Review article

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Atrial natriuretic factor: a protective role after acute renal ischemia?

Is there room for it in kidney transplantation?*

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Abstract. Because of the deleterious effects of acute tubular necrosis (ATN) after kidney transplantation, the search for new and effective means of protecting the kidneys from ischemic or nephrotoxic injuries continues. The beneficial effects of hyperhydration with mannitol or furosemide infusions in renal allograft recipients have now been well documented. The recent discovery by De Bold and coworkers that hypervolemia (by atrial distension) induces the release of atrial natriuretic factor (ANF) suggests an important physiopathological, and perhaps therapeutic, role for this natriuretic peptide in kidney transplantation. In addition to providing an overview of the current knowledge about ANF and its effects on both intact and ischemically injured kidneys, the physiological role of ANF in various situations, similar to those found in kidney transplantation, is analyzed. The effects of ANF on arachidonic acid metabolites and on the nephrotoxic side effects of cyclosporin are also reported. If the results of the preliminary experimental studies appear to be effective, further prospective clinical trials must be carried out to confirm them.

Key words: Atrial natriuretic factor, in kidney transplantation – Renal ischemia, atrial natriuretic factor

Acute renal failure (ARF) is a major problem in contemporary medicine. Five percent of all hospitalized patients are affected by some degree of ARF [9]. In various clinical situations, such as in intensive care medicine, following cardiovascular surgery, and after cadaver renal transplantation, the reported incidence of ARF fluctuates between 6% and 90% [9, 43]. Thus, the development of effective means to protect the kidneys against ischemic or nephrotoxic insults appears to be a prime necessity.

The discovery by De Bold and coworkers that an infusion of atrial extracts of mammals – including humans – into rats produced an important natriuresis seems to be a new and important step in the search for effective means for protecting the kidney against various injuries [17, 18]. Indeed, a 28-amino acid peptide was quickly identified as the causative factor of this effect, and this hormonal peptide, physiologically secreted by the atria, was named atrial natriuretic factor (ANF).

Atrial distension or the raising of atrial pressure after intravascular volume loading or similar procedures [42, 54] has been identified as the main stimulus of endogenous ANF release. The recent discovery of this natriuretic peptide must, therefore, be taken into consideration in the future to explain the various effects previously attributed to overloading in experimental or clinical reports.

ANF and the intact kidney

The action of ANF on the intact kidney appears not only to be as a powerful natriuretic substance but also as an elective vasodilatator of the preglomerular renal afferent artery with a concomitant efferent artery constriction [46, 47]. Furthermore, ANF inhibits the renin-angiotensin-aldosterone axis [36]. Thus, in several experimental as well as clinical studies, synthetic ANF infusion significantly increased the glomerular filtration rate (GFR), the urinary flow, and the total or fractional sodium excretion rates. All of these effects were, moreover, obtained with low doses of synthetic ANF (3 ng/kg per minute), reproducing physiological (30–40 pg/ml) or merely supraphysiological plasma levels (100 pg/ml) [1, 16, 20, 46, 55]. The use of higher doses of ANF (≥ 0.1 μg/kg per minute), inducing plasma levels 100–150 times higher than those in the physiological range, also increases the GFR and the natriuresis, but then produces a vasorelaxation and, therefore, a transient drop in mean blood pressure [20, 38, 46, 55]. Thus, ANF possesses both vascular and glomerulotubular effects on the intact kidney.

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ANF and the ischemically injured kidney

Several experimental studies in both rats and dogs were performed to investigate whether ANF keeps these effects after ischemic injury and whether ANF therefore appears to be a useful drug in protecting the kidney against ischemic or nephrotoxic injury.

ANF and renal function recovery after acute renal ischemia. In non-nephrectomized rats, a synthetic ANF infusion, inducing ANF plasma levels five to six times higher than baseline values, produced, after 30 min of renal artery occlusion (RAO), an improved GFR (+15%), an increased urinary flow (fivefold), and a sodium excretion rate comparable to that in a control group receiving only isotonic saline solution at the same rate (1 ml/h) [23, 24, 28]. Similar results, in terms of improved GFR and natriuresis, were reported by other authors in both rats and dogs after a RAO of 60 min [49, 60] and in the norepinephrine or glycerol-induced acute renal failure models [57]. Moreover, Nakamoto et al. clearly demonstrated that these effects remain established 24 or 48 h after RAO (in terms of a better creatinemia) and that the renal adenosine triphosphate regeneration (P-31 nuclear magnetic resonance) was significantly improved in ANF-infused animals during the reflow period [49].

Histologically, Shaw and colleagues showed that an ANF infusion after acute renal ischemia decreased medullary hyperemia and prevented intratubular cell shedding and granulocyte margination [60]. These results suggest that an ANF infusion can preserve GFR and reduce renal tissue damage in rats after renal ischemia.

