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Energy Dynamics in Chronic Heart Failure, Chronic Kidney Disease & the Cardiorenal Syndrome: A New Causal Paradigm

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INTRODUCTION

Societies across the globe now confront a rising burden of chronic disease on a scale never before seen in history. In recent decades deeply troubling increases in conditions such as the metabolic syndrome, diabetes, obesity, autoimmune disease, and chronic organ syndromes like heart failure (HF), chronic kidney disease (CKD), and non-alcoholic fatty liver have completely erased any putative gains 20th century medical science might have made in the control and prevention of disease.

According to the US Centers for Disease Control, 90% of the $4.1 trillion annual US healthcare expenditures is spent on chronic disease care [1]. There are no effective therapies for these conditions and treatment is by-and-large palliative.

Two of the most prevalent and complex syndromes now challenging medical science are HF and CKD.

First designated by the WHO as an emerging epidemic in 1997, HF continues to spread globally and now afflicts an estimated 64 million people worldwide and about 6-7 million in the US. HF is a debilitating syndrome characterized by functional impairments that impact quality of life and the ability to engage in daily activities. HF is now the leading cause for hospitalization (and re-hospitalization) in people over 60 years of age. Healthcare costs in the US continue to soar and are pegged to reach nearly $70 billion by 2030 [2-4].

CKD is an insidious, progressive disorder affecting about 850 million people worldwide – roughly 10% of the global population. In the US CKD affects about 11-14% of the adult population or about 37 million people. In the last three decades its prevalence has grown by nearly 30%. Many countries are now unable meet rising demand for dialysis treatment. Risk factors include diabetes and hypertension which also continue to escalate. According to the CDC expenditures for CKD in 2019 reached $87.2 billion with an additional $37.3 billion directed to end-stage kidney disease and treatments like dialysis and transplantation [5-6].

The contemporary predicament becomes more dire once one recognizes the failure of 20th century medical scientists to even accurately describe how the heart and kidneys function. The causal models they advanced to explain the functional deteriorations in HF and CKD are now widely recognized to have been wrong. Based on their flawed theories, existing treatments for these conditions are only band-aids that may or may not prevent downstream complications while having little or no effect on the underlying disease process. One cannot discuss the burgeoning epidemic of chronic disease without implicating experimental science.

Of equal concern is the failure of medical scientists to incorporate evidence that runs counter to their encrusted dogma. For 120 years they have clung to their archaic molecular/cellular paradigm, continuing to beat this long-dead horse, even though it fails to explain much of what is encountered in the laboratory or in day-to-day practice. It is said that consciousness always wakes up late. Certainly, this applies to medical science and the epidemic of chronic disease.

In the 1980s experimental evidence emerged that overturned the reigning 20th century model of cardiac function and, furthermore, pointed to the presence of an organized energy field in the blood originating through the contraction and dilation cycles of the heart. And yet, in a manner reminiscent of how, for thirteen centuries, Ptolemaic astronomers continued to explain planetary motion on the basis of their revolution around the earth, scientists persist in their attempts to explain energy dynamics on the basis of cellular and molecular mechanisms. The Ptolemaic system eventually became so convoluted that even astronomers didn't understand it. And once the correct explanation surfaced, geocentric astronomy collapsed into a heap and became a relic of history. Modern medical science seems destined to share the same fate.

In his acclaimed work *The Structure of Scientific Revolutions* (1962) science historian Thomas Kuhn describes the successive rise and fall of scientific paradigms [7]. Given that it is impossible for scientists to know what lies outside their frame of reference, by necessity all scientific theories are provisional and incomplete. Eventually scientists encounter phenomena their knowledge cannot explain necessitating cultivation of new knowledge and revision of spent theories. The entire history of experimental science consists of a series of conceptual boom-and-bust cycles.

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The epidemic of chronic disease has laid bare the flaws of the cellular/molecular perspective as well as the failures of experimental scientists to make proper adjudications. As in the case of geocentric astronomy, once evidence emerges that contradicts stated assumptions, a scientific theory is rendered invalid regardless of whether or not the science community chooses to accept it. We call such disruptive and revolutionary events a 'paradigm collapse'. In such circumstances the only option for scientists is to either acquiesce to reality or engage in denial and perpetuate what then becomes a collectively-shared delusion.

In this paper we examine HF and CKD through the lens of a new causal paradigm: as a conjoined energy deficiency syndrome whose progression is governed by impaired energy generation by the cardiovascular system leading to subsequent deterioration of blood energy dynamics. Due to the immense complexity of this topic our intention is not to go into unnecessary and laborious detail on specific cellular and molecular aspects of the syndromes but, instead, to use illustrative examples to establish overarching principles and to highlight the connection between the deteriorating energy field and *all* resultant aberrations. Indeed, once the energy dynamics are recognized cellular and molecular descriptions become superfluous. Our use of the term 'causal' is meant to imply that future breakthroughs in the treatment (and potential reversal) of these complex disease states necessarily entails recognition and correction of underlying energy deficits.

ENERGY FIELD DYNAMICS

One of the most significant turn of events in 20th century experimental medicine took place in the 1980s without most medical scientists even suspecting that the ground beneath their feet had begun to crumble. For most of the 20th century scientists conceived the heart to function in the manner of a mechanical pump, with blood propelled forward through the arteries during the systolic phase of the cardiac cycle. The diastolic phase of the cycle, on the other hand, was said to represent a period of passive relaxation.

This concept was originally advanced by William Harvey in 1628 in his seminal work *On The Motions of the Heart* in which he describes his discovery of the circulation of the blood [8]. Harvey's model was uncritically accepted by English physiologist Ernest Starling in the early 20th century and thereafter became dogma. The problem with the Harvey-Starling concept of cardiac function is that it doesn't explain how blood returns from the veins to the right side of the heart – just a small detail scientists overlooked for 350 years.

In the early 1980s physiologists discovered negative intraventricular pressures, i.e., a suction force, in the early diastolic phase indicating that diastole was not a time of passive relaxation but, instead, a period in which blood was actively drawn forward through the veins into the ventricular chamber [9-12]. In order for the ventricle to pump blood through the arteries it must first contain blood. A handful of studies later found the presence of spiral flow currents in arteries and veins which can only be explained on the basis of a suctional force [13-26].

By the late 1980s numerous studies affirmed the primacy of diastole in the cardiac cycle and, intriguingly, found that impaired outward movement of the ventricular and arterial walls, aka 'diastolic dysfunction' was the defining feature of a wide range of chronic conditions including hypertension, diabetes, obesity, depression, cancers, autoimmune diseases, as well as organ failure syndromes like HF and CKD [27, 28].

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During its cycles of contraction and dilation the heart generates an electromagnetic field which is responsible for diastolic expansion. In a series of earlier articles, we describe mechanisms at play in this phenomenon [29-31]. For over a century it has been recognized that the heart and blood contain large iron stores and, while iron's role in various chemical reactions has been extensively detailed, there has been little discussion as to whether it might play a broader role.

Equally the question arises as to the function served by nerves that course over the surface of the heart. Cardiologists claim these nerves cause the heart to contract but is this correct? As early as the 2nd century AD Roman physician Galen observed in animal experiments that when the heart was cut out and placed in a fluid bath it continued to dilate and contract, what is called cardiac automaticity. By the same token, transplanted hearts continue to function in recipients even though nerve conduction has been interrupted.

What happens during systolic contraction of the ventricle is identical to what happens during the induction of an external magnetic field by electrification of ferrous objects. As the ventricle contracts and iron stores are brought into closer apposition iron nuclei in the heart muscle and blood align and process synchronously on the basis of field interactions. Electrical potentials in the nerves saturate the field and induce formation of a three-dimensional magnetic field in the ventricular chamber leading to its expansion. Blood-borne energy dynamics also account for the phenomenon known as ischemic preconditioning (PC).

In 1986 Charles Murry et al., seeking to elucidate mechanisms at play in heart attack, tested whether intermittently reopening the coronary arteries to allow for brief return of blood flow altered the course of cellular injury [32]. In a control group of dogs, a coronary artery was clamped for 40 minutes to assess the extent of infarct damage. Another group underwent a series of four 5-minute arterial occlusions interrupted by 5-minute intervals of reperfusion. Afterward the artery was clamped for 40 minutes. To their complete surprise, animals that received PC pulses had only about 25% of damage as the control group.

The protection afforded by PC has been substantiated in many studies. When the PC sequence is applied prior to a prolonged ischemic episode a period of protection ensues that lasts about 2-3h during which ischemia-mediated damage is markedly reduced. Biochemical analysis suggests that PC slows the rate of ATP consumption, lactate accumulation, and development of tissue acidosis. Interestingly, diastolic function is preserved and the myocardium becomes resistant to potentially lethal arrhythmias. Such phenomena can only be explained on the basis of an influx of energy into the cardiovascular system [33-42].

A 1993 study found that PC pulses applied to one vascular territory of the heart protected the rest of the heart from prolonged arterial occlusion [43]. Several years later another study found reduction in myocardial infarct size in rabbits after administration of PC pulses to skeletal muscle [44]. Reports soon followed describing protection in organs besides the heart after PC pulses in distant vascular territories. Remote PC effects involving brain, liver, intestines, kidneys, stomach and lungs were described [45-58].

The PC response originates in the blood and spreads throughout the body. PC pulses applied to any vascular bed confer systemic resistance to prolonged ischemia. Remote PC induced by serial inflation-deflation of a blood pressure cuff in the extremities is now used prior to surgical procedures to limit operative and postoperative injury [59]. Reports suggest beneficial effects are transferable from one animal to another by

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transfusion of blood or bodily fluids [60-62]. It became recognized that the PC response could be induced by different means other than ischemia: hyperthermia, exercise, cardiac pacing, ethanol, volatile anesthetics, and a host of others including ozone [63-81].

A 1996 study ascribing a complex temporal signature to the PC phenomenon added another spin to the evolving picture [82]. The initial period of heightened resistance to ischemic injury disappears after about 2-3h but then protective effects recur in echo-like fashion about 24h later and persist for up to 48-72h; this is called the second window of protection. Researchers remain baffled as to its basis [83, 84]. As effects are associated with appearance of different mediator substances in the blood it appears to involve gene expression.

