



Newscasts from Vienna 2003 aim to provide a snapshot of the Congress proceedings: this activity is intended especially for cardiologists unable to attend the meeting, but it also represents a source of useful information available via the web after the meeting.

In order to provide first-hand, unbiased scientific information, authoritative professionals in cardiology were asked to report on their respective fields of expertise.

The ESC is privileged to have some of the finest European cardiologists acting as reporters for this important feature of [escardio.org](http://escardio.org).



The reports cover the most important symposia from Vienna 2003 and are organised following the chronology of the Congress.

**Claudio Ceconi, MD, FESC**  
Editor-in-Chief

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*The comments express the personal opinions of the authors, and do not necessarily reflect the official position of the European Society of Cardiology.*

## **Update on guidelines for pacemakers and implantable cardioverter defibrillators**

Dr. Cecilia Linde  
Stockholm, Sweden



### **Automatic implantable cardioverter / defibrillator**

Background for ICD treatment: In general *primary prevention* is used when therapy is given to a patient who has not yet suffered life threatening ventricular arrhythmia, but who are at high risk of such an arrhythmia.

*Secondary prevention* is used when therapy is given to a person who has suffered a cardiac arrest or syncopal/hypotensive VT.

### **Implementation of implantable cardioverter-defibrillator therapy for primary prevention – the North American perspective. (E. Prystowsky, Indianapolis, US)**

In spite of the increasing use of ICDs, sudden cardiac death remains as a substantial problem. In the US, the use of primary preventive ICDs are as great as secondary according to Dr Prystowski. The MADIT I and MUSTT criteria for primary prevention are Class I indications whereas the MADIT II criteria for primary prevention were given Class II a. Only Medicare does not reimburse for MADIT II criteria unless QRS > 120 ms. In Dr Prystowski's hospital, such a definition limits the number of suitable patients considerably with lack of hard evidence considering that the QRS width criteria was based on subgroup analysis.

### **Implementation of implantable cardioverter-defibrillator therapy for primary prevention – the North European perspective. (G. Breithardt, Münster, DE)**

The annual implantation rate of ICDs varies between US (200/ mill/ year) and Europe (maximum 50/ mill / year), as well as between the different European countries and inside countries e.g. Germany. According to a recent study, primary prevention constitutes 7% of ICD implantations in Europe compared to 50% in the US and 23% in Germany. An inside-Germany survey shows that the greater annual implantation rate implies more implantations for primary prevention. Likewise, screening for primary prevention varies. In the Euro Heart Survey on heart failure only <1% were on ICD therapy. There is thus a wide under-use of ICDs in Europe. This is despite the fact that Europe has the same guidelines (European Guidelines on the prevention of sudden cardiac death updated in 2003). Among the reasons for this discrepancy are the number of arrhythmia centers, economic matters, differences in health care systems and the need for more emphasis on cost-effectiveness in ICD studies.

**Conclusion:** Great emphasis should be given to implementation of guidelines for prevention of sudden death.

### **The European perspective: new pacemaker guidelines.**

**(P. Vardas, Heraklion, GR)**

Evidence from the European Pacemaker Registry shows differences in implantation rates between European countries that are pronounced, although not as extreme as regarding ICDs. Lack of European guidelines may contribute to heterogeneity in pacing indications and in implantation rates. Guidelines for cardiac pacing are under elaboration. In the future, joint US and European guidelines are desirable. The elaboration of guidelines is needed in the light of new indications for cardiac pacing especially concerning syncope, atrial fibrillation and cardiac biventricular pacing for heart failure.

**Conclusions:** European guidelines for cardiac pacing are needed.

### **The North American perspective on biventricular devices: current and evolving indications. (D. Benditt, Minneapolis, US)**

The use of biventricular pacing relies on the risks of right ventricular pacing, the benefits of biventricular pacing, the limited risks of biventricular pacing and the potential additional benefit of adding biventricular pacing to an ICD. Biventricular pacing is anticipated to constitute 30% of pacemaker implantations by 2004 in the US. The MOST, MUSTT, CTOPP and DAVID studies recently emphasised that right ventricular pacing increases the risk for death or heart failure-related hospitalisations even in patients with no prior history of heart failure. The MIRACLE and MUSTIC studies demonstrate symptomatic improvement by biventricular pacing in patients with severe heart failure and broad QRS. In the COMPANION study, biventricular pacing reduced heart failure-related hospitalisations in similar patients.

**Conclusions:** Biventricular pacing is expected to become more common both in the setting of secondary and primary prevention of heart failure.

## *Follow-up of cardiovascular disease trends*

Prof. Ulrich Keil  
Münster, Germany



This excellent symposium consisted of four presentations dealing with:

(1) Use of national mortality data for monitoring cardiovascular disease mortality trends in Europe. (S. Sans Menendez, Barcelona, ES)

(2) Monitoring coronary heart disease and stroke trends in Finland by myocardial infarction register studies over MONICA and post-MONICA period.  
(V. Salomaa, Helsinki, FI)

(3) Changing criteria for the diagnosis of myocardial infarction. Impact on monitoring trends. (H. Tunstall-Pedoe, Dundee, GB)

(4) Changing criteria and classification for stroke. Impact on monitoring trends.  
(K. Asplund, Umea, SE)

4 million people die from CVD each year (1998) in Europe. There has been a decline in age adjusted CVD rates in most western countries, with the exception of Greece, which however has relatively low CVD rates. In Russia there was a steep rise in CVD mortality after 1992 and thereafter a decline.

With regard to morbidity, 16 million people in Europe are admitted to hospital each year with some cardiovascular disease problem. This shows again the tremendous burden of disease and disability incurred by CVD and the universal burden on the European healthcare systems.

The example of Finland clearly shows that CHD and stroke rates can be reduced dramatically over very short time periods like two decades. The major causes of the dramatic decline of CVD in Finland over the last three decades were changes in nutrition and a decline in smoking.

The 7 countries study has also shown that the major determinants of population differences in CVD are nutrition habits and smoking. The major reasons why central European countries like Germany and Austria are not making great progress in reducing mortality and morbidity from CVD is that they are trailing behind with regard to adopting a healthy diet and refraining from smoking!

Monitoring of MI and stroke trends has continued in Finland also after the end of the WHO MONICA Project. Currently, results are available for the 15-year period 1983-1997. These results show that the steep decline in CHD mortality has continued and that this extends also to the older age groups (75+). The main part of this decline is due to the drop in sudden, out-of-hospital CHD deaths, which are the overwhelming majority of all CHD deaths.

Cardiovascular stroke has been traditionally defined by clinical signs. The issue has been raised as to whether modern imaging techniques could be applied to define stroke. Different techniques however give varying results and it is therefore problematic to propose new diagnostic criteria for stroke for epidemiological research.

Nevertheless, there is a need to re-evaluate the distinction between "transient ischaemic attacks" (TIA) and ischaemic stroke since the data based on brain imaging show that 20-40% of TIA's actually are ischaemic strokes with permanent lesions. This would result in an increase in stroke incidence.

In addition, there is a need to attempt to classify stroke events by stroke subtype and the pathogenesis. The obvious limitation for such an attractive classification is that it requires considerable resources and has thus become expensive and impractical for large-scale population-based studies.

## ***Heart Failure : Also a Skeletal Muscle Disease ?***

Prof. Piotr Ponikowski  
Wroclaw, Poland



### **Congress topic: 04.09 Metabolism / skeletal muscle/ ventilation**

Chronic heart failure (CHF) is no longer considered as haemodynamic disorder, being rather a systemic disease with involvement of the periphery. Among several peripheral organs which are affected in the natural course of CHF and involved in the pathophysiology of the CHF syndrome, skeletal muscle undoubtedly plays a crucial role.

During this symposium, alterations in the skeletal musculature were discussed together with their underlying causes and the potential clinical impact.

### **Skeletal muscle function in congestive heart failure. (O. Sejersted, Oslo, NO)**

Dr Sejersted presented his data on the impaired contractile properties of the skeletal muscle in the experimental model of CHF in rats. He pointed out that these changes are not associated with atrophy, detraining or reduced blood flow, being rather inherent to the muscle itself. Especially, slow twitch muscle become extremely slow during activity, probably due to slow turnover of the intracellular calcium. Interestingly, he discovered the upregulation of the proteins of the sarcoplasmic reticulum. Answering the question about the signals causing such subtle changes in CHF, he speculated about the role of proinflammatory cytokines.

### **Altered intracellular calcium release in skeletal muscles during chronic heart failure. (V. Adams, Leipzig, DE)**

Dr. Adams (Leipzig, DE) elegantly discussed alterations in intracellular calcium release in skeletal muscle in CHF. He stressed the role of down-regulation of SERCA activity described in several experimental models of CHF. However, he also mentioned that it has not been confirmed to occur in clinical circumstances of CHF. Getting into mechanisms, he focused on the reduced phosphorylation of phospholamban, hyperphosphorylation and nitrosylation of ryanodine receptor. Additionally, he hypothesized on the potential role of sarcolipin in CHF. He concluded that all these changes may lead to a decreased storage capacity of calcium ions in the sarcoplasmic reticulum which are available for the muscle concentration.

### **Skeletal muscle apoptosis in heart failure. (G. Vescovo, Vicenza, IT)**

Dr. Vescovo (Vicenza, IT) focused his interest on the process of apoptosis in the skeletal muscle. Referring to previous work from Dr. Hambrecht's group and his own data, he was able to document that apoptosis occurs in the skeletal muscle, being one of the possible cause of muscle atrophy. He showed that the magnitude of apoptosis correlates with impairment of the muscle function and the severity of exercise capacity. Among many potential mechanisms underlying apoptosis, he presented his own hypothesis on the role of proinflammatory cytokines, but adding to it a novel factor – sphingosine. He put forward a concept that in CHF cytokines (TNF-alpha) may in fact act via sphingosine which they release from diseased myocardium, and sphingosine act at the periphery causing some detrimental effects, apoptosis being one of them.

### **Oxydative metabolism in skeletal muscle during heart failure. (R. Ventura-Clapier, Chatenay-Malabry, FR)**

Dr. Ventura-Clapier (Chatenay-Malabry, FR) presented another part of muscle abnormalities in CHF – the evidence of impaired oxidative metabolism. In her experimental model of CHF she described decreased oxidative capacity of the skeletal muscle leading to an impairment of fine regulation in energy production and utilization and calcium homeostasis. She showed data documenting alterations in mitochondrial transcriptional factors. However, she was not able to detect these changes in the skeletal muscle of patients with end-stage CHF. She pointed out that ACE inhibitors given to all CHF patients she studied may partially be responsible for such a discrepancy.

In the concluding remarks the chairmen stressed the role of the abnormalities in the skeletal muscle in CHF either in the progression of the disease and as potential therapeutic target for future therapies.

## ***Implantable Informatics and Support Systems: This is the Future***

Prof. Hugo Ector  
Leuven, Belgium



### **The implantable loop recorder. (R. Kenny, Newcastle-upon-Tyne, GB)**

R.A. Kenny discussed "the implantable loop recorder". The primary function of the device is to capture an arrhythmic event. To be effective, external loop recorders require a high recurrence rate of events. For important but rare syndromes such as malignant syncope an implantable loop recorder can be indicated. The International Study on Syncope of Uncertain Etiology (ISSUE 1) has demonstrated the outcome in situations with tilt positive patients, bundle branch block and suspected tachycardia.

### **The implantable pressure recorder. (R. Sutton, London, GB)**

Monitoring heart rhythm alone does not suffice in the current setting. R. Sutton advocated the use of the implantable pressure recorder. The hemodynamic monitor is to be used as a warning system of decompensation. It can be used for titration and tailoring of drugs. The available "Chronicle" device (Medtronic Inc.) uses a pressure transducer in the outflow tract of the right ventricle. The device gives heart rate as well as pressure and trend data. A trial is underway.

### **Implantable device memory. (J. Clémenty, Pessac, FR)**

J. Clémenty reported on "the device memory". The current pacemakers and implantable cardioverter defibrillators provide extensive device automaticity with antibradycardia and antitachycardia therapies, diagnostic functions, and reports on device status. In the future, more meticulous adaptation to the physiologic status of the patient can be expected.

### **New sensors for informatics. (B. Lemke, Bochum, DE)**

B. Lemke brought up the need for new sensors. Nowadays piezoelectric and impedance sensors are commonly used. Reflectance oxymeters (for measuring oxygen saturation) still present with a high failure rate. The application of the fiberoptical sensing principle could help in the monitoring of cardiac output and contractility.

### **The total implantable device. (B. Lüderitz, Bonn, DE)**

In his presentation, B. Lüderitz discussed the "highly integrated self adjusting implant" with remote monitoring capability. He reviewed the possibilities of future telemedicine and home monitoring. Detection of silent or manifest ischemia and automatic drug delivery should be items to be included in the devices of this millennium. The advantages and possible implications of "therapy advisors" together with questions on the clinical efficiency of new sensors remain a matter of debate.

## ***Clinical seminars: Hypertension management:2003: confused, but at a higher level?***

Prof. Damiano Rizzoni  
Brescia, Italy



### **ALLHAT and JNC-7. (J. Probstfield, Seattle, US)**

The session was attended by a large audience. J Probstfield (Seattle, US), presented some of the results of the ALLHAT study, published in JAMA 2002. The aim of the study was to evaluate the effects of an ACE inhibitor, lisinopril, a calcium antagonist, amlodipine and a diuretic, chlorthalidone on fatal coronary heart disease and non-fatal myocardial infarction combined. No difference in the primary outcome was observed. However, the authors claimed that chlorthalidone had some advantage over the other two drugs in terms of incidence of heart failure and stroke.

The results of the ALLHAT trial formed the basis for the JNC-7 document (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension), in which the use of a diuretic as a first approach in hypertension treatment was suggested.

### **Are all trials performed equal? A European perspective on trials and what they way. (S.E. Kjeldsen, Oslo, NO)**

The reliability of the results of the ALLHAT trial, as well as their interpretation, were strongly challenged by S.E. Kjeldsen (Oslo, NO). According to the speaker, no validation of cardiovascular events by a specific end-point committee was provided, and especially for heart failure this may have determined an incorrect attribution of events. In addition, differences in achieved systolic blood pressure values were underestimated, and no information about previous antihypertensive treatment was provided, making it possible that many patients with subclinical heart failure on a diuretic therapy were abruptly shifted to a different drug. Amlodipine and lisinopril were further penalized by unusual drug combinations and by a high prevalence of blacks (in which diuretics are particularly effective) in the ALLHAT population. Therefore, it seems that the ALLHAT trial was "under-funded, under-monitored and under-reported".

### **Are all antihypertensives made equal? An Australian view. (C.M. Reid, Melbourne, AU)**

The conclusions of the ALLHAT trial were further challenged by the results of the ANBP-2 study, presented by C.M. Reid (Melbourne, AU), and published in the New Engl J Med 2003. In this study, anti-hypertensive treatment with an ACE inhibitor was associated with fewer cardiovascular events, compared with a diuretic. The speaker concluded by saying that "getting the right drug to the right patient at the right time" remains a major goal in treating hypertension.

### **Effects of antihypertensive therapy on the incidence of heart failure? (G. Noll, Zurich, CH)**

G. Noll (Zurich, CH) reviewed available data about the effects of antihypertensive treatment on the incidence of heart failure, remarking that it is highly improbable for an ACE inhibitor to be less effective than a diuretic in this regard.

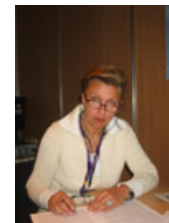
### **Glucose metabolism with antihypertensive drugs: what is the long-term impact? (J. Philippe, Geneva, CH)**

Finally, J. Philippe (Geneva, CH) suggested that an increased incidence of glucose disorders (both in terms of serum glucose levels or onset of new cases of diabetes), such as that observed in the diuretic arm of the ALLHAT trial, is supposed to have important effects in terms of cardiovascular morbidity and mortality in the medium-long term.

The chairman of the session (G. Mancia, Milan, Italy) concluded by inviting J. Probstfield to the podium for a short rebuttal.

## ***Genomics of Cardiac Diseases: A New Approach to Cardiac Pathophysiology***

Prof. Eloisa Arbustini  
Pavia, Italy



### **Bench to Bedside Symposium. In Collaboration with the International Society for Heart Research**

#### **How to elucidate the pathophysiology of familial cardiomyopathies?**

**(D. Keller, Paris, FR)**

Dagmar Keller (in collaboration with Lucie Carrier) opened the Symposium by dealing with the elucidation of the pathophysiology of familial cardiomyopathies. Hypertrophic cardiomyopathy (HCM) is characterised by phenotype heterogeneity: degree and distribution of hypertrophy, age at onset and severity of clinical manifestations vary among families and patients. The majority of HCM are familial (60%). The penetrance may be incomplete. To date, 12 causative genes are known: the last entry in the list of the disease genes is the CRP3/MLP (chr. 12.q15.1). HCM can be defined as "sarcomeropathy". In more than 80% of genotyped families, the disease genes are beta-MHC and MYBPC3 (40% and 42%, respectively in a series of 124 genotyped /197 investigated patients). More severe forms of HCM seem to be associated to complex genetic status: homozygous or compound heterozygous. The pathophysiology of HCM can be elucidated with different methods, ex vivo cellular studies, in situ analysis, etc.

Current knowledge on the pathophysiology of HCM include:

- **Type of mutation:** frameshift mutation induce the synthesis of unstable truncated proteins that are not detected in the cardiac myocytes. The pathogenic effect is that of a null allele with resulting haploinsufficiency. Vice versa, missense mutations produce stable proteins that are incorporated into the sarcomere where they exert a poison effect.
- **Sensitivity to calcium** that increases or decreases according to the mutated gene.
- **Energy metabolism:** 30% reduction of energy metabolism has been recorded, independently of the degree of hypertrophy.
- **Interactions among proteins** (i.e. acting sliding velocity has been shown to increase in hearts carrying pathologic mutations of HCM genes)
- **Enzymatic activity**, that is modified in the presence of disease-gene mutations.

#### **Importance of modifier and susceptibility genes in cardiomyopathies.**

**(M. Komajda, Paris, FR)**

M. Komajda discussed the role of modifier and susceptibility genes in cardiomyopathies, both HCM and dilated cardiomyopathy (DCM). Definitions: modifier genes modify the phenotypes (severity of the hypertrophy, remodelling, outcome, survival, tolerance to exercise, etc.), while susceptibility genes predispose to the development of the phenotypes, i.e. DCM. The types of studies that may outline the effects of modifier and susceptibility genes are case-control, sib-pairs, and transmission linkage disequilibrium (TDT) studies. Both susceptibility and modifier genes are involved in monogenic cardiomyopathies, namely familial diseases in which a causative role is played by the pathologic mutation of one or two of the disease-causing genes. HCM is familial in 60% of cases, while DCM is familial in 25% of cases. For HCM, several modifier genes are known: genes that code for ACE, Angiotensinogen, AgIIr1, Aldosterone synthase, Endothelin 1, Tumor necrosis factor alpha and other cytokines, Adrenergic receptors, PAF Acetylhydrolase, etc. For DCM, more frequently sporadic than familial, predisposition genes may play a major role. Data from prior studies document controversial results: for the ACE gene ID polymorphism, one of six studies provided positive association that has not been confirmed by five further studies. While polymorphisms in the ACE, Ag, AgIIr1, Aldosterone synthase, BNP, Adrenergic receptors are still unconfirmed, other genes such as ET1rA seem to be better candidates to predispose DCM. The ID ACE polymorphism seems to influence tolerance to exercise and survival. Gene polymorphisms are also candidates to influence **drug response**: the genetic background may help to identify good responders and poor responders to the different treatments used in patients with cardiomyopathy. For example, Beta2Receptor polymorphisms seem to influence the responsiveness to carvedilol in patients with congestive heart failure. A series of method- and sample-related problems are limiting our current knowledge: the candidate gene approach, the small sample size, the ethnical homologies and differences, the lack of replication of the results, the poorly defined functional significance of the polymorphic changes. Large population samples collected in collaborative studies are going to provide more reliable and precise answers in our population. The Eurogene Heart Failure Study (supported by Leduq Foundation) in which ten large European Cardiology Centres are involved, has collected 2000 patients, and constitutes an example of multicentric collaboration that may provide well-phenotyped patient population suitable for genetic studies.

#### **Use of proteomics to define cardiac phenotype during heart failure.**

**(V. Regitz-Zagrosek, Berlin, DE)**

Dr. Regitz-Zagrosek from Berlin illustrated the use of proteomics to define cardiac phenotype during heart failure. She gave the definition of Proteome, namely the complete set of chromosOMEs and their related **PROTE**ins. The approach to the study of diseased organs and tissues may move from proteomic rather than from a genomic basis. It implies the analysis of proteins that are present or absent in given tissues. The technology is costly and time-consuming, but the information can be uniquely useful for the understanding of the functional basis associated with the phenotypes and may indirectly address the identification of new disease genes. The phases in which such types of studies are conducted include protein extraction, from different tissues, cell fractionating, 2D electrophoresis, image analysis, spot excision, mass spectrometry, and bioinformatics. From a small tissue biopsy, it is possible to obtain a 2D gel with a thousand protein spots. Each spot can be quantitatively compared with reference proteins, and then specifically analysed. The proteomic studies are complicated by protein family complexity and high individual variability, also in relation to age and sex (i.e. several proteins are differently expressed in male and female hearts). Furthermore expressed proteins typically undergo post-translation changes such as

glycosilation, phosphorylation, and deamination that may complicate the understanding of the pattern of their expression. Overall the PROTEOME approach to research in heart failure is promising and is going to provide new insights in the understanding of the pathogenesis. One example of proteome-based ongoing studies is the analysis of cardiac peroxisome proliferation-activated receptor alpha (PPARalpha) in HCM and DCM. PPARalpha was found to be significantly increased in myocardial samples obtained from end-stage DCM hearts excised at transplantation versus the levels measured in normal hearts of donors that were not suitable for transplantation. Although no correlation was found between the levels of PPARalpha and age/LVEF, the elevated levels of PPARalpha mRNA in DCM cardiac energy production, compared with the decreased levels of PPARalpha found in HCM, suggest that specific cardiac metabolic programmes may be active in different types of cardiomyopathies.

## **Multifactorial genetics: a new approach to heart failure.**

**(H. Schunkert, Lübeck, DE)**

The final presentation was dedicated to multifactorial genetics as a new approach to heart failure. Dr. Schunkert from Lübeck, Germany, opened his presentation by recalling the complex and vicious circle that triggers and sustains congestive heart failure. This circle is articulated in steps, each with potential genetic implications. The causative agent is either genetically caused (monogenic) or influenced (multifactorial), the remodelling, the cardiac output variance, up to the neurohumoral pattern, are all phases in which genes may play some role. For example, in left ventricular hypertrophy caused by hypertension there is a long list of candidate genes to enter in some of the phases/items of LVH. They may influence the neurohumoral balance that underlines hypertension. The growth factor expression induced by the hypertensive status may influence the left ventricular hypertrophy, its severity and evolution. The genetic background may therefore constitute part of the hypothetical risk for LVH in hypertensive patients. A compound risk for LVH or Congestive Heart Failure (CHF) may result from the sum of genetic (about 45%) and environmental factors (40%), plus a percentage of chance that may escape predictability. In these types of studies, large numbers of patients are mandatory. The current need is that of addressing research to sum the effects of different polymorphisms. The combination of more polymorphisms in different genes could provide the additive weight gained by each of them when combined with others and in each individual. Genome wide association studies done with Single Nucleotide Polymorphism (SNP) analysis could provide the wide spectrum of candidate genes whose polymorphic changes, combined together in the same individuals, may define the genetic background for complex phenotypes such as heart failure. In small studies the strength of the association between polymorphisms and phenotypes may be informative (the example of lymphotoxin alpha and atherosclerosis) while in large family studies the informative value is high when specific phenotypes are present in several members.

*The comments express the personal opinions of the authors, and do not necessarily reflect the official position of the European Society of Cardiology*

## ***Cardiac Anatomy and Pathology Live: The Anatomy for the Interventionalist***

Prof. Antoine Lafont  
Paris, France



### **Anatomy for the Interventionalist : A New Session, a Must !**

**Live video demonstration. (S. Ho, London, GB)**

**Hands-on specimen demonstration.**

Who would have believed that spending two hours with an anatomopathologist showing us real hearts would have been such a wonderful experience? I was worried that it would be a relatively small meeting : the room of 40 seats was full, with more than 100 participants! This reveals a clear need for this completely new, educative session. In practical terms, Dr Ho, London, who had brought several normal and pathologic human hearts, started to show us via a camera (and did an excellent job) the anatomy of a normal heart, using the classical catheterisation route: inferior vena cava, the right atrium and its septum, the situation of the coronary sinus with regard to the mitral valve, the right ventricle, the left atrium with the 4 pulmonary veins, the ventricular septum and the situation of the conductive tissue. Abnormalities such atrial and septal defects, ductus arteriosus were perfectly accessible. Briefly, in the hands of Dr Ho, these hearts seem to restart to live, and this experience of real perception of the heart: for example, as an interventionist, I realized that my angiographic perception was less true than the CT images of the coronary arteries. A lot of practical questions regarding interventional cardiology were asked, showing the relevance of this new form of educational tool.

