Cardiorenal Syndrome
An Evolutionary Point of View
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In modern societies, lifestyle-related diseases, such as hypertension, diabetes mellitus, and obesity, are major causes of cardiovascular disease (CVD) and renal failure. In particular, chronic kidney disease (CKD), as defined by reduced glomerular filtration rate (GFR; <60 mL/min per 1.73 m²) and/or the presence of renal damage for >3 months, is a significant threat to public health. Recent epidemiological studies have demonstrated that CKD is a significant risk for cardiovascular events independent of classic risk factors, such as hypertension, dyslipidemia, and diabetes mellitus. The incidence and prevalence of CKD are increasing worldwide, and CKD is a significant health problem associated with high morbidity, mortality, and healthcare costs. One of the features of lifestyle-related diseases is that an apparently minor insult to the kidney, as manifested by microalbuminuria, is associated with a heightened incidence of CVD. Why? We may be able to find an answer in the process of the evolution of life.2,3 It is plausible that the structures and functions of vital organs and molecules essential for survival in the natural environment have now become villains that jeopardize our health in a modern society. The representative examples may include the renin-angiotensin-aldosterone system (RAAS) and the circulatory systems that deliver blood supply to the sites crucial for survival, such as the brain stem.

Cardiorenal syndrome is classified into 5 subtypes.4 This review mainly discusses the relationship among the kidney, heart, and brain in lifestyle-related diseases. However, an insight into the fundamentals of structures and functions of vital organs from an evolutionary point of view would help us understand the pathophysiological interactions in the other types of cardiorenal syndromes.

Structure of the Mammalian Kidney
In all creatures, the milieu intérieur is kept constant, and this stability is essential to various cellular functions and, therefore, maintenance of life.5 In mammals, the kidney is the primary organ responsible for the maintenance of the milieu intérieur of the body. The mammalian kidney has several unique futures; for example, it has both long-loop and short-loop nephrons and the juxtaglomerular apparatus (JGA). The JGA is composed of glomerular afferent and efferent arterioles, the macula densa, and extraglomerular mesangium. The fact that the JGA appears first in amphibian species in evolution suggests that the transition from aquatic life to terrestrial life required this particular structure and its functions.6 The primary functions of the JGA are the control of renin release and the autoregulation of renal blood flow and GFR. The macula densa, a plaque of specialized tubular epithelial cells, is the sodium sensor of the body that controls the rate of renin release and the tone of glomerular afferent arteriole. The first direct evidence for the role of the macula densa in the control of renin release and afferent arteriolar tone was reported by Ito and colleagues.7-9

Figure 1 illustrates the anatomic relationships of the renal vasculature and tubular segments. The major functions of the cortex are the creation of a huge amount of glomerular filtrate and reabsorption of most of the essential elements for life, whereas the major function of medulla is urine concentration and dilution. The kidney is one of the organs that receive abundant blood supply. Renal blood flow amounts to as much as 20% of cardiac output, >90% of which is distributed to the renal cortex. To maintain a high and stable GFR, efficient mechanisms of autoregulation exist in the cortex so that renal blood flow and GFR remain constant in the face of large variations in systemic blood pressure (BP). On the other hand, medullary blood flow is not well autoregulated, so that an increase in systemic BP results in an increase in medullary blood flow.10 This increase in medullary blood flow seems to be an essential component of pressure natriuresis.

Teleological Significance of the Structure and Function of the Kidney
The outer medulla is the anatomic site most susceptible to ischemic injuries.11 As shown in Figure 1, blood flow to the renal medulla is supplied by the descending vasa recta, which emanate from the efferent arterioles of the juxtaglomerular glomeruli. In the outer medulla, particularly in the inner stripe, descending vasa recta (containing arterial blood) and ascending vasa recta (containing venous blood) run side by side in opposite directions, forming a countercurrent circulation. Oxygen thereby diffuses from the descending to the ascending vasa recta, reducing the oxygen content as blood descends through the vasa recta vessels. In addition, oxygen consumption is very high in the outer medulla because of the...
high levels of active ion transport in the medullary thick ascending limbs of the loops of Henle (mTALs) and proximal straight tubules, thereby reducing the oxygen content even further in this region. In contrast, oxygen consumption is low in the inner medulla because there is no active transport by the thin loop of Henle, and, therefore, tissue oxygen tension is well preserved.

