibiteur de l'enzyme de conversion ou l'antagoniste de l'aldostérone);
4. des modifications électrophysiologiques comme la prolongation du potentiel d'action influençant l'apparition de potentiels tardifs, des troubles de l'utilisation du calcium intracellulaire ou des perturbations des échanges ioniques transmembranaires.

La prévention la plus efficace de la mort subite

par contrôle des arythmies ventriculaire en prévention primaire (sans antécédents rythmiques) ou secondaire (après objectivation d'arythmies ventriculaire) est le fait du défibrillateur implantable. Cependant, si l'on veut réduire le risque de développer une arythmie, il est nécessaire de mieux comprendre les mécanismes sous-jacents responsables de ces événements. Seule une meilleure compréhension de ceux-ci associée à un traitement préventif actif des pathologies responsables d'une insuffisance cardiaque diminueront le risque de développement d'arythmie fatale chez ces patients.

Déterminants moléculaires et cellulaires de la mort subite chez les patients en insuffisance cardiaque

Dr Hugues Abriel, Lausanne

Chez les patients en insuffisance cardiaque, dans environ 50% des cas, la mort est subite et imprévue. Dans la majorité de ces cas, le décès est causé par un épisode de tachycardie ventriculaire qui peut dégénérer en fibrillation ventriculaire. L'insuffisance cardiaque est un syndrome complexe qui est non seulement associé à une dysfonction ventriculaire, mais aussi à une instabilité électrique causée par un remodelage électrique (fonctionnel) et structurel du myocarde.

Récemment, un certain nombre d'approches pharmacologiques, ainsi que l'implantation d'un défibrillateur implantable, se sont révélés être des mesures diminuant la mortalité de ces patients. Cependant, les mécanismes précis qui génèrent le remodelage mentionné du myocarde restent encore très mal compris. Il en est de même des facteurs déclenchant les épisodes de tachycardie ventriculaire. Lors d'une récente revue de la littérature, Tomaselli et Zipes (*Circulation Research* 2004;95: 754–63) décrivent six modifications des propriétés cellulaires et moléculaires du tissu cardiaque qui peuvent générer les arythmies observées chez les patients en insuffisance cardiaque. (1.) La prolongation du potentiel d'action cardiaque et (2.) la dysrégulation du calcium intracellulaire peuvent tous les deux être à l'origine d'activités déclenchées tels que les post-dépolarisations précoces ou tardives qui peuvent générer des complexes ventriculaires prématurés. (3.) Les anomalies de la conduction représentent un facteur important dans la genèse des arythmies causées par des

mécanismes de «ré-entrées». Par ailleurs, (4.) l'ischémie chronique du myocarde et (5.) les altérations des voies de signalisation neuro-humorales sont aussi probablement des facteurs importants qui peuvent modifier les propriétés électriques du cœur. Finalement, des données récentes indiquent que (6.) des facteurs génétiques jouent probablement un rôle qui reste à définir dans la genèse de ces arythmies.

Nous allons présenter les principaux résultats obtenus grâce à l'étude de modèles animaux suggérant les nouvelles cibles fonctionnelles et moléculaires des approches thérapeutiques futures, qu'elles soient pharmacologiques, «device-based», ou mixtes.

Risikofaktor «Diabetes mellitus»

PD Dr. Peter Diem, Bern

Der «Diabetes Control and Complications Trial» (DCCT) [1] für Typ-1 und die «United Kingdom Prospective Diabetes Study» (UKPDS) [2] für Typ-2 – haben gezeigt, dass durch verbesserte Blutzuckereinstellung die Entwicklung und das Fortschreiten von mikrovaskulären diabetischen Spätmanifestationen signifikant reduziert werden kann. Klinisch nicht weniger bedeutend sind allerdings die makrovaskulären Diabetes-Komplikationen. Auch für die makrovaskulären Diabetes-Komplikationen bestehen zunehmend Hinweise auf eine pathogenetisch wichtige Rolle der Hyperglykämie:

- Eine epidemiologische Analyse der UKPDS-Daten ergab für eine einprozentige Reduktion des HbA_{1c} eine Risikoreduktion von 14% für Myokardinfarkte (95%-CI: 8–21%) [3].
- Zusätzlich haben mehrere RCT den Zusammenhang zwischen Hyperglykämie und makrovaskulären Erkrankungen untersucht. Obwohl keine der Studien primär eine signifikante Reduktionen der makrovaskulären Erkrankungen unter verbesserter Diabetes-Einstellung zeigen konnte, ergaben sich doch klare Tendenzen in diese Richtung. In einer eigenen Metaanalyse [4], welche intensivierte mit konventioneller Insulin-Therapie vergleicht, fanden wir sowohl für Typ-1- als auch für Typ-2-Diabetiker eine signifikante Reduktion des Risikos für makrovaskuläre Endpunkte.
- In der sog. Steno-2-Studie untersuchten Gaede et al. [5], inwiefern bei Patienten

mit Diabetes mellitus Typ 2 und Mikroalbuminurie eine schrittweise, multifaktorielle Intervention (mit Modifikation des Lebensstils, Nikotin-Karenz sowie intensivierter pharmakologischer Therapie von Hyperglykämie, Hypertonie, Dyslipidämie und Mikroalbuminurie) das Risiko, diabetische Spätkomplikationen zu entwickeln, senkt. Nach acht Jahren konnte auch für die kardiovaskulären Endpunkte eine eindruckliche und signifikante Senkung des Risikos belegt werden. Dabei betragen die absolute Risiko-Reduktion 20% und die NNT 5!

Die Bedeutung einer guten Blutzuckereinstellung für die Reduktion des Risikos, diabetische, mikroangiopathische Spätkomplikationen zu entwickeln, ist unbestritten. Immer mehr epidemiologische und klinische Daten deuten darauf hin, dass mit einer optimalen Blutzuckerkontrolle auch die erhöhte makrovaskuläre Komplikationsrate reduziert werden kann. Therapeutisch am erfolgreichsten dürfte allerdings ein multifaktorieller Approach sein.

Literatur

- 1 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med* 1993; 329:977–86.
- 2 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352: 837–53.
- 3 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
- 4 Stettler, et al. *Am Heart J*; in press.
- 5 Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999;353:617–22.

Lipoproteine: Wie viel ist zu viel?

Prof. Dr. Dr. h.c. Walter F. Riesen, St. Gallen

Die Dyslipidämie stellt einen der wichtigsten kardiovaskulären Risikofaktoren dar. Auf der Basis epidemiologischer Untersuchungen und klinischer Interventionsstudien haben verschiedene Expertengremien in den letzten Jahren die Grenzen der Serumlipidwerte und insbesondere des LDL-Cholesterins neu definiert. Die «3rd Joint Task Force of European and other Societies on Cardiovascular

Disease Prevention in Clinical Practice»- und die «National Cholesterol Education Program Adult Panel III»-Guidelines empfehlen einen LDL-Cholesterinwert unter 2,6 mmol/l für Patienten mit bereits vorhandener koronarer Herzkrankheit oder einem ebenso hohen kardiovaskulären Risiko aus anderen Gründen. Die Studien haben aber praktisch ausnahmslos gezeigt, dass, je tiefer der LDL-Cholesterinwert gesenkt wird, desto besser die klinischen Ergebnisse sind. Aufgrund der Daten der neuesten Studien (PROVE-IT, REVERSAL und TNT) sollten Patienten mit einem besonders hohen kardiovaskulären Risiko sogar einen LDL-Cholesterinwert unter 1,8 mmol/l haben. Bei Patienten mit einem geringeren globalen Risiko brauchen die Werte nicht unbedingt so tief gesenkt zu werden. Grundsätzlich gilt: je höher das Risiko, desto tiefer sollte der LDL-Cholesterinwert sein.

