NORDISK-BALTISK KARDIOLOGIKONGRESS, 13.-16.6, OG NORDISK INVASIV KARDIOLOGIKONFERANSE, 12.6.2013

I år var Norsk Cardiologisk Selskap vert for den nordisk-baltiske kardiologikongressen som ble avholdt på Holmenkollen Park Rica Hotel i Oslo. Møtet var i år derfor slått sammen med vårmøtet til NCS. Samtidig benyttet man anledningen til å arrangere den første nordiske invasive kardiologikonferanse på samme sted. Dette fant sted dagen før den nordisk-baltiske kongressen.

Den invasive konferanse besto av en rekke korte 8-minutters-innlegg før diskusjon. Dette var et vellykket konsept. Innleggene var konsise og diskusjonene interessante. Både forskningstrender og nyere kunnskap innen ST-elevasjonsinfarkt, rekanalisering av kroniske koronarkarokklusjoner og klaffefeil ble omtalt. Det var dels vanlige presentasjoner og dels kasuistikker. For en som nylig hadde vært på EuroPCR i Paris, ble dette en positiv opplevelse, både takket være kvaliteten på innleggene og temaene. Det faglige utbyttet var slett ikke dårligere enn i Paris. 55 leger og 40 fra industrien var påmeldt dette møtet.

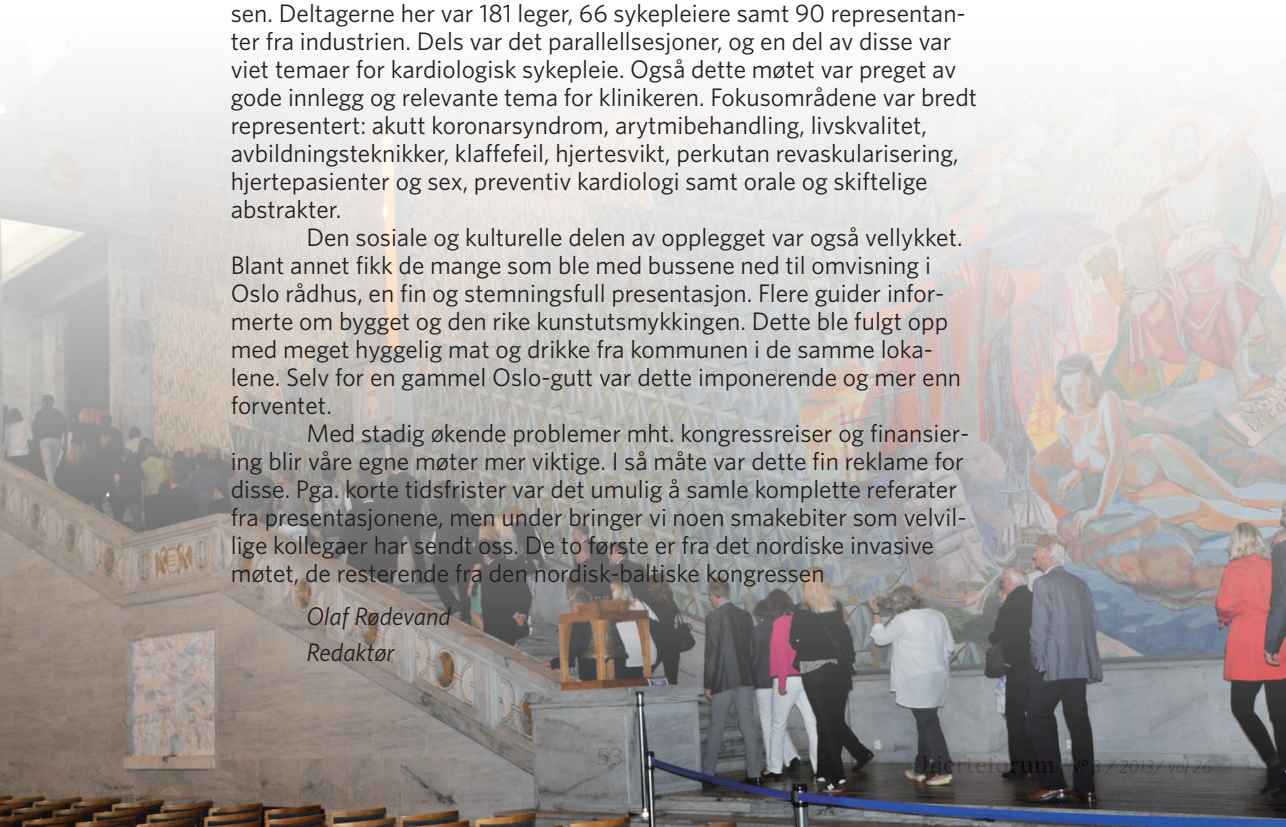
Hovedarrangementet var likevel den nordisk-baltiske kongressen. Deltagerne her var 181 leger, 66 sykepleiere samt 90 representanter fra industrien. Dels var det parallellsesjoner, og en del av disse var viet temaer for kardiologisk sykepleie. Også dette møtet var preget av gode innlegg og relevante tema for klinikeren. Fokusområdene var bredt representert: akutt koronarsyndrom, arytmibehandling, livskvalitet, avbildningsteknikker, klaffefeil, hjertesvikt, perkutan revaskularisering, hjertepasienter og sex, preventiv kardiologi samt orale og skiftelige abstrakter.

Den sosiale og kulturelle delen av opplegget var også vellykket. Blant annet fikk de mange som ble med bussene ned til omvisning i Oslo rådhus, en fin og stemningsfull presentasjon. Flere guider informerte om bygget og den rike kunstutsmykkingen. Dette ble fulgt opp med meget hyggelig mat og drikke fra kommunen i de samme lokalene. Selv for en gammel Oslo-gutt var dette imponerende og mer enn forventet.

Med stadig økende problemer mht. kongressreiser og finansiering blir våre egne møter mer viktige. I så måte var dette fin reklame for disse. Pga. korte tidsfrister var det umulig å samle komplette referater fra presentasjonene, men under bringer vi noen smakebiter som velvillige kollegaer har sendt oss. De to første er fra det nordiske invasive møtet, de resterende fra den nordisk-baltiske kongressen

Olaf Rødevand

Redaktør



STEMI OG AKUTT INTERVENSJON – MEDIKAMENTELL BEHANDLING KAN FORBEDRE PROGNOSE

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Det har vært en viktig utvikling av nye blodplatehemmende medikamenter og kombinasjoner av disse de senere årene til bruk ved ST-elevasjonsinfarkt. Acetylsalisylsyre (ASA) var først dokumentert med mortalitetsgevinst i *ISIS*-studiene på 1980-tallet. Senere har ADP-reseptorhemmere lagt til ASA og vist ytterligere gevinst. *CURE*-studien var først med å vise positiv effekt hos pasienter med akutt koronarsyndrom. *CLARYTY* i 2005 og *CLARITY PCI* bekreftet at klopidogrel pluss ASA var bedre enn ASA alene ved STEMI, også PCI-behandlet.

