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FROM METABOLIC DISORDERS TO CARDIOVASCULAR DYSFUNCTION

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Le ultime 4 decadi hanno testimoniato un'esplosione delle nostre conoscenze sulle funzioni e le disfunzioni dell'endotelio vascolare, il contenitore naturale del sangue, e sulle sue implicazioni per la salute e la malattia. Nella sua classica monografia, pubblicata nel 1954 e intitolata: "*Endothelium: Its Development, Morphology, Function, and Pathology*", Rudolf Altschul, Professore di Istologia all'Università di Saskatchewan, dedicò 124 pagine a tutti gli aspetti dell'argomento, e solo 20 pagine alle funzioni allora conosciute dell'endotelio. Nella prefazione di quel libro, commentò che "il numero maggiore di morte naturale per una singola causa in Nord America e probabilmente in molte altre parti del mondo è attribuibile alle malattie cardiovascolari", purtroppo ancora oggi vero dopo oltre mezzo secolo, e dunque con la sfida insita nella necessità di maggiori conoscenze. Egli aggiunse "...Lavorando sul problema dell'aterosclerosi, ho realizzato non solo quanto poco conosco sull'endotelio, ma anche quanto in più dovrei conoscere per la comprensione adeguata di questo processo".

Un avanzamento maggiore e relativamente più recente è stato l'apprezzamento che l'endotelio vascolare è un'interfaccia dinamicamente mutevole, le cui proprietà funzionali fondamentali – la permeabilità selettiva, la non-trombogenicità, l'inerzia naturale verso l'adesione leucocitaria, le funzioni autocrine, paracrine ed endocrine, come pure la replicazione cellulare e la morte cellulare – sono attivamente regolate attraverso l'azione sull'endotelio di vari mediatori endogeni (citochine, chemochine, fattori di crescita e di sopravvivenza). Questo modello concettuale dell'"attivazione endoteliale" comprende un ampio ambito di risposte funzionali che preparano la scena alla definizione delle cosiddette "disfunzioni endoteliali". E' interessante che il termine "disfunzione endoteliale" spesso inteso come sinonimo dell'alterata produzione di nitrossido, venne introdotto, prima della scoperta del nitrossido stesso, nel contesto delle alterazioni di multiple funzioni endoteliali – in particolare la stimolazione dell'adesione leucocitaria da parte di citochine proinfiammatorie, ed è oggi appunto inquadrabile nella teoria

dell'aterosclerosi come malattia "infiammatoria", in cui stimoli endotelio-tropi, tra cui le citochine interleuchina (IL)-1 e *tumor necrosis factor* (TNF), giocano un ruolo primario, a loro volta in grado di generare vie specifiche di amplificazione della risposta endoteliale.

Corollario importante di queste conoscenze è stata la dimostrazione che marcatori sistemici d'infiammazione, quali la proteina C-reattiva (C-reactive protein, CRP), predicono lo sviluppo di aterosclerosi e di eventi vascolari ad essa connessi. Conseguenza importante di queste conoscenze è stata la verifica che strategie d'interferenza con l'infiammazione vascolare siano in grado di ridurre eventi vascolari.

Tale prova del concetto si è avuta recentemente attraverso lo studio CANTOS, in cui un anticorpo monoclonale contro l'interleuchina 1-beta, canakinumab, si è dimostrata capace di ridurre eventi cardiovascolari in prevenzione secondaria in soggetti già trattati al meglio delle nostre conoscenze attuali, con buon controllo della colesterolemia, del sistema renina-angiotensina-aldosterone e del tono beta-adrenergico. Oggi dunque attivazione endoteliale, disfunzioni endoteliali, infiammazione vascolare, sono concetti embricati e fondamentali nelle nostre conoscenze sulla patogenesi della malattia vascolare, e pronti per la traslazione clinica, chiudendo il cerchio che dalla conoscenza di base sulle funzioni dell'endotelio nell'aterosclerosi porta a una riduzione degli eventi vascolari.

Fisiopatologia delle calcificazioni vascolari

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Nonostante l'apparente lontananza tra l'osteoporosi e le malattie cardiovascolari, in realtà queste due patologie sono strettamente correlate nella pratica clinica e questo ha portato ad ipotizzare che potesse esserci un meccanismo patogenetico comune. Da molti anni infatti è noto che i pazienti affetti da osteoporosi frequentemente vanno incontro a patologie vascolari che includono l'aterosclerosi e la calcificazione delle arterie. Alla base della stretta correlazione tra le due patologie sicuramente sono da considerare dei fattori eziologici che agiscono sia sul tessuto osseo che su quello vascolare e che sono rappresentati da età, infiammazione cronica, fumo di sigaretta, diabete mellito, deficienza estrogenica, ipovitaminosi C, D, K, presenza di lipidi ossidati e di radicali liberi e insufficienza renale. Data la stretta correlazione tra le due patologie un concetto interessante potrebbe essere che esiste un comune denominatore che agisce in parallelo sulle cellule sia ossee che vascolari.

E' ormai ampiamente noto che il paratormone (PTH) rappresenta l'ormone maggiormente implicato nell'omeostasi minerale e nel metabolismo osseo: il PTH infatti agisce mantenendo livelli adeguati di calcio e fosforo nel sangue ed ha una marcata influenza sul metabolismo minerale osseo. Oltre a questi ben noti effetti, attualmente sta crescendo l'interesse per altri meccanismi di azione, dato il ritrovamento del suo recettore in numerosi tessuti. In particolare l'interesse dei ricercatori si è rivolto al ruolo che ha nel sistema vascolare. I primi studi hanno indicato la presenza di R per il PTH a livello dei vasi sanguigni. Successivamente studi clinici hanno quindi evidenziato una correlazione tra iperparatiroidismo e malattie cardiovascolari. Non è ancora chiaro esattamente quale sia il preciso meccanismo di azione che porta il PTH ad indurre un danno nella parete arteriosa. Uno studio in vitro ha evidenziato come valori elevati di PTH conducano ad un

aumento della produzione e della riorganizzazione del collagene da parte delle cellule muscolari lisce vascolari. Inoltre studiando la cascata di eventi che si succedono al legame del PTH con il suo recettore è stato visto che, con meccanismo AMPc dipendente indotto dal legame PTH-R, si ha l'aumento dell'espressione di proteine chemiotattiche per i monociti, per cui si ha una amplificazione della migrazione monocitaria all'interno dell'endotelio vascolare e conseguentemente un aumento delle foam cells nella parete vasale.

Anche il sistema Osteoprotegerina-RANK-RANKL sembra essere coinvolto nel meccanismo di calcificazione. L'osteoprotegerina (OPG) è una glicoproteina di 401 aminoacidi che fa parte della superfamiglia dei recettori per Fattori di crescita tumorali (TNFR). Viene prodotta dal sistema cardiovascolare (cuore, arterie, vene), dai polmoni, dai reni, dall'intestino, dall'osso, da cellule emopoietiche e autoimmunitarie. L'espressione e la produzione di OPG è modulata da varie citochine (IL1, IL6, IL11, TNF-alfa), peptidi, ormoni e farmaci. Questa circola nel siero e lega come un recettore RANKL. RANKL è una citochina, prodotta da osteoblasti e cellule T attivate, che promuove la formazione, la fusione, la differenziazione, l'attivazione e la sopravvivenza degli osteoclasti, aumentando così il riassorbimento osseo e la perdita ossea. RANKL stimola il suo specifico recettore RANK, che è espresso da un numero ristretto di cellule, che includono progenitori e forme mature di osteoclasti, cellule T attivate e cellule dendritiche. Il legame di RANKL con RANK attiva una cascata di segnale intracellulare che coinvolge c-Jun, NF-kB e la via serina/treonina chinasi Akt/PKB. Gli effetti biologici di OPG sono opposti a quelli mediati da RANKL in quanto, legandosi a RANKL, agisce come un inibitore solubile e previene il legame di RANKL con il suo recettore RANK. A differenza quindi di RANKL che stimola il riassorbimento osseo, OPG previene il riassorbimento stesso e la perdita ossea. Per quanto riguarda il sistema vascolare, OPG è prodotta in vitro da cellule muscolari lisce e da cellule endoteliali e agisce come un fattore di sopravvivenza per le cellule endoteliali stesse. Le prime evidenze di un coinvolgimento del sistema della OPG nelle calcificazioni vascolari deriva da uno studio effettuato su topi OPG knock-out. Questi infatti vanno incontro ad una perdita ossea severa con fratture osteoporotiche multiple dall'età di un mese. Nei topi invece RANKL knock-out hanno un bassissimo numero di osteoclasti e sviluppano osteopetrosi. Inoltre sempre nei topi OPG knock-out si assiste ad un fenomeno di aterosclerosi precoce ed estesa sia a carico delle arterie renali

che dell'aorta a rapida evoluzione. L'ipotesi che il sistema RANKL/OPG possa rappresentare un legame tra osteoporosi e aterosclerosi è sottolineato in numerosi studi che hanno evidenziato una elevata prevalenza di malattie cardiovascolari in donne in postmenopausa e nella popolazione giovane con osteoporosi. Questo apparente paradosso dell'aumento di OPG in pazienti con osteoporosi e malattie vascolari è stato interpretato come un meccanismo controregolatorio che cerca di contrastare la progressione della malattia. Quindi per il ruolo non solo sul tessuto osseo ma anche su quello vascolare, OPG può rappresentare un meccanismo di legame tra le due patologie e i suoi livelli possono essere indicativi della gravità delle stesse.

