**Technical Note**

Glucose pump test: a new method for blood flow measurements

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**Abstract**

**Background.** A good test for monitoring blood flow ($Q_a$) must be accurate, rapid and economical in order to allow frequent easy measurements. The glucose pump test (GPT) is based on a constant glucose infusion as a dilutional indicator of $Q_a$.

**Methods.** GPT protocol requires a constant glucose infusion, by a syringe pump, into the arterial needle and two blood withdrawals from the venous needle, one basal before the infusion ($C_{a1}$), the other ($C_{a2}$) 11 s after the start of the infusion. At the bedside we measure glucose on $C_{a1}$ and $C_{a2}$. Knowing the infused glucose concentration ($C_i$) and the pump infusion rate ($Q_i$) we can easily calculate $Q_a = Q_i \times (C_i - C_{a2}) / (C_{a2} - C_{a1})$. We verified the accuracy of this new method by comparing it with the in vitro results from a circuit reproducing vascular access circulation, and in vivo comparing GPT-$Q_a$ with Doppler ultrasound in predialysis to the Transonic HD01-$Q_a$ during dialysis in 23 chronic haemodialysis patients.

**Results.** GPT-$Q_a$ values were highly correlated with the in vitro $Q_a = 1.01 \times \text{GPT}-Q_a - 16.6; r = 0.94$. There was agreement between the mean flow values of GPT and Doppler (927.5 and 927.1 ml/min, respectively; $P = \text{NS}$) while the mean value of HD01 was significantly lower (HD01-$Q_a = 690$ ml/min; $P < 0.001$ vs GPT-$Q_a$ and Doppler-$Q_a$). The regression analysis showed a good correlation between GPT and Transonic results ($r = 0.95$; HD01-$Q_a = 0.86 \times \text{GPT}-Q_a - 111.9$), while there was a significant difference between the two measurements (mean $\Delta 235 \pm 117$ ml/min; range from 15 to 451 ml/min). This difference could be caused by the large haemodynamic variations (different blood pressure, cardiac output, circulating effective volume, haematocrit) between pre-dialysis and intra-dialysis and in addition by the counter current flow during the reversal blood lines Transonic measurements.

**Conclusions.** GPT offers the advantage of a simple bedside procedure easily performed before dialysis: it does not interfere with the dialysis treatment and it is less intrusive for the patient as it does not involve reversal of the blood lines. The preliminary data indicate that our method could be a useful, simple and cheap test for monitoring access flow in every dialysis unit.

**Keywords:** constant infusion; glucose; vascular access

**Introduction**

A well functioning vascular access is vital for adequate dialysis and to limit morbidity in the chronic haemodialysis patient. In many years of clinical practice, native arteriovenous fistulas (AVFs) have proved to be the best permanent access with the fewest complications, while synthetic grafts (PTFE) have a limited average life and a larger number of complications [1].

Monitoring vascular access blood flow ($Q_a$), now facilitated by new methods, is certainly important, especially in grafts [1]. Increasing the frequency of these measurements could improve the possibility of predicting graft failure [2].

An ideal method for measuring $Q_a$ must be simple, quick and, if possible, economical.

After our successful experience using a glucose bolus as an indicator of vascular access recirculation [3], we tested a constant glucose infusion as a dilutional indicator of blood flow. The difference in glucose levels between a basal sample from the venous needle and a second sample during the infusion depends on blood flow, allowing its measurement: a high flow considerably dilutes the glucose infused, so there is only a small glucose increase and vice versa with a low flow (wide glucose difference).

