Treatment of Elderly Patients:
The Challenge of the Future

Keynote Speaker
Cornel Sieber
Erlangen-Nürnberg, D

From Friday,
September 25th, 2015, 6 pm
till Sunday,
September 27th, 2015, 2:15 pm

Opening: City Building Halle
Marktplatz, Halle (Saale)
Conference Site: Lion Building
Universitätsplatz 11, Halle (Saale)
Martin-Luther-University Halle-Wittenberg
Treatment of Elderly Patients: The Challenge of the Future

September 25\textsuperscript{th} – 27\textsuperscript{th} 2015

Heart Centre
University Hospital Halle (Saale)

in cooperation with

German National Academy of Sciences Leopoldina

DGGG - German Society of Gerontology and Geriatrics

DGTHG - German Society of Thoracic and Cardiovascular Surgery

European Section of the International Academy of Cardiovascular Sciences

Interdisciplinary Centre for Ageing Halle (IZAH)
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Treatment of Elderly Patients: The Challenge of the Future

- Meeting language English -

Friday September 25th 2015
Stadthaus Halle – City Building Halle

18:00 Opening

Andreas Simm

Address
M. Gekle, Dean of the Medical Faculty
R.-E. Silber, Heart Centre University Hospital Halle (Saale)

Keynote lecture and Schober award

Laudation Cornel Sieber
by Judith Campisi, Novato, USA

Keynote lecture:

Cornel Sieber
FAU – Friedrich-Alexander Universität, Erlangen-Nürnberg, D

“The elderly patient with frailty: from concepts to treatment”

20:00 Come Together
Saturday September 26th 2015
Löwengebäude – Lion Building

08:00 – 10:00 Session 1

Epidemiology / defining thresholds

Chair: George M. Martin, Andreas Simm

Increasing longevity – perspectives and challenges Jutta Gampe
Calculation of age-specific population-based reference intervals Till Ittermann
Is there a need for new cut-offs in the elderly and the frail? Stephan von Haehling
Reference intervals for geriatric patients – pros and cons Ursula Müller-Werdan

10:00 – 10:30 Coffee Break

10:30 – 12:30 Session 2

Vessel aging and diseases

Chair: Stefan Frantz, Hendrik Treede

Blood pressure strategies and goals in elderly patients with hypertension Peter Nilsson
Age-related accumulation of advanced glycation end products modifications reflect the vascular and cardiac function Andreas Simm
Vessels stiffness: from blood pressure to brain function Angelo Scuteri
Ageing and atherosclerosis Martin R. Bennett

12:30 – 13:30 Lunch Break
Saturday September 26th 2015

13:30 – 15:30 Session 3

Cardiac aging and diseases

Chair: Ursula Müller-Werdan, James Rudolph

Challenges and Chances of Cardiac Surgery in an Ageing Population  Hendrik Treede

Immunological phenomena in cardiac physiology and pathophysiology  Stefan Frantz

Cardiovascular risk in diabetes patients – a problem of long term and acute diabetes complications?"  Andreas Thomas

Long-term mechanical circulatory support (MCS) in the Elderly patient  Harriette Verwey

15:30 – 16:30 Poster Session / Coffee Break

16:30 – 18:30 Session 4

Frailty: from mice to humans

Chair: Angelo Scuteri, Martin R. Bennett

Frailty and Health Span in C. elegans and Mice  Thomas Johnson

Cellular senescence, ageing and wound healing  Judith Campisi

Geroscience in clinical practice: future perspectives  Andrea Maier

Frailty: from mice (rats) to humans. The electrophysiological effects  András Varró

20:00 Conference-Dinner (Landesmuseum für Vorgeschichte – Museum for Prehistory)
### Sunday September 27th 2015

#### 08:30 – 10:30 Session 5

**Multimorbidity: renal and cognitive function**

*Chair: Andrea Maier, Stephan von Haehling*

- Change of kidney function with age  
  Michael Gekle
- Challenges in the treatment of elderly patients with end stage renal disease: a clinical approach  
  Jeroen Kooman
- Successful Surgery - Challenging Recovery: Functional and Cognitive Recovery after Cardiac Surgery  
  James Rudolph
- Intensive Care reflected in multimorbidity and cognitive dysfunction  
  Hans-Jürgen Heppner

#### 10:30 – 11:30 Poster Session / Coffee Break

#### 11:30 – 11:45 Posterprice

#### 11:45 – 13:45 Session 6

**Ethical issues**

*Chair: Harriette Verwey, Cornel Sieber*

- The Ethical Struggle for Universal, High Quality, Affordable Health Care in the USA Lessons for the Developing World  
  George M. Martin
- Treatment of Elderly Patients: A View from Ethics  
  Andreas Suchanek
- Ethical reflections on vulnerability and human dignity in borderline situations of old age  
  Andreas Kruse
- The Treatment of Elderly Patients and their Protection in German Law  
  Christoph Mandla

#### 13:45 – 14:15 Farewell
The elderly patient with frailty: from concepts to treatment

Cornel Sieber

Frailty has over the years emerged as a true Geriatric syndrome, with a substantial overlap to sarcopenia (age-related loss of muscle mass). Frailty is an age-associated syndrome, depicted by a diminished endurance against internal and external stressors. Both syndromes have in common, that they negatively interfere with morbidity and mortality in older adults.

Research in the field of the frailty syndrome show clear translational approaches and as for sarcopenia, those results have and will even more in the future allow targeted interventions in multimorbid older adults, where mortality is not the most important endpoint, but much more the prevention or reversal of functional decline and by that loss of independence.

Within this described arena, the lecture will target on concepts of both frailty and sarcopenia from normal to „pathophysiological“ aging, with a special focus on, a) ongoing (inter)national projects (SPRINTT, Enable, ...) and, b) epidemiological and therapeutic The primary aim of the talk is to raise interest on integrated diagnostic and treatment approaches in a fast aging society away from a classical disease concept towards treatment strategies having functionality and prevention of disability as the primary focus.
In most developed countries life expectancy is increasing, with an average gain of about three months per year. While additional years previously were gained mostly by reductions of mortality for infants, children and young adults, the current improvement is predominantly due to reductions of mortality at old ages. This mortality decline is projected to continue and is assumed to gradually affect even the highest ages, thus leading to further increase in longevity.

We will discuss the implications of this projected increase in longevity such as the continuing rise in the numbers of the oldest-old, the current state of knowledge on the health status of the elderly, and the implications that this development will have for the health care systems in the future.
Calculation of age-specific population-based reference intervals

Till Ittermann

Reference intervals are widely applied in clinical practice, particularly for biomarkers. If a value outside of a reference interval is observed in an individual, the risk for a disease is increased indicating diagnostic significance. However, treatment decisions should not be drawn solely from a value outside of a reference interval, because reference intervals have no prognostic significance.

Reference interval calculation requires two steps. First a healthy population has to be defined. For this, data from large population-based studies is ideal, since exclusion criteria can be derived from study data, so that not only diagnosed but also previously undiagnosed diseases can be considered to define a healthy population. Data from such studies are also representative for the general population. Commonly, reference intervals for a parameter of interest are defined as its 2.5th and 97.5th percentile in the healthy population. Recently, quantile regression has received increasing attention as tool for reference interval calculation, because percentiles (e.g. 2.5th and 97.5th) can be directly modeled. A further advantage of quantile regression is that individual reference intervals can be calculated by introducing variables such as age, sex, smoking status and body mass index into the model. Thus, reference intervals of a parameter can be given for each year of age.

Three examples of reference interval calculation based on data from the Study of Health in Pomerania (SHIP) will be presented. Examples will include biomarkers (concentrations of thyrotropin and hemoglobin) and parameters of cardiopulmonary exercise testing (maximal oxygen uptake and maximal oxygen pulse).
Is there a need for new cut-offs in the elderly and the frail?

Stephan von Haehling

Cut-off values are used throughout all subjects of medicine and help tremendously in clinical decision-making. However, recent years have shown that some cut-off values may be considered as moving targets throughout the life span. This is true not only for cut-off values that have been accepted in recent years such as defining criteria of hypertension, but also those for the definition of overweight and obesity or muscle mass. Other examples embrace biomarker values such as those for N-terminal pro B-type natriuretic peptide or ferritin and transferrin saturation, the defining values of iron deficiency.

References:
Physiological ageing goes along with changes in homeostasis, resulting in alterations of body composition and organ functions even in the absence of overt disease. These changes in homeostasis are most evident in situations, when compensatory mechanisms are required to cope with an external stimulus challenging homeostasis. The red line of organ aging in fact is homeostenosis, which implies a narrowing of reserve in response to noxious challenges.

While age-related diseases have been studied thoroughly, much less is known about physiological organ ageing and the physiology of old age in general. The data basis for the clinically used routine measure (e.g. clinical chemistry, ECG, echocardiography, X-ray, scores in the ICU) stems from population of younger adults. While for the pediatric population some special reference values/intervals have been gathered to comply with the physiology of children’s organs, no such reference values for the geriatric population exist. Developing such reference data for the geriatric population is hampered by the substantial heterogeneity of the elderly, old and very old individuals.

