Objective: To compare the sequential changes in extracellular water (ECW) expansion in elderly patients receiving intensive care for severe sepsis with those in a similar group of younger patients.

Design: Inception cohort study.

Setting: Critical Care Unit and University Department of Surgery in a single tertiary care center.

Patients: A consecutive series of 14 patients older than 60 years (n = 8) or younger than 40 years (n = 6) with severe sepsis who completed sequential measurements of body composition during a 21-day period.

Main Outcome Measure: Sequential measurements of body composition including ECW by bromide dilution, total body water by tritium dilution, and fat-free body mass by dual-energy x-ray absorptiometry were performed during 21 days after resuscitation. Excess ECW was estimated from the difference between measured ECW and ECW predicted from fat-free body mass corrected to normal hydration.

Results: On the first study day, ECW was overexpanded by 9.05 ± 1.87 L (mean ± SEM) and 10.33 ± 1.79 L in the young and elderly groups, respectively (P = .66). Whereas the young group excreted most of this excess ECW by day 5 (P = .008), the elderly group remained overexpanded until day 10 before mobilization of ECW occurred (P = .003). The changes over time of ECW excess were significantly different (P = .02 for group × time interaction). The elderly group required more prolonged inotropic (P = .009) and ventilatory (P = .004) support and remained in intensive care longer (P = .008) than the young group.

Conclusions: The period of ECW expansion is more prolonged in elderly patients with sepsis and contributes to a poorer outcome from critical illness. This new finding is of fundamental importance to the treatment of elderly patients recovering from severe sepsis.

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ONE OF the hallmarks of aging is a decreased ability to respond adaptively to environmental challenges.1 This loss of physiological and metabolic reserve results in a diminished capacity to maintain homeostasis, and there is evidence to suggest that the mechanisms responsible for restoring body fluid composition to normal after injury or during critical illness may not function as effectively in the elderly as in younger patients.2,3 After resuscitation of the patient with sepsis, a period of obligatory extravascular sequestration of fluid occurs and results in over-expansion of the extracellular fluid volume.4,5 Current evidence suggests that elderly patients may respond less favorably to this large fluid load than younger patients, and we wondered if excessive or prolonged extracellular fluid expansion occurred and whether this contributed to a poorer outcome from critical illness. For this reason, we made sequential measurements of extracellular water (ECW) in a group of elderly patients with severe sepsis and compared the results with those obtained from a similar group of younger patients.

RESULTS

PATIENTS

Clinical details of the 14 patients are shown in Table 1. Six patients between the ages of 19 and 35 years formed the young group, in whom there were 2 cases each of meningococcal sepsis, pneumococcal pneumonia, and peritonitis caused by ruptured intra-abdominal abscesses. Eight patients between the ages of 60 and 72 years made up the elderly group, of whom 6 presented with peritonitis, 1 developed urosepsis complicating ureteric obstruction,
PATIENTS AND METHODS

Eight patients aged 60 years and older and 6 patients younger than 40 years who were admitted to our intensive care unit for the treatment of severe sepsis were studied. Criteria for entry were those of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, and severity of illness was assessed by means of the Acute Physiology Assessment and Chronic Health Evaluation II system without including points for age. Informed consent was obtained for each patient from their nominated next of kin before entry. These investigations were approved by the North Health Ethics Committee.

CLINICAL MANAGEMENT IN INTENSIVE CARE

Patients were treated in consensus fashion by a group of intensivists according to standard clinical guidelines. Circulatory resuscitation was guided by clinical assessment, including continuous monitoring of thoracic compliance, core temperature, pulse oximetry, intra-arterial blood pressure, and electrocardiography. For plasma volume expansion, physiological saline and colloid (~4% albumin, fresh frozen plasma, polygelatin, or pentastarch) were used with transfusion of packed red blood cells to maintain the hematocrit between 0.30 and 0.40. All patients received inotropic support with dopamine and/or norepinephrine, supplemented in some cases with epinephrine, dobutamine, or angiotensin. All patients without contraindications received digoxin. Amiodarone and/or direct-current cardioversion were used to control cardiac rhythm when required. Patients were given ventilatory assistance to achieve normoxemia and normocarbia, and positive end-expiratory pressure was limited to 15 cm H2O or less, unless required for alveolar flooding or hypoxemia despite an inspiratory oxygen fraction of more than 0.80. Patients were sedated with morphine sulfate and 1 presented with a cerebral abscess complicating acute mastoiditis. The Acute Physiology Score, which forms the major component of the Acute Physiology Assessment and Chronic Health Evaluation II score and is determined from the most deranged values of 12 physiological variables during the first 24 hours after admission to intensive care, was comparable in both groups, with median scores of 20 and 22 in the young and elderly groups, respectively (P = .80). Health status 3 to 6 months before admission was measured by the Chronic Health Evaluation component, a 4-level scale that rates a patient from good previous health to severe disabling chronic illness. None of the patients had chronic disease producing serious restriction of activity (class C). There was more comorbidity in the older patients, but only 1 patient (in the elderly group) had a history of congestive heart failure and none of the patients had a history of chronic renal failure. Six patients developed acute renal failure (3 young and 3 elderly) but only 1 patient (patient 11) received hemodialysis. All patients required at least 1 form of inotropic support. Two patients (1 young and 1 elderly) developed adult respiratory distress syndrome. Only 1 patient (patient 13) had major surgery beyond the first week of intensive care.

