Epidemiology of disease-related undernutrition and the impact on postoperative adverse outcome in cardiac surgery

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CHAPTER 9

GENERAL DISCUSSION
AND FUTURE PERSPECTIVES
Main findings

The general aim of this thesis was to investigate ways to improve identification of DRU and thereby treatment of undernourished patients undergoing cardiac surgery. Our data showed that 10-25% of cardiac surgery patients either are or become undernourished (Chapters 4, 5, 7). Moreover, our research clearly demonstrated that patients who are undernourished - based on low BMI, unintended WL, low FFMI or loss of muscle mass - have a higher risk for adverse outcome after cardiac surgery (Chapters 4, 5, 7). In addition, our data not only generated the fact that cardiac surgery patients with a higher preoperative FFMI were more able to respond to cardiac-surgery induced stress (Chapter 5), but also strengthened our hypothesis that patients with a higher preoperative FFMI were more capable of mobilizing muscle protein - favorable loss of muscle mass during surgery - resulting in a lower risk for adverse outcome (Chapter 7). In addition, patients not capable of regaining cardiac-surgery-induced protein losses during the postoperative recovery period experienced decreased vitality more often (Chapter 7).

In one of our other studies (Chapter 2) we observed that well-nourished patients undergoing cardiac surgery may be harmed by caloric overfeeding. Therefore, it is highly recommended to select and screen before you intervene. From our systematic review (Chapter 3) it was concluded that the screening tools MST (Chapter 3, Figure 3.1) and the SNAQ (Chapter 1, Figure 1.2) were the most accurate quick-and-easy tools available to implement screening for DRU in the general hospital inpatient population. Our systematic review showed that no studies on the accuracy of quick-and-easy undernutrition screening tools had been carried out in a cardiac surgery population. We observed that half of undernourished cardiac surgery patients were misclassified as well-nourished using the parameter unintended WL only, without the parameter low BMI (Chapter 4). Continued research by our group demonstrated that half of cardiac surgery patients with a low FFMI were still misclassified as well-nourished using both the parameters unintended WL and BMI to identify the undernourished (Chapter 5). In addition, neither the quick-and-easy nutritional screening tool SNAQ nor the MUST (both tools recommended in the Netherlands to screen for undernutrition at hospital admission (Chapter 1, Figure 1.2 & 1.3)) were able to identify an adequate number, i.e. more than 65%, of undernourished patients undergoing cardiac surgery (Chapter 8). These misclassifications have to be prevented. They may lead to inappropriate nutritional treatment and possible postoperative complications. Untreated undernutrition as well as overfeeding in the well-nourished may increase the occurrence of complications after cardiac surgery (Chapters 2, 4, 5, 7).

The results of our research underline the necessity of measuring body composition to identify DRU in cardiac surgery patients. To reduce the resulting extra workload
and the cost of measuring body composition as a screening tool, it may be of value to further develop an accurate, quick-and-easy nutritional screening tool which would easily identify those cardiac surgery patients at high risk for low FFMI. Further research on our CSSM - cardiac-surgery-specific MUST integrating age and gender - is recommended. Preliminary results demonstrated a relatively high sensitivity of 74% for the CSSM (Chapter 8). At the preoperative outpatient clinic nurses can use this quick-and-easy tool to establish undernutrition several weeks before surgery. After a patient is classified as undernourished, i.e. screened positive, preoperative referral to a dietitian for further diagnostic assessment and, if indicated, nutritional treatment should take place. To assess nutritional status and monitor therapy efficacy we advocate the use of BIS assessed FFMI, ICW and ECW although with caution (Chapter 6, Chapter 9, p. 159). To increase accuracy, we recommend the use of the DXA method to assess FFMI in parallel with BIS but with a lower frequency of assessment. To correctly interpret these body composition measurements and therapy efficacy fluid and inflammatory status should also be evaluated. In addition, information on exact body composition might be of additional benefit in treating those undernourished patients who have a simultaneous high fat mass, in other words treating the sarcopenic obese (see Future research, Chapter 9, p. 165). One can hypothesize that future interventions should not only aim to increase FFMI but should also aim to decrease fat mass thus reducing the risk for adverse outcome even more. To reduce the risk for adverse outcome nutritional therapy is probably particularly effective in combination with physical exercise (Chapter 9, p. 163).

