Development of the Biostator® Glucose Clamping Algorithm


The "glucose clamping" technique has been proposed as a method for the early detection of a beginning derangement of glucose homeostasis and thus for the possible prevention of maturity-onset diabetes. This technique interrupts the physiological glucose-insulin relationship by placing a patient's blood glucose concentration under an investigator's control, for quantification of the pancreatic beta-cell response during hyperglycemic clamps and of sensitivity of body tissue to exogenous insulin during normoglycemic clamps. We report the development of a glucose clamping algorithm for use with the Biostator® glucose-controlled insulin-infusion system (Horm. Metab. Res., Suppl. 8: 23–33, 1977). This algorithm adds simplicity and precision to the glucose clamping procedure and reduces operator effort to a minimum. We describe the early development of the algorithm with a model system and report evaluations made during animal studies and preliminary investigations with human subjects.

Additional Keyphrases: decreased sensitivity to insulin in maturity-onset diabetes • pancreatic beta-cells • data processing • estimating a patient's glucose metabolism rate • disorders of glucose homeostasis

The glucose clamping technique has been proposed as a valuable diagnostic tool for early identification of derangements in glucose metabolism in humans (1–3). In this technique the normal glucose–insulin relationship is interrupted by placing a patient's blood glucose concentration under an investigator's control. By "clamping" a patient's blood glucose concentration at a hyperglycemic value, with no addition of exogenous insulin, pancreatic beta-cell response to glucose may be observed. Likewise, by holding the patient's blood glucose concentration at a normoglycemic value, with programmed insulin infusion and feedback-controlled infusion of dextrose, the sensitivity of body tissues to insulin may be studied. This method offers clear advantages over oral glucose and insulin-tolerance tests (1). Unlike the oral glucose-tolerance test, the hyperglycemic clamp permits the time course of glucose metabolism by the body to be quantified and separated into the early and late phases of insulin secretion. The normoglycemic clamp with insulin infusion eliminates the danger of hypoglycemic excursions, possible with insulin-tolerance tests. The complex physiological responses to hypoglycemia are also avoided, thus providing a more reliable estimate of tissue sensitivity to insulin.

The glucose clamping method requires frequent measurement of blood glucose concentrations and subsequent infusion of dextrose doses to maintain the desired glucose concentration. Thus, the dextrose dose infused, under the proper conditions, is equal to the amount of glucose metabolized. An instrument capable of continuous monitoring and feedback control of blood glucose concentration would be well suited for this application.

The Biostator Glucose-Controlled Insulin-Infusion System (GCIIS) (4–6) has these features of closed-loop glucose control, providing glucose monitoring as well as infusion of insulin and dextrose, for computer control of blood glucose concentration within a preselected range. We have recently developed a glucose clamping control algorithm for use with the Biostator GCIIS. Early studies on a model system laid the groundwork for further evolution of the algorithm. The animal and human applications described here represent preliminary studies rather than a fully developed procedure.

Materials and Methods

The Biostator GCIIS (Life Science Instruments, Div. Miles Laboratories) is described in earlier publications (4–6). A computer-controlled infusion pump delivers insulin or dextrose in response to a signal from an electrochemical glucose sensor. Infusion is activated to maintain a patient's blood glucose concentration within a selected range.

Development of an algorithm suitable for use with the GCIIS and specifically tailored for glucose clamping has been developed and refined by in vivo experimentation and evaluation in dogs and humans. An early model is outlined in Figure 1. The reservoir, a stirrer, and external circulating pump represent the blood volume of a patient and the mixing action of blood circulation. Glucose disappearance is simulated by pump-controlled addition of water, causing an equal amount of overflow. The GCIIS is connected to the water reservoir through a double-lumen catheter and infusion tubing (for computer-controlled addition of dextrose) placed at opposite ends of the reservoir. This model is intended to assess the ability of the control algorithm to respond, by dextrose infusion, to various rates of glucose clearance and maintain the reservoir's glucose concentration at the pre-selected clamp value.

Further development of the algorithm was conducted through studies on two normal beagle dogs, maintained by Miles Laboratories, Inc., in a facility fully accredited by

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the American Association for Accreditation of Laboratory Animal
Animals. The dogs, weighing approximately 8 kg each, were anesthetized with Surital [sodium-5-allyl-5-(1-methyl-
butyl)-2-thiobarbiturate; Parke Davis, Detroit, MI 48207] and
connection to the GCIIS by means of a double-lumen catheter and an infusion line placed in either of the external jugular
veins. The dogs' blood glucose values were clamped at hyperglycemic concentrations of 1500 and 2000 mg/L for about
1.5 h at each concentration, with no insulin infusion. Nor-
moglycemic clamps were conducted at 800 mg/L for 3 h at
insulin-infusion rates of 1 and 10 milli-USP units/kg body wt
per minute.