RESUSCITATION AND CLINICAL OUTCOME

There was a median period of hemodynamic instability of 26 (13.3-70.5) hours in the young group and 31 (16.3-62.0) hours in the elderly group (P = .37). During this period when patients were resuscitated, the elderly group had a positive fluid balance (ignoring insensible fluid loss) greater than those in the young group (10.35 ± 3.10 L vs 6.94 ± 1.48 L), although there was no significant difference between them (P = .39). Total colloid infused during this period was 7.50 ± 1.30 L (including 172 ± 33 g of albumin) in the elderly group and 6.93 ± 0.70 L (136 ± 33 g of albumin) in the young group (P = .73). Table 2 shows the clinical outcome of the patients in the 2 groups. There was 1 death in the elderly group. When compared with young patients, elderly patients received significantly more prolonged inotropic (P = .009) and ventilatory (P = .004) support, and remained in intensive care (P = .008) and in the hospital (P = .005) longer than young patients.

BODY COMPOSITION AND WATER SPACES

Table 3 summarizes the sequential body composition measurements in the 2 patient groups during the 21-
While expansion at day 0 was not significantly different and remained essentially unchanged from day 5 to day 9.05 ± 1.87 L to 2.88 ± 1.85 L (P = .08) for the group × time interaction.

ECW EXPANSION

The Figure shows the changes in ECW excess in both groups. In the first 5 days of study, ECW excess fell from 9.05 ± 1.87 L to 2.88 ± 1.85 L (P = .008) in the young group and remained essentially unchanged from day 5 to day 21 (2.43 ± 1.42 L; P = .85). In contrast, ECW excess in the elderly group was 10.33 ± 1.79 L on day 0 and remained elevated during the first 10 days of study (P = .78) before declining to 4.90 ± 1.99 L (P = .008) by day 21. While expansion at day 0 was not significantly different between young and elderly patients (P = .66), at day 5 the elderly group was significantly overexpanded compared with the young group (P = .02). When compared with those in young patients, the changes over time of ECW excess in elderly patients were significantly different (P = .02 for the group × time interaction).

CONTINUING SEPSIS AND RENAL FUNCTION

In Table 3, the sequential measurements of CRP are also shown. The CRP level was uniformly elevated in all patients on day 0, had decreased on day 5, and by day 21 had normalized in both groups. There was no significant difference between the young and elderly groups in the rate of resolution of CRP (P = .07).

Table 4 shows the sequential measurements of creatinine clearance from the time of admission to intensive care through to the 10th study day. Mannitol was used in 5 cases, 4 in the elderly group and 1 in the young group. Renal function was similarly impaired in both groups at the time of admission to intensive care, but, whereas this had improved to normal limits by day 0 in the young group, renal function remained significantly impaired in the elderly patients throughout the first 10 days of study.
Our results show that the period of extravascular fluid sequestration is altogether more prolonged in the elderly critically ill, septic patient. Whereas young patients with severe sepsis mobilized most of the excess ECW within the first week after the onset of sepsis, elderly patients, by contrast, remained significantly overexpanded during the same period, and mobilization of this sequestered fluid did not occur until more than 2 weeks after the onset of sepsis. After 3 weeks, the measured ECW excess was still, on average, nearly 5 L. Moreover, when we examined the changes in ECW excess over time, there was a significant difference in the responses of the elderly patients compared with those of the young patients.

