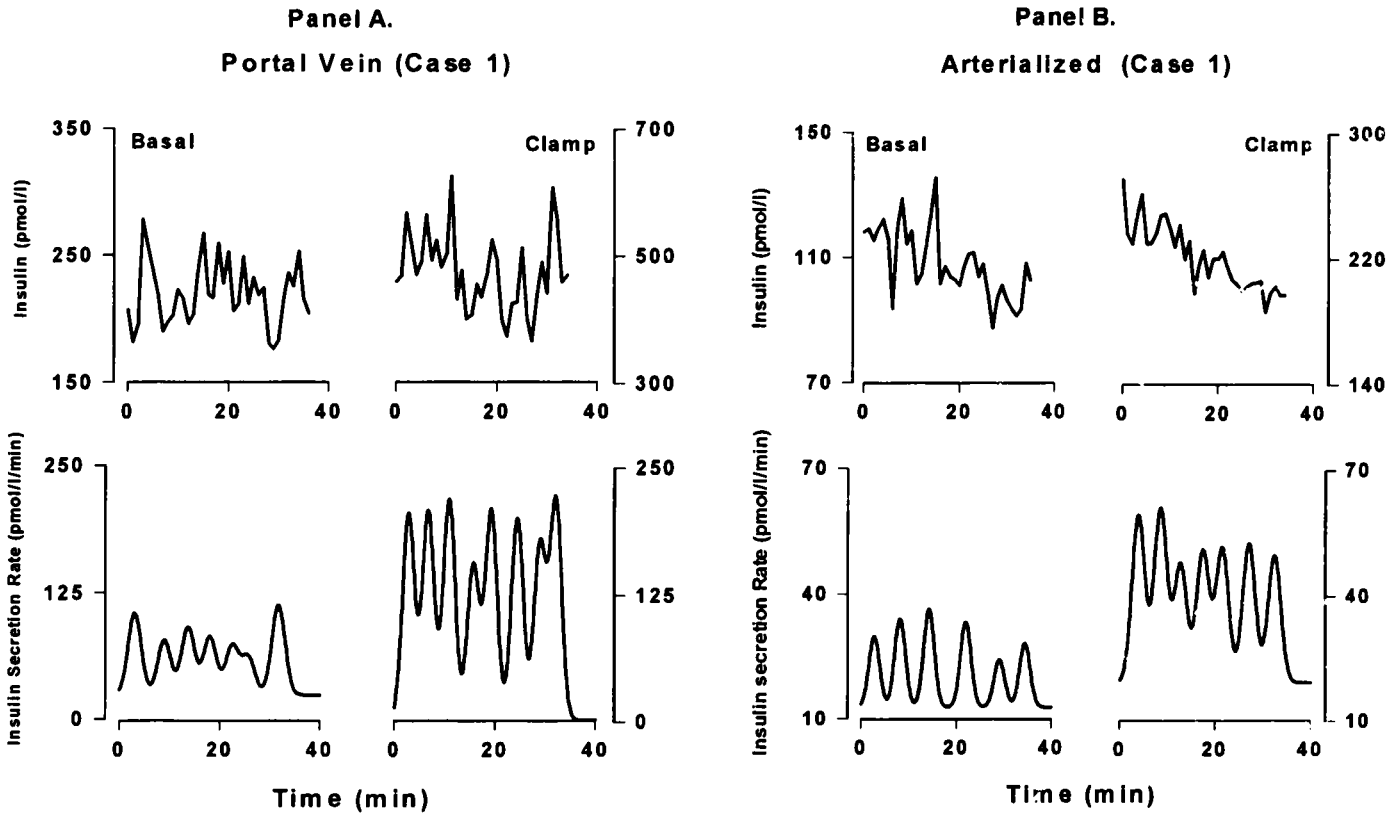

FIG. 4. A, The portal vein insulin concentration profile and corresponding deconvolved insulin secretion rates obtained during the intensive sampling periods in the basal state (*left panels*) and during the hyperglycemic clamp periods (*right panels*) for case 1. B, The arterialized insulin concentration profile and corresponding deconvolved insulin secretion rates obtained during the intensive sampling periods in the basal state (*left panels*) and during the hyperglycemic clamp periods (*right panels*) for case 1. Note that the insulin secretion rate is (mass units per volume of distribution)/time units. As the volume of distribution is unknown in the portal vein, these secretion units cannot be directly compared with those obtained from peripheral sampling.

formed (19). Cross-correlation analysis relates each portal vein insulin concentration to a corresponding value in the matching arterial series. This procedure consists of linear correlations carried out repeatedly at various time lags between the paired concentrations. Thus, at zero time lag, each portal vein plasma insulin concentration is compared with a time delayed measure (*e.g.* lag time minus 2 min) in the systemic circulation sample. By this means, an array of correlations can be collected that depend on the time matching of the two series.

To examine the relationship between pulses identified in the portal vein and systemic circulation we also performed peak concordance on these pulses from both sites. Peak concordance is a statistically independent (from cross-correlation) method to establish the relationship between detected pulses in two sampling sites. After identifying discrete insulin secretory bursts in the two time series (portal and peripheral), exact coincidence was defined by simultaneous pulse concordance (*i.e.* peak maxima occurred within one half-sampling interval of each other). Lagged coincidence was defined accordingly [*e.g.* with portal (+lags) or peripheral (−lags] peaks occurring first. The hypergeometric probability density (joint binomial distribution) was used to estimate the expected number of randomly concordant pulses, and the probability of falsely refuting the null hypothesis of pure chance concordance of the observed coincidences.

Results

Mean plasma glucose, insulin, and C peptide concentrations (Fig. 1)

The mean arterialized plasma glucose concentrations during the basal (fasting) and stimulated (hyperglycemic clamp) sampling periods were 5.3 ± 0.3 and 8.1 ± 0.1 mmol/L, respectively ($P < 0.001$). As expected, there was a rise in the mean arterialized (basal *vs.* stimulated, 209 ± 7.4 *vs.* 456 ± 16.8 pmol/L, $p < 0.001$) and mean portal vein (basal *vs.* stimulated, 440 ± 25.3 *vs.* 1020.7 ± 72.3 pmol/L; $P < 0.001$) insulin concentration after the increase in the plasma glucose concentration from 5.3 to 8 mmol/L during the hyperglycemic clamp. The mean arterialized C peptide concentration also increased with hyperglycemia (basal *vs.* stimulated, 1.8 ± 0.1 *vs.* 2.7 ± 0.1 nmol/L; $P < 0.001$), confirming an increase in insulin secretion in response to the glucose stimulus. Throughout the study in each subject, the portal vein insulin concentration was higher than the corresponding arterialized insulin concentration in both basal ($P < 0.001$) and stimulated ($P < 0.001$) sampling periods (Fig. 1).

Portal vein blood flow

The mean portal vein blood flow values in the two cases in which it was measured were 1.1 and 0.8 L/min. There was no change in the portal vein blood flow between the basal state and the hyperglycemic clamp.

Insulin concentration profiles (Figs. 2 and 3)

Inspection of the plasma insulin concentration profiles from the individual patients indicated the presence of re-