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Determination of capillary leakage due to recombinant interleukin-2 by means of noninvasive conductivity measurements

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Summary. One of the most common side effects of treatment with recombinant interleukin-2 (IL-2) is capillary leakage. Its genesis is not completely understood. The aim of the study was to determine whether capillary leakage can be monitored by means of a noninvasive conductivity technique and to study its starting point. Eight patients with advanced renal cell cancer were studied in a medium care section of the Department of Medical Oncology, University Hospital over 4 days during treatment sessions of continuous, intravenously administered IL-2 (mean dose of 15.6×10^6 IU·m^{-2}·day^{-1}). The fluid shift from the intravascular to the extra- and intracellular compartments was monitored by means of noninvasive conductivity measurements. Changes in blood volume were calculated from serial erythrocyte counts. The clinical parameters of capillary leakage (oliguria, positive fluid balance, and gain in mass) were recorded. The mean gain in mass was 9% after 4 days of IL-2 treatment. The extracellular fluid volume increased significantly [46 (SD 23.2)%; $P<0.01$], whereas the intracellular fluid volume did not change. The increase in blood volume (BV) amounted to 7% ($P<0.05$). The decline in albumin concentration was significantly more than the increase in BV [38 (SD 4.3)%; $P<0.01$], indicating capillary albumin leakage. The main changes were observed after the 2nd day of treatment. From this study, it is suggested that conductivity measurements are a suitable method to monitor capillary leakage induced by IL-2, and could be used to detect the exact onset and severity of this leakage. The leakage started within the first 24 h of treatment and was detected as a fluid shift from the intravascular to the extracellular space, while the intracellular compartment remained stable. These measurements could be useful during intervention studies with the aim of preventing this adverse effect of IL-2.

Key words: Interleukin-2 – Capillary leakage – Intracellular fluid volume – Extracellular fluid volume – Blood volume – Conductivity measurement

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Introduction

The administration of interleukin-2 (IL-2), either alone or in combination with adoptive transfer of lymphokine-activated killer cells, has been shown to mediate the regression of established metastases from a variety of tumours in both mice and men (Mazumder and Rosenberg 1984; Rosenberg et al. 1985, 1987). It has been shown that the amount of IL-2 that can be given is limited by its toxicity, especially the IL-2-induced increase in capillary permeability (Ettinghausen et al. 1988; Rosenstein et al. 1986). The capillary leak syndrome (CLS) is characterized by damage to vascular endothelial cells with resultant leakage of albumin from the vascular compartment. Fluid then leaks from the vascular space, causing, in the short-term, hypotension and, over longer periods oliguria, oedema and effusions. In extreme cases even interstitial pulmonary oedema can develop, which may require artificial ventilation to maintain adequate tissue oxygenation. The mechanisms by which IL-2 exerts its influence on vascular permeability are complicated and still not completely understood. A direct toxic effect of IL-2 on the blood vessels has not been thought to be likely, since in studies on nude and irradiated mice treated with IL-2 there was no evidence of any vascular leakage (Ettinghausen et al. 1988; Rosenstein et al. 1986). It has seemed more likely that IL-2 induces the CLS indirectly through the activation of other pathways, including the complement system, activation of polymorphonuclear neutrophils, generation or induction of vaso-active substance (e.g. phospholipase A2), and the release of other cytokines causing toxicity to the blood vessels (Baars 1993).

In animal models the IL-2-induced vascular leak has been quantified by measuring the extravasation of in-

travenously injected ^{125}I-labelled bovine serum albumin (Ettinghausen et al. 1988; Rosenstein et al. 1986). Therapeutic manoevres are urgently required to ameliorate IL-2 induced CLS and studies utilising these approaches will necessarily involve the accurate monitoring of the degree of vascular leakage. The CLS may be evaluated by sequential measurements of fluid balance and body mass, and changes in serum albumin concentration. Although these variables accurately reflect the degree of leakage over days, they are rather blunt tools and do not allow the measurement of leakage to be objectively performed over periods of hours. Radio-labelled albumin has also been used to evaluate the severity of CLS (Ettinghausen et al. 1988; Rosenberg et al. 1985) but this technique also suffers from the fact that it cannot be repeated several times per day or even daily. Therefore, a noninvasive conductivity technique of measuring fluid shifts within the body has been evaluated in patients being treated by IL-2. This method had been previously developed and validated in vitro (Meijer et al. 1989; de Vries et al. 1989) as well as in vivo in healty volunteers (Olthof et al. 1993) and in patients receiving haemodialysis (Kouw et al. 1992; de Vries et al. 1987; de Vries 1989). It measures intracellular (V_{ICF}) and extracellular fluid volume (V_{ECF}) in an accurate way. The V_{ICF} and V_{ECF} detected by the conductivity technique has been shown to correlate with the same variables measured by means of isotope dilution (Segal et al. 1991).

