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Nephrology Dialysis Transplantation

In-Depth Clinical Review

Advances in the cardiovascular assessment of patients with chronic kidney disease

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Abstract

Cardiovascular mortality is grossly elevated in patients with chronic kidney disease (CKD), and is associated with a wide variety of structural and functional abnormalities. These issues have driven additional attempts to further characterise these abnormalities to elucidate the pathophysiology involved, assess individual risk and/or target and monitor therapies specifically directed at the cardiovascular (CV) system. This review aims to assess the techniques that are currently available for the study of the CV system. This includes conventional assessments of the whole CV system from heart to peripheral microcirculation (although not deal with VC assessment), as well as the key functional consequences relating to stress induced cardiovascular reserve, perfusion and vasoregulation. In addition this review will introduce a variety of techniques aiming to expand the envelope of conventional measurements.

Keywords: cardiovascular disease; chronic kidney disease; imaging; metabolic stress; monitoring

Introduction

Cardiovascular (CV) mortality is grossly elevated in patients with chronic kidney disease (CKD), and is associated with a wide variety of structural and functional abnormalities. These issues have driven additional attempts to further characterize these abnormalities to elucidate the pathophysiology involved, assess individual risk and/or target and monitor therapies specifically directed at the CV system.

The key issue in these assessments is to appreciate that such structural and functional abnormalities occur within all elements of the CV system. Abnormal ventricular morphology is of critical importance, but equal stress needs to be placed on segmental function, quality and quantity of contractile function and left ventricular mass (LVM). Increasing appreciation of the importance of the peripheral circulation has markedly advanced our understanding of this area in recent years. This includes the need to image peripheral vascular calcification (VC) (ideally medial and intimal), particularly in conduit arteries. VC has multiple functional consequences [1], especially in altering the compliance of the conduit arterial segment, making detection and measurement of increasing arterial stiffness both a research and clinical imperative. The peripheral microcirculation is also important and may provide a window to understanding the behaviour of the microcirculation in critical central vascular beds.

The aim of this review is to assess the techniques that are currently available for the study of the CV system, whilst reviewing the specific importance of the data derived in the setting of CKD. This will include conventional assessments of the whole CV system from heart to peripheral microcirculation (although not dealing with VC assessment), as well as the key functional consequences relating to stress-induced CV reserve, perfusion and vasoregulation. This review will also introduce a variety of techniques aiming to expand the envelope of conventional measurements, particularly to provide information concerning the interface between metabolic stress and abnormalities of CV structure and function, in addition to advances in the continuous monitoring of the CV response to dialysis itself.

Cardiac imaging

Echocardiography

Conventional two-dimensional (2D) transthoracic echocardiography. Cardiac assessment by echocardiography is non-invasive, inexpensive to perform and generates detailed information about gross cardiac anatomy, objective quantification of LVM and the geometry of left ventricle hypertrophy (LVH), along with measures of function during systole and diastole. Prospective studies have shown the presence of LVH in most (70–80%) patients with end-stage renal failure, and this confers a poor prognosis. Indexing LVM (LVMI) to weight or body surface area confers

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difficulties with over- or under-estimation of LVMI due to the inherent variations in fluid volume status, body composition and nutritional status.

The most widely used method for quantifying systolic dysfunction is ejection fraction, derived from M-mode LV diameter measurements at end-systole and end-diastole. Systolic dysfunction measured by standard fractional shortening (FS) overestimates contractility in patients with concentric LVH (present in over one-third of dialysis patients), due to differential contractility within the inner and outer myocardial layers. Standard FS has been superseded by mid-wall FS, which allows for the phenomenon [2]. Zoccali *et al*. [3] demonstrated that mid-wall FS was superior to ejection fraction for the identification of asymptomatic dialysis patients with systolic dysfunction. In the same study, both parameters proved to be powerful independent predictors of new CV complications in dialysis patients. Importantly in ESRD, the independent negative effects on CV risk associated with both LVH and systolic dysfunction are additive [3], and the progression of these factors predicts CV events irrespective of their severity [4].

Notably, echocardiographic measures based on ventricular dimensions are sensitive to the degree of cardiac filling, which is important in dialysis patients where pre-load and after-load change as a function of fluid status. Other disadvantages of conventional echocardiography include the subjective interpretation and high inter-observer reporting variability [5], and semi-quantitative evaluation of regional systolic LV contraction.

