UPDATES IN CARDIOLOGY

Oxygen Therapy in Patients With Acute Heart Failure

Supplemental oxygen therapy (peripheral oxygen saturation 90% to 94% or partial arterial oxygen pressures <60%) has been practiced for more than a century and recommended in all hypoxemic management guidelines. It is a common method for treating acute heart failures, but its application on normoxemic patients is still highly controversial. According to many early clinical studies, hyperoxia and supplemental oxygen treatment can be devastating on patients whose oxygen saturation levels are normal: the accelerated output of reactive oxygen species reduces myocardial oxygen consumption and slows down coronary bloodstream, after which the patient suffers oxidative stress, and eventually undergoes a hyperoxia-induced vasoconstriction in his coronary, systemic, and cerebral vasculature.

Practitioners worldwide have repeatedly applied noninvasive mechanical ventilation to treat acute heart failure, even if performing a larger randomized controlled trial for it showed no substantial mortality difference in comparison to oxygen therapy.

Most of the studies considered for this article confirmed that extreme hyperoxia can be traced to increased left-ventricular filling pressures and impairment of cardiac relaxation. Acute heart failure was related to other hemodynamic irregularities, including coronary sinus blood flow and reduced cardiac output. The observed effects confirmed that oxygen level alterations are detrimental for the pulmonary capillary wedge pressure, and consequently for all cardiac functions.

Another systematic review on 61 patients reported that excessive oxygen therapy reduces coronary blood flow by 29%, increasing at the same time cardiovascular resistance. 4 of the 6 RCT analyses registered that treating acute conditions with supplemental oxygen caused 2-fold increase of the death risk.

Finally, more than 400 patients with ST-segment elevation myocardial infarctions were randomized during the AVOID trial (Aid Versus Oxygen in Myocardial Infarction), subjected to both supplemental oxygen and no supplemental oxygen treatment. As results showed, supplemental oxygen increased the size of their myocardial injury by 55%.

Hyperoxia is a human-developed rather than a nature-induced phenomenon. It affects the body in two ways: it induces vaso-constriction in the coronary, systematic, and cerebral vasculature, and accelerates endothelial production of reactive oxygen species that cause damage in the cellular tissue (mostly hydrogen peroxide and superoxide). The ROS production derives from three specific sources: nicotinamide adenine dinucleotide phosphate oxidants, nonenzymatic reactions (radiation), and mostly the obstructions in the mitochondrical electron transport chain. Once ROS production surpasses the tissue's antioxidant capacity, the bloodstream delivers unexpected oxygen levels, and this process results in immediate oxidative stress and detrimental cardiac damage. Reduced heart rates, on the contrary, have nothing to do with the sympathetic nervous system, but are caused by increased parasympathetic activity.

Oxygen therapy remains the cornerstone of AHF treatment, assuming it is applied in line with all factors and trial recommendations. The challenge is to consider all preserved/reduced ejection fraction populations, ventricular wall thickness, anemia, or presence of other coronary artery diseases. So far, there has only been a partial solution to this problem, namely developing automated oxygen delivery systems adjusted to the complexity of the patient's condition. (IM, MR)

Sepehrvand N., Ezekowitz, J.A., Oxygen Therapy in Patients With Acute Heart Failure, JACC: Heart Failure, Volume 4, Issue 10, pp. 783-790: 2016.

Carbamylated Low-Density Lipoproteins Induce a Prothrombotic State Via LOX-1

Chronic kidney diseases (CKD) are associated with a significant increased cardiovascular disease burden (CVD) and studies also show that CVD is the leading cause of death in patients with CKD, particularly in those undergoing hemodialysis with a 10 fold higher incidence of acute thrombotic events than the general population.

The frontrunner among primary/secondary CV prevention therapies is lipid lowering, even if reducing plasma cholesterol is not a definite guarantee for saving CKD patients' lives. Recent studies have shown that high levels of carbamylated low density lipoproteins (cLDL) have been found in the plasma of patients with CKD. Carbamylation represents a post-translational protein modification triggered by urea-derived cyanate.

Protein carbamylation can also appear at sites of inflammation driven enzymatically by phagocyte-induced inflammatory myeloperoxidase even when there is no renal disease. The incidence of major CV events may correlate with the levels of plasma protein carbamylation High-density lipoproteins and *ex vivo* lipoproteins may cause a chain of proatherogenic reactions inside the vascular cells which lead to detrimental CV events.

This study will examine the hypothetical connections between cLDL and thrombus formation promotion thus representing a correlation between CKD and CV events.

Native (nLDL) and modified LDL were isolated from the plasma of healthy donors and CKD patients undergoing hemodialysis and then ultracentrifugated. The same process was performed of plasma LDL from mice. The experiment was conducted on isolated mice.

C57Bl6 mice were given 2 mg/kg of cLDL and 2 mg/kg of low-density natural nLDL. The mice were anesthetized and then thrombus formation was induced by photochemical injury in the exposed right carotid artery, which was then monitored and stable vessel occlusion was defined as a blood flow below 0,1 ml.min for at least 1 minute.

Researchers executed real-time PCR to analyze mRNA and protein expressions, and aggregated the results with the ones performed on healthy volunteers' washed platelets or citrated whole blood. The gathered samples were incubated with the cLDLs and nLDLs (100mg/ml), thrombin, collagen, and ADP simulation.

None of the groups exhibited significant modifications in the activated partial thromboplastin and prothrombin times. PCR analysis, nevertheless, revealed higher plasminogen activator inhibitor type 1 mRNA expressions in carotid arteries from cLDL treated animals compared to nLDL-treated mice of controls and increased tissue factor in cLDL-incubated cells. In nLDL-treated mice no such difference in TF activity was spotted.