In our study, the prevalence of unintended preoperative WL, low BMI as well as low FFMI was rather low (4%, 5% and 8%, respectively), but still accounts for 13% of cardiac surgical patients. One may question whether DRU screening and intervention in all cardiac surgery patients will be cost-effective. However, the simplicity of the identification process, its short duration of less than 5 minutes, and the fact that in a vulnerable group of patients, risk can be reduced at a low cost and with no discomfort to the patient makes ‘nutritional conditioning’ a relevant risk control and patient safety issue. Waiting and planning time prior to surgery should be organized in such a way that the nutritional conditioning requirements can be met.

In conclusion, approximately one out of ten cardiac surgery patients is undernourished prior to surgery. To improve identification of DRU and thereby treatment of these patients, we advocate that FFMI be measured both during screening and during diagnostic assessment and that efficacy of therapy be evaluated. If a quick-and-easy undernutrition screening tool is preferred, we recommend further research into the cardiac-surgery-specific MUST (CSSM).
DRU and outcome after cardiac surgery

A lot of studies have investigated the association between BMI and adverse outcome after cardiac surgery, some of which contained a large number of patients. To the best of our knowledge no studies have been conducted on unintended WL or FFMI and adverse outcome in cardiac surgery patients. Engelman and colleagues evaluated a mixed cardiac surgery population of patients undergoing both CABG and valvular surgery. In this study which included more than 5000 patients (68% undergoing CABG), researchers found that a BMI of less than 20 was independently associated with increased mortality, incidence of pneumonia, stroke, renal failure, and re-exploration for bleeding. In a population of more than 4000 patients undergoing isolated CABG, Reeves and colleagues found an increased incidence of in-hospital mortality, infectious complications, renal failure, prolonged ventilation and prolonged length of hospital stay in patients with a BMI less than 20. Potapov and colleagues published the results of approximately 23 000 patients who underwent CABG or CABG with valvular surgery. The large number of patients in this study allowed researchers to separate patients into 20 separate BMI groups. The results of this study confirmed prior data in that patients with a low BMI were at increased risk for 30-day mortality, infections such as pneumonia and sepsis, re-intubation, re-exploration for bleeding and prolonged ICU stay. A recent study by Thourani and colleagues in more than 4000 patients undergoing valvular surgery demonstrated that patients with a low BMI up to 24 kg/m² had the highest in-hospital mortality when compared with patients with normal or high BMI. They all conclude that when compared with patients with higher BMI it is plausible that patients who are underweight may not have the necessary metabolic reserve to overcome the further increased catabolic stress resulting from a stressful operation. Other explanations that have been discussed are co-morbidities, severe heart failure, additional valvular surgery, more advanced age, and gender. Our studies assessing the association between DRU and adverse outcome were adjusted for age, gender, operative risk defined by the EuroSCORE, operative procedure, hypoalbuminaemia, inflammatory status, heart failure and operation time (Chapters 4, 5). Independently of these factors DRU was still associated with an increased occurrence of adverse outcome. In particular, low BMI and low FFMI were independently associated with an increased occurrence of postoperative infections and ICU stay. Most of these infections were of the respiratory tract. We hypothesized that mobilization of muscle mass proteins to deliver amino acids as substrate for the synthesis of acute phase proteins as part of the immune response, was hampered in those patients with a low FFMI (Chapter 1). Thus, patients with a low muscle mass are less able to handle infectious threats. Muscle mass functions as an important source of amino acids for protein synthesis and gluconeogenesis in times of stress and starvation. An addi-
tional explanation might be that a low FFMI reflects less respiratory muscle mass and function - muscle weakness - resulting in prolonged duration of mechanical ventilation. Prolonged mechanical ventilation is associated with pneumonia\textsuperscript{11}. Cardiac surgery patients who had preoperative inspiratory muscle training (IMT) had a significantly shorter duration of mechanical ventilation and a reduced occurrence of pneumonia\textsuperscript{12}. In conclusion, since there is biological plausibility and consistency with other studies we believe that our studies significantly support the hypothesis that DRU causes an increased risk for adverse outcome after cardiac surgery. More studies are needed to further explore the mechanism and the degree of causality according to the criteria for causation as described by Bradford Hill\textsuperscript{13}. Moreover, because no definite conclusions on causality can be drawn from cohort studies, a randomized controlled trial at FFMI and clinical outcome level should indicate if patients with a low FFMI benefit more from a nutritional and/or physical training program than those without a low FFMI.