PC comprises two opposing aspects: the immediate effect of the injurious agent and a protective counter-response in the blood to mitigate its impact. A dramatic example of the PC effect can be seen in the case of ozone, perhaps one of the most powerful PC agents yet discovered. We have documented its effects in previous papers. The protective response is mediated by red blood cells (RBCs).

RBCs are the first to experience the oxidative effects of ozone and to mount a response. Upon contact with ozonated fluids in the blood, RBCs undergo a transient dose-dependent decrease in energy flux, estimated to be in the 5-25% range over a period of 15-20 minutes, and then respond with a rebound surge of heightened metabolism and energy release along with outpouring of antioxidant substances. Ozone induces ATP and NADPH synthesis which spill into the blood to neutralize the oxidizing effects of ozone [85-89].

Heightened energy output by RBCs translates into increased blood flow and energy delivery to peripheral tissues. RBCs contain the enzyme nitric oxide (NO) synthase and generate large amounts of NO in response to oxidative stress that, in conjunction with their energy release into the blood, promotes diastolic function [90-101]. Ozone-related oxidative stress triggers activation of hypoxia inducible factor (HIF) which, in turn, augments release of vascular endothelial growth factor (VEGF) and erythropoietin (EPO) which stimulate angiogenesis, blood flow and oxygen delivery to peripheral tissues [102, 103].

The first phase of the PC response, aimed at generating increased blood energy levels, mediates subsequent events at the cellular level. Energy currents, carried in the extracellular fluid (ECF) space, enter cells via ion channel mechanisms and, in short order, enhance mitochondrial function and cellular energy metabolism as well as inducing a plethora of genes that counteract oxidative stress. The second window of protection is driven primarily by events at the cellular level as a result of gene induction [104-110].

The most striking effect of ozone PC is mitigation of the inflammatory response via suppression of NLRP3 inflammasome activity. All inflammation begins at the cellular level and is related to impaired mitochondrial function due to insufficient energy flow into the cell. Abnormal inflammasome activation is a prominent feature of numerous chronic diseases [111-115]. Inflammation in conjunction with impaired diastolic function is an invariant accompaniment of HF and CKD. The immediate effect of PC is augmentation of energy flow into cells throughout the body and alleviation of mitochondrial dysfunction [116-121].

PC is now regarded as the most powerful form of innate body-wide protection. It has been over three decades since its discovery and 10,000's of

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reports in the literature have detailed its various aspects. Molecular biologists have identified dozens of potential chemical mediators and various mechanisms—heat shock proteins, adenosine, various neurotransmitters, EPO, NO, oxygen-derived free radicals, ATP-sensitive potassium channels to name a few—and yet still have no compelling explanation [122-132]. Thomas Kuhn described this as 'paradigm-induced blindness'. But PC isn't just a protective mechanism intended to counteract physiological stresses. It is the means by which the cardiovascular system and blood function day-in and day-out to maintain energy flux into tissues throughout the body. Impairment of this primary energy generating system plays a causal role in the genesis of acute and chronic disease.

MICROVASCULAR DYSFUNCTION

In the 1970s and 80s cardiologists began to observe increasing numbers of people who presented with typical angina-like chest pain and who, on exercise stress-testing, developed ECG abnormalities consistent with myocardial ischemia but, surprisingly, were found to have normal appearing coronary arteries on angiography.

Named Cardiac Syndrome X in the 1970s, symptoms result from diastolic dysfunction at the microvascular level. Overall about 20-30% of individuals with angina have no discernable coronary plaques. Microvascular dysfunction is present in most or all of these people. In many cases blood inflammatory markers like C-reactive protein are also elevated. A preponderance of those affected are post-menopausal women [133-136].

Originally thought to be benign it is now regarded as a progressive condition linked to poor quality of life and increased mortality. As the micro-circulation cannot be directly imaged diagnosis is made largely by exclusion. Treatment is challenging and symptoms often refractory to medications which typically afford relief in other cases of angina.

Cardiac Syndrome X was another wake-up call for medical scientists that went unheeded. At the time angina was thought to be a result of arterial plaques in large and medium-sized arteries that restricted blood flow to the heart muscle. Based on this pathologic mechanism their solution was to surgically bypass the affected artery or to place stents across the lesion. But such mechanical approaches don't impact the underlying functional disturbance. It is now recognized that all individuals with coronary arterial disease have microvascular dysfunction.

In one study of over 51,000 people who underwent coronary stent placement for occlusive coronary plaques, recurrent angina developed in 28% by 12 months and 40% by 36 months. Total healthcare costs in these subjects were almost 2-fold higher in the first year alone [137-142]. Recurrent symptoms were attributed to microvascular dysfunction. Evidence has continued to accumulate in subsequent decades. By not addressing the primary functional disturbance in a timely manner, medical scientists have played a facilitating role in the expanding epidemic of HF.

Coronary microvascular dysfunction is not limited to the heart but, instead, is a body-wide process. As Galen claimed, the heart and vascular system functions as one. Multiple organs, including brain and kidneys, are affected [143-147]. Many with coronary microvascular dysfunction have abnormal brain perfusion and are at higher risk for neurologic problems like stroke. Microvascular dysfunction goes hand-in-hand with diabetes, hypertension, and the autoimmune diseases. Microvascular dysfunction, like the PC phenomenon, is a whole-body process.

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During periods of increased physical activity or emotionally stressful situations microvascular dysfunction impairs energy flow to the myocardium, aka 'decreased coronary flow reserve', producing scattered areas of muscle ischemia which evoke anginal symptoms. While coronary plaques typically affect particular geographic regions, microvascular dysfunction involves the entire heart. Consistent with its systemic nature, coronary flow reserve can be estimated by measuring waveforms in other vascular territories like the retinal arteries [148].

Impaired microvascular function results in diminished energy generation and mitochondrial dysfunction in endothelial cells causing inflammation [149-151]. Oxidative stress in endothelial cells, in turn, induces NLRP3 inflammasome formation and cytokine release triggering an immune response and the so-called cytokine storm. The response is not limited to the endothelium. Whether involving cardiac myocytes, renal tubular cells, or brain neurons, microvascular dysfunction sets into motion a spiral of chronic low-grade inflammation which, in turn, is exacerbated by risk factors like diabetes, hypertension, obesity, or elevated blood lipids [152-159].

The intertwined relation between microvascular dysfunction and endothelial inflammation is seen most vividly in arterial wall calcification. Calcium deposition takes place in vessels affected by chronic endothelial inflammation leading to loss of elasticity with stiff, non-compliant arteries [160-168]. Arterial wall calcification can occur anywhere in the body. Not surprisingly, breast arterial calcifications are associated with a higher risk for stroke and heart attack [169-171] (Figure 1).

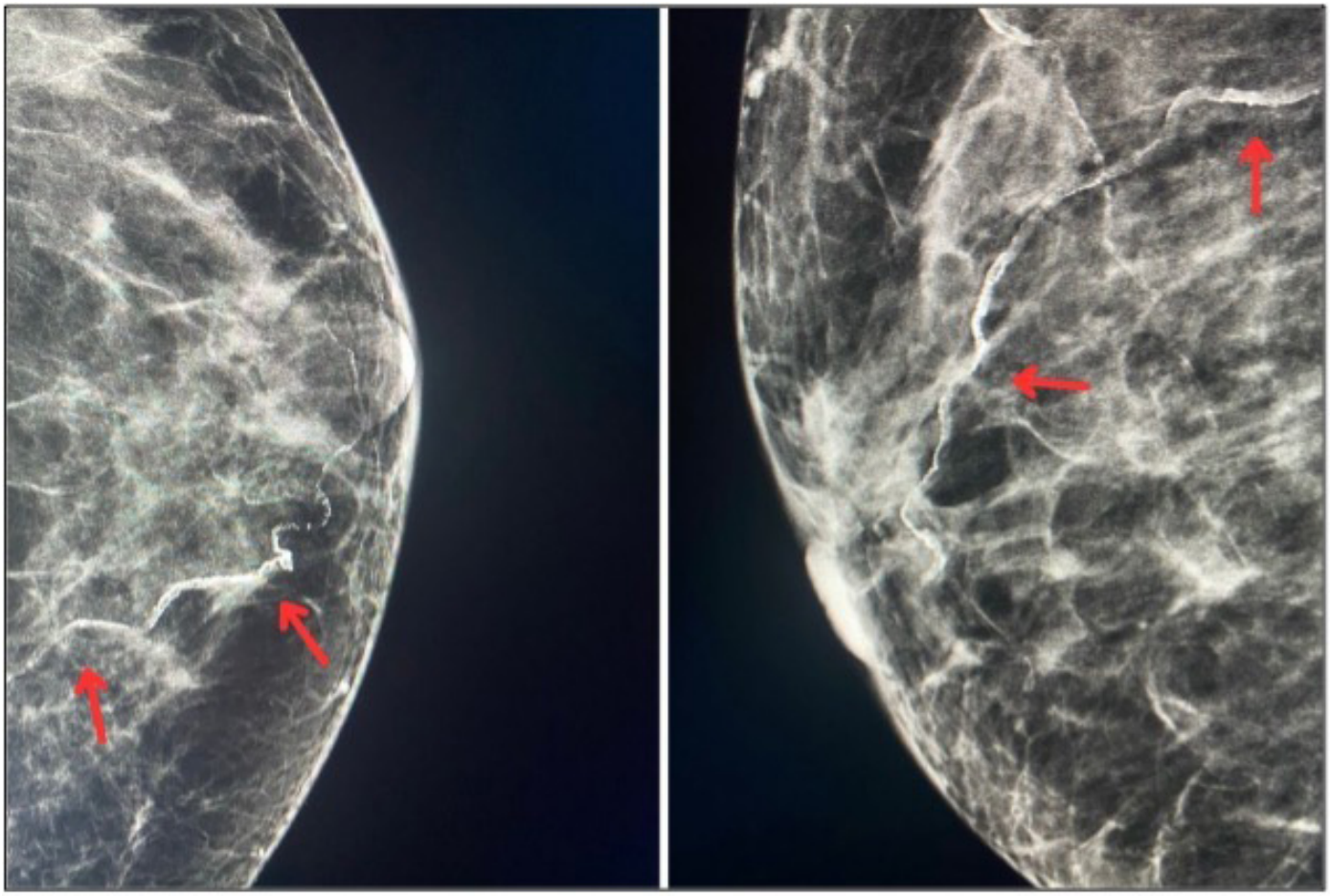

Figure 1: Breast arterial calcifications on mammography in a 64yo hypertensive, diabetic woman. (Courtesy of Eghosa Olomu, MD)

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Arterial calcification is associated with pathologic states like the metabolic syndrome, diabetes, autoimmune disorders, hypertensive disorders of pregnancy, cancers, even normal aging. In one large study of 30-49-year-old adults tested for coronary arterial calcification, over one-third (34.4%) had calcifications. More extensive calcification was associated with a 5-10-fold higher cardiovascular mortality [172]. Other studies found extensive systemic arterial calcification have a 3- to 5-fold higher all-cause mortality rate [173-176]. Calcifications may be present long before symptoms of heart disease, stroke, and/or signs of renal impairment appear (Figures 2 & 3).