I *PCI-CURE*-studien av pasienter med akutt koronarsyndrom (1) ble det vist reduksjon i endepunkter ved PCI også med forbehandling med ADP-hemmeren klopidogrel. Forbehandling med klopidogrel var tema i en ny meta-analyse (2) som ikke viste forskjell i mortalitet. Det var signifikant reduksjon i antall infarkt, men forbehandling økte ikke blødningstendensen.

De nyere ADP-reseptorhemmerne har større affinitet for ADP-reseptoren enn klopidogrel og har derfor vært forventet å gi bedre effekt. *PLATO*-studien (3) med 18624 pasienter med akutt koronarsyndrom viste at ticagrelor pluss ASA reduserte et sammensatt endepunkt med død, hjerteinfarkt eller slag versus klopidogrel og ASA i løpet av 12 måneders behandling uten å øke større blødning (*major bleed*), mens ikke-prosedyrerelatert blødning var noe økt. I denne studien hadde 38 % STEMI, og 43 % NSTEMI. Metningsdose med klopidogrel var 300 mg hos 60 % av pasientene, og 600 mg hos bare 20 %. Vi har således ikke data for ticagrelor ved STEMI mot klopidogrel som har fått høyeste metningsdose som nå er mest vanlig å bruke. Resultatene fra populasjonen med STEMI (38 %, n=7544) ble publisert i *Circulation* i 2010 av Gabriel Steg. Primært endepunkt var usikkert redusert med p-verdi på 0,07, hjerteinfarkt var signifikant redusert, og død redusert med p-verdi på 0,05. Forfatterne konkluderte med at resultatene for STEMI var konsistente med den positive hoved-*PLATO*-studien. En substudie på en hel kohort med STEMI er sannsynlig akseptabelt tolkbar, fordi det ikke dreier seg om en subgruppeanalyse med oppsplitting i enkelte variabler i dette tilfellet, og det er et stort antall randomiserte pasienter. *PLATO* har fått kritikk for at det ble diskrepans i hovedresultatet om man brukte en sentral bedømmelse av infarktdiagnose (positiv) eller infarktdiagnose bedømt av de enkelte forsøkslegene (negativt resultat).

TRITON-TIMI 38 (4) studerte ADP-hemmeren prasugrel versus klopidogrel hos 13608 pasienter med akutt koronarsyndrom. Metningsdose med klopidogrel var 300 mg, og 26 % av pasientene hadde STEMI. Det var signifikant økt blødning i prasugrel-gruppen, og sammensatt endepunkt av død, hjerteinfarkt og ikke-fatalt slag var signifikant redusert. Gruppen på 3534 pasienter med STEMI ble publisert i *Lancet* i 2009 av G. Montalescot. Det primære endepunktet var signifikant redusert hos STEMI-pasienter i likhet med i moderstudien.

Resultatet fra de to studiene er ikke direkte sammenlignbart pga. forskjeller i risikoprofil, metningsdoser av klopidogrel og andre forskjeller. Det er likevel gjort et forsøk på metaanalyse som indikerte at medikamentene hadde lik effekt, men med mindre blødning for pasienter som brukte ticagrelor (5). Det er innført anbefaling for prasugrel om redusert dose hos pasienter < 60 kg eller > 75 år og ved tidligere slag.

Det er nå tilgjengelig en intravenøs ADP-hemmer, cangrelor. *CHAMPION PHOENIX* cangrelor-studie på 11145 pasienter som gjennomgikk elektiv eller øyeblikkelig hjelp-PCI viste at det var signifikant redu-

sert primært endepunkt de første 48 timer, redusert stenttrombose og ikke økt blødning sammenlignet med klopidogrel (6). 55 % av pasientene som gjennomgikk PCI hadde stabil angina, 26 % NSTEMI og 19 % STEMI. Resultatet var konsistent for hele gruppen av diagnoser, men statistisk signifikant bare for gruppen med stabil angina.

Fibrinolyse er tilbake på arenaen med *STREAM*-studien (*New England Journal of Medicine* 2013) som viser at fibrinolyse ved STEMI innen 3 timer fra symptomdebut og mer enn 60 minutters transport til PCI er like bra behandling som primær PCI. Fibrinolysedosen ble halvert hos pasienter over 75 år. Alle pasienter ble vurdert med angiografi og evt. PCI 6-24 timer etter trombolyse. I et værutsatt land vil nok dette være nyttige studieresultater å ta med seg.

Konklusjoner for akuttbehandling av STEMI

Klopidogrel-forbehandling til PCI eller trombolyse f.eks. i ambulansen eller akuttmottak kan foreløpig fortsette som før, og gir sannsynlig reduksjon i endepunkter, spesielt infarkt (ikke mortalitet), uten å øke blødning. I tillegg til at klopidogrel brukes ved trombolyse er det også mest trygt ved økt blødningsrisiko, og i kombinasjon med warfarin. Randomiserte studier vedrørende forbehandling (*prehospital treatment*) er på vei for de nye ADP-hemmerne (ACCOAST og *ATLANTIC*).

Cangrelor intravenøst under PCI kan brukes hos pasienter med kvalme eller brekninger, de som skal til akutt kirurgi, eller hos dem med nedsatt tarmperfusjon eller andre årsaker til redusert absorpsjon av perorale medikament.

Ticagrelor og prasugrel er sannsynligvis bedre enn klopidogrel ved STEMI, men ticagrelor er enklest å bruke fordi det er færre kontraindikasjoner eller subgrupper som må ha dosereduksjon.

Etter forbehandling med klopidogrel med 600 mg vil det være naturlig å gi ny metningsdose med f.eks. ticagrelor neste morgen ved overgang til dette medikamentet.

GP IIb/IIIa-hemmere er ikke lenger rutinemessig anbefalt ved STEMI, men kan brukes ved mye trombemasse påvist under angiografi/PCI eller ved transport av høyrisikopasienter til PCI-senter. Bivalirudin bør foretrekkes foran GP IIb/IIIa-hemmere ved høyrisiko STEMI-PCI(ca. 20 % av pasientene?).

Dopamin øker mortalitet ved STEMI og kardiogent sjokk og anbefales ikke brukt, noradrenalin bør foretrekkes.

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STEM CELLS IS THE NEAR FUTURE

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Ischemic heart disease (IHD) is the most common cause of death and a major cause of hospital admissions in industrialized countries. Patients with chronic ischemic heart disease are treated both medically, with mechanical percutaneous revascularization and coronary bypass surgery. The treatment options have improved survival and quality of life of patients, but there is still a group of patients who have received all forms of conventional treatment of their disease, and who continue to have severe heart pain or heart failure.Therefore, new treatment modalities have had increasing interest.

Within research an increasing interest has moved towards an experimental treatment approach with regenerative stem cell therapy with the patient's own cells to re-establishment of blood vessels and heart muscle cells in the myocardium. There has been conducted many clinical treatment trials of patients with heart disease using different stem cell lines. The research groups have conducted clinical studies of patients with IHD using selected types of cells e.g. mononuclear cells, $CD34^+$ cells, $CD133^+$ cells, MSCs etc. (1,2). The results have been variable but with a clear trend for a treatment effect (1,2). It is not yet clear, whether one stem cell line is superior to another and also the most optimal delivery technic has been discussed.

