Ageing Research Reviews 70 (2021) 101408

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Haemodynamic frailty – A risk factor for acute kidney injury in the elderly

Neil G. Docherty [a,g], Christian Delles [b,g], Patrick D'Haese [c,g], Anita T. Layton [d,g], Carlos Martínez-Salgado [e,f,g], Benjamin A. Vervaet [c,g], Francisco J. López-Hernández [e,f,g,*]

[a] Diabetes Complications Research Centre, Conway Institute of Biomolecular and Biomedical Research, School of Medicine, University College Dublin, Dublin, Ireland
[b] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[c] Laboratory of Pathophysiology, University Antwerp, Antwerp, Belgium
[d] Departments of Applied Mathematics and Biology, and Schools of Computer Science and Pharmacology, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
[e] Institute of Biomedical Research of Salamanca (IBSAL), and University of Salamanca (USAL), Department of Physiology and Pharmacology, Salamanca, Spain
[f] National Network for Kidney Research REDINREN, RD016/0009/0025, Instituto De Salud Carlos III, Madrid, Spain
[g] Disease and Theranostic Modelling (DisMOD) Working Group, Spain

ARTICLE INFO

Keywords:
Elderly
Haemodynamic frailty
Dehydration
Acute kidney injury

ABSTRACT

Clinical frailty in the elderly is defined by a composite measure of functional psychomotor decline. Herein, we develop the concept of *haemodynamic frailty* (HDF), a state of increased predisposition to disease prevalent in the elderly and characterised by impairment of the network of compensatory responses governing the defence of circulatory volume and adaptive haemodynamic function. We review the factors predisposing the elderly to HDF, with a focus on the impaired capacity to sustain total body water balance. As a component of HDF, dehydration generates vulnerability to diseases caused by tissue hypoperfusion, including acute kidney injury. We provide a detailed mechanistic explanation of how dehydration and depletion of the intravascular volume impacts on renal blood flow to become an important element of the heightened risk of acute kidney injury (AKI) in the elderly. We bring these mechanistic considerations into the clinical context with reference to examples of how pre-renal (haemodynamic) and intrinsic (involving renal parenchymal damage) AKI risk is elevated in the setting of dehydration. Finally, we present HDF as a state of opportunity to prevent disease, for which diagnostic and interventional standards need to be refined. Further prospective studies are warranted to help clarify the clinical utility of assessing and managing HDF with regard to the mitigation of AKI risk in the elderly.

1. Context

The term "ageing society" has been coined to describe the increased representation of older persons in the global demographic (World population ageing, 2019). Currently, approximately 20 % of the EU population is above 65 years of age, with estimates indicating that by the end of the century, 15 % of the EU population will be 80 years of age or older (Population structure and ageing, 2020). Supporting individuals to live not only a long, but also a healthy and productive life represents a major societal challenge. From a medical perspective, this encompasses a need for more comprehensive understanding of the role that modifiable risk factors play in the aetiology of acute disease in the elderly, with the ultimate goal of finding solutions to help mitigate these risks.

2. Haemodynamic frailty

Frailty, as a medical term, has become synonymous with functional decline in advancing years, having been operationally defined by Fried et al. as meeting three out of the five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss (Fried et al., 2001). Scores estimating frailty are based primarily on the assessment of psychomotor skills, such as in the 66-item Frailty Index (Mitnitski et al., 2001), the FRAIL-NH scale (Kaehr et al., 2015) and the Canadian Study on Health and Aging Clinical Frailty Scale (CSHA CFS) (Artiles-Armas et al., 2019).

In offering a more expanded view, taking into account physiological vulnerabilities, Xue (Xue, 2011) defines frailty as '*a clinically recognizable state of increased vulnerability resulting from aging-associated decline in*

* Corresponding author at: Institute of Biomedical Research of Salamanca (IBSAL), University of Salamanca, Edificio Departamental, S-20 Campus Miguel de Unamuno, 37007, Salamanca, Spain.
E-mail address: flopezher@usal.es (F.J. López-Hernández).

https://doi.org/10.1016/j.arr.2021.101408
Received 11 December 2020; Received in revised form 6 July 2021; Accepted 10 July 2021
Available online 13 July 2021

reserve and function across multiple physiologic systems, such that the ability to cope with every day or acute stressors is compromised.' According to this definition, frailty is a pre-morbid and potentially modifiable condition (Donatelli and Somes, 2017) placing the individual at a state of increased risk of disease. An expanded multi-domain assessment of frailty would thus entail a review of systems in each patient (e.g. cardiovascular, excretory, respiratory, gastrointestinal, neurological), complemented ideally by the application of dynamic functional tests and the measurement of biomarkers (Partridge et al., 2018).

Within the frame of the cardiovascular system, adaptive haemodynamic control underpins the adequate performance of organs and tissues throughout the body. Defective haemodynamic regulation impairs the response to stressors, and confers vulnerability to a variety of diseases resulting from tissue hypoperfusion, including cerebrovascular and cognitive disorders (Liu and Zhang, 2012; Deng et al., 2018), dizziness (LZ, 2006; Rubenstein, 2006), stroke (Caplan et al., 2006), acute heart failure (Traber et al., 1993), hypovolaemic shock (Moore and Murtaugh, 2001), gastrointestinal disorders (Kreimeier, 2000) and acute kidney injury (AKI) (Makris and Spanou, 2016a). We propose the term *haemodynamic frailty* (HDF) to describe a state of increased predisposition to disease characterized by exhaustion or partial limitation of the haemodynamic reserve and adaptive haemodynamic responses. An inability to modulate regional perfusion and sustain circulatory volume in response to challenges such as fluid restriction or excess fluid loss represents an important source of HDF.

3. The propensity towards dehydration in the elderly and HDF

The human body is composed of up to 60 % water and appropriate body water balance is critical for survival (Lacey et al., 2019). One-third of body water is found in the extracellular space and is normally distributed in a ratio of approximately 4:1 between the extracellular interstitial and vascular compartments, with plasma accounting for approximately 60 % (3 L) of the effective circulatory blood volume (Seifter and Chang, 2017). Sex differences exist, with females having a lower percentage of total body water (TBW) than men (Ritz et al., 2008; Chumlea et al., 1999). TBW relative to body weight declines with age, due to fat accumulation and loss of lean mass. After adjusting for total body fat and fat-free mass, women but not men continue to show a small, but significant, negative linear association of TBW with age through a large portion of adulthood Chumlea et al., 1999).

At steady state, TBW is regulated by means of counterbalancing water gains from eating, drinking and metabolic water production, with both sensible (urine production, loss in faeces) and insensible (evaporation from lungs during breathing and perspiration) driven water loss. Non-haemorrhagic TBW loss "dehydration" can be classified with respect to whether serum plasma sodium concentrations are respectively 1) preserved relative to reference values (isotonic dehydration) 2) increased due to excess free water loss (hypertonic dehydration) or 3) decreased due to salt loss in excess of free water loss (hypotonic dehydration). TBW balance can be compensated acutely through fluid shifts between the ICF, the interstitial ECF and the blood plasma with longer-term corrections reliant upon neurohormonal regulatory responses governing renal control of water and electrolyte balance and the hypothalamic control of water intake. The mechanisms involved therein are multiple and synergistic. Hypernatremia and subsequent hypovolemia trigger the release of antidiuretic hormone (ADH) from the posterior pituitary and reduce atrial natriuretic peptide (ANP) secretion, resulting in decreased natriuresis and diuresis (Dos Santos Moreira et al., 2017). Baroreceptor-mediated responses stimulate thirst, increase heart rate and contractility and act alongside increases in peripheral resistance and salt and water retention in the kidney (Dos Santos Moreira et al., 2017; Kishi and Hirooka, 2013). Baroreceptor-linked neuroendocrine pressor responses are mediated by increases in sympathetic tone and activation of the renin angiotensin system. In healthy young individuals, the combined effects of these compensatory responses allow for rapid correction of hypovolaemic challenges of up to 10 % in magnitude. Further decrements diminish cardiac output due to decreased preload, with declines of 20 % or more resulting in reductions in systemic blood pressure (Kreimeier, 2000).

Table 1
Risk factors for dehydration in the elderly.

INTRINSIC	EXTRINSIC
• Older age and frailty	• Inadequate staff to assist
• Requiring assistance with foods and fluids	• Medications
• Incontinence	Diuretics
• Cognitive impairment/confusion	Laxatives
• Unawareness on the importance of hydration	
• Impaired renal function	
• Depression	• Residing in long-term care
• Decreased thirst	• Excessive heat
• Anorexia and low muscle mass	• Reduced access to water
• Hyperglycaemia	
• Acute illness, diarrhea and vomiting	

Adapted from (Lacey et al., 2019; Lorenzo et al., 2019; Ritt et al., 2017)

A reduced capacity to adaptively engage these synergistic responses is a defining characteristic of HDF in the elderly meaning that for less marked challenge to TBW, dehydration can be more likely to ensue. Indeed, dehydration, is common in the aged population, with an estimated prevalence of 20–30 % (Lorenzo et al., 2019). At least half of individuals aged 65 years or older are classed as either being actively dehydrated or at risk of becoming dehydrated (Population structure and ageing, 2020). Multiple intrinsic and extrinsic factors can perturb fluid balance in the elderly and underpin an overall increased risk of dehydration. Anthropometric and physiological changes associated with ageing *per se*, including loss of lean mass, gain of fat mass, tapering thirst and decreased urinary concentrating capacity can be considered as intrinsic features which promote a state of chronic hypertonic dehydration. Superimposition of accessory factors place the elderly at further risk of volume contraction with stimuli leading to isotonic dehydration (vomiting and/or diarrhea) and stimuli promoting hypotonic dehydration, e.g., diuretic use implicated. (Table 1). Collectively these phenomena explain how challenges to the extracellular fluid volume can more easily arise in the elderly and ultimately translate into ensuing medical complications and healthcare consumption.

Documented dehydration is associated with higher health care expenditure and mortality in the elderly. It is directly associated with an increase in hospital care, including admission to ICU and utilization of residency in short and long term care facilities (Frangeskou et al., 2015). According to US statistics, as far back as 1996, $1.36 billion was being spent on the treatment of hospitalized elderly patients with dehydration as their primary diagnosis (Kayser-Jones et al., 1999). Another report based on US data from 1999 estimated $1.14 billion in potential national saving from avoidable hospitalizations in these patients (Xiao et al., 2004). Over twenty years later, there remains an unmet need for the technology and protocols that would permit precise estimation of hydration status as part of routine work-up in hospitalised elderly persons (as well as in the general population).