Clinical studies on humans have been conducted under the
terms of an Investigational Device Exemption from the U.S.
Food and Drug Administration. The patients were connected
to the GCIIS by insertion of a double-lumen catheter and an
infusion line into forearm veins. Glucose clamp studies were
conducted at a normoglycemic concentration of 750 mg/L
at insulin-infusion rates of approximately 1 and 6 milli-
units/kg body wt per minute, representing a low and a high
infusion rate. Each individual was kept at the normoglycemic
value for approximately 3 h at the two different insulin-
infusion rates.

The glucose clamping control algorithm in its present form is:

\[
DR = WT \cdot KS \cdot [(BC - GY/10(3 + M)] + RC
\]

where:

\[
DR = \text{dextrose-infusion rate for clamp (mg/min)}
\]

\[
WT = \text{body weight (kg)}
\]

\[
BC = \text{desired clamp concentration (mg/L)}
\]

\[
GY = \text{present blood glucose concentration (mg/L)}
\]

\[
M = \text{slope of last 5-min glucose values}
\]

\[
KS = \text{constant to allow for differences in metabolism}
\]

\[
RC = 0.9 \text{RC}_{\text{preceeding}} + 0.1 (\text{DR}_{\text{preceeding}}/WT)
\]

RC is the static portion of the algorithm that determines DR
when the clamp concentration has been achieved.

In addition, provision is made to infuse insulin at a fixed
rate as follows:

\[
IR = RL \times WT
\]

where:

\[
IR = \text{insulin-infusion rate (milli-units/min)}
\]

\[
RL = \text{insulin-infusion rate (milli-units/kg per minute), selected by the operator}
\]

A hard copy printout of the data is produced by the Bio-
tator GCIIS printer module. The listing of the data, updated
each minute, includes: the blood glucose concentration, the
amount of dextrose infused each minute to maintain the
clamp, the amount of insulin infused each minute, and the
totals for insulin and dextrose infusion.

The data obtained from our glucose clamp studies are
presented as plots of blood glucose (mg/L) and dextrose-
infusion rate (mg/kg per minute) vs time (Figures 2–6). Al-
though the GCIIS provides an update for these values each
minute, we have simplified the charts to present glucose values
at 5-min intervals and dextrose-infusion at 10-min intervals.
The blood glucose values preceding the clamp values have
been omitted from the charts.

Results and Discussion

Glucose clamping experiments may yield valuable informa-
tion concerning the state of glucose metabolism in a
subject. For a normoglycemic clamp with a fixed insulin-
infusion rate, the dextrose-infusion rate may be used to esti-
mate glucose metabolism. This quantity is discussed by Rizza
et al. (7, 8) as being a valid estimate of glucose metabolism
when the dextrose-infusion rate has reached a steady-state
value as a function of time and when the glucose entering the
blood is from the exogenous source only. This latter condition
exists when the supply of endogenously produced glucose
entering the blood is completely suppressed. Rizza et al. (7)
show from their studies with 15 normal individuals that
complete suppression of endogenous glucose production oc-
curs at plasma insulin concentrations at or exceeding 50–60
milli-units per milliliter. During normoglycemic clamping
studies conducted by these investigators at insulin-infusion
rates of 0.5, 2.0, and 5.0 milli-units/kg body wt per minute,
steady-state insulin concentrations (mean ± SD) of 58 ± 4,
195 ± 9, and 570 ± 17 milli-units per milliliter, respectively,
were achieved within 30 min. Because our studies involve in-
ulin infusion rates of approximately equal magnitudes, we
assume complete suppression of endogenous glucose pro-
duction at the point where the steady-state dextrose-infusion
rate is achieved, and therefore use this value as an estimate
of the patient's glucose metabolism.

Results of Normoglycemic Clamps

Figure 2 demonstrates a normoglycemic glucose clamp (800
mg/L) on a normal, 8-kg male dog with insulin-infusion rates
of 1 and 10 milli-units/kg body wt per minute. The clamp was
maintained for 80 min at the low insulin-infusion rate and 100
min at the high infusion rate. The glucose value was main-
tained at 788 (SD 25) mg/L during the low insulin infusion and
784 (SD 32) mg/L during the high insulin infusion. The dex-
trose-infusion rate achieves steady-state at a value of 29.5
mg/kg per minute, about 170 min into the clamp.

Results of normoglycemic clamps on humans are shown in
Figures 3–5. Figures 3 and 4 represent normal individuals
clamped at a glucose value of 750 mg/L. The individual of
Figure 3, a normal woman, shows a mean blood glucose value
of 742 (SD 23) mg/L and a steady-state dextrose-infusion rate
of 2.5 mg/kg per minute about 80 min into the low insulin-
infusion rate clamp. The clamp with the high insulin-infusion
rate shows a mean blood glucose value of 739 (SD 20) mg/L
and a steady-state dextrose infusion rate of 6.0 mg/kg per
minute about 170 min into the clamp.