ANF, hypervolemia, and acute renal ischemia. Intravascular volume loading seems to be, through an atrial distension, the major physiological stimulus for endogenous ANF release [22, 42, 54]. To investigate whether the protective effect of overloading after acute renal ischemia was related to this ANF release, we studied another dog model. In non-nephrectomized dogs, left RAO was performed for 45 min. Three experimental groups were studied: *a control group* (normal hydration of 0.13 ml/kg per minute with isotonic saline during and 2 h after RAO); *an overload group* (acute volume loading with whole blood 1 ml/kg per minute during the 45 min of RAO, followed by a similar hydration of 0.13 ml/kg per minute 2 h after declamping); and *an ANF-infused group* (infusion of synthetic α 1–28 human ANF; 3.6 ng/kg per minute dissolved in isotonic saline and infused at a rate similar to that in the control group). As expected, a rise in cardiac filling pressures and a five times higher parallel ANF release were measured in overloaded animals. Two hours after declamping, the GFR was three times higher and the natriuresis ten times higher in overloaded animals than in the control group. The total or fractional sodium reabsorption and excretion rates followed a similar rise [25, 27]. In the ANF group, owing to very low doses of ANF infusion, reproducing comparable or merely supraphysiological (±120 pg/ml) ANF plasma levels as in loaded animals, the GFR dramatically increased (sevenfold), as did the natriuresis (15-fold) in comparison with the controls.

Moreover, the renin-angiotensin axis, stimulated by acute ischemia, was inhibited in the overloaded and ANF-infused dogs. The inference that the beneficial effects of volume loading after ischemia are, at least in part, mediated by an ANF release can, therefore, be postulated. This hypothesis seems reinforced by the recent report that the natriuretic effect of volume loading is inhibited by a simultaneous anti-ANF monoclonal antibody infusion [37].

ANF and hyperosmotic substances. Hyperosmotic challenge, such as with mannitol, has proved beneficial in early renal function recovery after acute renal ischemia [6, 64, 65, 69]. In this regard, we have observed in dogs that a slow mannitol infusion (1098 mosmol/kg; 0.13 ml/kg per minute), at a dose currently used in clinical situations, induces a rise in endogenous ANF release (reaching 120 pg/ml; twice as high as in controls). During this hyperosmotic infusion, neither cardiac filling pressures (atrial or pulmonary artery pressures) nor osmolarity changed. These results suggest that mannitol, per se, stimulated higher ANF production [27].

ANF, acute renal ischemia, and arachidonic acid metabolites. It is well known that arachidonic acid metabolites such as thromboxane A_2 (TXA_2) and prostacyclins (PGI_2) play a major role in the pathophysiological events involved during and after an acute ischemic insult [3, 44, 52]. We clearly demonstrated in rats that an ANF infusion (α 1–24 atriopeptin), after a RAO of 45 min, electively stimulated the prostacyclin synthetase and, therefore, produced a higher vasodilatative PGI_2 production. Therefore, the calculated TXA_2/PGI_2 ratio after an ANF infusion was similar to that in physiological conditions (sham-operated rats without ischemia) [28].

The higher release of vasodilating substances such as PGI_2 may explain the afferent artery vasodilatation observed with ANF infusion. Moreover, the redistribution of the renal blood flow to the inner cortex after an ANF infusion has recently been reported as mediated by this PGI_2 production [35]. To the contrary, the natriuretic ANF effect appears to be prostaglandin-independent since a cyclo-oxygenase inhibitor does not influence the natriuresis due to ANF. These results could shed some light on the mechanism underlying the vascular effects of the natriuretic peptide after ischemia.

ANF and nephrotoxic agents. An intravenous cyclosporin A (CyA) infusion, inducing CyA plasmatic levels (about 1700 ng/ml) four to five times higher than plasmatic levels usually measured in clinical kidney transplantation, produced an important drop in GFR and natriuresis in rats after acute renal ischemia (30 min of RAO). In contrast, a concomitant ANF infusion (0.5 μg/kg per minute) completely reversed these deleterious effects and, furthermore, produced an improved GFR and a higher natriuresis than in the control group receiving only saline solution [26]. These results might be correlated with the above-mentioned results in which ANF seems to be an elective stimulator of PGI_2 release. Indeed,

CyA, unlike ANF, produces a preferential TXA_2 production. In the same way, the nephrotoxic side effects induced by aminoglycosides, cisplatin, and contrast medium agents have recently been reported to be inhibited by ANF [12, 34, 58].

Acute renal failure pathogenesis and the possible protective role of ANF

A good understanding of the pathophysiology of ARF is a prime necessity in order to establish the natriuretic peptide as an effective means of protecting the injured kidney. Several successive periods occur during ARF and provide, therefore, various consequences [8].