This paper describes the first experience of using this technique in CLS and suggests that it may be a valuable tool for clinical researchers to use when studying ways in which IL-2-induced CLS may be reduced. It could also be useful in monitoring V_{ICF} and V_{ECF} during other physiological investigations.

Methods

Subjects. Eight patients (five women and three men) with advanced renal cell carcinoma and participating in a phase II protocol of the evaluation of IL-2 therapy were included in the study. Their mean age was 55.8 years (median 54; range 39–69 years). At the start, the condition of the patients was good. They had hardly any complaints due to the malignant disease and were able to perform their normal daily activities (Karnofsky performance index: 90%–100%; Karnofsky et al. 1948). None of the patients had received prior chemotherapy or suffered from cardiovascular or renal insufficiency. The study was approved by the Human Ethics Committee of the Free University Hospital and each patient gave informed consent.

The patients were admitted to the medium care section of the Department of Medical Oncology and treated with a cycle of IL-2, given as a continuous intravenous infusion over 96 h (4 days) in 2 l of 0.9% NaCl·day^{-1}. Five patients received $18 \times 10^6 \cdot m^{-2}$ IU (6 IU = 2.3 biological response modifier units; Smith 1988)·day^{-1}, one 12×10^6 IU·m^{-2} and two 9×10^6 IU·m^{-2}.

The patients' vital signs, including pulse, blood pressure and electrocardiogram were monitored continuously and a strict fluid balance was recorded by the nursing staff. Temperature was measured twice daily. Every morning, patients were weighed after micturition by the same individual and blood samples were drawn before breakfast for measurement of erythrocyte count, albumin, electrolytes, creatinine and osmolality (measured by a freezing-point depression).

Before the start of treatment and every 24 h after starting IL-2 treatment (day 1–4), the state of hydration of the patients was measured by a noninvasive conductivity technique which has been developed at the Department of Medical Physics of the Free University of Amsterdam (Meijer et al. 1989; de Vries 1989; de Vries et al. 1989). Four electrodes were placed around the circumference of the lower limb. The outer two were used to apply an alternating current (0.8 mA) with various frequencies (3–510 kHz), the inner two to measure the voltage decrease over the intermediate tissue. Since current strength was known, the conductivity (reciprocal of the impedance) could be calculated. Conductivity was calculated at low and high frequency.

The simplified electrical model on which this technique is based, consists of an extracellular pathway represented by a resistance and a parallel intracellular pathway represented by a resistance and a capacitor representing the cell-membrane. These two resistances and the capacitor represent the whole tissue (Kanai et al. 1982).

It is known that the capacitor has a high resistance at a low frequency (less than 5 kHz). Therefore, an alternating current of low frequency would only be conducted by the extracellular compartment. Since the resistance of the capacitor has been found to be very low at high frequency (greater than 250 kHz; Kanai et al. 1982), in that case the current is conducted by the intra- and the extracellular compartments. From in vitro studies, it is known that a linear relationship exists between conductivity and fluid volume. Measured conductivity data are expressed as percentages of the values of the 1st day. These data are translated to percentage V_{ICF} and V_{ECF} (de Vries et al. 1989). So, all V_{ECF} and V_{ICF} values have also been expressed as percentages of the starting value. Low frequency conductivity represents V_{ECF}, while high frequency conductivity represents V_{ECF} plus V_{ICF}. The difference between them gives V_{ICF}. This has been validated under in vitro (de Vries et al. 1989) and in vivo conditions (Segal et al. 1991), as well as in patients receiving haemodialysis (Kouw et al. 1992; de Vries et al. 1987). Baumgartner et al. (1989) have found that whole body impedance consists of the sum of the regional impedances of the arms and the legs. Segal et al. (1992) have shown that regional impedance of the limbs accurately predicts whole body V_{ECF} and total body water (V_{TBW}). By using the tetrapolar conductivity method there is no influence of the electrode-skin impedance.

The coefficient of variance of the measured intra- and extracellular conductivities have been shown to be 8% and 4%, respectively (Kouw et al. 1992).