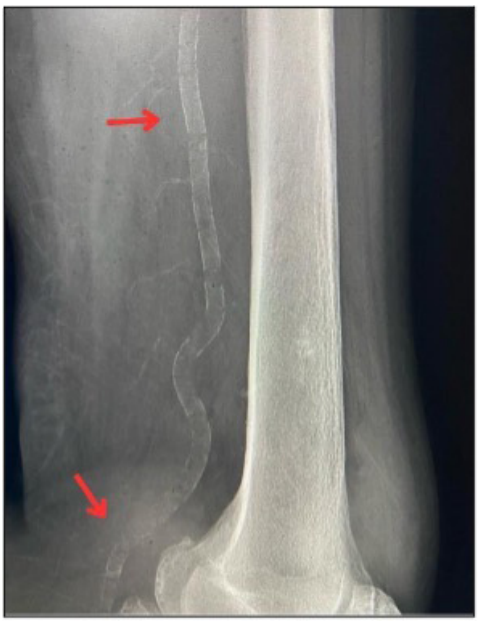

Figure 2: Vascular calcifications in the thigh of a 72 y.o. male with diabetes and CKD.

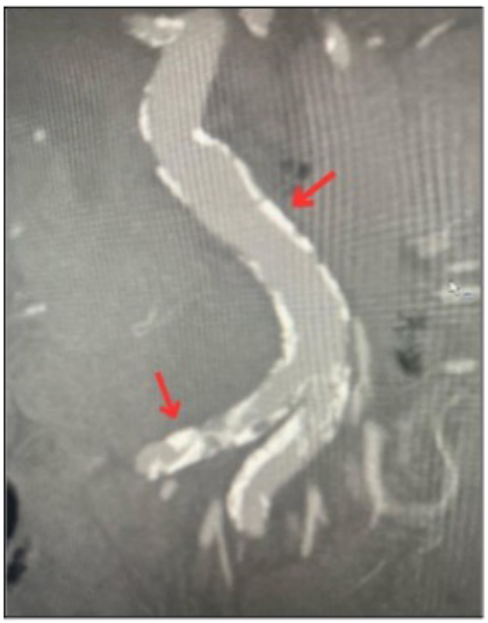

Figure 3: Dense calcifications on CT in the abdominal aorta of a 78yo male with hypertension and severe peripheral artery disease.

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Microvascular dysfunction is a central player in type II diabetes [177-181]. The relationship is bidirectional. Diastolic impairment promotes insulin resistance resulting in decreased delivery of insulin and glucose to cells; elevated blood glucose and insulin levels in turn induce further microvascular dysfunction. And these aberrations are plainly related to reduced blood energy secondary to diminished energy generation by the cardiovascular system.

Microvascular dysfunction and reduced energy flow to the kidneys induces activation of the renin-angiotensin system, release of vasoconstrictor substances by the adrenal glands, and systemic hypertension [182-188]. This too sets into motion a self-amplifying, bi-directional spiral of deterioration: hypertension worsens microvascular dysfunction and exacerbates endothelial inflammation which, in turn, further reduces energy flow to the kidneys. This intertwined relationship forms the basis of the so-called cardiorenal syndrome which isn't really a distinct syndrome but simply the recognition by medical scientists of a relationship between the two organs based on interdependency of energy flow.

Hypertension is the most common pathway leading into the deteriorating spiral of HF. Hypertension increases cardiac 'workload', i.e. the resistance against which cardiac muscle cells must function and induces adaptive remodeling of the heart and left ventricular hypertrophy (LVH) [189-193]. Microvascular dysfunction and inflammation promote deposition of fibrous tissue in cardiac muscle cells leading to progressive activity-related fatigue and, eventually, physical incapacitation. The stepwise transition from early hypertension to LVH to HF is governed entirely by microvascular dysfunction and reduced energy generation.

Microvascular dysfunction is an invariant feature in the spectrum of CKD and causally mediates its spiral of deterioration [194-195]. As in the heart impaired diastolic function triggers inflammation and immune activation. LVH compounds the pathologic process by adversely impacting renal blood flow, glomerular filtration and renal energy extraction. Abnormal waveforms, i.e., microvascular dysfunction, in the retinal arteries are predictive of progression to CKD [196].

The full implication of the intertwined cardiorenal dynamics come to bear in one grim fact: as CKD progresses one observes acceleration on a stage by stage basis of cardiovascular morbidity and mortality. Most people with CKD die of heart disease [197-206]. Likewise, treatments over the past half-century aimed at correction of hypertension resulted in blood pressure reductions and lower rates of heart attack, stroke and intracranial hemorrhage but had little impact on microvascular dysfunction or its progression to HF and/or CKD. Once again, medical scientists must shoulder a lion's share of responsibility for the expanding epidemic of HF and CKD.

A central theme in the genesis and evolution of HF and CKD is deterioration of the blood, the commonly shared milieu upon which all bodily functions depend. Not only does blood carry nutrients and growth factors that enable proper organ function, but its fluids – i.e. water – serve as a carrier for the organized energy field which orchestrates all cellular functions in the body. There has been little written in the modern medical literature about blood's primary causal role and yet for 1500 years it formed the basis for Roman physician Galen's system of humoral medicine [207]. His functionally-based system of medical thought and practice was arbitrarily discarded by chemically oriented scientists in the 18th century without ever refuting its claims.

The dynamic state of blood strongly influences the development and progression of HF and

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CKD. Blood accounts for about 7-8% of total body weight in the average adult with the RBC mass estimated to be about 2.3kg (5lb). RBCs are highly metabolically active and, through their iron-containing hemoglobin, generate large electromagnetic currents that course through the blood and ECF space. As we saw RBCs mediate the PC phenomenon.

Many studies substantiate the deleterious effect of anemia in chronic disease. Anemia is a frequent accompaniment of HF, CKD and chronic conditions like diabetes [208-223]. The relationship is bidirectional: the severity of anemia is often related to the stage and/or duration of the underlying disease; conversely, the presence of anemia directly impacts disease progression. Like hypertension and diabetes, anemia is associated with diastolic and microvascular dysfunction as well as diminished blood energy generation [224-228]. Anemia of any cause is independently associated with increased cardiovascular events like myocardial infarct, HF, and all-cause mortality. The critical element seems to be hemoglobin.

In diabetes hemoglobin (Hgb) undergoes irreversible glycation to form HgbA1C which has a markedly reduced (or absent) energy generating potential. HgbA1C is a reliable indicator for blood glucose control in diabetics and a powerful predictor for progression of diabetes and/or cardiovascular complications: higher blood glucose levels are associated with higher HgbA1C levels which, in turn, are directly related to worse outcomes. Chronic hyperglycemia is directly implicated with worsening of microvascular dysfunction [229-235].

Studies assessing mortality risk and HgbA1C levels found a continuous linear relationship between HgbA1C levels and all-cause mortality in diabetic and non-diabetic populations. Lowest mortality rates are seen with levels less than 5% and, with each 1% increment, the relative risk increases independent of all other risk factors. HgbA1C levels are momentary snapshots of blood energy status and the ability of RBCs to generate and maintain the body-wide energy field.

The intertwined nature of RBCs, Hgb and blood energy dynamics come full circle in the PC phenomenon: as diabetes, HF, and CKD progress, the PC response becomes blunted and, in advanced cases, disappears altogether [236-239]. This affirms the key role of RBCs in the generation and maintenance of blood energy levels. It also represents a major therapeutic challenge for any attempts intending to halt progression or to reverse the course of these debilitating and progressive conditions.

HEART FAILURE DYNAMICS

The failed systolic pump model of heart function advanced by William Harvey and Ernest Starling formed the basis for all notions of HF in the latter half of the 20th century not to mention serving as a flawed rationale behind a handful of largely ineffective therapies. Proper diagnosis and treatment of HF depends on accurate knowledge of the pathophysiology which must include energy dynamics.

Studies in the 1960s found that HF was characterized by elevated pressures in the left ventricular (LV) chamber coupled with reduced LV stroke volume, i.e., the amount of blood ejected with each contraction. Based on such evidence researchers devised an equation to estimate the efficiency of LV contraction— essentially a simple ratio between left ventricular stroke volume and the volume of blood in the ventricle at the end of the diastolic filling phase. A low left ventricular ejection fraction (LVEF) is suggestive of HF.

Clinical studies supported the predictive value of LVEF in the diagnosis of HF and, moreover, found

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that lower values were associated with worse clinical outcomes. Over the years LVEF became uncritically accepted as a universal criterion for assessment of LV pump function. International guidelines arbitrarily designated an EF of 45% or less as the cutoff for heart failure. For decades LVEF has been the primary means by which clinicians assess LV and heart function and make clinical determinations. But LVEF only gives an illusion of objectivity and certainty [240-242].