This new test, the glucose pump test (GPT), is easy, quick and economical, permitting frequent monitoring of vascular access blood flow. GPT is performed pre-dialysis, therefore not interfering with the dialysis session and not needing for the reversal of the blood lines.
Subjects and methods

GPT protocol

Before the start of dialysis we stick the arterial needle, pre-filled with 10% glucose facing the blood stream, and connect it to a syringe pump (Anestesia, Fresenius-Vial S.A., Brezins, France) filled with 10% glucose. We then place the venous needle downstream, take the basal blood sample (only 0.2 ml) and empty it with 2 ml of air (volume of the needle tube). We start the timing and the constant glucose infusion at the maximum rate ($Q_i$ = 20 ml/min with this pump) and after 11 s withdraw the second sample vigorously from the venous needle with a rapid and strong aspiration ($Q_a$ = 5 ml of blood in 2 s). The glucose in the two blood samples is measured with a glucometer (Profile, Lifescan, Milpitas, CA, USA). Figure 1 shows the procedure and the steady-state glucose infusion described by the glucose mass balance equation:

$$\left( Q_a \times C_{a1} \right) + \left( Q_i \times C_i \right) = C_{a2} \times \left( Q_a + Q_i \right)$$

and then

$$Q_a = \frac{Q_i \times \left( C_i - C_{a2} \right)}{\left( C_{a2} - C_{a1} \right)}$$

where, $Q_a$, access blood flow (ml/min); $Q_i$, constant infusion rate (ml/min); $C_i$, glucose concentration infused (mg/ml); $C_{a1}$, basal blood glucose concentration (mg/ml); $C_{a2}$, during infusion blood glucose concentration (mg/ml).

If the $C_{a2}$ sample is out of glucometer range (glucose > 600 mg/dl) due to a very low blood flow or to a high $C_{a1}$ (diabetic patient), it is possible to repeat the test reducing the infusion rate ($Q_i$ from 20 to 10 ml/min).

In vitro validation

A ring circuit with a short silastic segment (0.6×20 cm) and a peristaltic pump (BSM 22, Hospal, Bologna, Italy) was our vascular access model (Figure 2). Into the silastic tract we put two dialysis needles (15 gauge) 5 cm apart, the first needle facing the flow, the second downstream. A ‘Y’ connector just after the silastic part allowed the blood flow to shunt into a drainage bag during the glucose infusion. This bag was suspended on a balance to weigh the blood (weight-$Q_a$) during each test, in order to calculate the blood volume (blood weight/blood specific gravity) [4] and then the flow (blood volume/time).

Finally, the bag was also connected to a standard dialysis circuit to clear the glucose infused.

We repeated three tests according to GPT protocol, for six different levels of weight-$Q_a$ from 325 to 996 ml/min (maximum rate for BSM 22 pump) and obtained the GPT-$Q_a$ from equation 2.

In vivo validation

We validated this new method by comparing it with the Doppler ultrasound and ultrasound dilution method in 27 chronic haemodialysis patients (22 AVFs; five PTFE grafts), after informed consent. The Doppler ultrasound and GPT were performed consecutively in pre-dialysis and the Tran-sonic test was performed during the dialysis session. The GPT test was carried out twice in 18 patients in order to assess its reproducibility.

Doppler ultrasound measurements. The ultrasound measurements were carried out in pre-dialysis time with a colour Doppler machine (Image Point HX, Hewlett Packard, Andover, MA, USA) with a 7.5 MHz linear phased-array
transducer. The vascular accesses were evaluated in the longitudinal and transverse planes from the arterial anastomosis through the entire access. Vascular blood flow was calculated by multiplying the time-averaged velocity by the cross-sectional area of the intra-needle portion of the access.

**Transonic measurements.** \( Q_a \) was measured by ultrasound dilution technology (HD01 device, Transonic Systems Inc., Itaka, NY, USA) during dialysis (between the first and the last 30 min of dialysis) according to standard procedures recommended by the manufacturer [5]. HD01 sensors were pre-calibrated.

All measurements were run in duplicate and averaged.

**Statistical analyses**

Data are reported as means ± SD. The two data groups were compared by the paired Student’s t-test and the relationship between them was obtained by linear regression analysis and the Bland–Altman test [6]. The reproducibility of twice tests is calculated as averaged SD by pooling the individual (SD) of the \( N \) patients (\( N_i \)):

\[
Pooled \ SD = \sum \left( \frac{(SD_i^2)}{N_i} \right)
\]

From the pooled SD we obtained the coefficient of variation (CV = pooled SD/mean) for GPT and HD01. Similar analysis was performed for GPT *in vitro* and *in vivo*.