In order to determine whether these prothrombiotic effects are mediated by lectin-like oxidized LDL receptor 1 (LOX-1), scientists assessed mRNA expression levels in conditions of low interfering RNA, and their PCR experiments in cultured aortic smooth muscle cell (AoSMCs) showed that cLDL treatment didn't increase leucocytes, but did induce carotid artery tissue lysates LOX-1 mRNA.

The whole-blood analysis showed nLDL incubation on healthy subjects' washed platelets did not activate the platelets, contrary to cLDL incubation and collagen/ thrombin stimulation. The same experiment was performed excluding fibrinogen, where it was confirmed that ADP-induced p38 MAP-kinase phosphorylation caused LOX-1 to dislocate closer to the cells' surface.

This was the first evidence-based study to confirm that modifying LDL in CKD patients by in vivo/in vitro carbamylaion exerts prothrombotic effects on platelets and smooth vascular muscle cells, and does so through the LOX-1 receptor. Overall, it was concluded that cells express their LOX-1 receptors when incubated with cLDL, and that the LOX-1 receptor plays a critical role in platelet aggregation and ADP-induced binding of fibrinogen and modified lipoproteins. These findings could lead to a new lipid and LOX-1 targeting strategies in patients with CKD. (IM, MR)

Holy et al., Carbamylated Low-Density Lipoproteins Induce a Prothrombotic State Via LOX-1 Journal of the American College of Cardiology, Volume 68, Issue 15, pp. 1664-1676: 2016.

Computed Tomography for Planning Transcatheter Tricuspid Valve Therapy

Percutaneous transcatheter tricuspid valve therapy includes several treatment options for patients experiencing significant tricuspid regurgitation (TR); but who are considered too fragile for open heart surgery. Moderate to severe TR is a frequent occurrence in patients experiencing left-sided heart disease. Recently introduced therapies may open up options for these patients; many of whom are presently restricted to medicinal therapeutic treatments.

Current intervention techniques include the insertion of pledgeted sutures to reduce the TR level; positioning of a corkscrew anchor to reposition the dimension of the tricuspid annulus; the use of an inflated spacer device to fill the regurgitant orifice; and caval valve implantation. With each of these methods, a primary fear is that of impingement of the right ventricle artery, a situation that while rare, can lead to serious consequences.

This study proposes an initial systematic approach to define patient suitability for each of these devices, and discusses the use of computed tomography (CT) as a tool for planning and proceeding with each of these interventions.

Computed Tomogrpahy Measures and Models

Computed tomography is rapidly becoming the tool of choice to map, analyze, and build a comprehensive 3-D model of the geometry and anatomy of the tricuspid valve, the right ventricle, its spatial relationship

with the right coronary artery, the course of the right coronary artery, and the dimensions of the vena cava. These CT-derived measurements can be useful, and in some cases invaluable, in preparing to implement a specific therapy, or in determining whether a given therapy type should even be considered.

The study included 250 patients that were clinically referred to CT analysis prior to transcatheter aortic valve replacement. A 320-slice, multi-detector, 3D imaging scanner was used to conduct the analysis. In each case, the focus was to establish the relationship between the right coronary artery and the tricuspid valve annulus, and consisted of collecting a series of 2- and 4-chamber long-axis and short-axis views.

The dimensions of the vena cava were also assessed. These, and the other assessments led to the creation of 3D images. 2D Doppler echocardiography was also used as an imaging tool in the study to asses pulmonary artery and right atrial pressures.

The Study Group and Therapy Types

Baseline characteristics for this study included the patient's age, gender, body surface area, heart rhythm, presence or absence of diabetes, atrial fibrillation, or hypertension, and previous echocardiograph characteristics. The study group was evenly divided between male and female having a mean age of between 73 and 87 years. Patient's TR conditions were also considered.

The four therapy types included in the study were : the Mitralign system, involving the used or pledgeted sutures positioned to reduce the TR grade, the Tricinch System, which involved the positioning of a corkscrew anchor to reposition the tricuspid annulus dimension, the Forma Repair System, involving an inflated spaced to fil the tricuspid regurgitant orifice, and the Hereotopic Caval Implant System.

Conclusion

CT imaging has proved to be useful in preparing for each or these four therapy types, as well as indicating whether a proposed intervention can safely proceed. Future uses may include the use of 3-D software to recreate a patient's tricuspid valve apparatus. (IM, MR)

Van Rosendael et at., Computed tomography for Planning Transcatheter Tricuspid Valve Therapy, European Heart Journal, ,Volume 38, pp 665-674: 2017.

Contractility sensor-guided optimization of cardiac resynchronization therapy: results from the RESPOND-CRT trial

It is well known that cardiac resynchronization therapy (CRT) is an effective therapy for patients with medically refractory heart failure (HF), left ventricular (LV) systolic dysfunction (ejection fraction<35%), and a wide QRS complex.

The RESPOND-CRT study was a multicentre, double-blind, randomized controlled clinical trial, which enrolled patients with clinical indications for implantation of a de novo CRT defibrillator (with or without a pre-existing implantable cardioverter-defibrillator or pacemaker), according to current guidelines.

Poorly optimization of the atrioventricular (AV) and interventricular (VV) timings of the CRT device constitute the commonest variable that could adversely affect response. The optimal AV interval is integral to enhancing response to CRT, and a suboptimal AV interval may contribute to a decline in cardiac output, by up to 20%.

