

Proteinuria: Clinical Significance and Basis for Therapy

KT Woo, Y K Lau

ABSTRACT

Proteinuria is the hallmark of renal disease and proteinuria exceeding 1 gm a day in patients with renal disease augers a poorer prognosis. Proteinuria has been shown to be tubulotoxic and directly contributes to renal deterioration. Patients with non-selective proteinuria are more likely to have progressive renal disease. Diabetic patients with persistent microhaematuria have about 20 times the risk of developing diabetic nephropathy. In essential hypertension, the onset of de novo proteinuria after years of adequate BP control is a marker of subsequent decline in renal function. In glomerulonephritis, more severe proteinuria is associated with faster rate of progression. Even though the initial phase of proteinuria in patients with glomerulonephritis is usually of immunological origin, in the vast majority of patients with established disease, the latter progressive phase of proteinuric glomerulopathy is the result of glomerular hyperfiltration which shifts glomerular non-selective pores to larger dimensions resulting in excessive leakage of protein in the urine. Endothelial injury resulting from glomerular hyperfiltration causes increase in local generation of Angiotensin II in the kidney as part of the hemodynamic response. ACE inhibitors and angiotensin II receptor antagonists (ATRA) can improve glomerular pore-selectivity by remodelling the glomerular basement membrane. In addition, these agents also have beneficial effects by decreasing TGF- β production therapy decreasing mesangial cell proliferation, hence ameliorating disease progression in patients with diabetic nephropathy and IgA nephropathy. A number of recent clinical trials have shown that ACEI and ATRA therapy can retard the progression of renal deterioration in patients with NIDDM and those with IgA nephropathy and even restore normal renal function in those with mild renal impairment. Treatment and control of proteinuria in patients with renal disease should be regarded as important

as treatment of hypertension as it can prevent renal failure.

Keywords: Proteinuria, Disease progression, Therapy, ACE inhibitor, Angiotensin II receptor antagonist

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INTRODUCTION

Proteinuria is the hallmark of renal disease. Special tests on urinary proteins using selectivity indices, SDS-PAGE (Sodium dodecyl sulphate polyacrylamide gel electrophoresis) and Isoelectric Focusing (IEF) can predict response to therapy in patients with nephrotic syndrome. Proteinuria can also be used as a prognostic marker⁽¹⁾. Traditionally it has been thought that proteinuria is the result of diseased glomeruli. As the disease progressed proteinuria worsens. Patients with glomerulonephritis (GN) with more than 1 gm of protein excretion per day in the urine are more likely to have glomerulosclerosis or scarring of the kidney on renal biopsy and those exceeding 2 grams a day, a higher incidence of developing renal failure on follow up⁽²⁾.

PROTEINURIA AND DISEASE PROGRESSION

More severe proteinuria is associated with faster progression of the renal disease, and this correlation is stronger for those patients with nephrotic range proteinuria⁽³⁾. In essential hypertension, the onset of de novo proteinuria after a number of years of adequate blood pressure control is a marker of subsequent decline in renal function⁽⁴⁾. Diabetic patients with persistent microalbuminuria have about 20 times the risk of developing diabetic nephropathy⁽⁵⁾. Albumin excretion rate (AER) has been shown to correlate with the rate of decline in GFR in both IDDM and NIDDM patients. However at the stage of incipient nephropathy (AER 20 to 200 μ g/ml), it is more difficult to relate levels of microalbuminuria to subsequent progression. In a study of IDDM patients with long duration of diabetes mellitus (> 15 years), only five out of 18 progressed to clinical nephropathy in 10 years⁽⁶⁾. Therefore, albuminuria alone may not predict change in GFR in

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all diabetic patients. In a recent study, in 176 patients studied over a medium of five to eight years, baseline AER, male sex, presence of retinopathy, serum cholesterol and HbA1C were the strongest predictors for development of incipient nephropathy⁽⁷⁾. A complicating factor in the natural history of diabetes mellitus is that a subgroup of patients shows a decline in renal function without increasing AER.