**In conclusion**, this kind of workshop should be mandatory for the formation of an interventional cardiologist. Next year, we might propose 2 special sessions devoted for the interventional rhythmology and interventional cardiology.

## ***Spontaneous and Iatrogenic Microembolisation***

Prof. A. Gallino  
Bellinzona, Switzerland



### **Pathophysiology of coronary microembolisation. (A. Skyschally, Essen, DE)**

Prof. Skyschally from Essen, Germany, presented an experimental model in a dog for studying the pathophysiology of coronary microembolisation. By the use of injection of 40 µm plastic microspheres, it is possible to investigate the consequences of micro-infarcts and the behaviour of coronary flow and systolic myocardial wall thickening. Coronary flow decreases transiently during microembolisation with relatively rapid recovery; whereas systolic wall thickening impairs and does not recover in this acute animal experiment. The author gave some reasons for the imbalance and myocardial dysfunction: (1) histology shows micronecrosis, which however cannot explain completely the myocardial dysfunction; (2) infiltrating leukocytes are quite numerous in the microembolised areas; this inflammatory process is associated with an increase in TNF alpha, which is predominantly present and produced (in situ hybridization) around the microembolised area; infusion of TNF alpha mimics the progressive myocardial dysfunction; pretreatment with TNF alpha antibody prevents the myocardial dysfunction. Coronary flow reserve is diminished in the micro-infarcted area: this is probably induced by adenosine production in the non-micro-infarcted areas.

Preliminary experiments using steroids and/or statins seems to prevent myocardial dysfunction associated with micro-embolisation

Refs: Am J Physiol 2002;282:HG11-14, Circulation 2003;106:2180

### **Clinical relevance, prevention and treatment of spontaneous coronary microembolisation. (P. Camici, London, GB)**

The author stressed that the clinical model, as usual, is always more complicated and different than the animal model. Spontaneous microembolisation occurs following plaque ulceration or plaque fissure in the clinical setting of acute coronary syndrome. This has been explored in recent years by endoscopy and IVUS, the laboratory expression in clinical practice being elevation of troponin T and I and CK-MB. Iatrogenic emboli are more frequent during rotablation > atherectomy > surgery > stenting or angioplasty.

Clinical expressions of spontaneous microembolisation are acute coronary syndrome with ECG changes and arrhythmia. The similar work of Uren showed that reduction of CFR occurs in infarct-related areas, but also in remote non-infarcted areas. This may reflect a reflex between infarcted / non-infarcted areas.

Small coronary arteries and arterioles are the determinants of coronary resistance: they play also a very important role in the setting of microembolisation, as shown by the clinical research experiment of Camici's group, using an alpha blocker randomized to placebo, which was administered 4 days before PCI. The group under alpha blockers clearly presents an increased coronary flow reserve.

Altogether, treatment / prevention of microembolisation should definitely include aspirin and statins, anti-platelet and anti-thrombotic agents, for iatrogenic embolisation, the spectrum of the several devices. Warfarin, alpha blockers and anti TNF alpha may probably be tested in clinical trials in the near future.

Refs: J Am Coll Cardiol 2000;36:22-24, N Engl J Med 1994;331:222-7

### **Clinical relevance and prevention of coronary microembolisation during percutaneous interventions. (C. Di Mario, London, GB)**

Microembolisation during PCI includes platelet aggregates and plaque debris. Visualisation of microinfarcts can nowadays be detected by MRI, which shows focal infarctions not detectable by other diagnostic means.

Significant CK-MB release after PCI occurs in around 10%, and a fivefold increase is associated with increased mortality. Vein grafts are obviously more prone to microembolisation and are associated with 10% mortality at 1 year (fivefold increase of CK-MB).

Drug eluting stents are also associated with microembolisation in spite of low pressure expansion. The determinant measure even with this type of stent is stent length.

GP IIb/IIIa diminish significantly the occurrence of microembolisation but do not abolish this complication.

From IVUS studies, we have learned that plaque burden is associated with increased CK-MB, morbidity and probably mortality. A large reduction of the atherosclerotic burden by stent implantation is also associated with major increase in CK-MB.

From the devices, the Guard Wire was the first protection device showing a reduction of microembolisation. The Percusurge device is an efficient protection but is often associated with myocardial ischemia following occlusion of the distal vessel.

Filter devices are equivalent to protection; the main limitation being that they do not block all microemboli (<80µ). A recent comparison between filters and the Guard wire published by Stone et al in Circulation August 2003 showed equal results in terms of death, myocardial infarction and CK-MB elevation.

An important issue concerns the use of devices during primary PCI in acute myocardial infarction. The major problem being the artificial microembolisation by passing the complex atherothrombotic lesion with the protection device or with the filter. Promising results in this setting are the thrombectomy devices, (X-Sizer and the Excimer laser device, among others).

### **Clinical relevance and prevention of coronary microembolisation during coronary bypass surgery. (D. Taggart, Oxford, GB)**

Cardiac surgery is usually associated with serious neurological damage and intellectual function decrease (10-20%). There is no doubt that off pump aortocoronary bypass operations using arterial conduits definitely have diminished the risk of serious neurological damage. The author pointed to the importance of using arterial filtration particularly during on-pump aortocoronary bypass operations and to identify pre-operatively patients most prone to neurological complications.

## ***The Cutting Edge of Cardiovascular Magnetic Resonance: What's in the Pipeline***

Prof. Kieran Clarke  
Oxford, United Kingdom



### **Published Date Title Authors Topic**

The targeting of atherosclerotic lesions and vessel inflammation using paramagnetic nanoparticles, the detection of early fibrosis in myocarditis using delayed washout of contrast agents, imaging of tissue oxygen levels to detect stenosis, real time MR and glowing catheter tips to monitor interventions, and improved image resolution at 3 Tesla field strength were amongst the many exciting advances presented in this symposium on cardiovascular magnetic resonance.

### **Targeting thrombi and plaques. (S.A. Wickline, St. Louis, US)**

Dr Samuel Wickline (Washington University, St Louis) showed how MR imaging can be used to detect selected targets, such as fibrin in thrombi and tissue factor in smooth muscle cells, using high affinity antibody-directed ligands for those targets. The ligands are paramagnetic lipophilic chelates that bind to the target to decrease the relaxation times, allowing the target to be visualized using MR. Dr Wickline presented superb examples of targeting the nanoparticles to the  $\alpha_5\beta_3$  integrins in order to detect early atherosclerosis or inflammation of the vessel wall following angioplasty. Owing to the high sensitivity of the technique, these particles can also be used for early diagnosis, longitudinal evaluation of therapy, targeting drug delivery and to quantify the drug delivered to a particular area.

### **Tissue characterisation. (M.G. Friedrich, Berlin, DE)**

Dr Matthias Friedrich (Humboldt University, Berlin) presented clearly-defined images, using contrast enhanced magnetic resonance (CMR) techniques, of fibrosis caused by myocarditis and in hypertrophic cardiomyopathy. He also showed how patterns of delayed washout can aid in diagnosis and how triple inversion recovery T2-weighted imaging can be used to detect damage following acute myocardial infarction. Dr Friedrich also reported that BOLD MRI can detect the contrast resulting from different levels of oxygen in the tissue, thereby visualising ischaemic areas of the heart non-invasively. Finally, he described how <sup>1</sup>H spectroscopy of serum can be used to detect coronary artery disease.

### **Interventional cardiovascular magnetic resonance. (E. McVeigh, Bethesda, US)**

Dr Elliott McVeigh (NHLBI, NIH, Bethesda) described the use of 8 phased array receiver coils and fast gradients to decrease image acquisition times to 1,000 echoes per second and thereby allow real time imaging for guiding interventions. He showed impressive images of numerous catheter tracking methods, such as gadolinium coating and CO<sub>2</sub>-filled balloons, which allow real time interactions. One exciting use of this technique is to inject stem cells loaded with iron oxide into the infarcted heart – the injection visualized and targeted precisely to the periphery of the infarct. Thus, real time MRI can be used for diagnosis and for baseline function, as a guide for therapeutic delivery and to monitor the recovery of function after therapy.

### **All is better at 3T? (S. Kozerke, London, GB)**

Dr Sebastian Kozerke (University of Zurich, Switzerland) compared the latest 3T MR systems with 1.5 T systems, describing the various aspects that should be improved by using 3T, such as magnetic field homogeneity, which would allow faster acquisition times and greater signal to noise ratios. He described the difficulties encountered in using a 3T system for the heart, including distortion of the ECG signal (used for gating) by the high field, but presented the methods used to overcome the problems, such as using parallel imaging to increase the resolution and localized shimming to eliminate artifacts resulting from cardiac movement. These techniques resulted in faster cardiac imaging, eliminating the need for breathhold, and beautiful resolution of the coronary arteries in which the right and left coronary arteries could be imaged in the same scan. Finally, Dr Kozerke showed how tagging is improved by 80% by scanning at 3T and how diffusion tensor imaging can be used at 3T to detect Brownian motion of water to track fibre movement and structure.

*The comments express the personal opinions of the authors, and do not necessarily reflect the official position of the European Society of Cardiology.*

## ***A Second Point of View on Cell Cycle Proteins: A Future Target for the Treatment of Heart Failure?***

Dr. Katrina Bicknell  
 London, United Kingdom



Symposium organized in collaboration with the International Society for Heart Research.  
 This symposium highlighted the potential of cell cycle proteins as targets for the regeneration of the myocardium or treatment of detrimental cardiomyocyte hypertrophy.

### **Regulation of Cell Cycle in Cardiac Myocytes. (K.A. Bicknell, Reading, UK)**

The proliferative potential of the cardiomyocyte is progressively lost during cardiomyocyte development such that the majority of adult cardiomyocytes are unable to undergo cell division. Unable to divide, adult cardiomyocytes respond to increases in cardiac load by increasing the size of individual cells, the process of hypertrophy.

The loss of growth potential of the adult cardiomyocyte has been attributed to a cell cycle arrest in these cells. Flow cytometric analysis has demonstrated that the majority of myocytes (approx. 85%) are arrested in G0/G1 phases of the cell cycle and the remaining cells are arrested in G2/M. Indeed, the growth potential of the cardiomyocyte is reflected in the expressions of the positive and negative regulators of cell cycle progression. The expressions and activities of the positive cell cycle regulators (e.g. cyclin: cyclin dependent kinase (CDK) complexes) are significantly down-regulated in cell cycle-arrested adult cardiomyocytes compared to proliferating fetal cardiomyocytes. Similarly, the expressions of the negative regulators of cell cycle progression, the CDK inhibitors, are significantly up-regulated in adult cardiomyocytes compared to fetal cells.

During pressure overload-induced hypertrophy, a partial and transient reactivation of the cell cycle occurs in adult myocytes and a significant population of myocytes progress through the G1-S transition but accumulate in G2/M. This cell cycle reactivation is reflected in a transient increase in the expressions and activities of the G1-S acting cyclin:CDK complexes (e.g. cyclin D:CDK4 and cyclin E:CDK2) and a decrease in the expressions of the CDK inhibitors, p21 and p27. In view of the involvement of the cell cycle machinery in controlling the growth potential of the cardiomyocyte, strategies that target the cell cycle machinery might be of therapeutic benefit for both the treatment of detrimental hypertrophy or regeneration of the myocardium. For example, our laboratory has shown that the expression of the G2/M acting cyclin B1:CDK2 complex is down-regulated in cell cycle-arrested adult cardiomyocytes and that over-expression of cyclin B1 is sufficient to extend significantly the proliferative capacity of cell cycle arrested cardiomyocytes. Moreover, we have shown that E2F transcription factors play a critical role in regulating the development of cardiomyocyte hypertrophy and demonstrate that inhibition of E2F activity abrogates the induction of hypertrophy in neonatal cardiomyocytes.

### **Induction of Cell Cycle in Terminally Differentiated Cells. (M. Crescenzi, Rome, IT)**

In his presentation, Dr Crescenzi highlighted how information from the cell cycle regulation of the terminal differentiation of skeletal muscle can be used to elucidate the cell cycle regulation of differentiation in other cell types, such as neurons; adipose tissue and cardiomyocytes. Dr Crescenzi presented data from his laboratory investigating the regulation of the cell cycle machinery in skeletal muscle differentiation. Skeletal muscle offers an ideal model for studying terminal differentiation of cells *in vitro* since cultured myoblasts can be readily differentiated into myocytes by serum withdrawal and myocytes then fuse to form myotubes. Terminally differentiated myotubes are arrested in G1 phase of the cell cycle. To overcome this G1 block, Dr Crescenzi over-expressed the cyclin D1 and/or CDK4 in these cell cycle arrested cells. Over-expression of the cyclin D1:CDK4 complex was sufficient to push cells through the G1-S transition however cells then accumulated in G2/M.

### **Involvement of Cyclin D2 in Left Ventricular Hypertrophy. (P.K. Busk, Copenhagen, DK)**

In his presentation, Dr Busk presented data that demonstrated a role for cyclin D2 in controlling hypertrophic growth in adult cardiomyocytes. Dr Busk demonstrated that the expression of cyclin D2, and not cyclin D1 or D3, are regulated during pressure-overload induced hypertrophy. A cyclin D inhibitor, DIF1, which inhibits cyclin D expression, was employed to highlight the importance of cyclin D in the induction of hypertrophic growth. A role of cyclin D2 in controlling myocyte proliferation was also suggested, with data demonstrating that adenoviral-mediated over-expression of cyclin D2 resulted in a 2 fold increase in the number of neonatal cardiomyocytes present 6 days after infection compared to controls. Although DNA synthesis was increased in cyclin D2-infected cultures, the modest increase in cell number might suggest that another cell cycle block, e.g. the G2/M arrest, might be limiting the proliferation of these cultures.

### **Is Myocyte Renewal a Future Treatment of Heart Failure? (J. Leor, Tel Hashomer, IL)**

The area of myocyte renewal has gained much interest recently in view of the exciting developments in the use of stem cells or cell transplantation in the repair of the myocardium. In his presentation, Dr. Leor presented an elegant overview of the benefits and problems associated with cell transplantation, stem cell therapy and cell mobilization approaches to repair the damaged myocardium. Some of the problems associated with these therapeutic approaches included the possibility that transfer of beating human ES cells could result in the formation of a teratoma or that IV delivery of stem cells increases the mobilization to the lungs rather than the heart. In view of these concerns with stem cell and cell transplantation therapies, Dr. Leor suggested that strategies targeting the cell cycle machinery, if cell division could be induced in a controlled and safe manner, would represent a most promising approach to myocardial repair.

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## ***Cell cycle proteins: future target for the treatment of heart failure***

Dr. Pieter Doevendans  
Utrecht, Netherlands



The cycle of cell division is a complicated but highly conserved process. Cardiomyocytes are considered to be terminally differentiated cells and therefore resistant for cell division. Even under pathologic conditions, myocyte division is extremely rare or absent. In order for mitosis to occur cells must exist the resting or G<sub>0</sub> phase and enter the G<sub>1</sub> phase. Already in this switch many cell cycle promoting proteins like cyclins and cyclin dependent kinases are involved. In addition to these cell cycle stimulating proteins endogenous blockers of the cell cycle have been uncovered predominantly in the field of oncology as defects in cell cycle blockers could predispose an individual for malignancies. Cells go from G<sub>1</sub> phase into the S phase indicating DNA synthesis. The preparation for mitosis occurs in the G<sub>2</sub> phase and the M (mitosis) phase is the actual mechanical chromosome division.

### **Regulation of cell cycle in cardiac myocytes. (K. Bicknell, Reading, GB)**

Dr Bicknell, Reading UK gave an excellent overview of the cell cycle and all the proteins involved. Several groups have shown that cardiomyocyte can be forced into the S phase, but in general this does not induce complete mitosis. There appears to be a block in cardiomyocytes going from G<sub>2</sub> to M. For this transition the cyclin B1 and cyclin dependent cyclase 2 (CDC2) have been shown to be key proteins. Cardiomyocytes from mice can divide until 1 day after birth, in rats this period is extended to four days and in man 6 months has been reported. During maturation of cardiomyocytes the expression levels of both cyclin B1 and CDC 2 are gradually decreasing to almost undetectable levels in the adult stage. Transfection experiments were reported with vector containing cyclin B1 and GFP as separate proteins driven by the actin promoter. Overexpression of B1 in 3 day neonatal rat cardiomyocytes (still dividing) induced cell proliferation and the same was reported for cells harvested 5 days after birth (not dividing). They reported no marked increase in apoptosis, which is always a major concern when interventions are performed in the cell cycle.

Additional experiments were performed to define the role of cell cycle proteins in hypertrophy.

The effect of phenylephrine (PE) treatment of cardiomyocytes on expression levels of various E2f isoforms was analyzed. Three E2f isoforms were analysed at the protein level. E2F3a and E2F4 were upregulated upon serum suppletion and after PE treatment. The response of E2F5 was different in that levels were reduced upon serum treatment and normal in the presence of PE.

A blocking peptide was used to interfere with E2F mediated effects on transcription (AH2) The AH2 peptide interferes with E2F-DP binding. AH2 treatment was shown to block hypertrophy. In the presence of AH2 the induction of ANF expression was completely blocked. Clearly this data show the link between cell cycle and hypertrophy.

### **Induction of cell cycle in terminally differentiated cells. (M. Crescenzi, Rome, IT)**

The next speaker Dr M. Crescenzi (Rome Italy) showed his results in skeletal muscle. He compared protein levels in myotubes and myoblasts. His work was focused at earlier interventions in the cell cycle. He particularly focused on the transition of G<sub>0</sub> to G<sub>1</sub>. Comparing myotubes with myoblasts he showed higher levels of PCNA, cyclin D and E. In order to proceed to the G<sub>1</sub> phase cyclin E and A must be activated. This was demonstrated by overexpressing of the E1A protein. In the presence of E1A, myotubes dedifferentiate and reenter the cell cycle visible as mitosis. The majority of the cells go in apoptosis. Some cells start making colonies, but this is a rare event. In order to lift the block going from G<sub>0</sub> to G<sub>1</sub>, both Cyclin D1, as well as CDK4 were placed in adenoviral constructs for transfection. Surprisingly the high levels of protein lead to near physiological activity levels. Physiological activity levels were sufficient for the induction of cell division in myotubes. In the discussion again the issue of apoptosis came up. Dr Crescenzi stated that the probably the level of cyclin protein activity (not amount) will decide whether cells go into apoptosis or mitosis.

### **Involvement of cyclin D2 in left ventricular remodeling. (P. Busk, Copenhagen, DK)**

Dr Busk (Copenhagen, Denmark) showed his results in rats *in vivo*. Upon transverse aortic banding Cyclin D2 was induced at a constant level over a 12 week period. No changes were seen in cyclin D1 and D3 expression. The role of Cyclin D2 in mediating hypertrophy was further analyzed in *in vitro* experiments. By introducing DIF1 a specific blocker for Cyclin D the hypertrophic effect of PE on rat neonatal cardiomyocytes was completely reversed. Indicating a dominant role for cyclins in hypertrophy. In addition, the outcome of CyclinD2 overexpression was shown to increase cell numbers over time. These experiments were performed in both adult and neonatal cells.

### **Is myocyte renewal a future treatment of heart failure? (J. Leo, Tel Hashomer, IL)**

The session was concluded by Dr. Leo, who provided an excellent review on the current state of cell renewal for cardiac repair. He discussed cell transplantation, the mobilization of stem cells and the potential of cell cycle interventions. Important limitation is that most positive studies are all coming from one group. And all clinical trials with cell transplantation are positive, but obtained in poorly designed trials. He showed nice data on cell homing. The application route is crucial for homing as intravenous injection shows accumulation of stem cells in the lung. Intracavitary injections showed about 10% of the cells going to the heart. Post myocardial infarction more cells reside in the damaged area. Although his talk was sobering, he clearly was hopeful for future possibilities to use cell renewal for cardiac support in the next 5 years.

## ***Contractile Dysfunction in Heart Failure: From Molecular Mechanisms to Therapy***

Dr. Walter Paulus  
Aalst, Belgium



The origin of myocyte contractile dysfunction in heart failure still remains unknown and this well-attended symposium "from bench to bedside" tried to shed new light on recent advances in this field.

### **Molecular basis of contractile dysfunction in heart failure: the role of sarcoplasmic reticulum calcium uptake. (G. Christensen, Oslo, NO)**

Dr. Christensen focused on abnormal calcium reuptake by the sarcoplasmic reticulum (SR). Although it is still unclear if SR  $\text{Ca}^{++}$  ATPase expression is reduced, activity of SR  $\text{Ca}^{++}$  ATPase is clearly reduced in failing myocardium. Reduced SR  $\text{Ca}^{++}$  ATPase expression in heart failure could result from elevation of circulating cytokines such as IL6 or from altered levels of thyroid hormones, which are potent regulators of both SR  $\text{Ca}^{++}$  ATPase and phospholamban expression. When phospholamban gets phosphorylated, activity of SR  $\text{Ca}^{++}$  ATPase is greatly increased. In cardiomyocytes from failing hearts, this phosphorylation is reduced. Phosphorylation can occur at two sites: phosphorylation at Ser16 results from increased PKA activity and phosphorylation at Thr17 is under control of the calcineurin pathway.

### **Regulation of SERCA 2 activity in the failing human myocardium by calcineurin. (R.H. Schwinger, Cologne, DE)**

Deficient calcineurin controlled phosphorylation was explored by Dr. Schwinger. In myocardium of end-stage human heart failure he observed increased expression of calcineurin. This increase in calcineurin was responsible for both the induction of the hypertrophy gene programme and for the reduced phosphorylation of phospholamban. He also observed high calcineurin levels in myocardial biopsies of patients with left ventricular hypertrophy but the actual demonstration of reduced phosphorylation of phospholamban at Thr17 in hypertrophied myocardium still awaited confirmation.

### **Phospholamban: a promising therapeutic target in heart failure? (G. Hasenfuss, Göttingen, DE)**

Dr. Hasenfuss moved from SR calcium reuptake to SR calcium release. He recapitulated the recent evidence on hyperphosphorylation of the ryanodine receptor in failing myocardium. This hyperphosphorylation appears to be reversible following placement of a LV assist device and following betablocker therapy. The hyperphosphorylation leads to diastolic calcium leakage, reduced amplitude of systolic calcium release and arrhythmias because of augmented sodium-calcium exchange as a result of high diastolic myoplasmic calcium. The clinical correlates of these cellular abnormalities are familiar to all cardiologists and consist of reduced systolic shortening, diastolic LV dysfunction and ventricular tachycardia induced by delayed afterdepolarisations. This diastolic calcium leak from the SR is rapidly becoming a therapeutic target as it can be modified through gene transfer of FKBP12.6, a protein associated with the ryanodine receptor, through gene transfer of sorcin, another protein closely associated with the ryanodine receptor and through use of specific ryanodine receptor stabilizing drugs.

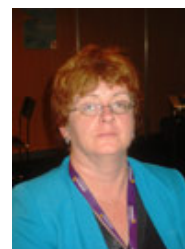
### **Suppression of heart failure progression by a pseudophosphorylated mutant of phospholamban via in vivo cardiac recombinant adeno-associated virus gene delivery. (K. Chien, La Jolla, US)**

The use of gene transfer to correct contractile dysfunction of failing myocardium was also the topic of the last speaker, Dr. K. Chien from La Jolla, CA. He focused on adeno-associated virus gene delivery of a phospholamban mutant. This phospholamban mutant mimicked hyperphosphorylation and resulted in a markedly restored SR function. Its administration to mice suffering of dilated cardiomyopathy because of a deficient cytoskeletal protein (MLP) prevented development of cardiomyopathy (phenotype rescue). Similar findings were also observed in post-infarct rats, who showed impressive reverse LV remodeling following administration of the phospholamban mutant. The importance of these findings has recently been corroborated by the discovery of phospholamban mutations in patients with familial dilated cardiomyopathy. The high attendance and the lively discussions following the presentations were testimony to the superb quality of the presentations.

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## ***Quality of Life Outcomes in Heart Disease: What Should be Assessed and How?***

Prof. Hannah McGee  
Dublin, Ireland



This symposium was the first opportunity at an ESC conference to address the topic of quality of life assessment. Since the mission statement of the ESC is to "improve the quality of life of the European population by reducing the impact of cardiovascular disease", it is particularly opportune that the topic feature on the scientific programme at this time.