Dehydration in the elderly may be considered as a key element of HDF, which can go uncharted and only become decisive in the development and progression of diseases, including AKI (Makris and Spanou, 2016a) (Fig. 1). The ability to accurately assess hydration status and circulatory volume alongside blood pressure (BP) control and adaptive reserve would allow for qualified assessment of the degree of HDF in at-risk individuals. Methods to accurately estimate hydration exist, including assessment of serum osmolarity and impedometry. Similarly, a number of non-invasive methods to determine intravascular volume are available, such as inferior vena cava (IVC) diameter and collapsibility index, left ventricular end diastolic index, left ventricular outflow tract (LVOT) velocity time integral (VTI), and end tidal CO_2 measurement. Yet, these technologies need to be selectively assessed, optimized and

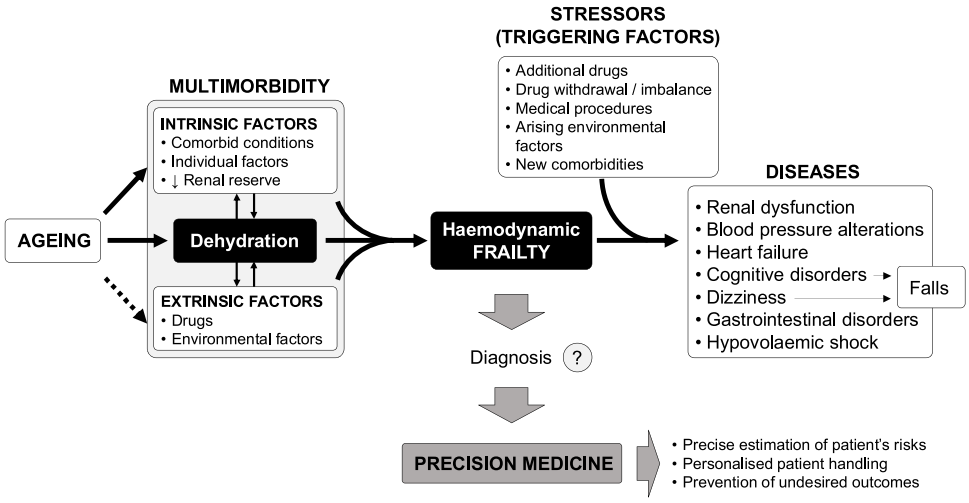

Fig. 1. Schematic depiction of the relation of dehydration and comorbidity, HDF and associated diseases triggered by environmental stressors in the elderly. Opportunity for precision and personalized medicine through the pre-emptive diagnosis of risk.

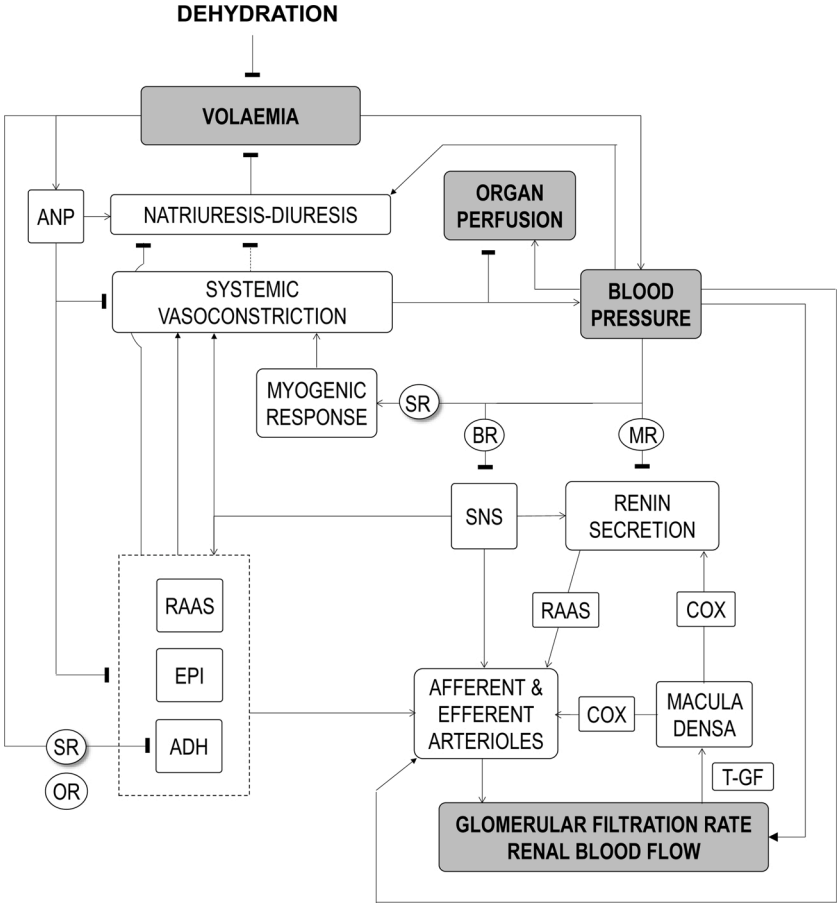

Fig. 2. Schematic representation of the haemodynamics regulation network depicting the main homeostatic mechanisms that maintain blood pressure, tissue perfusion and glomerular filtration during dehydration. ADH, anti-diuretic hormone; ANP, atrial natriuretic peptide; BR, baroreceptors; COX, cyclooxygenase; EPI, epinephrin; MR, mechanoreceptors; OS, osmoreceptors; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; SR, stretch receptors. T—GF, tubulo-glomerular feedback. Arrow-ended lines represent interactions involving activation, whereas blunt end lines represent inhibitions.

normalized for HDF estimation.

4. Acute kidney injury in the elderly

AKI, characterized by an abrupt decline in renal function, is increasing in incidence (Hoste et al., 2018). Within its recognised limitations in terms of sensitivity and specificity (Moledina and Parikh, 2018; Makris and Spanou, 2016b), the latest international consensus criteria [i.e., the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline] (Kellum et al., 2013) define AKI as typified increases in serum creatinine concentration (sCr) or reductions in urinary output (or both). AKI represents a major clinical issue associated with high levels of morbidity and mortality (Singbartl and Kellum, 2012). It also has significant repercussions from a healthcare economics perspective (Silver and Chertow, 2017). The most common acute sequelae of AKI are the need for dialysis and death. Longer term consequences include progression to chronic kidney disease and attendant increases in cardiovascular risk.

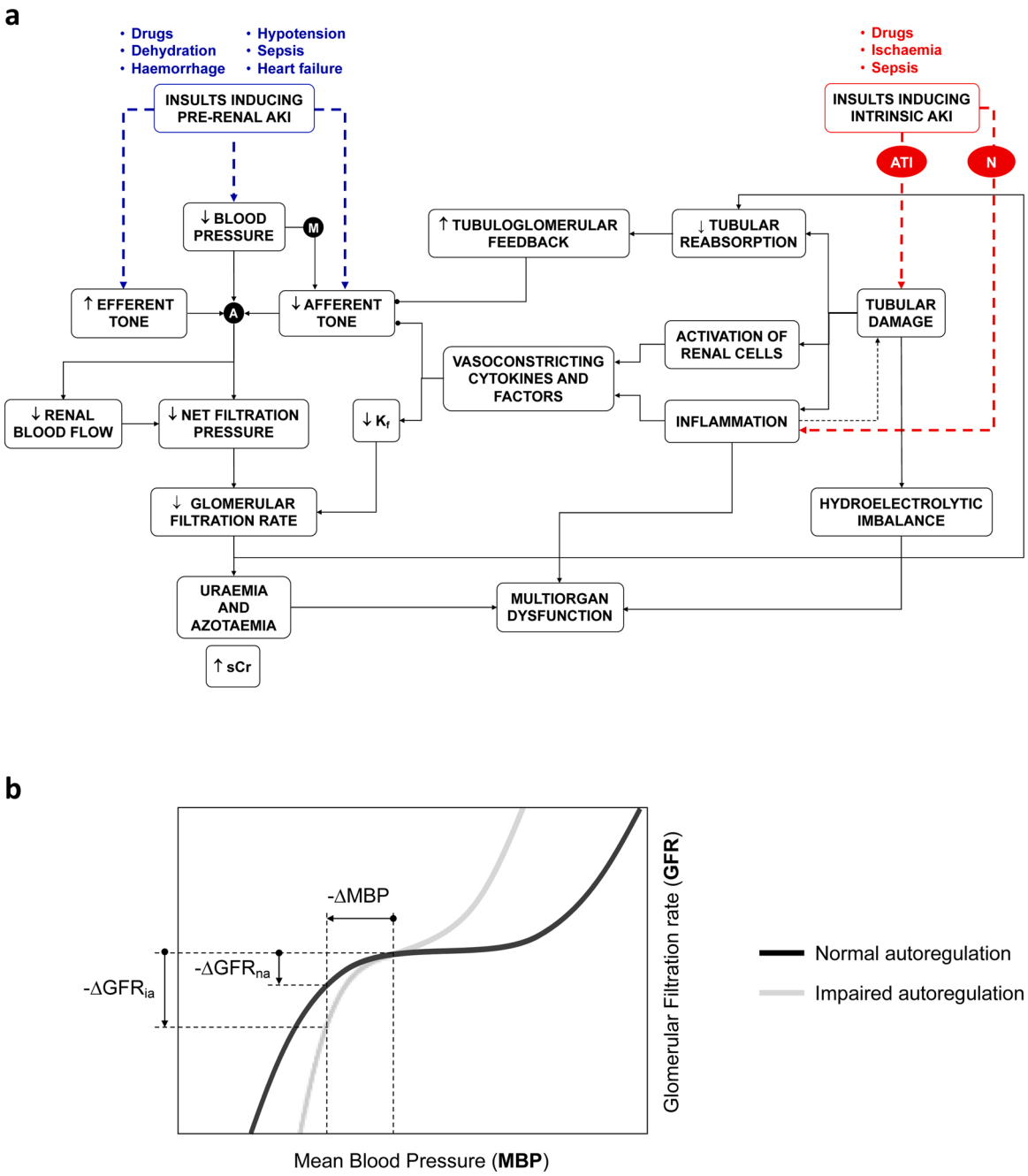

Fig. 3. **a)** Mechanisms of pre-renal and intrinsic AKI. **b)** Effect of autoregulation on the relationship between blood pressure and glomerular filtration rate. Graphical representation of the effect of a moderate drop in (mean) blood pressure (-ΔMBP) on glomerular filtration under normal and impaired autoregulation capacity. A, autoregulation. ATI, acute tubular injury. GFR, glomerular filtration rate. -ΔGFR_{na}, GFR drop under normal autoregulation conditions. -ΔGFR_{ia}, GFR drop under impaired autoregulation conditions. K_f, ultrafiltration coefficient. M, myogenic response. N, nephritis. sCr, serum creatinine. Arrow-ended lines represent interactions involving activation, whereas blunt end lines represent inhibitions.