Given the case prevalence of peritonitis and the greater number of surgical procedures in these patients...
(Table 1), it might at first sight appear that the elderly patients experienced a more severe and prolonged septic insult, and it could be argued that our results reflect this. However, we have shown that the severity of sepsis, as indicated by CRP levels on the first study day (Table 3), was comparable in both groups, while the levels of CRP also resolved at a similar rate, suggesting that there was no appreciable difference between the rates of resolution of sepsis in the 2 groups. Furthermore, when we compared peritonitis with nonperitonitis, the rate of resolution was similar. In the first 24 to 48 hours of admission to the intensive care unit that followed the initial septic insult, both groups had similarly deranged acute physiological variables (Table 1), and renal function was similarly impaired (Table 4). Both groups were resuscitated to the same end points, and in all 3 patients in the young group who had acute renal failure at the onset of sepsis, the renal response was almost immediate. By contrast, the responses of the 3 elderly patients who developed acute renal failure were poor, and, even in patients in whom renal function was not adversely affected after the onset of sepsis, creatinine clearance was markedly reduced compared with that in the younger patients; this is reflected by the overall values obtained for the group (Table 4). Finally, we found the individual responses of the elderly patients with peritonitis to be similar to those of the elderly without peritonitis; likewise, when we examined the responses of the young patients with peritonitis, we found these to be similar to those in the other nonperitonitis cases in the young group.

In critical illness, patients have to cope with considerably larger volumes of extracellular fluid than has been described in patients with other states of ECW expansion, such as heart failure, where ECW is of the order of 18 L or 266 mL/kg, compared with the 28 L or 362 mL/kg (Table 3) seen in the elderly patients with sepsis of this study (normal value, typically 15 L or 230 mL/kg). This places greater demands on renal and other homeostatic mechanisms to restore and maintain an adequate circulating volume. In light of the demonstrated changes in renal function, it may not be surprising that the ability of the elderly critically ill patient to excrete the enormous resuscitative fluid load becomes correspondingly impaired, predisposing to more prolonged extracellular fluid expansion. However, if these changes were simply the result of altered renal function, then the problems could be corrected by more aggressive diuresis or reducing the resuscitative fluid load by decreasing the volume of intravenous fluid administration. But large volumes of resuscitative fluid are necessary to maintain hemodynamic stability as a result of the continuous depletion of plasma volume caused by extravascular fluid sequestration; in addition, use of diuretics in the elderly patients of this study did not hasten mobilization of the sequestered fluid, while aggressive diuresis may actually compromise cardiovascular and renal function further by reducing the intravascular circulating volume and central filling pressures.

Extravascular sequestration of fluid is an obligatory phenomenon that occurs independently of organ function and is caused, in part, by an increase in capillary permeability but also by the structural and functional changes in the interstitial matrix and cell membrane. The interstitial fluid space comprises nearly 80% of the extracellular fluid volume and constitutes a dynamic compartment through which protein, water, and electrolytes continually pass, forming an interface between plasma and cells. It consists of a matrix or gel

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### Table 2. Clinical Outcome in the 2 Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Young (n=6)</th>
<th>Elderly (n=8)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic support, d</td>
<td>3 (2-8)</td>
<td>10 (4-24)</td>
<td>.009</td>
</tr>
<tr>
<td>Ventilatory support, d</td>
<td>4 (2-6)</td>
<td>9 (3-24)</td>
<td>.004</td>
</tr>
<tr>
<td>Intensive care, d</td>
<td>5 (3-10)</td>
<td>13 (5-24)†</td>
<td>.008</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>15 (7-29)</td>
<td>31 (11-120)†</td>
<td>.005</td>
</tr>
</tbody>
</table>

* Mantel-Cox log-rank test.
† One patient died 24 days after admission to the hospital.