In order to best provide a description of the organ physiology for clinical routine, age strata have to be defines and reference values for every age group should be gathered. This can be exemplified for ICU patients, whose organ failures have to be rated by scores.
Blood pressure strategies and goals in elderly patients with hypertension

Peter Nilsson

Hypertension is a major risk factor for cardiovascular disease on a global scale and appointed as the number one factor for overall mortality risk by the World Health Organization (WHO). It can lead to a number of cardiovascular complications in the elderly such as stroke and coronary heart disease, but also peripheral artery disease and cognitive impairment – a factor increasing the risk of dementia.

Even if the HYVET study could show clinical benefits by treating elevated blood pressure in “healthy” elderly 80+ years, it has been questioned whether this also applies to the frail elderly. To many clinicians it is not reasonable to over-treat a frail elderly patient with a number of co-morbidities and a reduced remaining life span. In fact, this circumstance could even be a motive to reduce drug dosage or even stop anti-hypertensive drugs all together. One complication is that some of these drugs with a potential blood-pressure lowering effect may also have other more pressing indications such as congestive heart failure (diuretics), ischemic heart disease (ACE-inhibitors, beta-receptor blockers) or angina pectoris (calcium antagonists, beta-receptor blockers or nitrates).

In recent guidelines from ESH and ESC on management of arterial hypertension from 2013 it was pointed out that there is strong evidence of benefits from lowering of BP by antihypertensive treatment in the elderly, limited to individuals with initial SBP of ≥160 mmHg, whose SBP was reduced to values <150 but not <140 mmHg. Therefore the recommendation of lowering SBP to <150 mmHg in elderly individuals with systolic BP ≥160 mmHg is strongly evidence-based. However, at least in elderly individuals younger than 80 years, antihypertensive treatment may be considered at SBP values >140 mmHg and aimed at values <140 mmHg, if the individuals are fit and treatment is well tolerated. A prospective meta-analysis compared the benefits of different antihypertensive regimens in patients younger or older than 65 years and confirmed that there is no evidence that different classes are differently effective in the younger vs. the older patient. In individuals older than 80 years with an initial SBP =160 mmHg it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian.

All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. The evidence for antihypertensive drug treatment in demented elderly is however lacking.

In a new sub-analysis from the HYVET study the authors found no evidence of an interaction between effect of treatment for hypertension and frailty as measured by a frailty index (FI). Both the trailer and the fitter older adults with hypertension appeared to gain from treatment. These new findings will be debated. It has, however, been questioned whether the HYVET study is really suitable to study frail elderly subjects at all due to its exclusion criteria.

In summary, treatment of hypertension seems to benefit the “healthy” elderly even 80+ subjects, but the role of this treatment in frail elderly and in subjects with dementia is currently debated. Clinical wisdom often has to substitute for the lack of firm evidence of how hypertension should be managed in frail elderly with many co-morbidities.
Age-related accumulation of advanced glycation end products modifications reflect the vascular and cardiac function

Andreas Simm

Advanced glycation end products (AGEs) seem to be involved in aging as well as in the development of diseases such as cardiovascular diseases, diabetes mellitus and renal failure. During aging, AGEs accumulate in matrix proteins like collagen and contribute to tissue stiffness. Whether non-invasive measurement of AGE accumulation in the skin may reflect function and protein modification of vessel and cardiac tissue is unknown.

In this study we analyzed the AGE-modifications in the collagens extracted from residual bypass graft material and cardiac tissue. Collagen types I and III (pepsin digestible collagen-, collagenase digestible collagen- and insoluble collagen fractions) were isolated from right atrial auricle of 72 patients and from veins of 52 patients. Collagen was quantified by 4-hydroxyproline assay and AGEs by the AGE intrinsic fluorescence. Skin autofluorescence was measured with a skin-autofluorescence reader.

The collagen AGE autofluorescence in patient material increased with patient's age and in diabetes mellitus. The pepsin digestible and collagenase digestible fractions were significantly less modified in comparison to the insoluble fraction. Decreasing amounts of extracted pepsin and collagenase digestible collagen correspond with increasing AGE autofluorescence. Skin autofluorescence is significantly linked to the AGE autofluorescence of the collagenase digestible and insoluble fraction from patient material. Skin autofluorescence and vessel stiffness significantly correlate to each other.

In conclusion we have found that skin autofluorescence and pulse wave velocity as non-invasive parameters significantly correlate with the AGE contained in graft material and therefore are strong predictors of vessel AGE modifications in patients with coronary heart disease.
Vessels stiffness: from blood pressure to brain function

Angelo Scuteri

Arterial stiffness, indexed as pulse wave velocity (PWV), a good marker of arterial aging, has been identified as a significant predictor of future CV events and cognitive decline. Arterial stiffness has a known dependence on actual blood pressure, that also increases with age.

Evidence will be presented regarding:
- Early Vascular Aging (EVA) precedes and predict hypertension;
- the pressure-dependence of PWV may vary with age, so that at older age changes in arterial stiffness may be independent of changes in blood pressure;
- brain is a major target organ of EVA and increased arterial stiffness represents a complex risk factor for dementia onset and progression.

The clinical and public health implication of these findings will be discussed.
Ageing and atherosclerosis

Martin R. Bennett

Atherosclerosis, the disease causing heart attacks and stroke, is the commonest cause of death in the UK, and very shortly in the world. An estimated 2.6M people in the UK have coronary artery disease and it accounts for >88,000 deaths pa (~224 people each day or one death every six minutes). Atherosclerosis is classed as a disease of aging, such that increasing age is an independent risk factor for the development of atherosclerosis. However, atherosclerosis is also associated with premature biological aging, as atherosclerotic plaques show evidence of cellular senescence characterised by reduced cell proliferation, irreversible growth arrest and apoptosis, elevated DNA damage, epigenetic modifications, and telomere shortening and dysfunction. Not only is cellular senescence associated with atherosclerosis, there is growing evidence that cellular senescence promotes atherosclerosis.

We will examine the evidence for ageing in atherosclerosis, the mechanisms underlying ageing including genomic, telomeric, epigenetic and mitochondrial DNA damage, cellular senescence, impaired nutrient sensing, and the functional consequences of vascular cell senescence.
Patients in need for cardiac surgery in 2105 are not all comparable to patients treated 10 years before. According to statistics from the German Society for Thoracic and Cardiovascular Surgery (GSTCVS) already 14% of patients who underwent cardiac operations in 2014 have been older than 80 years of age showing a steady increase over time. Along with age severity of co-morbidities is also increasing opening up a new scope of problems for cardiovascular medicine and cardiac surgery in particular. Operative risk stratification has become a major discriminator for therapy strategies but none of the published and commonly used risk scores reflects the individual risk of a specific patient perfectly. Neither frailty nor degree of aortic atherosclerosis are factors in the calculation of the most commonly used STS PROM and EuroSCORE risk scores. Addressing the need for less invasive and less compromising therapies new catheter based technologies have been developed in recent years to treat patients with structural heart disease especially in patients suffering from symptomatic aortic valve stenosis and functional mitral regurgitation. Transcatheter aortic valve implantation (TAVI) has meanwhile become a routine treatment for patients at elevated risk for surgery at older age and edge-to-edge mitral valvuloplasty by MitraClip implantation is commonly used as an alternative to surgical mitral valve repair. The most obvious advantage of those catheter based therapies is that they allow for treatment of patients who would not have been treated at all if surgery was the only option. The European Heart Survey published in 2005 revealed that only 30% of patients with symptomatic valvular heart disease aged over 80 years or with $\geq 3$ co-morbidities were referred for surgery at all. In effect the majority of patients treated by catheter interventions today would not have been treated 10 years before. And yet another question arises and needs to be answered: who is even too sick for TAVI or MitraClip? Today’s variety of treatment options require individual decisions that can only be taken by true Heart Teams consisting of cardiologists and cardiac surgeons in close cooperation who see the patient together and decide independent of department interests. This presentation is meant to give an update on modern treatment options for old patients with cardiac diseases on an individualized basis in the context of the Heart Team.
Immunological phenomena in cardiac physiology and pathophysiology

Stefan Frantz

Heart failure is a common disease with high mortality seeking for new pathophysiologic concepts to improve treatment. In recent years activation of the immune system was recognized to be important for disease progression. Indeed, we could show that the adaptive immune system, namely T-cells are involved in healing after myocardial infarction. Especially regulatory T-cells are able to increase M2-macrophages that improve healing, potentially by paracrine effects.

Whereas the role of inflammation under pathophysiologic conditions seems to evolve, the role of inflammation under physiologic conditions is unclear and has long been neglected. Our preliminary data show cardiac-resident leukocytes (M2-macrophages > B-cells > T-cells > granulocytes). The frequency of resident leukocytes found in cardiac muscle was 17.4 fold higher than in skeletal muscle. Moreover left ventricular function was compromised in aged mice and improved in lymphocyte-deficient mice.