Although AKI can affect individuals of all ages, it is especially relevant in the context of intensive and critical care medicine in the elderly (Hoste et al., 2015; Abdel-Kader and Palevsky, 2009), among whom mortality rates may reach 50 % or higher (Hoste et al., 2015). The incidence of AKI among the elderly is 3–55 fold higher (depending on the ages compared) than among younger individuals (Feest et al., 1993; Groeneveld et al., 1991; Ali et al., 2007; Pascual et al., 1990), and has doubled in a 10-year period (2009–2018) (Khan et al., 2017).

Increased susceptibility to AKI in the elderly is associated with reduced renal function, changes in renovascular reactivity, polypharmacy and comorbidities (Yokota et al., 2018) but dehydration *per se* can also be highlighted as a risk factor as will be discussed below.

5. Aetiopathology of acute kidney injury

Broadly speaking, AKI can be described as being pre-renal, intrinsic (renal) or post-renal in origin, with overlapping and discrete pathophysiological and molecular features in each case (Desanti De Oliveira et al., 2019). As shown in Fig. 3a, pre-renal AKI may result from the reduction of net glomerular filtration pressure or renal blood flow (RBF), as a consequence of low perfusion pressure (i.e., low blood pressure) or impaired renal autoregulation. Impaired autoregulation is caused by an altered equilibrium in the contractile status of the afferent and efferent arterioles. In the absence of parenchymal injury or senescence in the kidney, reductions in systemic blood pressure within the normal range

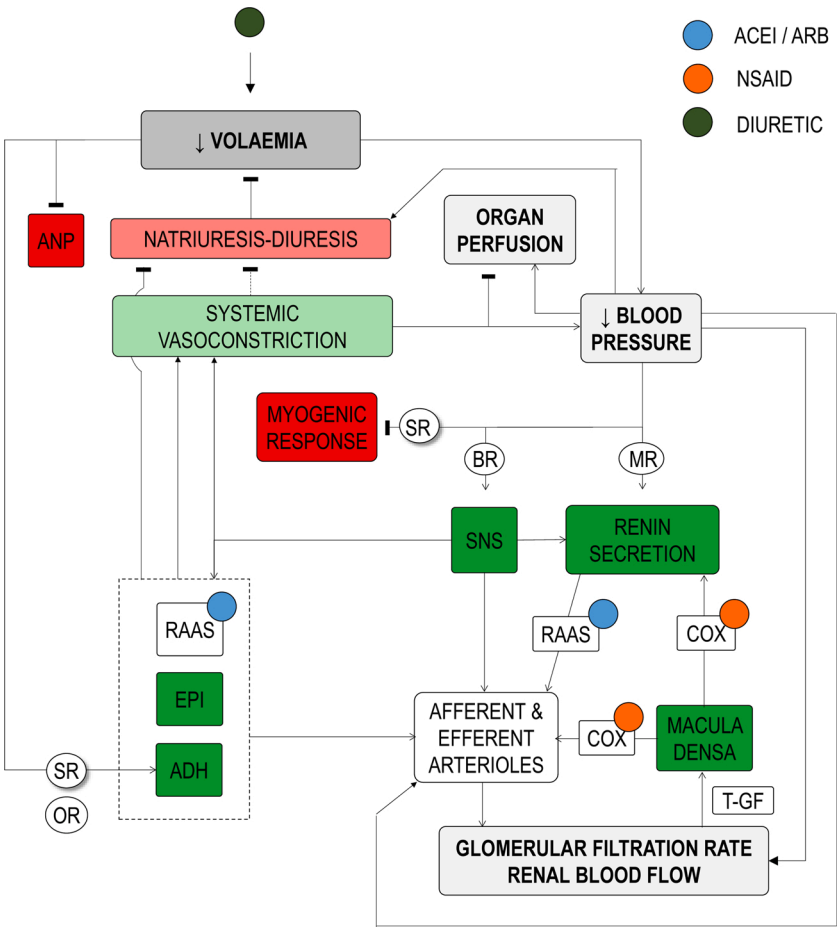

Fig. 4. Schematic representation of the handicapped response of the haemodynamics regulation network to a volaemic challenge (i.e., a diuretic treatment) in the presence of ACEIs or ARBs and NSAIDs, where blood pressure, tissue perfusion and glomerular filtration may be compromised (compare with Fig. 2). Activated mechanisms are depicted in green, and inhibited mechanisms in red. Half tones indicate partial (i.e., suboptimal) activation or inhibition. ACEI, angiotensin converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BR, baroreceptors; COX, cyclo-oxygenase; EPI, epinephrin; MR, mechanoreceptors; OS, osmoreceptors; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; SR, stretch receptors. T—GF, tubulo-glomerular feedback. Arrow-ended lines represent interactions involving activation, whereas blunt end lines represent inhibitions.

of renal autoregulation (80−180 mmHg) do not translate into significant alterations in the GFR, unless a loss of adaptive adjustment of the afferent and efferent arteriolar tone occurs (Fig. 3b) (Prieto-García et al., 2016a; Prieto-García et al., 2020). Intrinsic AKI (mainly in the form of acute tubular injury and tubulointerstitial nephritis) can activate tubuloglomerular feedback mechanisms that reduce GFR in the absence of reductions in systemic pressure (Lopez-Novoa et al., 2011). The reduction in GFR also relies on vasoactive mediators and pro-inflammatory cytokines released from activated tubular cells (Bonventre, 2007) which cause arteriolar vasoconstriction and thus a reduction in intra-glomerular pressure and RBF, and mesangial contraction which leads to a reduction of the ultrafiltration coefficient (K_f), (for review see (Lopez-Novoa et al., 2011)). Injury to the kidney arises along with systemic effects in distal organs (Druml, 2014; Kao et al., 2019; Singbartl and Joannidis, 2015). Independent of cause, a reduction in GFR may cause azotaemia and uraemia, and eventually cardiopulmonary congestion arising from salt and water retention (Glassford and Bellomo, 2017). Uraemia and azotaemia induce the dysfunction of other organs and may lead to death. Dehydration may be implicated in all three AKI sub-types but, as a component of HDF, the focus is on pre-renal and intrinsic AKI.

6. Dehydration as a component of HDF predisposes the elderly to pre-renal AKI

Because of multi-morbidity and physiological attrition, medication burden in the elderly is significant. Many drug families interact directly or indirectly with the components of the haemodynamic regulation network, thus becoming potential risk factors and stressors for haemodynamically frail patients. A classic example is the instance of AKI precipitated by combinations of anti-hypertensive medications and non-steroidal anti-inflammatory drugs (NSAIDs) (Prieto-García et al., 2020, 2016b).

Data from the US population indicates that the prevalence of hypertension increases with age: 22.4 % (within the 18–39 age range), 54.5 % (in 40–59 year-old individuals), and 74.5 % (age 60 and over) (Ostchega et al., 2020). The most prescribed antihypertensive drugs worldwide are diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). In most patients, blood pressure (BP) control is not attained with monotherapy, and double and triple therapies are implemented despite concerns of increased side effects (MacDonald et al., 2017). In fact, the most recent ESC/ESH 2018 guidelines recommend starting with at least two drugs (ACEI or ARB plus diuretic). Meanwhile, pain, often osteoarthritic in nature, is common in the elderly (Abbott and Fraser, 1998). Accordingly, non-steroidal anti-inflammatory drugs (NSAIDs) are very often administered acutely or chronically along with diuretics, ACEIs and ARBs, in a combination that is associated with a significant risk of AKI in susceptible individuals (Fig. 4). The addition of NSAIDs to antihypertensive therapy alters the haemodynamic equilibrium and leads to BP control dysregulation and pre-renal AKI in up to 22 % of patients (Lapi et al., 2013), with serious health and economic consequences (Prieto-García et al., 2016b). The AKI produced by the combination of NSAIDs, diuretics and ACEIs or ARBs has been termed “triple whammy AKI” (Prieto-García et al., 2016b; Boyd et al., 2000; Loboz and Shenfield, 2005; Fournier et al., 2014; Camin et al., 2015).

Clinical studies have shown that the incidence of AKI after single and double treatments (with these drugs) is lower than following triple therapy (Boyd et al., 2000; Heerdink et al., 1998; Thomas, 2000). With single treatments, only a few response mechanisms are inhibited, and