### Table 3. Sequential Measurements of Body Composition and C-reactive Protein During the 21-Day Study Period*

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 10</th>
<th>Day 21</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>BWt, kg</td>
<td>Young 74.95 ± 3.67</td>
<td>67.60 ± 3.82‡</td>
<td>63.52 ± 3.96§</td>
<td>61.85 ± 4.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Elderly 77.36 ± 5.62</td>
<td>77.10 ± 5.19</td>
<td>74.03 ± 5.72</td>
<td>67.35 ± 4.97§</td>
<td>.01</td>
</tr>
<tr>
<td>TBF, kg</td>
<td>Young 14.63 ± 1.86</td>
<td>14.02 ± 1.70</td>
<td>13.88 ± 1.87</td>
<td>13.06 ± 1.98</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>Elderly 17.14 ± 2.49</td>
<td>16.51 ± 2.17</td>
<td>16.05 ± 2.14</td>
<td>16.30 ± 2.30</td>
<td>.37</td>
</tr>
<tr>
<td>TBP, kg</td>
<td>Young 10.32 ± 0.97</td>
<td>9.35 ± 0.81§</td>
<td>8.99 ± 0.78</td>
<td>8.42 ± 0.71§</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Elderly 9.04 ± 0.51</td>
<td>8.65 ± 0.76§</td>
<td>8.35 ± 0.57</td>
<td>8.11 ± 0.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TBW, L</td>
<td>Young 46.53 ± 3.04</td>
<td>39.56 ± 2.99§</td>
<td>38.09 ± 2.97</td>
<td>36.21 ± 3.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Elderly 46.25 ± 3.67</td>
<td>46.61 ± 3.76</td>
<td>45.12 ± 3.85</td>
<td>38.87 ± 3.26§</td>
<td>.02</td>
</tr>
<tr>
<td>ECW, L</td>
<td>Young 24.29 ± 2.35</td>
<td>18.39 ± 1.99§</td>
<td>18.00 ± 0.85</td>
<td>16.32 ± 1.19</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Elderly 27.98 ± 2.74</td>
<td>29.28 ± 2.80</td>
<td>27.14 ± 3.48</td>
<td>20.31 ± 2.21‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>Young 35.5 (13-72)</td>
<td>9.5 (3.3-48)</td>
<td>8.6 (0.9-30)</td>
<td>0.0 (0.0-4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Elderly 26.5 (8.5-52)</td>
<td>10.2 (7-26)</td>
<td>10.1 (2.1-14)</td>
<td>3.7 (0.0-20)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*BWt indicates body weight; TBF, total body fat; TBP, total body protein; TBW, total body water; ECW, extracellular water; and CRP, C-reactive protein. Values are shown as mean ± SEM or median (range).
† Repeated-measures analysis of variance (after logarithmic transformation for CRP).
‡ P < .01 for paired t test vs preceding measurement.
§ P < .05 for paired t test vs preceding measurement.
component composed of a network of collagen and adhesive glycoproteins embedded in a gel of proteoglycans, and a fluid or sol component. The gel is normally unsaturated but readily takes up fluid when in contact with it. Proteoglycan filaments are extremely thin, coiled molecules made up predominantly of hyaluronic acid. They have the ability to coil and uncoil.20 Uncoiling of the matrix with loosely bound hyaluronic acid forms open helixes and causes specific sites on proteoglycans to become exposed to albumin within the sol compartment, facilitating accommodation of more albumin molecules (reduced albumin exclusion) and thereby increasing the uptake of water and electrolytes. Coiling covers these sites, closes the helixes in which hyaluronic acid becomes tightly bound, reduces albumin attachment, and causes exclusion of albumin from the gel compartment. This, in turn, reduces the extravascular flux of protein, salt, and water. Changes in the geometry of the interstitial matrix directly affects the compliance of the interstitial space (change in volume divided by change in pressure) and can thereby permit the storage of large volumes of fluid within the space.

Structural changes of hyaluronic acid and the interactions between collagen and proteoglycans that control the flow of albumin through the interstitial matrix are thus important factors in determining the fluid dynamics between the interstitial space and the intravascular compartment. The nature of the physiological control of interstitial space compliance is still largely unknown, but there is evidence to suggest that a renal factor may be responsible, since bilateral nephrectomy reduces interstitial space compliance 4-fold.30 There is a limit to the ability of the interstitial space to expand as long as the structure of the interstitium remains intact, and, in sepsis, oxidants released disrupt the structural integrity of the space, thereby allowing the space to expand beyond its limits.35 Moreover, there would be a delay in removal of this fluid because the structural proteins would have to be reformed to restore the integrity of that space. Conceivably, aging may be associated with an impairment in this process of change in interstitial matrix configuration causing reduced albumin exclusion, resulting in inappropriate expansion of the interstitial space that would cause delayed mobilization of sequestered fluid from this space.