Relative changes in blood volume (BV) were calculated from erythrocyte counts according to the equation:

$$BV_t = \frac{\mathrm{ery}_0}{\mathrm{ery}_t} \times 100$$

where BV_t is blood volume on day t, as a percentage of the starting value, ery_0 is erythrocyte count at the start of treatment, and ery_t is erythrocyte count on day t. The BV changes were calculated as changes in erythrocyte counts and not in packed cell volume because the dilution process used for automated counters may affect red cell volume and, therefore, measured packed cell volume, resulting in inaccurate calculations of changes in BV.

Statistical evaluation was performed using Wilcoxon's rank-sum test. A P-value of less than 0.05 was considered significant.

Results

Within 24 h from starting IL-2, fluid balance, defined as the sum of fluid intake (infusion fluid, fluid ingestion) minus fluid loss [an estimated rate of perspiration

Table 1. Percentage body mass and fluid changes during the 4 days of interleukin-2 treatment

	Start	Day 1	Day 2	Day 3	Day 4
Body mass (%)	100	102.1** (98.6–105.3)	103.9** (101.7–109.5)	108.4** (103.7–112.6)	109.5** (105.2–112)
Fluid balance ($l \cdot 24\ h^{-1}$)		+2.0 (0.6–2.3)	+2.0 (1.4–3.5)	+2.0 (1.6–4.3)	+2.6 (1.0–3.2)
Urine prod. ($ml \cdot 24\ h^{-1}$)		1415 (900–2180)	1235 (590–2740)	590 (500–2150)	650* (280–970)
V_{ICF} (%)	100	93.5 (89–106)	100 (82–102)	99 (83–108)	94 (86–110)
V_{ECF} (%)	100	102.5** (87.6–123)	121** (106–143)	131** (116–160)	144.5** (122–185)
BV (%)	100	103 (95–108)	102.5 (94–108)	112* (100–121)	107* (98–121)

Body mass, intracellular fluid volume (V_{ICF}), extracellular fluid volume (V_{ECF}) and blood volume (BV) are given as percentages of the starting value. Values are given as median and ranges.

* $P<0.05$, ** $P<0.01$ compared to start

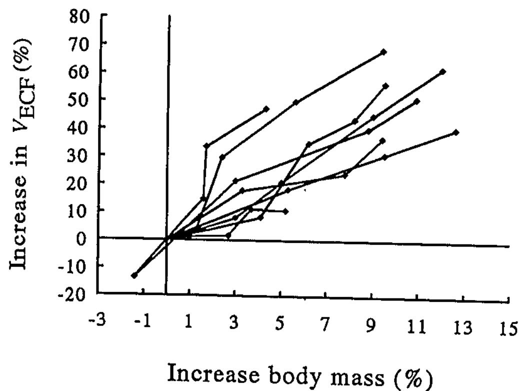

Fig. 1. The individual extracellular fluid volume (V_{ECF}) changes in relation to body mass changes caused by capillary leakage due to interleukin-2 treatment

of approximately 1000 $ml \cdot day^{-1}$ through the skin and the respiratory tract (Rose 1990), vomiting and urine output], became positive. The fluid balance was positive every day and led to a mean gain in mass of about 2% $\cdot day^{-1}$, and resulted in a mean total gain in mass of 9% by the end of treatment (Table 1). During day 3 and 4 urine production was less than in the first 2 days but only on day 4 was significant oliguria present.

By using noninvasive conductivity measurements, it was possible to discriminate between accumulation of the redistributed intravascular fluid in the extra- and intracellular spaces. Data showed that V_{ECF} increased by a mean value of 11.5% $\cdot day^{-1}$, resulting in an increase of 46% over the 4 days of IL-2 administration ($P<0.01$). The major change was observed on days 2 through 4. In comparison to V_{ECF}, V_{ICF} did not change (Table 1). Blood volume did not change significantly during the first 2 days, but increased thereafter.

Figure 1 shows that the increase in V_{ECF} caused by capillary leakage correlated well with the increase in body mass due to fluid accumulation (intra-individual correlation coefficients between 0.86 and 0.99). Blood pressure decreased significantly and pulse rate increased significantly during the 1st day and neither changed afterwards (Table 2).

As shown in Table 3, serum osmolality did not change significantly over the 4 days of treatment. Albumin concentration, however, decreased by an average of 38% by the end of treatment. The decrease in albumin concentration was noticed for the most part in the first 3 days. The decrease in albumin concentration was significantly more marked than the increase in BV. The measured electrolyte concentrations of serum did not change significantly during the treatment period.