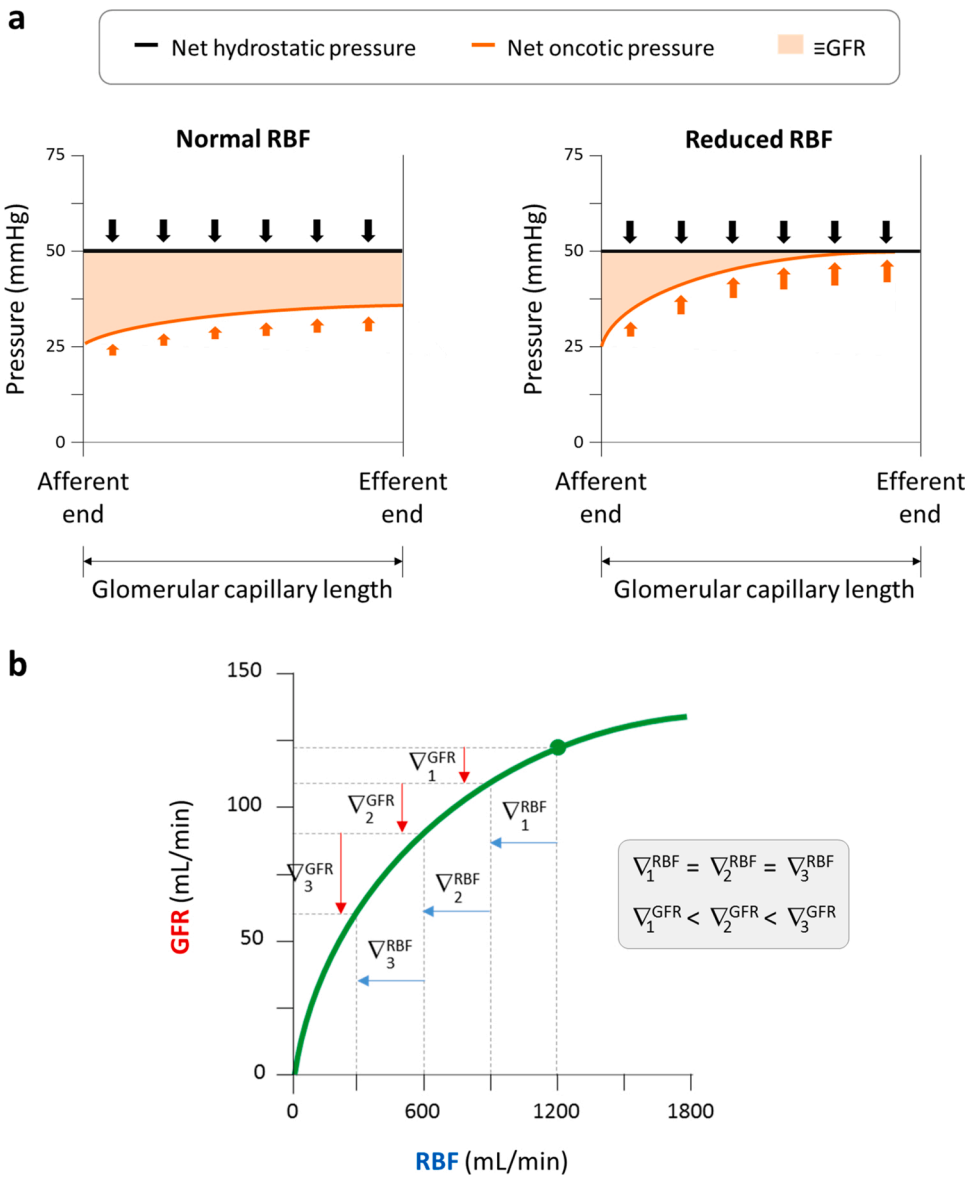

Fig. 5. a) Effect of RBF on GFR. Under normal conditions, net oncotic pressure does not grow enough to outweigh net hydrostatic pressure along the glomerular capillary length. However, when RBF is reduced, net oncotic pressure increases more steeply along the glomerular capillary length, so that GFR ceases when both pressures become equal. **b)** Graphical depiction of the relationship between RBF and GFR, illustrating that a given RBF translates in increasing GFR as the initial RBF decreases. GFR, glomerular filtration rate. RBF, renal blood flow.

compensation can still be attained by mechanisms remaining active. On the contrary, combinatorial therapy reduces redundancy normally maintained by the diversity of mechanisms that provide haemodynamic control, very significantly increasing the odds of BP dysregulation and AKI (Prieto-García et al., 2016b). AKI has been described in patients with chronic nephropathy treated with the triple whammy combination (Onuigbo and Agbasi, 2014).

However, additional factors are needed to explain why AKI occurs only in a fraction of patients treated with the three drugs (Prieto-García et al., 2016a). Clues to the importance of hydration status come from pre-clinical modelling in rats in which the triple whammy regimen only provokes AKI in animals that are dehydrated (Prieto-García et al., 2020). To this end, dehydration as a feature of haemodynamic frailty becomes the fourth element of a "quadruple whammy". Triple whammy AKI especially affects aged patients, in whom dehydration and comorbidities are most prevalent (as described above), and in whom the triple combination of drugs is most frequently prescribed (Loboz and Shenfield, 2005; Thomas, 2000; Lind et al., 2019). In dehydrated and hence highly haemodynamically frail patients, single and double therapies may also induce AKI, and comorbidities may substitute for the effect of drugs (Fig. 1). The incidence of AKI associated with NSAIDs is higher in older individuals (Zhang et al., 2017; Lucas et al., 2019; Turgutalp et al., 2017), also in the context of family medicine (Faber et al., 2019), and rises dramatically in dehydrated children (Patzer, 2008). The incidence of AKI associated to ACEI use is also higher in dehydrated children with heart failure (Terano et al., 2016), and in older patients Turgutalp et al., 2017).

7. Dehydration as a component of HDF also predisposes the elderly to intrinsic AKI

The elderly are also prone to intrinsic AKI (i.e., most commonly ischaemic and nephrotoxic AKI), due to renal attrition and accumulated comorbidities (Abdel-Kader and Palevsky, 2009). Older rats are also more sensitive to drug-induced intrinsic AKI (Ali et al., 1996; Beauchamp et al., 1992; Provoost et al., 1985; Pezeshki et al., 2017; Tarloff et al., 1996) and to renal ischaemia/reperfusion injury (Kusaka et al., 2012; Andrianova et al., 2018). Dehydration is also an independent risk factor for intrinsic AKI, and maintenance of a euhydrated state is a recognized practice for AKI prevention, including intrinsic AKI (Liu et al., 2019; KDIGO, 2012). In agreement, dehydration significantly amplifies intrinsic AKI in rats (Martinez et al., 1993; Obatomi and

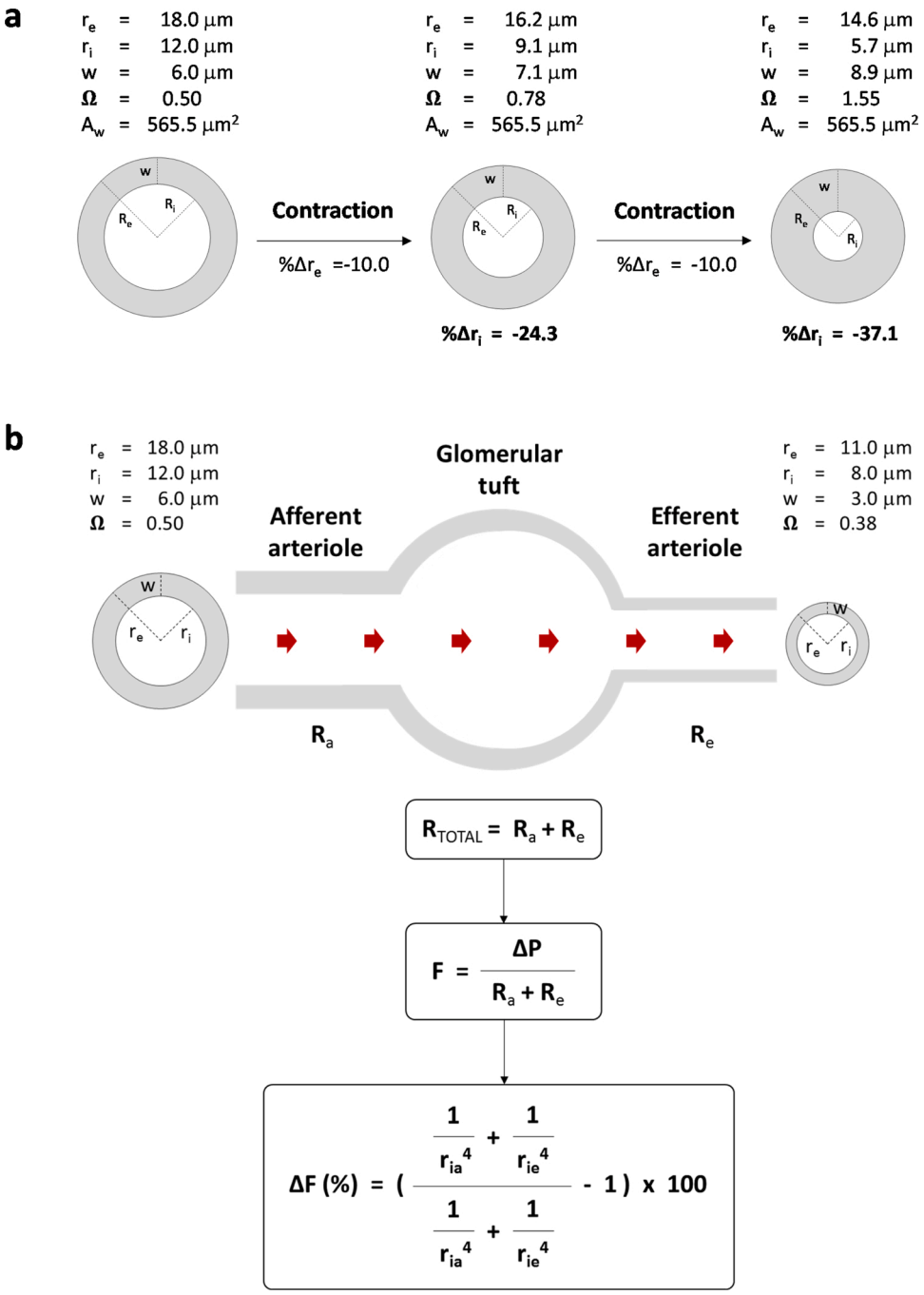

Fig. 6. a) Graphical illustration of the geometric amplifier effect, which augments the reduction in internal radius in arteries with higher wall-to-lumen ratio (Ω) during contraction, to accommodate the projection of the constant wall mass volume towards the lumen around a narrower size. As arteries contract, the inner radius must decrease more than the outer radius in order to maintain wall volume constant. The higher Ω, the more the inner radius must decrease compared to the outer radius. **b)** Illustration of the serial resistance exerted by the afferent and efferent arterioles. Afferent and efferent r_e, r_i, w and Ω represent values at normal perfusion pressure. Flow is inversely proportional to resistance, which is the sum of afferent and efferent resistance. In turn, resistance is inversely proportional to the fourth power of radius. Percentage incremental flow [ΔF (%)] resulting from afferent and efferent contraction or dilation can be calculated as a function of afferent and efferent r_e and r_i, provided that P stays constant after contraction or dilation of afferent and afferent arterioles. A_w, wall area. F, flow. P, pressure. R, resistance. R_a, afferent resistance. R_e, efferent resistance. r, radius. r_e, external (outer) radius. r_i, internal (inner) radius. r_{ia}, afferent r_i. r_{ie}, efferent r_i. w, wall thickness. Ω, wall-to-lumen ratio (i.e., w/r_i).