Aging is accompanied by a number of changes in the connective-tissue components of the interstitial matrix. There is accumulation of calcium salts, lipofuscin, and amyloid; thickening of the basement membrane; and changes in the chemistry of collagen.31 Collagen, which constitutes a major component of interstitial matrix and is secreted in soluble form, undergoes progressive chemical cross-linking with age, forming insoluble fibers that are relatively inert metabolically. These changes are primarily responsible for the progressive stiffness and rigidity of tissues characteristic of increasing age. Increased collagen cross-linking tends to increase the albumin-excluded fraction of the interstitial fluid volume, which would decrease the hydration of the interstitial tissue.22 Alterations in collagen with age could also account for derangements in the physicochemical properties of the collagen-proteoglycan matrix that impair its ability to coil and hinder mobilization of sequestered fluid from the matrix.

There are other mechanisms responsible for the restoration of circulating volume and acid-base homeostasis, such as baroreflex sensitivity33 and urinary concentrating ability,34 that may not function as effectively in the elderly. Excretion of an acid load by elderly subjects is more prolonged than in younger individuals.35 It is well recognized that glomerular filtration rate and renal blood flow decline with age,36,37 but wide ranges in renal blood flow and glomerular filtration rate produce little change in urine output. Loss of nephrons in the aging kidney that result in an obligatory solute diuresis and an intrinsic defect in solute transport in the diluting segment of the nephron impose inherent restrictions on the minimal osmolality that the renal tubule can establish.38 Although the ability to excrete an acute salt and water load is dependent on factors intrinsic to the kidney, overwhelmingly so is the ability to suppress antidiuretic hormone release and maintain a water-impermeable segment in the terminal nephron. Thus, an inappropriate, nonosmotic release of antidiuretic hormone that is common to sick elderly patients, coupled with an intrinsic defect in urinary dilution and a decline in glomerular filtration, will also potentiate excessive water retention and predispose to the prolonged overexpansion of extracellular water seen in elderly, critically ill patients.

The period after resuscitation when the phase of extravascular fluid sequestration occurs provides the great-

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**Table 4. Sequential Measurements of Creatinine Clearance From Day of Admission to the Intensive Care Unit**

<table>
<thead>
<tr>
<th>Group</th>
<th>Admission</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 10</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>1.02 ± 0.20</td>
<td>1.50 ± 0.10</td>
<td>1.53 ± 0.06</td>
<td>1.58 ± 0.08</td>
<td>.02</td>
</tr>
<tr>
<td>Elderly</td>
<td>0.88 ± 0.12</td>
<td>1.00 ± 0.09‡</td>
<td>0.91 ± 0.16‡</td>
<td>0.96 ± 0.12‡</td>
<td>.85</td>
</tr>
</tbody>
</table>

*Normal range, 1.5 to 2.3 mL/s. Values are mean ± SEM.
†Repeated-measures analysis of variance.
‡P < .01 for unpaired t test vs young.

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**Sequential measurements of excess extracellular water (ECW) in 8 elderly (open circles) and 6 young (solid circles) patients with sepsis. Asterisks indicate significant change from preceding measurement.**
est therapeutic challenge in critical illness. This problem is highlighted in the elderly patient with sepsis in whom this phase is inordinately prolonged and, with it, the need for more prolonged ventilatory and inotropic support. Large volumes of resuscitation fluid become necessary to maintain hemodynamic stability as a result of the continuous depletion of plasma volume, and prolonged overexpansion of extracellular fluid predisposes to pulmonary edema and respiratory failure as well as to postresuscitation hypertension consequent on massive intravascular influx of sequestered fluid.1,2 Transition to mobilization of sequestered fluid is therefore crucial, since it heralds organ system recovery and ultimately survival. The physiological mechanisms by which mobilization occurs are not fully understood, and while renal responses appear to be important, recovery of cell function and normalization of the interstitial matrix are paramount, since the obligatory extracellular fluid expansion is not caused by renal failure but by the inherent changes in the properties of the interstitial matrix.

These findings are of fundamental importance to the treatment of elderly patients recovering from severe sepsis, as we have shown that prolongation of the period of ECW expansion contributes to a poorer outcome from critical illness. It is apparent that the homeostatic mechanisms of the interstitial matrix or appropriate renal responses to counter ECW expansion cannot be relied on in the elderly patient, for even when these patients are out of intensive care and return to the ward 2 or more weeks after the onset of sepsis, this state of ECW expansion may persist. This highlights the magnitude of the problem and should draw the attention of clinicians caring for elderly patients recovering from severe sepsis to the need for continued vigilance to fluid balance and sodium restriction.

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Corresponding author: Graham L. Hill, MD, University Department of Surgery, Auckland Hospital, Private Bag 92024, Park Road, Grafton, Auckland 3, New Zealand.

REFERENCES


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