Although the structure of the kidney looks complex, there are certain principals in terms of the length of the loop of Henle and the interrelationship between tubular segments and vasculatures. The juxtamedullary nephron has a long loop, and its efferent arteriole gives rise to the descending vasa recta, whereas both the midcortical nephron and superficial nephron have a short loop, and their efferent arterioles form peritubular capillary networks. Some superficial nephrons have even shorter loops that remain within the cortex. In the medulla, the collecting duct is located at the midpoint between the vascular bundles of the vasa recta. The interbundle territory is organized with the long loops of the juxtamedullary nephrons lying closest to the vascular bundle. Shorter loops arising from superficial glomeruli are more peripheral and, therefore, closer to the collecting ducts. Because of these anatomic relationships, mTALs of the superficial nephron are the tubular segments most vulnerable to ischemic injuries, because their location is far from the vascular bundle. Indeed, it has been reported that the characteristic renal pathology of acute kidney injuries is the necrosis of mTALs close to the collecting duct.11

The above-mentioned structures enable the kidney to maintain a high GFR and a high reabsorption rate, whereas avoiding ischemic renal injuries even in the face of limited salt intake and low systemic BP. When sodium intake is low and systemic BP is reduced, the JGA increases renin release and autoregulates glomerular hemodynamics. An increase in renin release would raise the levels of circulating and intrarenal angiotensin II (Ang II). The autoregulation and preferential efferent (over afferent) arteriolar vasoconstrictor action of Ang II would mitigate a decrease in GFR in individual nephrons. In addition, there are heterogeneities in the vasoconstrictor actions of Ang II in the superficial and juxtamedullary afferent arterioles. By microperfusing the afferent arteriole in vitro, we have shown that vasoconstriction induced by intraluminal Ang II is much stronger in the superficial than in the juxtamedullary afferent arterioles, with maximal constriction being 70% and 30%, respectively.12 Because of the strong constriction of the distal branches (superficial afferent arterioles), intraluminal pressure in the proximal segment of the interlobular artery would be increased. These changes in intrarenal hemodynamics combined with the weak constriction of juxtamedullary afferent arterioles would decrease superficial single nephron GFR and increase juxtamedullary single nephron GFR. Thus, the heterogeneity of Ang II action may explain the redistribution of renal blood flow and GFR from superficial to juxtamedullary cortex induced by sodium depletion or administration of Ang II.13,14 Taken together, when Ang II is elevated, the total GFR remains relatively constant, whereas the fraction of glomerular filtrate passing through the juxtamedullary nephrons increases. On the one hand, this increase in filtered load of sodium to long-loop nephrons would facilitate efficient recovery of filtered sodium. On the other hand, an increase in tubular sodium load would increase oxygen demand in the juxtamedullary nephrons. However, mTALs of these nephrons are located in the vicinity of the vasa recta, and, therefore, oxygen supply would be enough to avoid ischemic injuries of this nephron segment. In terms of protection of mTALs of superficial nephrons, the most vulnerable tubular segment to ischemic injuries, the decreases in single nephron GFR combined with increased proximal tubular absorption (by increased filtration fraction and Ang II level) would greatly reduce the amount of sodium delivered to mTALs. This would reduce oxygen demand and prevent ischemic injuries of mTALs of the superficial nephrons.
Thus, a kidney is sophisticatedly designed structurally and functionally so that a high GFR and electrolyte balances are maintained even under a very low sodium intake and low systemic BP while protecting the kidney itself from ischemic injuries. When we look into the kidney from the teleological point of view, we can understand the necessity of its complex and well-organized structures and functions.

**Albuminuria as a Cardiorenal Risk**

Epidemiological studies have established that reduced GFR and increased urinary albumin excretion are related to heightened incidences of cardiovascular morbidity and mortality. Microalbuminuria is of particular interest, because it is a significant risk factor not only in diabetic and hypertensive subjects but also in the general population. Studies have now shown that albuminuria even within the reference range is associated with higher incidence and prevalence of CVD, and this risk increases in a continuous fashion with the degree of albuminuria. It is of note that albuminuria is a predictor for adverse cardiovascular events independent of the GFR, suggesting that albuminuria and reduced GFR have distinct mechanisms as cardiovascular risks.