### **Developing a "core" heart disease health-related quality of life questionnaire for Europe. (N. Oldridge, Indianapolis, US)**

The current pattern of quality of life instrument development in cardiology; i.e. with different specific questionnaires for different conditions was outlined. There are currently different measures for conditions such as angina, myocardial infarction and chronic heart failure. However, the need to measure quality of life is often to assess interventions (such as revascularization, pharmacological therapy or rehabilitation) which are used across these populations. Little can be made of the relative advantage of varying protocols if quality of life benefits or costs are expressed in different 'languages', i.e. using different questionnaires. This paper described the development of an ambitious project to develop a core heart disease quality of life questionnaire. It is being developed by members of the Working Group on Cardiac Rehabilitation & Exercise Physiology of the ESC and the European Health Psychology Society with Professor Oldridge, Professor Hugo Saner (CH) and Professor Hannah McGee (IE). Three existing scales which have good psychometric properties and have already been translated into a number of languages will be examined (the Seattle Angina Questionnaire, the MacNew Questionnaire and the Minnesota Living with Heart Failure Questionnaire). Other validated instruments will be included in the protocol to provide evidence on concurrent validity: the SF-36, the Hospital Anxiety and Depression Scale, the Global Mood Scale and the Type D Personality Scale. Development in each language requires a minimum of 315 participants. Thirty-one centres across 11 languages in Europe have been recruited to the study (Dutch, English, Flemish, Finnish, French, German, Italian, Norwegian, Portuguese, Spanish, and Swedish). At present about 30% of approximately 4,000 participants have been recruited. It is expected that the final core questionnaire will be available in late 2005. Discussion focused on the value of this single instrument for research and clinical practice across the boundaries of European countries and languages. Other specialties, in particular cancer and rheumatology have much more developed systems for cross-national and cross-language assessment of quality of life than does cardiovascular medicine. In cancer, in addition, there is the concept of a core short questionnaire for all cancer patients and specific add-on modules for specific cancers such as esophageal or prostate cancer. Having these instruments has permitted widespread inclusion of the concept in international clinical trials. It is hoped that this project will enable similar international cooperation in cardiovascular disease.

### **Quality of life in patients with atrial fibrillation after pharmacological or non-pharmacological interventions. (S. Stewart, Adelaide, AU)**

This paper highlighted the increasing burden of atrial fibrillation on the healthcare system. There is both an increasing incidence and an increasing rate of hospitalization per incidence of the condition. As prevalence rises rapidly with increasing age, the 'greying' of most populations means that the problem will continue to escalate. Many of the pharmacological management strategies, e.g. digoxin, exert significant negative effects on the quality of life of those taking them. Similarly non-pharmacological techniques, e.g. the MAZE technique were overviewed. The (relatively small number of) studies which have assessed quality of life in these populations were described. Many different instruments have been used which precludes a comprehensive assessment of the relative quality of life impact of the various techniques as yet. A vision for the future would be a situation where differing techniques (pharmacological or non-pharmacological) with relatively similar clinical profiles could be presented to patients in terms of the quality of life impact of each. Thus the patient's preference for treatment could be combined with the clinician's expertise in terms of selecting the best management strategy. In many current clinical situations, the clinician is trying to make this choice: "What would be best for this particular patient?". Quality of life assessment which could enable development of descriptions of the typical impact of an intervention on a population would improve the quality of information available both to the clinician and patient when making treatment preference decisions.

### **Quality of life changes following exercise training in patients with heart failure. (A. Cider, Gothenburg, SE)**

Exercise training is now widely advised for patients with heart failure. Numerous studies have demonstrated the physiological benefits of exercise training for these patients. However, if exercise training is to have a chance to be maintained in the community, it will be greatly assisted when patients can perceive a quality of life benefit for this exercise. This paper conducted an extensive literature review of quality of life assessment in randomised clinical trials of exercise for heart failure patients. Thirteen studies met the search criteria: 4 used generic measures (e.g. SF-36 or NHP), 4 used disease-specific measures (e.g. MLHFQ) and 5 used a miscellaneous set of other instruments. No studies showed poorer quality of life for those randomized to intervention. However, a number did not show benefit. Larger studies (N>50) were more likely to show benefits. It was concluded that there is some evidence of quality of life benefits of exercise for heart failure but that larger studies need to assess the level of such benefit and to examine sub-groups who benefit more or less from such interventions.

## ***Controversies in Chronic Heart Failure Therapy***

Dr. Massimo Piepoli  
Piacenza, Italy



The issues faced in this afternoon's "Controversies Session" were related to burning issues in heart failure therapy, i.e. a possible role for the concomitant use of more than just 2 autonomic-modulators (such as ACE-II, and BB with or without ARB), and whether there is still room for the cytokine antagonist after the initial discouraging evidence from earlier trials. This was reflected by the large participation of attendees: and at the end we left the large hall with few clear points but still large obscure hollows (but probably satisfied by the level of the discussions raised).

### **Triple combination of angiotensin-converting enzyme inhibitors, angiotension blockade and beta-blocker can be beneficial in chronic heart failure.**

**PRO: J. Cohn, Minneapolis, US**

**CONTRA: K. Dickstein, Stavanger, NO**

The first issue faced was the possible efficacy of the pharmacological combination of ACE-I, BB and ARB (important and open issue, also after the presentation of the CHARM result).

In this occasion, John Cohn played the role of the supporter of the benefit of this triple therapy, opposed by Ken Dickstein who was against. After extensive revision of the Val-HeFT data which showed a -13.2% reduction in the patient of the ARB arm, Cohn stressed the message that the combined therapy could be harmful and increase mortality came from a subgroup analysis. But, as also outlined in the discussion, we must be very careful in taking into account the messages coming from this kind of analysis.

At the same time based on subgroup analysis, the same speaker described that perhaps a particular type of heart failure patient may get benefit out of this combined therapy: ie. those on low dosage ACE-I, those with high plasma renin activity (>5.3 ng/ml/hr), and those on more unstable clinical condition.

But of course Ken had an easy job to counteract the evident weakness of this reasoning: those on sub-optimal ACE-I therapy should first optimise the dosage; thereafter in those patients with high renin activity level we should first identify the possible causes, such as for example hypovolemia, and stabilise those in unstable and progressive condition.

Finally, Cohn discussed the possible causes of the negative results showed in the Val-HeFT study, supporting the possibility that this was due simply to play of chance.

To address this last point, Dickstein performed a very critical revision of the patho-physiological importance of the neuro-humoral activation which plays a protective role in clinical emergency: its activation acutely compensates for reduced stroke volume, for example by increasing heart rate, stroke volume, or fluid retention. The combination therapy by inducing a full blockade of this response, particularly of the renin-angiotensive aldosterone system, can be harmful instead of protective, since it may play a vital role also in chronic state of heart failure. In fact also the MOXCON study showed that the simple and very effective suppression of the sympathetic activity by moxonidine could be dangerous.

The audience was left with the message that for the moment only the triple combination of BB, ACE-I and aldosterone inhibitor seemed to be the triple therapy which is of benefit in heart failure, while a further suppression of sympathetic tone, by the introduction of ARB could not induce any further effect. (But the investigators of the CHARM study may not agree!).

### **Tumour necrosis factor antagonism is still an option for treatment in chronic heart failure.**

**PRO: S. Anker, London, GB**

**CONTRA: H. Drexler, Hannover, DE**

The second controversy was really a contention among a young but enthusiastic research fellow (S. Anker his own definition) and the leading personality of Prof. H Drexler.

The background in favour of TNF inhibitors in CHF therapy was summarised by the young fellow: TNF is clearly increased at least in the more advanced CHF state, and it may be responsible for several ominous effects, such as cardiac dysfunction, Insulin resistance, endothelial dysfunction and catabolic metabolism. TNF is also a negative prognostic marker.

Thereafter, the flaws of the clinical trials performed which showed the negative effect of TNF inhibitors in heart failure patients, were stressed: too large dosages, inappropriate patient selection which, in the opinion of the speaker, seemed not to be severe enough to get any benefit from the cytokine activation. Instead a small substudy with lower dosage seemed to show beneficial results.

Also in this debate, the opposition rebated strongly point-by-point: firstly, there are several experimental data showing that cytokines and TNF in particular may play a protective role in acute inflammation, may confer resistance to injury. Secondly, several other factors are increased in CHF, but they may play a predictive role, and this does not imply that their blockade can be useful.

Furthermore the fact that the small substudy can indicate that a specific population may get any benefit out of a larger study, may lead to unwanted and questionable findings (such as identifying that some astrological influences may predict survival in AMI!).

More importantly, however was the last point raised in the debate, namely that CHF is a metabolic disorder and we must look for a metabolic drug able to block cytokines at this phase. But it was rebated that now we are already using drugs that are reducing cytokines concentration such as ACE-II, BB, and there are ongoing trials that will probably lead to the introduction of statins in the routine clinical practice also for CHF patients.

## ***Progression from hypertrophy to heart failure: new targets for therapeutic interventions***

Prof. Cees Van Echteld  
Utrecht, Netherlands



## **Cardiac failure: a complex evolutionary issue around four paradigms. (B. Swynghedauw, Paris, FR)**

The four paradigms that Dr. Swynghedauw addressed were:

1. Mechanoconversion: the cascade which leads to adaptation to stress is present in many species and involves common genes and intracellular signalling pathways. The cascade can be triggered by many factors and results in re-expression of a foetal gene program. The response can be modified by:
  2. Susceptibility factors such as senescence, diabetes and obesity. It was shown that in senescent failing myocardium increased NOS-1 expression compensates for decreased NOS-3 expression.
  3. Aetiology factors. For instance ischaemia per se can increase SERCA-2 expression, whereas in the hypertrophic heart SERCA-2 is down-regulated.
  4. Neurohormones and vaso peptides, which all have a reversible trophic effects.
- As targets for therapeutic interventions were mentioned the improvement of the economy of contractions, not contractility itself, and the attenuation of fibrosis.

## **The role of survival factors. (T.M. Suter, Bern, CH)**

Dr. Suter identifies three myocardial responses to stress: 1) An adaptive response leading to hypertrophy, 2) disorganisation of the sarcomere and 3) Apoptosis. The role of cytokines in these responses was emphasised and in particular the role of neuregulin (NRG). NRG is secreted from endothelial cells and the cardiomyocytes contain receptors for this cytokine. NRG induces hypertrophy and expression of a foetal gene program. NRG inhibits apoptosis via PI-3 kinase and the Akt signalling pathway. NRG affects the contractile proteins via the ERK  $\frac{1}{2}$  pathway. It was found that NRG attenuates doxorubicin induced myofibrillar damage through attenuation of doxorubicin induced increase of intracellular calcium. Increased calcium activates proteases in particular calpain, which is responsible for proteolysis of titin and desmin, leading to disorganisation of the sarcomere.

Obviously, increased secretion of neuregulin is an interesting new target for therapeutic intervention.

## **The role of inflammation. (K. Wollert, Hannover, DE)**

Dr. Wollert also addressed cytokine activation, which can be caused by neurohormonal dysregulation, left ventricular dysfunction, visceral oedema and hypoperfusion or ischaemia. The pro-inflammatory cytokines TNF $\alpha$  and IL-6 are increased in patients with depressed left ventricular ejection fraction. IL-6 promotes hypertrophy and has anti-apoptotic effects. All members of the IL-6 family interact through the gp130 receptor and decreased gp130 density is a critical event in the onset of heart failure during bio-mechanical stress. Special attention was focussed on the IL-6 member STAT-3 through a STAT-3 knock-out mouse. Infarct size in these mouse hearts was increased, but not the area at risk. Apoptosis was also increased but these hearts showed less hypertrophy after myocardial infarction. These KO mice develop dilated cardiomyopathy with increased fibrosis and decreased capillary density. In heart failure patients the fraction of phosphorylated gp130 is increased, whereas total and phosphorylated STAT-3 is decreased. Apparently, gp130 and STAT-3 are important protective factors and new targets for therapeutic intervention.

## **The role of energy metabolism. (H. Rupp, Marburg, DE)**

In hypertrophied hearts SERCA-2 is down-regulated and restoring the original SERCA-2 level may help to prevent RAAS activation. To up-regulate SERCA-2 etomoxir is proposed. Etomoxir is a CPT-1 inhibitor. CPT-1 transports fatty acids into mitochondria. Etomoxir therefore reduces fatty acid oxidation and increases glucose oxidation but interestingly is also an activator of the nuclear transcription factor PPAR $\alpha$ . How etomoxir increases SERCA-2 is not clear, but glucose metabolites may be involved. It was shown that after induction of cardiac hypertrophy, etomoxir prevented further hypertrophy and progression into dilatation. And in pressure overloaded hearts deactivation of PPAR $\alpha$  has been observed. Despite the fact that in hypertrophied hearts fatty acid oxidation is already decreased and glucose oxidation increased. Dr. Rupp is convinced that etomoxir is a promising new drug for the treatment of heart failure.

## ***New Concepts in Atherogenesis***

Prof. John Martin  
London, United Kingdom

This was a most interesting symposium in which the problem of atherosclerosis was analysed mostly from a basic science point of view, but also the clinical implications of the basic results were discussed.

### **Inflammation as a risk factor for atherosclerosis. (W. Koenig, Ulm, DE)**

### **Cytokines in Atherogenesis. (A. Tedgui, Paris, FR)\**

### **Hypomethylation of genomic DNA in atherosclerotic lesions. (S. Ylä-Herttuala, Kuopio, FI)**

### **New nuclear hormone receptors for mediating lipid action in atherosclerosis. (J.K. Liao, Cambridge, US)**

Prof. Koenig gave an in depth review of the role of inflammation in atherogenesis. He was balanced and critical, concluding that there was massive evidence that inflammation was involved, but cautioning that evidence for a causal relationship was still lacking. Prof. Tedgui described a convincing role of cytokines in atherogenesis in an elegant exposé of his own results.

Prof. Ylä-Herttuala presented new data on hypomethylation of genomic DNA. Dr. Liao discussed the role of nuclear receptors and particularly the effect of high dose dexamethasone on atherosclerosis in animals.

The presentations were convincing. However, even though each speaker presented convincing hypotheses supported by data, there was little overlap between them.

Stimulating discussion concerned the problem of whether the initiation and progression atherosclerosis was driven by the same cellular and molecular mechanisms that caused the final events of the acute coronary syndromes. There is clearly a need for more conceptual clarify in this area. A separate discussion explored the problem of whether there was one molecular or cellular cause of atherosclerosis, even though there may be many paths leading to that mechanism or whether there was more than one path that lead independently to atherosclerosis. In particular, there was discussion on whether smooth muscle cell intimal hyperplasia was a necessary condition for human atherosclerosis to occur, or not.

## ***Non-lipid Lowering Effect of Statins: Hypotheses and Facts***

Dr. Michael Marber  
London, United Kingdom



### **Statins: It's Not All in the Cholesterol!**

Is it just LDL cholesterol lowering that is important? I'm sure we are familiar with the arguments of agent specific effects that may be independent of cholesterol. This clinical seminar addressed four such possible effects. The authors used a wide range of statins in their presentations suggesting a class effect. I have therefore purposefully omitted the generic names of agents in this report.

### **Inhibition of matrix metalloproteinases by statins. (A. Chase, Bristol, UK)**

Dr Alex Chase (Bristol, UK) reminded us that statins are not that effective at reducing the anatomical severity of a stenosis but yet are very effective at reducing cardiovascular events. In addition they seem able to reduce systemic markers of inflammation such as CRP, perhaps independent of cholesterol lowering. This was perhaps best illustrated in the ApoE-deficient (knockout) mouse. In this model statins have no effect on cholesterol but do reduce plaque rupture and sudden death. This must mean that they "stabilize" atherosclerotic plaques in some way. Plaque instability is associated with a high content of macrophages and a thin fibrous cap. All these facts maybe related to the production by macrophages of proteolytic enzymes that breakdown the extracellular matrix, eroding the fibrous cap and thus destabilising the plaque. These enzymes are known as the Matrix Metalloproteinases (MMPs) and are classified according to their substrates, gelatin (gelatinases), collagen (collagenases) and stromelysin. The central hypothesis addressed by Dr Chase was that Statins reduce the expression by macrophages of some, or all, of these enzymes without affecting their relative abundance compared to their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs).

The in vitro experiments described by Dr Chase used lipid laden macrophages (foam cells) from cholesterol fed rabbits and human vascular smooth muscles cells (VSMCs) harvested from surplus saphenous vein. These cells were cultured in the presence and absence of a range of statins. In a concentration dependent manner a range of statins inhibited MMP protein content and activity without affecting the TIMPs. The mechanism of this effect was dependent on one of the consequences of HMG-CoA reductase inhibition, mevalonate starvation. This molecule lies immediately downstream of HMG-CoA and as well as the cholesterol biosynthesis pathway it is also involved as a precursor of geranylgeranyl pyrophosphate (GGP), a molecule involved in the post-translational activating modification, by geranylgeranylation, of the small G-proteins Rho and Rac. The effect of Statins on MMP expression could be rescued by the addition of exogenous mevolanate or GGP strongly implicating this synthetic pathway independent of cholesterol biosynthesis. Since statins did not alter MMP mRNAs it seems likely the Rho/Rac effect is mediated by a post-translational mechanism. These findings were reinforced by the review of clinical studies of atherectomy tissue that demonstrated MMP activity was reduced in those patients taking statins. In the questioning Dr Chase was asked if MMP inhibition could have a downside?. The response was that these same enzymes are also involved in migration of VSMCs to stabilize plaques and allow vessel growth (positive remodeling), however clinically there didn't seem to be a downside.

### **Role of statins in anti-oxidation. (A. Catapano, Milan, IT)**

The next presentation was given by Dr Alberico Catapino, Milan Italy and addressed the antioxidant effects of statins. He pointed out that oxidised LDL (oxLDL) in foam cells in the subendothelial region of plaques was something best avoided! Accumulation in this region was associated with the expression of adhesion molecules on the overlying endothelium that allowed leukocyte margination. In addition, circulating oxLDL was associated with clinical endothelial dysfunction as measured in forearm blood flow studies. This dysfunction could be reversed by the administration of vitamin C. However Dr Catapino questioned the clinical relevance of this observation since the largest of the randomized clinical trials of oral antioxidant vitamins have failed to show a reduction in acute vascular events, whilst the same trials (eg the Heart Protection study) or other studies of similar design, have almost universally shown that statins reduce coronary events. Dr Catapino then went on to show how statins could reduce oxidative stress. These mechanism included a reduction in LDL-cholesterol and thus ox-LDL, the upregulation of endothelial-type nitric oxide synthase, the downregulation of endothelial Angiotensin type 1 receptors and a down regulation of Lectin-like oxidized LDL receptor-1 (LOX-1), a major receptor for oxidized LDL on endothelial cells. Such effects could explain the documented reduction in circulating markers of oxidative stress that follows statin treatment in patients. However in Dr Catapano's view these effects are most probably related to cholesterol lowering since the molecular structures of the commonly used Statins do not suggest they have endogenous anti-oxidant activity. In addition, he pointed out that in the major statin trials there is the same linear relationship between LDL cholesterol and subsequent events whether patients are allocated placebo or statin. This last observation suggests that there are not "additional" mechanisms through which statins reduce events other than the reduction in LDL cholesterol.

### **Statins and platelet function. (V. Serebruany, Baltimore, US)**

The next presentation was given by Dr Victor Serebruany (Baltimore, USA). Dr Serebruany presented a clinical study designed to address a report that atorvastatin interferes with the anti-platelet action of clopidogrel. This report suggested that atorvastatin inhibited cytochrome P450 (CYP) 3A4 which was involved in the activation of clopidogrel (Circulation.

2003;7;107:32-7). Dr Serebruany addressed this report by an extremely thorough similarly designed study involving patients undergoing PCI and stent implantation. A relatively small number of patients were selected to match three criteria, clopidogrel and no statin, clopidogrel and any statin and clopidogrel and atorvastatin. Before, 4 and 24 hours after, receiving their pre-PCI clopidogrel platelet function was examined in incredible detail. As well as an array of function tests, including ADP aggregation, Dr Serebruany examined the surface expression of at least 15 functionally important platelet proteins. The overwhelmingly resounding finding was that the anti-platelet effects of clopidogrel were not inhibited by background atorvastatin, or other statin. However background statin therapy did seem to inhibit platelet function in particular the expression of SPAN-1, PAR-1 and PAR-4. The functional consequences of this were not presented in detail. However Dr Serebruany emphasized that his principle finding, atorvastatin did not inhibit the anti-platelet action of clopidogrel, was also borne out by the post-hoc analysis of the CREDO trial.

## **The effect of statins on angiogenesis. (S. Dimmeler, Frankfurt, DE)**

Dr Stefanie Dimmeler (Frankfurt, Germany), provided a beautifully illustrated presentation addressing the pro-angiogenic effect of statins. She started off by pointing out that not all is that beneficial since at least three independent groups have shown that although low concentrations of statins promote angiogenesis, high concentrations paradoxically inhibit angiogenesis. Dr Dimmeler then went on to present some of the ground-breaking work from her own group that has examined the effect of statins on the circulating endothelial progenitors thought to be important in angiogenesis, reendothelialisation and perhaps healing after MI. Dr Dimmeler showed very convincing data that cultured adult peripheral endothelial progenitors were much "healthier" if a statin was included in the medium. The inclusion of a statin, in a concentration and time-dependent manner, increased the yield of surviving endothelial cells. In addition they prevented senescence of these cells and thereby their ability to form colonies of proliferating endothelial cells. Using transcriptional profiling Dr Dimmeler suggested that these effects maybe through the downregulation of p27, upregulation of cyclins and the telomere-associated protein, TRF-2. Dr Dimmeler also summarized some of the other seminal work from her group that shows statins also have protective effects in these cells that are related to the activation of the protective kinase, Akt. The activation of this kinase protects these cells from oxidative stress and upregulates nitric oxide synthase activity. In addition these in-vitro effects of statins can be recapitulated in-vivo in both mouse and man. For example Dr Dimmeler presented data showing that peripheral circulating endothelial cell numbers, as measured by surface co-expression of CD133, CD34 and KDR, increased 4-fold after patients had received 28days of statin therapy.

In the questioning Dr Dimmeler was asked whether the proliferative effect of statins on endothelial progenitor cells meant these cells were kept in an undifferentiated proliferative state that prevented their transdifferentiation into cardiac myocytes? Dr Dimmeler stated that the contrary was in fact the case and her group had found that statins augmented such transdifferentiation.

## **Statins and tissue factor expression. (F. Cosentino, Rome, IT)**

The final presentation was by Dr Francesco Cosentino (Rome, Italy) and addressed the transmembrane pro-thrombotic protein, tissue factor. This protein, at the top of the amplificatory clotting cascade, collaborates with Factor VIIa in the activation of Factor IXa. It is also expressed at high levels in atherosclerotic plaques in endothelial cells, VSMCs and macrophages. Expression is further increased in culprit plaques in patients with acute coronary syndromes. Whilst in a porcine model inhibition of tissue factor, with recombinant tissue factor plasminogen inhibitor, prevented thrombus formation in balloon-injured arteries. Using a fat fed rabbit model of atherosclerosis Dr Cosentino showed that lipid lowering with statins reduced tissue factor content of atherosclerotic plaques and that this could occur independent of cholesterol lowering. The mechanism underlying this effect was examined in human aortic endothelial cells in culture where tissue factor expression was induced by thrombin. This induction was blocked by statins and rescued by mevalonate (see presentation by Dr Chase). Moreover the effect of statins on the inhibition of thrombin-induced tissue factor expression could also be inhibited at both the mRNA and protein level by the Rho kinase inhibitor Y27632, reinforcing the importance of activation of this kinase by GGP (see presentation by Dr Chase). In addition statin-induced activation of Akt was also implicated in the prevention of tissue factor expression, since inhibition of this kinase with the pharmacological inhibitor Wortmannin increased tissue factor expression. In addition there seemed to be cross-talk between the Rho and Akt kinase pathways.

The whole session was extremely well-attended. However, I suspect that many in the audience had thoughts similar to my own. It is usual to perform detailed pathological studies of drugs before the clinical trial evidence supporting their usage is proven. Although the investigators presented compelling data to show effects of statins independent of LDL-lowering, my view is that these are an "added bonus"; a freebie that complements the clinical data that compels the use of these drugs.

## ***The Adventitia: An Unrecognised Arterial Layer in Atherogenesis***

Prof. Gerard Pasterkamp  
Utrecht, Netherlands



Research on neointima formation and atherosclerotic disease focuses on cells and molecules within the intimal and medial layers. The adventitial layer is often neglected since it is located further from the luminal area. This session revealed that the adventitial layer is home to cells that are extremely potent in antigen recognition and capable of eliciting an inflammatory response.

## **The dendritic cell: the role of this antigen presenting cell in atherosclerotic disease (Y. Bobryshev, Sydney, AU)**

The dendritic cell is an antigen presenting cell that migrates to regional lymph nodes and activates T lymphocytes when antigens are encountered. The dendritic cell is present in the adventitial layer in normal arteries and in the intima in atherosclerotic arteries. Dr Bobryshev (Sydney) showed that dendritic cells are highly prevalent in rupture prone regions within the plaque. He also suggested that vascular dendritic cells that recognize antigens are part of a vascular type of "lymph node": the vascular associated lymphoid tissue (VALT). Dr Bobryshev also postulated an innovative idea how these cells could be used to sensitize the human immune system against antigen attacks by which atherosclerotic plaque destabilization could be prevented.

