odological difficulty in the placement of catheters in portal vein and hepatic vein in humans. Even when the isotopic tracers are not used, this arteriovenous (A-V) balance model enables to determine the net balance of substrate and amino acids across the tissue bed by measuring the concentrations of substrates or amino acids and the blood flow. This simple method without using isotopic tracers has classically been used for the last two decades to determine the metabolism of the peripheral tissue bed in critically ill patients.[36–44] When isotopic tracers of amino acids are used, more information about the total rate of appearance (Rat) of a substrate across the tissue bed such as leucine or phenylalanine can be obtained (Fig. 2). The measurement of net balance using isotopic tracers requires the calculation of blood, substrate concentration in the artery and the vein, and isotopic enrichment in the artery and vein.

Possible mechanisms and/or hypotheses to explain the alteration in protein metabolism in critical illness

Inefficient substrate oxidation: Evidences indicate that resistance to the normal protein anabolic effect of insulin may be an important mechanism leading to net catabolism in severe injury or sepsis.[45–48] A general dysfunction of insulin during critical illness has been reported to be the failure of insulin to exert its normal hypoglycemic action.[3,49] It has been proposed that the failure of insulin to normally stimulate glucose uptake and oxidation could lead to protein catabolism indirectly, as a consequence of a peripheral energy deficit.[47,48] Another possible scenario is that because of the inability of insulin to restrain the stimulatory effect of glucagon on the rate of glucose production and gluconeogenesis, due to the increased plasma glucagon to insulin molar ratio, there is an increased rate of protein breakdown to supply amino acids as substrates to fuel the accelerated rate of gluconeogenesis.[50,51] In other words, the recent work performed by Hesselgren *et al.*[45] indicated that in the skeletal muscle of septic rats there is an impairment of insulin to inhibit protein breakdown and to stimulate protein synthesis. To test the hypothesis that an increase in protein breakdown in critically ill patients is due to an impairment of peripheral glucose oxidation, Jahoor and Wolfe *et al.*[14] performed a study in patients with burn and sepsis using a euglycemic hyperinsulinemic clamp technique combined with simultaneous administration of dichloroacetate (DCA), that stimulates pyruvate dehydrogenase activity, to further increase glucose oxidation. They found that the administration of DCA to the patients with burn and sepsis during hyperinsulinemia elicited a significant increase in the rate of glucose oxidation and the percentage of glucose uptake oxidized compared with the hyperinsulinemic clamp alone. However, the response of leucine and urea kinetics to the clamp with the simultaneous administration of DCA was not different from the response to the clamp alone. These results have suggested that the maximum effectiveness of insulin to suppress protein breakdown is not impaired and that a deficit in glucose oxidation or energy supply may not play a major role in mediating the protein catabolic response to severe burn injury and sepsis.

Effects of catabolic hormones

In stressed patients, several circulating factors regulating substrate, protein and energy metabolism have been identified.[52,53] Glucagon, catecholamines and cortisol have been identified as the "stress hormones" that play important roles in critically ill conditions regulating substrate metabolism.[53] These are supported by the animal study, in which blockade of the response of glucagon and insulin by the infusion of somatostatin and simultaneous adrenergic blockade abolished catabolic responses typically seen in septic condition.[6] These hormones may partially be responsible for the catabolic response, because the administration of these hormones in normal human volunteers has been shown to reproduce many of the metabolic alterations observed during critical illness.[54] Hyperglucagonemia was observed in

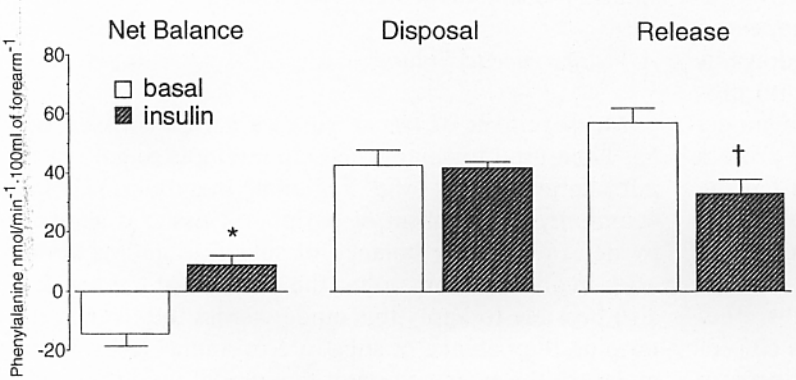

Fig. 2 Phenylalanine balance in and out from the forearm of the human volunteers. Infusion of stable isotope tracer of phenylalanine enables to calculate amino acid kinetics. Positive net balance is obtained after the local administration of insulin (*$P < 0.05$ vs. Basal). Positive net balance of phenylalanine is due to the significant decrease in release of phenylalanine from the forearm by the insulin infusion (†$P < 0.01$ vs. Basal). (From Ref. 43)