Stress cardiac imaging. Exercise-dependent techniques are limited by poor exercise capability in the majority of dialysis patients [6]. Nuclear imaging modalities such as thallium scintigraphy do not accurately detect coronary artery disease (CAD) [7]. Therefore, patients with CKD are often only considered suitable for pharmacological stress. Conventional dobutamine stress echo (DSE) measures indices of global and regional ventricular dysfunction, and relies on high-quality imaging and interpretation by experienced operators. Dobutamine increases heart rate and contractility via sympathetic stimulation, causing both transmural flow redistribution by arteriolar dilatation and increased oxygen consumption [8]. Dobutamine-related side effects have been variously reported in ∼10% of renal transplant candidates [9]. In contrast, dipyridamole causes transmural flow redistribution by inhibition of adenosine breakdown, leading to arteriolar vasodilatation, subendocardial steal and ischaemia caused by altering coronary haemodynamics in the presence of critical coronary stenosis.

DSE is sensitive and specific for coronary artery risk screening in renal transplant candidates [9]. However, doubts about applicability in patients with more severe CKD have led to renal disease currently not being categorized in the most recent 'Appropriateness Criteria for Stress Echocardiography' recommendations [10].

Dipyridamole stress echo provides similar prognostication to dobutamine testing in non-uraemic hypertensive patients [11]. An Italian study of dipyridamole stress echo for CAD screening in renal transplant candidates reported a low incidence of side effects and ischaemia compared to previous dobutamine studies. This population though did contain a low proportion of diabetics, and the end-points for identification of ischaemia were not entirely comparable to those used previously [12]. However, dipyridamole SPECT thallium isotope-based imaging in ESRD appears ineffective at identifying significant CAD and prognosis [7], with sensitivity significantly below that seen in non-renal controls and other similar population studies.

Tissue Doppler imaging. Myocardial tissue Doppler studies of LV base–apex contraction are useful in the identification of clinically occult LV dysfunction. Longitudinal ventricular contraction brings the base and relatively fixed apex together and supplements radial ventricular contraction [13]; measures of this are sensitive markers of LV dysfunction and detectible before other markers such as ejection fraction become impaired [14]. Longitudinal fibres in the LV are subendocardial; hence, these measures are particularly vulnerable to reduced blood coronary flow [15].

Fathi *et al*. [16] studied 145 unselected ESRD patients with age- and sex-matched controls in Australia. Tissue Doppler was performed only on those ESRD patients with a normal DSE. Diastolic velocity was impaired compared to controls, but there was no significant difference in systolic function. The overall number of risk factors did not predict LVM or volume. Studies have variously demonstrated early mitral annulus velocity, peak systolic and peak late diastolic velocities all to be independent of the pre-load in haemodialysis (HD) [17].

Tissue velocity imaging. Tissue velocity imaging (TVI) gives accurate quantification of LV filling pressures, myocardial contraction and relaxation. Myocardial velocities and strain rate quantify systolic function, whilst diastolic function is measured by myocardial velocities and isovolumetric relaxation time [18]. Of particular relevance to the study of dialysis patients, TVI can detect acute changes in LV function [19], and measurements (especially the isovolumetric velocities) are less dependent on ventricular load status than conventional Doppler echocardiography. TVI also gives additional detail regarding isovolumetric contraction, LV filling pressures and right ventricle function. TVI may lend itself to early detection of functional cardiac compromise in renal patients where suitably trained operators and appropriate equipment are available.

Assessment of asynchronous ventricular contraction. Myocardial performance can be affected by both reductions in contractility and *disordered* contraction of the ventricle, reducing efficiency or distorting outflow tract anatomy. This can be assessed using two-dimensional ultrasound speckle-tracking imaging as previously described by Notomi *et al*. [20]. Digital images with high frame rates are acquired and LV rotation and rotational velocity is analysed off line using a speckle-tracking algorithm. Two-dimensional strain as the main component of myocardial deformation can be measured, namely longitudinal, radial and circumferential strain. In addition, LV rotational velocity can be measured by tissue Doppler imaging from four points on the LV [21]. HD may well induce such changes,

already recognized with exercise-based stress, in patients with systolic and non-systolic dysfunction-based heart failure. Further evaluation of the application of these techniques is awaited.