Several studies have demonstrated the acute haemodynamic benefits of Echo-guided AV and VV timings optimization. Novel technology using the SonR contractility sensor enables this automatic optimization. Several studies have shown that cardiac contraction generates mechanical vibrations that propagate through the entire heart. The sensor records these as SonR signals that correlate strongly with LV dP/dt max, a measure of cardiac contractility.

Even though several studies have demonstrated the value of Echo-guided optimization in reducing the number of non-responders to CRT, clinicians do not perform this because of the lack of precision, availability of skilled staff, resources, and logistical challenges. This in turn has created a need for a simpler, automated approach to individualize the optimization of AV and VV intervals within patients.

This study demonstrated that contractility sensor-guided automatic optimization of CRT was safe and non-inferior to the AV and VV Echo-guided approach. The primary efficacy endpoint was the rate of clinical responders (comprising a nested composite of patients alive, without adjudicated HF-related events, with improvement in New York Heart Association class improvement of >1 level or quality of life improvement of at least 5 points, at 12 months). The primary efficacy endpoint of non-inferiority was met with a patient responder rate of 75.0% in the sensor arm vs. 70.4% in the Echo arm (P<0.001).

The SonR arm was observed to have reduced HF hospitalization rate. This could potentially have cost implications, as HF hospitalization is a major component of the overall cost related to the management of this cohort of patients. Importantly the sensor-strategy was notably better in patients with a past his-

tory of atrial fibrillation and renal dysfunction. This subgroup of patients can called sicker and with a bad haemodynamic, and therefore benefit from more frequent CRT optimization. The ability of the sensor strategy to frequently optimize and adjust for exercise periods may result in benefit in these patients, especially during the augmented stress of exercise and over the course of remodelling.

In what concerns long-term follow-up, the composite of death or HF hospitalization (pre-specified ancillary analysis) showed no significant difference in freedom from event between SonR and Echo over time

The Adaptive CRT (aCRTTM) study recently examined an algorithm enabling RV-synchronized LV and bi-ventricular pacing, in the setting of intact intrinsic AV conduction. This report demonstrated non-inferiority of the algorithm on the overall population when compared with Echo-guided optimization at 6 months of follow-up. aCRT seems to benefit to patients with normal AV interval at baseline while being potentially suboptimal for patients with prolonged AV. Unlike any of the above optimization strategies, the signal recorded by the SonR sensor reflects global ventricular contractility.

In summary, RESPOND-CRT is the first double-blind randomized controlled clinical trial examining the efficacy and safety of a contractility sensor-guided CRT optimization approach. Clinical response for most subgroups was in favour of the automatic optimization arm using the SonR sensor, especially in patients with a prior history of atrial fibrillation or renal dysfunction. (AP, RM)

Josep Brugada, Peter Paul Delnoy, Johannes Brachmann, Dwight Reynolds, Luigi Padeletti, Georg Noelker, Charan Kantipudi, Jose´ Manuel Rubin Lopez Wolfgang Dichtl, Alberto Borri Brunetto, Luc Verhees, Philippe Ritter, and Jagmeet P. Singh13, for the RESPOND CRT Investigators. European Heart Journal (2017) 38, 739–741.*

CT Angiography for the Detection of Coronary Artery Stenoses in Patients Referred for Cardiac Valve Surgery

Valvular heart diseases are quite common in industrialized regions, and are in most cases solved with surgery. Prior to the intervention, doctors recommend invasive coronary angiography (IPA), in order to detect coronary artery diseases (CAD) that could obstruct their work. But why is it so important to detect CADs? It is all because of the high mortality rates associated to valvular cardiac surgery, and the opinion that those can be reduced by combining these interventions with bypass surgery. Namely, what early CAD detection does is to stratify risk, and to determine the presence of concomitant coronary revascularization.

In recent years, another method used to detect CAD is coronary computed tomography angiography (CTA), but not routinely applied in patients undergoing cardiac valvular surgical treatment.

This article is a meta-analysis of 17 popular IPA-CTA studies, aiming to distinguish the method able to spot more CAD on patients undergoing elective valve surgery. The studies chosen used >16 detector row computed tomography scanning applied on patients with valvular heart disease scheduled for surgery and validated the results against IPA. The studies were performed on approximately 1,153 patients (mostly male, with an average age of 65 and a mean heart rate of 68 beats per minute). In 13 of those studies (4 tackling exclusively 70+ patients), the heart rate was reduced using beta-blockers, while contrast media application varied between 80 and 125 ml, and the radiation dose was somewhere between 2.55 and 26.0 mSv. Studies were selected carefully to avoid biased and inaccurate data, and resulted in satisfying high-quality scores.

For all 17 studies it was concluded that coronary CTAs is as realible and as effective as IPA in ruling out critical coronary arteries stenoses in valve surgery patients, and can thereof replace the widely accepted and standardized ICA method. However, this doesn't make the detecting power of CTAs universal: for instance, CTAs are not that good at depicting problems for AS patients, which is something to remember when treating arteriosclerosis. Some popular guidelines discuss the benefits of using ICA for examining 40+ patients, but the question remains whether those benefits can override aortic vegetation risks.

Coronary CTA is quite accurate when ruling out stenoses for all patients, but its role and unified application is still in need of definitive evidence. From what it has been concluded, CTA results were accurate for 64% of all patients (mostly ones with negative VHD results), but inaccurate for only 3% of them, where relying on CTA would have delivered wrong diagnosis.

Among other things, it is important to know that CTA is a faster, less complicated, and more cost-effective method for CAD examination, which provides incremental information, adjusted to cardiac valve morphology. Surgeons also find it useful to gain insights needed for aortic arch calcification and intrathoracic anatomy in general. (IM, MR)

Opolski et al., CT Angiography for the Detection of Coronary Artery Stenoses in Patients Referred for Cardiac Valve

Surgery JACC: Cardiovascular Imaging,Volume 9, Issue 9, pp. 1059-1070: 2016.