Un'altro mediatore coinvolto nel processo di calcificazione è rappresentato dalla MGP (Matrix GLA protein). La MGP è una proteina di 84 aa che fa parte di un gruppo di proteine che generalmente sono identificate come proteine vitamina K dipendenti o proteine GLA, che includono fattori della coagulazione (VII-IX), fattori anticoagulanti (proteina C e S) e l'osteocalcina, un costituente della matrice ossea che inibisce la formazione ossea stessa. Tutte queste proteine hanno in comune il fatto di possedere un numero di residui di un aminoacido inusuale, l'acido gamma-carbossi-glutammico (GLA), che viene sintetizzato con un meccanismo di modificazione post-trascrizionale vitamina K dipendente. L'attività biologica di MGP è strettamente dipendente dalla presenza dei suoi 5 residui di GLA. Deficit di vit K o uso di dicumarolici, impedendo la decarbossilazione di MGP, ne pregiudicano la funzione. MGP è stata originariamente isolata nell'osso ma oggi sappiamo che è anche espressa in molti altri tessuti che includono i reni, i polmoni, il cuore, la cartilagine e le cellule muscolari lisce della parete dei vasi. La funzione dei residui di GLA è di legare ioni calcio e cristalli di calcio, rimuovendo così l'eccesso di calcio dalla circolazione ed evitando lo sviluppo e la crescita di cristalli di calcio. Il ruolo in vivo di MGP sul metabolismo osseo e cartilagineo è sottolineato dal fenotipo dei topi MGP knock-out. Questi nascono normali, acquisiscono una bassa statura e in poche settimane sviluppano calcificazioni delle arterie con rottura e morte per emorragia. Negli uomini una mutazione del gene per MGP che porta alla produzione di una proteina anomala induce una malattia rara, "Sindrome di Keutel", caratterizzata da abnormi calcificazioni cartilagine. Negli individui affetti da questa sindrome è stata inoltre riscontrata calcificazione vascolare massiva, ad indicare un ruolo di MGP sul sistema vascolare anche nell'uomo. In uno studio

condotto su una popolazione giapponese è stato inoltre rilevato che i livelli di MGP sono più bassi nei pazienti con calcificazioni delle arterie coronariche rispetto ai soggetti normali e che all'aumento della gravità delle calcificazioni corrisponde un decremento dei livelli serici di MGP.

Un ulteriore passo avanti nello studio dell'associazione tra arteriosclerosi, calcificazioni vascolari e ridotta densità minerale ossea è derivato dagli studi sulla proteina Klotho. Klotho è un peptide circolante anti-invecchiamento. Il meccanismo d'azione di Klotho consiste nell'interferenza con la trasduzione dei segnali intracellulari innescati dal legame dell'insulina e del fattore di crescita insulino-simile con i rispettivi recettori di membrana. La delezione del gene che codifica per Klotho determina nell'animale da esperimento invecchiamento precoce, aterosclerosi, calcificazioni vascolari ed osteoporosi. Klotho è essenziale per la normale angiogenesi, esercita effetti anti-apoptotici nei confronti delle cellule endoteliali e protegge dallo stress ossidativo; per questo, il topo knockout per Klotho mostra una ridotta densità capillare e disfunzione endoteliale.

Renin-Angiotensin System a Crossroad from Hypertension to Vascular Complication

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The renin-angiotensin system (RAS) is one of the most important component of cardiovascular homeostasys. A dysfunction RAS plays a major role in determining functional and structural alterations at the level of macrovascular and microvascular circulation. From a mechanistic point of view, angiotensin II seems to be the most important actor in determining the cascade of events leading to endothelial dysfunction, sstructural changes and increased stiffness.

However, when in humans we analize the effect of drugs acting on the RAS by using ACE-inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) results are not similar and a clear difference of these two drug classes exists.

For instance the only available evidence that a RAS blocker can prevent atherosclerosis is with ACE-inhibitors while ARBs appear to be ineffective. In addition while it is well documented that ACE-Is can prevent myocardial infacrtion, again ARBs have no evidence of efficacy on this crucial clinical end-point (fig 1). Pharmacology can easily explain the superiority of ACE inhibitors as compared with ARBs, since the modes of action of these two drug classes are quite different. The inhibition of bradykinin degradation exerted by ACE inhibitors is an important aspect of their mechanism of action. In hypertensive patients, bradykinin can act on endothelium by a nitric oxide (NO)-independent pathway, possibly by the activation of endothelium-derived hyperpolarizing factors (EDHFs). Through this compensatory mechanism, bradykinin can evoke endothelium-dependent relaxation or tissue plasminogen activator (tPA) release, even in the presence of impaired NO availability, an effect not shared by other endothelial agonists, including acetylcholine. It is not surprising that in comparative studies in patients with hypertension or coronary artery disease, ACE inhibitors, but not ARBs, can

improve endothelial function in large arteries ().

In contrast, ARBs act biologically via a selective blockade of the AT1 receptor, leaving the other angiotensin receptors relatively unopposed. Importantly, as a consequence of the AT1 receptor blockade by ARBs, angiotensin II levels increase several fold through uncoupling of the negative feedback mechanism. Recent data suggest that AT2 overstimulation may be involved in promoting vascular growth, inflammation, and fibrosis.

A crucial aspect which needs to be taken into consideration is that the RAS has two distinct types of components: a circulating one (representing roughly 10% of the whole system), mainly devoted to BP regulation, and a tissue one (approximately 90% of the system), involved in tissue homeostasis. Whereas a low dose is sufficient to block the circulating RAS (though with the possible caveat of an insufficient duration of action), a high dose is necessary to reach the tissue RAS and effect organ protection Thus, the necessity to use RAS blockers at full dose is einforced by the evidence demonstrating that this is the only way to obtain a beneficial effect on target organ damage.

In the SECURE study, ramipril can prevent carotid artery placque progression onle at the dose of 10 mg daily, while it is not effective at the dose of 2.5 mg daily. This evidence is in line with a mechanistic study demostrating that ramipril 10 mg has a greater effect than ramipril 5 mg in improving NO availability in the brachial artery of hypertensive patients. In a similar way, DAPHNET study demonstrates that perindopril 8 mg daily is more effective in reversing carotid artery stiffness as compared to prindopril 4 mg daily. Finally, in IRMA study, the effect of irbesartan in reducing microalbuminuria is dose-dependent albeit a similar blood pressure control between the groups treated with 150 mg daily based therapy or 300 mg daily based therapy.
In conclusion, RAS is deeply involved in vascular alteration in hypertension.

Blockade of this system can lead to a beneficial effects for the patients, but strong evidence exist that ACE-is should be considered as first line agents as compared to ARBs.