Detection of HD-induced myocardial stunning. In patients with CAD but without CKD, transient myocardial ischaemia may lead to LV dysfunction that can persist after the return of normal perfusion. This prolonged dysfunction is known as myocardial stunning [22]. Repetitive episodes of ischaemia can be cumulative and have been shown to lead to prolonged left ventricular dysfunction. Myocardial stunning is thought to be a causative mechanism for heart failure, with stunning and hibernation existing as part of a single spectrum [23]. Conventional echocardiography is also utilized in the quantification of myocardial stunning during HD.

Two-dimensional echocardiography is performed serially throughout dialysis sessions using standard available equipment. Images are recorded prior to commencing dialysis (baseline), at 120 and 240 min during dialysis and 30 min after dialysis finishes (recovery). Standard apical two-chamber and four-chamber views (to visualize the LV endocardial border in two planes at $90°$ to each other) are recorded digitally for off-line analysis [24]. Endocardial borders (excluding papillary muscles) are traced semi-automatically. Maximal displacement of the endocardial border from a centre point is then measured over each of 100 chords around the LV wall, corrected for end-diastolic LV circumference and expressed as percentage SF.

Recently we have been investigating the hypothesis that HD treatment itself might be responsible for repetitive cardiac injury (manifested as dialysis-emergent myocardial stunning) and that this cumulative effect could be crucial in the development of heart failure. These acute changes are abrogated by appropriate modification of the dialysis treatment to avoid dialysis-induced relative hypotension, making the detection and assessment of this phenomenon and application of a dialysis-based intervention a tempting novel set of therapeutic strategies to reduce cardiac injury in HD patients.

We have now demonstrated that dialysis-induced myocardial stunning occurs in around two-thirds of HD patients, and is associated with intradialytic hypotension (IDH), excessive fluid removal and age (but not dialysis vintage or other pre-defined co-morbidities) [25]. Dialysis-induced myocardial stunning is also associated with an increased rate of intradialytic and post-dialytic ventricular arrhythmias (sudden cardiac death being the most common cause of CV mortality in this patient group [26]). Dialysis-induced stunning has a significant effect on 12-month survival, and in those patients who stun but survived 12 months, there was a reduction in absolute LV ejection fraction by around 10%, with segmental reductions in SF co-localizing to the ventricular segments that previously exhibited dialysis-induced transient changes. These patients also developed worsening dialysis-induced hypotension, setting up a potential vicious cycle of worsening dialysis-induced haemodynamic instability and cardiac damage (Burton JO, Jefferies HJ, McIntyre CW, submitted for publication).

Cardiac magnetic resonance imaging (CMR)

CMR may be used to examine anatomy and function of the heart. Increasing access to suitably specified scanners (in terms of both installed cardiac specific coils and appropriate software for ECG-gated study) is facilitating the use of CMR in both research and general clinical care.

Structure. Coronary artery MR is complex due to interference from cardiorespiratory motion and the small size and geometry of coronary vessels [27]. Multidetector-row and multislice computerized tomography (CT) offer excellent negative predictive value for proximal and main branch CAD, and in combination the modalities can give high-resolution information regarding significant stenoses and atherosclerotic burden [28].

Compared to CMR, overestimation of LVM by M-mode echocardiography parameters occurs in the presence of LVH and ventricular dilatation, and overestimation increases linearly with increasing LVM and chamber dimensions. Intra- and inter-observer variability is also significantly greater with conventional echo [29]. These factors have led CMR to be considered the technique of choice to measure LVM.

Contrast wash-out CMR can be utilized to look at ventricular fibrosis. A recent gadolinium CMR study of 134 patients with ESRD [30] demonstrated a focal subendocardial late gadolinium enhancement (LGE) in 14%, indicative of potentially silent myocardial infarction. This pattern is associated with increased LVM, dilatation and diastolic dysfunction. A further 14% exhibited diffuse LGE, indicative of diffuse myocardial fibrosis, which may be specific to uraemic cardiomyopathy. More general studies utilizing CMR as a tool to investigate prognosis and treatment outcomes are awaited.