## **The adventitial fibroblast: an inflammatory cell. (D. De Kleijn, Utrecht, NL)**

The fibroblast is another interesting cell. Dr de Kleijn (Utrecht) demonstrated that the fibroblast is an immunologically active cell capable of producing all types of cytokines and chemokines. The fibroblast uses toll like receptors (TLRs) to recognize exogenous and endogenous ligands. When the TLRs are activated, then intima formation is enhanced and plaque formation increases. The latter has been demonstrated in wild type and TLR deficient mice. More surprisingly, Dr de Kleijn showed that the TLR4 receptor is very important in expansive arterial remodeling upon plaque formation or flow increase.

## **Remodelling of vaso vasorum in atherosclerotic disease. (A. Lerman, Rochester, US)**

Dr Lerman (Rochester) showed that the arterial supply of the artery (vaso vasorum) is strongly altered when plaque formation occurs. With micro CT he nicely showed the effect of high cholesterol diet on vaso vasorum development in pig arteries. The vaso vasorum development rapidly enhanced when the cholesterol levels increased. Dr Lerman raised an interesting hypothesis: the endothelium of the vaso vasorum is disturbed in hypercholesterolemic conditions. This induces constriction of the vaso vasorum with subsequent lack of oxygen supply. Subsequently VEGF expression will increase with rapid vaso vasorum vessel formation as a consequence.

## **Adventitial manipulation and intimal thickening. (A. Kivela, Kuopio, FI)**

Dr Kivela (Kuopio) nicely summarized earlier reports that arterial injury elicits an inflammatory response. He developed a model in which the effect of adventitial injury could be investigated. When the adventitia is injured, more intima formation is observed. It remains difficult, however, to keep the shear stress constant when the adventitia is injured which could introduce an important confounder.

In conclusion: the adventitia is unrecognized in atherosclerotic research. This session clearly demonstrated that the adventitia is much more than a skeleton. The adventitia is a layer hiding highly immunologically

## ***New Perspectives on Sudden Death in High-Risk Populations***

Dr. Constandinos Vardakis  
Heraklion, Greece



New perspectives on sudden cardiac death (SCD) were discussed in this interesting symposium.

### **Sudden death in trials not focusing on arrhythmias. (S. Cobbe, Glasgow, GB)**

Prof. Stuart Cobbe addressed the incidence of SCD in trials not focusing on arrhythmias. In these trials, CAD and its complications are the principal cause of SCD in the community. Thrombolytic and anti-thrombotic agents, beta-blockers, ACE inhibitors and lipid lowering agents are effective in reducing its risk.

### **Sudden death in trials on biventricular pacing. (M. Schalij, Leiden, NL)**

Dr. M. Schalij focused on SCD in patients with a depressed LV uncton and biventricular pacemakers. Cardiac resynchronization, which improves cardiac function and structure, is not found to increase the incidence of SCD. However, a large number of such patients still die suddenly, thus ICD backup should be considered.

### **Sudden death and implantable cardioverter-defibrillator: update on ESC guidelines 2003. (A.J. Camm, London, GB)**

Prof. John Camm described that the guidelines process is exacting and dynamic and their regular review and update is an essential, ongoing procedure. According to the recent revision, ICD therapy is indicated for post MI patients with LVEF<30% (Class IIa), while for non-ischaemic dilated cardiomyopathy, the class is now changed to IIb. To strengthen these data, more trials for the same and adjacent indications are required, while detailed registries and audits of the use of devices are also recommended.

### **Cost efficacy of prophylactic interventions in high-risk patients. (L. Jordaens, Rotterdam, NL)**

Prof. L. Jordaens discussed the cost efficacy of prophylactic interventions in patients who survived serious arrhythmic events, especially despite conventional anti-arrhythmic therapy. ICDs significantly reduce mortality by approximately 40%, both as secondary and primary prevention. Despite the cost of ICD therapy, which was reported about \$7500, it is found to be cost-effective in high risk post MI patients and for secondary prevention.

## ***Endurance or Resistance Exercise Training in Patients with Heart Disease***

Prof. Helmut Drexler  
Hannover, Germany



### **Does it matter how you do exercise ?**

Despite regular jogging as an accepted means to prevent cardiovascular disease, other types of physical activities are very popular, i.e. to promote growth of muscle by fitness programs and weight lifting to become another Arnold Schwarzenegger. However, recent research suggests that the type of exercise might have implications for the cardiovascular adaptation. Dynamic exercise elicits shear stress at the level of the endothelium (the inner layer of arteries) raising the expression and activity of nitric oxide synthase, a key enzyme producing nitric oxide and mediating vascular dilation and protection. Isometric muscle contraction (i.e. weight lifting) without fall in systemic vascular resistance causes stretch of the vascular wall and induces radical formation which inactivates nitric oxide and exerts pro-atherogenic processes. **S Gielen (Leipzig, DE)** reviewed their results on underlying (basic) mechanisms for the beneficial effects of training clearly demonstrating that regular physical exercise is associated with beneficial vascular effects within weeks, even within the coronary circulation.

### **High intensity exercise is not required to get cardiovascular benefit**

**P Gianuzzi (Arona, IT)** pointed out and demonstrated convincingly that regular exercise activities are effective for prevention of cardiovascular disease, however, low levels of exercise intensity are sufficient and maximal exertion is not required to receive the benefits of such exercise activities. This clarification is highly welcome particularly for patients who suffered from a heart attack and are reluctant to test their limits of exercise capacity. It is more important to work out regularly (i.e. 4 times a week) than to work out once a week at the highest intensity levels.

### **Exercise training for heart failure or congenital heart disease**

Training programs for heart failure or in patients with congenital heart disease are still in their infancy because of fears of harming the patients. **JP Schmid (Berne, CH)** reviewed the different types of exercise training programs in patients with heart failure and showed that with some experience, training programs are both safe and effective in patients with heart failure, improving symptoms, morbidity and maybe even mortality. Exercise training programs can be extended to patients with adult congenital heart disease and even in children, as reported by **B Bjarnason-Wehrens (Cologne, DE)**. However, exercise programs in children need to include more playing and social components in order to sustain the compliance of these patients.

## ***Regulation of Coronary Microcirculation***

Prof. Mario Marzilli  
Siena, Italy

This symposium focused on the mechanisms regulating coronary blood flow, regional myocardial perfusion and the complex interactions between cardiac perfusion and function.

Coronary blood flow and myocardial perfusion need to be continuously adjusted to myocardial contractile performance and metabolic needs. Given the limited, if any, possible changes in oxygen extraction that is already near-maximal in basal conditions, adjustments result from a complex interplay of neural, metabolic and mechanical factors that modulate total coronary blood flow, and its distribution in the layers of the ventricular wall.

### **Neural regulation of myocardial perfusion. (O. Rimoldi, London, GB)**

The neural control of myocardial perfusion was discussed by Dr. Ornella Rimoldi. Starting from the pioneering work of Eric Feigl, which demonstrated the contribution of the sympathetic system to the regulation of coronary blood flow, Dr. Rimoldi presented a detailed analysis of the effects of sympathetic and parasympathetic receptors stimulation and/or blockade on coronary microcirculation. Dr. Rimoldi stressed the different responses to alpha and beta agonists and antagonists of different segments of the coronary vascular tree, explained how these responses depend upon the experimental conditions and emphasized the regional heterogeneity in neural effectors.

### **Endothelial and myogenic regulation of myocardial perfusion. (D.J. Duncker, Rotterdam, NL)**

Dr. Duncker, from Rotterdam, reported on his work on the endothelial and myogenic regulation of myocardial perfusion. Starting from a description of the resistance gradients along the coronary vascular tree, he presented a detailed analysis of species differences in the mechanisms regulating coronary microcirculation. He focused mainly on the canine and swine models, demonstrating striking differences in the response to pharmacologic interventions, including adrenergic and adenosine receptor stimulation-blockade, the human coronary microcirculation being closer to the swine model.

### **Capillary distribution of coronary blood flow. (H. Habazettl, Berlin, DE)**

Dr. Habazettl focused on the capillary segment of the coronary vascular network. He started with an analysis of the interplay between vessel diameter and blood viscosity and proceeded to a description of the myogenic reactions of coronary arterioles in situ demonstrating that myogenic responses are relevant even in the smallest arterioles. Metabolic stimuli, wall shear stress and transmural pressure gradients all contribute to capillary flow and may stimulate angiogenic adaptation. A mathematical model that includes shear stress, luminal pressure and circumferential stress can predict regional variations of metabolism and flow and heterogeneity of myocardial perfusion.

### **Effects of contraction, relaxation and ventricular volume on myocardial perfusion. (J. Schipke, Düsseldorf, DE)**

The effects of contraction, relaxation and ventricular volume on myocardial perfusion were discussed by Dr. Schipke. His lecture focused on the effects of cardiac pump function on coronary blood flow, translating the cyclic changes in intramural pressures associated with cardiac muscle contraction and relaxation in temporal and spatial flow heterogeneity. The systolic and diastolic distribution of coronary blood flow in the epicardial and endocardial layers of the left ventricle was analyzed in depth as well as the effects of ventricular volume changes.

Altogether, the four speakers gave a comprehensive picture of the complex mechanisms regulating myocardial perfusion at the microcirculatory level, stressing the close functional connections among the segments of the coronary vascular tree, and simultaneously emphasizing the regional gradients in metabolic, mechanical, and neural responses.

## ***Genetic Factors in Heart Failure***

Dr. Gilles De Keulenaer  
Antwerp, Belgium



### **How to identify candidate genes? (H. Schunkert, Lübeck, DE) Modifier genes – genes of susceptibility. (P. Charron, Paris, FR)**

Heart failure is a multifactorial and complex disease involving the responses of many, if not all, regulatory functions in the human body. Identifying genes that alter the course of this disease is therefore an extremely challenging task, especially since the role of these genes may vary in different environmental circumstances.

Strategies to approach this task can be based on the fact that the role of genes may manifest as a hereditary preservation of certain heart failure phenotypes, as pointed out by Dr. Schunkert. Chromosomal linkage analysis in families with a strong incidence of a certain type of heart failure, for example, is a powerful approach, but such families are hard to find and may direct the research to rare causes of heart failure. Other approaches like allele frequencies of single nucleotide polymorphisms of genes with known function may be helpful, and many of these studies are currently being performed. Pitfalls of these studies (for example the small study groups) may, however, give conflicting results as pointed out by Dr. Charron.

### **Animal models: potential and limitations. (M. Daemen, Maastricht, NL)**

Animal models may definitely help to study the problem, but as explained by Dr. Daemen, animal models of human disease may mimic human disease but still be profoundly different. For example, when studying ischemic heart disease, mouse models of atherosclerosis are available, but the question remains whether plaque rupture in a mouse artery is comparable with human plaque rupture. Studying local gene expression in a "ruptured mouse plaque", therefore, may only reflect part of what happens in a human plaque. Furthermore, these studies only concentrate on gene expression in a local environment, which is still much simpler than to study the effect of a gene on the whole organism, like certainly is the case in a complex disease like heart failure.

### **From gene to structure to function. (R. Knöll, La Jolla, US)**

Dr. Knoll finally illustrated how extensive the work can be once a gene is identified. By summarizing the work on LIM protein, a Z disc protein in mechanical stretch sensing, he illustrated how to proceed from gene to structure to function of a gene. This extremely laborious work, however, that involves studying protein-protein interactions and creating genetically altered mice, can lead to critical pathophysiological insights. The LIM protein gene work, for example, unmasked mysteries of the cardiomyocyte stretch sensor machinery, and showed that defects of this machinery leads to cardiomyopathy.

## ***Angioadaptation: Keeping the vascular system in shape***

Dr. Lino Gonçalves  
Coimbra, Portugal



Four contributions were presented in this session, promoted by the WG of Microcirculation, with the Chairpersons C. de Wit from Munich, Germany and M.M. Cicconi from Bari, Italy.

### **Adaptation to a new environment: hypertension and its treatment (E. Rosei, Brescia, IT)**

Professor Enrico Rosei, from Brescia, Italy, started his talk by saying that small arteries (< 350µm) suffer a remodelling process in response to arterial pressure increase. These changes can be evaluated by myographic techniques. The myographic techniques can be performed both in animals and in human sub-cellular tissue samples obtained by biopsy. By using these techniques he was able to show in humans that the reduction of these structural changes (at the level of the microcirculation) was possible with the use of some drugs, such as perindopril, cilazapril, lisinopril, nifedipine, isradipine, losartan and ibesartan, but not with other drugs such as atenolol and hidrochlorothiazide. Quite interestingly, the observed positive impact on vascular remodelling was observed despite similar hemodynamic effects.

He concluded that the structural changes in the resistance of small arteries are important predictors of a worse prognosis, and therefore can be used as an endpoint to evaluate the efficacy of the anti-hypertensive treatment.

### **Genetic mechanisms of adaptation. (H. Drexler, Hannover, DE)**

Dr. H. Drexler, from Hannover, Germany, introduced his talk by showing data that support the important role of angiogenesis in health and disease. He then turned his attention to the role of Cyr61 in several conditions. He showed data that support the contribution of vascular growth during development, postnatal development and following stress (such as pressure overload or ischemia). This vascular growth involves the activation of several different genes. He also stated that despite the importance of growth factors such as VEGFs, FGFs, PLGFs, other recently reported and studied factors such as Cyr61 seem to be involved in the angiogenic process. Transcriptional factors involved in anti-angiogenesis phenomenon may also be of vital importance to angiogenesis.

### **Change in number or size: angiogenesis versus arteriogenesis. (E. Deindl, Bad Neuheim, DE)**

Dr. Elisabeth Deindl, from Bad Nauheim, Germany, presented data that support the fact that arteriogenesis is the only physiologically relevant mechanism to compensate for the vessel occlusion. According to her data, arteriogenesis is not driven by ischemia itself, but by the shear stress associated with arterial occlusion. She concluded that monocytes' activation and migration is of utmost importance for arteriogenesis development.

### **Can we use it? Therapeutic options. (G. Ambrosio, Perugia, IT)**

Prof. G. Ambrosio, from Perugia, Italy, tried to answer several questions during his presentation:

Is angiogenesis feasible? According to several studies the answer is yes. Both protein-mediated, gene therapy-mediated, and endothelial progenitor cells-mediated angiogenesis was already reported in the literature and was associated with a reduction of myocardial ischemia and an improvement on myocardial function

Does it work? Fostering the angiogenic process has been possible in animals. However, in humans, several clinical trials came up with conflicting or marginal results. There are also some potential side effects that one should keep in mind when these forms of therapy are given to humans.

Will it have impact on clinical practice? It is still too soon to know whether angiogenesis will rise up to assume his place in the therapeutic armamentarium of cardiologists or other doctors that treat vascular diseases.

## ***Marfan Syndrome: Medical, Interventional and Surgical Treatment - Second point of view on Marfan Syndrome***

Dr. Francisco Calvo-Iglesias  
Vigo, Spain



The symposium was designed to discuss basic science and clinical issues with a special focus on molecular biology knowledge on treatments with stents versus surgery in Marfan patients.

### **New developments in genetics. (P.A. Handford, Oxford, GB)**

More than 500 mutations have been identified in various Marfan phenotypes. Mutations may cause structural or functional changes of the fibrillin, of these the latter has been less studied. The importance of calcium-binding sites was discussed; the presence of 43 sites and a high variability in calcium-affinity may explain the impact of structural changes.

Recent studies of patients with mild or serious presentations of Marfan Syndrome suggest that genetic classification might be used to identify patients with a high risk of complications. However, there are no data yet to prove if this will help in the clinical handling of the patients.

### **Clinical management and follow-up. (G. Jondeau, Boulogne-Billancourt, FR)**

The survival of Marfan patients has been significantly improved during the last years. It is important to establish the diagnosis early in order to implement lifestyle changes (sports, exercise), medical therapy (betablockers) or regular follow-up programs needed to identify patients in whom surgery should be undertaken. A survey revealed that on average 5.2 years pass from the first symptom until the patient was examined clinically and that the diagnosis would not be made before 2.8 further years had passed. More than 30% would have their condition recognized after 10 years. The importance of offering surgical treatment in a stable phase of the disease was demonstrated by serious outcomes in patients operated with an active dissection. In order to define patients needing surgery, follow-up programs with measurements of the aortic sinus valsalva are mandatory.

### **Stents in the Marfan aorta. (C.A. Nienaber, Rostock, DE)**

Aortic stents have been introduced in the management of Marfan patients with dissection, but the experience is limited. Of 6 cases treated with stents for palliative reasons, most had to be operated. There was a great caution given that the stents used presently have shortcomings in this special group of patients and that stents are the alternative only in very few patients.

### **Surgical management and follow-up. (M. Karck, Hannover, DE)**

The impact of surgical treatment was discussed. Four different surgical programs were presented: supracoronary replacement is not an alternative anymore, conduit implantation has been the "gold-standard", while the two newest approaches, Yacoub procedure or David reimplantation are more in focus. There was a special emphasis on valve-sparing procedures which is advantageous in young women since Coumadin treatment is not necessary. These procedures were regarded "un-effective" in 1996, but is now recognized to be a suitable alternative. However, the number of patients in treated is still very limited.

### **Conclusion**

The symposium revealed that molecular studies in the future may identify patients with a serious course, but the active and regular follow-up programs are still vital to identify patients with dilating aortic roots in whom surgical treatments may be indicated. Stenting of the aorta is to be done in only a minority of these patients.

## ***Marfan Syndrome: Medical, Interventional and Surgical Treatment***

Prof. Erik Thaulow  
Oslo, Norway



The symposium was designed to discuss basic science and clinical issues with a special focus on molecular biology knowledge on treatments with stents versus surgery in Marfan patients.

### **New developments in genetics. (P.A. Handford, Oxford, GB)**

More than 500 mutations have been identified in various Marfan phenotypes. Mutations may cause structural or functional changes of the fibrillin, of these the latter has been less studied. The importance of calcium-binding sites was discussed; the presence of 43 sites and a high variability in calcium-affinity may explain the impact of structural changes.

Recent studies of patients with mild or serious presentations of Marfan Syndrome suggest that genetic classification might be used to identify patients with a high risk of complications. However, there are no data yet to prove if this will help in the clinical handling of the patients.

### **Clinical management and follow-up. (G. Jondeau, Boulogne-Billancourt, FR)**

The survival of Marfan patients has been significantly improved during the last years. It is important to establish the diagnosis early in order to implement lifestyle changes (sports, exercise), medical therapy (betablockers) or regular follow-up programs needed to identify patients in whom surgery should be undertaken. A survey revealed that on average 5.2 years pass from the first symptom until the patient was examined clinically and that the diagnosis would not be made before 2.8 further years had passed. More than 30% would have their condition recognized after 10 years. The importance of offering surgical treatment in a stable phase of the disease was demonstrated by serious outcomes in patients operated with an active dissection. In order to define patients needing surgery, follow-up programs with measurements of the aortic sinus valsalva are mandatory.

### **Stents in the Marfan aorta. (C.A. Nienaber, Rostock, DE)**

Aortic stents have been introduced in the management of Marfan patients with dissection, but the experience is limited. Of 6 cases treated with stents for palliative reasons, most had to be operated. There was a great caution given that the stents used presently have shortcomings in this special group of patients and that stents are the alternative only in very few patients.

### **Surgical management and follow-up. (M. Karck, Hannover, DE)**

The impact of surgical treatment was discussed. Four different surgical programs were presented: supracoronary replacement is not an alternative anymore, conduit implantation has been the "gold-standard", while the two newest approaches, Yacoub procedure or David reimplantation are more in focus. There was a special emphasis on valve-sparing procedures which is advantageous in young women since Coumadin treatment is not necessary. These procedures were regarded "un-effective" in 1996, but is now recognized to be a suitable alternative. However, the number of patients in treated is still very limited.

### **Conclusion**

The symposium revealed that molecular studies in the future may identify patients with a serious course, but the active and regular follow-up programs are still vital to identify patients with dilating aortic roots in whom surgical treatments may be indicated. Stenting of the aorta is to be done in only a minority of these patients.

## ***Stem cells: Can the scientific excitement be translated into new treatments?***

Prof. Thomas Eschenhagen  
 Erlangen, Germany



The symposium addressed current strategies to translate the recent advances in the understanding of stem cell biology and tissue engineering into treatment options.

### **Electrophysiological properties of human stem cell derived cardiomyocytes. (L. Gepstein, Haifa, IL)**

Embryonic stem cells (ES cells) obviously have the greatest differentiation potential and propagation capacity, on the other hand the very same advantages give rise to the as yet not fully explored risk of tumor formation. Dr. Gepstein summarized the experience of his group with cardiac myocytes differentiated from human ES cells. Human ES cell-derived cardiac myocytes exhibit nodal-, atrial- and ventricular myocyte-like action potentials (most often atrial-like), depolarize and beat spontaneously (~60/min), express a strong sodium current and interconnect by connexin-positive gap junctions. When co-cultured with neonatal rat cardiac myocytes human and rat cells couple electrically and mechanically and beat in synchrony. When embryoid bodies (the cell aggregates ES cardiac myocytes are derived from) are injected into the LV of pigs in which the AV had been ablated, ES cells formed contact with the host myocardium and created an "escape pacemaker" that partly took over the endogenous His bundle escape rhythm.

**Conclusion:** Human ES cells give rise to cardiac myocytes with an early differentiation pattern that electrically and mechanically couple to host myocytes. Current questions relate to the efficacy of cardiac myocytes differentiation, selection protocols to yield a pure myocyte population. The latter point is of eminent importance with regard to tumor formation. Other open questions are how to upscale ES cell propagation, how to circumvent rejection and finally whether ES cells will give rise to arrhythmia.

### **Differentiation of adult progenitor cells into cardiomyocytes. (C. Badorff, Frankfurt, DE)**

Endothelial progenitor cells (EPC) hold great promise as being autologous in nature and easily obtained from the patient's own peripheral blood. EPC are cells that adhere when blood is put in cell culture dishes and that are positive for Dil-ac-LDL, a marker of endothelial cells. Dr. Badorff showed that approximately 10% of these cells, when co-cultured with neonatal rat cardiac myocytes, start to express markers of cardiac myocytes, i.e. they are simultaneously positive for Dil-ac-LDL and cardiac markers. This observation can also be made in neonatal rat cardiac myocytes pretreated with paraformaldehyde prior to co-culture, indicating that cell fusion, which could as well explain co-staining, is not necessary for the observed phenomenon. Interestingly, the capacity of EPC to differentiate in cardiac myocytes was shown to be lower in patients with ischemic heart disease and could be rescued by treatment of patients with statins. Therapy with EPC infusions is already tested in clinical trials.

### **Myocardial tissue engineered from stem cells. (T. Eschenhagen, Erlange, DE)**

How to apply stem cell-derived cardiac myocytes for therapy? In principle, these cells can be directly injected in the diseased myocardium. Alternatively, cells can be engineered to an artificial myocardial tissue in vitro and implanted as a tissue patch. Dr. Eschenhagen presented the approach of his group which utilizes liquid collagen to reconstitute neonatal rat heart cells to an engineered heart tissue (EHT). The ring/shaped EHT beat spontaneously (~60 min), exhibit a well differentiated heart tissue morphology including other cell types and spontaneous capillary and vessel formation, and a heart muscle like contractile behavior. Several EHT rings can be assembled in vitro and form large patches (1-2 cm) that can be surgically attached to a rat heart. Experiments in an infarct model show that, under immunosuppression, EHTs survive at least for 8 weeks, are strongly vascularized, exhibit terminal cardiac myocyte differentiation and homogenous electrical coupling to the host myocardium. The major open question is the optimal cell source for potential clinical applications.

### **Arrhythmogenic risk of embryonal stem cells. (S.C. Dudley, Atlanta, US)**

Besides the allogenic character and the risk of tumor formation (see above) one potential limitation of the ES cells approach is arrhythmogenicity. Dr. Dudley presented a detailed analysis of ionic currents of ES cell-derived cardiac myocytes from mice. As in humans these cells come at different electrophysiological flavors – nodal-, atrial- and ventricular myocyte-like, but at different percentage (5%, 15%, 80%). The main result was that the ventricular-like, i.e. those one is looking for, exhibit an unusually long action potential (3-4-fold longer than adult mouse), a slow propagation velocity and classical interventions to induce prolongation of action potential duration (low K<sup>+</sup>, quinidine, TEA, Bay K 8644) induce early and catecholamines induce late afterdepolarizations.

**Conclusion:** ES cell-derived cardiac myocytes have an arrhythmogenic potential. Whether this is relevant in the in vivo situation remains to be tested.

### **Safety and feasibility of myoblast transplantation. (P. Menasché, Paris, FR)**

The most advanced strategy in the field of stem cells is injection of skeletal myoblasts into the heart. Skeletal myoblasts can be derived from satellite cells that are present in skeletal muscle (10 g muscle biopsy). Dr. Menasché who pioneered this approach in patients presented the recent state of the art in this field. From animal experiments and the experience in a total of 70 patients treated up to now, the following conclusions can be drawn. The approach is feasible in terms of cell propagation and cell engraftment (survival rate after 2 weeks 5%). Skeletal myoblasts integrate into the host myocardium and survive for long time, but do not differentiate into cardiac myocytes and do not electrically couple to them. Animal experiments consistently demonstrate functional improvement. The first data in patients demonstrate an arrhythmogenic potential. The phase 2 trial is therefore conducted with a simultaneous implantation of an ICD. This will also allow exact quantification of the proarrhythmic potential.