The mechanisms of the association between albuminuria and CVD are still largely unknown and are a focus of intensive research and debate. It has been suggested that albuminuria not only reflects glomerular damage but also is a sensitive indicator of generalized endothelial dysfunction and capillary vasoconstriction that leads to penetration of atherosclerotic lipoproteins into the arterial walls. Studies showed that albuminuria was associated with endothelial dysfunction in the systemic circulation, but not all studies support this contention.

Microalbuminuria results from glomerular injuries and/or reduced tubular reabsorption of filtered albumin. It is unlikely that all 2 million nephrons within the human kidney contribute equally to a miniscule amount of albumin leaking into urine. It is more probable that some nephrons are damaged, leaking a substantial amount of albumin, whereas the majority of others are not. Indeed, by using immunohistochemical staining for albumin, Kralik et al reported that the kidney from albuminuric type 2 diabetic subjects showed a heterogeneous pattern of staining, suggesting that albuminuria originates only from a small fraction of nephrons. The question is whether the nephron damage occurs randomly among all of the nephrons or according to some principle. A random phenomenon would be difficult to explain such a close linkage between microalbuminuria and CVD, because there is no logical necessity. However, if there is a principle that causes nephron damage in certain subpopulations, and if the same principle applies to some mechanisms of CVD, then it would be able to explain the close linkage.

**Strain Vessel Hypothesis**

In hypertensive renal injury, considerable heterogeneities exist among different nephron populations. Specifically, tissue injury is most obvious in the juxtamedullary region and outer medulla in spontaneously hypertensive rats. Dahl salt-sensitive hypertensive rats, renovascular hypertension, and Ang II–induced hypertension. In addition, it has been shown that, in spontaneously hypertensive rats, glomerular lesions first appear predominantly in the juxtamedullary nephrons and then extend toward more superficial nephrons. Such distinct localization of renal injuries and mode of progression may be related to anatomic and functional heterogeneities of different nephron populations.

As shown in Figure 1, the juxtamedullary glomeruli are located deep in the cortex, and their afferent arterioles arise from either the initial segment of the interlobular artery or directly from the arcuate artery. In more superficial nephrons, their glomerular afferent arterioles branch off from the more distal segments of the interlobular arteries. Because glomerular capillary pressure is normally maintained at \( \approx 50 \text{ mmHg} \) by autoregulation in all nephrons, the pressure gradient across the afferent arteriole would be greatest in the juxtamedullary nephron. In other words, the juxtamedullary afferent arteriole is exposed to unusually high pressure for a vessel of its size \((\approx 20 \mu\text{m})\) and is destined to maintain strong vascular tone to provide this large pressure gradient in a short distance between the large arcuate artery and the glomerulus. In contrast, in the superficial nephrons, a more gradual pressure reduction occurs along the greater length of vasculature, including the entire interlobular artery and afferent arterioles. It is of note that the interlobular artery also participates in renal autoregulation, and, therefore, the feeding pressure of superficial afferent arterioles is substantially lower than that of juxtamedullary afferent arterioles.

There are many diseases and mechanisms proposed to cause microalbuminuria. As discussed above, however, regardless of the pathogenesis of microalbuminuria, the anatomic sites that are injured initially or more severely are the juxtamedullary afferent arterioles and glomeruli. It would be reasonable to expect that, in the early stages of hypertension, diabetes mellitus, or aging, renal injury occurs predominantly in the juxtamedullary nephrons, whereas the majority of other nephrons remain relatively intact. This would be expected to result in only minimal increases in urinary albumin excretion. Indeed, we observed that, in Otsuka-Long-Evans-Tokushima-Fatty rats, podocyte injuries, as measured by desmin staining, were evident only in the juxtamedullary but not superficial glomeruli in an early stage of developing albuminuria.