Within the recent years more focus within clinical stem cell therapy has moved towards the multi-potent mesenchymal stromal cells (MSCs) lines, which can be obtained from different tissues within the patient. Clinical studies are on-going with MSCs from the bone marrow and the adipose-derived stromal cells (ADSCs) from adipose tissue to evaluate their effect in reducing and repair damaged myocardial in IHD (3,4).

The total numbers of MSCs or ADSCs are limited within the tissues, but the cells can be isolated and culture expanded *in vitro* to reach a significant number for clinical therapy (2-4). It has been more and more obviously that isolation of ADSCs from adipose tissue at the abdomen could be an attractive method for harvesting cells for clinical use, since the tissue contains 300 times more MSC-like cells than bone marrow (5). Up to 1 % of adipose cells are estimated to be ADSC, while only 0.001 – 0.002 % of cells in bone marrow represents MSCs (6). Moreover, cells isolated from adipose tissue may also grow faster than bone marrow derived cells (6).

Our group has at Rigshospitalet Copenhagen University Hospital, Denmark established a Cardiology Stem Cell Centre and a stem cell culture facility approved by the Danish Medicines Agency for clinical studies. (7,8)

We have established the first in man clinical study with treatment with mesenchymal stromal cells from the bone marrow of patients with chronic coronary artery disease and normal cardiac pump function to improve blood flow in the heart muscle through the establishment of new small blood vessels (9,10). The mesenchymal stromal cells were isolated from bone marrow and cultivation expanded for 8 - 10 weeks. The last week the cells were stimulated towards endothelial progenitor cells with the vascular growth factor $VEGF\text{-}A_{165}$. The stem cells were then injected directly into the heart muscle using the NOGA-XP® system.

We have now followed the effect of therapy in all 31 patients for 3 years (9,10). It was feasible to establish in-hospital culture expansion of autologous MSCs and safe to treat the patients with intramyocardial injections of MSCs using the NOGA-XP® system. The treatments have in all patients been without any side effects. In the entire 3 years follow-up period, the patients treated with MSCs had significant increased exercise capacity ($p<0.001$), reduction in CCS class ($p<0.001$), angina

attacks (p<0.001) and nitroglycerine consumption (p<0.001), and improvements in Seattle Angina Questionnaire evaluations (p<0.001). MSC treatment improved left ventricular ejection fraction (p<0.001) and systolic wall thickening (p<0.02) at 6 months follow-up. There was a reduction in cardiac hospitalizations from the 3 years period before treatment to the 3 years follow-up period (p<0.001) (3).

On this background we have established two double-blind randomized placebo-controlled clinical trials. We have just finalized the one in 59 patients with heart failure caused by coronary artery disease evaluating the effect of mesenchymal stromal cells from the bone marrow in the formation of new blood vessels and heart (4). The patients were treated with either their own mesenchymal stem cells or saline (placebo) injected directly into the heart muscle in a 2:1 randomisation. The patients have been treated with no evidence of serious adverse reactions. In the other study, the effect of ADSCs from abdominal adipose tissue or placebo in a 2:1 randomization is tested in 60 patients with severe coronary artery disease without heart failure in order to form new blood vessels in the heart muscle (3). In this study, there also have not been any serious side effects to the treatment in the so far 48 patients which have been treated.

Conclusion

Clinical stem cell treatment of heart patients has already shown promising results. In the coming years, there will be generated more clinical data in larger patient populations. However, to establish stem cell therapy as a clinical therapy there will be a great need for conduction of large-scale single center or multicenter studies of mesenchymal stem cells to prove which treatment is the most optimal.

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INDICATIONS FOR CATHETER ABLATION IN ATRIAL FIBRILLATION

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Catheter ablation is a highly invasive and technically challenging procedure, requiring a lot of expensive equipment. It also takes resources for pre-examination and follow-up of patients.

It has therefore been an issue for continuous discussion over the last 10 years, which patients to select for this treatment.

Factors favouring ablation therapy include the possibility of improved symptom control compared to antiarrhythmic drugs. Pharmacological therapy of atrial fibrillation has limited efficacy, a risk of side effects, and requires regular use. On the other side, ablation therapy has an inherent risk of procedure related complications (2-5%), has a lower success rate particularly in persistent cases, is an expensive treatment, and limited capacity has been an issue at least in this country until quite recently.

The presentation is based on the 2012 Expert Consensus Statement from HRS/EHRA (doi:10.1016/j.hrthm.2011.12.016), and the 2012 focused update of ESC guidelines on atrial fibrillation (doi:10.1093/eurheartj/ehs253).

In the 2010 ESC guidelines, catheter ablation of paroxysmal atrial fibrillation got a class IIa indication, meaning "should be considered". "Level of evidence class A" means "supported by several randomized studies". This recommendation was upgraded in 2012 to a class I recommendation, meaning "is recommended" or "is indicated", both in Europe and the USA. The recently published practice guidelines form ACC/AHA, states the following limitations for the class I recommendation: The treatment should be performed at "Experienced centres", defined as centres performing > 50 atrial fibrillation ablations per year. Furthermore, it is valid only for selected patients who have failed antiarrhythmic drug treatment, and who have no additional complicating cardiac or pulmonary disease.

Concerning recurrent persistent atrial fibrillation, the data are sparser and the success rate more modest. The recommendation was class IIa, level of evidence B, in 2010, and this has not been changed.

Longstanding persistent atrial fibrillation, meaning atrial fibrillation that has been continuously present for 12 months or more, is associated with an arrhythmic substrate beyond the pulmonary veins. The class of recommendation was IIb, meaning "may be considered", in the ESC guidelines from 2010, This has not been changed, except that the evidence level has increased from "expert consensus" (level of evidence C) to "supported by one study" (level of evidence B). The reason for this somewhat limited enthusiasm concerning longstanding persistent atrial fibrillation is illustrated by the 5-years results from Hamburg, reporting single procedure success rate 20 %, multiple ablation success rate 45 %, and an average of 1.9 procedures/patient (range 1-5). However, if total atrial fibrillation duration was between 1 and 2 years, a more favourable outcome was found (77 vs 42 %, p=0.003) (Tilz et al, J Am Coll Cardiol 2012;60:1921-29).

Atrial fibrillation and heart failure often coexist. However, there are only sparse and somewhat conflicting data concerning the results of catheter ablation in this setting. The guidelines offer a quite weak recommendation of IIb (level of evidence B).

The ESC guidelines from 2010 for the first time accepted catheter ablation as a first line treatment option, but with a rather week recommendation of IIb (may be considered).

This recommendation has been strengthened in 2012, to IIa (should be considered). The upgrading of recommendation was mainly based on the multicentre, randomized *MANTRA-PAF* study conducted in Denmark, Sweden, Finland and Germany (N Engl J Med 2012;367:1587-95).

The *MANTRA-PAF* study randomized 294 patients to either radiofrequency ablation or anti-arrhythmic drugs as the first treatment for paroxysmal atrial fibrillation. After 24 months, 223 radiofrequency procedures had been performed in 140 patients in the ablation group (1.6 procedures per patient). In the anti-arrhythmic drugs group, 73% were still on drugs, but 58 patients (36%) had also been ablated due to insufficient symptom control. The data were analysed by *intention to treat*. The primary endpoints "burden of atrial fibrillation" (% of time with atrial fibrillation in each Holter), and "cumulative burden of atrial fibrillation" (% of atrial fibrillation in all Holters) did **not** show any statistically significant difference between the ablation and drug therapy groups. However, the ablation group showed numerically more patients free from atrial fibrillation in Holter recordings at all control intervals. This difference was statistically significant only at 24 months (p=0.007, secondary endpoint), not as cumulative data (p=0.10).