Meta-analysis of ARBs and ACE inhibitors trials conducted before 2006

ARBs vs comparators
(11 trials n=55 050)

ACE inhibitors vs comparators
(39 trials n=150 943)

RRR (%)

+1% +1% -8% +8%*

Global death, CV death, Stroke, MI

* P=0.03

RRR (%)

Global death, CV death, Stroke, MI

-9%*** -12%** -6% -14%***

** P=0.0005; *** P<0.00001
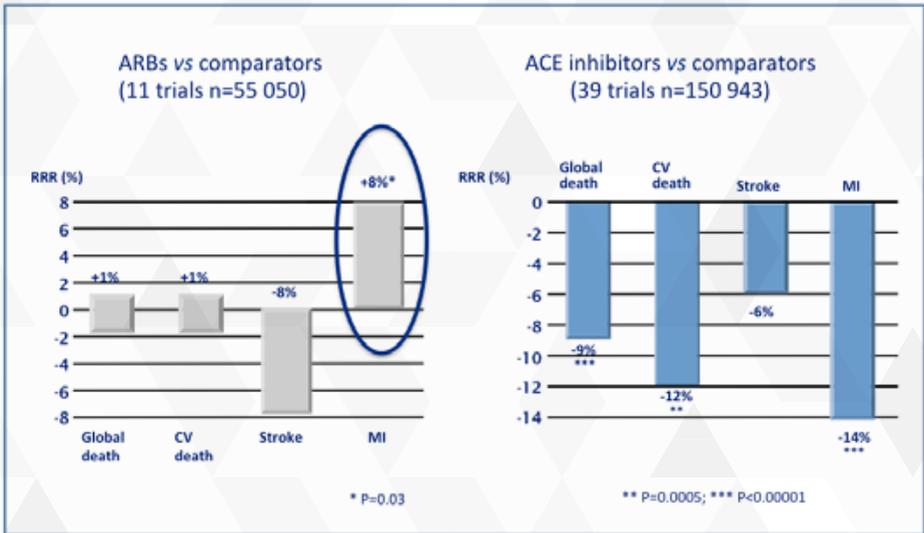
Adapted from Strauss MH et al. *Circulation* 2006

Right Ventricle and Pulmonary Adaptations in HFrEF and HFpEF

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The first issue that will be discussed is that the current understanding of pulmonary hypertension (PH) due to left heart diseases does not make any distinction between heart failure with reduced ejection fraction (HFrEF) as opposed to patients with heart failure and preserved ejection fraction (HFpEF) in terms of pulmonary hemodynamics. This is probably not true; it is fact demonstrated that in the systemic vasculature, the comorbidities which are more frequent ih HFpEF than in HFrEF largely determine a stiffer vasculature.

We compared the pulmonary hemodynamics in the two HF phenotypes, given similar values of pulmonary artery wedge pressure (PAWP), and demonstrated that PH-HFpEF patients had a significantly higher DPG as compared to PH-HFrEF patients.

The second issue that will be discussed is that the factors contributing to right ventricular (RV) dysfunction in heart failure patients may be different in the different contexts of HFrEF vs. HFpEF. We performed a study in a large multicenter population of patient with HFrEF or HFmrEF or HFpEF identifying the different clinical and echocardiographic factors associated with RV dysfunction in such patients. These differences might be useful in the future to design specific therapeutic interventions for such patients. In any case, regardless of the extent of LV dysfunction, RV dysfunction is a powerful independent predictor of poor prognosis in all heart failure patients.

Post-MI Ventricular Remodeling: Molecular and Structural Mechanisms

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Left ventricular (LV) remodeling that develops after an acute myocardial infarction (MI) is the pathologic process by which LV size, shape, and function are altered by mechanical, neurohormonal, and molecular factors. The acute loss of functional myocardium (cardiomyocyte necrosis) and the resultant abrupt increase in loading conditions, trigger unique biochemical intracellular signaling that initiates a sequence of structural changes within the residual remote viable myocardium that culminate in LV dilatation, cardiomyocyte hypertrophy, and increased LV chamber sphericity, all of which, while compensatory in nature, lead to increased LV wall stress and evoke an increase in myocardial oxygen consumption (MVO2). Ventricular remodeling may continue for weeks or months after an acute MI depending on the size, location, and transmurality of the infarct.

If the infarct is large and LV dilation is not sufficient to maintain cardiac output, compensatory activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) is triggered both regionally and globally giving rise, in part, to compensatory hypertrophy. Activation of SNS and RAAS also causes increased heart rate and vasoconstriction; factors that are useful in maintaining homeostasis but come at a cost of further increase in MVO2. When sustained, the increase in sympathetic drive (norepinephrine release) along with increased levels of angiotensin-II, aldosterone, and endothelin, lead to a cascade of adverse events that include de-novo injury and loss of constituent cardiomyocytes of the remote myocardial region, increased expression of pro-inflammatory cytokines and enhanced deposition of collagen in the cardiac interstitial compartment of remote

myocardium. These abnormalities, in turn, can lead to cardiomyocyte hypoxia, mitochondrial dysfunction and abnormalities in sarcoplasmic reticulum (SR) calcium cycling. This cascade of events, left unattended, will likely lead to the development of signs and symptoms of heart failure.

Accumulation of collagens in the myocardial interstitium termed "reactive interstitial fibrosis" (RIF), once established as part of the remodeling process, leads to increased LV stiffness that limits passive LV filling. RIF has also been implicated in promoting reduced capillary density and increased oxygen diffusion distance. These maladaptations give rise to cardiomyocyte hypoxia evidenced by increased expression of hypoxia-inducible factor-1 alpha (HIF-1α) in the remote compromised LV myocardium. The developing hypoxia triggers cardiomyocyte dysfunction and promotes cardiomyocyte apoptosis both of which contribute further to global LV dysfunction. Sustained sympathetic drive along with inflammation elicit abnormalities of the nitric oxide (NO) signaling pathway evidenced by dysregulation of the nitric oxide synthase (NOS) isoforms. The remodeled remote ventricular myocardium manifests down-regulation of endothelial NOS (eNOS) and up-regulation of inducible NOS (iNOS). Down-regulation of eNOS can lead to abnormalities of mitochondrial biogenesis while up-regulation of iNOS promotes inhibition of mitochondrial respiration thus setting the stage for structural, dynamic and functional abnormalities of mitochondria, the energy source servicing the contractile unit assembly. Constituent cardiomyocytes of the remodeled and dysfunctional LV manifest abnormalities of mitochondria that include reduced rate of ATP synthesis with excess formation of reactive oxygen species (ROS) as well as abnormalities of 1) fission and fusion, 2) mitophagy, 3) cardiolipin synthesis and remodeling, and 4) activities of complexes of the electron transport chain. This energy deprivation state further compromises the contractile function of cardiomyocytes leading to further compromise of global LV systolic and diastolic function. Dysfunction/disruption of the mitochondrial inner membrane also leads to the release cytochrome c into the cytosolic compartment of the cardiomyocyte triggering activation of caspase-3 and driving the cell into an apoptotic death spiral.

Progressive LV dysfunction, myocardial remodeling and imposed limits on energy supply in the face of increasing energy demands (increasing MVO2), set the stage for dysfunction of multiple energy requiring cellular process including key ionic pumps. Calcium cycling within the SR is rendered abnormal as evidenced by decreased expression and activity of SERCA-2a, hyperphosphorylation and leakage of ryanodine calcium release channels, and abnormalities of the sodium-calcium exchanger, all of which result in calcium overload of affected cardiomyocytes raising the specter of further cell death and development of life threatening arrhythmias. All these structural, cellular and molecular events that develop over time during the post-MI remodeling process act in concert to ultimately cause intractable congestive heart failure.

Endothelial Dysfunction and Mechanisms in CAD and HF

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Coronary atherosclerosis is the critical determinant of the clinical manifestations of coronary artery disease (CAD). Patients with both epicardial and endocardial coronary artery disease may have chronic hypoperfusion, which leads to increased myocardial stiffness secondary to chronic inflammation and fibrosis. Indeed, in addition obstructive epicardial disease, microvascular coronary disease is also both widespread and often under-recognized; the coronary vasodilator reserve decreases in proportion to degree of luminal stenosis of the coronary arteries. The presence of underlying CAD also contributes to the morbidity and mortality of patients with heart failure (HF), the leading cause of hospitalization in elderly. Despite improved medical management, HF prognosis is unfavorable, especially for heart failure with preserved ejection fraction (HFpEF); in contrast to heart failure with reduced ejection fraction (HFrEF), timely diagnosis of HFpEF remains a challenge and current standard therapy fails to improve prognosis.

Impaired coronary endothelial-dependent vasodilation was observed non-ischemic dilated cardiomyopathy, highlighting the implication of the endothelium in HFrEF regardless of the presence of atherosclerosis. Recently, it has been hypothesized that endothelial dysfunction plays a causal role in the development of HFpEF by postulating that the comorbid illnesses seen in HFpEF are the primary drive of a systemic inflammatory state, leading to coronary microvascular endothelial dysfunction. Indeed, elevated levels of inflammatory cytokines are seen in HFpEF patients.

In accordance with this paradigm, metabolic comorbidities drive left ventricular remodeling and dysfunction in HFpEF through coronary microvascular endothelial inflammation, which alters paracrine signalling from endothelial cells to surrounding cardiomyocytes. It is especially the fall in nitric oxide-cyclic guanosine

monophosphate-protein kinase G signalling that predisposes cardiomyocytes to develop hypertrophy and high diastolic resting tension. Microvascular endothelial dysfunction as a mechanism of LV remodeling in HFpEF differs from HFrEF, where eccentric left ventricular remodeling results from cardiomyocyte cell death pathways such as accelerated autophagy, apoptosis, or necrosis.