LVEF measurements are situation dependent and only moderately reproducible. They readily fluctuate with changes in blood pressure and heart rate. In that LVEF is based on blood volume, it is insensitive to primary functional indicators like muscle contractility and pressure. In the real-world ventricular contraction is diminished by elevated pressures in the ventricular chamber *before* systole, aka 'preload', which, in turn, are directly impacted by diastolic dysfunction; ventricular contractility is also impeded by the arterial pressures against which it must pump, aka 'afterload', which are increased in hypertension. The measurement of LVEF is also affected by the chosen imaging method which can result in variances of up to 10-20% [243, 244]. And for any given LVEF value the risk for poor outcomes is increased by coexisting conditions like diabetes, hypertension, anemia and kidney function.

The most serious blow, however, came in recent decades with the recognition that a large percentage of HF patients do not have reduced LVEF. Called heart failure with preserved ejection fraction (HFpEF), its incidence has spiked dramatically in recent decades and now accounts for more than 50% of chronic HF. HFpEF is more likely to affect women, the elderly, and people with comorbid conditions like diabetes and obesity. As with other forms of HF, treatment is largely ineffective [245-248].

Like Cardiac Syndrome X there are often no obstructing plaques in the coronary arteries and progressive deterioration is driven primarily by diminished flow reserve, i.e., impaired energy generation in the blood [249, 250]. This, in turn, manifests in microvascular dysfunction and inflammation throughout the circulatory system. Once mitochondrial function in cardiac myocytes is affected the pathological cascade associated with HF – muscle hypertrophy, remodeling of the heart wall, fibrosis and more – is set into motion. All observed pathology is downstream to the primary energy deficit. Experimental science has spent the last century studying wine in order to understand the grape.

Just as the discovery of active ventricular dilation in the 1980s overturned the reigning systolic pump model and forever changed notions of heart function, the recognition of HFpEF upends the existing model of HF and demands an entirely new conceptual framework. Systolic function and LVEF are only isolated aspects of the HF spectrum. As a clinical syndrome HF is a final common pathway into which multiple distinct functional disturbances ultimately merge and blend.

Given the volume of high-quality evidence that has surfaced in recent decades it is astonishing that medical scientists have yet to formulate a coherent explanation for HF — yet another example of paradigm-induced blindness. They describe three main entry points into HF: hypertension with activation of the adrenal axis and LVH, i.e., hypertrophic cardiomyopathy; those in which microvascular dysfunction and metabolic disturbances dominate, i.e., restrictive cardiomyopathy; and those in which primary inflammation of the heart as seen with viral myocarditis are responsible, i.e., dilated cardiomyopathy. In reality the three overlap and interpenetrate; there are few pure forms.

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While acknowledging the role of microvascular dysfunction and inflammation in all these precursor pathways scientists persist in their attempts to explain the various forms of HF on the basis of cellular and genetic mechanisms in much the same way Ptolemaic astronomers continued for centuries to use the geocentric model to explain planetary motions. Consciousness always wakes up late.

To observe the striking differences in cardiac morphology related to remodeling in the various forms of HF leaves little doubt that dynamic mechanisms are at play. The different patterns of remodeling can only be explained by opposing mechanical forces arising from within the blood and heart wall. The magnetic field in the blood is responsible for the outward motion of the heart and arteries while sympathetic constrictor nerves induce the opposing contractionary force. The disposition of such forces is influenced by real-time interactions between the heart, kidneys, and blood. In Galen's humoral system of medicine not only was blood the source of all energy flow in the body but each organ possessed its own special 'power'. Clearly the term power can be taken in a literal sense.

In hypertrophic cardiomyopathy as blood energy content diminishes the kidneys, through the renin-angiotensin system, activate the adrenal axis increasing heart rate and force of contraction thereby augmenting energy generation. While this boosts energy flux in the short term, over a protracted period it sets the stage for chronic hypertension and subsequent LVH [251-253]. This early phase of hypertrophic cardiomyopathy can often be seen in young and middle-aged adults with hypertension who present with isolated LVH in the absence of cardiomegaly (Figures 4 & 5).

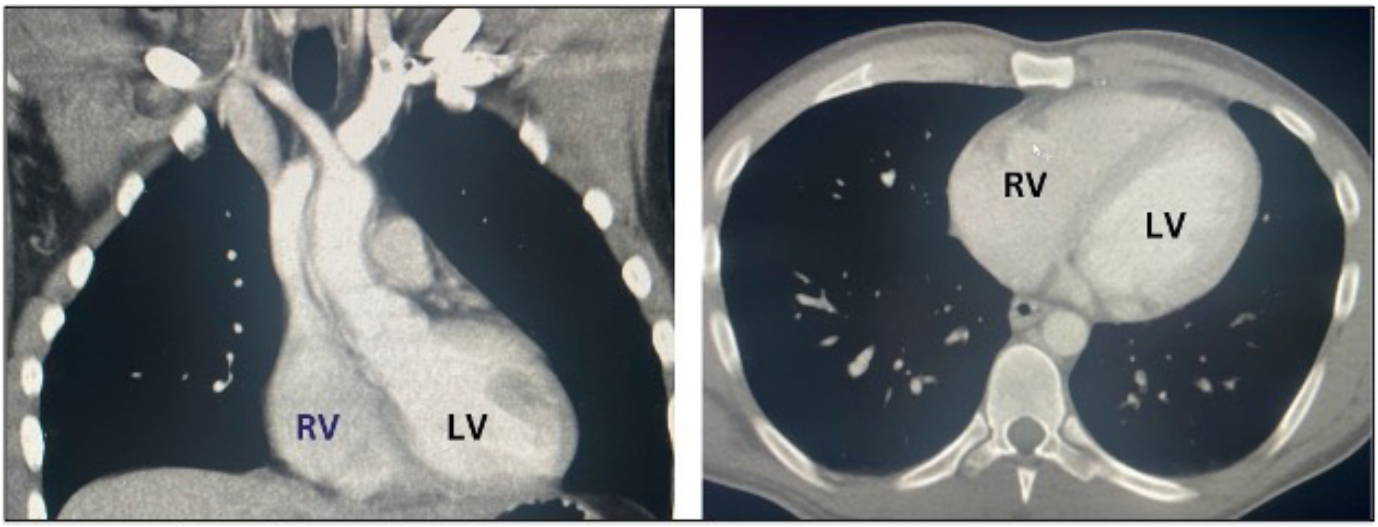

Figure 4: Normal appearing heart on coronal and axial contrasted CT images in a young adult.

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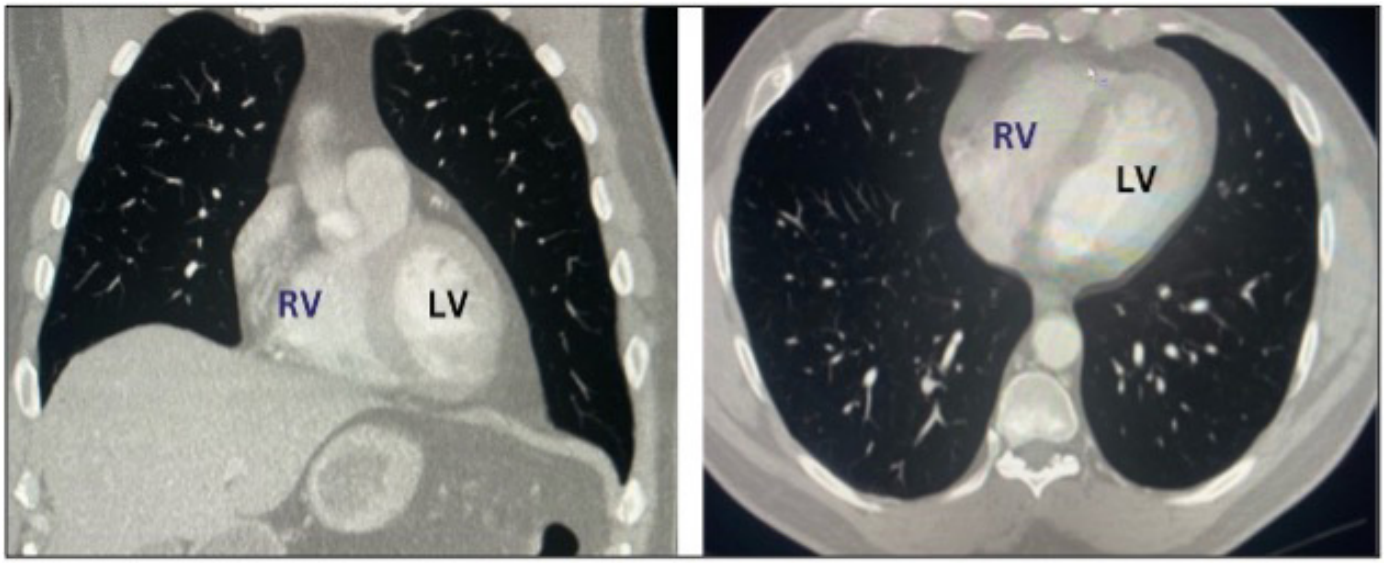

Figure 5: Coronal and axial contrasted CT images showing mild LVH without cardiomegaly in a hypertensive young adult.

As the energy deficit deepens cardiac remodeling markedly alters systolic and diastolic mechanics. Ventricular wall thickness continues to increase with the wall becoming stiff, noncompliant and fibrotic [254, 255]. Progressive diastolic dysfunction results in elevated end-diastolic pressures which 'back-up' into the left atrium, pulmonary arteries, and right ventricle (RV) causing their dilation and inducing cardiomegaly. Eventually wall thickening in the RV may occur but never to the extent seen in the LV. Individuals may develop pulmonary arterial hypertension as well [256]. After several decades of progressive deterioration full blown hypertrophic cardiomyopathy and HF ensue (Figure 6).