The total number of serious adverse events did not differ significantly between the groups in the *MANTRA-PAF* study, but the ablation group included 1 death due to a procedure-related stroke, and 3 cardiac tamponades. The authors comment that: *"... our data support the current guidelines recommending antiarrhythmic drugs as first-line treatment in most patients with paroxysmal atrial fibrillation"*.

It is well known that catheter ablation of atrial fibrillation is associated with a risk of clinical stroke or TIA in 0.5-1.0 % of procedures. However, many electrophysiologists are concerned by MRI studies reporting a 7-14 % incidence of "asymptomatic intracranial embolic events". Further concern may be expected by a paper from Jonathan Kalman's group in Australia, which was recently pre-published as an accepted manuscript in *Journal of American College of Cardiology* (Medi et al, DOI: 10.1016/j.jacc.2013.03.073). They report on 60 patients being ablated for paroxysmal atrial fibrillation, 30 patients with persistent atrial fibrillation, 30 patients being ablated for various supraventricular tachycardias (age matched), and 30 matched controls from the atrial fibrillation waiting list. General anaesthesia was used in all ablations. 8 neuropsychological tests were performed at baseline, 2 days and 3 months post-ablation. The main finding was an incidence of postoperative neurocognitive dysfunction of 20 % after 2 days, and still 13 % after 3 months. There was a positive correlation between this dysfunction and the duration of the procedure in the left atrium. The long-term implications of these subtle changes require further study.

Studies reporting outcomes of atrial fibrillation ablation predominantly have a limited follow-up of 1-2 years. Some studies of long-term follow-up have been presented, and a metaanalysis including 19 studies (6167 patients) recently appeared (doi: 10.1161/JAHA.112.004549). Single procedure success rate at latest follow-up was found to be 53 %, while overall multiple procedure success rate was more favourable at 80 %. The average number of procedures per patient was 1.5 (CI 1.36-1.67). Predictors of atrial fibrillation recurrence were found to be non-paroxysmal atrial fibrillation, reduced left ventricular ejection fraction or clinical heart failure, structural or valvular heart disease, and the duration of atrial fibrillation.

Conclusion

Catheter ablation has been upgraded to class I, level of evidence A indication for symptomatic, drug-refractory, paroxysmal atrial fibrillation

Catheter ablation as first line treatment is an option for paroxysmal atrial fibrillation (class IIa (B)), but in my opinion most patients still ought to try at least one class I or class III anti-arrhythmic drug prior to invasive treatment

In patients with longstanding persistent atrial fibrillation, or atrial fibrillation and heart failure, there is still only a weak recommendation for catheter ablation

(class IIb, level of evidence B/A). Individual selection of these patients is necessary

With current indications, atrial fibrillation ablation may lead to long-term freedom from atrial arrhythmia in 50-80 % of treated patients. However, this therapy probably only rarely is actually "curative"

CARDIAC CT - IS IT USEFUL?

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Cardiac CT angiography has in the last years evolved to be an important diagnostic tool in cardiology. Multicentre studies from Europe and United States have confirmed a high sensitivity (93%) and a reasonable specificity (79%). Most importantly the negative predictive value has proven to be very high, most often 97-99%, and accordingly, cardiac CT is useful to rule out coronary artery disease. Also, cardiac CT is able to stratify patients in different risk groups: from very low risk (patients without coronary artery stenosis) to higher risk (patients with non-significant and significant stenosis). Thus, cardiac CT has prognostic implications.

In patients suffering of possible stable angina pectoris, cardiac CT is, so far, not recommended by the ESC. However, an update of the guidelines from 2006 is to be presented at the next ESC in Amsterdam. In Denmark, cardiac CT is recommended in the workout of patients without previous cardiovascular disease and suspected stable angina pectoris (Figure 1), and last year 11500 scans were performed. Misinterpretation of coronary stenosis by cardiac CT is the most important issue to be solved in the future. The positive predictive value might be 50%. Thus to select the appropriate patients for invasive angiography a stress imaging like scintigraphy should follow a positive cardiac CT. The radiation dose was previously an important concern, but the dose has decreased significantly (from above 20 mSv to 2-3 mSv per examination), and is now at the level of an invasive angiography.

Also, pre-TAVI cardiac CT is highly valuable. Aortic annulus is a complex,

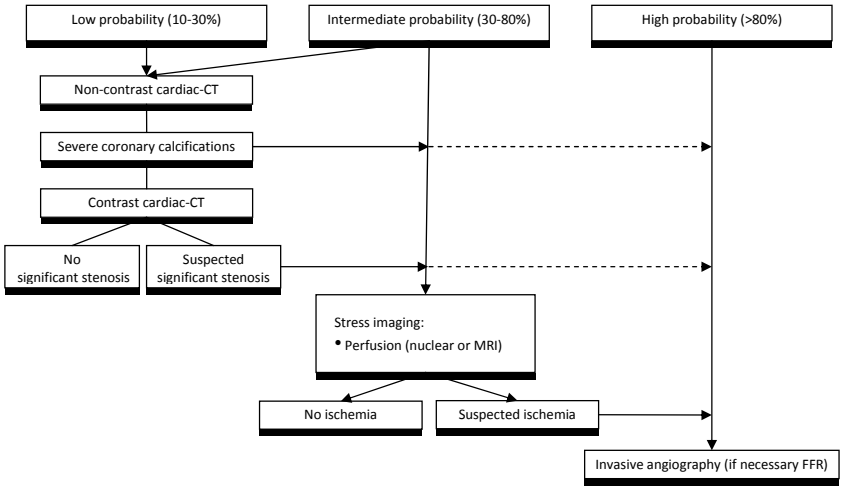

Figure 1. Symptomatic patients with suspected coronary artery disease (CAD). Estimation of pre-test probability of CAD using clinical history, biomarkers, ECG, echocardiography and optionally an exercise test

3-dimensional structure, and most often non-circular. Using 2D echocardiography it is difficult to measure the size of the annulus, and an inappropriate size of the prosthesis valve has an important impact on morbidity and mortality. However, cardiac CT is reliable and accurate and is able to reduce frequency of complications like paravalvular regurgitation.

Other indications could be evaluation of cardiac morphology and tumour mass prior to surgery, but maybe the most important indication is in cases with uncertainties after invasive coronary angiography or echocardiography. In such cases, cardiac CT might find "hidden" coronary anomalies or unexpected pulmonary veins draining into right atrium.

Cardiac CT is certainly useful in the daily clinical practice. However, cardiologist should be involved to be familiar with the weakness and strengths of the technique. Society of Cardiovascular CT has an annual meeting in July while the Nordic Symposium on Cardiac CT is scheduled every second year. We hope to see many of our Nordic colleagues in Odense in 2015. If interested in collaboration please mail to axel.diederichsen@rsyd.dk.