How to RESPOND to the quest to increase the effectiveness of cardiac resynchronization therapy?

Cardiac resynchronization therapy (CRT) is an electrical treatment based on biventricular or left ventricular (LV)-only pacing that was initially applied as a last-resort therapeutic solution for patients with severe heart failure (HF) associated with left bundle branch block.

A series of investigations reported that the proportion of responders to CRT is in the range of 57–67% among patients with moderate to severe HF.

A series of data from clinical studies support the concept that in acute evaluations AV delay optimization improves LV performance and stroke volume by allowing adequate diastolic filling of the left ventricle as well as reduction of diastolic mitral regurgitation. Similarly, acute evaluations with Doppler echocardiography showed that VV delay optimization may reduce or eliminate dyssynchrony and maximize cardiac output, with significant reduction of mitral regurgitation.

Therefore, optimization of suboptimal programming of AV and VV intervals could constitute the most common and correctable variable that may improve response to CRT. Traditionally, this has been done with use of echocardiographic techniques, but this requires exhaustive, iterative sampling that cannot be proposed for daily practice.

The influence of echocardiographic optimization of patients implanted with CRT has been the subject of controlled studies and one meta-analysis including data from 12 studies and 4356 patients. Those showed no significant differences in clinical or echocardiographic outcomes between patients who underwent AV and/or VV delay optimization and patients who underwent empiric device programming.

The RESPOND-CRT is a prospective, randomized, double blinded, multicentre, non-inferiority trial evaluating the effect of weekly, automatic CRT optimization based on a SonR contractility sensor vs. an echo-guided optimization of AV and VV timings. The SonR system uses an accelerometer sealed in the atrial lead to measure mechanical vibrations generated in the heart during isovolumetric contractions which are correlated with LV dP/dtmax. The device processes these signals through a specific algorithm, with the result of automatic optimization of AV and VV intervals, and it was performed weekly.

The primary efficacy endpoint of RESPOND-CRT was the 12- month rate of clinical responders (patient alive, without HF-related events, with improvement in functional class or quality of life). In a population sample of 998 patients, the rate of response was high (75.0% in the SonR group vs. 70.4% within the echo group). The noninferiority of SonR vs. echo-guided optimization was demonstrated, but not its superiority. In the long term, no significant differences were found in the composite of death or HF hospitalizations, while the risk of first HF hospitalization was significantly reduced in the SonR group.

In the approach to these complex evaluations, clinical outcome and clinical response may differ according to the setting where CRT has been applied (moderate to severe HF, mild HF, pacing for bradycardia in a patients with LV dysfunction, pacing following AV juction ablation in permanent atrial fibrillation with LV dysfunction).

The multitude of inter-related factors that may condition and modulate either a positive response to CRT and/or an improvement in outcome after implant of a CRT device with defibrillation capabilities suggest the need for multiparametric analyses performed on large data sets. (AP, RM)

Giuseppe Boriani - European Heart Journal (2017) 38, 739–741.

Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies

This review provides insights from published randomized control trials (RCTs), and offers recommendations for standardizing MI size assessment by CMR for the benefit of future studies.

Introducing primary percutaneous coronary intervention (PPCI) to treat acute ST-segment elevation myocardial infarctions (STEMI), has resulted in a substantial improvement in patient mortality. Data needed to in investigate therapies used for STEMI patients with the intent of reducing myocardial infarct (MI) size has been taken from randomized control trials (RCTs).

MI Size Quantification

The current gold standard for MI size quantification is CMR-LGE scanning (cardiac magnetic resonance by late gadolinium enhancement).

A recent analysis of the results of 10 RCTs disclosed that with every 5% incremental increase in MI size, the risk for hospitalization, heart failure, and all-cause mortality within a year, increased by 20%.CMR-LGE scanning is increasingly being used to quantify MI size, although guidance for CMR use is presently limited.

Methods

Researching this subject involved a systematic search of MEDLINE and Embase databases, and reviews of PubMed, Web of Science, and other publications. Information for inclusion in this study was limited to: trials that were conducted to investigate cardioprotective strategies for reducing MI size, patients that experienced cardiac symptoms with 12 hours of their onset, MI size as measured by CMR, and full-text RCT reports in English.

The study encompassed a total of 62 trials and 399 reports, and involved more than 10.000 patients.

CMR MI Size Measurements

MI size is dynamic, and accurate quantification is highly dependent on when CMR scanning is conducted during a patient's STEMI recovery and treatment. MI size tends to be overestimated when CMR scanning is performed too early; due to a likely presence of swelling or edema. Acute MI size tends to decrease significantly during post-STEMI days 1 through 7, but is relatively stable during days 3 and 4.

CMR scans of long-term, chronic MI size, tend to be taken at around the two-month period. These scans are conducted to provide information on post-STEMI lower ventricle remodeling, with follow-up scans conducted at 6 months in most trials.

In most trials, CMR/LGE imaging time was 10 minutes. Lesser imaging times tended to overestimate MI sizes. A clearer prognosis for full recovery could usually be obtained from a 25-minute session, but this was overly time consuming for most patients; which is why the 10-minute scan period is considered optimal.

Recommendations for Future RTCs

RCT patients should include those most likely to benefit from cardioprotective therapy for reducing

MI size. Measuring acute MI size offers a better choice for conducting a prognosis than chronic MI size.