**FFM using bio-impedance spectroscopy (BIS)**

Although of high potential, measuring FFM using the BIS method may lead to less accurate estimates of FFM in cardiac surgery patients than in healthy subjects\textsuperscript{14-16}. Cardiac surgery patients tend to have higher BMI, and extracellular fluid imbalances due to underlying cardiac disease are expected. Most probably these patient characteristics result in an overestimation of the metabolically-active part of FFM because of an expectedly high amount of extracellular water (ECW), and thereby an underestimation of DRU. FFM is calculated from ICW and ECW (Figure 1.1, Chapter 1). Moreover, in general more bias is to be expected in patients with obesity, extracellular fluid imbalances, weight loss or inflammation\textsuperscript{17-19}. Interpretation of BIS results remains a complex area because although it is clear that ECW increases in these states due to fluid surplus, it has not been clearly established to which degree this applies to intracellular water (ICW). ICW reflects nutritional status while ECW reflects fluid. Using BIS, an overestimation of ICW due to differing resistivity at tissue level caused by inflammation is a possibility\textsuperscript{17,20}. On the other hand, FFMI using bioelectrical impedance turned out to be a significant predictor of adverse outcome both in cardiac surgery (Chapter 5) and in other populations\textsuperscript{21-23}. In conclusion, we assume the BIS method to be reasonably useful in assessing low FFM in this cardiac surgery population, although only with caution. Its wide intra-individual variation compared with other methods may lead to misclassifications and thereby under or overtreatment (Chapter 6). However, it should be stressed that commonly used parameters such as unintended WL and BMI do not overcome these problems and are even less specific.
Undernutrition screening in cardiac surgery

From our systematic review (Chapter 3) it was concluded that the high applicability combined with clinically relevant sensitivity and specificity make both the MST (Chapter 3, Figure 3.1) and the SNAQ (Chapter 1, Figure 1.2) the most accurate tools available to implement in the general hospital inpatient population. The results of our systematic review also revealed that no studies have been carried out in a cardiac surgery population. To reach national consensus about nutritional screening tools to be used in a Dutch hospital population, the results of this review were presented and discussed at the national consensus meeting organized by the Dutch Dietetic Association and the expert group at the Academic Medical Center, Amsterdam (2005). Because of higher study quality and because its validation was performed in the Dutch setting, the SNAQ was judged of higher quality to be implemented as the DRU screening method in Dutch hospitals than the Australian MST.

A major subject of debate during the consensus meeting was the clinical relevance of registering the parameter low BMI in addition to unintended WL in order to identify the undernourished. Or, translated into nutritional screening tools, the question was; ‘Is the SNAQ method as accurate in identifying DRU as the MUST method?’.

The MUST includes BMI and the SNAQ does not (Figures 1.2 and 1.3). The MUST is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) to screen for DRU in the adult community setting.24 ESPEN advised the Nutritional Risk Score (NRS-200225) for the hospital setting, but this tool was judged by the experts visiting the Dutch consensus meeting as too complicated for daily practice. They concluded the MUST to be valid in the hospital setting. After the consensus meeting, the nutritional screening tools recommended to implement in Dutch hospitals were the SNAQ and if applicable the MUST.26

Currently, screening for DRU has been implemented in all Dutch hospitals. Most hospitals use the SNAQ and to a lesser extent the MUST. The Academic Medical Center (AMC) screens using the SNAQ at hospital admission. Which screening tool should be applied at the preoperative outpatient clinic is still subject of debate. The sensitivity of the SNAQ was reported to be 79% with a specificity of 83% in a mixed hospital population, and 59% and 94%, respectively in a preoperative high-risk outpatient population.27,28 It should be realized that these test characteristics are highly dependent on the reference standard used. Our study results demonstrated that a low BMI, or more specifically a low FFMI, are important parameters in identifying undernourished cardiac surgery patients. In comparison with a low FFMI, the sensitivity of both the SNAQ and MUST was low in cardiac surgery patients, 19% and 59%, respectively (Chapter 8). Nevertheless, although absolutely not optimal, even screening for DRU with the SNAQ remains valuable compared with no screening at all. The SNAQ does identify patients with unintended WL which is an
important well-established parameter of DRU in both surgical and chronic heart failure patients. In addition, it should be realized that even the extremely quick-and-easy SNAQ method remains hard to implement in daily practice. On the other hand, to reduce misclassifications and postoperative adverse outcomes, it is recommended that FFMI measurements be integrated to identify and treat the undernourished. To reduce extra workload and the cost of FFM measurements, further research on quick-and-easy undernutrition screening tools such as our CSSM integrating age and gender - is recommended. We observed a relatively high sensitivity of 74% for the CSSM (Chapter 8).