Cardiac function. Measured by CMR, around one-fifth of patients have abnormal end-diastolic volume (EDV) and cardiac output (CO) [31], which is lower than that reported in standard echocardiographic studies [32]. This may in part reflect the inability of the less healthy HD patients to lie flat for CMR. Visualizing the proximal aorta by CMR can also be used to measure pulse wave velocity (PWV) as a marker of arterial stiffness [33]. The recognition of problems associated with the use of gadolinium-containing contrast in patients with severely impaired renal clearance certainly is limiting the use of CMR. However, it should be noted that standard CMR looking at ventricular size and global/segmental function is performed contrast free.

Positron emission tomography

Positron emission tomography (PET) is an imaging technique that offers unrivalled specificity and sensitivity, and represents the gold standard for the study of tissue perfusion, including myocardial blood flow (MBF). PET can also be used to measure coronary flow reserve (as an important marker of demand ischaemic potential), and with glucose-based isotopes can be used to study myocardial metabolism.

Using $H_2{}^{15}O$ (which has a short half-life) as the radiolabelled tracer allows repetitive MBF measurements at short intervals. Also, because it is metabolically inert, it equilibrates rapidly between the vascular and extra-vascular spaces, meaning that uptake by the heart does not vary despite wide variations in flow rate [34].

Gated imaging using ^{13}N-NH_3 in combination with PET has recently been suggested as a feasible and useful tool in the simultaneous assessment of myocardial perfusion, left ventricular functions and contractile function of the heart [35]. ^{13}N-NH_3 is an established and routinely used method for the quantitative imaging of MBF at rest and under stress conditions and for measuring coronary flow reserve [36]. Ammonia PET though has the disadvantage compared to water PET of having a lesser degree of tissue extraction (typically only one pass with water), which reduces the resolution of segmental perfusion measurements in damaged fibrotic hearts for ammonia compared to water-based studies.

We have recently successfully utilized water PET to demonstrate significant reductions in global and segmental myocardial perfusion during HD in patients with normal gross coronary artery anatomy [37]. The expense and limited availability of PET scanning with appropriate isotope availability mean that this technique is still very much a research tool.

Measurement of arterial compliance

Arterial walls alter their structure and function in response to atherogenic and atherosclerotic factors, as well as changes in the haemodynamic burden. As a result, the structural changes can include activation and proliferation of smooth muscle cells and rearrangement of cellular elements and extracellular matrix of the vessel wall [38]. This disruption of the architecture with the increase of hydroxyapatite crystals, collagen and loss of elastic fibres results in a reduction in arterial compliance and an increase in arterial stiffness.

This change in arterial compliance results in marked functional CV change. The rapidly returning reflected pulse wave reinforces the central (aortic) systolic blood pressure (BP) peak at the expense of the usual reinforcement of the diastolic BP. This results in the widening of pulse pressure [39].

Although direct study of these central waveforms is precluded in normal clinical practice, the change in morphology of the pulse wave can be quantified from a computer reconstruction, using a validated transfer function, of this central wave form derived from the measurement of a peripheral (usually radial) pulse. Detailed discussion of pulse wave analysis is beyond the scope of this article.

Measurement of PWV, increasing with increasing arterial stiffness and reducing distensibility to pressure, provides a better, less composite, measure of arterial stiffness than augmentation alone. This can be measured by a variety of techniques. The most commonly applied are either ultrasound based, or rely on the assessment of the arterial wave form at separated peripheral sites (either simultaneously or ECG gated with a single tonometry probe) [40]. There are however a burgeoning number of devices becoming available.

The more recent developments rely on a far lower level of operator skill than previous methods. A detailed discussion of all of these options is beyond this review's scope, but the full range at present are summarized in Table 1.

Autonomic functional assessment

Baroreflex sensitivity

Autonomic dysfunction is common in patients receiving dialysis, and those with significant CKD. Short-term regulation of BP is largely controlled by appropriate autonomic nervous activity through the baroreflex arc [41]. Baroreflex sensitivity (BRS) is therefore well recognized as an integrated assessment of the autonomic nervous system [42]. BRS is not constant, and is affected by multiple factors. The involvement of drug treatment [43], endothelial dysfunction/paracrine factors [44], posture [45] and age [46] have all been demonstrated. Such dysfunction is associated with an increased incidence of cardiac arrhythmias [47], falls propensity, intradialytic haemodynamic instability [48,49], cardiac damage, metabolic syndrome [50], CV events and all-cause mortality after myocardial infarction [51] and in heart failure.