Plummer, 1993). Dehydration reduces diuresis and elimination of some drugs (such as aminoglycoside antibiotics), thus contributing to drug accumulation and nephrotoxicity (Lecompte et al., 1981; Inouye et al., 1982), an issue which currently is receiving particular interest in the pathophysiology underlying the development/aggravation of toxin-induced chronic interstitial nephritis in agricultural communities (CINAC) (Vervaet et al., 2020; Johnson et al., 2019). But the kinetics of many drugs are not affected by hydration. Yet dehydration may sensitize to nephrotoxic AKI through its impact on the core physiological mechanisms of haemodynamic regulation and the pathophysiological mechanisms of intrinsic AKI. As described, dehydration triggers synergistic responses aimed at restoring blood volume, BP and GFR (Fig. 2) (Thornton, 2010). During dehydration, RBF is significantly reduced (Hope and Tyssebotn, 1983; Kirkebø and Tyssebotn, 1977; Wyler et al., 1983), whereas GFR may also be moderately reduced or remain constant, depending on the balance of the effect on RBF, the degree of vasoconstriction incrementing intra-glomerular hydrostatic pressure (Giebisch and Windhager, 2009), and the effect of ADH and angiotensin (and other factors) on mesangial contraction decreasing K_f (Dworkin et al., 1983; Schor et al., 1981).

Because RBF is a main and independent determinant of GFR (Fig. 5a), it is precisely this reduction in RBF which primes an exaggerated reduction in GFR by stimuli causing intrinsic AKI. This amplified response is the consequence of the non-linear relation between RBF and GFR (Fig. 5b), with a decreasing slope as RBF increases (Mullens and Nijst, 2016). Accordingly, a reduction in RBF caused by dehydration sets the equilibrium on a steeper position in the curve, implying that further reductions in flow caused by intrinsic AKI-inducing agents will reduce GFR more than at basal conditions (where the RBF-GFR relation is less steep) (Fig. 5b). Because of the relation of flow to the fourth power of the

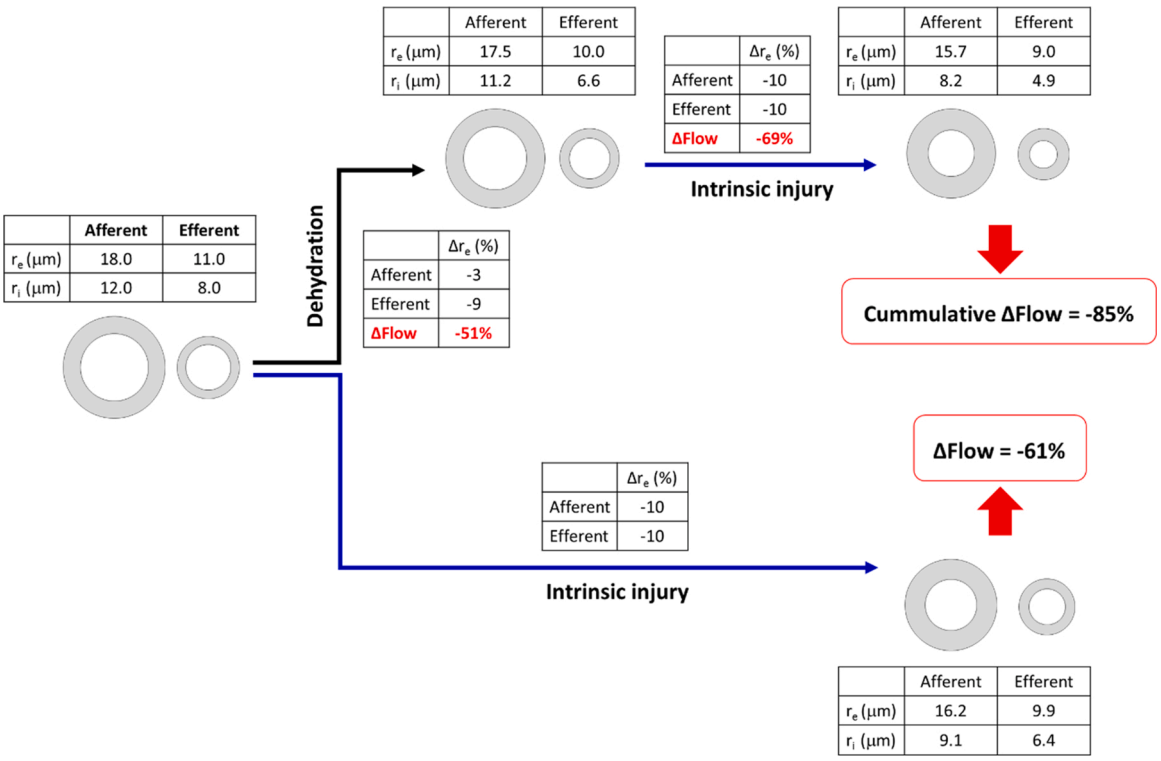

Fig. 7. Exemplifying case on the effect of intrinsic AKI on RBF in normohydrated and dehydrated individuals. r_e, external (outer) radius. r_i, internal (inner) radius.

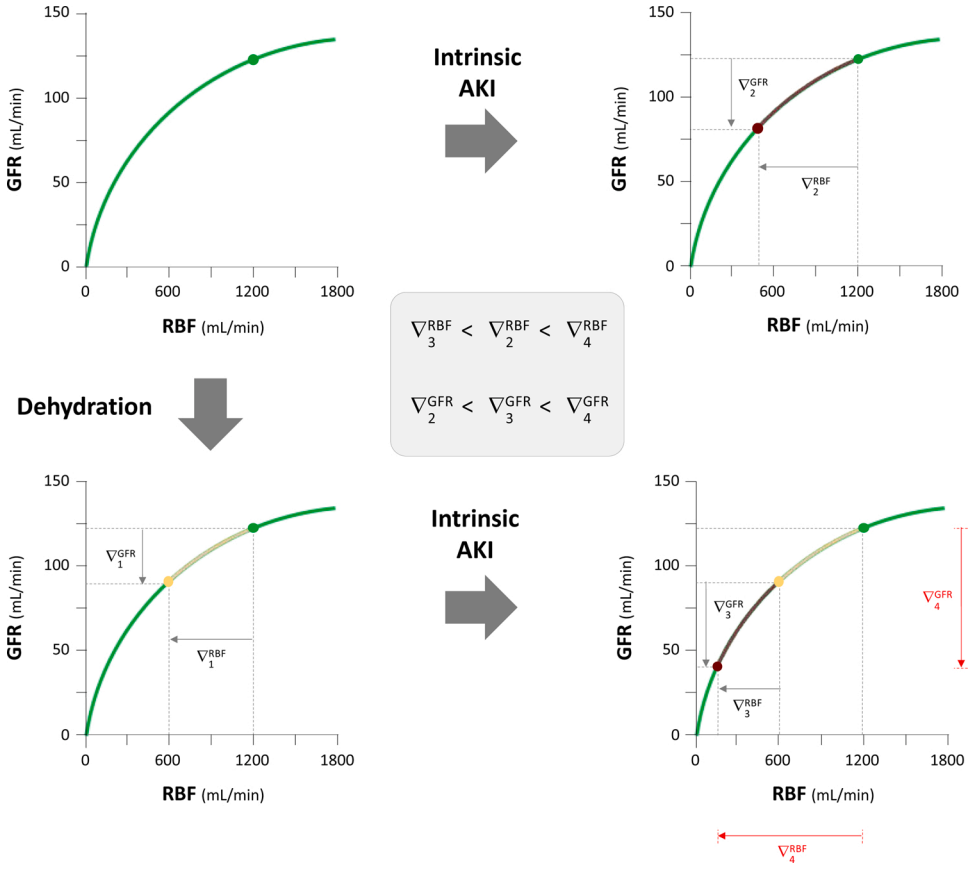

Fig. 8. Translation to GFR of the RBF reductions produced by intrinsic AKI (as from Fig. 9) in normohydrated and dehydrated individuals, illustrating that the amplification effect of dehydration. Green dots show the point of normal renal function in the RBF-GFR relationship (i.e., the starting point for intrinsic AKI in normohydrated individuals). Yellow dots represent the conditions reset by dehydration (i.e., the starting point for intrinsic AKI in dehydrated individuals). Brown dots mark the result of intrinsic AKI in both conditions. GFR, glomerular filtration rate. RBF, renal blood flow.

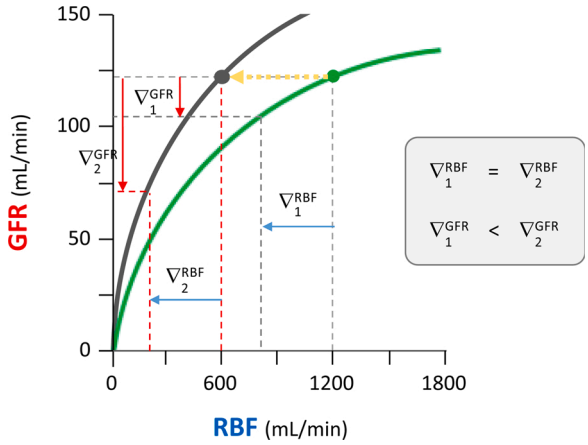

Fig. 9. Graphical depiction of the effect of RBF reduction under normohydrated and dehydrated conditions with preserved GFR. A given reduction in RBF causes a more pronounced effect on GFR in dehydrated individuals. The green dot shows the point of normal renal function in the RBF-GFR relationship (i.e., the starting point for intrinsic AKI in normohydrated individuals). The grey dot represents the reset condition produced by dehydration with preserved GFR (i.e., the starting point for intrinsic AKI in dehydrated individuals in whom GFR is maintained). GFR, glomerular filtration rate. RBF, renal blood flow. The yellow dashed arrow represents the effect of dehydration with maintained GFR.

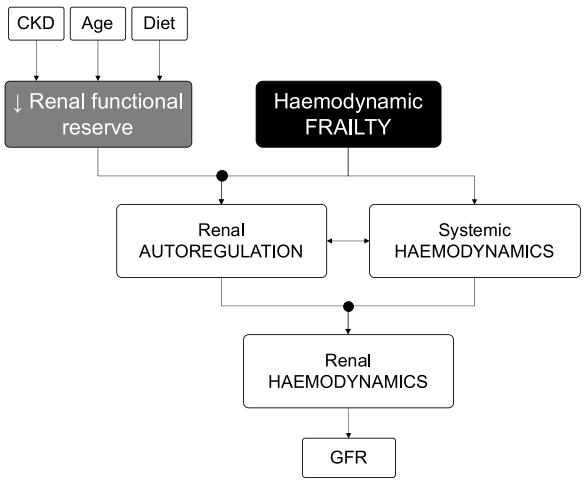

Fig. 10. Interaction of haemodynamic frailty with the loss of renal functional reserve in the generation of predisposition to AKI.

radius (i.e., the Poiseuille relationship), achieving the same proportional reduction in flow requires a significantly larger reduction in radius from a more contracted than from a more dilated state. This would partially offset the amplification of the effect of dehydration, as AKI would act on more contracted arterioles in dehydrated individuals. However, as the vascular 'geometric amplifier' (Folkow, 1987, 2000) works in the opposite direction it will augment the reduction in the internal radius in arteries with a higher wall-to-lumen ratio during contraction (Fig. 6).