Structural and Myocardial Dysfunction in HFrEF and HFpEF

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The European Society of Cardiology (ESC) published new guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) 1. The new nomenclature includes separating patients with HF into 3 distinct groups depending on the left ventricular ejection fraction (LVEF): preserved LVEF (≥50%) -HFpEF, mid-range LVEF (40–49%) -HFmrEF, and reduced LVEF (≤40%) -HFrEF. Although there have been several studies that argue for and against stratifying HF patients by LVEF, the latest guidelines continue to focus mainly on the LVEF as the central determinant of prognosis in HF. However, further characterization of HF phenotype using etiology, comorbidities, and nonresponse to therapy among the 3 proposed groups are not incorporated into the definition. It is important to identify pathophysiological mechanisms and specific etiologies that underlie the clinical status, beyond the simplistic definition of preserved, mid-range, and reduced LVEF.

So far, HFmrEF does not have specific diagnostic and therapeutic management. Among these three ESC proposed HF "phenotypes", the most well-known is HFrEF, which has specific diagnostic and therapeutic flow-charts. HFrEF is the consequence of many cardiac pathologies: ischemic heart disease is the most frequent but also valvulopathies, myocarditis, cardiomyopathies and advanced hypertensive cardiopathy are able to lead to this condition. Structurally HFrEF is generally characterized by regional or global left ventricle dysfunction up to an eccentric dilation. On the other hand, HFpEF is associated to normal value of LVEF with one condition able to reduce cardiac output as hypertensive cardiopathy, left atrium enlargement, supraventricular arrhythmias, severe mitral or aortic valvulopathy, and so on. Similar, to HFrEF, patients with preserved LVEF have

poor prognosis in terms of rehospitalization and mortality. Furthermore, it is necessary to highlight that the determination of LVEF from 2D echocardiographic images with Simpson's biplane technique is relatively unreliable, with intra and interobserver variability of up to 13% and 15%, respectively, because of foreshortened views and geometric assumptions2. Moreover, LVEF calculation is sensitive to changes in hemodynamic loading conditions. This is what occurs in patients with mitral regurgitation who have preserved LVEF despite severe ventricular dysfunction3,4. The consequence of such variability in measurement and sensitivity to loading conditions may lead to a significant overlap among the 3 proposed categories that are separated by only a few percentage points. Moreover, calculating LVEF is considered a simple method to estimate ventricular function, but in fact it may be too simplistic.

Probably the use of LVEF is misleading and confusing. The structural and myocardial dysfunction needs a more accurate evaluation in order to correctly assess systolic and diastolic function using advanced echocardiographic techniques such as TDI, strain rate and speckle tracking. Nevertheless, in order to identify the cause underlying the myocardial dysfunction, the use of cardiac magnetic resonance that is able to perform a tissue characterization is fundamental.

Therefore, it is important to decipher pathophysiological mechanisms that underlie the functional status, beyond the simplistic definition of preserved, mid-range, and reduced LVEF.

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Myocardial Ischemia and Coronary Disease Two Sides of the Same Coin?

Leonardo Bolognese

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Traditionally, the detection of ischemia has been considered to indicate severe anatomical stenosis (**1**). This paradigm, however, does not adequately consider the complicated relationship among coronary artherosclerotic disease, coronary arterial blood flow, myocardial ischemia, and adverse cardiac events.

In fact, comparative analyses have demonstrated that the relationship between ischemia and anatomical stenosis may be neither consistent nor perfect. For instance, the nuclear substudy of the COURAGE trial (**2**) illustrated that 40% of patients with >70% stenotic lesions have either no or only a mild degree of myocardial ischemia. In addition, 20% of lesions with 70% to 90% stenosis in the FAME trial had demonstrated FFR >0.8 (**3**). Similarly, in a prospective study by Park et al. (**4**), 57% of lesions with >50% anatomical stenosis had FFR >0.8. These data suggest that it is possible to have no ischemia in the presence of significant stenosis. On the other hand, 16% of lesions with <50% luminal stenosis in the study by Park et al. (**4**) and 35% of lesions with 50% to 70% stenosis in the FAME trial (**3**) demonstrated FFR <0.8, or the presence of ischemia with no significant stenosis. These findings emphasize the importance of factors beyond luminal stenosis that may contribute to inducible ischemia. Compositional changes within the plaque, diffusivity, eccentricity, as well as shear stress and other factors may provide insightful clues as to patterns of discordant physiological and anatomic parameters. Furthermore, coronary microvascular dysfunction (in the absence of obstructive coronary artery disease) may be operational. Thus, discordance would occur with physiological abnormalities or ischemia without a high-grade stenosis along with stenosis without ischemia.

In patients with ischemic heart disease, there is a long-believed paradigm linking a reduction in ischemic burden to prognostic improvement (**5**). Current evidence supports that the risk of cardiac adverse events is largely the result of the presence

and extent of coronary atherosclerotic disease, whereas provokable ischemia in stable patients merely serves as a surrogate for the underlying coronary artery disease **(6)**. Contrary to widespread perception, there is no conclusive evidence for provokable myocardial ischemia as an independent predictor of outcome, but there is strong evidence for the atherosclerotic disease burden being independently predictive of adverse events. The International Study of ComparativeHealth Effectiveness With Medical and Invasive Approaches (ISCHEMIA; NCT01471522) trial will be well positioned to conclusively disentangle the relationship between coronary anatomy and myocardial ischemia for guiding clinical management, and the investigators should seize this opportunity to, for example, test the value of ischemia evaluation over an assessment of coronary artery disease burden for risk assessment and treatment effectiveness **(5)**.

Given the failings of the epicardial stenosis paradigm, it is time to embrace a new, more enlightened paradigm that considers the many other known causes of myocardial ischemia including atherosclerotic burden, vasospasm, microvascular angina, and endothelial dysfunction in the evaluation of every patient with angina or ischemia.

Current evidence reminds us that that atherosclerosis, not stenosis or ischemia, is the primary disease process. Instead, stenosis severity represents a secondary anatomic consequence of atherosclerosis on coronary lumen size, whereas ischemia is a tertiary physiologic consequence of atherosclerosis and luminal narrowing on intracoronary flow. Although atherosclerosis, stenosis, and ischemia are all well-accepted predictors of outcome, it has remained generally unknown to date their relationship to each other. Certainly, atherosclerosis-defined ischemia does not necessarily have to be dependent on and defined by only on a given cut off value of stenosis severity.

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The Role of miRNAs in Coronary Artery Disease

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MiRNAs have been described two decades ago. These are small (approximately 22 nucleotides in length), non-coding RNA molecules that are able to regulate gene expression at a post-transcriptional level. Several lines of evidence have indicated that single miRNAs regulate the expression of multiple genes, while the expression of single genes can be regulated by multiple miRNAs. As a matter of fact, miRNAs have been shown to be pivotal regulators of complex biological processes associated with multiple cardiovascular pathologies, including left ventricular hypertrophy, ischaemic heart disease, heart failure, hypertension and arrhythmias. For instance, miR-1, miR-21, miR-133a, miR-499, and miR-208a/b have been associated with coronary artery disease, acute coronary syndromes, and myocardial injury, while miR-223, miR-191, miR-126, and miR-150 have been associated with platelet activation. In addition, based on evidence on the presence of circulating miRNAs, they have been evaluated as potential biomarkers in patients with heart failure and patients with acute coronary syndromes. At this point in time, no data supports the future use of miRNAs as an alternative to traditional biomarkers – such as cardiac troponin – for the diagnosis of acute coronary syndromes. Whereas, miRNAs might play a clinical role for risk stratification in the context of secondary prevention after an acute coronary syndrome. A similar role of miRNAs could be imagined in other major clinical settings in which an accurate risk stratification is pivotal. Moreover, the concept of miRNA-based therapy is developing. Synthetic antagonists of miRNAs (antagomiRs) are currently in phase II trials for the treatment of chronic hepatitis C virus infection. Along this line, preclinical investigations suggest that miRNAs could represent a therapeutic tool in cariovascular disorders ranging from heart failure to dyslipidaemia. Notwithstanding, several challenges related to specificity and targeted delivery will need to be addressed prior to the possible implementation of miRNAs in the diagnosis and treatment of cardiovascular diseases.