**Conclusion:** The skeletal myoblast injection is a feasible approach that entered the first controlled clinical trials. The proarrhythmic potential and the clinical efficiency will be crucial questions of this promising approach.

**In summary,** ES cell-based and tissue engineering approaches are still in their early days. The former for unresolved safety and efficacy issues, the latter for the problem of ideal cell source. The EPC and the skeletal myoblast strategy, in contrast, are already under clinical evaluation, but many questions with regard to efficacy, safety and mechanism of action appear open and await answers which will be provided by the ongoing controlled clinical trials and solid experimental research.

## ***The Effect of Exercise and Cardiac Rehabilitation on Arrhythmias***

Prof. Etienne Aliot  
Nancy, France



### **Chronic endurance exercise is pro-arrhythmogenic in athletes. (H. Heidbuchel, Leuven, BE)**

Dr. H. Heidbuchel reviewed the literature on the impact of chronic endurance exercise on arrhythmias. There is a higher incidence of atrial fibrillation in people who exercise regularly (more than 3 hours per week) compared to the general population, even if they present less underlying cardiac disease. He focused on the role of bradycardia and increased vagal tone and the possibility of dilatation, ventricular hypertrophy, microfibrosis.

The University of Leuven studied 256 cases of atrial flutter in patients with (52%) or without (48%) underlying heart disease. Atrial flutter patients had a relative risk of developing atrial fibrillation of 1.8.

As far as ventricular arrhythmias are concerned, it seems that they don't have "per se" a poor prognosis when patients do not have any underlying cardiac disease. On the other hand, a series of 46 patients with severe ventricular arrhythmias (non sustained ventricular tachycardia, sudden death and syncope) were followed for 4.7 years. Among these 46 patients, 59% had manifest right ventricular arrhythmogenic cardiomyopathy and 30% probable right cardiomyopathy (only 5% presented with hypertrophic cardiomyopathy or coronary abnormalities). During follow-up, 18 major events were observed. The only factors of risk stratification were the age of the patients (younger) and the results of the EP study (ventricular arrhythmia inducibility). This emphasizes the need for thorough assessment of such patients.

Endurance exercise may lead to functional and structural changes. Arrhythmias in athletes are rare, and an underlying heart disease is often identified.

### **Spectrum of sudden deaths in athletes (A. Biffi, Rome, IT)**

Dr. Biffi presented the experience of the Institute of Sport (Rome) since 1963. 32,000 athletes have been screened, of whom 855 were disqualified and only 7 presented with sudden cardiac arrest. Dr. Biffi emphasized the difference in the etiologies of sudden cardiac death between the USA and Italy. In sportsmen less than 35 years old, hypertrophic cardiomyopathy represents 36% of the cause of the sudden cardiac death in the US compared to 3% in Italy. Conversely, arrhythmogenic right ventricular cardiomyopathy was present in 23% of the cases in Italy, versus 3% in the USA.

Italy is one of the rare countries which perform cardiac screening in all athletes and disqualify them from competition in case of abnormalities. For example, in a series of athletes with ventricular arrhythmias, 71 presented with more than 2000 PVCs or more than 1 NSVT, and all were disqualified. During the follow-up, one died suddenly. The other 255 athletes of the series who presented with less than 2000 PVCs and no NSVT were followed and didn't present any arrhythmic events. It's interesting to note that firstly, 7 athletes in the first group presented with right ventricular abnormalities, versus 0 in the second group. Secondly, the disqualification was pronounced independently of the presence or not of an underlying cardiac disease.

### **Autonomic balance after exercise training in cardiac patients (S. Adamopoulos, Athens, GR)**

Exercise training has a positive influence on the neuro-hormonal situation experimentally and clinically. In cardiac heart failure, physical training decreases the level of tumor necrosis factor, improves skeletal muscle metabolism, the mitochondrial oxidative capacity and the baroreflex sensitivity. Physical training improves symptoms, ventilatory response and exercise tolerance. The impact of such training on the prognosis has yet to be defined.

### **Preventive measures and risk stratification. (J.L. Mont Girbau, Barcelona, ES)**

Dr. Mont Girbau showed the difficulty of preventive measures, mainly related to cost-effectiveness. He insisted on the importance of minimal screening for athletes including at least clinical examination and electrocardiogram. In this presentation, he also presented a series of 180 patients with or without lone or vagal atrial fibrillation. In this series, people who exercise regularly presented with more frequent vagal atrial fibrillation than the control group.

*The comments express the personal opinions of the authors, and do not necessarily reflect the official position of the European Society of Cardiology*

## ***Making Cells Make a Difference – Origins of Cellular Diversity in the Heart***

Dr. Paul J. Barton  
London, United Kingdom



This exciting Basic Science Session highlighted emerging concepts in early cardiac development with particular reference to cellular identity.

### **Development of electrical activity in the heart (A. Mooman, Amsterdam, NL).**

This presentation addressed the origin and specification of cardiac conduction tissue. Central to this process is a complex regional and temporal pattern of gene expression involving members of the Tbx family of transcription factors previously known for mutations in Tbx-5 which underlie Holt Oram syndrome, and of Nkx2.5. Tbx 2 and Tbx 3 in particular appear to be involved in the development of the myocyte cellular lineage leading to formation of the conduction system (sinus node, AV junction, AV node and proximal AV bundle branches). The data point to important regulatory mechanisms and may be of importance not only in our understanding of cardiac development but also of targets for potential cellular manipulation in the treatment of conduction system defects.

### **Regionalisation of the myocardium during cardiac development (D. Franco, Jaen, ES).**

The theme of regional specification was continued in this talk. The data focused both on global regional myocyte identity (specification of atrial and ventricular myocytes and of left and right sides) and on the specific expression of ion channel gene. The data highlighted both the chamber specificity of particular ion channels (e.g. KCNE1 and KNCE3 being restricted to ventricular and atrial myocytes) but also served as an important reminder of the transmural gradients of expression seen with these genes.

### **Role of connexins during cardiac development (D.Gros, FR).**

This presentation continued the theme of conduction system development by describing detailed information on the expression of connexin gene expression. Connexins demonstrate a complex pattern of developmental and region specific expression. Connexin 40 (Cx40) is expressed throughout the atrium the AV node but in the ventricle it is restricted to the conduction system. Transgenic heterozygous mice where described where the green fluorescent protein (GFP) gene had been "knocked in" at the Cx 40 gene locus. These mice present a unique and elegant opportunity to re-examine the distribution of Cx 40 gene expression by revealing GFP fluorescence. Moreover, as this can be done directly in living tissue it allows the conduction characteristics of identified fibers to be examined *in situ*. Such animals offer a unique resource for further investigations into the developing and adult conduction system.

### **Signaling during heart valve formation (R. Poelmann, Leiden, NL).**

The development and cellular origins of heart valves were elegantly discussed during this presentation. Heart valves derive from a complex set of interactions between regions of extended extracellular matrix mainly consisting of collagen, and cells derived from endocardium, neural crest and pericardium. Experiments using chick quail chimeras were used to investigate the contribution of these cells by allowing the origin to be accurately determined. All three cell types contribute to the formation of valve tissue. Additional data were presented to demonstrate the importance of shear stress related gene expression in the subsequent development. The data trace potential origins of cardiac developmental abnormalities and raise important issues relating to the possible need for cellular diversity for tissue engineering of a valve.

## ***Flies, worms, fish and sea-urchin eggs: what can primitive organisms tell us about human cardiovascular disease?***

Prof. Qingbo Xu  
London, United Kingdom



## **Regulation of the cell cycle: from sea-urchin eggs to inhibitors of restenosis. (M. Boehm, Bethesda, US)**

## **Wnt, Frizzled, Disheveled: fruit-fly genes with emerging roles in cardiovascular development and disease (M. Blankesteyn, Maastricht, NL)**

## **Apoptosis and unstable atherosclerosis: could we have done it without *C. elegans*? M.R. Bennett, Cambridge, GB)**

## **Zebrafish, an organism that makes heart development transparent! (W. Rottbauer, Heidelberg, DE)**

This symposium addressed the impact of several models for studying the cellular and molecular mechanisms of cardiovascular diseases in humans. Four speakers in this session are Drs M Boehm (Bethesda, USA), M Blankesteyn (Maastricht, the Netherlands), MR Bennett (Cambridge, UK) and W Rottbauer (Heidelberg, Germany). Each speaker presented the data obtained from investigating sea-urchin eggs, fruit-fly genes, *C. elegans* and Zebrafish to address basic issues of cell signaling, cell cycle, apoptosis and organ development. The basic information of this symposium is that every model described by the authors has advantages emphasizing one aspect of the molecular process of cells. For instance, Zebrafish is an animal that is easy to breed and manipulate the gene which generates a phenotype similar to human cells. To test the function of human genes, which can be introduced to the organism, we can learn how these genes work in vivo. However, we have to keep in mind that these primitive models can mainly be used to study the basic mechanisms of cell and molecule processes in vivo and in vitro, which are not suitable for directly interpreting the data into the pathophysiological conditions in humans.

## ***The Vascular System Under Immune Attack***

Prof. Juan Carlos Kaski  
London, United Kingdom



Over the past decade evidence has accumulated indicating that atherosclerosis is an inflammatory condition. Atherosclerotic lesions contain inflammatory cells i.e. macrophages, dendritic cells and T lymphocytes and it is established that atherosclerotic disease is associated with signs of local and systemic inflammation. Moreover, increased levels of inflammatory markers are able to predict cardiovascular risk in patients and also in apparently healthy subjects. This Basic Science Symposium chaired by Prof. A. Tedgui (Paris) and Prof J.C. Kaski (London) focused on the role of immune cells in atherogenesis and cardiovascular disease.

### **T-cells and atherosclerosis – new insights (F.A. Machs, Geneva, CH)**

In this session F.A. Mach (Geneva) addressed the problem of T-cells in atherosclerosis and reviewed the available evidence regarding the role of T-cells in animal and human atherosclerosis. T-cells in atherosclerotic lesions are mainly of the CD4 subtype and albeit fewer, CD8 T cells can be also found. T-cells play a role in early atherogenesis and plaque vulnerability. They recognize protein antigens presented to them by macrophages and dendritic cells. T lymphocytes in atheromatous lesions are largely from the Th1 subtype and produce the potent cytokine interferon gamma (IFN-g) and other pro-inflammatory cytokines. IFN-g is an immune activating cytokine, which activates macrophages and induce inflammatory responses. It has been also shown that IFN-g impairs collagen synthesis by smooth muscle cells and may thus have a plaque destabilizing role. There is abundant experimental evidence that IFN-g potentiates atherosclerosis and the absence of this cytokine results in reduced lesion size in the experimental animal. Th1 cells appear to be particularly important during early phases of atherosclerosis but studies suggest also a role in plaque instability. Oxidised LDL (ox-LDL) cholesterol is a candidate antigen in atherosclerosis that is recognized by T cells. The immune response to ox-LDL has a pathogenic role in atherosclerosis and may represent a therapeutic target. A co-stimulatory molecule, CD40 L, expressed by B cells and dendritic cells is and other necessary for T-B cell co-operation and is activated by IFN- cytokines. Specific blockade (anti CD40L antibodies) of CD40L reduces atheroma formation in experimental animals. In experimental studies, modulation of T-cell responses within plaques results in reduced recruitment of monocytes and less atheromatous lesions. Reduced expression (or KO) of the CXCR3 receptor reduces atherosclerosis.

### **Dendritic cells and endothelial dysfunction (M. Weis, Munich, DE)**

Dendritic cells (DC), the most potent antigen-presenting cells are likely to have an important role in atherosclerosis, as discussed by M Weis (Munich) in this session. DC induce and modulate T-cell activation and have been found in both early and established atheromatous plaques and in the borders of necrotic tissue during MI. Work by Weis et al. indicates that DC are upregulated during endothelial activation and increased endothelin-1 concentrations also stimulate DC adhesion. Their binding to endothelial cells can be inhibited by statins and increased DC adhesion can be reversed by the administration of endothelin-1 blockers. DC "monitor" the vessel wall in search for antigens. In the presence of coronary artery disease risk factors DC show increased adhesion, migration and accumulation. They have been shown to invade atheromatous plaques. DC are of different subtypes and exert different modulatory actions on T-cell function. In humans, DC of the Langerhans cell and interstitial types belong to the myeloid pathway and produce IL-12. Interstitial DC produce IL-10, an anti-inflammatory cytokine. Another pathway includes plasmacytoid DC, which secrete IFN-g/g. Adhesion molecules are necessary for DC to exert their functions i.e. VCAM-1 is required for cell adhesion and migration.

### **Regulatory T cells and atheroprotective immunity. (G.K. Hansson, Stockholm, SE)**

G. Hansson (Stockholm), who has pioneered work in the field of immunity and atherosclerosis, presented data from his own group and others, particularly investigations by A. Tedgui's group, regarding atheroprotective immunity. T-cells have multiple roles in atherosclerosis such as activation and recruitment of macrophages and other T-cells, inhibition of collagen synthesis by SMCs and antibody production. T-cells infiltrate lesions and produce IFN-g. T-cells are modulated not only by pro-inflammatory cytokines but also by anti-inflammatory molecules (i.e. IL-10 and TGF- $\beta$ ), which represent a "brake" to the pro-atherogenic action of these cells. T regulatory cells exist which an anti-inflammatory and modulate the activity of Th1 lymphocytes. TGF-  $\beta$  fibrogenic molecule, exerts an important modulatory action on Th-1 lymphocytes and it has been shown in experimental studies that T-cells that cannot recognize TGF-g exacerbate atherosclerosis. TGF-  $\beta$  KO mice show a dramatic increase of atherosclerotic lesions, which is associated with a massive increase in IFN-g production. Evidence exists that immunization with a number of antigens can exert protective effects in experimental models. Different immune effector responses can be elicited against the same antigen and this can explain the protective actions observed with immunization techniques using antigens that have been identified as pro-atherogenic in different studies. Modulation of atherosclerosis by T-cells and other inflammatory cells and their products is a complex process that still require further understanding

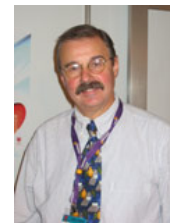
### **Empiric versus mapping guided pulmonary vein isolation (D.J. Wilber, Chicago, US)**

The isolation of pulmonary veins to treat atrial fibrillation with catheter techniques follows different approaches. Targeting the located electrophysiological focus of the induction of atrial fibrillation is the pathophysiological approach and results in a minimum area to ablate. The risk of missing potentially arrhythmogenic areas results in a lower success rate. The empiric guided technique by routinely isolating all four pulmonary veins is technically more demanding and requires more sophisticated imaging equipment. Nevertheless, the results of this technique show a trend towards more success and fewer complications.

Conclusion: A combination of the empiric and mapping guided pulmonary vein isolation techniques are proposed. Whether there is a substantial difference between the electrogram-guided segment isolation versus anatomic isolation technique is still uncertain.

## ***Ablation of Pulmonary Veins Triggering Atrial Fibrillation: 5-Year Experience***

Dr. Christian Leuner  
Bielefeld, Germany



This Symposium addresses the main topics of the actual experiences in the interventional treatment of atrial fibrillation and diminishing the procedure inherent risks.

### **Non-pulmonary vein foci: do they exist? (D. Shah, Geneva, CH)**

Reviewing the literature there is growing evidence that there are a substantial amount of extra pulmonary vein foci triggering atrial fibrillation. In early publications Haissaguerre published a rate of 6% of these foci. In more selected cases with special awareness of this problem, rates up to 45% had been published. In one of the latest publications from Lin, WS et al. published in *Circulation* 2003, information is given about the main regions where these foci could be found. Main places were left atrial posterior free wall 38.3%, superior vena cava 37.0%, crista terminalis 3.7%, ligament of Marshall 8.2%, coronary sinus ostium 1.4%, and interatrial septum 1.4%. More foci had been located by extensive mapping techniques in other places, but not all foci had been able to initiate atrial fibrillation.

Conclusion: There should be more awareness about the existence of non pulmonary –vein foci, especially in cases of recurrence of atrial fibrillation after pulmonary vein isolation.

### **Role of imaging in pulmonary vein isolation (N. Marrouche, Cleveland, US)**

To achieve the best results in ablation of atrial fibrillation, several different technical approaches have been developed. Catheter techniques to locate the arrhythmic substrate and isolate the pulmonary veins completely without provocation of pulmonary vein stenoses are now available. The imaging techniques to guide the catheters to the correct position are still unsatisfactory. In addition to the currently available techniques, N. Marrouche from the Cleveland Clinic demonstrates the additional benefits of Intracardial Echocardiography (ICE). The direct location of a circular catheter and the ablation catheter is possible and the morphology of all pulmonary vein ostia can be visualized. Visualizing the appearance of microbubbles during ablation helps to avoid complications by adjusting the ablation energy. Further developments of imaging techniques will integrate 3D- ICE, KATO and CT or MRI information. The main interest in the new imaging technique is to reduce the current, long duration of the interventions.

Conclusion: The introduction of intracardial Echocardiography in addition to the already used imaging techniques reduces complications and procedure duration in the ablation of atrial fibrillation.

### **Which patient should undergo pulmonary vein isolation? (T. Arentz, Bad Krozingen, DE)**

There are different approaches to the selection of patients to whom the ablation of atrial fibrillation should be offered. Since there are no convincing data from multiple studies that there are substantial prognostic benefits for all treated patients, there is a need to select the highly symptomatic candidates, drug resistant to class I and III anti arrhythmic drugs. The complexity of the procedure, the limited success rate and the still quite substantial complication rate provide evidence in favour of selecting the patients with good risks. These are patients with paroxysmal atrial fibrillation, a left atrium diameter less than 45 mm on echocardiography and younger than 65 years.

Conclusions: Pulmonary vein isolation should be offered to highly selected symptomatic patients because a substantial prognostic benefit has not been proven up to now.

### **Significance of pulmonary vein stenosis after electrical isolation. (R. Cappato, San Donato, IT)**

In 1997 the first peer reviewed article describing a pulmonary vein stenosis as a consequence of a pulmonary vein ablation was published. The evidence that focal ablation of the antiarrhythmic substrate deep within the ostium of the pulmonary vein is the main reason for stenosis development, resulted in a major change in techniques. It resulted in the electro-/anatomical and the completely anatomic procedures. The pathophysiological basis of the development of the stenosis is well defined. It mainly results from a fibrotic process. Stenosis more than 70% provoke symptoms such as dyspnea, cough, haemoptysis, pleuritic pain or palpitations. Symptoms are mostly misinterpreted and in 50% of cases, visible changes in the chest x-ray are not correct interpreted. The treatment is balloon dilatation, if necessary with stenting, lobectomy or surgical reconstruction of the pulmonary veins. The actual risk for a hemodynamically relevant pulmonary stenosis according to the speaker is about 0.6%. This raises the question of whether there is a real benefit for a routine assessment for pulmonary stenosis after pulmonary vein isolation.

Conclusion: After the change of technique for the electric isolation of the pulmonary veins to a more anatomic approach, the rate of significant pulmonary vein stenosis is significantly reduced. The timely recognition of pulmonary vein stenosis is still problematic.

### **Empiric versus mapping guided pulmonary vein isolation (D.J. Wilber, Chicago, US)**

The isolation of pulmonary veins to treat atrial fibrillation with catheter techniques follows different approaches. Targeting the located electrophysiological focus of the induction of atrial fibrillation is the pathophysiological approach and results in a minimum area to ablate. The risk of missing potentially arrhythmogenic areas results in a lower success rate. The empiric guided technique by routinely isolating all four pulmonary veins is technically more demanding and requires more sophisticated imaging equipment. Nevertheless, the results of this technique show a trend towards more success and fewer complications.

Conclusion: A combination of the empiric and mapping guided pulmonary vein isolation techniques are proposed. Whether there is a substantial difference between the electrogram-guided segment isolation versus anatomic isolation technique is still uncertain.

## ***Stem Cell Therapy in Cardiac Regeneration and After Myocardial Infarction***



Prof. Gianluigi Condorelli  
Rome, Italy

### **Contribution of bone-marrow derived stem cells to myocardial revascularization. (E. Gunsilius, Innsbruck, AT)**

Dr. E. Gunsilius demonstrated that endothelial progenitor cells contribute substantially to neovasculogenesis in the heart after transplantation. His group used human models such as leukaemia and transplanted patients, in which donor stem cells can be recognized from recipient cells by specific chromosomal markers, demonstrating that bone marrow cells of the recipient contributed by approximately 25% to transplanted heart neovascularization.

### **Stem cells in skeletal and cardiac muscle. (N. Rosenthal, Monterotondo, IT)**

Dr. Nadia Rosenthal, from Monterotondo (Rome) stressed the importance of IGF-1 in skeletal and cardiac tissue repair. Dr. Rosenthal determined that the tissutal muscle form of IGF-1 induces skeletal muscle hypertrophy without affecting the heart, while circulating IGF-1 does induce cardiac hypertrophy. Moreover, mice overexpressing the IGF-1 muscle specific isoform had an increased skeletal tissue repair after injury, suggesting that IGF-1 increases stem cell differentiation into skeletal muscle. In cardiac muscle, mIGF-1 expression induces hypertrophy without the activation of markers of pressure overload hypertrophy. In the first weeks of life, animals show cardiac hyperplasia, while later on in life mice showed cardiac hypertrophy. Therefore, IGF-1 is a cytokine that might be used in the future for muscle tissue repair.

### **Therapeutic strategies: injection or enhanced mobilisation: (B. Nadal-Ginard, Boston, US)**

Dr. Bernardo Nadal-Ginard presented a revolutionary picture of the heart as a proliferative organ. His group claims that local cardiac stem cells are very critical for tissue repair. According to Nadal-Ginard, these cells are localized in specific niches, particularly in the atrium. They express c-Kit on the surface and can therefore be sorted out using this antigen, can be cloned and expanded in vitro, expressing markers of cardiac, skeletal and smooth muscle differentiation. His group presented data showing that cells expanded in vitro are able to repair infarcted hearts, generating new cardiomyocytes that contract better than the old ones and that are able to improve cardiac function substantially. His group claims that stem cells could be stimulated to migrate from their niches and replicate after injection of IGF-1 and Hepatocyte Growth Factor in ischemic zones of the myocardium. Therefore, they believe that using HGF and IGF-1 it is possible to mobilize local cardiac stem cells and induce them to proliferate.

### **Stem/progenitor cell therapy in patients: neovascularisation and cardiac regeneration? (A. Zeiher, Frankfurt, DE)**

Dr. Andreas Zeiher's group demonstrated that hematopoietic stem cells "primed" to become endothelial cells though a brief treatment with VEGF, are incorporated into new vessels. Using murine infarct models, Dr. Zeiher's group demonstrated that "stem cells" primed with VEGF localize to the infarcted area. Next, Dr. Zeiher showed the results of a small trial in which circulating progenitor cells were injected in patients with acute myocardial infarction, together with standard therapy, including primary angioplasty. The group of patients treated with stem-cells showed an improvement of cardiac function, assessed by LV angiography, echocardiography, FDG-PET as compared to patients receiving the conventional treatment only. The effect was more remarkable in patients with larger myocardial infarction. The infusion of stem cells is safe, since there were no major complications in the treated group. This treatment has also been applied to patients with ischemic heart failure. Initial data are promising also for this type of patients. Larger, randomised, multicentre trials are needed to confirm these initial positive results.

## ***Stress Echocardiography in Challenging Cases: Any Help from Doppler Myocardial Imaging***

Dr. Marco Campana  
Gussago, Italy



### **Rationale for the quantification of regional myocardial function during stress echocardiography. (T.H. Marwick, Brisbane, AU)**

T.H. Marwick introduced the session with an overview of the rationale for the need of improving stress echocardiography with quantification. Current limitations of qualitative analysis - left ventricle wall motion score - and possible improvements by using Tissue Doppler Imaging (TDI) have been identified, and summarized as follows:

- a) *overall diagnostic accuracy*: evidence of improvement for beginners, not for expert readers;
- b) *quality of images*: TDI is less dependent on image quality, but some limitations still remain;
- c) *learning curve*: TDI reduces, but does not eliminate the difference between experts and beginners;
- d) *reproducibility*: TDI improves reproducibility, with some limitations in subsets like "low image quality" and "one vessel disease" ;
- e) *small ventricular cavities*: TDI helps, but some limitations still remain;
- f) *single vessel disease*: some evidence of improvement with TDI;
- g) *multi vessel disease*: no evidence of improvement with TDI;
- h) *follow-up*: no evidence of improvement with TDI;

### **Diabetic patients (H. von Bibra, Munich, DE)**

H. von Bibra then illustrated the potential advantages of TDI in diabetic patients. Stress echocardiography limitations in these patients are represented by lower blood pressure and heart rate during stress, silent myocardial ischemia, and less specific ST changes on ECG tracing. This can be true for a large population, due to the fact that post-prandial (2 hours after the meal) hyperglycemia, besides fasting glycemia, is related to the risk of cardiovascular disease.