Altogether, the composite effect of the RBF-GFR relation, the lumen size (i.e., internal radius)-RBF relation and the geometric amplifier derived from dehydration amplifies the effect of intrinsic AKI-inducing stimuli on GFR decline. This is exemplified in Figs. 7 and 8. Intrinsic injury is induced in kidneys during dehydration and under normal conditions, in which the effect of afferent and efferent tone on blood flow is illustrated. For the same injury (i.e., same percentage reduction in external radius, meaning same percentage contraction of external media wall cells), a further overall reduction in renal blood flow is seen in dehydrated kidneys, despite the specific effect of AKI on RBF being smaller in dehydrated animals. This smaller effect in RBF nevertheless causes a deeper drop in GFR, as it starts from a steeper region of the RBF-GFR relationship (Fig. 8). Even if the GFR is maintained during dehydration, the reduction in RBF still magnifies AKI (Fig. 9). AKI magnification increases with the intensity of dehydration or, more accurately, with the reduction in RBF produced by dehydration. Additionally, increased blood viscosity (i.e., as indicated by increased osmolarity and haematocrit potentially resulting from dehydration) would also amplify the reduction in RBF caused by a given reduction of internal radii, by a factor equal to the increase in viscosity.

Combined with the effect of dehydration, the overall effect of AKI is significantly magnified. Intrinsic injury uncovers, leverages and accrues to the concurrent effect of dehydration resulting in damage amplification. This is especially relevant from a clinical perspective, because an initial GFR reduction caused by dehydration may often develop unnoticed, unless the GFR reduction is sufficiently strong. In fact, significant reductions in GFR (over 50 %) are needed for serum creatinine (the internationally recognized standard and most frequently used biomarker of renal function impairment) to increase and exceed the normality range (Moledina and Parikh, 2018; Makris and Spanou, 2016b; Ronco et al., 2012). Consequently, intrinsic injuries will cause a more severe AKI in dehydrated than in normohydrated individuals, in terms of GFR reductions, for the same level of parenchymal damage inflicted. Moreover, injuries causing no damage in normohydrated individuals might cause an overt AKI in dehydrated individuals.

8. Loss of renal functional reserve and HDF interact to potentiate vulnerability to AKI

Renal functional reserve (RFR) represents the capacity of the kidneys to increase GFR in response to certain physiological or pathological stimuli or conditions (Sharma et al., 2014; Palsson and Waikar, 2018). This has led to the concept that, in chronic and acute pathological states, RFR is recruited to maintain renal function before basal GFR begins to decrease (Jufar et al., 2020). In the pathological continuum, a subclinical reduction of RFR precedes the decline in GFR and is considered a sign of established disease, and a state of vulnerability. Kidneys with exhausted or very limited RFR can no longer buffer additional insults and are thus more susceptible to AKI. A reduced RFR is a predictive factor for AKI risk independent of hydration status. RFR is articulated through afferent (and efferent) vasodilation and involves an increment in RBF. By affecting renal haemodynamics and autoregulation, RFR status is also a major element interacting with HDF to determine susceptibility to AKI (Fig. 10). Individuals with reduced RFR as a consequence of age-related decline in functioning nephron number and impaired renovascular reactivity, such as the aged and CKD patients, are thus more vulnerable to HDF-inducing conditions. The capacity for RFR to sustain GFR is reduced in the elderly as nephrons are progressively lost (Sharma et al., 2014; Ciro et al., 2007; Fuiano et al., 2001). However, RFR can be relatively well preserved in aged subjects, in those that maintain high GFR levels (i.e., $>$ 100 mL/min/1.73 m^2) (Fliser et al., 1993), suggesting that it is nephron loss, and not age-related mechanistic wearing, the cause of RFR reduction.

9. Perspectives

We have highlighted how a relative inability to effectively sustain water balance represents a central aspect of HDF in the elderly which can predispose or sensitize individuals to pre-renal and intrinsic AKI. Accordingly, accurate assessment of hydration status would provide a unique window of opportunity for patient-centred precision and preventive (P4) medicine aimed at attenuating HDF (Morley and Vellas, 2017). Pre-emptive diagnosis of risk is a tool for double edged intervention. On the one hand, stressors (i.e., drugs, toxins, medical procedures, life conditions and habits, etc.) may be avoided in high-risk patients, in order to prevent disease. On the other hand, less frequently recognized but equally important, convenient stressors may be allowed

with confidence in well hydrated and haemodynamically stable patients. These convenient stressors, such as drugs or procedures may provide patients with optimal handling and enhanced quality of life. Individual evaluation of hydration as a critical element of HDF is a direct method to estimate risk in a truly personalized manner, as complementary to scoring risk factors (i.e., comorbidities), which basically utilize population-based statistics. New methods and tests to easily and cost-effectively evaluate HDF and prospectively assess the benefits of doing so with regards to mitigating the risk of AKI in the elderly and other at-risk populations is merited.

Funding

CD is supported by the British Heart Foundation Centre of Excellence grant (ref. RE/18/6/34217). ATL is supported in part by the Canada 150 Research Chair program and by the Natural Sciences and Engineering Research Council of Canada, via a Discovery award. CM-S and FJL-H are supported by grants from the Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, Spain [refs. PI18/00996 and RETICSRD016/0009/0025 (REDINREN)].