**Results**

**In vitro**

The mean \( Q_a \) for GPT (from equation 2) and for blood weights were, respectively, 649 ± 36 and 639 ± 17 ml/min (\( P = \text{NS} \)) with a mean difference between the two measurements of 9.8 ± 81 ml/min (range from –131 to 141 ml/min). The correlation between weight-\( Q_a \) and GPT-\( Q_a \) was good \(( r = 0.94)\) with a regression equation, weight-\( Q_a = 1.01 \times \text{GPT-} Q_a - 16.6; (n = 18) \) (Figure 3). The pooled SD of GPT triplets was 47.9 ml/min showing a good *in vitro* repeatability (CV = 7.4%).

**In vivo**

We had only 24 Transonic results (three failed tests with no results due to a troubled basal line) and 26 Doppler results (one test lost due to faulty software) out of 27 patients analysed with the GPT. Finally, 23 patients were analysed with all three methods and Table 1 summarizes the main results. The mean flow values of GPT and Doppler ultrasound were close while the mean HD01 value was significantly lower \(( P < 0.001 \) vs GPT-\( Q_a \) and Doppler-\( Q_a \)). Figure 4 shows the correlation between GPT and Transonic results. A highly significant correlation was obtained \(( r = 0.95)\) with a regression equation: HD01-\( Q_a = 0.86 \times \text{GPT-} Q_a - 111.9.\) There was a significant difference between the two measurements with mean \( \Delta 235 ± 117 \) ml/min (range from 15 to 451 ml/min). This difference did not correlate with the average of the two measurements \(( r = 0.29)\) according to the Bland–Altman analysis [6]. This means the difference

<table>
<thead>
<tr>
<th>Comparison</th>
<th>GPT (ml/min)</th>
<th>HD01 (ml/min)</th>
<th>Doppler ultrasound (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_a ) mean</td>
<td>927.5 ± 392</td>
<td>690.5 ± 356</td>
<td>927.1 ± 539</td>
</tr>
<tr>
<td>( Q_a ) median</td>
<td>806</td>
<td>555</td>
<td>766</td>
</tr>
<tr>
<td>Range</td>
<td>336–1639</td>
<td>235–1315</td>
<td>224–1760</td>
</tr>
</tbody>
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HD01-\( Q_a \) vs GPT-\( Q_a \), \( P < 0.01 \); HD01-\( Q_a \) vs Doppler-\( Q_a \), \( P < 0.001 \).

**Fig. 3.** Correlation between the *in vitro* programmed blood flow (weight-\( Q_a \)) and the GPT results.

**Fig. 4.** Correlation between Transonic HD01 and GPT blood flow measurements in 23 patients.
between the two measurements was not influenced by the magnitude of flow.

The regression analysis between ultrasound and GPT results (Figure 5) showed a good correlation ($r=0.88$) but a regression line different from identity, Doppler-$Q_a = 1.21 \times \text{GPT-}Q_a - 199.9$ with a mean difference between the two measurements of $0.4 \pm 265 \text{ ml/min}$ (range from $-606$ to $476 \text{ ml/min}$).

Comparison of Doppler ultrasound and Transonic results showed the worse correlation ($r=0.87$) and very different data (mean $\Delta 237 \pm 287 \text{ ml/min}$; range from $-262$ to $782 \text{ ml/min}$) and a regression equation: $\text{HD01-}Q_a = 0.58 \times \text{Doppler-}Q_a + 156$.

The repeatability of GPT and Transonic showed a similar good coefficient of variation (CV$_{\text{GPT}} = 8.1\%$; CV$_{\text{HD01}} = 8.2\%$).

**Discussion**

The GPT is a dilution method based on glucose infusion into the arterial needle and two glucose determinations on blood samples from the venous needle, a basal one before the infusion and another during it once the glucose steady state ($\sim 10$ s) has been reached.

The blood flow rate dictates the difference between the two glucose levels: a high flow considerably dilutes the glucose infused, so there is only a small glucose increase and vice versa with a low flow (wide glucose difference).

The well-known principles of indicator dilution technique had already been applied to measure fistula blood flow [7]. Other authors proposed a constant infusion of isotope indicator as a steady-state dilutional method for measuring graft flow [8,9]. All these methods have fallen into disuse because they used tracers that are difficult to measure, and the radioactive substances give disadvantages for patients and operators in routine use.