POSTCARDIAC ARREST CARE

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The survival after out-of-hospital cardiac arrest (OHCA) has increased by 50-100% during the last decade in Scandinavia. In Denmark, 30 days survival after OHCA is now about 10%. The better prognosis is probably due to improvement of all aspects of the chain of survival including increased focus on post cardiac arrest care at the hospital.

Recent studies have documented significantly better survival after OCHA when admitted to a tertiary care centre than when admitted to non-tertiary hospitals. It may therefore be relevant to centralize the treatment of these patients. Most, but not all, registry studies reports increased survival if the patients are sent for acute coronary angiography and percutaneous revascularisation (PCI), but there is a severe selection bias in all these studies. A randomized trial will be needed to evaluate whether acute PCI will improve the prognosis in all OHCA patients. It seems reasonable to offer acute PCI to all STEMI patients, and to handle other OHCA patients with subacute coronary evaluation and revascularisation if needed after awakening until such a trial is available.

All comatose OHCA patients with ventricular tachycardia or ventricular fibrillation as initial rhythm should be treated for 24 hours with mild therapeutic hypotermia at 32-34°C. This has been shown by a few small to midsize randomized studies. The beneficial effect of therapeutic hypotermia after cardiac arrest may be substantial, but the current body of evidence is not conclusive. In addition, there are several unknown factors including optimal target temperature, optimal cooling time, and optimal cooling method. Major trials on some of these issues are on their way. In addition to patients with ventricular tachycardia/ventricular fibrillation, comatose OHCA patients with asystoli as primary rhythm can also be considered for hypothermia treatment, especially when the arrest was witnessed and resuscitation was attempted without delay. But initial asystoli carries a much poorer prognosis. Registry studies also indicate that post cardiac arrest and post hypothermia fever should be avoided.

If the patient does not wake up after the hypothermia treatment prognostication should in most patients be postponed to at least 72 hours after normotermia has been reached – usually about 5 days after the cardiac arrest. SSEP and EEG may help in this prognostication, but has to be combined with a clinical neurological examination. CT, MR as well as some biochemical markers also caries prognostic information in these patients.

KARDIOGENT SJOKK

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Prognose

Til tross for alle fremskritt i kardiologien de siste årene, inkludert akutt revaskularisering av hjerteinfarkt, er mortaliteten ved kardiogent sjokk fortsatt på mellom 40 og 60 % i de fleste registre. Overlever pasienten de første 30 dagene er imidlertid prognosen svært god. 90 % av pasienten med sjokk som overlevde de første 30 dagene i *GUSTO-1* levde etter 1 år (55 % døde de første 30 dager).

Definisjon

Kardiogent sjokk er definert som en tilstand med misforhold mellom oksygentilførsel og forbruk i kroppens organer som medfører vevshypoksi i kombinasjon med kardial funksjonssvikt. Vanligvis er årsaken til den reduserte vevsperfusjonen nedsatt hjerteminuttvolum.
Pasienter i kardiogent sjokk har:

- Systolisk blodtrykk < 90 mmHg i ≥ 30-60 min etter oppstart av volumterapi.
- Tegn på redusert organperfusjon, dvs. kalde, klamme ekstremiteter, oliguri og redusert bevissthetsnivå.
- Hemodynamiske målinger fra lungearteriekateter: hjerteindeks < 2,2 l/min/m^2 ved PCWP > 15-18 mmHg. Blandet sentralvenøs oksygenmetning (SvO_2) fra lungearteriekateter < 60 % eller sentralvenøs oksygenmetning ($SvcO_2$) fra et sentralt venekateter (CVK) < 70 %.

Monitorering

Pasienter bør monitoreres med arteriekran, CVK, urinkateter, kontinuerlig hjerterytmeovervåkning og repeterte ekkokardiografiundersøkelser. Hos selekterte pasienter vil en ha behov for kontinuerlig monitorering av hjerteminuttvolum og karmotstand. Da kan en benytte pulsbølgeanalyse-prinsippet (f eks. PICCO, Vigileo/FloTrac) eller et lungearteriekateter.

Stabilisering

Initialt må pasienten stabiliseres raskt med tanke på respirasjon, sirkulasjon og hjerterytme. CPAP/ikke-invasiv ventilasjonsstøtte initialt, men lav terskel for intubasjon som tillater høy PEEP-behandling som sikrer oksygenering og som også kan medføre redusert pre- og afterload.

Intraaorta-ballongpumpe (IABP)

Bruk av aortaballongpumpe er fortsatt aktuelt selv om *IABP-SHOCK II*-studien fra 2012 ikke viste effekt av slik behandling. Imidlertid inkluderte denne studien kun pasienter med kardiogent sjokk som følge av et akutt hjerteinfarkt. F.eks. var pasienter med myokarditt ekskludert. I tillegg var infarktpasienter med mekaniske komplikasjoner ekskludert. Pasienter med ventrikkelseptumruptur, myksomer eller papillemuskel- eller chordaruptur skal derfor fortsatt ha IABP.

Behandle utløsende årsak

Det er viktig og identifisere og behandle utløsende årsak:

- *Revaskularisering,* kardiogent sjokk har oftest iskemisk årsak
- *Konvertering* av takyarytmier
- *Temporær pacing* ved bradykardi/blokk
- *Akutt kirurgi* ved mekaniske komplikasjoner
- *Perikardtapping* ved tamponade
- *Sirkulasjonssvikt – behandle utløsende årsak:*
  - sepsis, anemi, lungeemboli, tyreotoksikose etc.

Revaskularisering

Revaskularisering ved iskemisk årsak er eneste behandling som er dokumentert i kontrollerte kliniske studier. *SHOCK*-studien fra1999 viste at 30 dagers mortalitet ble redusert fra 53 til 44 % i gruppen randomisert til tidlig revaskularisering med PCI eller ACB-kirurgi.

Inotropi/pressor-behandling

Skal ikke gis til pasienter med akutt hjertesvikt hvis de ikke er preget av hypotensjon med systolisk blodtrykk < 85 mmHg eller viser tegn til sviktende organperfusjon. Ved mindre uttalt hypotensjon kan en forsøke vasodilatasjon med f.eks. lavdose nitroprussid. Hvis hjertet har kontraktil reserve, kan slagvolumet øke når *afterload* senkes.

- Vasodilatasjon: Nitroglyserin/ nitroprussid
- Inotropi og vasodilatasjon: Dobutamin/ levosimendan
- Inotropi og vasokonstriksjon: Dopamin/ adrenalin
- Dominerende vasokonstriksjon: Noradrenalin, fenylefedrin, vasopressin.

Alle adrenerge agonister inkluderte fosfodiesterasehemmere øker intracellulært cAMP og kalsium. Dette gir økt oksygenforbruk, større infarkter og økt arytmitendens. Adekvat vevsperfusjon, ikke blodtrykk, bør styre behandlingen. Bruk lavest mulig doser. Inotropi (f.eks. dobutamin, evt. levosimendan, særlig for å oppheve beta-blokade) forsøkes ved lavt blodtrykk (< 85 mmHg) og hypoperfusjon for å øke hjerteminuttvolumet. Ved behov for vasopressor for å øke blodtrykket velges dopamin eller noradrenalin. *SOAP*-studien fra 2010 (sjokk forårsaket av sepsis, hypovolemisk sjokk eller kardiogent sjokk) viste hyppigere forekomst av arytmier i gruppen randomisert til dopamin og bedre overlevelse i gruppen randomisert til noradrenalin i subgruppen av pasienter i kardiogent sjokk. Det er derfor et rasjonale for å velge noradrenalin fremfor dopamin ved behov for vasopressor.