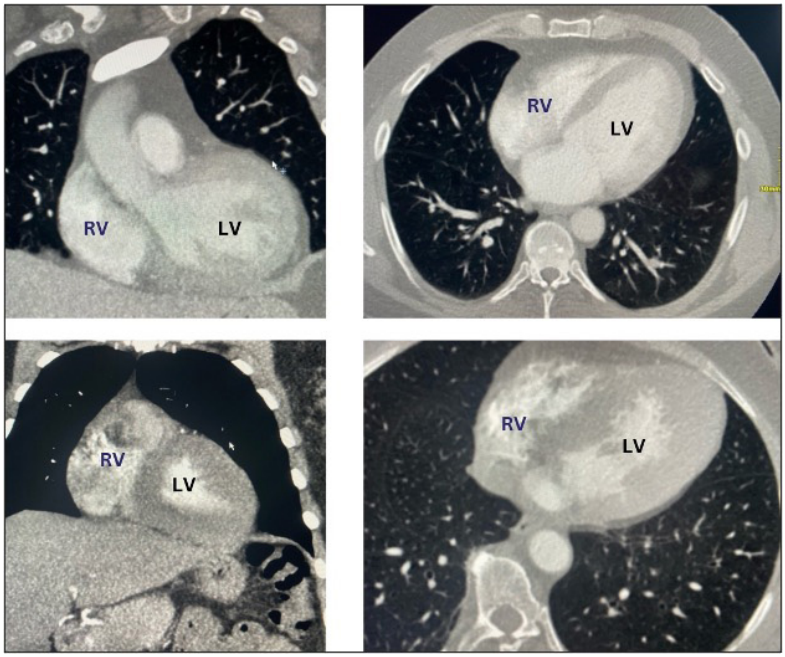

Figure 6: Coronal and axial contrasted CT images of cardiomegaly with moderate (top two images) and severe (bottom two images) LVH and hypertrophic cardiomyopathy.

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The blood-borne metabolic pathway into HF, i.e., restrictive cardiomyopathy, evolves differently. Subjects are usually middle-aged or older adults with a history of obesity and/or diabetes who develop recurring episodes of angina-type chest pain (with or without coronary plaques) and progressive inability to perform normal daily activities [257-260]. Rhythm disturbances, especially atrial fibrillation (AF), may occur [261, 262]. In one study, among people with new onset AF, 37% had coexisting HF; in people with known HF up to 60% developed AF. This same population is also more likely to present with primary pulmonary arterial hypertension and/or signs of right-sided HF like edema in the lower extremities.

As opposed to early hypertrophic HF, the energy deficit in restrictive cardiomyopathy is global, affecting all regions of the heart and both systole and diastole. But the primary driver is diastolic dysfunction. During periods of increased activity there is rapid buildup of pressure in the cardiac chambers impeding blood flow, hence the term 'restrictive,' that persist long after cessation of activity and may even precipitate congestive failure [263]. In this pattern of remodeling the heart is more likely to develop concentric enlargement all four chambers and take on a more globular appearance (Figure 7).

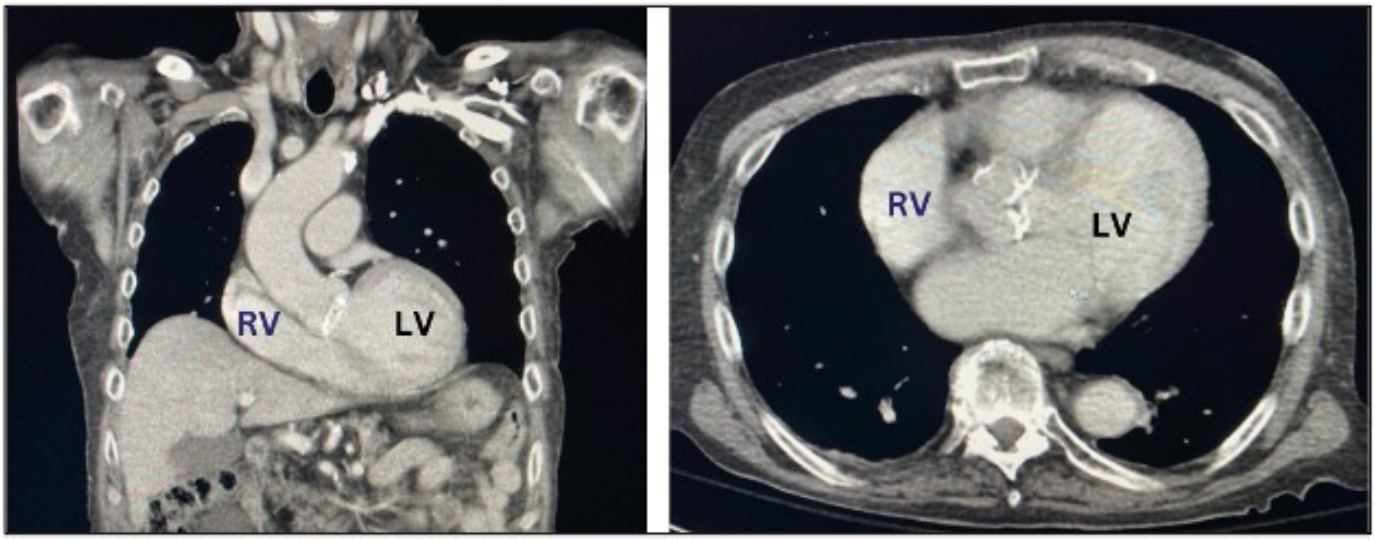

Figure 7: Coronal and axial contrasted CT images of 67yo male with diabetes and HFpEF.

The third entry path into the HF syndrome, dilated cardiomyopathy, is related to chronic myocardial inflammation [264-266]. The most common cause appears to be viral myocarditis. Affecting any age group, it is being seen in young and middle-aged adults with increasing frequency. It presents frequently as deteriorating cardiac function in the absence of abnormal intraventricular pressures or coronary artery disease. Because myocardium is the primary target there is enhanced arrhythmogenic potential and risk for sudden death [267].

Chronic myocardial inflammation resembles an autoimmune disorder with activation of pro-inflammatory cytokine pathways and autoantibodies directed against cardiac muscle [268-271]. In dilated cardiomyopathy progressive destruction of heart muscle occurs with loss of contractility leading to primary systolic HF. The most common imaging finding is a diffusely enlarged thin-walled heart with disproportionate dilation of the chambers (Figure 8).

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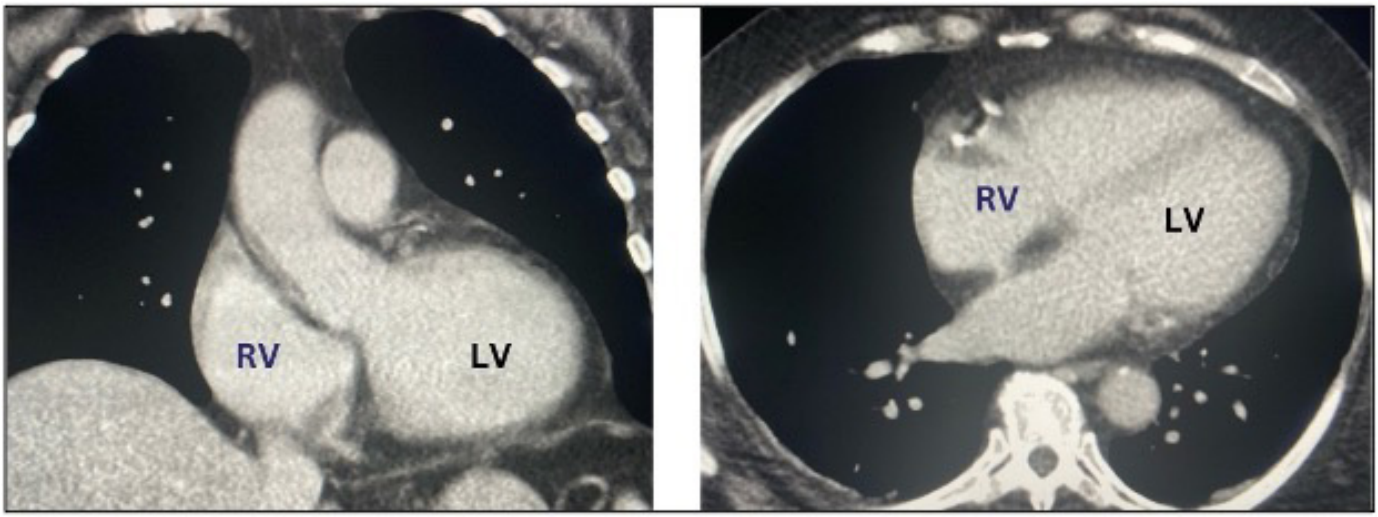

Figure 8: Contrasted coronal and axial images in a 50yo male with dilated cardiomyopathy. Etiology unknown.

The energy dynamics responsible for the globular 'water pouch' morphology in dilated cardiomyopathy reveal yet another example of flawed reasoning based on the obsolete systolic pump model. Once negative intraventricular pressures in early diastole were discovered researchers claimed they resulted from 'elastic recoil' of the fibrous cardiac skeleton induced by the torsional rotation of the myocardium during systole. This is utterly ridiculous. How does this explain the marked cardiomegaly and disproportionate dilation of the chambers when there is insufficient muscle to generate such a torsional force? The outward expansion of the heart and arteries originates in the blood.

CHRONIC KIDNEY DISEASE

Progressive renal failure sets into motion an ever-widening nest of morbid consequences – hypertension, anemia, electrolyte imbalances, metabolic acidosis, and mineral bone disease (MBD) not to mention at least a 20-fold higher incidence of adverse cardiovascular events compared with the general population. Given the broad impact of such conditions on healthcare systems across the globe the astronomical costs attendant with CKD are not at all surprising [272].

In 1812 a paper appeared in the journal *Medical-Chirurgical Transactions* by a Dr. Wells who related his experiences with various forms of 'dropsy,' i.e., edema, which is due to accumulation of fluid in the ECF space beneath the skin [273]. By then chemists had developed methods to analyze urine for the presence of proteins like albumen. Among 29 patients with 'dropsy of the skin,' i.e., edema in the lower extremities, 23 had protein in their urine. Proteinuria is now regarded as a primary sign of acute renal injury and chronic kidney disease.

Wells further observed that dropsy was often associated with chest symptoms like cough and difficulty in breathing. A number of individuals had 'hydrothorax,' i.e., fluid in the pleural space, suggesting chronic HF. Two-thirds of such cases had protein in their urine. Wells concluded that this clinical constellation constituted a distinct pathologic syndrome.