In conclusion, ideally patients should be screened and referred for DRU at the pre-operative outpatient clinic several weeks prior to cardiac surgery, at the time of hospital admission, and weekly after surgery as well as monitoring nutritional intake during hospital admission and at postoperative hospital appointments. Consequently, the waiting period and also the early and long-term postoperative phases can be used to increase patients’ reserve capacity of metabolically-active FFM by means of nutritional interventions combined with exercise programs to optimally respond to operative stress.

**Definition and reference standard of DRU**

Diagnostic accuracy in terms of sensitivity and specificity is highly dependent on the reference standard defined. Currently, there is still no consensus-based definition of DRU. In 2009 Soeters and Schols stated that two major pathogenetic factors lead to DRU and should be integrated in the assessment of DRU: 1) undernutrition (by means of a negative nutrient balance) and 2) inflammatory activity. Undernutrition and inflammatory activity should be of such magnitude that this leads to: 1) changes in body composition, specifically loss of BCM; and 2) loss of function including muscle function (force and endurance), cognition and immune function. Last year, the European and American Society for Parenteral and Enteral Nutrition (ESPEN, ASPEN) published a proposal for an etiology-based diagnosis of adult starvation and disease-related undernutrition in the clinical practice setting. This International Consensus Guideline Committee proposes the following terminology for nutrition diagnosis integrating interaction between inflammatory response and nutritional status: 1) starvation-related malnutrition, when there is chronic starvation without inflammation, 2) chronic disease-related malnutrition, when inflammation is chronic and of mild to moderate degree, and 3) acute disease or injury-related malnutrition, when inflammation is acute and of severe degree. The strength of this terminology is that it includes diagnostic as well as therapeutic implications. If inflammation is absent then even advanced undernutrition due to starvation can be readily treated with appropriate nutritional resuscitation. The pres-
ence of inflammation often limits the effectiveness of nutritional interventions. A positive response to nutritional intervention will also require successful medical treatment of the underlying disease or condition. Nutrition therapy is an important supportive measure to facilitate effective medical treatment, although the prognosis for individuals with this type of undernutrition will be largely determined by the predisposing disease or condition. The Committee ends by concluding that development of associated laboratory, functional, food intake and body weight criteria in support of these diagnoses and their application to routine clinical practice will require further discussion and validation. In addition, to reach consensus for the optimal definition and to operational DRU, an international Delphi study was performed interviewing experts on the field\textsuperscript{32}. It was concluded that deficiencies of energy or protein and decrease in FFM were most often mentioned as being particularly important in defining DRU. Elements important to operational DRU were unintended WL, BMI, and no nutritional intake. Opinions on cut-off points regarding these elements differed strongly among experts. Soeters and Schols\textsuperscript{6} propose the items unintended WL, BMI and nutrient intake to screen for undernutrition and to assess those positively screened for undernutrition by measuring body composition - FFM, BCM, muscle mass, ICW, ICW/ECW ratio - and function. In light of these recently published suggestions to make a working definition for DRU, our reference standard for DRU formulated in 2005 (Chapter 3) ‘Unintended WL or another changing anthropometric over time’ and ‘an estimate of the current body composition status such as BMI’ aggregated with FFMI in 2010 (Chapter 5) seems justified in our cardiac surgery population. Especially, since we demonstrated that all these items are independently associated with adverse outcome. As well as unintended WL, BMI and FFM, a variety of other anthropometric parameters that estimate body composition and more sophisticated techniques that measure body composition exist\textsuperscript{34}. It is clear that highly accurate techniques to measure body content such as in-vivo neutron activation analysis and also dual energy X-ray absorptiometry (DXA) have the disadvantages of relatively high cost, need specialized measurement facilities, and are not commonly available\textsuperscript{34,35}. Practically, when diagnosing a patient’s nutritional status most of the time only a history of body weight is available. As the next step, clinical trials assessing nutritional interventions combined with physical exercise programs on outcome should be performed to confirm the effectiveness of our formulated reference standard for DRU in cardiac surgery. These trials should stratify for the presence of DRU and inflammatory activity\textsuperscript{6,33,36}. As a result, a population-specific reference standard for DRU can be formulated that is capable of identifying those patients benefiting from nutritional intervention by improved function and outcome. Once a reference standard for DRU is formulated, it will be useful to develop an accurate quick-and-easy undernutrition screening tool as these are better applicable in daily clinical practice. To further refine the ref-
erence standard of DRU, systemic approaches to monitor and treat DRU in daily
dietetic practice should be registered in an electronic database also including data
about etiology, function and clinical outcome.