ESC retningslinjer fra 2012 fremhever manglende dokumentasjon for valg av behandling ved kardiogent sjokk og er relativt lite spesifikke. I stedet kan en anbefale de tysk- østerrikske retningslinjer fra samme år som i detalj gir forslag til behandling av kardiogent sjokk.

GENETIC TESTING FOR INHERITED ARRHYTHMIA SYNDROMES

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In the past decade a lot of new scientific discoveries have been made in the field of cardiovascular genetics. These have led to a deeper understanding of a number of arrhythmias, especially monogenic disorders such as the long QT syndrome (LQTS). The Heart Rhythm Society and The European Heart Rhythm Association have published a joint consensus statement on the state of genetic testing for channelopathies and cardiomyopathies[1].

The yield of genetic testing for a given channelopathy is quite variable and not all clinical cases are accounted for by known genetic variants. Therefore, a negative genetic test does not rule out the clinical disease in the index case.

Pre and post genetic test counselling should include a discussion on the risks, benefits and implications of the results. Treatment decisions should be based on a comprehensive patient evaluation and not just the results of the genetic test. The cost of genetic testing is not insignificant, although the price is expected to decrease in the near future.

Genetic testing is available and recommended in certain clinical scenarios in the LQTS, especially types 1-3, catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome and hypertrophic cardiomyopathy. Genetic testing for the causative mutation in family members is frequently indicated. For details of indications for testing the reader is referred to the consensus document[1].

The percentage of sudden unexplained death in autopsy series of individuals under 35 years is in the range of 15-40%. The expected yield of post mortem testing for the most common mutations causing serious channelopathies (KCNQ1, KCNH2, SCN5A and RyR2) is 15-25%. The high cost of genetic testing should be weighed againts the potential life saving impact for surviving family members.

A clinically focused initial evaluation is advised for those who have suffered sudden unexpected death. A determination of the clinical scenario should be followed by a comprehensive autopsy. Careful family history and evaluation of first degree relatives should be done next if necessary. If the cause of death is still unexplained more detailed evaluation may involve genetic testing. The consensus statement recommends collection of tissue samples for all cases of sudden unexplained death. Either comprehensive or targeted genetic testing may be considered in attempt to establish probable cause and is recommended if circumstantial evidence points toward the LQTS, Brugada syndrome or CPVT. Mutation-specific testing is recommended for relatives following identification of the sudden unexplained death mutation.

There are a number of known risk variants for atrial fibrillation (AF). However, our understanding of the genetics of AF in still in the early stages. Genetic testing for common arrhythmias such as AF is currently not recommended.

In summary, there are growing data on the role of genetics in the development of arrhythmias. Genetic testing is becoming clinically relevant for some channelopathies and cardiomyopathies. On the other hand, genetic testing for complex common disease is not yet recommended. Doctors caring for patients with arrhythmias need to be aware of the indications for and limitations of genetic testing.

HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;12:1077-1109.

DOES MYOCARDIAL DEFORMATION IMAGING IMPROVE THE INTERPRETATION OF STRESS ECHOCARDIOGRAPHY?

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Several experimental studies showed that stress-induced ischemia caused predictable deterioration of regional myocardial function: reduction and delay of contraction with concomitant shift of deformation from systolic to post-systolic phase [1]. Therefore quantitative imaging was assumed to allow detection of early ischemic phenomena, which often can not be assessed visually. In clinical studies, the peak velocity response for both systole and diastole has been shown to be significantly lower during stress in mal-perfused myocardial regions [2-5]. Prominent post-systolic velocity was shown to be sensitive and early marker of acute ischaemia [6]. Later investigations proposed a reduced strain and strain rate, increased ratio of post-systolic shortening to maximal segmental deformation, delayed relaxation measured by transverse strain at peak stress for ischemia detection [7-10]. The translation of these tools into routine clinical practice raises the question of choice: which is the most accurate and the most reliable parameter?

Our study aimed to identify the best ultrasound quantitative parameter for prediction of at least one stenosis ≥70% stenosis per patient. 151 patients (age 61.77 ± 9.21) were included in the study without previous myocardial infarction in order to have homogenic group in terms of baseline measurements. We performed extensive side-by-side comparison of multiple markers using methods available in daily practice: 98 measured and calculated parameters including systolic, post-systolic, diastolic velocity, strain and strain rate parameters were obtained with pulsed wave doppler myocardial imaging (PW-DMI), colour-coded doppler myocardial imaging (CC-DMI) and speckle tracking imaging (STI) at rest and during stress [11]. The rationale of applying all these techniques during the same dobutamine stress test is based on the awareness that each of them has inherent advantages and limitations. Direct comparison of physiologically different parameters as well as similar markers obtained by different methods should allow the reasonable choice of the most reliable predictor of CAD for practical use.

The total number of all investigated segments was 1359. The stored images of 38 segments (2.8%) due to poor image quality were excluded from the analysis. Data of 1321 (97.2%) segments were finally analysed. Ischemia was visually assessed in 60 (39.7%) subjects: rest and peak WMSI was 1.02 ± 0.05 and 1.36 ± 0.21, respectively. A total of 53 (35.1%) patients had ≥70% coronary stenosis. All parameters were evaluated in 9 out of 16 segments, discriminated according to our previous DMI study [6] as most representative for three coronary territories using factor statistical analysis. Separate analysis was made for each evaluated myocardial segment, taking into account known base-to-apex and wall-to-wall differencies of myocardial velocity and strain/strain rate. Basal inferoseptal, basal inferior and mid inferior segments were attributed to right coronary artery (RCA); mid inferoseptal, apical inferoseptal, basal anterior and mid anteroseptal segments were attributed to left anterior descending (LAD); basal inferolateral and mid inferolateral segments were attributed to left circumflex artery (LCX). The difference between stenosed and non-stenosed segments were significant, but relatively small comparing to standard deviations. Our results confirmed the relation of 40 quantitaive parameters of regional myocar-

dial function to the obstruction of coronary arteries. Markers included blunted response of systolic velocity, prolonged time-to-peak systolic velocity, reduced E′ wave velocity and E′/A′ ratio, reduced systolic and post-systolic strain, ratio of post-systolic index, reduced strain rate and their changes during stress. They were 23 velocity, 10 strain and 7 strain rate markers specific for each segment location. Among stenosis predictors there were 9 rest parameters, 19 stress parameters and absolute or relative changes of 12 markers from rest to stress.

The strongest single predictors of stenosis appeared to be stress E′ wave velocity (PW-DMI, basal inferior segment, cut-off 7.53 cm/s, and CC-DMI, mid anteroseptal segment, cut-off 3.5 cm/s) and stress systolic strain (CC-DMI, mid inferolateral segment, cut-off -16%). However, based on the results, we coud not discriminate one or two robust predictors, sufficiently powerful for stand-alone use, as all of them demonstrated only limited pedictive value.