Thus, lymphocytes seem to be important under pathophysiologic and physiologic conditions.
Cardiovascular risk in diabetes patients – a problem of long term and acute diabetes complications?

Andreas Thomas

The quality of metabolic control in regards to the prognosis of diabetes is evaluated predominantly based on the established HbA1c level. However, this marker only reflects the average glucose concentration rather than glucose level fluctuations. Most significantly, HbA1c does not allow any conclusions regarding the risk of hypoglycaemia or vasotoxic peaks, while it is only a limited predictor for the quality of glucohomeostasis. However, various experimental studies suggest that glucose excursions have an influence on the development of vascular damage, hence avoiding such excursions is key in the absence of evidence to the contrary.

A diagnostic tool is available by means of continuous glucose monitoring (CGM). The indispensable effectiveness of evaluating CGM profiles and their significance in terms of the prognosis for diabetes can be supported by models such as the “glucose pentagon”, even if valid clinical data are not yet available in this area. There are a range of treatment options available for minimizing glycaemic variability. These are summarized at the end of this presentation.
Long-term mechanical circulatory support (MCS) in the Elderly patient

Harriette Verwey

Technological advances and good patient management resulting in excellent survival rates have expanded the use of MCS devices.

Nowadays it is quite common to treat even hemodynamically unstable patients and elderly.

In general indication for treatment with long-term MCS in general are:

- Patients with symptoms of severe congestive heart failure, NYHA class III - IV and an estimated 1 year survival less than 50%
- Refractory to optimal medical treatment and no other treatment options such as cardiac resynchronisation therapy
- Patients awaiting heart transplantation who become hemodynamically unstable or with compromised end-organ function

Timing of surgery mostly based on the INTERMACS classification has become an important criteria in lowering operative mortality. As technology improves and long term results of MCS are getting better the question raises whether we should also treat elderly patients with long-term MCS.

From recent publications it has become clear that patients, age 70 and above have a higher early mortality rate when compared to patients younger than 70 years. The long term results however are not inferior to the results achieved in the younger population. Is it only age that count? Older age has proved to be a marker for increased fragility in patient tolerance for other important risk factors.

Frailty in elderly mechanical support patients is associated with higher risk of death and has therefor become an important patient selection criterion.

Routine assessment of frailty e.g gait speed, functional status and cognition, degree of caregiver support and advanced care planning are therefore mandatory.

It is of utmost importance to have clear indications and contraindications for long term MCS in patients with advanced age while taking into account the severity of fragility. Absolute age will no longer be a selection criteria for implantation of long term MCS in elderly.

Drews T et al. Mechanical circulatory support in patients of advanced age. Eur J Heart Fail 2010;12:990-4
Frailty and Health Span in C. elegans and Mice

Thomas E. Johnson

The last 30 years has seen a revolution in the approach we take to studying aging. Mike Klass and I pioneered the new approach by identifying and characterizing a C. elegans mutant (age-1) that can live as much as ten times longer than the normal control. Any one of several dozen additional mutant genes in C. elegans, Drosophila, yeast, and mice can also extend life, although far less dramatically than in C. elegans. As these animals age, they show decreased movement and increased frailty.

We have asked several questions about the nature of nematode frailty in the longevity mutants and in long-lived worms derived by non-genetic approaches. Primary among these questions is whether the increased longevity by longevity mutants is accompanied by postponement of frailty as assessed by movement capabilities. In general, increased longevity is associated with increased healthspan. Frailty occurs at older ages and most forms of life extension (mutations, genetic selection, environmental manipulation, drug treatments, and stochastic approaches) all result in extended health span. Frailty seems to be postponed in proportion to the increase in life span, in most cases (Newell et al., in preparation).

More recently we have begun analyses of frailty in long-lived mouse mutants that were selected for increased resistance to paraquat (1, 2). Increased stress resistance can be used as a surrogate marker to enrich for longevity mutants. We then used forepaw grip strength to ascertain whether mutant mice showed increased robustness by.

The system used to select for paraquat resistance can also be used to identify mutations conveying increased resistance to any stressor that can be used in mass selection. Another example of this is the identification of genetic variants that can lead to increased survival or organs during storage at ultra-low temperatures (Cypser et al., in preparation).

Relevant Papers:
Cellular senescence, ageing and wound healing

Judith Campisi

Cellular senescence is a multi-faceted stress response that irreversibly arrests cell proliferation and engages a complex senescence-associated secretory phenotype (SASP). The senescence growth arrest prevents the development of cancer by halting cells at risk for malignant transformation. The SASP, which comprises numerous cytokines, chemokines, growth factors, proteases and small metabolites, serves to optimize tissue repair and regeneration in the face of damage. Despite these beneficial effects, the SASP can be deleterious, especially when senescent cells are chronically present such as when accumulate during aging and at sites of age-related pathology.

Using a combination of complex cell culture models and genetically modified mice, we explored the dual nature of the senescence response. In a mouse model of cutaneous wounding, we show that senescent cells are essential for optimal wound healing, and promote wound healing by secreting the SASP factor PDGF-AA. On the other hand, senescent cells that accumulate with age and remain persistently present after therapies such as ionizing radiation or DNA damaging chemotherapy can promote tissue degeneration, most likely by fueling chronic inflammation. Our findings provide new insights into the dual nature of the senescence response, and suggest rational approaches to maintaining the beneficial effects, while minimizing the deleterious effects.
Gerontology in clinical practice: future perspectives

Andrea Maier

During the last centuries human life expectancy steadily increased prominently due to improvement of hygiene and disease related medical intervention. Increasing life expectancy goes along with age related morbidity and with a huge heterogeneity of individual life history trajectories. The pathophysiological mechanisms related to aging are still under investigation, but recent research on methodologies such as heterochronic parabiosis and pathways such as senescence show promising results for future interventions. However, translation of the results obtained using animal models to individual life trajectories requires the understanding of the interaction of aging and disease as well as environmental factors, which will be discussed in the lecture.
Mice and rats are traditionally and often used for physiological experiments with the intention to extrapolate the obtained results to human. In recent years, this issue has become even more important since transgenic mice preparations have become widely available. In cardiac electrophysiology and cellular calcium handling, however, the relevance of data obtained in mice and rats should be treated with particular caution. The heart rate of rats and mice are in the range of 300 to 500 beats/min which results in significant differences in calcium handling and repolarization mechanisms. The latter implies that different transmembrane ionic currents are expressed in mice and rats compared to human to secure safe and relatively rapid repolarization that provides proper time for diastole. Therefore, mice and rats unlike human and other mammalian cardiac ventricular tissue lack the plateau phase of the action potential and negative force frequency relation. These and other differences result in important differences in the mechanisms of arrhythmias and drug effects also including neurohormonal modulation. In this context, it is important to emphasize the significance of non-rodent ion channel transgenic models for future studies. The present overview will provide and discuss published and non-published experimental data from the lab of the author and from the literature as well.

In conclusion, in cardiac electrophysiological, arrhythmia and pharmacological experiments mouse and rat data should be used with particular care when extrapolating them to human implications.
Change of kidney function with age

Michael Gekle

The kidney undergoes age-related changes, reaching full functionality after the age of 5 years and suffering a progressive decline in renal function (e.g. glomerular filtration and excretion of xenobiotica) as well as a in the regulatory range of renal function (e.g. matching sodium and potassium excretion to dietary intake) starting at the age of 15-20 years.

Renal function decline is not only a function of age but also of gender, race and genetic background. Pathogenetically, mediators of chronic inflammation, oxidative stress and the renin–angiotensin–aldosterone (RAAS) system are relevant factor determining renal ageing, due to an enhanced of incidence of cellular damage combined with reduced repair capacities. In addition cardiovascular diseases play a significant role.

Features of renal aging include several functional alterations (e.g. reduction of glomerular filtration, proximal tubular secretion, vitamin D3 synthesis, titratable acid excretion, responsiveness to hormones rate, regulatory flexibility) that can also translate into macroscopic and microscopic changes. Assessment of renal function has to account for age-related changes and is confronted with the challenge to differentiate between age-based physiological alterations and true pathological situations that require the appropriate intervention.

Increasing mechanistic knowledge of age-related renal changes can lead to feasible dietary recommendations and pharmacological approaches to exert beneficial influence on renal function decline in the elderly. However, currently no kidney specific approaches are available and the recommendations include the proper lifestyle modifications as for other organ systems.
Challenges in the treatment of elderly patients with end stage renal disease: a clinical approach

Jeroen Kooman

The number of geriatric patients on dialysis has increased in the past decade. This is due to demographic factors and a wider acceptance of elderly patients on dialysis. Nevertheless, the prevalence of frailty and comorbidity in elderly ESRD patients is high. Recent studies have questioned the effect of dialysis on quality of life in frail elderly patients with severe comorbidity and showed limited survival benefit in this specific patient group. However, other studies have shown acceptable quality of life in elderly patients start on dialysis.