References

Abbott, F.V., Fraser, M.I., 1998. Use and abuse of over-the-counter analgesic agents. J. Psychiatry Neurosci. 23 (1), 13–34.
Abdel-Kader, K., Palevsky, P.M., 2009. Acute kidney injury in the elderly. Clin. Geriatr. Med. 25 (3), 331–358. https://doi.org/10.1016/j.cger.2009.04.001.
Ali, B.H., Bashir, A.K., El Mugamer, I.T., Tanira, M.O.M., 1996. Gentamicin nephrotoxicity in the rat: influence of age and diabetes mellitus. Hum. Exp. Toxicol. 15 (1), 51–55. https://doi.org/10.1177/096032719601500109.
Ali, T.Z., Khan, I., Simpson, W., et al., 2007. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J. Am. Soc. Nephrol. 18 (4), 1292–1298. https://doi.org/10.1681/ASN.2006070756.
Andrianova, N.V., Jankauskas, S.S., Zorova, L.D., et al., 2018. Mechanisms of age-dependent loss of dietary restriction protective effects in acute kidney injury. Cells 7 (10), 178. https://doi.org/10.3390/cells7100178.
Artiles-Armas, M., Roque-Castellano, C., Conde-Martel, A., Marchena-Gómez, J., 2019. The comprehensive complication index is related to frailty in elderly surgical patients. J. Surg. Res. 244, 218–224. https://doi.org/10.1016/j.jss.2019.06.011.
Beauchamp, D., Gourde, P., Theriault, G., Bergeron, M.G., 1992. Age-dependent gentamicin experimental nephrotoxicity. J. Pharmacol. Exp. Ther. 260 (2), 444–449. Accessed August 29, 2020. https://pubmed.ncbi.nlm.nih.gov/1738093/.
Bonventre, J.V., 2007. Pathophysiology of acute kidney injury: roles of potential inhibitors of inflammation. In: Acute Kidney Injury, Vol 156. KARGER, pp. 39–46. https://doi.org/10.1159/000102069.
Boyd, I.W., Mathew, T.H., Thomas, M.C., 2000. Cox-2 inhibitors and renal failure: The triple whammy revisited. Med. J. Aust. 173 (5), 274. https://doi.org/10.5694/j.1326-5377.2000.tb125642.x.
Camin, R.M.G., Cols, M., Chevarria, J.L., et al., 2015. Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDS: "The Triple Whammy. Nefrologia 35 (2), 197–206. https://doi.org/10.1016/j.nefro.2015.05.021.
Caplan, L.R., Ka, S.W., Gao, S., Hennerici, M.G., 2006. Is hypoperfusion an important cause of strokes? If so, how? Cerebrovasc. Dis. 21 (3), 145–153. https://doi.org/10.1159/000090791.
Chumlea, W.C., Guo, S.S., Zeller, C.M., Reo, N.V., Siervogel, R.M., 1999. Total body water data for white adults 18 to 64 years of age: the Fels Longitudinal Study. Kidney Int. 56 (1), 244–252. https://doi.org/10.1046/j.1523-1755.1999.00532.x.
Ciro, E., Plati, A.R., Mazzullo, T., et al., 2007. Renal function and functional reserve in healthy elderly individuals. J. Nephrol. 20, 617–625.
Deng, Y., Wang, L., Sun, X., et al., 2018. Association between cerebral hypoperfusion and cognitive impairment in patients with chronic vertebra-basilar stenosis. Front. Psychiatry 9, 455. https://doi.org/10.3389/fpsyt.2018.00455.
Desanti De Oliveira, B., Xu, K., Shen, T.H., et al., 2019. Molecular nephrology: types of acute tubular injury. Nat. Rev. Nephrol. 15 (10), 599–612. https://doi.org/10.1038/s41581-019-0184-x.
Donatelli, N.S., Somes, J., 2017. What is Frailty? J. Emerg. Nurs. 43 (3), 272–274. https://doi.org/10.1016/j.jen.2017.03.003.
Dos Santos Moreira, M.C., Naves, L.M., Marques, S.M., et al., 2017. Neuronal circuits involved in osmotic challenges. Physiol. Res. 66 (3), 411–423. https://doi.org/10.33549/physiolres.933373.
Druml, W., 2014. Systemic consequences of acute kidney injury. Curr. Opin. Crit. Care 20 (6), 613–619. https://doi.org/10.1097/MCC.0000000000000150.
Dworkin, L.D., Ichikawa, I., Brenner, B.M., 1983. Hormonal modulation of glomerular function. Am. J. Physiol. - Ren Fluid Electrolyte Physiol 13 (2). https://doi.org/10.1152/ajprenal.1983.244.2.f95.
Faber, S.J., Scherpbier, N.D., Peters, H.J.G., Uijen, A.A., 2019. Preventing acute kidney injury in high-risk patients by temporarily discontinuing medication - an observational study in general practice. BMC Nephrol. 20 (1), 449. https://doi.org/10.1186/s12882-019-1636-z.
Feest, T.G., Round, A., Hamad, S., 1993. Incidence of severe acute renal failure in adults: results of a community based study. Br. Med. J. 306 (6876), 481–483. https://doi.org/10.1136/bmj.306.6876.481.
Fliser, D., Zeier, M., Nowack, R., Ritz, E., 1993. Renal functional reserve in healthy elderly subjects. J. Am. Soc. Nephrol. 3 (7), 1371–1377.
Folkow, B., 1987. Structure and function of the arteries in hypertension. Am. Heart J. 114 (4 PART 2), 938–948. https://doi.org/10.1016/0002-8703(87)90591-6.
Folkow, B., 2000. The debate on the "amplifier hypothesis" - some comments. J. Hypertens. 18 (4), 375–378. https://doi.org/10.1097/00004872-200018040-00003.
Fournier, J.P., Sommet, A., Durrieu, G., Poutrain, J.C., Lapeyre-Mestre, M., Montastruc, J.L., 2014. More on the "triple Whammy": antihypertensive drugs, non-steroidal anti-inflammatory agents and acute kidney injury-a case/non-case study in the French pharmacovigilance database. Ren. Fail. 36 (7), 1166–1168. https://doi.org/10.3109/0886022X.2014.917943.
Frangeskou, M., Lopez-Valcarcel, B., Serra-Majem, L., 2015. Dehydration in the elderly: a review focused on economic burden. J. Nutr. Health Aging 19 (6), 619–627. https://doi.org/10.1007/s12603-015-0491-2.
Fried, L.P., Tangen, C.M., Walston, J., et al., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 56 (3), M146–M157. https://doi.org/10.1093/gerona/56.3.m146.
Fuiano, G., Sund, S., Mazza, G., et al., 2001. Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. Kidney Int. 59 (3), 1052–1058. https://doi.org/10.1046/j.1523-1755.2001.0590031052.x.
Giebisch, G., Windhager, E., 2009. Glomerular filtration and renal blood flow. In: Boron, Walter F., Boulpaep, Emile L. (Eds.), Medical Physiology A Cellular and Molecular Approach, 2nd ed. Saunders/Elsevier, Philadelphia, PA, p. 767.
Glassford, N.J., Bellomo, R., 2017. The role of Oliguria and the absence of fluid administration and balance information in illness severity scores. Korean J. Crit. Care Med. 32 (2), 106–123. https://doi.org/10.4266/kjccm.2017.00192.
Groeneveld, A.B.J., Tran, D.D., Van der Meulen, J., Nauta, J.J.P., Thijs, L.G., 1991. Acute renal failure in the medical intensive care unit: predisposing, complicating factors and outcome. Nephron 59 (4), 602–610. https://doi.org/10.1159/000186651.
Heerdink, E.R., Leufkens, H.G., Herings, R.M.C., Ottervanger, J.P., Stricker, B.H.C., Bakker, A., 1998. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch. Intern. Med. 158 (10), 1108–1112. https://doi.org/10.1001/archinte.158.10.1108.
Hope, A., Tyssebotn, I., 1983. The effect of water deprivation on local renal blood flow and filtration in the laboratory rat. Circ. Shock 11 (2), 175–186. Accessed August 29, 2020. https://pubmed.ncbi.nlm.nih.gov/6640859/.
Hoste, E.A.J., Bagshaw, S.M., Bellomo, R., et al., 2015. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 41 (8), 1411–1423. https://doi.org/10.1007/s00134-015-3934-7.
Hoste, E.A.J., Kellum, J.A., Selby, N.M., et al., 2018. Global epidemiology and outcomes of acute kidney injury. Nat. Rev. Nephrol. 14 (10), 607–625. https://doi.org/10.1038/s41581-018-0052-0.
Inouye, S., Niizato, T., Komiya, I., Yuda, Y., Yamada, Y., 1982. Mode of protective action of fosfomycin against dibekacin-induced nephrotoxicity in the dehydrated rats. J. Pharmacobiodyn. 5 (12), 941–950. https://doi.org/10.1248/bpb1978.5.941.
Johnson, R.J., Wesseling, C., Newman, L.S., 2019. Chronic kidney disease of unknown cause in agricultural communities. N. Engl. J. Med. 380 (19), 1843–1852. https://doi.org/10.1056/nejmra1813869.
Jufar, A.H., Lankadeva, Y.R., May, C.N., Cochrane, A.D., Bellomo, R., Evans, R.G., 2020. Renal functional reserve: from physiological phenomenon to clinical biomarker and beyond. Am. J. Physiol. – Regul. Integr. Comp. Physiol. 319 (6), R690–R702. https://doi.org/10.1152/AJPREGU.00237.2020.
Kaehr, E., Visvanathan, R., Malmstrom, T.K., Morley, J.E., 2015. Frailty in nursing homes: the FRAIL-NH scale. J. Am. Med. Dir. Assoc. 16 (2), 87–89. https://doi.org/10.1016/j.jamda.2014.12.002.
Kao, C.C., Yang, W.S., Fang, J.T., Liu, K.D., Wu, V.C., 2019. Remote organ failure in acute kidney injury. J. Formos. Med. Assoc. 118 (5), 859–866. https://doi.org/10.1016/j.jfma.2018.04.005.
Kayser-Jones, J., Schell, E.S., Porter, C., Barbaccia, J.C., Shaw, H., 1999. Factors contributing to dehydration in nursing homes: inadequate staffing and lack of professional supervision. J. Am. Geriatr. Soc. 47 (10), 1187–1194. https://doi.org/10.1111/j.1532-5415.1999.tb05198.x.
KDIGO, 2012. Clinical practice guideline for acute kidney injury. Kidney Int. Suppl. 2, 124–138.
Kellum, J.A., Lameire, N., Aspelin, P., et al., 2013. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit. Care 17 (1), 204. https://doi.org/10.1186/cc11454.
Khan, S., Loi, V., Rosner, M.H., 2017. Drug-induced kidney injury in the elderly. Drugs Aging 34 (10), 729–741. https://doi.org/10.1007/s40266-017-0484-4.
Kirkebø, A., Tyssebotn, I., 1977. Effect of dehydration on renal blood flow in dog. Acta Physiol. Scand. 101 (3), 257–263. https://doi.org/10.1111/j.1748-1716.1977.tb06006.x.
Kishi, T., Hirooka, Y., 2013. Sympathoexcitation associated with Renin-Angiotensin system in metabolic syndrome. Int. J. Hypertens. 2013, 406897. https://doi.org/10.1155/2013/406897.
Kreimeier, U., 2000. Pathophysiology of fluid imbalance. Crit Care 4 (SUPPL. 2), S3. https://doi.org/10.1186/cc968.
Kusaka, J., Koga, H., Hagiwara, S., Hasegawa, A., Kudo, K., Noguchi, T., 2012. Age-dependent responses to renal ischemia-reperfusion injury. J. Surg. Res. 172 (1), 153–158. https://doi.org/10.1016/j.jss.2010.08.034.