From the hemodynamic point of view, the juxtamedullary afferent arterioles are small and short vessels that are exposed to a high and pulsatile pressure and destined to maintain strong vascular tone to provide a large pressure gradient in a short distance. We refer to these kinds of vessels as "strain vessels." Thus, microalbuminuria may be an early marker of vascular damages of strain vessels within the body. Other strain vessels exist most notably in the central nervous system, where many perforating arteries arise directly from large high-pressure arteries, such as anterior, middle, or posterior cerebral arteries, and penetrate into the brain tissues (Figure 2). As in the case of juxtamedullary afferent arterioles, these perforating arteries are exposed to a high pressure and destined to maintain high vascular tone to provide large pressure gradients from their parent arteries to brain tissue.
capillaries. It is well known that the sites of hemorrhage or infarction in the brain are frequently the areas of blood supply governed by these perforating arteries. Thus, “strain vessels injuries” may explain the link between vascular damage and microalbuminuria in the kidney and stroke.

Central Hemodynamics as a Possible Link Between Albuminuria and CVD

Unlike strain vessels in the kidney and central nervous system, coronary arteries do not provide a pressure gradient. However, they are also under high-pressure hemodynamic conditions with a strong vascular tone, having the common features of the strain vessel. It is well known that coronary blood flow depends primarily on diastolic and not on systolic BP. Coronary arteries arise directly from the aorta, and during the systolic phase there is little coronary blood flow because intramyocardial vessels are compressed because of myocardial contraction. This creates a unique situation that, during the systolic phase, the entire epicardial segments of coronary arteries, including small arteries just before their entering the myocardium, are exposed to a very high pressure, because there is little outflow. Studies have shown that coronary arteries (particularly small-sized segments) exhibit myogenic responses, so that when intraluminal pressure is elevated, they would contract strongly to maintain vascular integrity. In addition, Hashimoto and Ito have shown recently that central pulse pressure is closely related to changes in renal hemodynamics (resistive index of renal segmental artery) and urinary albumin excretion rate. It has been reported that a high pulse wave velocity and altered central hemodynamics are associated with high event rates of CVD independent of BP measure at the upper arm. Thus, central hemodynamics may be a common basis for the associations among albuminuria, stroke, and coronary arterial disease. Unlike other small vessels in peripheral circulation where blood flow and pressure are rather constant, the strain vessels are exposed to pulsatile pressure and flow, and, therefore, stiffness of large arteries would have a great impact on the burden imposed on strain vessels.

Albuminuria and Salt Sensitivity of BP

One of the features of microalbuminuria is the close association with salt sensitivity of BP, and this association is observed even in normotensive subjects. Salt-sensitive hypertension is characterized by glomerular hypertension, microalbuminuria, and a higher mortality and morbidity of cardiovascular events.

There are many mechanisms involved in the salt sensitivity of BP, and one such mechanism may be impaired pressure natriuresis. When salt is ingested with meals, various neurohormonal changes, such as inhibition of the RAAS and enhanced production of prostaglandin and NO, occur and thereby increase GFR and reduce tubular sodium reabsorption. It has been shown that, in humans, ingestion of a high protein meal induces a substantial (~40%) increase in corti-
cal blood flow. Although there is no report on the measurement of medullary blood flow in humans, animal experiments have shown that an acute infusion of saline or amino acids increases medullary blood flow and that an increase in medullary blood flow promotes natriuresis. The postmeal natriuretic response seems to be accounted for by an early (0–90 minutes) increase in glomerular filtered load of sodium and a late (90–180 minutes) reduction in tubular sodium reabsorption. These acute changes in renal function play an important role in achieving daily sodium balance, and when these changes fail to accomplish a complete sodium balance, extracellular volume increases, resulting in an elevation in BP. This elevation in BP then increases sodium excretion (pressure natriuresis), and one of the mechanisms of pressure natriuresis is the increase in medullary blood flow.