Therefore, the decision whether or not to start dialysis may be difficult for both the clinician and patient. In the process of shared decision making, a balance should be pursued between life expectancy and quality of life. Risk scores can be of help in facilitating shared decision making, but not as a definite tool to withhold dialysis. However, in the elderly patient with severe comorbidity, conservative care can sometimes be a reasonable alternative to dialysis.

The care of elderly patients on dialysis includes, but also transcends optimal prescription and individualization of dialysis therapy. Therefore, care for the elderly with end-stage renal disease should be undertaken by a multidisciplinary team with special dedication to a multidimensional approach in this population.

In this lecture, various clinical aspects regarding the treatment of elderly patients with ESRD will be addressed.
Successful Surgery - Challenging Recovery: 
Functional and Cognitive Recovery after Cardiac Surgery

James Rudolph

Cardiac surgery is a common operation that, generally, improves the function of patients. Within those patients is a proportion that struggle to return to cognitive and physical function. This presentation will examine the evidence regarding cognitive and functional recovery after cardiac surgery. Key discussion points will target measurement of these outcomes in the preoperative, perioperative, and long-term timeframes; the impact of delirium on recovery, and strategies to improve understanding of the causes of the recovery. At the end of this presentation, learners will be able to describe the value of preoperative risk stratification, to identify challenges with measurement in the perioperative period, to understand the value of avoiding complications in the perioperative period, and to critically examine the literature in this field.
Intensive Care reflected in multimorbidity and cognitive dysfunction

Hans-Jürgen Heppner

Due to the demographic shift there are increasing numbers of geriatric patients admitted to acute care hospitals in all disciplines. The increase of chronic diseases and medical improvement leads to more and more older patients participating in modern treatment tools in intensive care medicine. Ageing developments are changing the challenges facing medical care and the management of intensive care medicine in geriatric patients in relation to multimorbidity, impending disabilities and functional impairments. So health care providers find themselves not only confronted with decisions regarding the appropriate care, but also the impact of the disease and its treatment on the functional and cognitive status of the patient. Geriatric patients with their age depended functional decline and multimorbidity are threatened by immobility, malnourishment and are at high risk of complications and in need of care due serve illness and there is a special risk during intensive care treatment.

We have to distinguish between normal aging, the continuous loss of function, the decline in organ function and the pathological changes. Multimorbidity and frailty are the two major pillars in taking care of critically ill elderly patients. The presence of comorbidities influences treatment and management of diseases in critically ill patients. Those comorbidities often have a significantly impact on patients' quality of life, burden of disease, and survival. Quality of life and self-reported health status decrease with an increasing number of comorbidities.

In acute care treatment is to check, whether the therapeutic standards are conferrable.
- Does the patient suffer from constraints in quality of life because of the disease?
- Does the patient endure therapy without constraints?
- Which therapy is reasonable?
- What does the elderly patient want?

Cognitive impairment, acute or chronic is also a challenge in treating critically ill elderly. There is multifactorial nature of delirium and need for thorough evaluation to unravel them. In intensive care treatment sepsis and metabolic abnormalities are the most common etiologies of Delirium. Most of the causes are treatable and have favorable outcome therefore every intensivist must be diligent in recognizing, evaluating, and treating delirium. Dementia and intensive care treatment seems to be a contradiction in terms. In these cases advanced directories are helpful and initiating ICU treatment should always be balanced carefully. Cognitive impairment is regarded as the main risk factor for delirium; unfortunately, within daily clinical workload, these deficits often remain undetected.

Mortality among old patients is high, but functionality and comorbidity have a great impact on the outcome. Structural and functional organ changes play an important role in the treatment of critically ill geriatric patients. Therefore basic geriatric knowledge should be part of the curricula for intensive care medicine.
The United States pays about twice as much per capita for health care than any other developed country yet, with the exception of outcomes for some cancer treatments, its health metrics rank near the bottom of those of peer nations, including appalling statistics for maternal and infant mortalities. The leading cause of bankruptcies in the US is attributable to medical expenses, a situation virtually unknown among most peer nations. Despite recently introduced legislation (the Affordable Care Act) many millions of Americans remain uninsured. Many millions more will remain dangerously underinsured, particularly lower socioeconomic groups of people who can only afford the cheapest levels of medical insurance and thus are subject to unaffordable co-payments. Even those who can afford “platinum” coverage may find themselves within a community that is “out of the network” of their private insurance companies and thus become responsible for all medical expenses.

How is it possible for such a dysfunctional health care system to have evolved in the richest country in the world? Are there lessons here for the developing world? We shall discuss contrasting ethical and political values among Americans as underlying issues. First, there is a division amongst those who embrace the ethic of actuarial fairness and those who embrace the ethic of community solidarity (DA Stone, Journal of Health Politics, Policy and Law, 18:257-317, 1993). Second, there is the widespread view that regards health care as a commodity requiring comparative shopping, free enterprise and profit. Third, there is a political system that permits vast sums of money in support of the “lobbying” of legislators and thus, well justified expectations that these legislators will support special corporate interests. These factors have effectively prevented an obvious solution – a single payer system of publically funded universal health care. Various forms of such a system are of course in place in other developed countries, including those with a mix of public and private institutions. The key to cost containment is the creation of a single bargaining agent. The keys to the enhancement of public health include the amelioration of extreme socioeconomic disparities, a universal system of health care that emphasizes primary care and preventive medicine, and major investments in both basic and translational biomedical research. Regarding the latter, it is important to point out the potential contributions to public health of a single payer system of health care, as it would greatly expedite population-based epidemiological, medical genetic, clinical and health economics research, including research that is relevant to our goal of enhancing the healthspans and lifespans of our populations.
From an ethical perspective, the question as to how to treat elderly patients seems to have an obvious answer: caring for them and treating them with respect and fairness, thus ensuring their autonomy and dignity. This answer is appropriate, but it might leave out the basic challenge, namely how to do so under economic pressure.
Ethical reflections on vulnerability and human dignity in borderline situations of old age

Andreas Kruse

In the middle of the ninth decade of life we can observe significant changes in the physical and cognitive parameters which remind us of a morphological change of the whole organism and this is accompanied by a growing vulnerability in terms of physical and organic brain disease. This does not mean that all these elderly people will suffer severe physical and cognitive losses. However, the probability of such losses does detectably increase and this can be deduced by the fact that, in the ninth decade of life, chronic physical diseases, as well as the various forms of dementia, are significantly more likely and what needs to be considered here is that it is precisely this advanced age which is showing a remarkable demographic dynamic, it is here that we are finding the steepest population growth. This means that we have to increasingly not just concern ourselves with vulnerability, but also the transience and finitude of human existence. We must find cultural forms of dealing with this borderline situation in order to support people in accepting these borders and to realise their self-design potential in these borderline situations – a social and cultural task – and indeed a political one. Particularly in such borderline situations of increased vulnerability, respect for human dignity must be expressed and that everything possible is done to ensure that no degradation of human dignity is allowed to take place. It is important that this human dignity can 'live', can be 'realised', and this is only possible in relationships with other people, in the encounters with others, in taking part. Precisely for this reason is it so important for us to repeatedly reflect upon our images of old age, above all the vulnerability of age, we need to reflect upon our images of transience and finiteness and, against the background of this reflection, we should arrive at an affirmation of age – with age in its vulnerability, too.
The Treatment of Elderly Patients and their Protection in German Law

Christoph Mandla

I. If one speaks about elderly patients, one must keep in mind that he can also talk about himself. In few years, we will all be elderly patients. Everything that concerns the elderly patients nowadays will also most probably concern us in the future. In modern societies, almost the entire life is governed by the law. There is hardly an area for which there are no rules. This raises the question of whether there are regulations that relate only to the elderly and also especially the elderly patients.

II. The answer may surprise you, there are many standards that meet the elderly and protect them well, but the protection is not explicitly related to the age, however to certain characteristics that mainly the elderly have. Because many standards relate especially to the elderly and to the elderly patients, the impression is generated that there are standards solely directed to protect elder people.

1. Starting with the Basic Law (Grundgesetz – GG), the constitution of the Federal Republic of Germany, there is no standard that specifically refers to the age. Even art. 3 para. 3 GG, protects equality and indeed refers to sex, ancestry, race a. s. o. but does not refer to the age. In Social Security Code of long term care insurance (SGB XI), the age is also not highlighted under care neediness, see law sec. 1. para. 4. In para. 4a. the law refers to both sexes and different cultural needs, however it does not even comment on the age. In pension law, SGB VI, the age is highlighted in sec. 35, which regulates the retirement age.

2. The civil law is primarily regulated in the Civil Code (Bürgerliches Gesetzbuch – BGB). There are rules on advance directive provisions that are particularly relevant for elderly patients, although they apply to all adults, including the younger. (By the way, in the law of the treatment contract, sec. 630a BGB, there is also no specific reference to the age of the patient.)

