Pathophysiology of oedema in idiopathic nephrotic syndrome

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Abstract

The decrease in plasma protein and colloid osmotic pressure (COP) in the nephrotic syndrome is accompanied by a decrease in tissue-fluid protein and COP. The latter protects against a fall in blood volume. However, the range and speed of this protective mechanism are limited, and a decrease in blood volume can be expected if plasma COP is below ~10 mmHg, or (temporarily) if the protein loss starts very fast. In addition, due to this protective mechanism volume retained by the kidneys cannot effectively expand blood volume, explaining that hypertension is rarely grave and pulmonary congestion unusual, whereas peripheral oedema can be gross. The renal derangement leading to volume retention involves a decreased filtration per nephron, increased tubular reabsorption, and decreased sensitivity to ANP but the relation between these changes is incompletely resolved.

Keywords: nephrotic syndrome; oedema; pathophysiology

Transcapillary fluid balance

The notion that plasma volume (blood volume) is decreased in the nephrotic syndrome (NS) stems from the fact that in the Starling equilibrium, which dictates that the plasma colloid osmotic pressure (pCOP) is a major driver for plasma fluid to be retained in the vascular compartment. According to this equation, a decrease in pCOP such as follows from renal protein loss results in an increased fluid shift to the interstitium. But how about interstitial COP (iCOP)? Would that remain unchanged during hypoproteinaemia? Of course not. There is a continuous dynamic exchange and equilibrium between vascular protein, in particular albumin, and interstitial albumin, which is essential for normal blood volume regulation [1]. This exchange is so effective, that if pCOP drops from the normal value of 24–14 mmHg, i.e. by 10 mmHg, the iCOP will drop by approximately the same amount, say from 14 to 4 mmHg [2]. Consequently, the drop in pCOP is compensated for by an equal drop in iCOP, which prevents a fluid shift from plasma to interstitium, or, in other words, prevents a drop in plasma and blood volume.

Indeed, blood volume measurements are generally normal or even somewhat increased in the NS [3]. Blood pressure is also mostly normal or even increased, which would be difficult to understand if blood volume would be low. A good case for the idea that blood pressure is indeed elevated rather than low is made by the observation in adults [4] as well as in children [5] that blood pressure drops after steroid-induced recovery from the NS. In these patients, plasma renin activity is often higher after recovery from the NS [4,6], also pointing against a decreased blood volume in the nephrotic phase. However, the case for plasma renin is more complex, as some patients may have extremely high concentrations [7].

The parallel decreases in plasma and iCOP help to maintain a normal fluid distribution and blood volume during normal hydration state, but at the same time have great consequence for the distribution of volume that is retained by the kidneys. In normoproteinemic conditions such retained fluid will expand both blood volume and interstitial volume. As it is, interstitial expansion will accelerate lymphatic flow and replace albumin from interstitial space to the blood. The increased blood albumin mass will keep part of the retained fluid in the blood compartment, which is important, as that will form the physiological basis for stimulation of renal volume excretion, and restoration of the balance.

During hypoproteinaemia, interstitial albumin concentration is low, virtually zero if hypoproteinaemia is severe. In these conditions, fluid retained by the kidney will not, or in any case less, expand blood volume, as

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there is no tissue-fluid albumin to be replaced to the
blood. Therefore, in the NS the excess volume is mainly
distributed to the interstitium, and blood volume
remains within normal limits irrespective whether total
hydration is normal or increased. Consequently, fluid
overload can in general be removed without causing
hypovolaemia. The absence of a blood volume increase
despite overhydration averts severe hypertension and
pulmonary congestion, which are uncommon in the
NS. This explains why patients with the NS have a
much higher tolerance for fluid retention and are more
severely overhydrated when referred for treatment than
patients with chronic renal failure. We found that out
when we followed patients with chronic renal failure or
with the NS during their clinical treatment for
overhydration [8].