The ideal timeframe for performing an acute MI size CMR is during days 3 through 5; with a follow-up scan in 6 months. Manual quantification of MI size by experience operators is preferable.

When semi-automated techniques are used, the results should be validated. MI size should be presented as a lower ventricle percentage when possible. (IM, MR)

Heerajnarain et al., Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies Journal of the American College of Cardiology Volume 10, Nomber 3, 2017

Percutaneous tricuspid valve therapies: the new frontier

Approximately 1.6 million patients in the U.S. moderate to severe tricuspid regurgitation (TR). Only a small fraction undergoes tricuspid surgery (about 8000 every year). Many forego surgery because of the high risks involved. Percutaneous procedures are however becoming an attractive alternative approach for these high-risk patients. Percutaneous approaches used in aortic and mitral valve treatment are already widespread, of which several are being explored for tricuspid valve treatment.

Surgical Treatment and Therapeutic Concepts

Roughly half of those with mitral valve regurgitation experience TR. These patients are often at risk of developing significant to severe TR following mitral valve replacements; or, the development of functional TR (FTR) following left-sided valve surgery – leading to a negative prognostic impact on survival in both cases.

Standard surgical treatment for functional TR involves tricuspid annuloplasty to resolve problems associated with the angular dimensions. Unfortunately, successful mitral regurgitation solutions cannot be directly applied tricuspid valve (TV) repair because of anatomical differences between the two. Several promising transcatheter tricuspid annuloplasty concepts approaches are under study or in work however.

The Mitralign system has been used to treat FTR patients. A steerable catheter is advanced in the right ventricle, across the tricuspid valve (TV), and through the annulus. A second catheter is used to deliver suture pledgets to help reduce the annual area. The number of these treatments has been small, but basically successful.

The TriCinch is another catheter-based device designed to perform tricuspid annular clinching. In this approach, a corkscrew is implanted in the proximity of the mid part of the annulus. Once secured, a stent is coupled to the implant, tension is applied, and the stent is then deployed in the inferior vena cava to maintain that tension. Recent implementations of the TriCinch approach have had favorable results.

A third approach, TRAIPTA, involves delivering a circumferential implant along the atrioventricular groove, after which tension is applied to the implant to modify the geometry of the TV annulus. This procedure is relatively safe, although it cannot be used in patients with previous heart surgery.

The Millipede system involves the use of a repositionable and retrievable ring that can be implanted

surgically or by catheter. Its repositionability however, brings with it a high risk of complete atrioventricular blockage.

Caval Valve Implantation consists of implanting the various prostheses via a low-pressure venous system. The procedure has met with success, but there is no consensus on which of the devices implanted would be an ideal choice.

Other approaches include the FORMA device in which a TV spacer device is delivered through venous access and anchored to the right ventricle apex; a Mitraclip device, which is an appealing approach but has yet to be attempted due to various challenges; and Transcatheter TV replacements, which have yet to be attempted on humans.

Transcatheter-based techniques have rapidly evolved in recent years; many of which appear quite feasible, although few data are available. Most of these approaches have progressed to less invasive procedures, where imaging is expected to play an increasingly important role in live guidance. (IM, MR)

Taramasso et al., Percutaneous tricuspid valve therapies: the new frontier European Heart Journal, Volume 38, pp. 639-647: 2017.

Reducing salt intake

The results of a recently published survey of blood pressure (BP) trends around the world have shown that the number of adults with an elevated BP has nearly doubled between 1975 and 2015 and now affecting 1.13 billion persons worldwide. In fact, mean systolic and diastolic BP have decreased in high income Western and Asian Pacific countries and have rather increased in low- and middle-income countries, suggesting a progressive shift of the problem towards poorer regions of the world.

One of the objectives of the Open Working Group on Sustainable Development Goals endorsed by the UN General Assembly is to reduce the mortality due to non-communicable diseases, including hypertension, by 33% by 2030.

These latter include a limited alcohol consumption, an increase in physical activity, tobacco cessation, weight loss, and a limitation of salt intake. All these interventions have been reported to lower BP and to improve cardiovascular outcomes. A reduction of salt intake is considered today as the best buy intervention for non-communicable diseases prevention and control.

A reduction of salt intake to 5–6 g of sodium chloride (NaCl) per day is recommended by the World Health Organization as well as by almost all international guidelines for hypertension management. The majority of persons around the World are consuming between 8 and 10 g NaCl per day and sometimes even much more. Thus, there is not enough evidence demonstrating that lowering sodium intake from 10–6 g NaCl provides clinical benefits unless people are hypertensive.

In fact, as long as renal function is intact, there should not be any correlation between sodium intake and BP because of the pressure/natriuresis phenomenon. However, as renal function declines for any reason including aging, obesity, metabolic syndrome, or a renal disease, BP remains high when people are on a high salt intake because it is needed to increase salt excretion and to maintain sodium balance.

Recent data have clearly shown that potassium intake is a modulator of the association between salt intake and BP. Moreover, that a higher potassium intake is associated with a lower incidence of cardiovascular and renal events when patients are on a high sodium intake. This would suggest to increase potassium intake with the consumption of fruits and vegetables.

Today, potassium intake is below the recommended target of 3 g/day in almost all countries and the target urinary potassium excretion of >100 mmol/ dL is rarely found in epidemiologic surveys. An equilibrated sodium and potassium intake should lead to a ratio of urinary Na/K excretion of 1 whereas today, it is around 2.5. The drawback is that in many countries, fresh fruits and vegetables are expensive whereas unhealthy foods with high sodium, sugar and fat contents are relatively cheap and accessible to the populations.