Areas under the curve in ROC analysis were 0.63 - 0.72 for 16 PW-DMI, 12 CC-DMI, 12 STI markers. Interestingly, similar ability to predict significant CAD was reported for strain rate, strain parameters and post-systolic index (AUCs 0.67 – 0.71, 0.64 - 0.66, and 0.60 – 0.63, respectively) in the study of Hanekom et al. Sensitivity, specificity and accuracy of single predictors ranged from 40.0% to 93.3% (95% CI 22.7%; 99.2%), from 34.2% to 88.7% (95% CI 25.6%; 94.1%) and from 45.8% to 80.0% (95% CI 37.5%; 87.2%), respectively. Youden index ranged from 0.20 to 0.52 (see Table 3). Meanwhile, sensitivity, specificity and accuracy of visual DSE evaluation was 82.4% (95% CI 77.4%; 85.2%), 92.6% (95% CI 83.4%; 97.5%) and 86.0% (95% CI 79.5%; 89.6%), respectively, Youden index 0.75. *Comparing AUCs of WMSI (0.88) with each quantitative marker, it was found that visual DSE evaluation was significantly better than all discriminated quantitative predictors* (P < 0.05).

Referring to other investigations, MYDISE, perhaps the only known multicenter study, demonstrated similar limited sensitivity (67-69%) and specificity (60-67%) of systolic velocities before correction by heart rate, age, and gender [12]. Several other previous publications also could not demonstrate incremental benefit of quantitative parameters to visual wall motion assessment. In the study of Cain et al [5], the accuracy of myocardial Doppler velocities was lower comparing to wall motion scoring. Strain rate imaging in the report of Voigt et al [7] was found to be comparable with conventional visual assessment. Investigating the accuracy of Doppler-based and two-dimensional strain imaging, Hanekom [9] did not find significant differences between quantitative and visual assessment.

The next question was - might the combination of several parameters enhance the power of quantitative tools? We built and tested multiple logistic regression models, while the highest predictive ability (AUC 0.86, accuracy 81%) was achieved with full Integrated model, combining visual and quantitative markers of both methods together (Figure 1), but it looked really cumbersome and far from practical. Next step was to use automated vendor-suggested software: parameters of 18 myocardial segments were manually approved and automatically exported to Excel tables using commercially available software (Echopac PCBT08, GE Healthcare). According to ROC analysis the most informative 18 parameters for at least one stenosis per patient

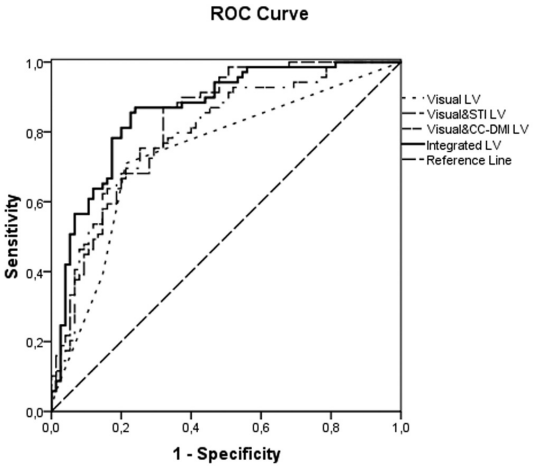

Figure 1. Performance of several models - combination of different quantitative parameters

were selected consuming the tracking of 2- and 4-chamber views at rest and during stress. Created software automatically makes the prognosis of significant stenosis, and its performance looked very promising in model derivation cohort (Figure 2). Performance is improving while the number of included patients is increasing and stabilizes over 70 patients. However, when applied in new study group for model validation, predictive value significantly dropped down (Figure 3).

Summarizing published and our own experience, one could perceive some systemic problems with application of quantitative methods for stress echocardiography. First of all, these are technical challenges - strain techniques are known to be vulnerable to considerable noise in the signals, and other artefacts; less accurate tracking at higher heart rates is observed; potentially inadequate spatial and temporal resolution, angle-dependency and high beat-to beat variations are known limitations [13]. Methodology of research in stress echo is really complicated, as segment- or at least level-specific criteria should be applied. In general, looking to particular segmental parameters may represent too large compression of data extracted from the whole LV. Mutual interaction of ischemic and non-ischemic segments possibly may diminish the differences between the groups. At last, we have to realize substantial variability of measurements as coefficients of correlation for inter- and intraobserver variability in our research ranged from 0.53 to 0.85. This variability seems to be not less than in visual assessment and may mask ischemic changes in deformation.

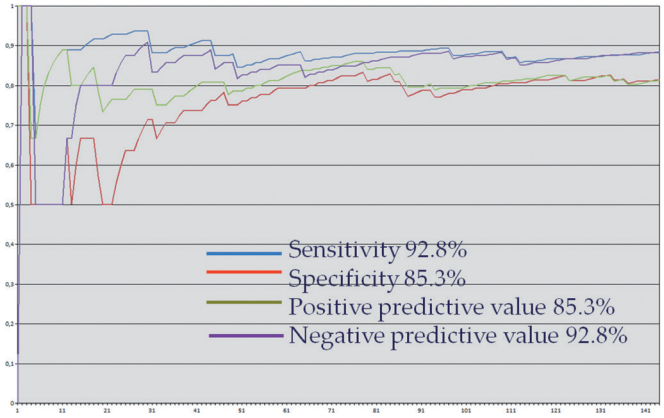

Figure 2. Performance of automated model for predicting at least one stenosis per patient: model derivation

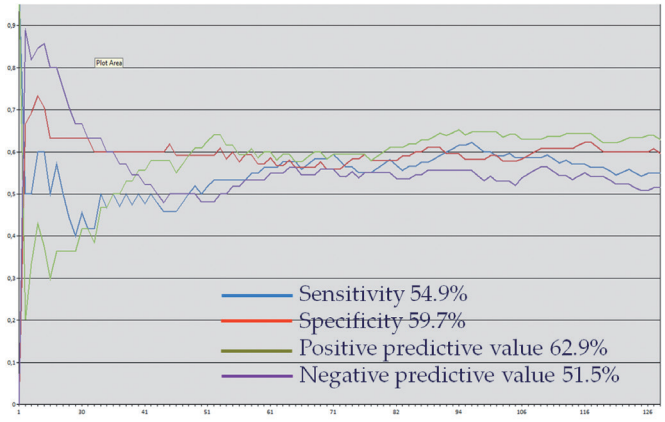

Figure 3. Performance of automated model for predicting at least one stenosis per patient: model derivation

Today quantitaive methods are not recommended for use in stress echocardiography in expert consensus statement issued by the European Association of Echocardiography [14]. As many other clinical decisions, echo stress tests continue to be evaluated subjectively. Perhaps, this is not a disadvantage, as the whole set of visual data goes to super complex neural computer – human brain, which generates the interpretation of the test.