Table 2. Patients characteristics from the start to the end of the interleukin-2 treatment

	Start	Day 1	Day 2	Day 3	Day 4
[a] Mean arterial pressure (mmHg)	113.5 (89–133)	91.5* (83–116)	82* (77–94)	86.5* (75–96)	93.5* (74–102)
[b] Pulse ($beats \cdot min^{-1}$)	74 (58–96)	84* (75–109)	95* (76–105)	90* (67–100)	91* (78–102)
Temperature (°C)	36.4 (36.1–38)	37.8 (37.2–39.3)	37.7 (37.0–38.1)	37.9 (37.2–38.5)	37.7 (37.0–38.3)
Mass (kg)	70.7 (62–89.7)	73* (62.8–90.6)	74.5* (63.5–92.1)	76.5* (65.5–93)	78* (67.8–94.4)

[a, b], Mean values of three daily measurements in each patient; values are median and ranges; * $P<0.05$ compared to start

Table 3. Serum values and relative changes of the albumin concentration

	Start	Day 1	Day 2	Day 3	Day 4
Osmolality (mosmol·kg^{-1})	292 (288–300)	291 (280–307)	282 (276–299)	283.5 (281–298)	282 (275–299)
Creatinine (µmol·l^{-1})	107.5 (77–123)	97 (72–127)	108 (79–279)	154.5 (83–271)	131 (89–259)
Albumin (g·l^{-1})	36.5 (28–42)	31* (23–37)	27.5* (23–33)	24* (18–28)	22* (19–26)
Albumin (%)	100	86* (76–90)	77.5* (69–82)	64* (63–76)	60* (58–68)
Sodium (mmol·l^{-1})	140.5 (137–142)	139 (137–143)	139 (134–141)	140.5 (134–141)	140 (128–144)
Potassium (mmol·l^{-1})	4.6 (4.0–5.4)	4.4 (3.7–5.2)	4.0 (3.5–5.9)	4.1 (3.7–5.1)	4.0 (3.7–4.7)

Values are given as median and ranges; * $P<0.01$ compared to start

Discussion

The administration of IL-2 is capable of inducing lasting remissions in a proportion of patients with advanced renal cell carcinoma or malignant melanoma. Most effective IL-2 administration programmes are, however, accompanied by considerable toxicity, probably resulting from endothelial cell damage which leads to capillary leakage and it is important to get information on the pathogenesis and severity of CLS due to IL-2. For this purpose, it is necessary to monitor V_{ECF} and V_{TBW}. The severity of CLS in patients undergoing IL-2 treatment is normally estimated by a gain in mass and decline in serum albumin concentration. These variables are, however, not very precise for the exact estimation of CLS.

If one wants to measure V_{ECF} and V_{TBW} by means of dilution methods, it is necessary to use three tracers, namely one for V_{ECF} (e.g. bromide; de Planque et al. 1965), one for V_{TBW} (e.g. tritiated water or antipyrine; Soberman et al. 1949) and one for BV (e.g. Evans blue; Guyton 1991). All these tracers have their own equilibration time, half-life time and intrinsic breakdown. During *static* measurements, the error of these dilution techniques has been found to be substantial (4%–10%; McGrath et al. 1976). If one wants to use the same tracers for measurements during *dynamic* conditions, the problem becomes extremely difficult. The concentration of the three tracers will decrease with time due to biological breakdown and due to dilution of the tracer into other, unintended compartments (Aukland and Nicolaysen 1981). In theory, measurements of fluid changes with time due to interventions should be possible by these techniques, but the errors would be large (Rose 1990). Therefore, we studied the degree of capillary leakage by means of noninvasive conductivity measurements in eight patients receiving continuous IL-2 treatment.

Groeneveld et al. (1987) have found that in the porcine septic shock model, microvascular permeability is not the same in different organs (in the abdomen it is higher than in the lungs). We studied microvascular permeability in the muscles which form the only tissue with capillary leakage in the limbs. It was not however investigated as to whether CLS is of the same degree of severity in muscles as in other organs. However, a good correlation was found between the increase in V_{ECF} and gain in mass. Therefore, CLS in muscles would seem to be representative for the whole body (situation).