In summary, prevention of non-communicable diseases such as hypertension implies the implementation of numerous public health strategies. Intervention on sodium and potassium intakes is only one facet of the problem but it is certainly the most cost-effective now, also with improving childhood nutrition or fighting against adiposity, smoking, physical inactivity, and air pollution. (AP, RM)

Giuseppe M, Suzanne O, Paul KW, Martin M, Anna D, Friedrich CL, Khalid A, Fernando L, Albertino D, Dorairaj P, Giuseppe LT, Michael W, Martin O, Sidney CS, Jagat N. European Heart Journal (2017) 38, 697–704.

Refining Statin Prescribing in Lower-Risk Individuals

The Veterans Affairs/Department of Defense, the American College of Cardiology/American Heart Association and the Joint British Societies released a number

of studies during 2013/2014 that confirm the benefits of statin treatment. Their findings were complemented by additional evidence on statins' positive effects, focusing on patients whose atherosclerotic cardiovascular disease risk is lower than 7, 5%. This article discusses the best statin strategies to apply on low-risk patients.

Clinicians are no longer struggling to approve statin treatments, but to select optimal candidates for lipid-decreasing drug therapy. As the American Heart Association suggests, statin treatment should also be applied on patients whose atherosclerotic cardiovascular diseases (ASCVD) score levels are lower than 7.5%. A Copenhagen General Population Study confirmed this opinion, and demonstrated that more than 20% of all ASCVD events happen to people who were never considered for statin therapy. Prior to these studies, there was hardly any accurate risk estimation method, and the only approach targeted as 'safe to apply on all patients' was Pool Cohort Estimation combined with clinical-patient discussions.

The first study considered for this article is an ACC/AHA report promoting clinician-patient discussions as the best method to reveal important factors, including evidence of genetically-induced hyperlipidemias, low-density lipoprotein cholesterol (160 mg/dl), and family history of ASCVD conditions.

The second analysis was conducted by Yeboah, looking to improve risk reclassification considering coronary artery calcium (CAC) scores and family history of ASCVD as independent predictors. Both studies confirmed that CAC scores improve low-risk reclassification.

Pletcher et al. used the established CAC model to make assumptions concerning statin's cost-effectiveness, and concluded that 'statin-for-all' was a more cost-effective solution than measuring CAC for each patient. For 10 years, he observed statin treatment effects on 10,000 50 years old women with high cholesterol, and concluded that statins caused more than 60 cases of myophaty, but prevented 32 myocardial infarctions, and prolonged total life expectancy by 1,108 years. Measuring CAC for 2,500 of those women required an investment of approximately $2.25 million, and led to 9 cases of radiation-caused cancer compared to the 45% of benefits it can provide.

Most studies from 2013 provide evidence that supports prescribing statin therapy to low-risk asymptomatic patients. Still, this is not a universally applicable solution because of the inherent limitations of risk estimation that has to be performed in advance. Most of the modern studies recommend it for patients with 4-5% risk levels, while there are also such that target its effectiveness depending on the average age or the gender of patients.

What is already a fact is that CAC scores are quite successful in disseminating low risk patients that should be excluded from this therapy and can help identify those at high risk and should be used in assessing patients requiring more precise evidence to reclassify assessment of potential net benefit (or lack thereof) from statin use. (IM, MR)

Pender et al., Refining Statin Prescribing in Lower-Risk Individuals Journal of the American College of Cardiology, Volume 68, Issue 15, pp. 1690-1697: 2016.

The year in cardiology 2016: valvular heart disease

There is a linear relation between ageing of the population and the prevalence of valvular heart disease (VHD), that is estimated to double before 2050.

Aortic stenosis

Transcatheter aortic valve implantation is currently considered the treatment of choice for inoperable patients and the preferred alternative for high-risk patients. A total of 750 patients underwent, TAVI with a self expandable device (CoreValve) or surgical AVR. After 3 years, TAVI was associated with significantly reduced all-cause mortality or stroke (37.3% vs 46.7%: P=0.006)and better aortic valve haemodynamics compared with surgery.

In the PARTNER 2 randomized trial, 1011 intermediate-risk patients were assigned to TAVI and 1021 to surgical AVR. At 2 years no significant differences were observed between the two groups in the primary end point of all cause mortality or stroke.

In another study, the latest generation SAPIEN 3 device was evaluated in 1077 intermediate-risk patients and the outcomes in this population were compared with those observed in intermediate-risk patients treated with surgical AVR in the PARTNER 2 trial. Comparison with the surgical group revealed that for the primary composite endpoint of mortality, strokes, re-interventions and moderate or severe aortic regurgitation at 1 year, TAVI with SAPIEN 3 was superior to surgical AVR. These findings support the extension of the clinical indications of TAVI to elderly patients at intermediate risk with severe AS.

A recent meta-analysis of all available randomized trials comparing the safety and efficacy of TAVI vs surgical AVR reveals that TAVI was associated with a significant survival benefit throughout 2 years of follow-up.

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Aortic regurgitation

Aortic regurgitation (AR) can result from degeneration of a previously implanted bioprosthesis. This situation in high-risk patients can be treated with transcatheter aortic valve-in-valve implantation. An 8-year single-centre experience with this procedure has been recently reported in a large number of patients with failed aortic bioprosthesis. Percutaneous closure with plugs improves patient prognosis, is potentially associated with less mortality and morbidity than reoperation, and may be considered in selected high-risk patients.

Mitral regurgitation

A large series of patients submitted to primary mitral repair for isolated degenerative mitral regurgitation (MR) over 1 decade was analysed and the effect of recurrent MR was evaluated. The 15-year incidence of recurrent moderate or greater MR was 13.3%, and the incidence of mitral reoperation was 6.9%.

