Letter to the Editor: “Can early plasma elimination rate be used to quantify renal clearance of macromolecules?”

Carl M. Öberg and Bengt Rippe
Department of Nephrology, Lund University, Lund, Sweden

TO THE EDITOR: The purpose of this Letter to the Editor is to address a number of issues in the study by Vuchkova et al. (29) that may warrant correction or further clarification. In their study, plasma elimination of a bolus dose of albumin and IgG is used as an indirect measure of renal protein loss. This is problematic for several reasons. First, the major determinant of the plasma clearance of albumin (and IgG) is not renal excretion, but the transcapillary escape rate (TER) from plasma to extravascular compartments, being ~5%/h for albumin (i.e., ~5 g/h) in man (22, 23) and higher during disease states such as septic shock (4, 14), hypertension (23, 25), and diabetic nephropathy (12, 21). This value, however, does not describe the renal clearance of these proteins, which was the matter of interest in the study by Vuchkova et al. (29). Only a miniscule part of TER represents renal clearance, even during heavy proteinuria. The elimination rate of interest, which perhaps should have been measured in the experiment, is the fractional catabolic rate (FCR), since a small part of FCR represents urinary loss and proximal tubular catabolism of plasma proteins (24). The FCR_{albumin} is ~2%/h in humans, corresponding to a half-life of human serum albumin of ~17 days. It is estimated that ~10% of the FCR is due to renal catabolism which implies a glomerular sieving coefficient of albumin of ~6-8·10^{-5} (assuming little or no tubular reuptake of intact albumin). About 15% is catabolized by the liver and up to 10% leaks into the gastrointestinal tract while muscle and skin (endothelium) account for most of the FCR (24). Likely, it is possible to measure a small increase in FCR in nephrotic animals due to increased renal loss. However, the measurement of FCR requires waiting 2–3 days postinjection until the plasma curve becomes approximately monoeXponential (18, 26). Thus the time period for the experiment (24 h) was not properly designed to measure renal clearance (see Fig. 1).

For example, the elimination rate found in the study for both albumin and IgG is ~2%/h. This value is lower than TER, which may be due to the longer time course (24 h) of the experiment, allowing significant lymphatic return of tracer to the circulation from extravascular compartments (10). Hence, a monoeXponential disappearance of tracer molecules over a longer period of time than the first 50–60 min cannot describe the disappearance (and reappearance) of tracer molecules in the circulation. Another example is the elimination rate found for neutral Ficoll which is much lower (~4% for Ficoll_{55Å}) than TER for Ficoll_{55Å}, being ~23% (2). Again, the likely cause for such a markedly low elimination rate is the significant return of Ficoll from extravascular compartments to the circulation. Interestingly, this implies a higher recirculation rate for Ficoll from the extravascular compartments compared with albumin and IgG. A high recirculation rate would also explain why the apparent elimination rate of Ficoll in the nephrotic animals was essentially the same as that in controls. With such a high turnover rate of Ficoll, the expected increase in TER in the nephrotic animals (21) would be difficult to measure without using a much shorter time period for the experiment.

The capability of healthy glomerular capillaries in restricting leakage of large plasma proteins through the glomerular barrier is crucial for normal renal function. One of the hallmarks of kidney disease is the failure of the glomerular capillary barrier in restricting plasma proteins, leading to proteinuria (on the order of a few grams per day). The concept of a highly selective glomerular filtration barrier has been challenged by the albumin retrieval hypothesis stating that the mechanism behind proteinuria is the failure of the proximal tubule in reabsorbing proteins. Albumin is thought to be more permeable through the glomerular capillary wall, due to a high glomerular sieving coefficient of 0.03–0.08 (11, 15). To maintain plasma levels, most of this albumin would need to be reabsorbed largely intact, since the daily amount of albumin produced by the liver is only ~10–12 g (26). Thus the tubular reuptake of intact albumin is a crucial assumption in the albumin retrieval hypothesis. However, there is an overwhelming body of evidence showing that proteins that are reabsorbed in the proximal tubule are degraded in lysosomes and released into the circulation as amino acids (5–8, 17). By contrast, there is little or no proteinuria. The elimination rate of interest, which perhaps should have been measured in the experiment, is the fractional catabolic rate (FCR), since a small part of FCR represents urinary loss and proximal tubular catabolism of plasma proteins (24). The FCR_{albumin} is ~2%/h in humans, corresponding to a half-life of human serum albumin of ~17 days. It is estimated that ~10% of the FCR is due to renal catabolism which implies a glomerular sieving coefficient of albumin of ~6-8·10^{-5} (assuming little or no tubular reuptake of intact albumin). About 15% is catabolized by the liver and up to 10% leaks into the gastrointestinal tract while muscle and skin (endothelium) account for most of the FCR (24). Likely, it is possible to measure a small increase in FCR in nephrotic animals due to increased renal loss. However, the measurement of FCR requires waiting 2–3 days postinjection until the plasma curve becomes approximately monoeXponential (18, 26). Thus the time period for the experiment (24 h) was not properly designed to measure renal clearance (see Fig. 1).