INTRINSIC TOXICITY OF FILTERED PROTEINS

Hitherto, it was believed that proteinuria is the result of damage to the kidneys but recently, evidence suggest that the converse is also true, that proteinuria can also directly cause renal damage.

When there is excessive leakage of protein in the renal tubules, the proximal tubular cells (PTC) become overloaded with protein. Lysosomes present in the PTC when they engulf excessive proteins, would swell and rupture and release injurious lysosomal enzymes which cause tubulointerstitial damage and fibrosis and with time, give rise to renal failure. In the second mechanism, protein overload of the PTC also triggers the release of certain growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β) which are mitogenic to the PTC. They cause excessive production of collagen as well as interstitial cell proliferation, eventually leading to fibrosis and renal failure. Finally, protein overloading of the PTC causes the activation of transcriptase genes which in turn trigger genes encoding vasoactive and inflammatory mediators, the release of these lead to vasoconstriction and inflammation of the renal tissue with injury and renal failure⁽⁸⁾.

PROTEIN TRAFFIC, INTERSTITIAL INFILTRATES AND DECLINING GFR

Over the last decade, there is accumulating evidence that the severity of proteinuria is correlated with tubulointerstitial infiltrates mainly comprising CD4 Type T lymphocytes and monocytes. There is also evidence that the degree of tubulointerstitial injury predicts renal function decline better than the severity of glomerular damage⁽⁹⁾.

There are two reasons why tubulointerstitial lesions occur in patients with renal diseases who have proteinuria. Tubulointerstitial inflammation is a reaction to ischaemic obliteration of peritubular capillaries that follows obsolescence of glomerular tuft^(10,11). The other reason is that the tubulotoxic effect of proteinuria leads to interstitial inflammation because of release of vasoactive amines and inflammatory mediators resulting from protein overload of the lysosomes.

In general two mechanisms are in play whether we refer to tubular or glomerular injury. The first mechanism is due to immunologic injury from the tubulointerstitial nephritis or the glomerulonephritis. The other mechanism is injury resulting from the effects of protein overload whether on the tubules or the glomerulus specifically either on the proximal tubular cell (PTC) or the GBM. In terms of therapy, immunologic injury can be modified by immunomodulation therapy and protein overload injury can be modified by measures aimed at reduction of proteinuria through non-immunological therapy to reduce hyperfiltration.

PROGRESSION OF RENAL DISEASE AND PROTEIN SELECTIVITY

There is evidence that in certain renal diseases like focal and segmental glomerulosclerosis, IgA nephritis, lupus nephritis and diabetic nephropathy, the degree of interstitial mononuclear cell infiltrates correlate with the rate of renal functional decline⁽¹²⁾. The presence of chronic tubulointerstitial lesions in these diseases are correlated with declining renal function⁽¹³⁾. What these diseases have in common is non-selective proteinuria. In IgA nephritis the non-selective proteinuria was correlated with tubulointerstitial lesions and a higher incidence of renal failure⁽¹⁴⁾.

In contrast to the above diseases in Minimal Change Disease (MCD), interstitial infiltrates seldom develop despite heavy proteinuria. The obvious reason is that the period of heavy protein excretion in the renal tubules is of short duration since MCD responds promptly to steroids. The other reason is the difference in the quality of the proteinuria. In MCD patients have selective proteinuria and excrete albumin which is relatively innocuous compared to the larger immunoglobulins like IgG in nonselective proteinuria which can alter expression of tubular activation molecules much more than albumin. In addition non-selective proteinuria normally includes complement components C 5 to 9 which enters tubular fluid and allows complement mediated injury resulting in tubulointerstitial inflammation and injury as in focal and segmental glomerulosclerosis and diabetic nephropathy.

BASIS FOR TREATMENT OF PROTEINURIA USING ACEI AND ANGIOTENSIN II RECEPTOR ANTAGONIST (ATRA)

Local generation of Angiotensin II in the kidney, formed in excessive amounts in response to hemodynamic injury to the endothelium in glomerular hyperfiltration shifts glomerular non-selective pores to larger dimensions (i.e. patients with non-selective proteinuria become even more non-selective).