The 2-year outcomes of a randomized trial comparing mitral valve repair with mitral valve replacement with preservation of the whole subvalvular apparatus, in patients with severe ischaemic MR showed that no significant difference in LV reverse remodelling or survival was observed. The rate of recurrence of moderate or severe MR at 2 years was higher in the repair group than in the replacement group (58.8% vs 3.8%, P<0.001). As a consequence, patients in the repair group had more serious adverse events related to heart failure (P=0.05) and more cardiovascular readmissions (P=0.01).

The 2-year outcomes of another randomized trial comparing coronary artery by-pass grafting (CABG) alone with CABG plus mitral valve repair in patients with moderate ischemic MR showed that the mean left ventricular end-systolic volume index was not significantly different between the two groups. Mortality was also similar (10.6% vs 10.0%, P = 0.78).

The German transcatheter mitral valve interventions (TRAMI) registry prospectively enrolled 828 patients submitted to MitraClip therapy (median age 76 years, and median logistic EuroSCORE I: 20.0%). One year mortality was 20.3%. Quality of life improved remarkably after MitraClip implantation.

Mitral stenosis

Pre-operative pulmonary hypertension has been shown to affect the long-term outcome in a large series of patients operated on for mitral stenosis (MS). Ten-year survival after mitral valve surgery was significantly lower in the moderate-severe pulmonary hypertension group, compared with the normal pulmonary artery pressure-mild pulmonary hypertension group (58% vs 83%; P=0.001). According to this finding, patients with MS and mild pulmonary hypertension should be considered for mitral valve surgery.

A multicentre retrospective review of clinical outcomes of 64 patients with MS and severe mitral annular calcification submitted to transcatheter mitral valve replacement using balloon-expandable TAVI valves was performed. Access was transatrial in 15.6%, transapical in 43.8% and transseptal in 40.6%. In this preliminary experience, the procedure was associated with significant adverse events, and 30-day all-cause mortality was 29.7%. Only very symptomatic patients with limited therapeutic options should be considered for this modality of treatment at this stage.

Tricuspid regurgitation

A recent study showed that in patients with moderate TR or tricuspid annular dilatation undergoing mitral valve repair, concomitant tricuspid annuloplasty was safe, effective and associated with improved long-term right-sided remodelling. No difference in patient survival, late functional status, progression of TR or tricuspid valve reoperations has been found in a recent retrospective study comparing patients treated with suture annuloplasty and those submitted to ring annuloplasty.

When isolated severe TR occurs in a context of right heart failure or develops late following left-sided valve surgery, the surgical risk is generally high. The TriCinch device allows transfemoral fixation of a corkscrew in the annulus of the tricuspid valve in proximity to the anteroposterior commissure.

Tricuspid regurgitation can also be treated with edge-to-edge repair using the MitraClip system. Another device used to reduce TR is the FORMA System, which is a valve spacer/occluder positioned within the tricuspid orifice, creating a platform for native leaflet coaptation to reduce the regurgitant jet.

In total there was a lot of new evidence in the domain of VHD during the past year and it is expected that it will be incorporated into the upcoming ESC/EACTS on VHD to be published next year. (AP, RM)

Ottavio Alfieri and Alec Vahanian, European Heart Journal (2017) 38, 739–741.

The year in cardiology 2016: heart failure

The most important novel recommendations of the 2016 ESC guidelines on diagnosis and treatment of HF can be summarized in the following points.

(1) A novel algorithm for the diagnosis of HF in the non-acute setting has been proposed : the measure of natriuretic peptides (NPs), is recommended as a first step in all patients with suspected HF. The role of NP levels is mainly for excluding HF, due to the their very high negative predictive value.

(2) Transthoracic echocardiography in patients with suspected or established HF to stratify the patients with chronic HF in: reduced (heart failure reduced ejection fraction (HFrEF) LVEF <40%), mid-range (HFmrEF, LVEF: 40-49%) preserved ejection fraction (HFpEF, LVEF >/=50%).

(3) A revised algorhytm for the treatment of patients with chronic HF has been proposed. All patients with symptomatic HFrEF should receive a combination of an Angiotensin-converting enzyme (ACE)-I [or Angiotensin receptor blocker (ARB) if ACE-I not tolerated], a b-blocker and a mineralocorticoid antagonist (MRA). If a patient still remains symptomatic sacubitril/valsartan is recommended to replace ACE-I and also the use of diuretics in patients with signs and/or symptoms of congestion.

(4) In the management of a patient with HF, comorbidities should be taken into account. For diabetes and hyperkalaemia new treatments are available. Metformin is safe to use in patients with HFrEF, and it should be the treatment of choice in patients with diabetes and HF, even if contraindicated in patients with severe renal or hepatic impairment. Recently, empagliflozin, an inhibitor of sodium-glucose cotransporter 2, has been shown to be able to reduce the rate of hospitalizations for HF in patients with diabetes at high-cardiovascular risk, including patients with HF.

With respect to hyperkalaemia (>6.0 mmol/L), two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for use.

New findings on the treatment with RAS inhibitors and NEP inhibitors

The ATMOSPHERE trial showed that the addition of aliskiren to enalapril did not result in a reduction of the risk of death from cardiovascular causes or hospitalization due to HF, as compared with enalapril alone, but did cause more hypotension, renal dysfunction, and hyperkalaemia.

Another papers have been published in 2016 reinforcing the favourable evidences on the use of sacubitril/valsartan as a replacement therapy of enalapril, defining better the population of patients who might receive a benefit from this new ARNI compound. Sacubitril/valsartan was effective at reducing cardiovascular death (either due to sudden death or worsening HF and HF hospitalization throughout the LVEF spectrum, considering, that only patients with HFrEF have been included in the trial.