3. a) With an advance directive provision, sec. 1901a BGB, everyone who has the full age and ability to consent, has the right to powerfully decide what tests and treatments he/she wishes or refuses for the case when in the future he/she may not even be able to explain this. Medicines are committed to these rules. For every person who cannot care his life concerns and matters, because he/she has become incapable of giving consent is assigned a guardian by the court, sec. 1896 para. 1 BGB. This guardian has to implement the will of the patient. In case of conflict that means when the doctor and the guardian disagree about the will of the patient, the court decides.

b) In order not to be dependent on a guardian assigned by the court, but each can authorize a representative who has the same duties of the assigned guardian, sec. 1896 para. 2.2 BGB. Usually people choose a close relative, the spouse, children of their own or a friend.

c) The third instrument is the guardian provision, sec. 1901 para. 3 BGB. With this provision, one can decide which person the court should assign as a guardian and which duties to be fulfilled.

4. This means that the protection of elderly patients is better, the more they protect themselves in advance. When they fully take precautions, it is also possible to combine advance directive provision with an authorization of a representative. Even the guardian has to decide in the interest of the patient and not to generalize, he still might not be the right person to reflect and apply the best duties on behalf of the patient. Thus a double dependency is clear: Elderly patients are not only dependent on how they are treated by the medical system, but also they are mainly dependent on what they have done for their protection when they were still capable to take precautions. It is also favorable for elderly patients who have the capability to consent to have people at their side to help them, without that they are completely helpless.

III. Elderly patients are therefore best protected if they make provisions for their protection. This however is ensured only by another person and it shows at this point our permanent dependence on others.
Posters
(in alphabetical order)

Sunday 27th of September
from 11:30 to 11:45

The Poster Award Ceremony
(1) Molecular interactions of crystallins in the human eye lens preventing cataract formation

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The human eye lens contains a highly concentrated and long-lived mixture of 15 different proteins, called eye lens crystallins. These proteins rely on well-balanced inter-protein interaction in order to avoid aggregation and/or phase separation potentially leading the turbidity of the lens and cataract.

To understand the unique organization of the crystallins in a highly concentrated surrounding, we supplement crystallin extracts from vertebrate lenses with recombinant and $^{15}$N/$^{13}$C isotope labeled crystallin. Isotope filtered high-resolution Nuclear Magnetic Resonance (NMR) spectroscopy reveals at an amino acid residue level interactions of the respective crystallin with the lens extracts.

Viscosity measurements of complete eye-lens homogenate consisting of alpha-, beta- and gamma- crystallins in comparison with the pure alpha-crystallin provides an almost ideal Arrhenius behavior indicating less pronounced intermolecular interactions. This reflects the nature of the transparent eye lens where a high number of very weak intermolecular interactions in a highly concentrated colloidal system prevent aggregation and phase separation. During age-related cataract the balance of these weak interactions gets lost.
(2) Age dependency of the voluntary wheel-running activity of mice

Babett Bartling¹, Samiya Al-Robaiy¹, Holger Lehnich², Bernhard Hiebl², Andreas Simm¹,²

¹ Clinic of Cardio-thoracic Surgery, Heart Centre of the University Hospital Halle (Saale) and ² Centre for Medical Basic Research, Medical Faculty, University Halle (Saale)

Physical activity has turned out to be an effective form of non-medicamentous therapy for many diseases including age-related diseases. To examine specific mechanisms underlying the beneficial effect of physical activity, mice are often used as laboratory animals and running wheels introduced into the housing cages as exercise system. However, less is known about the long-term running profile of laboratory mice for both sexes in which simultaneous aging of the mice plays an additional role. Therefore, we constructed and tested a running wheel system which allows constant recording of the activity of mice for a long period of time. We recorded higher wheel-running activities for females than for males along with an age-dependent reduction for both sexes. Sex-dependent differences in the running activity were maximal in juveniles and declined steadily with increasing age. Moreover, females vary more in their running activity than males. Additional records of 24-month-old mice indicated highly reduced wheel-running activities at old age, which was mainly caused by lower running velocities but not by shorter running durations. In summary, we demonstrated the simultaneous influence of sex and/or age on level and pattern of the wheel-running activity of laboratory mice. These data might be a helpful tool to design and interpret mouse studies investigating the effect of physical activity on age-related diseases.
(3) The biomarker skin autofluorescence predicts the outcome in cardiac surgery

Britt Hofmann, MD, PhD a; Kathleen Jacobs a; Alexander Navarrete Santos, PhD a; Andreas Wienke, PhD b; Rolf-Edgar Silber, MD, PhD a; Andreas Simm, PhD a

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Aim- During ageing, advanced glycation end products (AGEs) accumulate in extracellular matrix proteins like collagen and contribute to a decline in organ function. We aimed to assess whether AGE accumulation measured as skin autofluorescence has a prognostic value for the outcome of cardiac surgery patients.

Methods and Results- Between April 2008 and January 2012, data from 334 consecutive patients undergoing isolated coronary artery bypass grafting were prospectively recorded. Skin autofluorescence was measured using an autofluorescence reader. To verify whether the measured skin autofluorescence correlates with the postoperative outcome in cardiac surgery patients, this parameter was assessed in a multiple logistic regression analysis with other preoperative parameters like age, diabetes, renal function e.g. and the established cardiac surgery risk score systems like the EuroScoreII and the STS Score. Skin autofluorescence as non-invasive marker of tissue glycation provided the best prognostic value in identifying patients with major morbidity risks after coronary artery bypass surgery (OR 2.87; p=0.0004).

Conclusion- Measurement of the AGE related skin autofluorescence as a non-invasive tool provides incremental prognostic value in identifying patients with major morbidity risks after cardiac surgery.
(4) Role of lymphocytes for myocardial physiology and aging

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Aim: In the present work we comprehensively characterized the cardiac-resident leukocyte populations, and addressed for the first time how the lymphocytes take part in cardiac physiology and aging.

Methods and results: Flow-cytometrical analysis of perfused-digested murine (C57BL6/J) hearts revealed a cardiac-resident leukocyte population comprising M2-macrophages > B-cells > T-cells > granulocytes. Of note, the number of resident leukocytes found in cardiac muscle was 17.4 fold higher than in skeletal muscle. A light-sheet microscopy analysis revealed that cardiac B-cells are distributed in specific clusters along the myocardium, but no specific pattern for cardiac T-cells have been identified. In order to further investigate the roles of different lymphocyte subsets in cardiac physiology, we characterized the cardiac phenotype of different immune-deficient mouse strains (RAG1KO, \(\mu\)MT, CD4KO, MHCIIKO, and OTII) lacking lymphocytes, B-, and T-cells, and expressing transgenic T-cell receptors, respectively. Briefly, we found that both B-cell and CD4+ T-cell deficient mice presented decreased capillary density, and VEGFa expression within the myocardium, suggesting that these cells might play a role in promoting angiogenesis under basal conditions. Furthermore, we observed that the cardiac-resident leukocyte compartment shifted towards a pro-inflammatory differentiation profile in macrophages and T-cells during aging. This correlated with the development of a functional decline and increased expression levels of chemokines and proinflammatory cytokines including CCL5, CXCL13, TNF, and gamma-IFN in the myocardium. Furthermore, we observed an accumulation of CD44+, CD62L-, FOXP3- CD4+ T-cells in heart-draining lymph nodes of aged mice. Upon in vitro restimulation these activated/ memory T-cells displayed a proinflammatory phenotype expressing TNF and gamma-IFN, but not IL-10. Most strikingly, age-related cardiac inflammation and dysfunction were significantly attenuated in different CD4+ T-cell-deficient and T-cell receptor transgenic strains.

Conclusion: The data indicate a novel role of lymphocytes for cardiac physiological homeostasis. Especially, CD4+ T-cells contribute to spontaneous myocardial inflammation and functional decline during aging.
(5) Glycation and Wnt signaling

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The canonical Wnt/β-catenin signaling pathway plays multiple roles during embryonic development and tumorigenesis but is also linked to multiple processes in ageing including stem cell biology, DNA damage response and ROS signaling, metabolic regulation and cellular senescence. Hyperglycaemia as observed with high incidence in elderly people has been shown to activate the hexosamine pathway and to result in advanced glycation endproducts (AGEs). AGEs accumulate during ageing as non-enzymatic protein modifications and frequently impair protein structure and function. Interestingly high glucose levels have been shown to also modulate Wnt/β-catenin signaling activity. In this context, we here addressed if Wnt signaling is affected by AGE modifications.
Reactive dicarbonyls as important precursors of Advanced Glycation Endproducts cause endothelial cell dysfunction

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Background
Advanced Glycation Endproducts (AGEs) are posttranslational modifications resulting from the non-enzymatic reaction of amino acid side-chains with carbohydrates. Glyoxal and Methylglyoxal are dicarbonyls involved in the formation of AGEs. Circulating AGEs and dicarbonyls are directly in contact with endothelial cells (ECs) from the vasculature and are able to modulate intimal EC properties. The effect of endogenous AGEs and dicarbonyls on primary ECs isolated from the vessel of patients suffering from heart diseases has been poorly studied. In this study the effect of in vivo glycated albumin as model of endogenous AGEs, MGO and GO on primary human endothelial cells was investigated.