Experimental and human evidence suggest that ACEI tend to improve non-selective proteinuria, but how they do so is still speculative. The improvement in the selective properties of the glomerular capillary wall induced by ACEI could be the result of changes in the morphometry, as reflected by changes in the macromolecular organisation of the protein matrix in the GBM or the slit-diaphragm of the podocytes. This is consistent with recent findings that ACEI reduce RNA expression for extracellular matrix components in experimental diabetes⁽¹⁵⁾ as well as in an immunological rat model with massive proteinuria⁽¹⁶⁾.

ACE inhibitors in animals and humans reduce the log-normal component of the assumed pore size distribution⁽¹⁷⁾ and more importantly, cause the shunt pathway to become less pronounced by reducing the radius of large nonselective pores⁽¹⁸⁾.

ACEI / ATRA THERAPY

Several studies have shown that at comparable BP reduction, ACEI lowered proteinuria and rate of GFR decline more effectively than other hypotensives⁽¹⁹⁾. In patients with IDDM with nephropathy, ACEI reduces microalbuminuria and delays progression to macroalbuminuria in incipient diabetic nephropathy⁽²⁰⁾. Most of the studies done, like those of Lewis are in IDDM⁽²¹⁾. For NIDDM nephropathy, the results of ACEI therapy are still controversial. In PIMA Indians, who have a high incidence of NIDDM, in those with established diabetic nephropathy with macroalbuminuria, a three year randomised control trial showed a better antiproteinuria effect and slower rate of GFR decline in the group treated with enalapril compared to conventional antihypertensives. In Afro Americans too with NIDDM, ACEI therapy had more antiproteinuric effect and slower rate of GFR decline better than conventional treatment with calcium channel blockers^(22,23).

In another trial on normotensive NIDDM patients with microalbuminuria and normal renal function, the risk of progression to macroalbuminuria was 18% in patients who received enalapril compared with 60% in those who did not⁽²⁰⁾.

Recently⁽²⁴⁾ in a randomised multicentre control trial, RENAAL (Reduction of End points in NIDDM with Angiotensin II Receptor Antagonist, Losartan), involving 1513 patients from 29 countries with NIDDM of which 751 patients in the treatment group were on Losartan 50 mg to 100 mg daily compared to 762 patients given placebo, both groups also continuing treatment for hypertension with conventional BP medicine, excluding ACE inhibitors and other Angiotensin Receptor Blocker (ATRA) there was a 28% reduction in development of End

Stage Renal Disease among the patients treated with Losartan.

In the group of patients with non-diabetic chronic nephropathies, ACEI therapy has been shown to decrease proteinuria and preserve renal function⁽²⁵⁾. In Lewis' study⁽²¹⁾, urinary protein decreased in the ACEI group compared to the control group where proteinuria actually increased. There is evidence to suggest that the decrease in proteinuria with ACEI therapy is related to improvement in size-selectivity of the GBM^(26,27) and not so much on the result of lowering of glomerular capillary pressure⁽²¹⁾.

In patients with hypertension and proteinuria, the effect of BP control overrides the effect of proteinuria⁽²⁸⁾, in other words there is less dependence on protein reduction in such patients. ACEI and Angiotensin II Receptor Antagonist (ATRA) are the only anti-hypertensive agents that reduce proteinuria even with no change in BP. The antiproteinuric effect of ACEI is drug specific and not dependent on reduction of intraglomerular hypertension alone as in the non-nifedipine calcium channel blockers which are BP dependent. The other feature to note regarding the antiproteinuria effect of ACEI is that the effect of ACEI on proteinuria is dependent on sodium restriction⁽²⁸⁾. To maximize the effect of ACEI on proteinuria, patients should be on a low salt diet. Nifedipine uniformly failed to reduce proteinuria and also does not protect renal function. In fact the use of nifedipine may even worsen proteinuria⁽²⁹⁾. It is a good rule that when using drugs to reduce proteinuria, if proteinuria increases despite therapy it may mean that the drug is increasing the proteinuria. It would be good practice therefore to restrict sodium intake or prescribe a thiazide diuretic to such patients.