According to our strain vessel hypothesis, microalbuminuria indicates the existence of damage in juxtamedullary afferent arterioles and glomeruli and, therefore, impairments of the downstream medullary circulation. Because the medullary circulation plays a crucial role in the mechanisms of pressure natriuresis, microalbuminuria may be related to impaired pressure natriuresis and, therefore, salt sensitivity of BP. In addition, in the early stages of juxtamedullary glomerular injuries, there may be functional alterations in vasa recta. Namely, glomerular hypertension/hyperfiltration in the juxtamedullary glomeruli may cause constriction of descending vasa recta and thereby functionally impair renal medullary circulation. It is of note that mTALs of the juxtamedullary nephron are located close to the vasa recta that supply blood to the medulla. Mori and colleagues have demonstrated the presence of tubulovascular cross-talk in which NO or superoxide produced by the mTALs can diffuse into pericytes of descending vasa recta. By microperfusing mTAL segments in vitro, Abe et al. demonstrated that an increase in sodium chloride concentration of the tubular perfusate stimulates superoxide anion production and decreases NO. Thus, hyperfiltration in juxtamedullary nephrons would increase sodium delivery to their own mTAL and stimulate superoxide production, which, in turn, may cause vasoconstriction of the descending vasa recta. Thus, our strain vessel hypothesis may explain close interrelationships among microalbuminuria, salt sensitivity of BP, and cerebrocardiovascular mortality and morbidity. It should be noted, however, that other factors, such as the RAAS and insulin sensitivity, also play a role in salt sensitivity of BP.

CKD Components as Cardiorenal Risks
As mentioned above, in such diseases as hypertension, diabetes mellitus, and obesity, vascular injuries occur first in the strain vessels. The renal manifestations of the injuries are microalbuminuria and salt sensitivity of BP, and both would be significant risk factors for CVD because they may indicate strain vessel injuries in other vital organs. As endothelial and vascular damage become advanced, more and more glomeruli are injured, resulting in a substantial amount of albuminuria and reduced GFR. In addition, proteinuria induces tubulo-interstitial damage within the kidney, thereby contributing to a further decline in GFR. Therefore, overt albuminuria is a strong risk factor for both renal and cardiovascular events in subjects with hypertension, diabetes mellitus, and/or obesity.

In contrast to lifestyle-related diseases, overt albuminuria does not seem to be a significant risk factor for CVD in primary glomerular diseases. Urine abnormality is the first sign of primary glomerular disease, and its manifestation is often proteinuria (macroalbuminuria) rather than microalbuminuria. The degree of urine abnormalities reflects the degree of glomerular injury but not strain vessel injuries. Therefore, albuminuria alone may not be a risk factor for CVD because strain vessels are not the primary sites of injuries.

Once renal function is reduced regardless of the original cause, numerous nonclassic risk factors come into play for further aggravation of renal dysfunction and endothelial and vascular injuries. They include oxidative stress, inflammation, bone-mineral disorder, anemia, and so forth. Both classic and nonclassic risk factors induce renal damage, and renal dysfunction further aggravates classic risk factors, as well as nonclassic risk factors, thereby forming a vicious cycle. Both classic and nonclassic risk factors are powerful accelerators of atherosclerosis. It has been shown that even moderate renal dysfunction is associated with enhanced oxidative stress and inflammation, which, in turn, accelerate atherosclerosis in the general circulation.

An Evolutionary Point of View and Perspectives
Why do we have such vulnerable structures as strain vessels or the RAAS that may cause organ damage? From the evolutionary point of view, we speculate that unique structures such as strain vessels in vital organs, as well as neurohormonal systems such as the RAAS, would have been essential for creatures on the land to survive under their natural environments. All creatures, in their natural environments, were constantly facing the danger of circulatory collapse and starvation. Given the generally difficult access to salt and a high risk of wound injuries, hypotension and hypoperfusion of vital organs were the principal challenges with which they had to cope. For this purpose, the complex and well-organized renal structures, sophisticated integration of various renal functions, and the potent vasoconstrictor and sodium-retaining actions of RAAS were all indispensable. In addition, to maintain the perfusion of the vital tissues, such as brain stem, it was necessary to develop circulatory systems in which vessels are branched off directly from the large arteries and deliver blood to the tissue. Without sufficient evolutionary time to adapt to the modern diets of the rapidly developed industrialized societies, the organisms were not designed to cope with high salt intake, hypertension, and obesity, as reviewed elsewhere. Taken together, the close link between CKD and CVD may be viewed as an inevitable consequence destined by evolution. In other words, although we human beings enjoy the benefits of many developments after the industrial revolution, we have to keep in mind that our fate is still governed by the natural laws of evolution. Thus, perspectives from an evolutionary point of view may explain why hypertension and diabetes mellitus, unforeseen
in the concept of evolution, preferentially affect vital organs such as the brain, heart, and kidney.

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