Stress echocardiography diagnostic accuracy in diabetic patients improves by using TDI.

### **Heart transplant patients. (G.A. Dérumeaux, Rouen, FR)**

G. Derumeaux dealt with the theme of transplanted hearts. These show some differences in characteristics of ischemia and coronary artery disease with respect to the general population, with an incidence of 10-25% at one year, and 40-70% at ten years. In such patients, sensitivity of traditional stress tests is low, being 21-27% for ECG, 50-66% for SPECT, and 25-50% for stress echocardiography.

The use of TDI during dobutamine stress echocardiography in transplanted hearts improves the accuracy for non expert readers, reduces the learning curve, and improves reproducibility.

### **Women. (A.G. Fraser, Cardiff, GB)**

A.G. Fraser illustrated TDI data obtained during stress in women. The feasibility of TD-stress echo is higher for dobutamine than exercise stress test, and the long axis views give better results than short axis. Regarding "peak systolic velocity" in normal hearts during stress, women show a difference of -1.5 cm/sec with respect to men in all myocardial segments, suggesting that different tables for normal values should be used for the two sexes. TDI could be useful in particular for those patients with intermediate pre-test probability of coronary disease.

### **Assessing contractile reserve. (F. Wiedermann, Wurzburg, DE)**

F. Wiedermann showed how dobutamine stress echocardiography with the help of TDI can distinguish different myocardial conditions like normal, acute ischemia, stunning, non-transmural and transmural infarction, and viability, when velocities are carefully evaluated together with temporal events during cardiac cycle.

**In conclusion**, TDI is more than a promising tool, being ready for routine clinical use in several situations, when we need to improve sensitivity and specificity of stress echocardiography.

## ***The complex link between thrombosis and inflammation***

Dr. C. Kluft  
Leiden, Netherlands

**Thrombosis in the absence of inflammation. (D. Fitzgerald, Dublin, IE)**

**Thrombosis in the presence of inflammation. (L. Biasucci, Rome, IT)**

**Cross-talk between platelets and inflammatory cells.  
(U. Rauch, Berlin, DE)**

**Clinical implications. (A. Maseri, Milan, IT)**

Patients with AMI with and without preceding instability and inflammation cannot yet be rationally approached as different groups

An important question is how patients with a myocardial infarction with preceding instability with inflammation, and patients with myocardial infarction "out of the blue" without preceding increased inflammation differ in terms of the cause of thrombosis, thrombus composition, need for intervention and prognosis.

Among patients with AMI, those with preceding instability and AMI "out of the blue" are about equally prevalent and can be considered as two categories of patients (Maseri).

Detailed summaries of pathways of thrombosis were provided.

Thrombosis in the absence of inflammation is a wrong concept, the process itself is inflammatory, including important contributions of platelets which may be considered as inflammatory cells (Fitzgerald). Genetic variations in platelet proteins and ligands reveal that platelet adhesion is important (Fitzgerald).

It is more appropriate to distinguish between a situation with and without preceding increased inflammation.

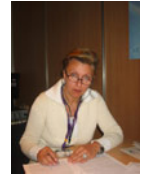
Biasucci reviewed pathways involved in increased risk and activation of thrombosis when inflammation is present. In addition to inflammation-induced changes in the systems, one of the specific links to thrombosis may be CRP, which has been reported to increase tissue factor expression.

Inflammation promotes platelet-leukocyte interaction involving P-selectin resulting in addition in increased microparticles with tissue factor (Rauch). This potentially stimulates propagation of thrombi.

There are clear clinical and biochemical indications that patients with pre-existing instability and inflammation are different from those with AMI "out of the blue" The knowledge is incomplete and clinical implications have not yet been systematically studied to obtain a basis for a rational, different approach to these two categories of patients (Maseri, Biasucci). Antithrombotic regimens have met with limited success and have an inherent bleeding risk. A desired target would be the final inflammatory pathway leading to stimulation of coagulation (Maseri).

## Exercise in Patients with Hypertrophic Cardiomyopathy

Prof. Eloisa Arbustini  
Pavia, Italy



### Left ventricular hypertrophy and exercise. (P. Spirito, Genoa, IT)

The symposium was opened by Paolo Spirito (Genova, Italy) who dealt with left ventricular hypertrophy and exercise tolerance in HCM. Left ventricular hypertrophy is the main feature of HCM. The histological hallmarks are myocyte disarray, fibrosis and small vessel disease. The mismatch between the myocardial mass and coronary circulation is elicited by exercise and the lactate metabolism is abnormal during pacing studies. The perfusion abnormalities are confirmed by imaging study. Therefore, exercise may induce ischemia and ischemia may trigger ventricular tachyarrhythmias and sudden death. In fact, most sudden deaths occur during sport activity and exercise (Maron, Circulation 1993: 44% SD in athletes are caused by HCM). The magnitude of hypertrophy is variable in HCM patients: the risk of SD versus thickness values <15mm, 16-19mm, 20.24mm, 25-29mm and  $\geq 30$ mm has been reported to be 0%, 2.6%, 7.4%, 11% and 18.2%, respectively. Symptoms do not reflect the risk: they may be mild in patients with severe left ventricular hypertrophy. Furthermore it has been shown that there is no close relation between blood pressure response during exercise and left ventricular hypertrophy. Therefore the conclusions are that there is no relationship between magnitude of left ventricular hypertrophy and exercise tolerance in patients with HCM. Indeed, most patients with extreme left ventricular hypertrophy ( $\geq 30$  mm) have no or only mild functional limitation. Nevertheless, **intense exercise remains a potential trigger for sudden death in HCM and should be avoided independent of the magnitude of the hypertrophy.**

### Exercise a useful tool to distinguish different types of hypertrophy.

(W. McKenna, London, GB)

The role of exercise as a tool to distinguish different types of hypertrophy was then discussed by William Mc Kenna (London, UK) who concentrated on exercise testing in HCM. Metabolic gas exchange measurements during maximal upright exercise provide accurate and reproducible measure of exercise capacity. Maximal exercise testing with gas exchange, blood pressure and heart rate measurements provides useful information to support diagnosis, guide management of symptoms and assess risk of sudden death. In HCM, data in 846 consecutive patients revealed peak VO<sub>2</sub> ranging from 30 - 160% of predicted values. A VO<sub>2</sub> max of <50% predicted is most often associated with non sarcomeric contractile protein HCM including mitochondrial disease, Fabry's Disease and associated skeletal myopathies. There is a very poor correlation of symptoms and objective measures of exercise capacity. Reporting of symptoms is understated in those with disease development during adolescence. Continuous measurement of the systolic blood pressure during maximal upright exercise reveals **abnormal vascular responses in approximately 25% of the young patients. This subset is at significantly increased risk from sudden death.** Those with a normal blood pressure response in the absence of other risk factors can be reassured that they are not at increased risk of sudden death.

### Sport and risk of sudden death. (A. Pelliccia, Rome, IT)

Antonio Pelliccia (Rome, Italy) discussed the risk of sudden death and sport in HCM. The speaker addressed three major questions:

1. Is the risk of SD increased by sport participation in patients with HCM? More than 30% of SD in athletes are associated with HCM. Most HCM athletes collapse during or immediately after a training session or in the context of a competitive event. A series of data support the conclusion that **regular exercise increases the risk of sudden death in HCM** and, at present, HCM is the leading cause of sudden death in competitive athletes in the world, except in Italy where a specific law for screening of athletes is in force.
2. Can HCM athletes be identified before sudden events? Cardiovascular screening should be performed in all competitive athletes. EKG provides useful information while history data are proven to have scarce utility and physical examination may be unremarkable, especially in non-obstructive HCM. In a large series of 33,735 athletes who underwent cardiovascular screening (Corrado et al in 1997), 3016 (9%) had EKG abnormalities. The echocardiographic study documented HCM in 22 of 3016 (0.07%). In a further series of 4450 athletes free from known cardiovascular diseases (Pelliccia), 12 were proven to have structural cardiovascular diseases (including Marfan syndrome, myocarditis, mitral valve prolapse, etc.) but none had HCM. Therefore, **screening athletes with 12-lead electrocardiography has the potential to identify unsuspected HCM**, due to the large proportion (> 90%) of detectable abnormalities.
3. Can the follow-up of HCM patients disqualified from sport indirectly provide information on the overall risk of SD? Dr Pelliccia stated that **avoiding intense sports and competition might decrease risk of sudden death.** However, scientific evidence is missing and specific investigation in this field is especially needed. The recently constituted ESC Study Group dedicated to Sport and Cardiology will provide guidelines and will work to solve unanswered questions.

### Importance of intracavitary gradient. (M. Borggreffe, Mannheim, DE)

M. Borggreffe (Mannheim, Germany) discussed the **importance of the intracavitary gradient**. The pathophysiology of left ventricular obstruction was outlined, discussing all variables that may enter in the mechanism of the obstruction (anterior mitral valve motion and pushing of the leaflet onto the septum, orifice reduction, abnormal intracavitary pressure generation, the flow that invests the mitral valve (angle of attack), cordal slack, the extent of left ventricular hypertrophy, as well as elongated mitral valve). Overall, the obstruction is usually associated with more severe symptoms. The systolic murmur brings the patient to medical attention, and in case of high ventricular pressure in obstructive HCM the prognosis is poorer than in the absence of obstruction. In Maron's series (JAMA 1999) the prognosis was shown to be worst in the presence of intracavitary gradient. This data has been recently confirmed (NEJM 2003) in 1101 patients: 273 (25%) had resting gradient  $> / = 30$  mmHg with a RR of death of 2.0. It was concluded that intracavitary gradient  $> 30$  is frequent and that the clinical significance is that of a poor prognosis. The increase of the left ventricular pressure actually increases wall stress, and induces myocardial ischemia and cell death. Interventions aimed at reducing the obstruction and lowering the intraventricular pressure could positively reflect on the risk of sudden death. Dr. Borggreffe reported a series of 10 patients with obstructive HCM: their history was characterised by sustained ventricular tachyarrhythmias. They all were SD survivors and all had inducible VT/VF at PES. The post-operative follow-up (13±2 years) documented the absence of inducible VT/VF. He concluded his presentation by stating that although the **gradient is not the disease**, it is associated with less favourable outcome.

### Exercise after transcatheter ablation of the hypertrophic septum.

(H.J. Kuhn, Bielefeld, DE)

Dr. H. Kuhn (Bielefeld, Germany) gave the last lecture. He discussed **exercise after transcatheter ablation of the septum (TASH)**. Exercise testing was shown to play an important role for diagnosis and for post-interventional evaluation of obstructive HCM: the gradient reflects the degree of obstruction during exercise. After TASH, consistent benefits are measured with exercise testing in obstructive HCM. Similar benefits are also seen in patients with exercise intracavitary gradient only. He reported the data obtained in a series of 468 patients treated in Bielefeld using the GASP-Technique (non-echocardiographic gradient, angiocardiology, programmed stimulation-guided technique). Athletes who have a positive cycle-ergometry test performed the exercise Doppler echocardiography that was used for the validation of the reduction of the alcohol amount in a dose-ranging study (stepwise reduction from 3.9 ml to 0.6 ml). It could be shown that **very similar effects occurred in patients undergoing low dose treatment in exercise testing (gradient reduction and maximal oxygen uptake), including amelioration of the quality of life and significant improvement of the prognosis.** The rate of adverse effects was remarkably reduced. It was recommended to perform TASH with a maximum of 1.5 ml per therapeutic session (on average 0.8 ml) of ethanol. This dose replaces the 2-4 ml per session usually injected by the vast majority of centres performing septal ablation.

## ***Pacemakers, Implantable Cardioverter-Defibrillators and Electromagnetic Interference***

Dr. Cecilia Linde  
Stockholm, Sweden



This symposium addressed the clinically relevant problems for carriers of pacemakers and implantable-cardioverter defibrillators and electromagnetic interference

### **Electromagnetic interference by mobile phones in pacemaker function. (M. Santini, Rome, IT)**

Mobile phones may generate electromagnetic fields which could interfere with the pacemaker (PM) function. Mainly three different types of transient interference may be observed : an increase in the paced rate, asynchronous pacing or a complete inhibition of the pacing function. No permanent malfunctioning or reprogramming has been reported. GSM mobile phones may cause some type of changes in the PM function if the phone is used < 10 cm from the PM. Interference is more likely during switching on-off or ringing. Although no significant interference has been reported in patients with ICD (Implantable Cardiac Defibrillators) over-sensing between mobile phone and the programmer head has been demonstrated. New technologies will be used in future devices to avoid electromagnetic interference.

**Conclusion:** Patients submitted to permanent pacing or ICD therapy should be reassured to use mobile phone and to keep their mobile >10 cm from the device. During follow up, mobile phones should be switched off.

### **Studies of pacemaker and implantable cardioverter defibrillator triggering by electronic anti theft devices. (H. Ector, Leuven, BE)**

Interactions between electronic anti-theft systems (EAS) and PM or ICDs are a theoretically possible but rarely reported except under extreme circumstances as evidenced by two studies. Whereas PMs can be temporarily inhibited, accelerated or paced in an asynchronous mode, ICDs may deliver inappropriate shocks. Clinically relevant complications only occur as a result of direct contact or prolonged exposure. No case of permanent reprogramming has been reported. A normal or slow walk through the EAS gate is without risk for the PM or ICD patient. The FDA recommends the patient to be aware that EAS systems may be hidden in entrances and to practice a policy of "Don't linger, don't lean". In the year 2000, the European WGs of Arrhythmia and Pacing issued the same recommendations.

**Conclusion:** Interaction with EAS and PM/ ICD is unlikely. Patients should be encouraged not to linger or lean on such equipment.

### **Do airport metal detectors interfere with implantable pacing devices? (C. Kolb, Munich, DE)**

A total of 203 PM and 151 ICD patients were studied concerning interaction of standard airport metal detectors gates. In none of the PM patients were sensing or pacing anomalies or spontaneous reprogramming detected. No inappropriate tachyarrhythmia of the ICD was seen.

**Conclusion:** Patients may safely pass the metal detector gates at airports and this practice is to be preferred over hand-held metal detectors.

### **Pacemakers in the magnetic resonance imaging (MRI) environment; safety considerations (F. Duru, Zurich, CH)**

Previously, 6 deaths of pacemaker patients have been reported during MR imaging procedures. Lately, safe MR imaging in paced patients has also been reported. Strong magnetic forces during MRI may temporarily alter pacing mode, result in inappropriate pacing with the risk of life threatening arrhythmia, particularly in non pacemaker dependent pacing. Radio-frequency (RF) and gradient fields of the MR scanner may cause changes in pacing rate or temporarily inhibit pacing.

Telemetry use and the access to an external defibrillator during the procedure could increase safety. However, the heating by the RF-field may cause burning of the heart muscle around the tip of the electrodes. These effects can be reduced but not completely avoided by using low field MR systems and by limiting the procedures to head and lower extremity scans.

**Conclusion:** At present MR imaging should be avoided in the pacemaker patient.

### **Do we need pacemakers and implantable cardioverter defibrillators resistant to magnetic resonance imaging? (W. Irnich, Giessen, DE)**

There are different influences of MRI: The static magnetic, the gradient and the high frequency fields. The magnetic field theoretically could dislodge pacemakers and electrodes. The gradient fields could influence pacers to inhibit or revert to asynchronous pacing whereas the high frequency fields produce high temperature at electrode tip to 65 degree C with the risk of burn. Methods to reduce these risks were discussed.

**Conclusion:** Compatibility between PMs and ICDs and MRI can be reached if the MRI is triggered by the pacing spike and the scan duration is limited to the refractory period. A prerequisite is a programmable reed contact function of the implantable PM/ICD. Such an algorithm may become mandatory in future devices.

## ***New Therapeutic Tools in Atherothrombosis***

Prof. Freek Verheugt  
Nijmegen, Netherlands



**Developing strategies to inhibit athero-thrombosis.  
(L. Badimon Maestro, Barcelona, ES)**

**Low molecular weight heparin and pentasaccharide. (S. Mehta, Hamilton, CA)**

**Tissue factor pathway inhibitors. (M. Eto, Zurich, CH)**

**Oral antithrombins. (L. Wallentin, Uppsala, SE)**

Both platelets and the coagulation cascade are involved in the thrombotic complication in atherosclerosis, the so-called *atherothrombosis*. Interference with both physiological systems can reduce the risk and often catastrophic consequences of atherothrombosis. Antiplatelet therapy may consist of aspirin, clopidogrel and glycoprotein IIb/IIIa antagonists. Aspirin is still the major antiplatelet agent, in that it significantly reduces cardiovascular death, (re)infarction and stroke in vascular patients (BMJ 2002 meta-analysis in 144,000 patients in over 300 placebo-controlled trials). Clopidogrel, a platelet ADP receptor blocker, further reduces this risk on the short and longer term in patients treated for non ST-elevation acute coronary syndromes with or without coronary intervention (2 major trials including over 15,000 patients). Finally, platelet glycoprotein IIb/IIIa blockers have only been shown effective in the cath lab. Patients undergoing intervention for stable angina or non-ST elevation acute coronary syndromes have less periprocedural MIs with these expensive agents, but without a clear effect on early and late mortality (over 30,000 patients tested in over 20 major trials).

Drugs interfering with the coagulation cascade (*anticoagulants*) are mainly used in acute coronary syndromes (heparin and low-molecular weight heparin) and long-term (vitamin K antagonists, also called oral anticoagulants) after myocardial infarction. Both heparin and oral anticoagulants need close therapy monitoring (apTT and INR respectively). Low molecular weight heparin can be given subcutaneously and do not need monitoring.

### **New strategies**

New antiplatelet drugs are not on the horizon really. Possibly, a second generation ADP receptor blocker by Lilly with a tighter bond to the platelet ADP receptor will be evaluated shortly. Glycoprotein IIb/IIIa blockers will probably not be tested outside the cath lab except in the pre-hospital setting of ST-elevation myocardial infarction ahead of primary angioplasty (facilitated PCI). In a post-hoc analysis of the ADMIRAL trial abciximab lead to a better TIMI-3 flow prior to primary angioplasty (21%) compared to placebo (10%). Yet, prePCI thrombolytic therapy opens up may more occluded vessels (up to 33% of the culprit vessels with 50 mg rt-PA bolus in PACT). So, likely lytic therapy rather than IIb/IIIa blockers will be evaluated and probably used ahead of primary PCI to speed up reperfusion in STEMI.

More new tools are or will be available in anticoagulant therapy. First, the specific factor-Xa inhibitor pentasaccharide (fondaparinux, or Arixtra<sup>®</sup> by Sanofi) will be tested in 2 megatrials against enoxaparin: OASIS-5 in non STE ACS, and OASIS-6 in STEMI. Secondly, a new oral direct thrombin inhibitor (ximelagatran, or Exanta<sup>®</sup> by AstraZeneca) has shown to be as least as effective as warfarin in stroke prevention in atrial fibrillation (SPORTIF-III, *Lancet* in press). These results will be repeated in the SPORTIF-V study to be presented at AHA 2003. Furthermore, ximelagatran has been evaluated against placebo after MI in the ESTEEM trial presented here at ESC 2003 and published in the September 6 issue of *Lancet*. The drug significantly reduced reinfarction and stroke at no increased major bleeding risk, but with transient liver enzyme abnormalities in about 5% of patients. Finally, oral factor-Xa inhibitors will be tested shortly in non-STE ACS. The major advantage of blocking high in the coagulation cascade is the low amount of drug needed to inhibit thrombin generation: one molecule Xa is responsible for the generation of at least 50 molecules of thrombin. Going even higher in the coagulation cascade is to inhibit tissue factor. Parenteral tissue factor (pathway) inhibitors will be tested shortly in arterial thrombosis after positive pilot results in elective PCI.

## ***Pulmonary Embolism: Sluggish Progress towards a Breakthrough?***

Prof. Nazzareno Galiè  
Bologna, Italy

The diagnostic strategy and the treatment of acute pulmonary embolism have faced steady progresses in the past years and they were reflected in the presentations of the symposium.

### **Diagnostic strategy based on clinical probability, lower limb ultrasonography and spiral computed tomography. (G. Simonneau, Clamart, FR)**

Prof Gerald Simonneau of Clamart (FR) reviewed the different diagnostic algorithms that have been proposed. In particular, he presented the data of the ESSEP study that involved 14 centers in France and evaluated the specificity of spiral CT scan in the diagnosis of acute pulmonary embolism. A normal CT scan accompanied by a normal venous ultrasound scan of the lower limbs identified a group of patients with a reduced risk of thromboembolic events, in particular if the clinical probability of acute pulmonary embolism is low and they are outpatients. In these subjects, anticoagulant treatment can be avoided. In cases with high clinical probability or inpatients with low probability, the risk of recurrences without anticoagulant treatment is 5% over three months.

### **Risk stratification based on cardiac troponins and brain natriuretic peptides. (P. Pruszczyk, Warsaw, PL)**

Dr Piotr Pruszczyk of Warsaw (PL) presented recent data on the risk stratification of patients with acute pulmonary embolism based on biological markers such as cardiac troponin T and brain natriuretic peptides. Increased levels of cardiac troponin T identify patients with a high risk of mortality, particularly in association with echocardiographic signs of right ventricular dysfunction, even in absence of hypotension. Elevated levels of brain natriuretic peptides are also directly correlated with the severity and the outcome of the patients. Nevertheless, the precise role of these biomarkers in therapeutic decision making and in particular in the choice between anticoagulation alone or associated with thrombolysis is still not clear and should be validated in appropriate prospective clinical trials.

### **Modern treatment of pulmonary embolism. (S. Hustedt, Aarhus, DK)**

Prof Sven Hustedt of Aarhus (DK) reviewed the different options available for the anticoagulant treatment of patients with acute pulmonary embolism. He confirmed that early therapy with low molecular weight heparins is the treatment of choice in subjects who do not undergo thrombolysis, followed by oral anticoagulants. In addition, in particular subsets in which oral anticoagulant treatment is difficult (e.g. cancer or anorexic subjects) low molecular weight heparins can be used also after hospital discharge. Unfractionated heparins followed by anticoagulants is still the most appropriate strategy in patients treated with thrombolysis. The optimal duration of oral anticoagulant treatment is three months in the absence of persistent risk factors for recurrences. The role of the new anticoagulants such as pentasaccharides and melagatran/ximelagatran in patients with venous thromboembolic disease is currently under evaluation by controlled clinical trials.

### **Thrombolytic therapy in sub-massive pulmonary embolism: the final answer? (S.V. Konstantinides, Göttingen, DE)**

Prof. Stavros Konstantinides of Göttingen (DE) discussed the indication of thrombolysis in acute pulmonary embolism, which is clearly required in patients with hypotension. In subjects with normal blood pressure and echocardiographic signs of right ventricular overload (so-called sub-massive pulmonary embolism) the indication for thrombolysis is not clear because the data are derived by small trials that have never demonstrated an improved survival. The use of thrombolysis in this context seems to reduce recurrences and the need for additional interventions. The final answer for the indication of thrombolysis in sub-massive pulmonary embolism should be based on a long-awaited controlled clinical trial aimed to demonstrate an improvement in the survival of the patients.

## ***Treatment for viral myocarditis and inflammatory cardiomyopathy: who should be treated?***

Prof. Bert Andersson, Sweden



The debate concerned an area in which there are – as yet – no evidence based therapies available. The questions addressed during the debate have, however, been debated in the cardiology community for decades. The debate had attracted considerable interest as judged from a fully occupied conference hall.

### **Viral myocarditis should be treated**

**PRO: U. Kuhl, Berlin, DE**

**CONTRA: A. Keren, Jerusalem, IS**

U. Kuhl started to present the experience from his group in Berlin regarding detection and treatment of persistent virus within the myocardium in patients with chronic myocarditis. Their experience was that therapy with interferon effectively cleared virus from the myocardium, accompanied with signs of improvement in left ventricular function and symptomatology. The performed studies were small and uncontrolled, and therefore a prospective placebo controlled multicenter study has been launched to test the hypothesis that virus can be cleared from the myocardium.

Keren pointed to the fact that no randomized study had been performed to show that antiviral therapy was effective. Dr Keren showed results from other investigators that had found evidence that viruses within the myocardium were in fact associated with a favourable prognosis.

The debate following was lively and concerned which patients to select for virus identification, as there is a high degree of spontaneous clearance. The speakers agreed that selected patients could be candidates for antiviral therapy but that controlled studies were needed.

### **Inflammatory cardiomyopathy should be treated.**

**PRO: B. Maisch, Marburg, DE**

**CONTRA: P.J. Richardson, London, GB**

B. Maisch had the opinion that inflammatory cardiomyopathy should be treated, but that conventional histology was not the tool to identify such patients. With immunohistochemistry, inflammatory markers could be detected within the myocardium, giving the opportunity to treat a patient with immunosuppression, immunomodulation or immunoabsorption. His group had positive experience in this field, and Dr Maisch also referred to a recent randomized study by Wojnicz, using steroids and azathioprine.

P.J. Richardson had the contra-standpoint and presented data of poor results from previous controlled trials with immunosuppression in patients with cardiomyopathy and myocarditis. However, these studies had not selected patients with modern laboratory techniques. Dr Richardson also emphasized that myocardial inflammation could be a transient phenomenon.