The individual of Figure 4, a normal but obese woman,
demonstrates a mean blood glucose value of 742 (SD 19) mg/L
and a dextrose infusion rate of 1.0 mg/kg per minute about 40
min into the low insulin-infusion rate clamp. At the high in-
ulin-infusion rate, the mean blood glucose value is 748 (SD
12) mg/L and the dextrose-infusion rate is 3.3 mg/kg per
minute about 110 min into the clamp.

The individual of Figure 5 is a woman with maturity-onset
diabetes. The insulin-infusion rates used for this subject are
slightly greater (1.1 and 6.6 milli-units/kg body wt per minute)
than those for the other two women. At the low insulin-
infusion rate, this individual demonstrates a mean blood glucose
value of 750 (SD 20) mg/L and a steady-state dextrose-infusion rate
of approximately 0.5 mg/kg per minute immediately into the
clamp. At the high insulin-infusion rate, the mean blood
maturity-onset diabetic, and may be a sign of an early derangement in glucose
metabolism.

Studies of this type on a population of normal and diabetic
subjects should permit compilation of a data base classified
according to the magnitude of the metabolic derangement.
The glucose clamping procedure may then be used as a
INSULIN INFUSION RATE = 1 m Units/kg/min  
INSULIN INFUSION RATE = 10 m Units/kg/min

Fig. 2. Plot of a normoglycemic glucose clamping study (600 mg/L) on a normal dog at insulin-infusion rates shown. Blood glucose concentration (G) and dextrose-infusion rate (DR) plotted as a function of time.

INSULIN INFUSION RATE = 0.9 mUnits/kg/min  
INSULIN INFUSION RATE = 5.3 mUnits/kg/min

Fig. 3. Plot of a normoglycemic glucose clamping study (750 mg/L) on a normal woman at insulin-infusion rates shown. Blood glucose concentration (G) and dextrose-infusion rate (DR) plotted as a function of time.
**Fig. 4.** Plot of a normoglycemic glucose clamping study (750 mg/L) on a normal, obese woman at insulin-infusion rates shown. Blood glucose concentration (G) and dextrose-infusion rate (DR) plotted as a function of time.

**Fig. 5.** Plot of a normoglycemic glucose clamping study (750 mg/L) on a diabetic woman at insulin-infusion rates shown. Blood glucose concentration (G) and dextrose-infusion rate (DR) plotted as a function of time.
screening procedure for the detection of the early stages of maturity-onset diabetes. In turn, this may provide incentives for the development of medications to re-establish normal insulin-receptor function and thus prevent full manifestation of the disease. Maturity-onset diabetes is usually characterized by loss of tissue sensitivity and responsiveness to insulin, perhaps related to an abnormality of the insulin-receptor function on cells (7, 8).

Results of Hyperglycemic Clamps

In contrast to the maturity-onset type, juvenile-onset diabetes is characterized by lack of insulin secretion in response to a dextrose challenge, owing to defective or missing pancreatic beta-cells. Hyperglycemic clamping of an individual’s blood glucose concentration, with no infusion of exogenous insulin, should permit assessment of beta-cell function.

At this time, we have not used the Biostator glucose clamping algorithm for hyperglycemic clamps on human subjects. However, Figure 6 demonstrates results for a normal, 8-kg dog clamped at hyperglycemic concentrations of 2000 and 1500 mg/L, as analyzed with the Biostator glucose clamping algorithm. The left side shows a 2000 mg/L clamp for 100 min; the mean blood glucose value is 1967 (SD 29) mg/L. The dextrose-infusion rate shows a steady increase throughout this period and reaches a plateau at approximately 49 mg/kg per minute. This plateau probably represents the steady-state response of the pancreatic beta-cells to the hyperglycemic blood glucose value. Beyond this point, the amount of dextrose required to maintain the clamp shows a decrease and may indicate a decrease in glucose metabolism. This decrease continues when the clamp value is lowered to 1500 mg/L, where it is maintained for 80 min at a mean blood glucose value of 1507 (SD 44) mg/L.

Advantage of the Algorithm

Before the development of the glucose clamping algorithm, the Biostator GCIIS had been used for glucose clamping studies (9–11), but the operator had to rely on trial-and-error selection of the dextrose-infusion rate to maintain the clamp value. Now the dextrose-infusion rate is continuously updated by the glucose clamping algorithm.

The ability to maintain a “tight” clamp, that is, one with a minimum deviation from the target value, is needed to avoid stimulation of unwanted physiological responses. The mean blood glucose value of our normoglycemic clamps on humans is 743 mg/L (SD 18 mg/L). The target clamp value is 750 mg/L. The glucose clamping algorithm should permit maintenance of a glucose clamp with less deviation from the target value than was previously possible with the GCIIS control algorithms.

Use of the glucose clamping technique, which is greatly simplified by the development of the glucose clamping algorithm, should contribute to a better understanding of disorders in glucose homeostasis, and permit early recognition of metabolic derangement preceding full manifestation of maturity-onset diabetes.

Studies to evaluate the efficacy of the GCIIS and the glucose clamping algorithm in clinical situations are continuing.

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References