In 1827 English physician Richard Bright described 25 cases of dropsy, many of whom had proteinuria and which, on subsequent postmortem examination, were found to have marked pathologic changes in the kidneys [274]. Thereafter the triad of dropsy, proteinuria, and kidney dysfunction

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became known as Bright's disease. Bright later described an association between proteinuria and LVH. Decades later investigators found that elevated blood pressure often occurred before the onset of proteinuria and seemed to play a mediating role. The functional basis for these intertwined pathologies would remain obscure for nearly 150 years.

Based on the systolic model of heart function, renal impairment was thought to be a consequence of diminished arterial inflow to the kidneys. The 20th century concept of renal failure held that the kidneys interpreted diminished renal arterial inflow as indicating fluid depletion. To correct this the kidneys responded in two ways: they increased retention of sodium and water by the collecting tubules (which led to volume overload and edema), and they activated the renin-angiotensin system in order to raise cardiac output and increase renal blood flow (which led to hypertension). But this explanation never held water.

A 2008 study examining circulatory dynamics associated with worsening renal function in HF patients found that the arterial flow model failed to explain the deterioration. The strongest determinant was elevated right atrial pressure, i.e., diastolic dysfunction [275]. A study in 2009 study also found that increased venous pressure was the most important factor leading to worsening of renal function [276].

Elevated central venous pressure (CVP), i.e, backward failure, is now recognized to be the primary driver of deteriorating renal function. Transmission of elevated CVP into the kidneys raises intrarenal pressure which secondarily restricts arterial inflow. The kidneys *aren't* reabsorbing more sodium and water. Instead, due to increased back-pressure, the normal pressure gradient between arteries and veins is diminished so that less urine and sodium can be filtered. This same mechanism explains proteinuria. Impaired RV diastolic function also causes accumulation of fluid in the ECF space of the lower extremities causing edema. For over 200 years dropsy could not be explained on the basis of the Harvey-Starling systolic model. Now the answer is obvious. Why didn't scientists ever put 2+2 together?

The relation between increased renal vein pressure and decreased kidney function was recognized well over a century ago but never incorporated into the conceptual framework. In 1861 German physiologist Ludwig observed in lab animals that as renal vein pressures increased urine flow decreased. In 1931 Winton described a 'steeply graded' linear relation between renal venous pressure and urine flow [277]. Arterial inflow was less significant than elevated venous pressure. In the 1980s studies found that transient compression of the renal veins decreased the filtration rate of urine along with sodium excretion [278-280]. Such dynamics are in play with antihypertensive therapies.

In the 1990s studies found that antihypertensive treatments with angiotensin converting enzyme (ACE) inhibitors designed to block activation of the renin-angiotensin system delayed progression of CKD and reduced proteinuria, in some cases by up to 40-80%. Studies found increased endothelial-dependent dilation, i.e., diastolic function, which in turn reduced venous back-pressure [281-290]. Not only was the systolic framework incapable of explaining such findings it actually prevented researchers from interpreting results correctly. And yet current methods used to evaluate renal function don't even consider diastolic function.

To gauge severity of CKD a quantitative method known as glomerular filtration rate (GFR) is used, a ratio between the concentration of creatinine in the urine versus in the blood adjusted for 24-hour urine volume. For decades GFR has been regarded as a benchmark for estimation of renal function

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but, like LVEF, it involves some shaky assumptions and statistical hocus-pocus.

Creatinine, a breakdown product of muscle metabolism, is freely filtered by the glomeruli and excreted into the urine. But renal tubules also secrete it into the urine so it doesn't just reflect glomerular filtration. Creatinine levels in the blood fluctuate according to physical activity, age, dietary protein intake and hydration status. Individuals can have significant elevations in blood creatinine without impaired renal function and, conversely, relatively normal blood creatinine levels in the presence of impaired renal function.

In recent decades a statistically derived method has been widely used called estimated GFR (eGFR) that takes into account factors like age, gender, and body mass. A 2019 report analyzed 70 studies comparing eGFR with measured GFR in 40,000 renal transplant patients and showed that eGFR often varied by 30% or more and incorrectly staged 60% of CKD patients [291, 292]. The eGFR method is but an estimate of an estimate. And it assumes that glomerular filtration is the only function that matters.

No doubt a primary function of the kidneys is to filter fluids, ions, solutes and impurities from the blood. But is there more to renal function than meets the eye? And how do blood energy dynamics fit into the picture? By necessity kidney function must entail not only elimination of wastes and superfluous materials but extraction of energy from the filtered arterial fluids so as to preserve blood energy content, otherwise large amounts of energy would be lost down the toilet.

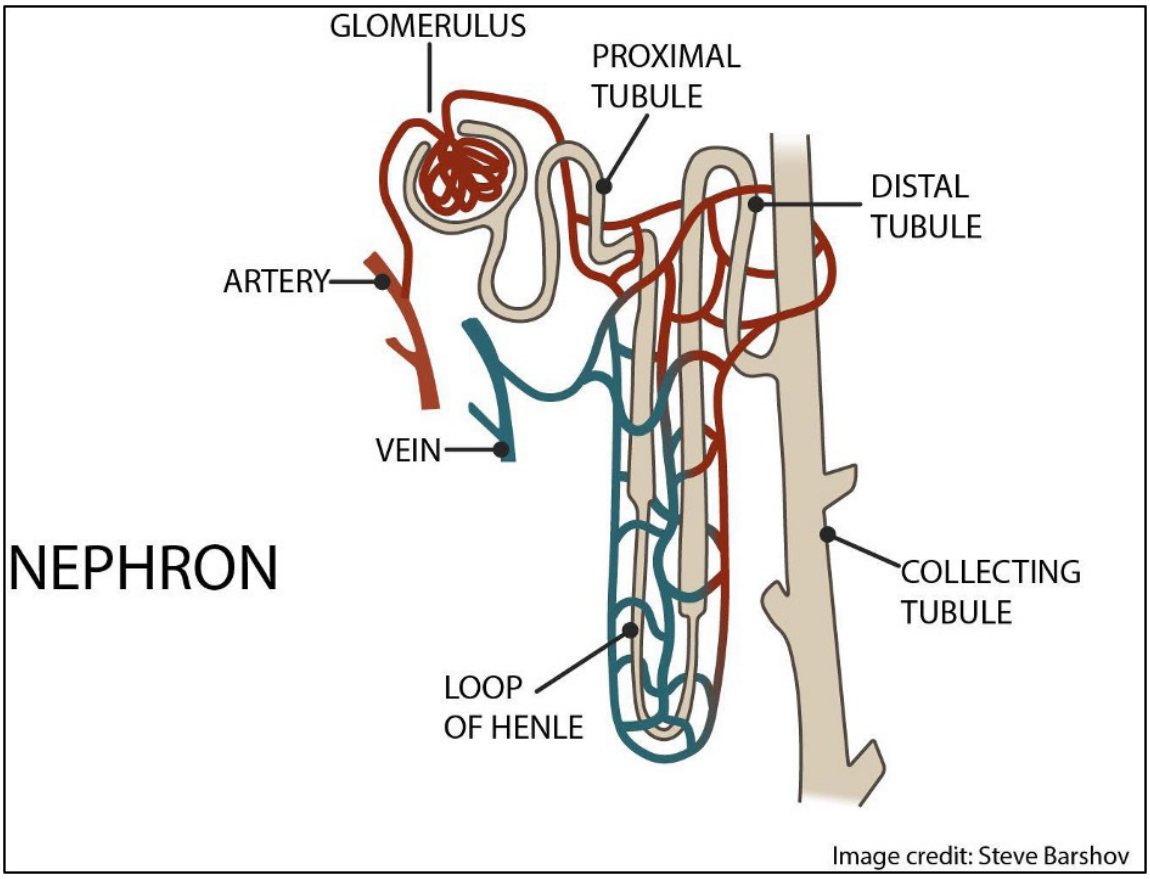

Figure 9: Small venous tributaries lie in close proximity to the collecting tubules. Reabsorption of glomerular filtrate back into the vascular system is effected by suction pressure generated by the right ventricle during diastole.

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Observe in Figure 9 that energy-laden arterial blood, once filtered by the glomerulus, passes through the renal collecting tubules. The tubules lie in close proximity to tiny venules and it is the suctional force of the RV that draws energy currents and fluid back into the venous system. Moreover, the energy content of the filtered fluid itself creates the directional flow gradient along which the fluid and ions move back into the venous system, in the manner that electrical currents always travel along voltage gradients.

The defining attribute of healthy kidney function is not glomerular filtration but the ability to concentrate urine [293-296]. As they remove wastes and spent materials from the tubular filtrate, the kidneys extract an ultra-pure fluid with high energy content which returns to the vascular system via the renal veins. This enriched fluid – which definitionally is ECF – enables venous blood to efficiently bind oxygen during passage through the lungs and to undergo energetic transformation in the heart. As the kidneys fail, the quality of the blood deteriorates. For this reason, we regard the kidneys as guardians of the ECF space. Deterioration in ECF energy content plays into the amplifying spiral of CKD (Figures 10 & 11).

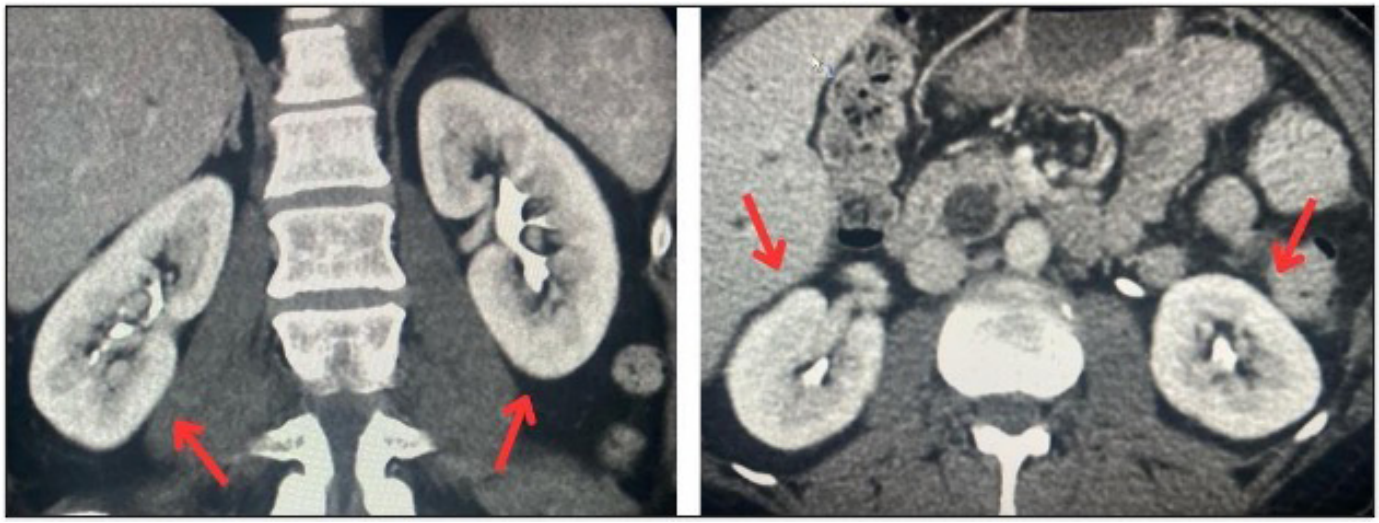

Figure 10: Contrasted coronal and axial CT images of normal appearing kidneys in a young adult.