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3D ECHOCARDIOGRAPHY IN CLINICAL PRACTICE

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The most significant developments in echocardiography in the last decade are the real-time 3D echocardiography (RT3DE) and 3D transoesophageal echocardiography (3D TEE). The clinical use of these new techniques has broadened significantly. Why use RT3DE in every-day clinical practice? RT3DE provides potentially faster image acquisition; there is less need to rely on geometric assumptions when quantifying volumes, mass and function; it is easier to understand 3D structure of the heart and relations of various structures to one another and last and not least it is easier to demonstrate echo findings to those who are echo-challenged. We in Tartu University Hospital use RT3DE and 3D TEE for quantification of left ventricular (LV) volumes and function, for evaluation of LV dyssynchrony, in decision making in valvular heart disease, in left atrial appendage evaluation and in guiding some intracardiac interventions (DSA and PFO closures).We have also started to use 3D stress echocardiography (3DSE).

The advantage of 3D imaging in quantification of LV volumes and function is the improvement in the accuracy of the evaluation by elimination of errors caused by foreshortened views. RT3DE has shown high correlation with the CMR reference values and high reproducibility.

In evaluation of LV dyssynchrony systolic dyssynchrony index (SDI) is calculated as a standard deviation of the time to reach minimal regional volume in different LV segments, given in % of the cardiac cycle. Several studies have shown that SDI is reliable in the evaluation of LV dyssynchrony. RT3DE is a promising tool for improved patient selection, in optimization of CRT therapy and in predicting response to CRT.

In valvular heart disease 3D TEE is used for perioperative planning in mitral valve surgery. It is a useful tool in segmental analysis of mitral valve, in quantification of valve stenosis and regurgitation and in evaluation of complex valve disease.

3D stress echocardiography is also a very promising tool for use in clinical practice. Now side-by-side display of the cropped images has become available. So-called iRotate (bi- and triplane) stress echocardiography can be a bridge form 2D to 3DSE. Several authors have shown that success rate of adequate LV segment visualization in 3DSE is equal or even better compared to 2D. 3DSE enables faster image acquisition and shorter analysis time. Multislice display of 3D data set of the LV makes segmental analysis more accurate.

INDICATIONS FOR MITRAL VALVE RECONSTRUCTIVE SURGERY

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Mitral regurgitation (MR) is a leading cause of heart valve disease according to EuroHeart Survey, competing with degenerative aortic stenosis. Obviously, it is more pronounced in advanced age group (12). MR has a direct negative impact on population survival, especially in patients with far advanced symptoms of NYHA functional classes. Even patients with asymptomatic MR, whose effective regurgitant orifice area is ≥40mm^2, demonstrate up to 40% mortality rates in a five-year period. Cardiac events among patients with asymptomatic MR have also increased quite significant. In some articles it is shown to be up to 60% in five years in a group of patients suffering from severe MR, even in asymptomatic patients (4). Decrease of survival because of MR, including asymptomatic patients, raises a question whether it should be treated surgically in early stages or later stages when left ventricular remodeling, arrhythmias and/or pulmonary hypertension become more pronounced, as it is suggested in the latest guidelines (10).

Fundamental research might answer some of those questions and declare that a volume overload stress has early negative impact on left ventricular function and remodeling. Appearance of mast cells within the left ventricular or the left atrial myocardium in patients with severe MR, even in asymptomatic patients, leads to myocyte degeneration, death and interstitial tissue remodeling with changes at the genetic, molecular, subcellular and cellular levels (1,3,13,14). Therefore, early and proper diagnosis or patient screening of MR is becoming significantly important.

Diagnostic criteria for imaging techniques such as echocardiography or cardiac magnetic imaging are probably becoming most important. Traditionally, regarding grading of MR, nowadays along with the quantitative grading of MR there are more sensitive markers in the armamentarium of echocardiography like left ventricular systolic strain, especially strain rates which are altered in predilated or dilated ventricles and even in normal, but volume overloaded ventricles. Calculated effective regurgitant orifice area using PISA method is less sensitive and less correct compared to anatomic regurgitant orifice area calculations from 3D transesophageal echocardiography. Standards such as cardiac magnetic resonance imaging and transesophageal echocardiography, especially calculating anatomical regurgitant orifice area, probably should become a golden standard in evaluating severeness of MR (11,16).

The left ventricular diastolic diameter changes quite in a limited range up to 1.6% per year after surgery, it raises a question whether left ventricular dimensions should become or remain a criterion for indications of cardiac surgery (7). There is also another important issue regarding female sex and MR. It seems that only 5.7% of women, compared to 9.6% of men, reach the classical surgical threshold of left ventricular end systolic diameter which is considered to be critical at ≥45mm. However, women have smaller bodies and indexing for body surface area (BSA) the same mitral valve regurgitation severity will demonstrate greater left ventricular and left atrial enlargement. Therefore, greater attention should be paid to estimation of MR in the female group of patients (2).

Results from the 1980s and 1990s show improvement of the surgical techniques during the last decades in repairing mitral valves (6,19). However, reoperation rates after mitral valve repair remain up to 16% to 20% in a twenty-year period after surgery (5). Causes of failure to repair mitral valve or MR recurrence are also interconnected with the stage of MR as a disease (8). There is a group of valve-

related complications: underlying valve disease, Barlow disease or fibroelastic deficiency. Advanced myxomatose changes are associated with higher repair failure rates. Prolapse of both leaflets or prolapse of the anterior leaflet demonstrates higher valve repair failure rates (15,18). Of course, there are issues associated with surgical skills and techniques or procedure-related issues, where no annuloplasty ring or chordal shortening techniques have been used or the operator has low volume of mitral valve surgery. In this group of patients, higher failure rates are expected. Increasing age of patients with increased comorbidity rate raises a question. However, there is enough data from scientific papers, also Medicare and Medicaid services analyses showing that outcome of isolated mitral valve repair in older patients (≥75 year old) provides better outcome results compared to mitral valve replacement (19). Nowadays even following new American and European guidelines regarding MR, real life presents three surgical timing tactics advocating when and how to deal with patients having severe MR, both in symptomatic and asymptomatic stages. Guidelines suggest operating on MR when developing severe clinical symptoms. However, as it has been said before, there are surgical tactics that even asymptomatic patients, especially those who have been revealed suffering from severe MR, should be operated on, and this approach is suggested by the Cleveland Clinic Foundation (9). They showed that less than 0.5 % mortality rate can be achieved in this group of patients with a high repair rate, up to 95%. Their material also shows that mortality rates increase to almost the double and tenfold when NYHA class I group of patients was compared to NYHA class III or IV. It is not only because pressure of failing heart, but also because of increased comorbidities such as renal failure, sepsis and atrial fibrillation. Survival rates according to new NYHA functional class are also far better in a repair group of patients with NYHA I class symptoms compared to NYHA class IV. The truth is most likely somewhere in between. The technique of "watchful waiting" has been proposed by Austrian group of surgeons (17) to follow asymptomatic patients suffering from severe MR. The appearance of symptoms like elevated pulmonary artery pressure, atrial fibrillation, left ventricular dilatation or heart failure symptoms, would serve as an indication for surgery. Management of severe chronic primary MR most probably should account for several factors such as reparability of patient heart valve which in turn depends on quality of mitral valve tissue, surgical skills, training and volume of repair operations of each hospital. Individual statistical data such as mortality, morbidity, reparability and durability of mitral valve repair before offering this type of surgery to manage severe MR in asymptomatic patients should be accounted before offering mitral valve repair to asymptomatic patients. On the contrary, "watchful waiting" tactics or existing guidelines should be followed.

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