In the DANISH trial, a randomized controlled trial, 556 patients with symptomatic systolic HF (LVEF </=35%) not caused by coronary artery disease were assigned to receive an implantable cardioverter-defibrillator (ICD), and 560 patients were assigned to receive usual clinical care (control group). The primary outcome of the trial was death from any cause. The conclusion was that ICD implantation for primary prevention in patients with HFrEF, not caused by CAD, did not reduce the rate of long-term all-cause mortality.

Prevention of HF:

Systolic blood pressure

In the SPRINT trial, 9361 subjects with a SBP of 130mm Hg or higher and an increased cardiovascular risk, but without diabetes, had been randomly assigned to a SBP target of less than 120 mmHg (intensive treatment) or a target of less than 140 mmHg (standard treatment). The trial was stopped early after a median follow-up of 3.26 years due to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group This beneficial effect was obtained in a context of an increase of serious adverse events such hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls.

Diabetes mellitus

After some disappointing results obtained in trial testing inhibitors of dipeptidyl peptidase 4 (DPP-4), two recent trials showed that the treatment of diabetic patients with the glucagon-like peptide 1 (GLP-1) analogues, liraglutide and semaglutide, reduced the rate of occurrence of major cardiovascular events.

Influenza vaccination: an old story never appropriately implemented

Patients with HF are at increased risk of experiencing cardiovascular and respiratory-related hospitalizations compared with the general public, and for those with influenza infection these risks are substantially elevated. The *UK National Institute for Health and Care Excellence* (NICE) and the *American Heart Association* (AHA) recommend annual influenza vaccination, as well as the recent ESC Guidelines.

TRUE-AHF—challenging the early-intervention hypothesis in acute heart failure

TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure) was designed to evaluate the effect of a 48-h infusion of ularitide on the short-term clinical course of patients and the long-term risk of cardiovascular death. The study drug ularitide, a chemically synthesized analogue of urodilatin, leads to systemic and renal vasodilation, diuresis and natriuresis, inhibition of the renin-angiotensin system. As compared with placebo, ularitide was accompanied by significant decreases of signs of intravascular decongestion. The 1069 patients receiving placebo experienced more episodes of persistent or worsening HF in the first 48 h than did the 1088 patients receiving ularitide. These results question the concept that early (and short term) intervention with a vasodilator could reduce wall stress and myocardial injury during the critical initial period of acute HF and therefore that an early treatment is able to decrease the long-term risk of cardiovascular death. (AP, RM)

Aldo Pietro Maggioni and Frank Ruschitzka, European Heart Journal (2017) 38, 705–71.*

Tricuspid regurgitation diagnosis and treatment

Primary tricuspid regurgitation (TR) is caused by congenital or acquired abnormalities of the tricuspid valve. Secondary TR, which is moderate to severe, results from leaflet abnormalities or annular dilation. TR is not an uncommon condition, as it occurs in 65% to 80% of the population. 10% or less of all TR is primary, with causes ranging from radiation therapy and drugs, to the presence of pacemaker and defibrillator leads. Most TR is secondary in nature, although not all cases of secondary TR are severe.

Traditional thinking is that TR is best managed medically; with the focus being on the underlying cause. Secondary or chronic TR can however represent a real danger should it cause a right ventricular (RV) volume overload resulting in an irreversible RV myocardial damage. This has led to a trend favoring the use of surgical techniques to resolve serious TR issues.

Evaluating TR Severity and Treatment Options

3D echocardiography is the primary tool used in evaluating TR severity. Echocardiology can allow visualization of the three tricuspid valve (TV) leaflets simultaneously, along with the amount of annular dilation that may be present. The TV orifice is the largest of the four heart valves. Its 30-35 mm diameter annulus changes shape throughout the cardiac cycle. Cardiac Magnetic Resonance Imaging is a preferred alternate source for TV evaluations.

Conservative treatment options are limited for patients experiencing severe TR, and showing signs of right heart failure. Unfortunately, mortality is generally poor following TV surgery; although it is improving. Early mortality decreases when patients with severe TR undergo surgery before the symptoms themselves are allowed to become severe. Performing corrective TR surgery at the same time a patient is undergoing left-sided heart surgery has become standard practice. Moderate TR surgical solutions are safer however. These surgeries are often performed in conjunction with mitral valve repair, and often result in a reduction of heart failure symptoms.

Repair, Replace, and Valve Therapy

Options to be considered for those with primary TR are whether to repair or replace the TV, although there is no perfect prosthetic replacement valve currently available. In secondary or functional TR, the trend currently favors surgical repair, although persistent severe TR is more likely to be an outcome than it is in instances of replacement. Annuloplasty is another approach, in which annular rings are implanted to correct TR.

Replacement is indicated over annuloplasty in cases of primary TR, or in cases of secondary TR where life expectancy is an issue. Fewer options for percutaneous therapy exist, although there has been a reported success involving transcatheter tricuspid repair. This, however, is a single case report.

Summary

Primary TR is caused by pathological abnormalities of the TV apparatus. Secondary TR is far more common and if often associated with heart disease. Patients undergoing surgery for heart disease are sometimes treated for moderate or severe TR at the same time. Advanced therapies for TR are still in the development stages. (IM, MR)

Arsalan et al., Tricuspid regurgitation diagnosis and treatment European Heart Journal, Volume 38, pp 634-638: 2017.

IM, Dr. Irina Macovei; AP, Dr. Alina Popa;
MR, Dr. Mihaela Rugină