Diastolic Filling and Relaxation: the Significance of LV, LA, RV Strain from Echo Lab to Clinical Practice

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Diastolic filling disturbances belong to all forms of heart failure (HF) and its early detection could be mandatory also for prevention. Left ventricular (LV) strain, particularly its derived diastolic parameter "the early diastolic strain rate (LVSRe)" has currently become an important parameter to evaluate LV diastolic function and LV filling pressures and could be extremely helpful in HF reduced EF (HFrEF) and especially in the difficult clinical diagnosing of heart failure with preserved EF (HFpEF). In addition, left atrial (LA) and right ventricular (RV) strain have shown significant clinical utility in patients with LV diastolic dysfunction. In detail, findings show that LA strain measurements are useful to detect early cardiac alterations in patients with risk for cardiac abnormalities with preserved LV systolic and diastolic dysfunction. In addition, HF is also associated with significantly higher RV diameter, increased RV thickness, worse RV diastolic function assessed by tissue Doppler and strain rate, and worse RV systolic function. The best correlations with RV GLS in patients eg with HFpEF were LV GLS, LV and RV wall thickness, and TAPSE, indicating a role for RV strain analyzing's not only in HFrEF but also for HFpEF.In effect, several studies have proven the clinical utility of these new parameters to determine LV diastolic dysfunction and elevated LV filling pressures as well as to determine the cardiovascular prognosis in patients with both preserved and reduced LVEF. In this presentation, it will be presented the clinical evidence that support the potential use of LV, RV, and LA strain in the clinical practice.

Left ventricular (LV) strain, particularly its derived diastolic parameter "the early diastolic strain rate (LVSRe)" has currently become an important parameter to evaluate LV diastolic function and LV filling pressures. In effect,

several studies have proven the clinical utility of this new parameter both in patients with preserved and reduced LVEF. In this presentation, it will be presented the clinical evidence that support the potential use of LV strain, particularly its derived diastolic parameter "the early diastolic strain rate (LVSRe)", in the clinical practice.

Is it Possible to Establish Diastolic Dysfunction Degree During Atrial Fibrillation? The Role of Echo and Cardiac NMR

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Incidence of atrial fibrillation (AF) is continuously increasing, despite considerable advances in the management of patients with this type of arrhythmia, with AF remaining a source of considerable morbidity and mortality worldwide. Lifetime risk for development of AF is 1 in 4 for people 40 years of age and older, while it has been estimated that the number of adults with AF in the European Union will more than double from 2010 to 2060.

Cardiac imaging has explored the mechanisms through which atrio-ventricular diastolic derangement increases the risk of nonvalvular AF, with guidelines giving precise indications on how to assess left ventricular diastolic function and left atrial pressure in AF patients. Assessment of diastolic function in this condition, however, is limited by cycle length variability, absence of an organized atrial activity and frequent occurrence of atrial enlargement regardless of filling pressures. Thus, new indexes, not yet necessarily validated for AF patients, are proposed in the guidelines. Among these indexes those potentially capable of describing the delicate atrio-ventricular interactive relation should convey the strongest pathophysiological information and be less influenced by R-R' variations, if they can be comprehensively acquired in 1 single beat.

Previously, we have demonstrated that the atrial conduit contribution to ventricular filling, as obtained from a single-beat simultaneous left atrial and ventricular pyramidal full-volume 3D dataset, has a direct relationship with the degree of underlying ventricular diastolic impairment in heart failure patients. More recently we have also shown that conduit quantitation is also able to predict 1 month AF recurrence in a population of persistent AF patients imaged immediately

after electrical cardioversion. These findings support the concept that conduit, independently of the imaging technique used to quantify it, reflects intrinsic atrial pathology, that cannot be sufficiently explained by ventricular pathology only and thus it could be proposed as a clinically effective tool for exploring the link between AF and diastolic dysfunction, in excess of ventricular derangement.

New and Traditional Techniques in Cardiac RM: Its Additive Role in Heart Failure

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Cardiovascular Magnetic Resonance (CMR) plays an important complementary role to echocardiography in the assessment of patients with heart failure, as stated in the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.

CMR can provide a precise and accurate assessment of left (and right) ventricular ejection fraction using a 3D technique (post-processing planimetry of each short axis slice) which does not rely on geometrical assumptions. This can aid the selection of patients' candidate for device implantation. But the major additive role of CMR is on the non-invasive myocardial tissue characterisation of the dysfunctional myocardium, and the opportunity to identify and quantify myocardial oedema or fibrosis and scarring as the substrate for the dysfunction. Oedema imaging is performed using a T2-weighted sequence, a sequence sensitive to the content of water in the tissue. Fibrosis/scarring imaging is performed after 15-20min of the administration of a gadolinium-based contrast agent (late gadolinium enhancement, LGE imaging). The wash-in and wash-out kinetics of the contrast agent is different in normal vs diseased myocardium. Importantly, the contrast accumulation in the diseased myocardium follows the pathophysiology of the underlying disease. In particular, it is possible to identify and distinguish an ischemic vs non-ischemic pattern of disease. The ischemic pattern has a subendocardial or transmural LGE distribution, whilst the non-ischemic patterns varied among epicardial, mid-wall, circumferential subendocardial or patchy LGE. Given the ability to identify the underlying causes of heart failure in most patients, CMR can used as a gatekeeper for invasive angiography. Epicardial LGE can be suggestive of myocarditis, whilst mid-wall LGE is not pathognomonic of a single disease but in keeping with dilated cardiomyopathy either idiopathic, post-myocarditis, alcoholic cardiomyopathy and others. The LGE technique can be applied to both dilated or hypertrophic

phenotypes. Again, based on the LGE pattern of distribution a differential diagnosis of hypertrophic cardiomyopathy, Fabry's disease, hypertensive heart disease, cardiac sarcoidosis or other can often be established.

Novel techniques for myocardial tissue characterisation include native T1 mapping, T2 mapping and extracellular volume of distribution (ECV), known as myocardial relaxometry techniques. Both native T1 and T2 mapping are contrast-free techniques, whilst ECV requires the administration of contrast agent. T2 mapping is a novel technique for the identification of myocardial oedema with higher reproducibility than the traditional T2 weighted sequences. Native T1 mapping measures myocardial fibrosis, but it is a composite of myocardial and interstitial fibrosis, whilst ECV uniquely identifies interstitial fibrosis. Both native T1 mapping and ECV provide a semiquantitative measurement of myocardial fibrosis, and literature is increasingly demonstrating its incremental prognostic role. Whilst the myocardial relaxometry techniques have been part of the research domain, these techniques are almost ready for clinical applications, complementing the LGE assessment.

Right Ventricular Dysfunction in Heart Failure: the Dark Side of the Moon

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Right ventricle (RV) was for a long timelargely ignoredin the consideration of left-sided heart failure (LHF). However, in the last twodecades, several studies have clearly demonstrated thatright ventricular dysfunction (RVD) is not only common in LHF but its presence also strongly contributes to increasedmorbidity and mortality.

The distinction between RVD and right heart failure may be resembledto that between LV systolic dysfunction and LHF. The former is defined by abnormal values of functional parameters,whereas the latter is defined by haemodynamic decompensationwith typical clinical signs and symptoms.RVD is present when a measure of RV functionfalls outside the recommended range of normal.Right heart failure is a clinical diagnosis with signs and symptomsof systemic congestion in combination with structural and/orfunctional abnormalities of the right heart. It is important to acknowledge that staging phases of RVD andright heart failure vary of time and some patients may not haveRVD at rest, but rather during exercise. In contrast to LHF, there is currently no clear staging of right heartfailure, although attempts have been made to develop a stagingsystem.

Prospectivestudies are urgently needed to clarify the mechanisms underlyingright heart remodelling and dysfunction, and to provide effectivetreatments that improve morbidity and mortality.The ability to distinguish amongRHF caused by LHF, pulmonary vascular obstructive disease,and intrinsic RV pathology should be improved through novel hemodynamicindexes and biomarkers. Although RV imaging made substantial progress,more advances are warranted, particularly in relatingmeasures of systolic and diastolic performanceto indexes of load. Considerable advance in biventricular support technologies,particularly durable devices with applicabilityto broader patient populations is expected.

Therefore, greater focus on the often neglected rightside of the heart is warranted as well as introduction of standardized endpointsof right heart dysfunction and failure in future clinical trials.