BRS as a marker of the fundamental control of BP is of great physiological significance in the study of HD. Impaired BRS has been demonstrated in patients who are unstable on HD [52]. Furthermore, transfer from conventional haemodialysis three times weekly to nocturnal haemodialysis increases BRS [53], although further work is required to evaluate outcomes associated with what are at least theoretical benefits in terms of CV outcomes.

Measurement of BRS

Initial BRS measurement methodology was based on the assessment of the CV response to both pressors and vasodilators [54]. These were both invasive, and only provided a snapshot view of resting BRS. Contemporary techniques however focus on spontaneous BRS assessment. Whilst invasive techniques have been utilized [55], non-invasive continuous BP recording by devices such as the Finometer (FMS, Amsterdam, The Netherlands), which reconstructs central haemodynamics from digital photoplethysmography via validated transfer functions, allows the calculation of spontaneous BRS both at rest [56] and during interventions such as HD [57] and PD [58]. BRS is calculated from the regression slope between continuous inter-beat interval and beat-to-beat BP changes. Three consecutive changes in the R–R interval in the same direction were required before a phase shift calculation (incorporated into Finometer software) is performed [59].

BRS may be computed from such recordings via either frequency-domain or time-domain techniques. Frequency-domain techniques rely on spectral analysis, whilst time-domain techniques quantify BRS by regression analysis of the relationship between systolic BP and pulse rate change. Whilst detailed analysis of the relative merits of these techniques is beyond the scope of this review, different techniques have been shown to produce broadly consistent

Table 1. Devices available for the assessment of arterial stiffness

Device	Manufacturer	Technique	Assesses	Benefits	Issues
SphygmoCor	AtCor Medical	Applanation tonometry + ECG	PWVPWA (AIx)Central BP	Can assess any arterial segment Calculation of central BP from peripheral site	Operator dependent, training and validation required
Vicorder	Skidmore Medical	Simultaneous BP cuff	PWV	Rapid assessment	New—validation in progress No PWA
PulseTrace PCA2	Cardinal Heath (MicroMedical)	Digital photoplethys-mography	PWV via PWA	Rapid assessment Portable	Reproducibility and correlation to PWV
PulseTrace PWV	Cardinal Heath (MicroMedical)	Doppler + ECG	PWV	Can assess any arterial segment	Outcome data
Complior	Artech Medical	Simultaneous pulse sensors	PWVCentral BP	Can assess any arterial segment	—
DynaPulse 200	PulseMetric	Brachial artery distensibility via BP cuff	PWACentral BP + haemodynamics	Rapid assessment Can be used in patient's home	No direct assessment of PWV
CVProfilor DO-2020 CVProfilor MD-3000 HDI/Pulsewave CR-2000	HDI Diagnostics	Radial automated applanation Tonometry + brachial BP cuff	PWACentral haemodynamics (CR-2000)	Differentiates large + small artery stiffness	No direct assessment of PWV
HEM-9000 AI	Omron	Automated radial applanation tonometry	PWA (AIx)	Automated assessment	No PWV or central BP
VP-1000VP-2000	Omron	BP cuffs + ECG Applanation tonometry (VP-2000)	Peripheral PWV PWA (Carotid AIx) (VP-2000)	Rapid assessment	No central PWV assessment

results [60]. Reproducibility is also similar between techniques [61].

Recent interest in the relative activity of the baroreflex arc has led to the development of Baroreflex Effectiveness Index (BEI), expressed as the ratio of baroreflex-mediated to non-baroreflex-mediated BP changes [62]. In a cohort including pre-dialysis, HD and PD patients, reduced BEI predicted all-cause mortality [63].