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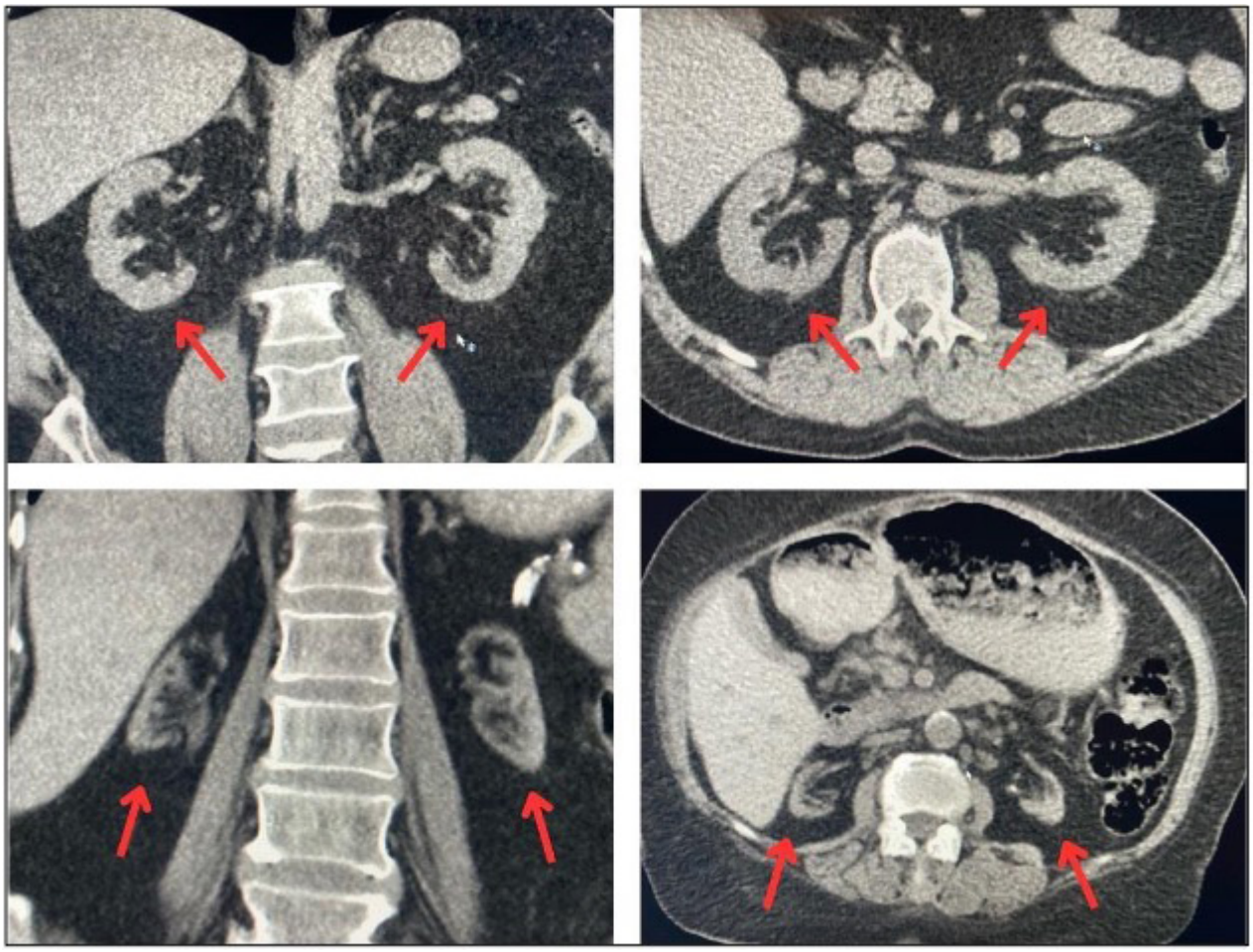

Figure 11: Coronal and axial contrasted CT images in moderate CKD (top two images) and end-stage renal disease (bottom two images). Note loss of volume associated with progressive cell death & fibrosis.

The kidneys are highly metabolically active and receive about 25% of blood flow from the heart. The concentration of mitochondria in renal cells is second only to cardiomyocytes. Mitochondria synthesize energy substances like ATP and NADPH which drive cellular activity [297-301]. During periods of oxidative stress when mitochondrial function is disrupted, reactive oxygen species are produced which damage cellular structures and trigger inflammation. This, in turn, elicits an immune response via NLRP3 inflammasome and cytokine pathways that, ultimately, results in cell death [302, 303].

Chronic low-grade inflammation with impaired mitochondrial function is the hallmark of CKD. In healthy kidneys, fibroblasts are responsible for maintenance of renal architecture. During prolonged ischemic injury fibroblasts are activated and functional tissue is gradually replaced by connective tissue. Progression of CKD forms a nearly invariant common pathway that builds in step-by-step fashion: diastolic dysfunction → impaired renal tubular function → proteinuria → cytokine-mediated inflammation → progressive cell death and loss of function → activation of fibroblasts → renal fibrosis and scarring. Due to its silent nature CKD is not usually diagnosed until in advanced stages [304-307].

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VITAMIN D AND THE ECF SPACE

By the early 20th century it was known that sunlight, ultraviolet light and cod liver oil were effective in preventing and reversing rickets, a metabolic bone disease, the incidence of which had skyrocketed in industrialized urban areas within upper northern latitudes [308-310]. In the 1920s researchers discovered that the active principle in cod liver oil was vitamin D which, through unknown mechanisms, effected transformation of ambient light energy resulting in the amelioration and reversal of the bone and mineral pathology of rickets. We describe the means by which such energy transfers occur in an earlier piece [311].

In the 1980s reports began to surface documenting deficient vitamin D levels in various infectious and autoimmune disease like tuberculosis, multiple sclerosis, diabetes, inflammatory bowel disease rheumatoid arthritis, psoriasis and more [312-339]. In that chronic inflammation is indicative of deficient energy flux we can assume that vitamin D mediates energy transfers in the body.

In the general population low vitamin D levels are associated with increased all-cause and cardiovascular mortality [340-352]. Vitamin D deficiency in healthy populations is associated with increased arterial stiffness, microvascular dysfunction and inflammation [353-356]. Conversely, vitamin D supplementation leads to improvement in vascular dilation and reduction in LVH as well as inflammation [357-359]. Quite clearly vitamin D plays an active role in the body's energy economy.

Vitamin D deficiency is common among people with CKD and is associated with progression of disease and adverse cardiovascular outcomes. Low vitamin D levels trigger activation of the renin-angiotensin system and are associated with hypertension, impaired diastolic function and inflammation [360-362]. Vitamin D deficiency disrupts the endocrine axis between the kidneys, parathyroid glands and bone compartment setting into motion the syndrome known as CKD-MBD (mineral and bone disorder), a plethora of abnormalities driven by hormones like PTH and FGF-23 whose effects escalate the deterioration [363-367].

In 1969 researchers discovered the vitamin D receptor which mediates the effects of vitamin D at the cellular level. Over the ensuing decades vitamin D receptors were found in over 30 tissues throughout the body including kidneys, skin, bone, intestines, pancreatic β-cells, prostate, breast, muscle, adipose tissue, as well as the immune system. Activated vitamin D influences at least 500 different gene activities through receptor-mediated epigenetic mechanisms [368].

Given such widespread biological impact one would expect vitamin D to be a panacea for every conceivable form of inflammation but such is not the case. For every study showing benefits with vitamin D supplementation another finds no effect [369]. Some studies find that vitamin D administration in CKD improves clinical outcomes in MBD and reduces proteinuria; others find it has no effect on either CKD progression or cardiovascular outcomes [370-374]. Why are results so mixed? It would appear that the rate-limiting step lies not in synthesis of vitamin D but its conversion into a biologically potent state.

Through photosynthesis-like mechanisms, radiant energy in the skin induces vitamin D formation which, subsequently, is transformed to its intermediary $25(OH)D_3$ and, finally, to the highly-active $1,25(OH)_2D_3$ form, which is said to be 500-fold more biologically active. These latter two energy-requiring steps are effected by the ubiquitous superfamily of enzymes known as the cytochrome p450 system. Studies suggest their activity is dependent on water-borne energy currents and/

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or external radiant energy [375-378]. And herein lies the basis of the vitamin D-associated bone pathology in CKD.

All physiological functions in the body, including outward dilation of the heart and arteries, are effected through conformational changes of proteins which, as with the heart, represent states of polarization and depolarization. To be biologically active proteins must acquire a so-called hydration shell, consisting of multiple layers of water molecules, which is instrumental in determining not only 3D protein structure but the folding process itself [379-384]. Energy disposition in the ECF not only plays a primary role in conformational changes in normally folded proteins but in pathological states like the protein misfolding disorders [385-389].