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Current and Novel Tools for Congestion Detection in Heart Failure

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Systemic congestion is one of the principal features in acute heart Failure (AHF). Around 90% of patients hospitalized for an acute episode experience some degree of fluid overload at peripheral or pulmonary level. Indeed, current treatment and Guidelines are focused on symptoms relief, congestion solution and organ perfusion maintenance. Unfortunately, the detection of congestion by traditional clinical examination is often inaccurate, therefore it could varies in relation with clinical presentation and underlying pathophysiological mechanisms responsible for cardiac dysfunction. The principal determinants of the clinical picture are the hemodynamic status, primary cardiac disorder, systemic pressure and organ perfusion/damage. Traditionally, the definition and classification of the HF syndrome identifies different entities: pulmonary edema, right HF, HF with acute coronary syndrome, hypertensive HF and cardiogenic shock. Another important criteria is the distinction between impaired or preserved systolic function (HFrEF vs HFpEF) that may influence initial management and strategy. Finally, the clinical classification of patients with AHF describes different categories of patients such as 'wet' or 'dry', 'warm' or 'cold', and contemporarily identifies elevated filling pressures and organ perfusion damage as the primary hemodynamic derangements in HF. On the basis of pathophysiological profiles, the clinical presentation of AHF can be featured in a wide range of clinical pictures. Every picture reflects a specific hemodynamic profile and the consequent different congestion pattern. Despite the fact that fluid overload is commonly observed in AHF patients and congestion is the predominant clinical profile in this setting, it is often the "tip of the iceberg" of preliminary conditions starting from increased left ventricular filling pressure, cardiac workload, peripheral vasoconstriction and neuroendocrine overdrive. These determinants lead to a progressive organs deterioration related to fluid accumulation involving the kidney, lung, liver and intestine. Management

and systemic improvement of organ function should become a future target to reduce mortality and hospitalization. The clinical diagnostic assessment is based on dyspnea severity (the severity of dyspnea), peripheral edema, jugular venous distention, additional cardiac murmur, and chest radiography. This approach has several limitations and needs to be integrated with additional laboratory and diagnostic imaging tools. Besides the natriuretic peptide measurement linked to increased filling pressure and hemodynamic derangement, other biomarkers such as pro adrenomedullin, Hs troponin, galectin-3, and cystatin-C, are now available and they could provide information on systemic congestion, HF severity, and specific organ damage. Recently, hemoconcentration and plasma osmolarity have been achieved to monitor systemic fluid overload and as prognostic markers. Diagnostic imaging is likewise important to non-invasively detect LV filling pressure, cardiac output, right side heart failure and central venous pressure. A rapid ultrasound scan at admission can easily provide essential information on Ejection fraction, tricuspidal regurgitation severity, right ventricle dysfunction /dilatation, vein cava collapse and dimension. During ultrasound examination, it is also possible to recognize the pulmonary congestion status by lung comets measurement and contemporarily to evaluate pleural effusion. A new emerging factor partially neglected during congestion evaluation is the interstitial space: reduced venous capacitance associated with increased vascular resistance and reduced lymphatic drainage, which could lead to interstitial disruption and electrostatic force alteration with glycosamminoglicane derangement. Systemic bioimpedance examination is an additional methods to analyze peripheral and interstitial congestion occurring during the hypovolemic status and fluid redistribution in more advanced stages.

Overall, an integrated approach should take the following into account: clinical evaluation, underlying pathophysiological conditions generating HF impairment, systemic and lung congestion assessment by a systematic model. Evaluating all of these features at admission and discharge, could be a good approach to avoid recurrent episodes and to outline a future target for HF management.

The Role of the Kidney in Diuretic Resistance

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Heart failure is a syndrome characterized by insufficient blood flow to all organs, especially the kidney. As a response, the kidney will respond by autoregulation to try to keep glomerular filtration rate (GFR) stable, resulting in an increase in filtration fraction. In parallel, because of the activation of the renin angiotensin aldosterone system, via a maladaptive mechanism, the kidney is stimulated to retain excessive amounts of sodium and consequently water. This results in further impairment of heart (and kidney) function, and a further increase in salt and water retention, which is the vicious circle in the syndrome of heart failure. To get rid of the excessive water (and salt), physicians use (loop) diuretics to stimulate sodium and potassium excretion in the loop of Henle, with subsequent water excretion. In patients with relatively preserved GFR, preserved renal blood flow, relatively low central venous pressure and diuretic naïve, this will most often lead to a strong effect of the diuretic. In acute heart failure, this so-called diuretic response (how much water/sodium/weight can be lost by a certain amount of loop diuretic), is strongly associated with outcome. It actually is also the main target for therapy in acute heart failure: how to get rid of excessive water in as limited amount of time and with as limited dose of diuretics as possible. With every dose of diuretics, the effect of the drug is counterbalanced by proximal and distal tubular reabsorption of sodium (and subsequent water). This means that the effectiveness of loop diuretics is sometimes hampered by this phenomenon; the net result being a lower than usual diuretic response. When a diuretic response is really low, this is called diuretic resistance. Causes of diuretic resistance are incompletely understood, but include the mentioned tubular reabsorption proximal and distal of the loop of Henle, tubular hypertrophy, low renal perfusion, high central and renal venous pressure, and possibly unknown mechanisms.

In the end, it is especially this group of patients with diuretic resistance that require intensive management, monitoring and treatment, although to date there have been no randomized trials to specifically target diuretic resistance.

Hyponatremia in Heart Failure: Clinical and Pathophysiologic Role

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Hyponatremia, defined as serum sodium (Na+) <135 mmol/L, is the most common electrolyte disorder in hospitalized heart failure patients. Both admission and hospital acquired hyponatremia are associated with an increased risk for adverse outcomes including prolonged hospital stay, need for discharge to a short or long term care facility, and all cause mortality. Hyponatremia frequently poses an important therapeutic challenge in ADHF, because simple substitution treatment – as with other deficiencies – cannot be easily performed and an obvious concern for harmful fluid overload exists. Moreover, the pathophysiology of hyponatremia is often dilutional rather than depletional in decompensated HF.

Importantly, ubiquitous use of powerful Na+ wasting diuretics in this context hampers differentiation between both conditions, which require a totally different approach. This talk therefore aims to provide a pathophysiology based assessment and management strategy for the important clinical challenge of hyponatremia in decompensated HF, based on currently available evidence.

Figure:

Flowchart – Initial approach to hyponatremia in acute decompensated heart failure (J Am Coll Cardiol. 2015 Feb 10;65(5):480-92.)

HYPONATREMIA
Serum Sodium < 135 mmol/L

↓

Plasma hypotonicity?
(<285 mOsm/L)

↙ ↘

NO: PSEUDOHYPONATREMIA

1. Laboratory artefact
   CAVE: - Elevated triglycerides/cholesterol
            - monoclonal gammopathy

2. Effective osmoles
   - HYPERGLYCEMIA!!!!
   - Hypo-osmolar radiocontrast
   - Ethanol, methanol, ethylene glycol
   - Mannitol

YES: HYPOTONIC HYPONATREMIA

STOP DISTALLY WORKING DIURETICS
- Thiazide-type diuretics
- Mineralocorticoid receptor antagonist
- Amiloride

POTASSIUM & MAGNESIUM SUBSTITUTION
- Serum potassium ≥ 4 mmol/L
- Serum magnesium ≥ 0.85 mmol/L

Serum sodium ≥ 125 mmol/L & no volume overload: fluid challenge with 1L 0.9% NaCl

→   Serum sodium increase: DEPLETIONAL HYPONATREMIA

→   Serum sodium decreased/unchanged: DILUTIONAL HYPONATREMIA

DIAGNOSIS

DEPLETIONAL HYPONATREMIA ⟷ **DILUTIONAL HYPONATREMIA**

1. History and clinical examination:

   - Acute gastro-intestinal or third-space losses
   - Hypovolemia
   - High-dose or combination of diuretics

   - Edema, ascitis, pleural effusion
   - Hypervolemia

2. Urinary osmolality:

   Adequately suppressed ⟷ Inadequately suppressed
   (<100 mOsm/L)   (≥100 mOsm/L)

3. Urinary sodium:

   Depleted ≤50 mOsm/L

TREATMENT

DEPLETIONAL HYPONATREMIA ⟷ **DILUTIONAL HYPONATREMIA**
Sodium substitution: Promote free water excretion:

$$\frac{[Na^+]_{INFUSATE} + [K^+]_{INFUSATE} - [Na^+]_{SERUM}}{(\alpha \times Body\ weight\ [Kg]) +1}$$

1. AVP Antagonists
2. Improve distal nephron flow

α = 0.6 in children and non-elderly men
α = 0.5 in non-elderly women and elderly men
α = 0.45 in elderly women

Bio Humoral and Haemodynamic Derangement

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CRS type II is defined as kidney injury in the setting of chronic heart failure. Many are the mechanisms underlying kidney damage. These encompass low perfusion inducing glomerular damage, splancnic congestion leading to tubular damage, neuroendocrine and inflammatory factors.1,2 In CRSII the heart-kidney crosstalk is as such that kidney damage, once established, produces a vicious circle that in turn leads to a further heart damage . Splancnic congestion due to RV failure and consequent kidney tubular congestion and damage can paly also a role. Tubular cells when get into apoptosis release many factors, including NGAL andf pro inflammatory cytokines. These may in turn produce a further heart damage with perpetuation of the heart/kisnear/heart cross talk and damage. NGAL can also interfere in teh heart with metalloproteinase clivage and induce further negative remodelling.