Clinical implications and future research

Identification of DRU in cardiac surgery

For now, to correctly identify and therefore treat undernutrition prior to cardiac
surgery, we advocate measuring FFMI in all cardiac surgery patients, or at least in
those patients at high risk for low FFMI. To screen for DRU, we recommend BIS
assessed FFMI in addition to low BMI and unintended WL. If a quick-and-easy
undernutrition screening tool is preferred, we recommend the (cardiac-surgery-spe-
cific) MUST in preference to the SNAQ. We advocate that dietitians use BIS to
measure and evaluate FFMI, ICW and ECW during further assessment although with
cautions. In clinical practice the differentiation between ICW and ECW for the cor-
correct interpretation of nutritional state is essential, and the evaluation of nutritional
therapy should include dynamic assessment of body composition. DXA is limited
by its inability to differentiate the hydration state of FFMI. To increase accuracy, we
advocate the use of the more sophisticated DXA method to assess FFMI in parallel
with BIS but with a lower frequency of assessment. Moreover, from DXA measure-
ments skeletal muscle mass can be estimated. Skeletal muscle mass is the compo-
nent of FFMI most sensitive to losses in disease and ageing. Fluid and inflam-
atory status have to be integrated into the nutritional assessment of cardiac surgery
patients to correctly interpret BIS and DXA measurements and therapy efficacy. It
should be emphasized that effectiveness of these selection strategies on body com-
position or outcome level after cardiac surgery has not yet been demonstrated.
Future research should demonstrate to what extent cardiac surgery patients with
DRU benefit from a nutritional intervention.

Nutritional interventions combined with physical exercise

Our research in cardiac surgery patients (Chapter 5) and studies in other patient
populations demonstrated that a low FFMI increases the risk for postoperative
adverse outcome (postoperative complications, longer hospital stay, increased
occurrence of the systemic inflammatory response syndrome, mortality and poorer
quality of life). We hypothesized that a low FFMI reflecting less muscle mass
represents insufficient nutritional reserve to cope with operative stress. To improve
FFMI and thereby reduce the risk for adverse events, nutritional therapy is probably
particularly effective in the context of anabolic interventions such as physical exer-
cise. Therefore, we recommend the next step should be to study the additional effect
of preoperative nutritional interventions combined with physical exercise at body level