There are some limitations to the compensatory
power of the transcapillary albumin redistribution
mechanism. First, there is an end to the amount of
interstitial albumin. The normal interstitial albumin
mass in an average adult is ~250 g, and the iCOP
~14 mmHg (but less in depending extremities). This
means that when pCOP has dropped by >14 mmHg
(or <10 mmHg), the gradient between pCOP and
iCOP must have decreased. In those circumstances the
blood volume cannot be maintained. This is the case in
severe NS, such as occurs in children with minimal
lesions NS, or, particularly, congenital nephrosis [9].
In adults such extreme situations occur less often,
and then mostly in MLNS or amyloidosis (‘malignant
proteinuria’). We have confirmed this principle in
dogs, in whom progressive hypoproteinaemia was
induced by repetitive plasmapheresis. These dogs, who,
in contrast to the NS, have normal kidneys, appeared
able to excrete a volume challenge when the artifi-
cially decreased pCOP was allowed to rise above
9 mmHg [10].

The second limitation concerns the speed of albumin
circulation between plasma and interstitial compart-
ment, probably 24 h for a complete circle. This means
that with a sudden strong loss of plasma proteins, such
as can occur in the initial phase of a minimal lesions
NS, mobilization of interstitial albumin may be too
slow to compensate for the decrease in pCOP. A
temporary decrease in effective blood volume is the
result, but the circulation can recover within a day,
when mobilization of interstitial protein is completed.
This leads to the interesting situation that initially a
patient may show symptoms of hypovolaemia at a
moderately decreased plasma protein concentration,
whereas these symptoms have disappeared later,
although plasma protein has dropped further. This
sequence of events is found particularly in the initial
phase of minimal lesions NS, again more often in

The third limitation is that the physiological decrease
in blood volume that occurs during standing is
enhanced during hypoproteinaemia. This implies that
upon standing a subnormal effective circulation may
arise in patients in whom pCOP is around the critically
low level [12].

Sodium retention in the NS

The observation that patients with NS retain volume in
the absence of a low blood volume implicates that it is an
intrinsic renal abnormality. However, measurements of
blood volume have been criticized as not sufficiently
accurate to exclude (impending) hypovolaemia [13].
Other observations in humans present convincing
evidence that the kidney in the NS indeed has an
intrinsic inability to excrete sodium. Patients with
incipient minimal lesions NS start to retain sodium
when plasma albumin is still normal [11,14]. Patients
with established minimal lesions NS, in whom recovery
is induced with steroids start to excrete the excess
volume when plasma albumin concentration has hardly
changed from its hypoproteinaemic level [6,15]. The
other observation is that experimental hypervolaemia,
either induced by head-out water immersion or by iso-
concentrated albumin infusion (iso-oncotic, to avoid the
acute sodium retaining effect of hyperoncoticity)
induces only limited increase in sodium excretion in
NS patients, not in proportion with the large amounts
of fluid overload [16,17].

The nature and localization of the renal impairment
to excrete sodium has not yet been elucidated.
Understandably, evidence in humans is indirect and
circumstantial. The general notion is that, when
patients are actively retaining sodium (i.e. in a positive
sodium balance), increased tubular sodium reabsorp-
tion occurs throughout the nephron. Instead, when
patients have stable nephrotic oedema, but are not
actively retaining sodium, their renal sodium handling
appears to be normal [14].

In rats with experimental puromycin nephrosis, a
model of minimal lesions NS, proximal tubular sodium
reabsorption was increased, and insufficiently suppress-
able by volume loading [18]. In unilateral puromycin
nephrosis, sodium retention by the affected kidney was
localized in some distal part of the nephron, as proximal
reabsorption was decreased [19]. There is evidence that
the distal nephron in the NS has decreased sensitivity to
the action of atrial natriuretic peptide. In humans,
studies using various forms of volume expansion
showed insufficient natriuretic response despite eleva-
tion of plasma ANP to at least normal levels [20,21].
ANP resistance can be demonstrated specifically in the
affected kidney of experimental unilateral nephrosis
[22], and isolated kidneys of nephrotic rats [23]. Isolated
inner medullary collecting cells from rats with experi-
mental nephrosis show diminished sensitivity to atrial
natriuretic peptide, a disturbance that can be resolved
by inhibition of degradation of its second messenger
cGMP [24]. This is indeed an intriguing finding,
however, it is completely unresolved how this abnor-
mality is related to the glomerular disturbance of the NS.

References

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