The debate that followed raised questions about the safety of repeated myocardial biopsies and side effects of immunoactive therapy. In summary, this session brought forward a fruitful debate in an area of great interest, and in which active research is ongoing, hopefully leading to emerging therapies.

## ***Bench to Bedside: Role of Gender in Cardiac Remodelling and Arrhythmogenesis***

Dr. Sylvain Richard  
Montpellier, France



It is believed that, in heart, women fare much better than men. But this is not always true as explained in this session.

### **Oestrogen actions in the heart. (P.A. Doevendans, Utrecht, Netherlands)**

Dr. P.A.F.M. Doevendans (Utrecht, the Netherlands) presented important aspects of "*Estrogen actions in the heart*". He reminded us that left ventricular (LV) mass is greater in men than in women. Gender-related factors may modulate the response to pathophysiological factors involved in LV hypertrophy. From this perspective, estrogen has beneficial short and long-term effects. After pointing out that estrogen receptors (ERa and ERb) are well-represented in cardiomyocytes of both males and females, Dr. Doevendans distinguished two types of effects. "Long-term" genomic effects are mediated via ERa and ERb and lead to changes in gene expression (e.g., L-type Ca channel, ANF). "Rapid" non-genomic effects may involve NO metabolism, ion homeostasis and intracellular transduction pathway. He showed that estrogen attenuates the hypertrophic response to pressure overload in mice, and antagonizes phenylephrine-induced cardiomyocytes hypertrophy in cultured myocytes.

### **Gender and signalling for hypertrophy via the Akt pathway. (M. Sussman, Cincinnati, US)**

Dr. M. Sussman (Cincinnati, USA) delivered a talk entitled "*Gender and signalling for hypertrophy via the Akt pathway*". Young women possess higher levels of nuclear-localized phospho-Akt<sup>473</sup> relative to comparably aged men or postmenopausal women. Akt is an important protein kinase regulating a broad range of physiological functions. He reported that nuclear overexpression of Akt was capable of increasing cell number without cardiac mass increase, generating more "engines" to power contractility and better protection from myocytes drop out, in mice. At the myocyte level, Ca dynamics were enhanced with supraphysiologic mechanisms. He also mentioned effects on cardiac progenitor cells. To conclude, M. Sussman emphasized that Akt is anti-apoptotic and anti-senescent, with pro-growth and pro-contractile effects. He suggested that selective estrogen receptor modulators should be investigated according to their effect on the cardiovascular system.

### **Cellular mechanisms of gender-specific repolarisation. (M. Rosen, New York, US)**

Dr. M.R. Rosen from New-York, USA, reported on "*Cellular mechanisms of gender-specific repolarization*". Women have longer corrected QTc intervals than men and are more prone to develop *Torsades de Pointe* when taking drugs that prolong repolarization. These drugs have in common a blockade of the repolarizing outward K currents I<sub>Kr</sub>. Dr Rosen showed a transmural dispersion of the L-type Ca current (I<sub>CaL</sub>) (epicardium > endocardium) in rabbit females, but not in males, consistent with gender differences seen electrophysiologically in the ascending branch and descending slopes of the T-wave and cellular action potential duration (longer *plateau*). This dispersion contributes to increase action potential duration and QT intervals in females, thereby, promoting drug- and congenital long QT syndrome-related arrhythmias. I<sub>Kr</sub> blockers (e.g. dofetilide) favour early afterdepolarizations and fatal arrhythmias. Both clinical and experimental data implicate gonadal steroids (both testosterone and estradiol) as determinants of gender-related differences.

### **Gender and susceptibility to arrhythmias: clinical implications. (H. Tan, Amsterdam, NL)**

Dr. H.L. Tan from Amsterdam, the Netherlands, reviewed a variety of pathophysiological situations – acquired or inherited – supporting "*Gender and susceptibility to arrhythmias: clinical implications*". For example, he mentioned that testosterone shortens the QT and that gender effects are often age-dependent. He reported that the Brugada syndrome (an autosomal defect linked to SCN5A Na channel mutation) is more prevalent and malignant in males. In contrast, dl sotalol induces *Torsades de Pointe* more frequently in women than in men. In the case of ischemic heart diseases, females lag behind males, probably because they have less coronary artery disease and less tendency to develop arrhythmias leading to sudden death.

In conclusion, sex is a potent modulator of cardiac function. In heart disease, being a male or a female has both advantages and disadvantages, depending on the period of life and hormonal exposure. Increasing our knowledge of gender-related differences may open new perspectives for the development of sexy therapeutic strategies.

## ***A Second Point of View on Informatics, Patient Management and Research***

Prof. Peter Macfarlane  
Glasgow, United Kingdom



**Impact of informatic tools on research and patient care: the ACC experience. (W.S. Weintraub, Atlanta, US)**

**Tailoring therapy to individuals: clinical and research needs for common databases. (D. Cianflone, Milan, IT)**

**Optimising patient care and research: European cardiovascular data registry. (M.L. Simoons, Rotterdam, NL)**

**Cardiac catheterization and interventions: the first software for international interoperability of databases. (C. Pristipino, Rome, IT)**

Weintraub described the collection of the ACC database for assessing effectiveness of cath lab procedures in different hospitals with varying numbers of procedures. Cianflone described how databases might be used in future to tailor therapy to an individual's needs on the basis of experience while Pristipino elaborated on methods designed to allow French and Italian cardiovascular databases to be merged. Finally, Simoons briefly discussed the potential role of the European cardiovascular data registry in optimizing patient care.

Macfarlane summarized by saying that although databases were not "sexy", their collection played a vital role in the future of evidence-based cardiological practice.

## ***How can informatics improve patient management and research***

Prof. Grzegorz Opolski  
Warsaw, Poland



### **Registry for every cardiovascular patient?**

#### **Impact of informatic tools on research and patient care: the ACC experience. (W.S. Weintraub, Atlanta, US)**

Dr W.S. Weintraub (Atlanta, US) showed how the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) is used for research and patient care. ACC-NCDR is established to provide a uniform and comprehensive database for analysis of cardiovascular procedures across the US. Data are collected and reported according to uniform guidelines since 1998. Up to now, data from more than 1,300,000 patients (pts) admissions and more than 500,000 percutaneous coronary intervention (PCI) have been collected. Dr Weintraub introduced version 3.0 of ACC-NCDR with new and modified elements. Data from ACC-NCDR were used for example to examine the relationship between hospital PCI volume and adverse outcomes. Results showed that PCI volume was not a significant independent predictor of mortality or urgent CABG. Although overall risk-adjusted mortality was higher for acute myocardial infarction pts undergoing PCI at sites performing less than 200 procedures per year, more than 50% of these sites had lower overall risk-adjusted mortality rate. The ACC-NCDR committee plans to perform follow-up at 6 months in selected group of pts from this Registry.

#### **Tailoring therapy to individuals: clinical and research needs for common databases. (D. Cianflone, Milan, IT)**

Dr D. Cianflone (Milano, IT) discussed the necessity for common databases. Qualitative databases, searchable with a common protocol, are being established in collaborating centres to provide ready-access to "how to" aspects of implementation and link individuals and institutions concerned with the practice of cardiovascular disease prevention. It is intended that access to this information will reduce developmental costs and facilitate collaboration. Areas of interest for case-studies include: worksite health promotion, school health, community-based heart health initiatives, risk factor screening programs, major national campaigns, professional education, dissemination of clinical guidelines and cardiac rehabilitation. Solution for these issues could be the use of World Wide Web technology with multiplatform access via web browsers and simple, standardized user interface.

#### **Optimising patient care and research: European cardiovascular data registry. (M.L. Simoons, Rotterdam, NL)**

Dr M.L. Simoons (Rotterdam, NL) gave an overview of European Cardiovascular Data Registry. The Euro Heart Survey programme provides systematic cardiovascular surveys, which will contribute to improved cardiovascular patient care in Europe. The surveys are designed to have a flexible approach to major cardiovascular topics while maintaining rigorous standards and are, therefore, adapted to the needs of both industry and medical community programmes. The registry will bring together patient-related data and knowledge base. The first results from the registry will be presented next year. Dr Simoons stated the positive impact of competition between different vendors of integrated data systems.

#### **Cardiac catheterization and interventions: the first software for international inter-operability of databases. (C. Pristipino, Rome, IT)**

Dr C. Pristipino (Rome, IT) demonstrated the first software for international inter-operability of databases in cardiac catheterization and interventions (GB Cardio ANMCO). Results from data from Italy and France proved that the international interoperability of cardio-databases is possible and feasible. They suggest that common prospective databases will significantly improve disease understanding and management. In his presentation, Dr Pristipino stated that GB Cardio ANMCO is ready to share at European level, with potential population of 120 million inhabitants. His further plans include development of stable virtual or physical connection, improvement of core data sets, expansion of common fields, and widening area of interest to acute coronary syndromes, echocardiography and electrophysiology.

**In conclusion**, informatics – mainly by means of registries – not only provide valuable data regarding diagnosis, management and outcomes of pts in the "real world", but it might also serve as the decision-making tool for shaping more effective healthcare in the cardiovascular field.

## ***Arterial Stiffness: A New Diagnostic and Prognostic Tool***

Prof. Denis Clement  
Ghent, Belgium



The clinical importance of the vascular system has been neglected for years by many cardiologists. However, last years, it has been recognized that blood vessels possess characteristics that can predict future cardiovascular events such as myocardial infarction and stroke.

### **Arterial wall elastic properties. (M.F. O'Rourke, Sydney, AU)**

The concepts of vascular compliance and thickness have brought another way to approach peripheral hemodynamics on top of the earlier concept of peripheral resistance. When examining an arterial wave, one should reflect that it is constituted by several parts including an important reflection wave that is due to the backward movement of blood when contacting the resistance of the blood vessel wall; this wave normally falls within the diastolic part of the arterial curve, but can come earlier during systole, when the vessel wall becomes thicker and less elastic. This is typically the case in elderly subjects, causing augmentation of the systolic pressure clinically known as systolic hypertension. Analysis of this phenomenon automatically leads to the study of the vessel wall characteristics and among these, vascular wall thickness.

### **How to evaluate arterial stiffness? (C. Giannattasio, Monza, IT)**

The oldest way to approach vascular wall characteristics is to measure pulse wave velocity. This can be determined quite easily by measuring the time difference between the pulse waves arriving at two locations such as the carotid and the femoral artery. The stiffer the wall, the quicker the velocity of the pulse. Often distensibility is used derived from vessel diameter (determined by ultrasound) and pulse pressure (difference between systolic and diastolic pressure). There is a clear relation with age, ambulatory blood pressure and intima/media thickness. Above all, these parameters correlate with survival and cardiovascular events. Unfortunately, methods to evaluate these parameters are still too cumbersome to be used in daily practice but great progress is being made in recent years.

### **What causes arterial stiffening? (J. Cockcroft, Cardiff, GB)**

Both structural as well as functional factors play a role. Among the functional factors, endothelium influences the process significantly because of the control on vasoconstriction and vasodilatation. On top of this, clearly all factors controlling vascular tone come into consideration such as the sympathetic system and the renin-angiotensin system. Among the structural factors, genetic influences play a role (see studies in twins), inflammation of the vascular wall and synthesis/breakdown of the elastic layers. Again, this leads to understand why it all changes with age but many other influences come into action (for example arterial hypertension, calcification of the wall).

### **Pulse pressure and arterial stiffness: epiphenomena or prognosticators? (M. Safar, Paris, FR)**

The finding that these parameters clearly function as indicators of long term prognosis brings the analysis of vascular wall thickness far above solely academic importance. Professor Safar is the world-wide expert in this issue and spent a greater deal of his academic life studying these interesting new issues. He comes to the conclusion that over the age of 50 years, pulse pressure is one of the most important parameters predicting cardiovascular morbidity and mortality. Measurement of an easy parameter such as pulse wave velocity should be added to our list of parameters to determine prognosis.

### **Modification of arterial stiffness: is it feasible?**

Obviously, when accepting the importance of arterial stiffness in prognosis, one would want to influence it to improve prognosis. Clearly, this can be done and several studies with antihypertensive agents have shown that it is possible to decrease thickness and improve pulse velocity. Studies should be set up to see whether this improvement is also directly linked to improvement of long term prognosis.

This symposium is opening a complete new way to study cardiovascular prognosis. The topic is presently still made slightly difficult by some technical factors although measurement of pulse wave velocity is easy. Clearly, study of the vascular system is highly informative to the cardiologists who should not forget that blood vessels are a fully integrated part of the cardiovascular system.

## ***Avoiding Overuse of Drugs and Interventions: Sparing Pills and Pennies***

Prof. Raffaele De Caterina  
Chieti, Italy



### **Can We Avoid Overuse of Drugs and Interventions?**

In a time of constrained resources, the bulging of new treatment options in Cardiology demands a clear rationalization of their use. Giving everything to everyone is not only impossible from a purely economical standpoint, but has the risk of exposing patients to the risk of unnecessary and often potentially dangerous procedures. This Symposium was organized with the aim of covering five important areas of cardiovascular research in which there is a clear risk of overusing drugs and treatments.

#### **In whom should we spare aspirin in primary prevention? (C. Patrono, Rome, IT)**

Carlo Patrono, from the University of Rome, Italy, elaborated on the choice of patients in whom we should refrain from using aspirin in primary prevention. Despite the popular belief that aspirin is an innocuous drug, it is associated with a sizeable risk of bleeding events, related both to its direct effects on the gastro-intestinal mucosa and to its ability to interfere with haemostasis. The benefit of aspirin in preventing thrombosis clearly outweighs the risk in secondary prevention of cardiovascular disease. However, when in primary prevention we move towards healthier and healthier populations, the risk/benefit ratio substantially decreases, and becomes close to that for values of absolute risk of cardiovascular events around 1% per year. When we are considering treating such types of patients, we need to address the risk/benefit ratio and possibly abstain from the use of aspirin.

#### **In whom can we avoid statins? (T.R. Pedersen, Oslo, NO)**

Terje R. Pedersen, from the University of Oslo, elaborated on the use of statins. Here, inappropriate or unwarranted use in cardiovascular disease is admittedly rarer, because the risk/benefit ratio is favourable in the vast majority of patients, with the exception of possible interaction with other drugs and the use in very-low-risk populations.

#### **In which post-myocardial infarction patient can we spare an implantable cardioverter-defibrillator? (A. Leenhardt, Paris, FR)**

Antoine Leenhardt, from Paris, France, addressed the issue of the implantable cardioverter-defibrillator in patients after an acute myocardial infarction with a low (<40%) ejection fraction. These devices have a Class I indication (full appropriateness) in these patients when a spontaneous ventricular tachycardia is detected and this is inducible at an electrophysiological test. However, other than in this category, many other patients might benefit. Given the high cost of the device, non-invasive markers of a high susceptibility to fatal arrhythmias should be studied prospectively to assess the most appropriate indications of the implant.

#### **In whom with unstable coronary syndromes can we avoid glycoprotein IIb/IIIa inhibitors? (R. Wilcox, Nottingham, GB)**

Robert G. Wilcox, from the University of Nottingham, UK, addressed the issue of the routine use of glycoprotein IIb/IIIa antagonists in unstable coronary syndromes. These are expensive drugs associated with a clear increase of major bleeding episodes, and find now a clear place in the medical armamentarium when patients with unstable coronary syndromes undergo a percutaneous intervention. Outside of the catheterization laboratory, however, their use is much more debatable. In fact, their use is accompanied by no clear decrease in mortality, some decrease in myocardial infarction (usually clinically inconsequential), likely balanced by an increase in serious bleeding. Their routine use in this setting is therefore, arguably, very much debatable.

#### **In whom submitted to a percutaneous coronary intervention could we avoid stenting? (B. Meier, Berne, CH)**

Bernhard Meier, from Bern, Switzerland, addressed the issue of avoiding the use of stenting during percutaneous interventions. Stenting is probably useful in only 25% of the procedures. The use of routine stenting in the treatment of all dilated lesions is likely to be a clear example of overuse, since most dilatations cannot be improved (and could possibly actually be harmed) by stenting. The same of course applies for the excessive use of the newcomers in the area, the even more expensive drug-eluting stents, which are now likely to be implanted in most cases for lesions that would not even require plain stenting. Here the experience of the interventional cardiologist probably plays a major role for containing the escalation of costs, something certainly not favoured by the current trends.

In summary: a Session to promote meditation on reading carefully the results of trials and keep in mind on the one hand the Hippocratic dictum "First do not harm", and – on the other – that we all live in a world of limited resources., ...despite the glittering of cardiological exhibits.

## ***Update on Free Radicals in Cardiac Pathophysiology***

Dr. Barbara Casadei  
Oxford, United Kingdom



This excellent symposium reviewed new evidence highlighting previously unrecognized roles of free radical production in myocardial and vascular signaling.

### **Mechanisms of myocardial ischaemic preconditioning and hibernation: role of free radicals and nitric oxide (Dr R Schultz, Essen, DE)**

Dr Schultz reviewed evidence in support of a negative inotropic effect of endogenous nitric oxide (NO) during ischemia and the potential role of myoglobin as a myocardial buffer of NO in pathological conditions where excessive NO release may compromise left ventricular function. He also showed that reactive oxygen species (ROS) are a crucial player in mediating the protective action of 'classic' myocardial preconditioning effected by a preceding bout of ischemia.

### **Effects of free radicals on cardiac excitation-contraction coupling (G. Hasenfuss, Göttingen, DE)**

But what is the mechanism by which ROS modulate myocardial function? Dr Hasenfuss addressed this issue by showing that a short application of ROS causes delayed myocardial diastolic contracture by inducing intracellular calcium overload. He dissected the potential mechanisms involved in intracellular calcium handling to conclude that ROS-mediated inhibition of the plasmalemma sodium pump may lead to an increase in intracellular sodium, which in turn would be exchanged for calcium by the sodium/calcium exchanger resulting in calcium overload and myocardial contracture.

### **Ischaemic preconditioning in vessels: overview on new paradigms. (C. Dessy, Brussels, BE)**

As reviewed by Dr Dessy, most of the pathways involved in ROS-mediated signaling in the myocardium can be demonstrated in the vascular system where ROS are also mediating 'preconditioning' of the endothelial layer in response to ischemia. This is a novel field of research, which has already provided evidence that have potentially exciting clinical implications. The possibility that a bout of peripheral ischemia (e.g., circumscribed to the forearm) may protect another vascular bed against ischemic injury (i.e., the new paradigm of 'remote preconditioning') is an exciting finding particularly if it could be applied to the coronary circulation.

### **Myocardial NADPH oxidase and its implication in cardiac disease. (A.M. Shah, London, GB)**

However, the domain of ROS biology is no longer limited to ischemia and reperfusion, but is now also including myocardial growth. Dr Shah clearly demonstrated that ROS production by the NAD(P)H oxidase system is instrumental in mediating angiotensin-induced left ventricular hypertrophy and in stimulating myocardial fibrosis in response to left ventricular pressure overload. Intriguingly, Dr Shah's data also suggest that microdomain compartmentalization of different isoforms of the NAD(P)H oxidase may be crucial in determining their downstream signaling pathway and molecular targets. As for the NO synthases, the function of the NAD(P)H oxidase is showing a complexity and a spectrum of activity that we are only beginning to understand.

## ***Computer Applications in Cardiology***

Dr. Willem Dassen  
Maastricht, Netherlands



### **Prognostic value of the non-linear dynamicity measurement of atrial fibrillation waves detected by GPRS internet long-term electrocardiogram monitoring. (S. Khor, Budapest, HU)**

The first presenter, Dr S Khor from Budapest, addressed the prognostic value of non-linear techniques to predict paroxysmal atrial fibrillation (PAF), using extended length (28 days) Holter registrations in patients suffering from PAF and sinus rhythm recurrence within one day. After an extensive overview of methods used in the non-linear analysis there was unfortunately only limited time left to discuss the clinical results in detail.

The question was raised whether a prediction of PAF recurrence should not be based on the analysis of sinus rhythm recordings.

### **Continuous 12-lead ST monitoring adds prognostic information to TIMI risk score in patients with non-ST-elevation acute coronary syndromes. (M. Zairis, Piraeus, GR)**

In the second presentation Dr Zairis from Piraeus, Greece described how in 397 patients with non-ST elevation acute coronary syndromes (NSTACS) continuous ST-segment monitoring for 24 hours could identify a group of 101 pts with at least one transient ST-segment shift lasting at least one minute. In the total group, the incidence of the composite endpoint of cardiac death, new MI or urgent revascularization (the primary endpoints) was 24.4 %. The presenter showed a significant difference in risk in composite endpoint incidence between the subgroups of TIMI Risk Score for NSTACS, with or without ST-segment shift.

### **Towards enhanced, personal, intelligent and mobile systems for early detection and interpretation of cardiological syndromes. The EPI-MEDICS project. (J. Fayn, Lyon, FR)**

The EPI-MEDICS project was presented by Dr J. Fayn from Lyon, France. In this project the ECG of a patient can be monitored using a simple portable and intelligent Personal ECG Monitor. Based on build-in intelligent self-adaptive serial ECG processing and decision making techniques, a number of different levels of alarm could be generated. Using wireless communication protocols like Bluetooth and GSM/GPRS alarm messages can be automatically transmitted to an emergency call center. Currently the first field tests are being conducted.

### **Feasibility of seamless remote monitoring of pacemaker patients. (M. Santini, Rome, IT)**

In the presentation of Dr Santini of Rome, Italy the feasibility of remote monitoring of pacemaker patients was discussed. On a daily basis, pacemaker data were automatically transmitted to a mobile phone which relayed them to the attending physician. Out of 122 patients, 116 had enough GSM coverage and were able to set the system up correctly. Altogether, 8515 messages were sent. In 21 patients the monitoring was not completely successful, because more than 3 contacts were necessary to maintain monitoring or the interval without messages exceeded 5 days.

The success rate of automatically generated reports as compared to manually initiated ones illustrated the importance of proper training in using the device.

### **CARIS-NT: development of a multi-tier, component-based multicentre cardiology information system to support regional healthcare. (E. van der Velde, Leiden, NL)**

Dr E. van der Velde from Leiden, The Netherlands presented an overview on the CARIS-NT project. The purpose of this major project was the migration from a Client/Server oriented cardiology information system to a new, multi-tier architecture-based one. This migration will allow access to the central database also from other hospitals using a web-based front end via a secure connection. Problems to be solved include the diversity of hospital information systems used in the various hospitals together with the lack of a universal patient identification number.

### **A variable valve area lumped parameter model of left-ventricular filling. (G. Szabo, Heidelberg, DE)**

In the final presentation of Dr G Szabo from Heidelberg, Germany, a computer model of left ventricular filling was discussed. Based on measurements in six animals, atrial and ventricular pressures and flows during diastolic filling were modeled. There was a very good agreement between measured and calculated parameters like transmitral flow curves. Further evaluation using patient data obtained during invasive procedures are planned in the near future.

In conclusion, it was an interesting session illustrating the large diversity of applications in cardiology of computers and new communication technology.

## ***Tissue Factor: A key Player for Thrombosis and Inflammation***

Prof. Giuseppe Ambrosio  
Perugia, Italy

### **Role of plaque and blood-borne tissue-factor in atherothrombosis. (J. Badimon, New York, US)**

Over the last few years, there has been a surge of interest over the role of "tissue factor" in a variety of pathophysiological conditions. Once thought to be just one of many components of the coagulation cascade present in tissues (hence its name), it is now recognized to have multiple localization and multiple functions.

Tissue factor catalyzes the formation of thrombin upon activation of coagulation factors VII and X. The "classical" notion was that tissue factor is typically localized in the adventitia of vessels. Thus, it would be responsible for "physiological" hemostasis, in that it would get in contact with other coagulation factors only upon exposure of adventitia to blood, such as upon vascular trauma. We now know that tissue factor has further reaching actions.

Comments: This piece of information is of particular clinical relevance. It provides a biochemical explanation as to why not only massive plaque rupture, but even subtler plaque ulceration can give rise to massive intravascular coagulation.

### **Role of tissue factor pathway on post-ischaemic microvascular inflammation. (P. Golino, Naples, Italy)**

The second talk was by Dr. P. Golino (Naples, Italy). This talk reviewed the evidence about another source of tissue factor, and also about other roles than promoting coagulation. Dr. Golino nicely demonstrated that, whereas normal endothelium does not express tissue factor, mRNA as well as enzyme activity are rapidly produced in endothelial cells exposed to oxidants or injured by ischemia/reperfusion. In addition, convincing evidence was provided to indicate that tissue factor, both through direct interaction with specific membrane receptors, as well as secondary to its stimulating thrombin production, can activate neutrophils, monocytes, and endothelial cells, thus contributing to local "inflammatory" injury in postischemic hearts.

Comments: These observations have a particular pathophysiological relevance. On the one hand, exposure of tissue factor on coronary endothelium of reperfused hearts may be associated with intravascular coagulation at the microcirculatory level, thus contributing to the "no-reflow" phenomenon of incomplete distal reperfusion upon relief of coronary artery occlusion. On the other hand, they indicate that activation of the coagulation cascade may also contribute to maintaining a vicious cycle of inflammatory injury in post-ischemic hearts.