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- FFM, muscle mass -, function and clinical outcome in patients undergoing cardiac surgery. In a recent review it was concluded that preoperative exercise therapy can be effective for reducing postoperative complication rates and length of hospital stay after cardiac surgery. Two studies assessed preoperative inspiratory muscle training in candidates for CABG surgery at high risk for postoperative pulmonary complications, and one in candidates for elective CABG surgery not specifically at high risk. One study assessed preoperative exercise training (not further specified) in low-risk candidates awaiting elective CABG surgery. These preoperative training sessions varying between two to ten weeks resulted in higher inspiratory muscle strength, fewer pulmonary complications (specifically pneumonia), and shorter length of hospital stay. No data on metabolically-active body mass were available. In the setting of cardiac rehabilitation, chronic heart failure and in elderly patients, early postoperative resistance exercise training, has been shown to be safe and of additional value to aerobic regimes to increase muscle strength and mass, clinical status, exercise capacity and quality of life. In guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) it is stated that surgical patients with severe undernutrition benefit from nutritional support for 10-14 days prior to major surgery even if surgery has to be delayed. Also studies assessing practical approaches using oral nutritional supplements (ONS) i.e. sip feeding using standard high-caloric protein-rich formulas suggest additional benefit with regard to body composition, quality of life and complications in patients with chronic heart failure as well as in surgical patients. It should be stressed that a major methodological problem of studies assessing the effect of sip feeding is that the optimal amount of protein (1.5 g/kg) for optimal synthesis has almost never been prescribed. Tepaske et al. found fewer postoperative infections in cardiac surgery patients at high risk for infection when preoperatively fed with an ONS with essential amino acids for a minimum of five days. It has been suggested that specific amino acid supplements increase muscle mass in the elderly. In COPD patients FFM increased more in patients attending a rehabilitation program that included amino acid supplements than a similar rehabilitation program without amino acid supplements. The other way around, Biolo et al showed that mobilization instead of bed-rest improves nutrition utilization. Wolfe and co-workers from Texas, and Van Loon and co-workers from Maastricht, the Netherlands, have published several studies about nutritional interventions combined with physical exercise. Data suggest that not only the exact composition and amount of an amino acid supplement are important, but also the timing of ingestion of the supplement in relation to the exercise. Although overall results suggest that nutritional interventions combined with physical exercise have a beneficial effect at body composition level, results of clinical studies comparing the effect of different strategies on clinical outcome in patients are lacking. In conclusion, future research should further unravel the mechanism behind DRU.
and its etiology such as inflammatory activity, specific nutritional interventions and possible benefits\textsuperscript{60}. Adverse effects should be monitored, especially in those patients at high risk for overfeeding (\textit{Chapter 2}). Additionally, a large multicentre clinical trial stratifying for the presence of inflammatory activity\textsuperscript{6,33} should reveal if undernourished patients awaiting elective cardiac surgery benefit from nutritional intervention (ONS, 1.5 g protein/kg) combined with physical exercise therapy in particular resistance training. This intervention program should be started two to six weeks preoperatively and continued during the early and long-term postoperative phases. To effectively identify undernourished cardiac surgery patients low FFMI should be measured in addition to low BMI and unintended WL. As a result, recovery after cardiac surgery may be improved.

\textbf{Sarcopenic obesity}

An interesting subgroup comprises those cardiac surgery patients with a high fat mass but also a low FFMI - the sarcopenic obese\textsuperscript{61}. Additional analyses of our data showed that one-quarter of patients with a low FFMI did have a high fat mass\textsuperscript{62}. We hypothesized that the adverse effects of a low FFM and high fat mass interact resulting in an aggravated risk on adverse outcome. As suggested by other investigators, obesity directly affects inflammation which in turn negatively influences muscle mass, contributing to the development and progression of sarcopenic obesity\textsuperscript{63}. Results from a study in the elderly demonstrated that sarcopenic obese subjects were two to three times more likely to develop disability than participants who only had sarcopenia or were only obese\textsuperscript{64}. One can hypothesize that in saropenic obese subjects preoperative nutritional interventions and physical exercise programs reduce the risk for adverse outcome after cardiac surgery even more than in non-obese sarcopenic subjects. This is because not only is FFM increased but also fat mass is decreased. In conclusion, future research should unravel if specific combinations of body composition require specific combinations of nutritional and physical exercise treatment.

\textbf{General conclusion}

DRU is a widespread problem that has been consistently associated with adverse outcome. Without standardized screening protocols at best only half of undernourished patients are identified and treated. To correctly identify and treat undernourished patients awaiting cardiac surgery FFMI should be measured in addition to BMI and unintended WL only two to six weeks prior to surgery. If screening for DRU is positive, further diagnostic assessment incorporating body composition should take place. Based on this assessment a patient-tailored dietary treatment can be prescribed and its effect evaluated. Consequently, the waiting period and also the early and long-term postoperative phases can be used to increase the patients’ reserve capacity.
of metabolically-active FFM by means of nutritional interventions combined with exercise programs to optimally respond to operative stress. As a result, recovery after cardiac surgery may be improved.

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