Methods
Primary culture ECs were isolated by enzymatic digestion from residual bypass graft material (HSVECs, human saphenous vein endothelial cells) from patients suffering from coronary heart disease. HSVECs were stimulated with different concentrations of low and high in vivo modified BSA, GO and MGO. The cells were chronically stimulated 3-4 days and then analyzed according to various functional parameters.

Results
Our preliminary results show that GO leads to morphological changes in HSVECs. MGO only in combination with GO induces morphological changes of HSVECs. Furthermore it was found that GO and MGO induce senescence in the cells, demonstrated by increased p21 protein expression and SA-β-Gal (senescence-associated β-galactosidase) activity. Both dicarbonyls decreased mRNA expression of cell-adhesion molecules and affect the expression of different receptors for AGEs (RAGE ↑; SR-AI ↑; AGE-R complex ↓; SR-AI ↓; FEEL-1 ↓). In addition, the permeability of HSVEC monolayer decreased after chronic treatment with GO/MGO and with high in vivo-modified BSA.

Conclusion
Our findings suggest that elevated levels of dicarbonyls and/or AGEs can damage the endothelium and thus promote the development of vascular dysfunction. The elucidation of the mechanisms by which GO/MGO act is ongoing.
(7) Alteration of markers of intestinal barrier function are associated with age-associated liver damage in mice

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Results of epidemiological studies suggest that besides general overnutrition and an unhealthy diet age is also a risk factor for the development of non-alcoholic fatty liver disease (NAFLD). Furthermore, alterations of intestinal barrier function and an increased translocation of bacterial endotoxin have been shown to be associated with the development of NAFLD. Results obtained in animal studies suggest that tight junctions in the gastrointestinal tract are remodeled during aging. However, if remodeling of intestinal tight junctions is associated with the increased vulnerability of the liver during aging has not yet been fully clarified. Starting from this background the aim of the present study was to determine if markers of intestinal barrier function are altered in old mice and if so, if this is associated with liver damage. Markers of liver damage were determined in liver tissue of 12 week and 24 months old male C57BL6 mice fed standard chow. Concentrations of the tight junction proteins occludin and zonula occludens-1 (ZO-1) were determined in duodenum, ileum and colon. Liver to body weight ratio, plasma ALT and AST levels but also histological signs of hepatic inflammation and fibrosis were significantly higher in old mice than in young animals while no signs of liver steatosis were found. Furthermore, number of CD8α positive cells was also significantly higher in old animals when compared to young mice. While in tissue obtained from duodenum and ileum protein levels of both occludin and ZO-1 was markedly lower in old mice than in young animals, similar differences were only found for ZO-1 in colon. Taken together, our data suggest that despite being fed standard chow old mice developed liver inflammation and beginning fibrosis and this is associated with lower levels of tight junction proteins in small and large intestine.
(8) Generation of human iPSC-derived neural stem/progenitor cells and their differentiation into glutamatergic and GABAergic neurons

Matthias Jung, Jovita Schiller, Bernadette Harwardt and Dan Rujescu
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Genetic variations are often associated with psychiatric diseases such as Schizophrenia. Specific DNA variations presumably affect the neural development, resulting in dysfunctions of neural cells. Non-viral reprogramming of human somatic cells into pluripotent stem cells (iPSCs) provides a useful tool for the in vitro-modeling of such diseases. Here, well-established human iPSCs were differentiated into neural stem cells (NSCs). Transcript analysis of specific markers (GPM6A, S100B, PAX6) confirmed neural cell fates within stable populations of NSCs. Double immunostaining of Ki67, SOX2 and NESTIN also demonstrated cell proliferation and neural stem cell identity. To receive functional neurons, we performed an in vitro neurogenesis. Within 8 weeks, NSCs generated both neuronal fated cells (NeuN, TUBB3, NEFL) as well as glial progenitors (GFAP, O4). The regional identity of these cells was confirmed through the expression of telencephalic and hippocampal markers (FOXG1, OTX1, PROX1, AUTS2). The rhombencephalic markers NKX2.2 and OLIG2 were also detectable. Functional analysis of mature neurons was realized through whole-cell patch-clamp recordings and verified the presence of specific postmitotic neuron subtypes such as excitatory glutamatergic cortical cells. Additionally, we transferred the differentiation model and the culture conditions to a 3D culture system. The generation of neurospheres from NSCs enables the mimicry of different brain regions including the cerebral cortex. Within 4 weeks, we generated cerebral organoids. The presence of early neural cell fates was confirmed through transcript and protein expression of specific markers such as PAX6, SOX2 and NESTIN. In contrast, post mitotic neural cells were identified through immunostaining of Ki67 as well as NeuN and TUBB3. Specific neuron subtypes such as GABAergic (GABA) and glutamatergic neurons (TBR-1) were detectable. Organoids cell displayed forebrain and hindbrain identities (FOXG1/NKX2.2). Together, these results confirmed the efficient neural differentiation of human iPSCs using two different culture systems. Adherent as well as 3D culturing enables functional studies of healthy and diseased human cortical development. Thus, in vitro disease modeling will help to investigate neuronal dysfunctions associated with specific genetic variations.
Klotho deficient mice are a well-established mouse model of premature aging. As its main function, Klotho is considered to act as an obligatory co-receptor for FGF23 in the kidney where it regulates calcium and phosphate homeostasis in a Vitamin D dependent manner. However, Klotho is also present in hypothalamic paraventricular and periventricular neuroendocrine nuclei as well as in the anterior pituitary where its role remains enigmatic. Our analysis of Klotho deficient mice revealed various alterations in the hypothalamic-pituitary system including a strong activation of the hypothalamus-pituitary-adrenal (HPA) axis and a reduced expression of GH, FSH, LH and prolactin in the anterior pituitary. These neuroendocrine abnormalities may be caused by the loss of Klotho in the hypothalamus and/or pituitary system but could also be an indirect consequence of the changes in Vitamin D homeostasis due to absence of Klotho in the kidneys.

In order to distinguish between these two possibilities we set Klotho deficient mice on a Vitamin D free diet after weaning, as this treatment has been shown to normalize calcium and phosphate levels. Analysis of pituitary hormone expression revealed normal levels of FSH, LH and prolactin whereas GH remained to be reduced.

As a second approach, we addressed the function of Klotho in hypothalamic neurons by taking advantage of conditional Klotho deficient mice crossed with a forebrain neuron-specific CamK cre mice. However, transcript levels of pituitary hormones were not altered in these Klotho fl/CamK cre animals indicating that Klotho deficiency in hypothalamic neurons does not compromise pituitary functions.

Overall, our data demonstrate the importance of Klotho in major endocrine axes. Ongoing studies will reveal the impact of these endocrine changes to aging.
Cysteine-S-glutathionylation is a reversible post-translational modification occurring under oxidative stress. Here, we tested how transcription factor FoxO1a activity is affected by the absence of its cysteine residues and whether glutathionylation of FoxO1a might occur. A V5-tagged cysteine-deficient mutant of human FoxO1a (all 7 cysteines were replaced by serines) was generated by site directed mutagenesis, followed by transfection of HepG2 human hepatoma cells or HEK293 human embryonic kidney cells to overexpress either wild type (WT) or Cys-deficient V5-FoxO1a. Neither insulin-induced phosphorylation of FoxO1a nor its nucleocytoplasmic shuttling was attenuated in cysteine-deficient FoxO1a. Moreover, no alteration of basal FoxO1a DNA binding activity (EMSA) was noticed in the Cys-deficient version versus WT under normal culture conditions. However, exposure to diamide, a thiol-oxidizing agent, revealed that, while FoxO1a-DNA interaction was attenuated in the WT form, this oxidant-induced attenuation was less prominent in the cysteine-deficient mutant. Furthermore, transactivation of a FoxO-responsive element-driven reporter gene was less prominent in cells overexpressing Cys-deficient FoxO1a than in those transfected with WT FoxO1a. Moreover, immunoprecipitation and Western blotting analyses (reducing/non-reducing) of diamide-exposed cells overexpressing WT or mutant FoxO1a suggest that oxidant-induced FoxO1a interaction with cofactors is attenuated in the Cys-deficient mutant. In summary, these data suggest that cysteine residues in FoxO1a, while not affecting insulin-induced phosphorylation and nucleocytoplasmic shuttling, are important mediators of FoxO1a/DNA interaction under conditions of oxidative stress. Moreover, these data point to glutathionylation of FoxO1a and/or yet to be identified cofactors under exposure to oxidants, suggesting a regulation of FoxO activity through S-glutathionylation.
Atrial fibrillation (AF) is associated with increased risks of stroke, cardiac failure, and mortality. Since, due to the lack of sufficient markers, the discrimination and classification of AF subtypes (paroxysmal, persistent, and long-standing persistent) is inadequate, the underlying mechanisms and pathology of AF remain elusive. The aim of this study is to proteomically analyze the left atrial appendage tissue obtained from patients suffering from AF.