ACE I/D POLYMORPHISM AND RESPONSE TO ACEI/ATRA THERAPY

Since ACE inhibitors decrease ACE activity, ACE inhibitor therapy in patients with IgA nephritis would be expected to reduce renal injury in these patients. We have shown that ACEI therapy does lead to decreased proteinuria and retardation of the progression of renal failure in IgA nephritis. In our study we also showed that Angiotensin II Receptor Antagonist (ATRA) is as effective as ACEI in decreasing proteinuria and preservation of renal function⁽³⁰⁾.

It has been postulated that ACEI/ATRA (ACE inhibitor/Angiotensin receptor antagonist) may decrease proteinuria in patients with glomerulonephritis by its action on the Glomerular Basement Membrane. We performed a study⁽³⁰⁾ to examine the relationship between the response of patients with IgA Nephritis (IgA Nx) to ACEI (Enalapril)/ATRA (Losartan)

therapy by decreasing proteinuria and its effect on the Selectivity Index (SI) in these patients. Forty-one patients with biopsy proven IgA Nx entered a control trial with 21 in the treatment group and 20 in the control group. The entry criteria included proteinuria of 1 gm or more and or renal impairment. Patients in the treatment group received ACEI (5 mg)/ATRA (50 mg) or both with three monthly increase in dosage. In the control group, hypertension was treated with atenolol, hydralazine or methyldopa. After a mean duration of therapy of 13 ± 5 months, in the treatment group there was no significant change in serum creatinine, proteinuria or SI but in the control group, serum creatinine deteriorated from 1.8 ± 0.8 to 2.3 ± 1.1 mg/dl ($p < 0.05$). Among the 21 patients in the treatment group, 10 responded to ACEI/ATRA therapy determined as decrease in proteinuria by 30% (responders) and the other 11 did not (non responders). Among the responders, SI improved from a mean of 0.26 ± 0.07 to 0.18 ± 0.07 ($p < 0.001$) indicating a tendency towards selective proteinuria. This was associated with improvement in serum creatinine from mean 1.7 ± 0.6 to 1.5 ± 0.6 mg/dl ($p < 0.02$) and decrease in proteinuria from mean of 2.3 ± 1.1 g/day to 0.7 ± 0.5 g/day ($p < 0.001$).

After treatment, proteinuria in the treatment group (1.8 ± 1.6 g/day) was significantly less than in the control group (2.9 ± 1.8 g/day) ($p < 0.05$). The post treatment SI in the responder group (0.18 ± 0.07) was better than that of the non responder group (0.33 ± 0.11) ($p < 0.002$). Eight out of 21 patients in the treatment group who had documented renal impairment had improvement in their renal function compared to two in the control group ($\chi^2 = 4.4$, $p < 0.05$). Of the eight patients in the treatment group who improved their renal function, three normalised their renal function.

Our study suggest that ACEI/ATRA therapy may be beneficial in patients with IgA Nx with renal impairment and non selective proteinuria as such patients may respond to therapy with improvement in protein selectivity, decrease in proteinuria and improvement in renal function. ACEI/ATRA therapy probably modifies pore size distribution by reducing the radius of large nonselective pores, causing the shunt pathway to become less pronounced resulting in less leakage of protein into the urine.

Individual antiproteinuric response to ACEI/ATRA therapy varies depending on ACE gene polymorphism as those with the DD genotype respond better to the antiproteinuric effect of ACEI/ATRA therapy^(31,32). Yoshida⁽³²⁾ in a study examining the role of the deletion polymorphism of the ACE gene in the progression and therapeutic responsiveness of IgA nephropathy using the ACEI lisinopril reported that the ACEI lisinopril

significantly decreased proteinuria in the DD genotype patients but not in the II or ID genotype. Similar findings have also been reported by Moriyama⁽³³⁾.