Initiation phase. With renal vasoconstriction, the decrease in the renal blood flow and the rise in renal vascular resistance are the first pathological signs observed at the beginning of ARF. The stimulation of the renin-angiotensin-aldosterone axis and the secretion of vasoconstrictive prostaglandins such as TXA_2 are well documented during this phase.

Many vasoactive agents (secretin, acetylcholine) have already been reported to reverse the renal vasoconstriction and the decreased RBF, but in clinical situations, dopamine (a beta receptor agonist) seems to be of relevant clinical use [31]. The vasodilatation of the preglomerular artery, the inhibition of the renin-angiotensin axis, and the PGI_2 release noted with ANF in the previous studies may suggest a theoretical interest of this peptide during this initiation phase.

During the *ischemic period*, a decrease in the cellular adenosine triphosphate (ATP) concentration, a rise in the intracellular sodium and free cytosolic calcium, and, finally, a shift from aerobic to anaerobic metabolism are the most important cellular events [2, 5, 15, 48, 66]. Cell swelling and membrane damage are the prompt results of these intracellular events.

Similarly, in organ preservation, the swelling of the cells appears to be the prominent sign of ischemic injury [53]. However, kidney perfusion with hypotonic solution, which produces a similar degree of cell swelling [39], is less damaging than a comparable degree of anoxic cell swelling. This fact confirms the notion that anoxic damage involves more than merely cell swelling and explains preservation lesions.

To date, the relationship between cellular anoxic swelling and ANF remains unexplored. On the other hand, during this period, the role of the calcium channel blockers seems to be of the utmost importance [29, 59].

The *vascular reflow period* is one of the most important phases affecting the resulting renal impairment. Indeed, the reflow provides oxygen, substrates, and ATP for membrane repair. Nevertheless, this vascular reflow is also associated with the formation of oxygen-free radicals, with a rise in nonionized calcium within the cells, and the removal of the protective effect of the extracellular acidosis [33].

Moreover, despite this adequate reoxygenation of renal tissues and the normalization of the RBF, the lesions of ARF persist and the GFR remains depressed. These facts seem to be in accordance with the role of tubular components during the *maintenance phase* of ARF. Tubular swelling and/or obstruction by intraluminal debris are the two major tubular events involved.

Several agents have been beneficial in clinical and experimental studies during this phase of ARF. Hyperosmotic diuretics, such as mannitol, protect the kidney against ischemic injuries through a rise in RBF and a possible role as free radical scavenger. Mannitol also prevents tubular cell swelling and, therefore, reduces the severity of intratubular obstruction [6, 64, 65, 69].

Other loop diuretics, such as furosemide, which inhibit glomerulotubular feedback, are commonly used in clinical transplantation, but their efficiency in protecting from ARF still remains controversial [41]. Moreover, the use of dopamine with furosemide should be more effective against ARF since it results from the association of agents affecting both vascular and tubular components. The calcium channel blockers, which can increase the RBF and prevent vascular and tubular damage by decreasing cellular calcium uptake, represent another very important approach to reducing the deleterious effects of renal ischemia. Nevertheless, in clinical studies, the calcium channel blockers seem to be more effective when they are infused before an ischemic insult and, consequently, have less clinical relevance. Thus, these calcium blockers are probably useful in kidney transplantation since they can be used in the donor and during organ preservation [29, 59].

The role of the natriuretic peptide with regard to these considerations therefore seems interesting during the initiation phase and during the reflow period since its important natriuretic effect could be useful in preventing tubular obstruction. Moreover, ANF improved ATP regeneration during the reflow period [49]. The possible effect of ANF upon cellular swelling has not yet been explored; however, ANF has recently been recognized as preventing the mobilization of the hormone-induced intracellular calcium in cultural mesangial cells.

ANF and patients in end-stage kidney failure

The plasma concentration of immunoreactive ANF has been reported to be markedly increased in patients with congestive heart failure and in those with chronic renal failure [21, 56, 61]. This may be due to a combination of volume overload, an altered renal metabolism of the peptide, and the release of a prohormone that has a longer plasma half-life than α R-ANF. After kidney transplantation, on the other hand, ANF levels decrease with normalization of the creatinine clearance [19]. Despite the high levels of endogenous ANF in patients with end-stage renal disease (ESRD), recent reports clearly demonstrate that, as previously described in healthy volunteers, ANF has the same effect in patients with ESRD or nephrotic syndrome. Indeed, a higher sodium excretion rate, improved GFR, and a transient drop in blood pressures were documented with an ANF infusion (bolus or infusion) at a dose similar to that used in healthy subjects [10, 67, 68].