Microcirculation

Assessment of microcirculatory function

Microcirculatory function may be assessed indirectly (via surrogate humoral markers including asymmetric dimethy-larginine and endothelins) or directly by assessing the vasodilator response to various stimuli, including ischaemia (typically post-occlusive), hyperthermia or drugs. Iontophoretic drug provocation with acetylcholine (ACh) and sodium nitroprusside (SNP) allows separation of the endothelial-dependent (ACh) and endothelial-independent (SNP) pathways. Both Laser Doppler flowmetery (LDF) and Laser Doppler imaging (LDI) utilize a low-power laser to detect blood flow in dermal capillaries, either at a fixed point (LDF) or scanning over a limited area (LDI). Their use has been demonstrated in CKD [64]. There are however, significant methodological constraints with both techniques, and thus specific care must be taken with many factors, including the environment, site of assessment and drug delivery [65].

Cutaneous microcirculatory changes may have a direct bearing on the development and clinical course of VC. The maintenance of flow to vulnerable critical visceral circulations is essential to maintain health, and abnormalities of microcirculatory function may be important in the overall pathophysiology of this process and the development of CUA. There are currently no data available on the distribution of directly calcified microvessels in patients with CKD. Abnormal cutaneous microcirculation has been identified in patients receiving HD [66] and further reductions in microcirculatory function have been shown to be present in HD patients with large-vessel VC [67].

The cardiac microcirculation is becoming increasingly recognized as being important in the development of demand-induced myocardial ischaemia [68]. Impaired coronary flow reserve is determined by the maximum flow resulting from stress vasodilatation of both epicardial coronary arteries and the microcirculation. In health, 90% of MBF takes place through vessels $<150\ \mu m$ [69]. Myocardial ischaemia is well recognized as occurring in HD patients in the absence of large-vessel coronary disease [70]. There are no data currently available on the presence of significant calcification within the coronary microcirculation itself. Impaired microcirculatory function in ESRD patients is associated with increased LVM and arterial remodelling [71].

The assessment of subcutaneous dermal capillaries is a primary method for the assessment of the microcirculation. These vessels are representative of the microvascular supply to the heart [72] and kidneys [73]. This might allow study of the relatively accessible microcirculation to provide a window to critical central vascular beds. Abnormalities of

endothelial function demonstrated using LDF can provide additional quantification of CV risk when used in conjunction with conventional risk scores [74]. LDF also appears to be able to document endothelial cell dysfunction in ESRF patients prior to clinical evidence of CV disease or diabetes mellitus [75].

Continuous haemodynamic monitoring

Despite sequential improvements in HD technology, IDH occurs in 20–30% of HD treatments. In addition to the unpleasant symptoms experienced by patients, a fall in BP during HD is an independent risk factor for mortality [76]. There has been a recent increase in the appreciation that haemodynamic instability during HD is capable of producing recurrent cardiac injury (myocardial stunning) and that this cumulative effect could be crucial in the development of heart failure.

The ability to continuously monitor the CV response to HD, and potentially to assess the success or otherwise of an introduced intervention to improve a patient's stability may become more important in the general care of vulnerable HD patients. At present, the available techniques have largely been limited to a research application, but are well enough validated and robust enough to be considered in limited general clinical use.

Continuous pulse wave analysis

The Finometer allows continuous non-invasive pulse-wave analysis at the digital artery. The technology utilizes the finger-clamp method to record digital artery pulse waveform, and from this reconstructs a central aortic waveform that allows calculation of a full range of haemodynamic variables on a continuous basis, for each heart beat [77]. These include BP, pulse rate, stroke volume, CO and peripheral resistance. This technology is becoming increasingly used to assess chronic dialysis patients [78,79]. Previous work has validated the Finometer against invasive haemodynamic measurements in normals, unstable intensive care patients and in cardiac surgery patients, a proportion of whom had VC [80]. This has shown the Finometer to be accurate in tracking relative change. Measurement of CO though has been demonstrated to compare well with echocardiogram-based measures [81] in ESRD patients.

Thoracic bioimpedance and bioreactance

More recently, bioimpedance has come to the forefront for non-invasive CV monitoring. This technique was founded on the concept that electrical conducting properties of the thoracic space vary with the amount of blood contained therein. The method entails the measurement of changes in the electrical impedance of the chest cavity, which are subsequently highly related to changes in the amount of blood contained within the aorta. Analysis of the rate of change of aortic blood volume can readily be related to CO, but does not allow the measurement of beat-to-beat BP or systemic vascular resistance. Bioimpedance offers an easy-to-use, cost-effective CO measurement modality.