MALDI Imaging mass spectrometry (MALDI-IMS) was used for differentiation and classification of pathophysiological AF subtypes, through the direct (in situ) analysis of formalin-fixed paraffin embedded (FFPE) left atrial appendage tissue. FFPE left atrial appendage tissue resected routinely during MAZE procedures in surgery were collected of patients with paroxysmal, persistent, and long-standing persistent arrhythmia. Sections were dewaxed and trypsin solutions were applied directly onto the section using an automated spraying device. Spectra were acquired at a mass range of m/z 800-3500Da and lateral resolution of 80 µm. Two hundred laser shots were acquired per pixel and random walk of 50/position. Data analyses were performed using SCiLS Lab software.

Component analysis of MALDI Imaging data by probabilistic latent semantic analysis results in a clear discrimination in the first 3 components of atrial fibrillation. By using receiver operating characteristic analysis (AUC > 0.7) characteristic intensity distribution of given m/z values, which are discriminative for the considered cluster, was determined to distinguish between paroxysmal vs persistent AF, and persistent vs long-persistent AF, m/z values was determined between persistent vs long-persistent AF (1.59±0.12 vs 6.85±3.02, p = 0.02).

The tissue-based proteomic approach provides clinically relevant information to be beneficial in improving risk stratification in AF patients. In the future the obtained information might be considered as new biomarker to support the diagnosis of the severity of AF status. They also suggest new criteria to determine the most appropriate surgery for each AF subtype to improve postoperative outcomes.
Extracellular microRNA as a Biomarker for gender specific differences in patients undergoing coronary artery bypass graft surgery (CABG)

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Background: Coronary artery disease (CAD) and consequently ischemic heart disease (IHD) is leading cause of death both in Germany as well as worldwide. Female gender is preventive at young age and a risk factor at old age resulting early mortality after coronary artery bypass graft surgery (CABG). It remains unclear why the risk of elderly women is higher than of elderly men.

Objectives: Analysis of gender specific differences on the basis of micro RNAs analysed in pericardial fluids.

Methods: 20 patients (10 female+ 10 male) with age 70±3 yrs admitted for elective isolated CABG (Coronary artery bypass graft surgery) were included for this prospective study. We will collect pericardial fluid, plasma, mammary artery and right atrial appendage (RAA) as biological samples from patients. For RNA isolation, the miRNeasy serum/plasma Kit and miRNeasy mini Kit (Qiagen, Hilden, Germany) are used. RNA from pericardial fluids will be analysed with μRNA Microarrays from Affymetrix to get a μRNA profile and with real time PCR (miRCURY LNA™ microRNA PCR / Exiqon, Vedbaek, Denmark) for validation. The study was approved by the local ethic committee.

Results: Intact RNA can be isolated from all samples. The RNA amount from pericardial fluid is sufficient to get a respective μRNA profile using array technology. Using real time PCR, the expression of the housekeeping hsa-miR-103a-3p as well as selected cardiac specific hsa-miR-208a-3p and hsa-miR499a-5p μRNAs could be verified. Further preliminary results will be presented.

Conclusion: Cardiac μRNA isolated from the pericardial fluid are master regulators of the cellular metabolism and should be an optimal target to explain gender differences in patients undergoing CABG surgery.
Maternal insulin-dependent diabetes mellitus affects embryonic microRNA expression during the preimplantation period: Insights from a rabbit model

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MicroRNAs (miRs) are a class of highly conserved small (19-24 nucleotides) non-coding RNAs. They are involved in various biological processes such as development and embryogenesis. Recent studies suggest that miRs are also regulators and markers of placental development with a relationship between aberrant microRNA expression during pregnancy and placental insufficiency. Metabolic disorders like diabetes mellitus affect placenta function already at the time of trophoblast differentiation with potentially long-lasting effects on offsprings’ health. We hypothesise that diabetes-related placental dysfunction may be identified by the expression of specific trophoblast miRNAs. Therefore, we have analysed the influence of a maternal type 1 diabetes mellitus (T1DM) on miR expression in vivo in maternal (plasma, endometrium) and embryonic samples (embryoblast and trophoblast cells, blastocyst cavity fluid), using the rabbit as experimental model. Diabetes was induced in female non-pregnant rabbits by alloxan treatment two weeks prior to mating. In in vitro experiments we examined direct effects of insulin, glucose and LIF on embryonic miR expression.

MiR-27b, -141, -191 and -222 were expressed in maternal plasma and endometrium, in embryoblast and trophoblast cells and in blastocyst cavity fluid. They were affected by maternal diabetes. Furthermore, we detected an altered mRNA expression of miR target genes in blastocysts developed under diabetic conditions. In in vitro experiments we used LIF, insulin and glucose to stimulate embryonic miR-27b, -141, -191 and -222. In vitro data indicate that changes in maternal hormones and metabolites are reflected by an adapted miR regulation in embryos from diabetic mothers.

We show that miRs are expressed in blastocyst cavity fluid where they might serve as communicator between embryoblast and trophoblast cells. Furthermore, maternal diabetes leads to a downregulation of miRs in both embryonic compartments and maternal plasma, demonstrating that miRs could serve as biological markers as early as during the preimplantation period.

Our findings demonstrate that maternal diabetes leads to enhanced BCAA concentrations and a disturbed BCAA metabolism in embryos. It affects embryonic mTOR activation with likely changes in mTOR signalling.
(14) The role of protein glycation on protein degradation

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Ageing cells accumulate protein aggregates due to a decline of 20S/26S proteasome dependent protein degradation. Proteolytic insufficiencies are also involved in age-related diseases like Parkinson or Alzheimer disease and cataract. The reason for this phenomenon is unknown, but several observations suggest that posttranslational protein modifications like glycation play a role. For example, an age-related increase in the content of glycated proteins and protein aggregates showed an inverse relationship to lifespan. However, it is not understood why glycated, misfolded proteins cannot be degraded via the 20S/26S proteasome and accumulate over time. A better understanding of the molecular mechanisms of age-related protein degradation deficiencies is necessary to develop novel therapies for patient treatment. Our goal is to experimentally address several questions: (1) Are glycated proteins targeted by the ubiquitin proteasome system (UPS) for degradation and (2) is there a general stress response to glycation, e.g. upregulation of UPS components (e.g. ubiquitin, Ubc4/5, p97/Cdc48, ubiquitin ligases (E3s))? (3) Does protein glycation directly interfere with polyubiquitination at lysine residues? To tackle some of these questions we have developed a novel in vitro UPS substrate, that allows to measure protein folding and protein half-life of glycated and unmodified proteins.
Modulation of transcriptional mineralocorticoid receptor activity by casein kinase 2

Stefanie Ruhs¹, Nicole Strätz¹, Katja Quarch¹, Antonia Masch², Mike Schutkowski, Michael Gekle¹ and Claudia Grossmann¹

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The mineralocorticoid receptor (MR) is a ligand-dependent transcription factor that contributes to electrolyte homeostasis and blood pressure control. In the renocardiovascular system it can also mediate aging-related pathophysiological processes including inflammation, endothelial dysfunction and vascular remodeling. An important aspect of the deleterious action of MR is the requirement of additional stressors like a parainflammatory micromilieu. There are indications that during vascular aging, parainflammation increases which then augments pathological MR activity and leads to vascular changes. One of the underlying molecular mechanisms may be posttranslational modification of the MR. Based on sequence analysis, we identified casein kinase 2 (CK2) as a promising candidate for MR phosphorylation.

CK2 is a very well conserved ubiquitously expressed serine/threonine kinase that possesses over 300 substrates implicated in signal transduction and gene expression. It is additionally involved in cell cycle regulation and proliferation. Recent investigations indicate that the activity and expression of casein kinase 2 (CK2) is enhanced by inflammatory stimuli.