Die Studien mit Statinen und der damit verbundene Fokus auf das LDL-Cholesterin haben aber auch gezeigt, dass mit einer mittleren LDL-Cholesterinsenkung von ca. 30% eine relative Risikoreduktion in der gleichen Grössenordnung erreicht wird. Selbst bei stärkerer LDL-Senkung bleibt immer noch ein Restrisiko bestehen, welches grösser als die Risikoreduktion ist. Neuere Therapieansätze beinhalten deshalb nicht nur die Senkung von LDL-, sondern die gleichzeitige Erhöhung von HDL-Cholesterin.

Für HDL-Cholesterin existieren keine Zielwerte. Es hat sich aber gezeigt, dass Werte unter 1,0 mmol/l mit einem erhöhten Risiko vergesellschaftet sind. Therapeutisch sollte eine Erhöhung des HDL-Cholesterins um ca. 25% angestrebt werden. Eine derartige Erhöhung kann mit neuen Medikamenten (Niaspan, Rimonabant, CETP-Inhibitoren u.a.) erreicht werden.

Früherkennung der Atherosklerose

PD Dr. Roberto Corti, Zürich

Arteriosklerotische Läsionen nehmen einen dynamischen und unvorhersehbaren Verlauf. Neue bildgebende Verfahren, die in vivo die Untersuchung arteriosklerotischer Läsionen erlauben, können unsere Kenntnisse deutlich

erweitern. Insbesondere können sie wichtige Informationen über den natürlichen Verlauf des Prozesses liefern und haben somit enorme Möglichkeiten zur besseren Beurteilung der Prognose.

Akute koronare Ereignisse stehen im Mittelpunkt der koronaren Herzkrankheit. Während Patienten mit stabiler Angina pectoris eine gute Prognose aufweisen und nur mit einer Häufigkeit von 3% pro Jahr kardiovaskuläre Ereignisse erleiden, steigt das Todesrisiko bei unbehandelter instabiler Angina pectoris bis zu zehnmal an. Entsprechend kommt der Risikostratifizierung für die klinische und therapeutische Entscheidungsfindung grosse Bedeutung zu. Die Ruptur und Erosion der Oberfläche sogenannter vulnerabler Plaques und die daraus resultierende Änderung der Plaquegeometrie und Thrombusbildung sind zwei wichtige Mechanismen, die bei akuten koronaren Ereignissen eine Rolle spielen. Vulnerable Plaques sind meist relativ klein, neigen aber wegen des hohen Lipid-Gehaltes oft zur passiven Ruptur aufgrund mechanischer Stimuli. Dazu kommt ein Makrophagen-abhängiges Phänomen aktiver Plaque-Ruptur aufgrund von Matrix-Abbau durch Metalloproteinasen. Plaque-Ruptur und Plaque-Erosion mit Thrombusbildung sind die weitaus häufigsten Ursachen des tödlichen Myokardinfarktes.

Mittels neuer bildgebender Verfahren wie MR können die risikobestimmenden pathologischen Charakteristika arteriosklerotischer Plaques dargestellt werden. Das MR erlaubt die nichtinvasive Darstellung arteriosklerotischer Plaques und die Charakterisierung ihrer Komponenten in vielen Gefässgebieten.

Therapeutisch steht bei der instabilen Angina pectoris die «Plaque-Passivierung» im Vordergrund, d.h. die Verhinderung oder Hemmung der Thrombusbildung und Blockierung der Vasokonstriktion in den epikardialen Koronarien und der Mikrozirkulation. Lipidsenker stabilisieren Plaques und verbessern dadurch langfristig die Prognose. Mittels MR konnten wir zeigen, dass lipidsenkende Medikamente (Statine) die Grösse der Plaques und ihren Lipid-Gehalt reduzieren, was zur Stabilisierung der Plaque führt. Das MR erlaubt somit die Erforschung neuer kardiovaskulärer Therapiestrategien.