### **Physiological location and function of intravascular tissue factor. (B. Engelmann, Munich, DE)**

In the final talk, Dr. Engelmann (Munich, DE), reviewed the evidence for yet another source of tissue factor. Through elaborate biochemical and ultrastructural experiments he demonstrated that significant amount of tissue factor can be found in the blood, in an active form. This additional tissue factor does not come as a soluble molecule. Rather, it can be found within "cell particles" of a few hundred microns. These particles for the most part derive from activated platelet and activated endothelial cells.

Comment: The importance of this observation lies in the fact that it provides additional support to the hypothesis that inflammation and coagulation do cooperate. In fact, cell activation is expected to translate into increased tissue factor levels, which in turn could further promote inflammation in addition to being a powerful coagulation stimulus.

## ***Understanding Reperfusion Injury (Bench to Bedside)***

Prof. Frank Rademakers  
Leuven, Belgium



### **Pathophysiology for the clinician. (M. Ovize, Lyon, FR)**

### **Microcirculatory changes: can contrast echo help? (S. Kaul, Charlottesville, US)**

### **Changes in regional function: contribution of strain and strain rate imaging. (G. Sutherland, Leuven, BE)**

### **Evaluating the progression of injury: the role of magnetic resonance imaging. (D. Pennell, London, GB)**

Reperfusion injury occurs as a result of the restoration of blood flow to a previously ischemic region. While the opening of the infarct related artery is the main strategy to limit infarct size, this action by itself causes further damage to the tissue and could be deleterious. Several strategies can be undertaken to limit the negative effects of reperfusion, but to do so, we need to understand the mechanisms underlying this entity.

Myocardial stunning contributes to reperfusion injury (free radicals, calcium overload) but usually is reversible. The irreversible components include the no-reflow phenomenon and reperfusion necrosis and these are the true targets for intervention. The duration of ischemia, residual blood flow and mechanical loading of the muscle are major determinants of the extent of no-reflow. The mechanisms involved are smooth muscle swelling, white blood cell capillary plugging, interstitial myocardial oedema, microvascular spasm, microthromboembolism and plaque embolism. Pharmacologic therapies targeted towards thrombosis (IIb/IIIa inhibitors) and inflammation but also glucose/insulin (fatty Acid accumulation), cyclosporine, adenosine, calcium antagonists have shown results, as have mechanical techniques (recovery baskets during PCI) to limit the extent of no-reflow. To test these interventions in clinical practice we need in vivo imaging modalities that can show us the presence, extent and impact of no-reflow and reperfusion injury.

Both echo and CMR have this potential. Contrast echo can measure microvascular integrity and the reaction to a vasodilatory stimulus. M-mode echo can identify wall thickness increases due to oedema and it can measure the intrinsic contractile properties of the muscle through tissue Doppler. In partial wall infarcts the presence of an ischemic pattern with early systolic stretch, late systolic decreased thickening and post systolic thickening but a preserved response to dobutamine, indicates the presence of both contractile reserve and flow reserve. CMR has the spatial resolution and capacity to show the 3D extent of the key components of acute ischemia and reperfusion, ie microvascular obstruction, necrosis and oedema without the need to use a vasodilatory stimulus. Using these new tools it will be possible to test the therapies, investigated in animal research, in the relevant clinical human situation.

## ***Diagnostic and Therapeutic Dilemmas in Managing Patients with Devices***

Prof. Bernd Lüderitz Philippe Ritter  
Bonn, Germany St. Cloud, France

### **Problems with Pacemakers and ICDs: Better management is mandatory**

#### **Unexplained fever (E. Alt, New Orleans, US)**

Unexplained fever in patients with implanted devices poses diagnostic and therapeutic dilemmas. Firstly, only 20-35% of all patients with infections, especially with chronic device infections, develop fever. Other aspects such as local swelling, pain and patient history are helpful to establish the diagnosis of device infection. Secondly, fever in patients with implanted devices can, but is not necessarily related to the device. If not other source of infection is found in these patients, blood cultures, TTE and TEE help to determine about 50% the device to be the source of fever. Thirdly, total device and lead removal is the therapy of choice from which only very defined cases should be deviated.

#### **Symptomatic venous obstruction (A. Oto, Ankara, TR)**

Venous obstruction is the most common complication of the transvenous pacemaker and ICD implantation. It has been reported in up to 35% of cases. However, most are asymptomatic, and less than 5% are symptomatic. Special care should be taken in patients with cut abandoned leads, in the elderly, in patients with low ejection fraction, with previous temporary pacing leads and in the presence of systemic infections.

#### **Syncope in the paced patient (M. Brignole, Lavagna, IT)**

Despite pacemaker/ lead failure may be regarded as a specific cause of syncope in paced patients, this is rarely observed in the real world, accounting for about 7% of all patients. The most common cause of syncope is hypotension, either due to dysautonomia or to neurally mediated reflex. At particular risk of occurrence of syncope are those patients with implanted pacemakers, because of vaso-vagal syncope and sick sinus syndrome. Despite all investigations, about one third of cases of syncope remain unexplained.

#### **Pocket ulceration (R. Sutton, London, GB)**

Pocket ulceration is an avoidable problem by use of good technique. Its occurrence is usually disaster for the whole system generator and leads. A radical approach to solution to the problem of pocket ulceration is justified.

#### **Ventricular arrhythmia storm in the implantable cardioverter-defibrillator patient (E. Manios, Heraklion, GR)**

Electrical storm in ICD patients is a loosely defined situation. Therefore, controversy exists among relevant studies. However, it may be fatal and represents a true medical emergency. Amiodarone and beta-blockade can control arrhythmia and improve prognosis.

## ***Ventricular Resynchronisation for Wide QRS Heart Failure: Unresolved Issues***

Dr. Paulus Kirchhof  
Münster, Germany



### **Unresolved issues in Cardiac Resynchronisation therapy**

Cardiac resynchronization therapy (CRT) by continuous biventricular pacing improves cardiac function in patients with severe heart failure and asynchronous ventricular activation. The speakers in this session discussed unresolved issues in the clinical implementation of this form of therapy.

#### **How to select responders? (A. Auricchio, Magdeburg, DE)**

Dr. Auricchio discussed current techniques to select patients that will profit from CRT. A combination of electrophysiological (QRS duration, left ventricular activation maps) and hemodynamic measurements (echocardiographic strain rate, acute improvement of dp/dT during catheterization) will help to predict who will profit from CRT.

#### **Is left-ventricular pacing efficient in resynchronisation? (JJ Blanc, Brest, FR)**

Dr. Blanc reported that univentricular left ventricular pacing may be sufficient to achieve CRT: In small studies, left ventricular pacing improves both acute hemodynamic measurements and functional capacity after 3-6 months to a similar degree as biventricular pacing. This is supported by observational data that relate asynchronous left ventricular contraction rather than global electrical asynchrony to worsening heart failure and cardiac death. Large, randomized trials are needed to test the effects of univentricular left ventricular pacing.

#### **Resynchronisation therapy. Is it a class I or II A indication? (P. Vardas, Heraklion, GR)**

Dr. Vardas reviewed indications for CRT. For the target population (NYHA III-IV on optimal medical therapy, LVEF < 35%, QRS duration > 130ms with LBBB pattern, PR interval > 150ms), all trials (PATH-CHF, MUSTIC, MIRACLE, INSYNC) show improvement in functional capacity and QoL after 3-6 months of CRT. A recent meta-analysis suggested that CRT may reduce mortality, but ongoing trials (COMPANION, CARE-CHF) will answer this question. This will determine whether CRT will become a class I indication as opposed to the current class IIa status.

#### **Do resynchronisation devices require a tailored follow-up strategy? (C. Linde, Stockholm, SE)**

Dr. Linde called for specialized follow up during CRT therapy. Device testing and re-programming can optimize left ventricular synchronization during follow-up (prolongation of battery life, adaptation of AV delay and in some patients of VV delay). Optimal medical CHF and atrial fibrillation therapy are of paramount importance. Specialized follow-up, potentially with the help of "heart failure nurses", may improve long-term benefits of CRT. This needs to be formally tested in clinical trials.

#### **Should an implantable cardioverter-defibrillator always be used with biventricular pacing? (L. Padeletti, Florence, IT)**

Dr. Padeletti discussed the need for combination devices offering defibrillator (ICD) therapy in addition to CRT. Pathophysiologically, CRT could have both antiarrhythmic (synchronization of activation) and pro-arrhythmic effects (increased dispersion of repolarization). Some clinical observations suggest that CRT can reduce arrhythmic events. In the COMPANION trial, however, CRT+ICD combination devices improved survival at 1 year. Further studies will determine which CRT patients need an ICD.

## ***Risk estimation as a tool for cardiovascular disease prevention***

Prof. De Backer  
Ghent, Belgium



This was a highly informative and educational symposium on total multifactorial risk estimation as a tool for cardiovascular disease (CVD) prevention.

### **Why assess total cardiovascular disease risk. (D. Wood, London, GB)**

Prof. D. Wood addressed the question of why total CVD risk should be assessed. Indeed, in patients with established disease, in patients with diabetes and in people with extremely elevated risk factors, the total risk for recurrence or for a first event is already very high. No further risk estimation is needed in them. They should be given maximal attention.

However, in the large majority of asymptomatic apparently healthy people, intuitive risk estimation is frequently wrong due to over- or underestimation of total risk due to the complex synergistic interaction between different risk factors. In such a situation, a risk estimation tool can help and should be used.

### **How to assess total cardiovascular disease risk estimation. (I. M. Graham, Dublin, IE)**

Prof. I. Graham reviewed the different tools that are available, both in terms of different options and different sources of data. The pros and cons of each were discussed. The SCORE (Systematic Coronary Risk Evaluation Project) was presented. It seems to have several advantages for European populations with great possibilities for future adaptations at national level, and for the integration of new risk markers.

### **Absolute risk, relative risk, attributable risk and rate-advance periods, (H.W. Hense, Münster, DE)**

Prof. H. W. Hense addressed the question of what can be derived from risk charts in terms of estimates of absolute risk, relative risk, attributable risk and rate-advancement periods. He illustrated very clearly, with examples on the SCORE risk chart, how all this can be derived and used in clinical practice.

It became clear that such a risk estimation model is not only a tool for deciding on the intensity of the preventive action that is needed in a given individual. It can also be used as an educational tool in order to improve the doctor-patient communication.

### **Risk estimation as an interactive tool. (T. F. Thomsen, Glostrup, DK)**

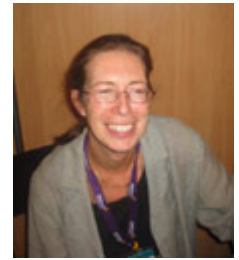
This was further elaborated by Prof. T. Thomsen, who introduced SCORECARD as the new official European electronic cardiovascular risk management system. This new system will become available early next year as an interactive treatment guide for the clinician based on the ESC recommendations on CVD prevention.

# ESC Congress Report 2003



As a new feature of the web-based news coverage of the ESC Annual Congress, 'From the Bench: Basic Science News' is devoted to the more basic research presented in Vienna.

Abstract sessions, highlighting the most recent data and contributions in the areas of cardiac and vascular biology, have been selected. Reports will be provided by experts in the field giving perspective to these new findings.



Yours sincerely,

Prof. Karin Sipido F.E.S.C.  
Editor

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## *Electrical remodeling and arrhythmogenesis: novel insights*

Professor Antonio Zaza

Abnormal expression/function of sarcolemmal and sarcoplasmic reticulum membrane proteins can both contribute to arrhythmogenesis in myocardial remodeling. Several intriguing findings in this area have been presented in this session.

Spontaneous activity is at the basis of triggered arrhythmias, because of abnormal depolarization and pacemaker activity. For the latter, a specific current, called  $I_f$ , and encoded by the HCN gene, is very important. It is normally absent in ventricular myocytes, which also normally do not have a pacemaker activity. This may change during hypertrophy and heart failure, contributing to the arrhythmias in these conditions. The work presented by Dr. Cerbai identified increased expression of the HCN2 channel isoform as the molecular basis of increased ventricular automaticity in endothelin-induced hypertrophy in rat myocytes.

In addition to a focus of abnormal activity, changes in conduction are an important determinant in the genesis and maintenance of arrhythmias. Dr Salameh described opposite changes in the expression of connexin 43, a gap junction protein, in dilated versus hypertrophic cardiomyopathies, although both conditions are characterized by an increased risk of reentrant arrhythmias. His findings suggest that the expression level of gap junctional proteins may not be the primary determinant of arrhythmogenic conduction abnormalities in such conditions, but that other factors must be involved.

Abnormal Ca handling is important for contractile alteration, but also for electrophysiological remodeling because it affects all Ca-sensitive membrane currents, as e.g. the Na/Ca exchanger. This mechanism could be of importance in atrial fibrillation. Atrial enlargement was found to be associated with an increased probability of spontaneous calcium release from the SR in human myocytes (by Dr. Hove-Madsen). On the other hand, in myocytes from patients with atrial fibrillation Ca current density was reduced (study by Dr. Greiser). The amplitude of contractions, reflecting Ca release from the sarcoplasmic reticulum was also reduced. In contrast to the reduced force developed during electrically stimulated contractions, the response to rapid cooling was normal, reflecting a normal sarcoplasmic reticulum calcium content. Put together, such findings may suggest that atrial remodeling may be associated with an abnormal function of sarcoplasmic reticulum calcium release channels and of their coupling to sarcolemmal calcium channels.

Dr. Workman also studied remodeling during atrial fibrillation looking at the Na/K ATPase, generating the so-called Na-pump current. He showed that the properties and density of the Na-pump current were altered, and this could contribute to the electrical remodeling as well as to changes in Na handling. The latter then can tie back into altered Ca handling.

These reports illustrate the many mechanisms that will contribute to the increased incidence of arrhythmias in cardiac remodeling, and that many of those may involve altered Ca handling as well.

## ***Presence and therapeutic potential of stem cells in coronary artery disease***

Prof. P.A. Doevendans  
Utrecht, Netherlands

Some of the key questions in stem cell research were addressed in five lectures. Can we identify the cells for instance in the adult organism? This subject was raised and answered by Dr Sainz from Paris, who showed the presence of SP cells in mouse aorta. It is important to realize that there are several different methods to isolate stem cells. The recognition of SP cells is based on staining characteristics of cells. Adding Hoechst dye added to cells will stain stem cells less than other cells. This difference can be detected by a robot using fluorescence to sort cells. The image provides something like a scatter plot, where the cells with low staining intensity can be identified in the left lower panel. As the staining of the cells is different from the main population they have been named the side population (SP) cells. SP cells can be harvested from any tissue. She showed that these cells are also present in the aorta in adult mice. Where these cells are coming from and what their potential role in pathophysiology could be is still unclear. Important is the further studies she performed to show the mixed population of cells present among the SP fraction. More than 90% of the cells were SCA1+ (membrane protein detected in stem cells) while less than 10% express CD34 (membrane protein detected in endothelial progenitor cells).

This indicates that just isolating a group of cells based on morphology (mononuclear cells) or staining characteristics (Hoechst) are useful to isolate cells including stem cells. However the percentage of stem cells is unclear and whether the appropriate cells are there for specific applications is unclear.

The differentiation potential of stem cells was further analyzed by Dr Pesce (Rome). He studied the effect of a cytokine (Stromal derived factor 1) on differentiation. The cell source were hematopoietic stem cells. He isolated cells that expressed another marker (c-kit, stem cell factor receptor). A detailed analysis was performed to check whether SDF helps to push c-kit+ cells into the direction of the endothelial cell lineage. In the presence of collagen and fibronectin SDF appeared to be a very potent factor for endothelial cell differentiation in vitro (cell culture). Blocking integrin adhesion completely blocked this phenomenon. Apparently this factor directs endothelial cell formation, once precursors attach to the extracellular matrix.

Also Dr Ninci (Freiburg) has been looking at the influence of growth factors (VEGF) on cell differentiation. In this study the source were bone marrow derived macrophages. The model presented focused on the role of macrophages in arteriogenesis. Several techniques were presented including microarray, real time PCR (to determine RNA levels) and protein analysis. She showed that macrophages express receptors (flk and flt1) for VEGF. She showed that at the protein level the expression of cytokines (Monocyte Chemoattractant Protein 1 and 5) is down regulated, while Cadherin is upregulated. These results indicate that the cells gradually move from the inflammatory phenotype to cells contributing to the vascular structure.

Fundamental studies in patients with an acute myocardial infarction were presented by Dr Ferrario (Padua, Italy). His group performed an important straightforward analysis in patients presenting with acute myocardial infarction. They determined the number of circulating endothelial progenitor cells in serum at the time of admission, and several later timepoints. The results revealed a dramatic increase in the number of CD34+ cells, on admission gradually decreasing in the following weeks. In addition an increase in SCF and VEGF levels was observed. These data would suggest that mobilization of stem cells if beneficial should be stimulated a few days after the infarct. However there were no data to show that pts with a strong response have a better outcome.

The last abstract was another essential report on a stem cell study in primates. Baboons were treated with C-CSF and SCF just prior or shortly after MI. The effect of stem cell mobilization post MI was assessed with advanced techniques to determine blood flow, left ventricular function, and infarct size. Infarct size was assessed with in vivo imaging (PET) and histological analyses. The results of the study showed a sustained increase in circulating EPCs in the treated animals. These enhanced EPC numbers could have contributed to the increased myocardial blood flow observed. There was no reduction in infarct size nor was there any improvement in left ventricular function. The model used was a complete or chronic myocardial infarction based on an occluded vessel.

One of the chairman (Dr P. Doevendans, author) was invited to summarize this session. He stressed the lack of fundamental knowledge in stem cell biology. This was illustrated by the data from the first three abstracts as these studies are still focusing on stem cell recognition, selection and differentiation. Little pieces of information were provided here, suggesting induction of differentiation into endothelial cells by SDF in the correct environment (Pesce) and the modification of macrophages by VEGF (Ninci). Also the recognition of stem cell in mouse aorta tissue (Sainz) is part of stem cell biology. In a patient study the natural course of stem cell mobilization was addressed which is crucial for any clinical intervention study using stem cell factors. The results in monkeys clearly showed an effect of mobilized EPCs on blood flow but not on infarct size. All groups look at different stem cell populations and sources.

To this day there is no proof for any transdifferentiation of EPCs in large animals or man into the cardiomyocyte phenotype. It is crucial to perform preclinical studies to determine the relationship between the number of cells mobilized or injected and improvement of function. Hopefully, these studies are ongoing.

## *Targetting signaling pathways in left ventricular hypertrophy*

Gianluigi Condorelli, MD, PhD

**Presentation Title(s):** -Blocking p193 and p63 pro-apoptotic pathways has positive effects on cardiac morphology and function after myocardial infarction

-Gene Transfer of the mechanically-induced gene IEX-I inhibits cardiac hypertrophy in vivo

-Targeted Disruption of RyR2 in the heart suppresses pressure overload-induced cardiac hypertrophy but impairs cardiac function

Activation of E2F transcription factor in cardiac hypertrophy

**Presented by:** Dr. R. Hassink, Dr. P.C. Schulze, Dr. Y. Zou, R. Hinrichsen

Cardiac hypertrophy has long been seen as a compensatory and adaptive response to increased demands on the heart. The structural changes are accompanied by functional changes, and it is now thought that many aspects of this remodeling are actually contributing to the progression of disease. Therefore a lot of research is aimed at gaining insight into the mechanisms underlying this hypertrophic response, as illustrated by the studies presented at this session.

Dr. R. Hassink from Utrecht, NL, demonstrated that blocking apoptosis through the inhibition of the tumor suppressor and apoptosis inducer p53 and another protein called p193 in cardiomyocytes ameliorates cardiac function and preserves myocardial viability after myocardial infarction, even 6 months after myocardial infarction. These results were obtained using a mouse model whereby negative interfering p53 and p193 were overexpressed in the cardiomyocyte compartment.

Dr. P.C. Schulze from Cambridge, USA, showed that a gene called IEX-1 can prevent pressure overload hypertrophy. Gene transfer studies in vivo and in vitro and elegant histological analyses were used to determine the anti-hypertrophic effects of IEX-1. Therefore, this novel gene may represent an important negative regulatory feed-back mechanisms in the early phase of cardiac hypertrophy.

Dr. Zou from Chiba (JP) presented data on a mouse model of heterozygous knockout of Ryanodine Receptor type 2. The heterozygous knockout mouse model demonstrated that RyR2 is involved in the control of cardiomyocyte hypertrophy, beside its role in the control of Ca<sup>2+</sup> flux from the sarcoplasmic reticulum. In fact, its absence increases the expression for fetal gene expression in the heart after pressure overload.

Dr. R Hinrichsen from Copenhagen, DK, demonstrated the importance of the transcriptional factors E2F in cardiac hypertrophy. E2Fs control cellular proliferation, while terminally differentiated cardiomyocytes do not proliferate. Dr. Hinrichsen demonstrated that E2F activity is indeed activated by hypertrophic stimuli and is important for the hypertrophic response.

The pathways leading to hypertrophy are clearly diverse and complex. Studies as presented here are examining a specific detail of this network. Future research will have to integrate these data, and establish their role in the various conditions that can lead to cardiac hypertrophy.

## *Young Investigator's Award on Thrombosis Session*

Raffaele De Caterina, MD, PhD

The Young Investigator's Award on Thrombosis was established in 1999 by the Working Group on Thrombosis of the European Society of Cardiology to promote original research on thrombosis within the Society by investigator less than 35 years old. Since then, each year, the 5 best abstracts submitted for the ESC Congress and fulfilling the admission criteria have been selected for presentation in front of a Jury.

The three best investigations are awarded prizes of 1000, 500 and 250 Euros, and a Diploma, presented during the Award Ceremony. This year the Jury has been composed by: Prof. Raffaele De Caterina and Prof. Gilles Montalescot (Chairmen of the Session); Prof. Steen Dalby Kristensen, Prof. Keith A. Fox, Prof. Christian W Hamm.

The presenters this year were:

- **G. Vilahur** (Barcelona, SP): Effects of a novel platelet selective NO donor, aspirin + clopidogrel and combined therapy in inhibiting flow and lesion-dependent thrombosis;
- **N. Qamar** (Leicester, GB): Increased platelet reactivity in healthy young individuals with a two-generational family history of premature myocardial infarction;
- **H. Turhan** (Ankara, TR): Increased soluble adhesion molecules in patients with slow coronary flow;
- **N. Slavina** (Moscow, RU): Both ticlopidine and clopidogrel prevent acute phase elevation of von Willebrand factor in non-ST-elevation acute coronary syndromes;
- **R.J. Curtin** (Dublin, IE): Using the PFA-100 and serum thromboxane B2 to measure aspirin resistance in patients with cardiovascular disease.

Criteria for the assignment of the prizes are the originality of the presented research, methodology, quality of the presentation and responses to questions raised during the discussion. This year the prizes have been awarded to the following three investigators:

- **R.J Curtin** (Dublin, IE): winner of the first prize
- **N. Qamar** (Leicester, GB): winner of the second prize
- **G. Vilahur** (Barcelona, SP): winner of the third prize

The Working Group on Thrombosis congratulates the winners and all the finalists in general for the quality of research presented, and wishes all of them a successful research career.

## *Young Investigators Award in Basic Science*

Prof. John Martin  
London, United Kingdom

The prestigious award for the best presentation in basic science was decided today. Five scientists under the age of 35 years presented their work to a jury comprised of Dr. JJ. Mercadier, P. Benlian, G. Hasenfuss and J. Martin. The standard of the science presented was universally outstanding, leaving the judges with a difficult decision. The result were announced at the Awards Ceremony on Tuesday September 2nd. The titles of the presentations and the names of the presenters are as follows (in order of presentation):

- The pro-angiogenic factor CYR61 is highly expressed after myocardial stress and depends on activation of PKC and MAPKs.  
**K. Kaminski** (Bialystok, PL)
- Regulation of the growth arrest and DNA damage-inducible gene 45 (GADD45) by peroxisome proliferator-activated receptor gamma in vascular smooth muscle cells.  
**D. Bruemmer** (Berlin, DE)
- Is Skp-2 the missing link between the extracellular matrix and vascular smooth muscle cell proliferation?  
**M. Bond** (Bristol, GB)
- Altered phosphorylation status of phospholamban, PLB, and its contribution to the negative  $[Ca^{2+}]_i$ -frequency relationship in the MLP<sup>-/-</sup> mouse with heart failure.  
**G. Antoons** (Leuven, BE)
- Matrix metalloproteinases-9 and -12 have opposite effects on atherosclerotic plaque stability.  
**J. Johnson** (Bristol, GB)

The Jury considered the innovative and methodological qualities of the work, the strength of the mechanistic insights, the quality of the presentation, and the discussion with the jury members. The Awardees were:

First prize, **D. Bruemmer** (Berlin, DE)

Second prize, **G. Antoons** (Leuven, BE)

Third prize, **K. Kaminski** (Bialystok, PL)