The accuracy of bioimpedance for continuous monitoring of CO is affected by background electrical interference and changing hydration status, rendering this technique not useful for continuous haemodynamic monitoring of dialysis [82]. These factors are additive to the other limitations of bioimpedance including variances in skin conductivity, patient movement and lack of clinician attention to exact placement of skin-contact electrodes.

New Bioreactance™ technology (Cheetah Medical Inc., Indianapolis, USA) is based on the appreciation that changes in aortic blood volume induce small changes in the frequency of electrical signals propagating across the thorax. These small changes are highly correlated with blood flow and can thus be used to accurately and consistently report the CO. Similar to bioimpedance-based methods, the Bioreactance system (NICOM™) relies on pairs of electrodes delivering a low alternating current, sensed for its propagation characteristics along the thorax by the other electrode pairs. As Bioreactance measures frequency and not amplitude, the exact location of the electrodes is far less important and allows filtering of the electrical interference noise typically encountered in hospital settings. The accuracy and reproducibility for this technique has already been demonstrated in animal studies [83] and patients, allowing direct comparison to conventional thermodilution methods [84]. In theory, this method should also be far less sensitive to changes in hydration.

Metabolic stress

Patients with CKD, and in particular those on renal replacement therapy, are subject to a tremendous degree of metabolic stress [85]. The mechanisms as to how these chemical stresses translate to the observed aberrant structural and functional CV changes are poorly understood. One of the important metabolic consequences seen is the development of advanced glycation end-products (AGEs). These are produced from a series of complex and sequential reactions collectively called the Maillard reaction. Furthermore, both carbonyl and oxidative stress favour AGE formation and subsequent deposition within tissues [86]. These products also accumulate in CKD, due to reduced renal clearance. Hyperglycaemia favours, but is not required for, AGE formation [87]. Accumulation of chemically stable AGEs on long lived proteins may serve as a measure of cumulative metabolic stress [88] and affects the structure and function of proteins, enhanced cytokine production and activation of transcription factors *via* binding to specific receptors (e.g. receptor for AGE) [89]. AGEs are not routinely measured in clinical practice as they are difficult to analyse in complex bodily fluids such as blood, and the more significant tissue-bound compounds have previously required biopsy.

AGE deposition within tissues can now be assessed by the use of skin ultraviolet (UV) autofluoresence (AF). This device (AGE Reader, Diagnoptics, Groningen, The Netherlands) utilizes a UV source at a specific range of wavelengths [90]. It is non-operator dependent and relies on resting the forearm of the subject onto the device. A connected personal computer then analyses the degree of AF and correlates that to known normal ranges. Although

the measurement is quick and non-invasive, the technique is limited by the range of skin pigmentation that will allow AF to be measured at all.

Skin AF has been demonstrated to correlate well with skin biopsy AGE levels [91]. Skin AF has been shown to be predictive of complications [92] and cardiac mortality in diabetic patients, useful in the assessment of chronic graft dysfunction and outcomes in renal transplant patients [93] and predictive of mortality in HD patients [94]. Furthermore, the cross-linking of structural proteins caused by tissue AGE deposition may result in reduced tissue compliance. Diastolic cardiac dysfunction, predominantly as a result of defective ventricular relaxation has been associated with increased skin AF.

Techniques aimed at bridging our understanding of the metabolic to the functional hold the promise of significantly improving our ability to detect these critical drivers of CV disease and target current and emerging therapies towards them.

Conclusion

The range of techniques that are becoming available for the CV assessment of the patient with CKD are rapidly expanding. Full exploitation of this suite of methods requires further collaboration with other specialities to access imaging expertise and to appreciate new insights that might be particularly relevant to the complex functional and structural CV abnormalities that result in the appalling magnitude of CV events that our patients are subject to.

Clearly further work is needed in the generation of yet more methods to increase our understanding of the pathophysiology at work, but the greater requirement is to explore and establish the place for techniques already available for patient care. This will require an increased ability to merge information pertaining to the different elements of the CV system to appreciate the effects as a whole, as well as discriminating between which are likely to remain as research tools and which have future relevance to day-to-day patient care. What is clear though is that there is certainly a need to move above and beyond a reliance on current basic measures, such as crude peripheral BP, as our principal source of information concerning the CV status of our patients.

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