Lacey, J., Corbett, J., Forni, L., et al., 2019. A multidisciplinary consensus on dehydration: definitions, diagnostic methods and clinical implications. Ann. Med. 51 (3–4), 232–251. https://doi.org/10.1080/07853890.2019.1628352.
Lapi, F., Azoulay, L., Yin, H., Nessim, S.J., Suissa, S., 2013. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 346 (7890). https://doi.org/10.1136/bmj.e8525 e8525.
Lecompte, J., Dumont, L., Hill, J., du Souich, P., Lelorier, J., 1981. Effect of water deprivation and rehydration on gentamicin disposition in the rat. J. Pharmacol. Exp. Ther. 218 (1), 231–236. Accessed August 26, 2020. https://pubmed.ncbi.nlm.nih.gov/7241381/.
Lind, K.E., Raban, M.Z., Georgiou, A., Westbrook, J.I., 2019. NSAID use among residents in 68 residential aged care facilities 2014 to 2017: an analysis of duration, concomitant medication use, and high-risk conditions. Pharmacoepidemiol. Drug Saf. 28 (11), 1480–1488. https://doi.org/10.1002/pds.4866.
Liu, K., yun, Zhou L., yang, Li D., et al., 2019. A novel rat model of contrast-induced nephropathy based on dehydration. J. Pharmacol. Sci. 141 (1), 49–55. https://doi.org/10.1016/j.jphs.2019.09.003.
Liu, H., Zhang, J., 2012. Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. Int. J. Neurosci. 122 (9), 494–499. https://doi.org/10.3109/00207454.2012.686543.
Loboz, K.K., Shenfield, G.M., 2005. Drug combinations and impaired renal function - the "triple whammy. Br. J. Clin. Pharmacol. 59 (2), 239–243. https://doi.org/10.1111/j.0306-5251.2004.2188.x.
Lopez-Novoa, J.M., Quiros, Y., Vicente, L., Morales, A.I., Lopez-Hernandez, F.J., 2011. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 79 (1), 33–45. https://doi.org/10.1038/ki.2010.337.
Lorenzo, I., Serra-Prat, M., Yébenes, J.C., 2019. The role of water homeostasis in muscle function and frailty: a review. Nutrients 11 (8). https://doi.org/10.3390/nu11081857.
Lucas, G.N.C., Leitão, A.C.C., Alencar, R.L., Xavier, R.M.F., Daher, E.D.F., 2019. Silva Junior GB da. Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. J. Bras. Nefrol. 41 (1), 124–130. https://doi.org/10.1590/2175-8239-JBN-2018-0107.
LZ, R., 2006. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 35 (Suppl 2), ii37–ii41.
MacDonald, T.M., Williams, B., Webb, D.J., et al., 2017. Combination therapy is superior to sequential monotherapy for the initial treatment of hypertension: a double-blind randomized controlled trial. J. Am. Heart Assoc. 6 (11) https://doi.org/10.1161/JAHA.117.006986.
Makris, K., Spanou, L., 2016a. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin. Biochem. Rev. 37 (2), 85–98. Accessed April 12, 2020. http://www.ncbi.nlm.nih.gov/pubmed/28303073.
Makris, K., Spanou, L., 2016b. Acute kidney injury: diagnostic approaches and controversies. Clin. Biochem. Rev. 27 (4), 153–175. Accessed September 9, 2020. https://pubmed.ncbi.nlm.nih.gov/28167845/.
Martinez, F., Deray, G., Dubois, M., et al., 1993. Comparative nephrotoxicity of carboplatin and cisplatin in euvolemic and dehydrated rats. Anticancer Drugs 4 (1), 85–90. https://doi.org/10.1097/00001813-199302000-00011.
Mitnitski, A.B., Mogilner, A.J., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 1, 323–336. https://doi.org/10.1100/tsw.2001.58.
Moledina, D.G., Parikh, C.R., 2018. Phenotyping of acute kidney injury: beyond serum creatinine. Semin. Nephrol. 38 (1), 3–11. https://doi.org/10.1016/j.semnephrol.2017.09.002.
Moore, K.E., Murtaugh, R.J., 2001. Pathophysiologic characteristics of hypovolemic shock. Vet. Clin. North Am. Small Anim. Pract. 31 (6), 1115–1128. https://doi.org/10.1016/s0195-5616(01)50095-9.
Morley, J.E., Vellas, B., 2017. Patient-centered (P4) medicine and the older person. J. Am. Med. Dir. Assoc. 18 (6), 455–459. https://doi.org/10.1016/j.jamda.2017.04.001.
Mullens, W., Nijst, P., 2016. Cardiac Output and Renal Dysfunction Definitely More Than Impaired Flow. J. Am. Coll. Cardiol. 67 (19), 2209–2212. https://doi.org/10.1016/j.jacc.2016.03.537.
Obatomi, D.K., Plummer, D.T., 1993. Influence of hydration states on the acute nephrotoxic effect of gentamicin in the rat. Toxicology 80 (2-3), 141–152. https://doi.org/10.1016/0300-483X(93)90177-T.
Onuigbo, M.A., Agbasi, N., 2014. "Quadruple whammy"- a preventable newly described syndrome of post-operative AKI in CKD II and CKD III patients on combination "triple whammy" medications: a Mayo Clinic Health System, Eau Claire, Wisconsin experience. Niger. J. Clin. Pract. 17 (5), 649–654. https://doi.org/10.4103/1119-3077.141440.
Ostchega, Y., Fryar, C.D., Nwankwo, T., Nguyen, D.T., 2020. Hypertension prevalence among adults aged 18 and over: United States, 2017–2018. NCHS Data Brief, No 364. Hyattsville, MD.
Palsson, R., Waikar, S.S., 2018. Renal functional reserve revisited. Adv. Chronic Kidney Dis. 25 (3), e1–e8. https://doi.org/10.1053/j.ackd.2018.03.001.
Partridge, L., Deelen, J., Slagboom, P.E., 2018. Facing up to the global challenges of ageing. Nature 561 (7721), 45–56. https://doi.org/10.1038/s41586-018-0457-8.
Pascual, J., Liaño, F., Marcén, R., Naya, M.T., Orte, L., Ortuño, J., 1990. Incidence and prognosis of acute renal failure in older patients. J. Am. Geriatr. Soc. 38 (1), 25–30. https://doi.org/10.1111/j.1532-5415.1990.tb01592.x.
Patzer, L., 2008. Nephrotoxicity as a cause of acute kidney injury in children. Pediatr. Nephrol. 23 (12), 2159–2173. https://doi.org/10.1007/s00467-007-0721-x.
Pezeshki, Z., Maleki, M., Talebi, A., Nematbakhsh, M., 2017. Age and gender related renal side effects of cisplatin in animal model. Asian Pac. J. Cancer Prev. 18 (6), 1703–1705. https://doi.org/10.22034/APJCP.2017.18.6.1703.
Population structure and ageing. https://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing. Accessed April 5, 2020.
Prieto-García, L., Pericacho, M., Sancho-Martínez, S.M., et al., 2016a. Mechanisms of triple whammy acute kidney injury. Pharmacol. Ther. 167, 132–145. https://doi.org/10.1016/j.pharmthera.2016.07.011.
Prieto-García, L., Pericacho, M., Sancho-Martínez, S.M., et al., 2016b. Mechanisms of triple whammy acute kidney injury. Pharmacol. Ther. 167, 132–145. https://doi.org/10.1016/j.pharmthera.2016.07.011.
Prieto-García, L., Vicente-Vicente, L., Blanco-Gozalo, V., et al., 2020. Pathophysiological mechanisms underlying a rat model of triple whammy acute kidney injury. Lab. Invest. (July) https://doi.org/10.1038/s41374-020-0473-9.
Provoost, A.P., Adejuyigbe, O., Wolff, E.D., 1985. Nephrotoxicity of aminoglycosides in young and adult rats. Pediatr. Res. 19 (11), 1191–1196. https://doi.org/10.1203/00006450-198511000-00016.
Ritt, M., Jäger, J., Ritt, J.I., Sieber, C.C., Gaßmann, K.-G., 2017. Operationalizing a frailty index using routine blood and urine tests. Clin. Interv. Aging 12, 1029–1040. https://doi.org/10.2147/CIA.S131987.
Ritz, P., Vol, S., Berrut, G., Tack, I., Arnaud, M.J., Tichet, J., 2008. Influence of gender and body composition on hydration and body water spaces. Clin. Nutr. 27 (5), 740–746. https://doi.org/10.1016/j.clnu.2008.07.010.
Ronco, C., Kellum, J.A., Haase, M., 2012. Subclinical AKI is still AKI. Crit Care 16 (3). https://doi.org/10.1186/cc11240.
Rubenstein, L.Z., 2006. Strategy to prevent falls and fractures in Ireland' s ageing population introduction and overview of approach. Age Ageing 35 (June (Suppl 2)), ii37–ii41. https://doi.org/10.1093/ageing/afl084, 2008.
Schor, N., Ichikawa, I., Brenner, B.M., 1981. Mechanisms of action of various hormones and vasoactive substances on glomerular ultrafiltration in the rat. Kidney Int. 20 (4), 442–451. https://doi.org/10.1038/ki.1981.160.
Seifter, J.L., Chang, H.Y., 2017. Extracellular acid-base balance and ion transport between body fluid compartments. Physiology 32 (5), 367–379. https://doi.org/10.1152/physiol.00007.2017.
Sharma, A., Mucino, M.J., Ronco, C., 2014. Renal functional reserve and renal recovery after acute kidney injury. In: Karger AG, S. (Ed.), Nephron - Clinical Practice, Vol 127, pp. 94–100. https://doi.org/10.1159/000363721.
Silver, S.A., Chertow, G.M., 2017. The economic consequences of acute kidney injury. Nephron 137 (4), 297–301. https://doi.org/10.1159/000475607.
Singbartl, K., Joannidis, M., 2015. Short-term effects of acute kidney injury. Crit. Care Clin. 31 (4), 751–762. https://doi.org/10.1016/j.ccc.2015.06.010.
Singbartl, K., Kellum, J.A., 2012. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 81 (9), 819–825. https://doi.org/10.1038/ki.2011.339.
Tarloff, J.B., Khairallah, E.A., Cohen, S.D., Goldstein, R.S., 1996. Sex- and age-dependent acetaminophen hepato- and nephrotoxicity in Sprague-Dawley rats: role of tissue accumulation, nonprotein sulfhydryl depletion, and covalent binding. Fundam. Appl. Toxicol. 30 (1), 13–22. https://doi.org/10.1006/faat.1996.0038.
Terano, C., Ishikura, K., Miura, M., et al., 2016. Incidence of and risk factors for severe acute kidney injury in children with heart failure treated with renin–angiotensin system inhibitors. Eur. J. Pediatr. 175 (5), 631–637. https://doi.org/10.1007/s00431-015-2680-8.
Thomas, M.C., 2000. Diuretics, ACE inhibitors and NSAIDs - The triple whammy. Med. J. Aust. 172 (4), 184–185. https://doi.org/10.5694/j.1326-5377.2000.tb125548.x.
Thornton, S.N., 2010. Thirst and hydration: physiology and consequences of dysfunction. Physiol. Behav. 100 (1), 15–21. https://doi.org/10.1016/j.physbeh.2010.02.026.
Traber, D.L., Meyer, J., Traber, L.D., 1993. Cardiac function during hypovolemia. Pathophysiology of Shock, Sepsis, and Organ Failure. Springer, Berlin Heidelberg, pp. 194–199. https://doi.org/10.1007/978-3-642-76736-4_14.
Turgutalp, K., Bardak, S., Horoz, M., Helvacı, I., Demir, S., Kiykim, A.A., 2017. Clinical outcomes of acute kidney injury developing outside the hospital in elderly. Int. Urol. Nephrol. 49 (1), 113–121. https://doi.org/10.1007/s11255-016-1431-8.
Vervaet, B.A., Nast, C.C., Jayasumana, C., et al., 2020. Chronic interstitial nephritis in agricultural communities is a toxin-induced proximal tubular nephropathy. Kidney Int. 97 (2), 350–369. https://doi.org/10.1016/j.kint.2019.11.009.
World population ageing 2019. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf. Accessed April 5, 2020.
Wyler, F., Stalder, G., Kaeslin, M., Hof, R.P., 1983. Hemodynamics in experimental hypernatremic dehydration with special reference to individual organ blood flow in shock and after rehydration. Pediatr. Res. 17 (11), 919–925. https://doi.org/10.1203/00006450-198311000-00017.
Xiao, H., Barber, J., Campbell, E.S., 2004. Economic burden of dehydration among hospitalized elderly patients. Am. J. Health. Syst. Pharm. 61 (23), 2534–2540. https://doi.org/10.1093/ajhp/61.23.2534.
Xue, Q.L., 2011. The frailty syndrome: definition and natural history. Clin. Geriatr. Med. 27 (1), 1–15. https://doi.org/10.1016/j.cger.2010.08.009.
Yokota, L.G., Sampaio, B.M., Rocha, E.P., Balbi, A.L., Prado, I.R.S., Ponce, D., 2018. Acute kidney injury in elderly patients: narrative review on incidence, risk factors, and mortality. Int. J. Nephrol. Renovasc. Dis. 11, 217–224. https://doi.org/10.2147/IJNRD.S170203.
Zhang, X., Donnan, P.T., Bell, S., Guthrie, B., 2017. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC Nephrol. 18 (1) https://doi.org/10.1186/s12882-017-0673-8.