For example, the elimination rate found in the study for both albumin and IgG is ~2%/h. This value is lower than TER, which may be due to the longer time course (24 h) of the experiment, allowing significant lymphatic return of tracer to the circulation from extravascular compartments (10). Hence, a monoeXponential disappearance of tracer molecules over a longer period of time than the first 50–60 min cannot describe the disappearance (and reappearance) of tracer molecules in the circulation. Another example is the elimination rate found for neutral Ficoll which is much lower (~4% for Ficoll_{55Å}) than TER for Ficoll_{55Å}, being ~23% (2). Again, the likely cause for such a markedly low elimination rate is the significant return of Ficoll from extravascular compartments to the circulation. Interestingly, this implies a higher recirculation rate for Ficoll from the extravascular compartments compared with albumin and IgG. A high recirculation rate would also explain why the apparent elimination rate of Ficoll in the nephrotic animals was essentially the same as that in controls. With such a high turnover rate of Ficoll, the expected increase in TER in the nephrotic animals (21) would be difficult to measure without using a much shorter time period for the experiment.

The capability of healthy glomerular capillaries in restricting leakage of large plasma proteins through the glomerular barrier is crucial for normal renal function. One of the hallmarks of kidney disease is the failure of the glomerular capillary barrier in restricting plasma proteins, leading to proteinuria (on the order of a few grams per day). The concept of a highly selective glomerular filtration barrier has been challenged by the albumin retrieval hypothesis stating that the mechanism behind proteinuria is the failure of the proximal tubule in reabsorbing proteins. Albumin is thought to be more permeable through the glomerular capillary wall, due to a high glomerular sieving coefficient of 0.03–0.08 (11, 15). To maintain plasma levels, most of this albumin would need to be reabsorbed largely intact, since the daily amount of albumin produced by the liver is only ~10–12 g (26). Thus the tubular reuptake of intact albumin is a crucial assumption in the albumin retrieval hypothesis. However, there is an overwhelming body of evidence showing that proteins that are reabsorbed in the proximal tubule are degraded in lysosomes and released into the circulation as amino acids (5–8, 17). By contrast, there is little or no
evidence supporting tubular uptake of intact albumin and even less evidence supporting tubular uptake of Ficoll or other polysaccharides on a larger scale as is suggested by Vuchkova et al. (29).

In conclusion, if most of the proteins that leak across the glomerular filtration barrier are catabolized into amino acids, then the glomerular sieving coefficient of albumin (and indeed IgG) is likely to be very low, as has been noted by several authors (9, 16, 19, 27). In addition, the permeability for Ficoll both in the GFB and synthetic membranes apparently lies somewhere between that of globular proteins and dextran (1, 3, 13, 20, 28). For example, if the plasma clearance of a bolus dose of albumin was only due to renal excretion, this would imply a plasma half-life of ~2,000 h, corresponding to a TER of <0.04% (i.e., >50 times less than that measured by Vuchkova et al.) (29). Regardless of what opinion one may hold about the true sieving coefficient of albumin and/or the role of glomerular permeability in kidney disease, early plasma elimination of macromolecules cannot be used to measure renal clearance since the disappearance of tracer molecules to other body compartments is much greater than that to the urinary space.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: C.M.O. provided conception and design of research; C.M.O. prepared figures; C.M.O. drafted manuscript; C.M.O. and B.R. edited and revised manuscript; C.M.O. and B.R. approved final version of manuscript.

REFERENCES