Recently studies have also demonstrated that ACEI, apart from remodelling the GBM, the improvement in pore selectivity being one of the end results, may also have beneficial effects on the mesangial cells by decreasing TGF- β production thereby decreasing mesangial matrix production, hence ameliorating the disease process in IgA Nx where there is mesangial cell proliferation⁽³⁴⁾. In addition, ATRA has been shown to exert an antiproliferative effect on mesangial proliferative GN. This could help to further explain the improvement in renal function in patients with IgA Nx on ACEI/ATRA therapy⁽³⁴⁾. In order for this to occur the injury must be still at the stage where it is possible for amelioration of the renal lesions and possibly remodelling of the renal architecture. Patients with more advanced renal disease with glomerulosclerosis and thickening of the GBM, are less likely to respond to therapy with improvement in SI and serum creatinine. In this respect, we found that patients with serum creatinine exceeding 3 mg/dl are less likely to recover renal function though therapy with ACEI/ATRA may retard their long-term progression to end stage renal failure.

REFERENCES

1. Woo KT, Lau YK, Lee GSL, Wei SS, Lim CH. Pattern of proteinuria in IgA nephritis by SDS-PAGE: Clinical Significance. *Clin Nephrol* 1991; 36:6-11.
2. Woo KT, RPS Edmondson, AYT Wu, GSC Chiang, HS Pwee, CH Lim. The natural history of IgA nephritis in Singapore. *Clin Nephrol*, 1986; 25:15-21.
3. Cameron JS, Turner DR, Heaton J, Williams DG, Ogg CS, Chantler C, Haycock GB, Hicks J. Idiopathic mesangiocapillary glomerulonephritis. Comparison of types I and II in children and adults and long-term prognosis. *Am J Med*, 1983; 74:175-92.
4. Ruilope LM, Alcazar JM, Hernandez E, Moreno F, Martinez MA, Rodicio JL. Does an adequate control of blood pressure protect the kidney in essential hypertension? *J Hypertens* 1990; 8:525-31.
5. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T. The natural course of microalbuminuria in insulin-dependent diabetes: A 10-year prospective study. *Diab Med* 1995; 12:482-7.
6. Forsblom CM, Groop PH, Ekstrand A, Groop LC. Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration. *Brit Med J* 1992; 305:1051-3.
7. Gall MA, Hougaard P, Borchjohansen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus - prospective, observational study. *Brit Med J* 1997; 314:783-8.
8. Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. *Kidney Int* 1997; 51:2-15.
9. Jackle I, Gunther H, Von Gise H, Alt JM, Bohle A, Stolte H. Kidney function and protein excretion in relation to pathomorphology of glomerular diseases. *Contrib Nephrol* 1988; 68:128-35.
10. Bohle A, Von Gise H, Mackensen-Haen S, Stark-Jakob B. The obliteration of the post-glomeruli and tubuli functional interpretation of morphologic findings. *Kin Wochenschr* 1981; 59:1043-51.
11. Heptinstall RH. Chronic glomerulonephritis, end-stage kidney and visceral changes in chronic renal failure, in *Pathology of the Kidney* (3rd ed), edited by Heptinstall RH, Boston, Little, Brown and Co. 1983; pp:601-36.