The reversibility of kidney damage in CRSII is still debated. Neither in animal studies, nor in heart failure clinical trials, this hypothesis has been ever demonstrated. One possible future development is the use of stem cells to ameliorate kidney function by acting on paracrine mechanisms, decreasing inflammation, repairing tissue damage and producing organ favorable remodeling. These has been shown preliminarly in diabetic nephropathy and in models of kidney damage with mesenchymal bone marrow stem cells.

The attached cartoon summarizes the heart-kidney crosstalk and the possible mechanisms of kidney repair induced by stem cell transplantation.

Unmet Need and Future Directions around Heart Failure

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The incidence, prevalence and burden of disease associated with heart failure are increasing. Effective treatments for hypertension and ischaemic heart disease delay the onset of heart failure into older age, but older patients usually have several different medical conditions making the effective management of heart failure more complex and difficult. Polypharmacy is a major problem.

Patients' expectations are also increasing. Patients hope that health professionals will relieve their symptoms, reduce future morbidity and disability, maintain their ability to live independently and, providing these goals can be achieved, prolong life.

For patients with heart failure, the control of congestion and the prevention of arrhythmias are of key importance in achieving some of these goals. However, even if congestion and arrhythmias are controlled, outcome may be determined by comorbidity, frailty and senility. Every threat is also an opportunity. The next great breakthroughs in heart failure care must deal with these issues.

Arrhythmias and Sudden Death in Heart Failure Patients with Preserved Ejection Fraction (HFPEF)

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Many patients with chronic heart failure (HF) die suddenly of arrhythmia despite the use of medical therapies. Drug therapy (in particular beta-blockers), but also the Implantable Cardioverter Defibrillator (ICD) has proven to be effective to reduce the sudden cardiac death rate in HF patients wih reduced ejection fraction (EF).

Relative to the patients with HFREF, the prevalence of HFPEF is increasing. The latter is related to the aging of the population, and many patients have a history of hypertension. So far, no drugs have been proven to improve prognosis in these patients. In the most recent European Society of Cardiology HF guidelines no clear recommendations for drug therapy of HFPEF was made. As a result, the prognosis is dismal, with a 1-year mortality ranging from 10-25%.

Data on the mode of death in HFPEF is not widely available. One of the reasons is because there is lack of uniformity in the definitions used to classify death in HFPEF (*population-based studies* most commonly report cause of death, clinical trials most commonly report mode of death). Based on data of a few moderately comparable HFPEF studies, including I-PRESERVE, CHARM-Preserved and TIME-CHF, sudden cardiac death was the most common mode of death (26-28%), followed by HF death (14-21%). When comparing mode of deaths between HFPEF with HFREF, cardiovascular death is more common in HFREF. Approximately 30% of all deaths in HFPEF is due to non-cardiovascular cause. As a consequence, the proportion of sudden death might be lower in patients with HFPEF than in HFREF, albeit still 25-30% of all cardiovascular deaths. Uncertainty remains regarding the incidence of sudden cardiac death, arrhythmic death, and incidence of sustained ventricular tachyarrhythmias. Clarifying the uncertainty is of great importance to understand the true incidence of arrhythmic death and incidence of

sustained ventricular tachyarrhythmias, and may possibly identify specific HFPEF patients who will benefit from ICD implantation.

We are currently conducting a study to determine the presence and significance of arrhythmias in patients with HFPEF (The **V**entricular tachyarrhythmia detection by **I**mplantable Loop Recording in **P**atients with **H**eart **F**ailure and Preserved Ejection Fraction, **VIP-HF** registry). This VIP-HF registry will importantly contribute to the knowledge on the occurrence of and risk factors for ventricular (tachy) arrhythmias in patients with HFPEF.

Current and New Challenges in Sudden Death Prediction

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Despite a rapidly developing base of knowledge, mstly during the past 30 years, about the arrhythmic mechanisms and myocardial substrates of sudden cardiac death (SCD), that resulted from clinical, imaging, electrophysiologic and interventional advances, important challenges remain for the prediction and prevention of SCD. Progress requires the detection of clinical marker that are able to identify individuals at high risk to experience lethal ventricular tachyarrhythmias. An ideal risk stratification strategy would identify within the general poulation those individuals who will experience SCD and exclude those who will not experience SCD. Multiple invasive and noninvasive tests have been evaluated, but currently no optimal strategy for risk stratification exists.. The current widely used strategy of stratifying risk on the basis of the left ventricular ejection fraction in patients with either ischeminc or nonischemic cardiomyopathy shows many limitations. In fact, the majority of patients who will experience SCD do not have a low ejection fraction, and many patients with a low ejection fraction may be at low risk for SCD. Beyond the ejection fraction, tissue characterization by contrast enhanced cardiac magnetic resonace is an emerging test for identifying patients with mycardiac scar, which confers an increased risk of life-threatening ventricular arrhythmias. The long-term Italian experience of systematic ECG screening of young competitive athletes resulted into a substantial reduction of sport-related SCD. However, either genetically-determined concealed myocardial substrates or ion channel disorders, which may be missed at preparticipation screening, still represent potential causes of SCD in young individuals without previous alarming symptoms or clinical signs.

Targeting SCD prediction as a research priority is paramount, with the hope that progress in the understanding of the genetic predisposition to SCD will contribute in parallel with clinical markers to more efficiently identify at risk individuals.

Cardiomems. A progress in HF Home Monitoring

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Heart failure (HF) exacerbations leading to hospital admissions are a growing burden to people experiencing HF and to society because of the associated cost. The related hospital resources rate of use represents the highest ones within the entire health care management program in the western world and is currently extending into the eastern developing countries [**1**].

HF is the most frequent cause of hospitalization in patients older than age of 65 [**2**], whose number will almost double over the next 50 years. It poses an increasing problem for global healthcare systems. The burden is further worsened in patients, in which, the primary disease is complicated by co-morbidities like diabetes and renal failure. In this setting MEDICARE database reports nearly 25% re-hospitalizations within 30 days and 67% within 1 year [1].

Those alarming data advocate a great need to develop and implement strategies to reduce the risk of hospitalization in this rising ill population.

CardioMEMS (Abbott, Sylmar, California), a permanently implanted device, has been developed aiming to accomplish this goal. CardioMEMS received Food and Drug Administration (FDA) approval in 2014 for HF hospitalization reduction in NYHA functional class III patients.

The CardioMEMS sensor measures pulmonary artery pressures (PAPs), which can be monitored by a clinical HF team that adjusts medical therapy with the goal of preventing HF worsening.

In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association

[NYHA] functional Class III Heart Failure Patients) multicenter randomized controlled study [3] the HF management led by longitudinal access to PAPs was associated with substantial reduction in rates of HF hospital admissions. The benefit persisted in the overall duration of the randomized follow-up. Much importantly, data were consistent in patients with both preserved and reduced ejection fraction, addressing PAPs as the most effective marker of patient clinical status.

A question remained to be answered: was CHAMPION study experience a unique exploit or it was well reproducible in real world HF context?

Retrospective analysis, conducted in the "real world" St. Jude Medical Merlin database on the stored de-identified CardioMEMS transmissions, suggests the hemodynamic-guided HF therapy can achieve PAPs reduction even larger than those observed during the CHAMPION trial [4]. Although those data did not allow to link the PAPs reduction with adjustment of guideline-directed medical therapies to the meaningful decline of HF hospitalizations rate in the implanted patients.

A more advanced retrospective investigation was performed on a MEDICARE cohort of 1,114 HF patients receiving CardioMEMS implants[5]. In these HF population there were 1,020 HF hospitalizations in the 6 months before, compared with 381 after, 139 deaths, and 17 ventricular assist device implantations and/or transplants in the 6 months after implantation (hazard ratio [HR]: 0.55; 95% confidence interval [CI]: 0.49 to 0.61; p<0.001). This lower rate of HF hospital admissions was associated with a 6-month comprehensive HF cost reduction of $7,433 per patient (IQR: $7,000 to $7,884). In the analyses restricted to 6-month survivors data were confirmed. Similar decrease in HF hospital resources costs were observed in the subset of 480 patients with complete data available for 12 months before and after implantation (HR: 0.66; 95% CI: 0.57 to 0.76; p < 0.001). On the basis of such evidence we would be tempted to conclude the ambulatory hemodynamic monitoring should have wider implementation in "real-world" HF management.

The study data have not been generated in a controlled environment and monitored patients underwent close selection to receive the expensive, invasive

monitoring device. The point could be relevant by considering the CardioMEMS system may have limitation on PAPs interpretation as this might not mirror immediate changes in left ventricular filling pressure while pulmonary vascular resistances are elevated. In the study population the CardioMEMS monitoring was associated with one avoided HF hospitalization for about every 2 devices implanted. The benefit size was even larger than the one achieved in the pivotal controlled CHAMPION trial.