However, glucose is an ideal tracer because it is harmless, easy to measure and economical. Our method is simpler than previous ones because it requires only two needles (the same used for haemodialysis) rather than three and only two small blood samples rather than eight [9]. The third needle was used in the previous methods to measure the cardio-pulmonary recirculation as constant infusion last $>1$ min. In the GPT, the infusion steady state is reached in a few seconds, before the return of cardio-pulmonary recirculation (sample $C_{a2}$ at $11$ s).

Dilution methods for measuring blood flow rely on complete mixing of the tracer so that dilution depends exclusively on blood flow. This mixing can be improved by: (i) tracer infusion facing blood stream; (ii) sufficient distance between the needles in the same venous branch; (iii) no effluent venous side-branches close to the arterial needle; (iv) turbulent blood flow; and (v) constant cross-sectional area (steady flow).

These features are typical of grafts, but also of many native AVFs. These conditions are valid both for Transonic HD01 and GPT. The three methods had similar mean values except for HD01, which showed a significantly lower mean. It is difficult to account for this difference. The fact that ultrasound Doppler and GPT are both pre-dialysis tests while HD01 is intra-dialysis suggests that blood flow may change during the dialysis session and, in addition, by reversing the blood lines as requested by HD01 method.

Several physiological mechanisms may be at play. The effect of potentially large haemodynamic variations (different blood pressure, cardiac output, circulating effective volume, haematocrit) between pre-dialysis and intra-dialysis may influence access blood flow. The countercurrent peristaltic flow (created by the blood pump in the reversal blood lines position) may alter the basal pre-dialysis blood flow. Krivitski and Depner [10] directly measured the effect of the reversed pump flow on the vascular access flow in an experimental study using a sheep with an implanted graft. They observed a $Q_a$ decrease in the order of up to $100 \text{ ml/min}$ (with a basal $Q_a$ of $920 \text{ ml/min}$ and a reversed $Q_h$ of $230 \text{ ml/min}$). This significant influence is obviously greater for higher $Q_h$ (from $200$ to $300 \text{ ml/min}$) or lower $Q_a$ as well showed by Bos et al. [11].

There were some differences also between GPT and Doppler results, particularly in patients who had older, fistulae with large aneurysms (19 AVFs and only four PTFE grafts in our 23 patients with three tests compared). In these, measuring blood flow with Doppler ultrasound may be inaccurate because the cross-sectional area is not a circle and the time-averaged velocity sampling is very difficult (turbulent flow). Doppler measurements are also affected by the presence of venous side-branches between the needles, while dilution methods are not.
as showed by Krivitsky and Depner [10]. An advantage of Doppler method is that it provides both estimation of blood flow and anatomical morphology including direct view of stenosis.

All these pitfalls in blood flow measuring makes the $Q_a$ values extremely variable [2] and its clinical benefit uncertain and still questioned especially in native AVFs [12–17]. There is a need for large randomized prospective studies to further elucidate this crucial point.

In conclusion, our method offers the advantage of a simple bedside procedure easily performed before, during or after and even out of dialysis (for example in transplant patient where identifying high access flows may aid in clinical decision making). The pre-dialysis GPT is the simplest because it does not interfere with the dialysis treatment and it is less intrusive for the patient since it does not involve reversal of the blood lines.

GPT, in addition, may be more accurate than intradialysis methods since before haemodialysis, haemodynamics may be more stable and comparable and blood flows less variable. Further investigations need to be performed to prove this latter point as well as to decide if GPT will have enough predicting value to identify critical lesions for preventive purposes in a surveillance protocol. If so, its ease and speed would make this test a good screening tool in the general haemodialysis population.

Acknowledgements. We are grateful to the non-profit association ‘Comitato assistenza malati Tigullio’ for the donation of the syringe pump and the colour Doppler ultrasound machine to our Hospital. Part of the data was presented as posters at the World Congress of Nephrology in San Francisco, October 13–17, 2001.

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Received for publication: 10.4.02
Accepted in revised form: 12.7.02