Baars et al. (1992) have shown that polymorphonuclear neutrophils (PMNN) are activated during systemic administration of IL-2. These PMNN preceded the induction of complement system activation, measured by increased C3a levels. Mier et al. (1990) have shown that peak levels of tumour necrosis factor (TNF) occurred 2 h after IL-2 administration. Furthermore, they have shown that administration of dexamethasone with IL-2 prevented the in-vivo generation of TNF resulting in an amelioration of the observed perturbation of PMNN function and a reduction in the degree of hypotension and organ toxicity. All these toxicity mechanisms are activated within the first 24 h after starting treatment and are known to cause enhanced capillary permeability and this enhanced capillary permeability will disturb the Starling equilibrium across the capillary membrane expressed as:

$$J_v = K_f[(P_c - P_t) - \sigma(\pi_c - \pi_t)],$$

where J_v expresses the net volume flow across the capillary wall, K_f the filtration coefficient (equalling the product of the hydraulic conductivity and the surface area), P_c the capillary hydrostatic pressure, P_t the interstitial fluid pressure, σ the Staverman reflection coefficient, π_c the capillary colloid osmotic pressure, and π_t the interstitial colloid osmotic pressure. The augmented capillary permeability can be translated as a decrease in σ (Taylor et al. 1984). The colloid osmotic pressure gradient ($\pi_c - \pi_t$) will also decrease due to the protein shift from intravascular to the interstitium (Guyton 1992). Besides the K_f will also change. Since K_f is directly proportional to the radius of the pores to the 4th power and the pore sizes will increase, K_f will also increase. All these factors together will lead to a fluid shift towards the interstitium, resulting in an increase in P_t. As a result of this the lymphatic safety

factor will decrease (Taylor et al. 1984). As a result the interstitium will be expanded due to the fluid accumulation.

Our data indeed showed (V_{ECF} increase, albumin concentration decrease, mean arterial pressure decrease and pulse increase) that a fluid shift occurred from the intravascular to the extracellular part of the interstitium also starting within 24 h and being most pronounced on the 2nd day. In spite of the extracellular compartment changes, the intracellular compartment remained remarkably constant (Table 1). This was probably due to the fact that fluid losses from the intra- to the extravasal compartment were iso-osmotic, leading to an unchanged extracellular osmolality. Figure 1 shows that, with respect to individual differences, the increase of the V_{ECF} correlated with the increase of body mass. Mean gain in mass was less than expected on the basis of the fluid balance. This was probably caused by increased sweating due to intermittent fever.

In spite of capillary leakage, BV remained stable during the first 2 days and increased slightly during day 3 and day 4, probably due to intravenous administration of 0.9% NaCl used to dissolve the IL-2. This BV increase cannot be the only explanation for the decline in serum albumin concentration during the study. From Table 1 and 3 it can be concluded that the decrease in serum albumin concentration was only partly caused by an increase in BV, but was largely due to capillary leakage. Urinary albumin loss cannot be implicated as a cause of the hypo-albuminaemia, since this was not observed in our patients. These data show that proteins pass through the endothelial barrier during CLS. The data presented in this paper showed that conductivity measurements can be applied to the study of CLS induced by IL-2. The measurements were well-tolerated and could be performed several times a day, if necessary. Not only does this technique allow the frequent assessment of fluid leakage from the vascular space to the tissues, but also provides data relating to the relative distribution of this fluid between the intra- and extracellular compartments. It might be useful during further research to consider the cause, exact onset and possible treatment of this syndrome. It could also be applicable in other clinical situations of accumulation of interstitial fluid.

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References

Aukland K, Nicolaysen G (1981) Interstitial fluid volume: local regulatory mechanisms. Physiol Rev 61:556–43

Baars JW (1993) Interleukin-2 toxicity: mechanisms and management. In: Wagstaff J, Kluwer BV (eds) Interleukin-2: the state of the art. Dordrecht, The Netherlands, pp 45–69

Baars JW, Hack CE, Wagstaff J, Eerenberg-Belmer AJM, Wolbink GJJ, Thijs LG, Strack van Schijndel RJM, van der Vall HLJA, Pinedo HM (1992) The activation of polymorphonuclear neutrophils and the complement system during immunotherapy with recombinant interleukin-2. Br J Cancer 65:96–101

Baumgartner RN, Cameron Chumlea W, Roche AF (1989) Estimation of body composition from bioelectric impedance of body segments. Am J Clin Nutr 50:221–6

Ettinghausen SE, Pini RK, Rosenberg SA (1988) Increased vascular permeability in organs mediated by system administration of lymphokine-activated killer cells and recombinant interleukin-2 in mice. J Natl Cancer Inst 80:177–88

Groeneveld ABJ, Heidendal GAK, den Hollander W, Nauta JJP, Thijs LG (1987) Noninvasive assessment of regional albumin extravasation in porcine septic shock. J Crit Care 2:245–255