In our experiments inhibition of CK2 concentration-dependently reduced genomic MR activity at a glucocorticoid response element. An HSP90-dependent interaction of different CK2 subunits with the MR could be shown by co-immunoprecipitation. Predicted phosphorylation sites of the MR were validated by peptide array and site-directed mutagenesis experiments. As underlying molecular mechanism for CK2-mediated enhanced MR activity we found altered DNA-binding of phosphorylated MR with no effect on nuclear shuttling. Furthermore, we could demonstrate that in a parainflammatory micromilieu, CK2 enhances aldo/MR signaling and function. Overall, our results suggest that CK2-dependent phosphorylation of MR enhances genomic MR activity by facilitating DNA-binding, thus promoting pathophysiological vascular changes.
(16) Reactive species modify NaV1.8 channels and affect action potentials in murine dorsal root ganglia neurons

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Dorsal root ganglia (DRG) neurons are important relay stations between the periphery and the central nervous system and are essential for somatosensory signaling. Reactive species are produced in a variety of physiological and pathophysiological conditions and are known to alter electric signaling. Here we studied the influence of reactive species on the electrical properties of DRG neurons from mice with the whole-cell patch-clamp method. Even mild stress induced by either low concentrations of chloramine-T (10 µM) or low-intensity blue-light irradiation profoundly diminished action potential frequency but prolonged single action potentials in wild-type neurons. The impact on evoked action potentials was much smaller in neurons deficient of the tetrodotoxin (TTX)-resistant voltage-gated sodium channel Na\textsubscript{V}1.8 (Na\textsubscript{V}1.8\textsuperscript{-/-}), the channel most important for the action potential upstroke in DRG neurons. Low concentrations of chloramine-T caused a significant reduction of Na\textsubscript{V}1.8 peak current and progressively slowed down inactivation at higher concentrations. Blue light had a smaller effect on amplitude but slowed down Na\textsubscript{V}1.8 channel inactivation. The observed effects were less apparent for TTX-sensitive Na\textsubscript{V} channels, rendering Na\textsubscript{V}1.8 as an important reactive-species-sensitive component in the electrical signaling of DRG neurons, potentially giving rise to loss-of-function and gain-of-function phenomena depending on the type of reactive species and their effective concentration and time of exposure. The mechanisms described here might be relevant for alterations in rapid electrical signaling observed in aged tissue or under age-related pathophysiological conditions.
A maternal diabetes mellitus type 1 downregulates embryonic glyoxalase 1 in early pregnancy

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Diabetic pregnancy is associated with higher metabolic stress for the embryo and fetus due to changes in glucose, lipid and amino acid metabolism. In maternal serum increased glucose levels lead to formation of reactive α-dicarbonyls like glyoxal (GO) and methylglyoxal (MGO). In most tissues the glyoxalase system (glyoxalase (GLO) 1 and 2) detoxifies reactive α-dicarbonyls thus protecting cells against malfunction or inactivation of proteins by advanced glycated end products (AGES). A maternal diabetes during early pregnancy leads to an accumulation of AGES in the preimplantation embryo (Haucke et al. 2014).

The aim of this study was to analyze the influence of a maternal diabetes mellitus on GLO1 expression and activity in preimplantation embryos. An experimental diabetes mellitus type 1 was induced in female rabbits before conception and maintained during the preimplantation period. GLO1 expression and activity were investigated in 6 day old blastocysts from healthy and diabetic rabbits by RT-PCR, Western Blot and enzyme assay.

GLO1 was expressed in both cell compartments of the blastocyst, the embryoblast and the trophoblast. Blastocysts from diabetic rabbits showed a decrease in GLO1-protein amount and activity, indicating that maternal hyperglycemia impairs embryonic GLO1 expression.

Therefore we cultured day 6 blastocysts with 0, 10 and 25 mM glucose, 100 µM MGO and 250 or 500 µM GO for 6 and 2.5 hours, respectively. In absence of glucose GLO1 protein amount was decreased, while enzyme activity of GLO1 did not change. MGO and GO had no impact, neither on GLO1 protein amount nor on GLO1 enzyme activity.

We show that a maternal diabetes mellitus leads to a decrease in GLO1 protein amount and GLO1 enzyme activity in preimplantation embryos. The downregulation of embryonic GLO1 expression correlates with increased AGE levels, indicating that the embryonic glyoxalase system is disturbed and its protective function is impaired in embryos from diabetic mothers.

(Supported by EU FP7-EpiHealth 278418, Epihealth-NET and the Wilhelm Roux Programme, MLU Faculty of Medicine)

A contribution of alpha-2 macroglobulin in the naked mole-rats anti-aging strategy?

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Longevity and cancer-resistance are one of the most important features of the naked mole-rat (NMR), an underground living animal domiciled in the Rift Valley in East Africa, which lifetime is extended up to 30 years. To investigate the reasons for its longevity makes this species eminent for aging and cancer researchers. Recently a 140fold higher alpha-2 macroglobulin (A2m) mRNA liver expression was found in the NMR compared to the short living mouse. In humans a negative correlation between A2m and age is known, showing the highest A2m blood concentrations at birth.

Investigating the molecular weight of NMR A2m by different gel electrophoretic analysis, we could show a comparable protein structure of the human and NMR A2m, as a tetrameric protein of approx. 720kDa, which is able to bind its specific receptor LRP1. NMR plasma displayed a 2fold higher A2m concentration (8.3±0.44 mg/mL vs. and 4.4±0.20 mg/mL) than human plasma.

Using 1% NMR plasma in the culture medium increased the adhesion of human fibroblasts and PC-3 (prostate carcinoma) cells. The increase in adhesion came along with an increased CD29 and CD44 protein expression under 1% NMR plasma supplementation.

We reported similarities but also distinct differences in the protein structure and function of the NMR-A2m. Because of its capability to increase adhesion of fibroblasts and tumor cells we refer A2m to play a central role in the anti-cancer strategy in NMRs and suppose A2m as a mediating molecule responsible for the longevity in this species.

Supported by the “Europäische Sozialfond” – ESF 100098250
(19) Effect of dietary Advanced Glycation Endproducts on NF-kB signaling pathway in a human embryonic kidney reporter cell line

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Background: Advanced glycation end products (AGEs) are the result of a non-enzymatic reaction of proteins with reactive carbohydrates. Heat-processed foods contain high amounts of AGEs. Using the water soluble fraction, it has been shown that dietary AGEs from bread crust have antioxidative and cardioprotective effects, probably mediated by NF-kB signaling pathways. However, previous findings indicated, that the alcohol-soluble fraction of bread crust revealed the highest antioxidative potential. Therefore, in this study the effect of different bread crust extracts on NF-kB activation in a HEK reporter cell line was elucidated.

Methods: The bread crust was extracted with PBS (fraction I), ethanol (fraction II) and 2-propanol (fraction III). Afterwards, we determined the AGE-level of these three bread crust fractions by fluorescence measurement and slot blot analysis. To investigate the influence of these fractions on NF-kB activation, we used a GFP-linked reporter cell line NF-kB/293/GFP-LucTM. The GFP expression was analyzed by flow cytometry. The expression of the AGE-binding receptor RAGE was determined by realtime RT PCR.

Results: The slot blot analysis showed that all three bread crust fractions contain a detectable amount of AGE modifications. Thereby, the highest level of protein-bound AGEs was found in the water-soluble bread crust fraction I. In contrast, the AGE-specific fluorescence of fraction I and II was less than in fraction III suggesting a higher content of fluorescent AGEs in the hydrophobic bread crust fraction. This finding was confirmed by the results of the GFP expression analysis in the NF-kB/293/GFP-LucTM cells. Although all bread crust fractions led to an activation of NF-kB in these cells, the fraction III showed the highest effect. Moreover it was found, that the mRNA expression of RAGE in NF-kB/293/GFP-LucTM cells occurs independently from the stimulation with the three bread crust fractions.

Conclusion: Our data showed for the first time, that the three bread crust fractions stimulate the NF-kB signaling pathway in a HEK reporter cells line with different degrees. The highest intensity on NF-kB activation was found after stimulating cells with bread crust fraction III, which indicates that the AGE modification extracted with 2-propanol have the highest antioxidative effect. Furthermore, there was no correlation between the RAGE mRNA expression and the activation of NF-kB in HEK reporter cells by the three bread crust fractions.
Multiple Valve Surgery in Octogenarians – Take care for the Porcelain

Manuel Wilbring, Sebastian Arzt, Utz Kappert, Konstantin Alexiou, Sems-Malte Tugtekin, Klaus Matschke

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Objectives
Cardiac surgery progressively is faced with more and more elderly patients. Due to their unique physiology and susceptibility to morbidity, tailor-made treatment strategies are warranted. Herein we describe the clinical and follow-up results after multiple valve surgery in octogenarians.

Patients and Methods
Since 2000 a total of 3,323 patients older 80 years underwent cardiac surgery. Out of these, 101 patients (3.0%) received multiple valve surgery. Mean patient’s age was 82.0 years +/- 1.9 years. Computed logistic EuroSCORE averaged 25.3 +/- 19.5%. Mean follow-up time was 277 +/- 47 days, equaling a total of 442 patient-months.

Results
Surgery consisted of double valve procedures in 88.1% and in 11.9% of triple valve surgery. Mean hospital stay was 16.1 +/- 9.7 days, hospital mortality 13.9%. During follow-up 43.8% of the patients died. Corresponding 6-months and 1-year survival was 40.1% and 28.6%, respectively. Main postoperative morbidity consisted of respiratory failure (17.3%), stroke (2.2%), delirium (22.3%) and renal failure (13.8%). Only 40 patients (39.6%) were free from postoperative complications. If any complications occurred, hospital mortality dramatically increased from 5.0% to 20.0%.

Conclusion
Octogenarians are demanding patients. Occurrence of any complication after multiple valve surgery resulted in multiplied mortality. Particularly in the era of TAVI, the indication for multiple valve surgery should be made with a jealous watch on medical condition, complaints and patient’s motivation. It has to be discussed, whether catheter-based treatment of the leading vitium might suffice or not.
# List of Speakers A – J

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