12. Mackensen-Haen S, Bohle A, Christensen J, Wehrmann M, Kendziorra H, Kokot F. The consequences for renal function of widening of the interstitium and changes in the tubular epithelium of the renal cortex and outer medulla in various renal diseases. *Clin Nephrol* 1992; 37:70-7.
13. Bohle A, Wehrmann M, Bogenschutz O, Batz C, Muller CA, Muller GA. The pathogenesis of chronic renal failure in diabetic nephropathy; Investigation of 488 cases of diabetic glomerulosclerosis. *Pathol Res Pract* 1991; 187:252-9.
14. Woo KT, Lau YK, Yap HK, Lee GSL, Chiang GSC, Lim CH. Protein selectivity: A prognostic index in IgA nephritis. *Nephron* 1989; 52:300-6.
15. Nakamura T, Takahashi T, Fukui M, Ebihara I, Osada S, Tomino Y, Koide H. Enalapril attenuates increased gene expression of extracellular matrix components in diabetic rats. *J Am Soc Nephrol* 1995; 5:1492-7.
16. Ruiz-Ortega M, Gonzalez S, Seron D, Condom E, Bustos C, Largo R, Gonzalez E, Ortiz A, Egido J. ACE inhibition reduces proteinuria, glomerular lesions and extracellular matrix production in a normotensive rat model of immune complex nephritis. *Kidney Int* 1995; 48:1778-91.
17. Deen WM, Bridges CR, Brenner BM, Myers BD. Heteroporous model of glomerular size selectivity: Application to normal and nephrotic humans. *Am J Physiol* 1985; 249:F374-89.
18. Remuzzi A. Mathematical description of transport of water and macromolecules through the glomerular capillary wall. *Curr Opin Nephrol Hypertens* 1995; 4:343-8.
19. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *Br Med J* 1992; 304:339-43.
20. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. *JAMA* 1994; 271:275-9.
21. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456-62.
22. Bakris GL, Copley JB, Vicknair N. Blood pressure reduction and progression of diabetic nephropathy in african americans(AA): A five year follow-up (abstract) *J Am Soc Nephrol* 1995; 6:446.
23. Bakris GL, Copley JB, Vicknair N, Leurgans S. Effect of nondihydropyridine calcium antagonists (NDCAs) on progression of nephropathy from noninsulin dependent diabetes (NIDDM). (abstract) *J Am Soc Nephrol* 1995; 6:446.
24. Werner K. Public Affairs Home Page Press Release (Merck). Cozaar significantly reduced progression of kidney disease in patients with most common form of diabetes: [wysiwyg://8/http://pubaff.merck.com/media/051901.htm](http://pubaff.merck.com/media/051901.htm)
25. Praga M, Hernandez E, Montoyo C, Andres A, Rulope LM, Rodicio JL. Long term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. *Am J Kidney Dis* 1992; 20:240-248.
26. Morelli E, Loon N, Meyer T, Peters W, Myers BD. Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes* 1990; 39:76-82.
27. Remuzzi A, Perticucci E, Ruggenenti P, Mosconi L, Limonta M, Remuzzi G. Angiotensin-converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. *Kidney Int* 1991; 39:1267-73.
28. Heeg JE, De Jong PE, Van Der Hem GK, De Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 1989; 36:272-9.
29. Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: An updated meta-analysis. *Nephrol Dial Transplant* 10 (Suppl 9) 1995; 39-45.
30. Woo KT, Lau YK, Wong KS, Chiang GSC. ACE/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis: *Kidney Int* 2000; 58:2485-91.
31. Vleming LJ, Van Kooten C, Van Dijk M. The D-allele of the ACE gene polymorphism predicts a stronger antiproteinuric response to ACE inhibitors. *Nephrology* 1998; 4:143-9.
32. Yoshida H, Mitarai T, Kawamura T. Role of the deletion polymorphism of the angiotensin converting enzyme gene in the progression and therapeutic responsiveness of IgA nephropathy *J. Clin. Invest.* 1995; 96:2162-9.
33. Moriyama T, Kitamura H, Ochi S. Association of angiotensin I-converting enzyme gene polymorphism with susceptibility to antiproteinuric effect of angiotensin I-converting enzyme inhibitors in patients with proteinuria. *J. Am. Soc. Nephrol.* 1995; 6:1674-8.
34. Nakamura T, Obata J, Kimura H, Ohno S, Yoshida Y, Kawaihi H, Shimizu F. Blocking angiotensin II ameliorates proteinuria and glomerular lesions in progressive mesangioproliferative glomerulonephritis. *Kidney Int.* 1999; 55:877-89.

11th General Scientific Meeting Anaesthesiology - The Next Odyssey

Date : 22 & 23 September 2001

Venue : Mandarin Hotel, Singapore

Jointly organized by : Chapter of Anaesthesiologists, Academy of Medicine, Singapore and Singapore Society of Anaesthesiologists

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The topics of the four symposia cover exciting developments and advances in basic sciences and clinical practice. These include inter alia Translational Research (Dr Chan Yew Weng, SGH), Genomics (Dr Kon Oi Lin, NCC), Immunomodulation (Dr Ng Kim Swee, CGH), Pain (Dr Stephen Schug, Royal Perth Hospital) and Monitoring (Dr Gan Tong Joo, Duke University Medical Centre).

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