Guyton AC (1991) Textbook of medical physiology, 8th edn. Saunders, Philadelphia

Kanai H, Haeno M, Sakamoto K (1982) Electrical measurement of fluid distribution in legs and arms: estimation of extra-cellular and intra-cellular fluid. IEEE Front Eng Health Care 7:273–6

Karnofsky DA, Abelman WH, Craver LF, Burchenal JH (1984) The use of nitrogen mustards in the palliative treatment of carcinoma with particular reference to bronchogenic carcinoma. Cancer 1:634–69

Kouw PM, Olthof CG, Ter Wee PM, Oe PL, Donker AJM, Schneider H, De Vries PMJM (1992) Assessment of post-dialysis dry weight: an application of the conductivity measurement method. Kidney Int 41:440–4

Mazumder A, Rosenberg SA (1984) Successful adoptive immunotherapy of established pulmonary metastases with lymphokine-activated killer cells and recombinant interleukine-2. Science 225:1487–9

McGrath BP, Tiller DJ, Horvath JS, Johnson JR (1976) Measurement of extracellular fluid volume in patients on maintenance hemodialysis. Kidney Inter 9:57–9

Meijer JH, Vries PMJM de, Goovaerts HG, Oe PL, Donker AJM, Schneider H (1989) Measurement of transcellular fluid shift during hemodialysis, I. Method. Med Biol Eng Comput 27:147–51

Mier JW, Vachino G, Klemper MS, Aronson FR, Noring R, Smith S, Brandon EP, Laird W, Atkins MB (1990) Inhibition of Interleukin-2 induced tumor necrosis factor release by dexamethasone: prevention of an acquired neutrophil chemotaxis defect and differential suppression of Interleukin-2 associated side effects. Blood 76:1933–40

Olthof CG, Vries PMJM de, Kouw PM, Oe PL, Schneider H, Lange JJ de, Donker AJM (1993) Non-invasive conductivity method for detection of dynamic body fluid changes: in vitro and in vivo validation. Nephrol Dial Transplant 8:41–46

Planque BA de, Geyskes GG, Van Dongen R, Dorhout Mees EJ (1965) Simultaneous determination of extracellular volume and blood volume with the Volemetron. Clin Chim Acta 11:270–7

Rose BD (1990) Clinical physiology of acid-base and electrolyte disorders, 3rd edn, McGraw-Hill, New York

Rosenberg SA, Mule JJ, Spiess PJ, Reichert CM, Schwarz SL (1985) Regression of established pulmonary metastases and subcutaneous tumor mediated by systemic administration of high-dose recombinant interleukin 2. J Exp Med 161:1169–88

Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, Linehan WM et al (1987) A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukine-2 or high-dose interleukine-2 alone. N Eng J Med 316:889–97

Rosenstein M, Ettinghausen SE, Rosenberg SA (1986) Extravasation of intravascular fluid mediated by systemic administration of recombinant interleukine 2. J Immunol 137:1735–42

Segal KR, Burastero S, Chun A, Coronel P, Pierson RN, Wang J (1991) Estimation of extracellular and total body water by multiple-frequency bioelectrical-impedance measurement. Am J Clin Nutr 54:26–9

Smith KA (1988) Interleukine-2: inception, impact and implications. Science 240:1169–75

Soberman R, Brodie BB, Levy BB, Axelrod J, Hollander V, Steele JM (1949) The use of total body water in man. J Biol Chem 179:31–42

Taylor AE, Parker JC, Allison RC (1984) Capillary exchange of fluid and protein. In: Shoemaker WC, Thompson WL, Holbrook PR (eds) Textbook of critical care. Saunders, Philadelphia, pp 359–367

de Vries PMJM (1989) Determination of intracellular and extracellular fluid volume by means of non-invasive conductivity measurements. Method, in vitro validation and clinical application during haemodialysis and haemofiltration. Thesis, Free University Press, Amsterdam

de Vries PMJM, Meijer JH, Oe PL, Van Bronswijk H, Schneider H, Donker AJM (1987) Conductivity measurements for analysis of transcellular fluid shifts during hemodialysis. Trans Am Soc Artif Intern Organs 33:554–6

de Vries PMJM, Meijer JH, Vlaanderen K, Visser V, Oe PL, Donker AJM, Schneider H (1989) Measurement of transcellular fluid shift during hemodialysis, II. In vitro and clinical evaluation. Med Biol Eng Comput 27:152–8