ANF and kidney transplantation

The reported incidence of ARF in renal transplantation reaches ±10% in grafts from living related donors, but ranges from 6% to 90% in cadaver renal allografts following the various transplant centers [11, 43, 63].

In several situations ARF is not foreseeable and cannot be prevented, although in clinical renal transplantation the most commonly involved causative factors are, at the present time, well documented. Indeed, acute tubular necrosis (ATN) remains the most common cause of ARF in the early post-transplantation period. Hyperacute rejection and vascular or urinary surgical complications may be possible sources of ARF but they are now uncommon. Nephrotoxic agents, particularly cyclosporin A (CyA), may also contribute to ARF [32].

ATN may occur secondarily to intrinsic factors relating to the donor, to the graft itself, and to the recipient's characteristics and management. Indeed, adequate hemodynamic donor management in which prolonged hypotension, hypovolemia, and the need for vasopressor drugs can be avoided has thus been the first important step in lessening the incidence of postoperative ATN. Moreover, the technique of in situ cold perfusion precludes the deleterious first warm ischemic period.

As for the graft itself, it is well documented that an increased cold and/or warm ischemic time is followed by a somewhat parallel rise in delayed graft function incidence [11, 30]. New preservation solutions, such as University of Wisconsin solution, thus appear to be fundamental [40]. Good preservation methods are equally important since long-term graft survival, even in the cyclosporin era, is more related to the respect of good matches than to total ischemic time [50, 51]. It therefore seems clear that reducing the average ischemic time to under 24 h is still difficult since immunologic screening for ABO and HLA compatibilities, detection of preformed cytotoxic antibodies, and organ sharing within various contries must all be carried out.

During this cold ischemic period, ANF appears to retain the protective effects previously described with warm ischemia. Indeed, the inclusion of ANF in a flushing solution (Collins) allows for improvement of the in vivo inulin clearance in the rat after renal transplantation [71].

Finally, the hemodynamic parameters of the graft's recipient appear to be of prime importance in decreasing the incidence of ATN in cadaver renal allografts. Indeed, in experimental studies it is well documented that volume overloading protects the kidney against acute ischemic insults through an enhancement of the RBF, an improved GFR, and a higher urinary flow or solute excretion [7, 70]. Likewise, in clinical studies, Carlier et al. clearly demonstrated that hyperhydration of the graft recipient decreased the rate of ATN from 36% in patients receiving restricted fluids to 6% in overloaded patients [13]. These results suggest the mediation of a humoral factor since the kidney had been denervated during the harvesting. Our experimental results allow us to hypothesize that ANF could be, at least in part, this humoral mediator. This inference is furthermore reinforced by the fact that the correlation between ANF levels and cardiac filling pressures in renal transplant recipients has recently been established [14].

In relation to allograft recipient management, it has recently been reported that moderate hydration associated with mannitol infusion before declamping also decreases the incidence of ATN from 53% in a control group to 4.8% [64, 65]. The higher endogenous ANF release that we measured in dogs infused with mannitol (at a dose similar to that in these clinical studies) reinforces the interest of this physiological, and perhaps therapeutic, peptide.

It can be concluded that following acute renal ischemia in various experimental models, ANF provides beneficial effects that protect the kidney against ischemic insult. Indeed, the natriuretic peptide improves the GFR, produces a higher diuresis and natriuresis, inhibits the angiotensin-renin system, and finally causes a preferential secretion of vasodilatative substances such as PGI_2. Moreover, in these models, ANF prevents the nephrotoxic side effects of cyclosporin A. All of this suggests important applications in human kidney transplantation, all the more so since similar protective effects with ANF were recently reported in dog autografts after 24 h of cold ischemia [45].

Furthermore, it is likely that ANF is the humoral factor that could at least partially explain the beneficial effects of volume loading or hyperosmotic challenges upon the denervated, ischemically injured kidney.

The clinically relevant usefulness of ANF in kidney transplantation is related to the fact that beneficial effects were obtained when ANF was given immediately after the ischemic injury and also that these protective effects were obtained with low, and merely supraphysiological, doses which did not induce undesirable side effects. Recent clinical studies in patients with end-stage renal disease or nephrotic syndrome demonstrate that ANF keeps these natriuretic effects in patients with higher plasma ANF levels and encourage researchers to carry out clinical trials in kidney allograft recipients. Randomized clinical trials must be performed in order to determine the best management of ANF for use in these patients and to choose the appropriate type of infusion and duration.

The results of all the aforementioned experiments are interesting, but it is also clear that ANF is not always able to reverse the renal function of the oligoanuric kidney when it is already in the maintenance phase of acute ARF [4, 62]. This fact reinforces the necessity of using ANF just before declamping and secondarily with a continuous infusion of very low doses for several days.

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