The unexpected results should drive a greater focus on post-market clinical data collection from multiple sources as FDA closely seeks. Those must include claims, electronic health records, and high quality registries while employing advanced analytic approaches to determine device safety and effectiveness to support decision-making before to provide extensive adoption of a high cost, technically high demanding monitoring system in the unselected real world subjects [6] .

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# Hyperuricemia a New Old Disorder: Relationship and Potential Mechanisms in HF

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Cardiovascular diseases are the major cause of death in the Western world as a consequence of the extensive prevalence and the inadequate control of cardiovascular risk factors in the general population. Elevated levels of serum uric acid are ethiological mechanism in the development of gout and is also significantly associated with an increase in the relative risk of CV diseases in addition with the more consolidated CV risk factors (e.g. hypertension, lipid disorders, diabetes). The hypothesis linking uric acid with cardiovascular disease is based on the demonstration that a overactivation of the biochemical pathway leading to urate production can be responsible for an increased oxidative stress leading to CV disease (**Figure 1**). The patogenetic role of elevated serum uric acid does not apply exclusively to the development of CV disease, but also to the worsening of prognosis of established cardiac disorders including heart failure (HF). Hyperuricemia is very common in patients with HF mainly as a consequence of the large use of diuretics and can significantly affect the clinical outcome either in terms of incidence of gout or worsening in renal function. The presence of hyperuricemia has been proven to significantly increase mortality in patients with heart failure with an increase in the relative risk of death in patients with reduced and preserved EF% (**Figure 2**). The negative impact of hyperuricemia is more evident in patients with preserved renal function and this support a dual mechanism of potential damage from elevated levels of serum uric acid. In particular the results of the studies involving heart failure patients are supporting the primary role of over-production of uric acid associated with an enhanced oxidative stress as a responsible for the increase in mortality. This support the possibility that CV disease associated with hyperuricemia can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in oxidative stress and serum uric acid. The trials carried out so far have be conducted in an unselected population of HF patients reporting conflicting results. The treatment of hyperuricemia with allopurinol and oxipurinol is associated with a trend toward

a positive impact on clinical prognosis of patients with HF while the results of the EXACT-HF study have shown a tantalizing reduction in the rate of hospitalization that did not reach the statistical significance because of the small sample size. further studies are need to better understand the characteristics of the population who could benefit from xantine-oxidase inhibition. In conclusion elevated levels of serum uric acid can directly and indirectly contribute to the development of heart failure and may worsen the clinical outcome. A more systematic evaluation and treatment of serum uric acid in patients with HF is warranted for the future.

Figure 1   Urate production pathways
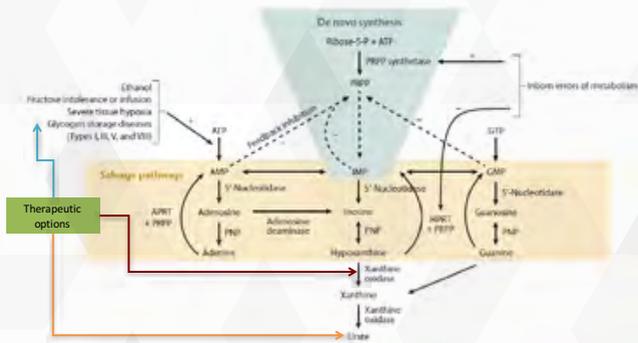
Mandal A. et al. Annu Rev Physiol. 2015;77:323-45

Figure 2   Kaplan-Meier plots for all-cause mortality and HF hospitalization in patients with HFrEF, HFpEF
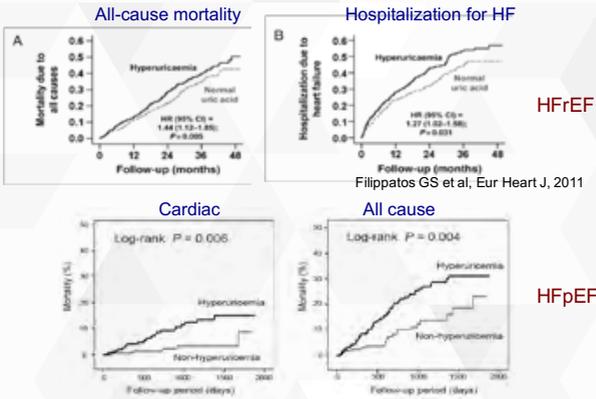
Filippatos GS et al, Eur Heart J, 2011

Shimizu T_ et al, _Am J Physiol Heart Circ Physiol, 2015

Diuretic Response and Diuretic Efficiency a New Target in HF Patients

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Congestion and volume overload are the primary cause for symptoms and ADHF hospitalizations. It has been demonstrated that residual congestion or the degree of decongestion is strongly related to adverse outcomes (**1-5**). Qualitatively the goals of ADHF therapy are easy to define: **1)** Achieve true euvolemia. **2)** Ensure stable to improved blood pressure, renal function, and electrolyte levels. **3)** Maintain or titrate guideline directed medical therapy while accomplishing the above. However, these goals are remarkably hard to define quantatatively. This is driven by the complexity body fluid homeostasis where multiple body fluid compartments are in equilibrium with an interaction of pressure-volume interactions. (**6**) We have an inability to measure clinically the majority of relevant body fluid spaces, and those we have access to are generally poor fidelity. Furthermore, many patients (even if we could measure euvolemia) can't achieve true euvolemia with stable blood pressure and renal function. As such, the reality is even more complicated in that each patient's individual best-case approximation of euvolemia involves the interaction between fluid, pressure, and their specific cardiac and renal physiology.

Treating a volume expanded patient with ADHF can be conceptually split into two components: **1)** the diuretic response and **2)** the degree of volume overload. Importantly, the response to the diuretic is temporally uncoupled from the absolute volume status of the patient. An analogy can be drawn that euvolemia is the destination, the severity of volume overload the distance from the destination, and the diuretic response the speed at which one is moving toward the destination. As a result, patient with severe volume overload can also have an excellent diuretic response, and a euvolemic patient can have severe diuretic resistance. The primary tool clinicians use to judge diuretic response is net fluid output and changes in body weight, but these parameters are known to lack precision.(**7,8**) Notably, the

correlation between fluid and weight loss, two metrics which ostensibly should be measuring the same thing is only ~r=0.5 indicating there is only about 25% overlap in the information provided by either metric.**(9)** Given that we have a very limited ability to measure euvolemia (i.e., arrival at the destination) and we often are blind to the rate of natriuresis (the speed we are traveling toward the destination), and that symptoms and signs of HF can often improve with only a fraction of volume overload being treated, it is not surprising that many patients are discharged with significant residual volume overload. Furthermore, physicians are often fearful of overdiuresis leading to significant renal injury, despite the fact that this appears to be an uncommon complication.**(10)**

As a result of the above there are several important priorities: **1)** We need to develop better ways to define euvolemia on an individual patient level. **2)** We need better ways to estimate how far away the patient is from their ideal fluid status. **3)** We need better ways to determine the rate at which we are moving toward euvolemia (diuretic response). Furthermore, when we are able to discern non-response of the patient, we need better therapeutic approaches to accelerate progress when we run into diuretic resistance or cardio-renal limitations. While it will involve substantial investment and time to develop comprehensive approaches to define euvolemia, an easier task with more immediate reward will be to develop better metrics to guide diuretic progress. An example is given of what we are doing at Yale to implement some of these principles. This involves measuring urinary composition and this predicting diuretic response in real time. **(11)** This is coupled to a nurse driven diuretic titration pathway that allows the diuretic to be uptitrated or held based on the natriuretic response to each dose.

Next a brief overview of our knowledge deficits is made regarding diuretic resistance. Loop diuretic infusion is used as an example. Based on existing knowledge, loop diuretic should offer profound diuretic advantage based on several pharmacokinetic advantages. First off, a constant infusion of diuretic avoids the post diuretic period of compensatory sodium reabsorption. **(12)** Secondly, by infusing the diuretic slowly and avoiding spikes in plasma levels as seen with bolus, there is lest "wasting" of the diuretic with plasma levels over the renal ceiling level where no additional natriuresis occurs with higher plasma levels. **(13,14)**. However, we have seen in clinical trials that there is no meaningful

advantage to loop infusion with some signal for higher rate of adverse events such as death or rehospitalization. **(15,16)** Next discussion of the relatively limited role renal function plays in determining diuretic response in acute heart failure, contrary to traditional wisdom. **(17,18)**

In summary, despite the central nature of volume status and diuretic therapy, we have a remarkable inability to measure euvolemia, diuretic response/resistance, and have an inadequate understanding of the mechanisms underlying diuretic resistance in contemporary human heart failure patients. Additional research in these domains is desperately needed.

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