The hydration shell surrounds hydrophilic domains of most intracellular proteins and organizes into a complex semi-crystalline matrix with gel-like consistency. Hydration shell water has physical properties distinct from that of water in the adjacent fluid spaces including net negative charge, higher pH, and increased density. Such physical differences implicate a voltage gradient and energy flow. When the ECF is energy-depleted, function of enzymes like the cytochrome p450 system is disrupted thereby impeding energy transfers and, in the case of vitamin D, formation of highly-active $1,25(OH)_2D_3$. As the function of the kidneys deteriorates so too does the energy content of the ECF.

The trail of escalating bone pathology begins in the kidneys [390-392]. Normally blood calcium and phosphate are tightly regulated and fluctuations are offset by altered absorption in the gut and/or excretion by the kidneys. With progressive death of renal cells and deterioration in ECF energy status two things happen: insufficient conversion of vitamin D into active $1,25(OH)_2D_3$ to meet energy needs, and, impairment of tubular reabsorption and/or secretion of calcium and phosphate. This leads to increased phosphate in the blood and loss of calcium in the urine [393, 394]. Parallel to this progressive leeching of minerals from the bone, i.e., osteoporosis, takes place with heightened fracture risk [395].

In response to altered renal function bone cells release a substance called fibroblastic growth factor-23 (FGF-23) which worsens the situation [396-400]. While increasing urinary phosphate excretion, FGF-23 blocks synthesis of vitamin D, impairs microvascular dysfunction, accelerates arterial calcification, promotes LVH, and activates fibroblasts leading to progression of CKD and fibrosis. The parathyroid glands join in the fray by increasing secretion of the hormone PTH to augment vitamin D synthesis and normalize bone metabolism which, once again, amplifies the spiral of deterioration [401-403]. A blow-by-blow description of events is pure overkill. All downstream pathology follows on the heels of microvascular dysfunction and impaired energy generation which, in turn, lead to worsening renal function, attenuation of energy flow into the ECF space, and acceleration of bone pathology.

OMNIA INCIPIT IN SANGUINE

In this final section we return to where we began – the organized blood-borne energy field – and consider the implications of this profoundly transforming rediscovery.

If, as Galen claimed, everything begins in the blood, and if, as we now see, both HF and CKD are manifestations of a progressively expanding energy deficit, then, as a self-evident principle, all therapeutic attempts must be oriented toward replenishment and restoration of the debilitated energy economy. Therapies must address dynamic causes, which is to say microvascular and diastolic

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dysfunction, otherwise there will be no stabilization or reversal of HF and CKD. We catch a glimpse of this principle at play in current therapeutics.

In 2014 a new class of hypoglycemic agents, the sodium-glucose transport (SGLT2) inhibitors, was introduced for the treatment of diabetes. Under normal circumstances all filtered glucose is reabsorbed into the blood by the renal tubules with no spillage into the urine. A class of receptors in the proximal renal tubule known as the SGLT2s reabsorbs about 80% of the glucose. SGLT2 inhibitors block function of these receptors leading to increased loss of glucose in the urine and resultant lowering of blood sugar levels [404-406].

Clinical studies affirmed improved glycemic control but it soon became apparent their actions extended far beyond lowering blood sugar. SGLT2 inhibitors induced weight loss, lowered hypertension, reduced cardiac arrhythmias, decreased proteinuria, delayed CKD progression, and improved outcomes in HF [407-414]. Effects were mediated by increased microvascular and mitochondrial function [415-423]. SGLT2 inhibitors are also associated with significant reductions in Hgb A1C [424, 425]. Improved microvascular function must be related to increased energy generation by RBCs related to decreased blood glucose levels [426, 427].

For obvious reasons SGLT2 inhibitors are not a final solution but the accidental discovery of beneficial effects points in a potentially fertile direction: therapeutic strategies should be aimed at enhancing RBC function and restoration of the PC response. Gradual optimization of PC should, over time, augment energy dynamics in the blood, ECF space and intracellular milieu. This would seem to be the best (and possibly only) option for potential reversal of these conditions. On the other hand, failure to address energy dynamics will result in predictable consequences as our final example illustrates.

Anemia is a very common complication of CKD and HF. Overall about 25% of those with CKD develop anemia and by the time end-stage disease supervenes at least 75% are affected [428-430]. The prevalence of anemia in HF ranges from about 10% to 70% which is also stage-dependent [431]. In both cases anemia is associated with diminished quality of life, progression of disease, increased hospitalization rates, and higher mortality.

Treatment of anemia remains controversial and far from ideal. Over the past three decades, iron supplementation, blood transfusions, and erythropoiesis-stimulating agents (ESAs) like EPO have been the mainstay but each has a downside. Oral and intravenous iron are associated with gastrointestinal side effects and infusion reactions. Excess iron induces free radical damage in cells and increases the risk of infection. Blood transfusions are associated with autoimmune reactions and autoantibody formation [432-434].

Since their release in 1989 ESAs have been regarded as the standard of care despite a black box warning alerting users to an increased risk for death, heart attack, stroke, blood clots, increased risk of tumor progression and shortened overall survival. And raising Hgb too much also worsens outcomes. Recent studies found increased risk of death and adverse outcomes with ESAs when attempts were made to raise Hgb into normal range [435-438]. This is undoubtedly related to diminished blood energy generation; attempts to stimulate RBC synthesis pull energy away from other vital functions; they rob from Peter to pay Paul.

Based on such pitfalls the search for a more suitable means to address the anemia problem continued eventually leading back to the PC phenomenon. In the early 1990s scientists identified a substance they called 'hypoxia inducible factor' (HIF) which is released during the early ischemic phase of the PC response and which appears to play a key role

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in mediating its effects. HIF induces a plethora of genes including those involved in production of RBCs, EPO and iron-transport proteins. Its potential to coordinate RBC synthesis and iron metabolism led many to regard HIF as an ideal successor to the ESAs for addressing the anemia dilemma [439-446].

But HIF is rapidly degraded by an enzyme, prolyl hydroxylase, and its effects are short-lived. To overcome this snag scientists developed a group of compounds known as the prolyl hydroxylase inhibitors (HIF-PHIs) that block its degradation and prolong its activity. In recent years dozens of clinical trials have evaluated the effect of these agents on anemia outcomes in CKD and, finally, in 2019 they were approved for use in various European and Asian countries although not in the US. Unfortunately, the HIF-PHIs performed little better than ESAs.

The effect of HIF-PHIs on RBC production was similar to that of the ESAs or, in research jargon, 'non-inferior'. And while they might improve iron metabolism, supplementation is still necessary. And then there is the thorny problem of side effects. In a pooled analysis of four major clinical trials, one of the agents, roxadustat, had a 6-fold higher incidence of venous thrombosis, 4.8-fold increase in pulmonary embolism, a 5.4-fold increase in seizures and a 2.4-fold increase in septic shock compared with placebo. It was also associated with higher adverse cardiac events and all-cause mortality [447-449]. Other reported side effects of the HIF-PHIs include gastrointestinal erosions, progression of renal fibrosis, hyperkalemia, activation/reactivation of cancers, progression of diabetic retinopathy and pulmonary arterial hypertension [450]. Doesn't the safety profile look just a bit worrisome?

The question raised by such results has less to do with the relative efficacies of HIF-PHIs versus ESAs but, instead, why do each of them have such marginal effects on anemia correction and improvement in outcomes? The answer can only be found in the deterioration of the blood-borne energy field. Both agents obviously activate specific energy-requiring functions in targeted cells but if energy status is marginal then results will be less than desirable. The profusion of side effects, especially those involving the vascular system such as clot formation, indicate energy is being actively drawn out of the blood for other functions. The inescapable conclusion is that any attempt to modify outcomes in HF and CKD, or their morbid consequences, must address the energy equation.

EPILOGUE

We have shown that the origins of HF and CKD, two of the most ubiquitous organ failure syndromes globally, lie not in the cellular and molecular domains as scientists have long claimed but, instead, are energetic in nature and related to the intertwined impairment of heart and kidney function culminating in progressive deterioration of the blood-borne energy field.

The inability of the cellular/molecular paradigm to accurately explain such happenings constitutes a classic paradigm collapse as described by Thomas Kuhn and, concurrently, signals the rise of a new energy-based paradigm in medicine. By the same token it underscores the urgent need for new diagnostic and therapeutic approaches to stem the rising black tide of chronic disease across the globe. There is precious little time for foot-dragging and dawdling on this immensely impactful issue.

Late 19th century psychoanalyst Pierre Janet argued that the sole purpose of consciousness is 'to attend to the function of reality'. Its purpose is not to devise abstract theoretical systems that have little bearing on real world events but to faithfully integrate the evidence that reality presents to the senses. For

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much of the 20th century medical scientists fell into a dogmatic slumber that precluded them from seeing the true nature of phenomena before their eyes.

We observe first-hand the sheer determining power of paradigm: one 'sees' what one is conditioned to see. Scientists, by instinct and training, are herd creatures who follow the well-trodden path and, by convention, are constrained in their ability to explore outside established boundaries. Such attributes are no longer conducive to discovery and innovation. Paradigms become totalizing (as in totalitarian) ways of perceiving reality. But intractable problems like HF and CKD cannot be solved using the same mode of thought that created them. This is the most important take-home lesson from the failed 20th century experimental medicine experiment.

True science is more than interminable experimentation and generation of data; it demands integration of evidence into a comprehensive and internally coherent framework that mirrors the function of reality. By the same token description and explanation are not one and the same. As a paradigm moves more deeply into abstract theorizing it runs the risk, like Ptolemaic astronomy, of creating an entirely fictional world of thought *even when based on objective facts*. Facts are real, how they are explained is another matter altogether.

Since the mid-18th century, based on the writings of philosopher David Hume, it has been recognized that no scientific theory can ever be proven. It is impossible to know what lies outside one's spatial or temporal frame of reference. 20th century scientists seem to have forgotten this crucial point: all scientific knowledge is tenuous and provisional. There is no place for hubris and dogmatism in science.

Based on the work of 20th century science philosopher Karl Popper it is established that the *only* way science advances is through refutation of existing hypotheses. We have met this demand vis à vis demonstration of the incompleteness of the cellular/molecular framework and it is now incumbent upon scientists to refute assertions advanced in this paper. In the event refutation is not forthcoming then the dynamic energy framework must be accepted as provisionally correct.

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