Letters

Haemoglobinopathy diagnosed on HbA_{1c} analysis

A 55-year-old Caucasian man attending our hospital for type 2 diabetes mellitus, diagnosed elsewhere 3 years ago, recently underwent glycosylated haemoglobin measurement by high-performance liquid chromatography (HPLC) using a Menarini HA8140 A1c analyser. In addition to HbA and A_{1c} peaks, a third peak (*see* Fig. 1) was noted. Subsequent haemoglobinopathy analysis, using a Hb Gold HPLChromatogram (Drew Scientific), confirmed this as HbC (36·5%).

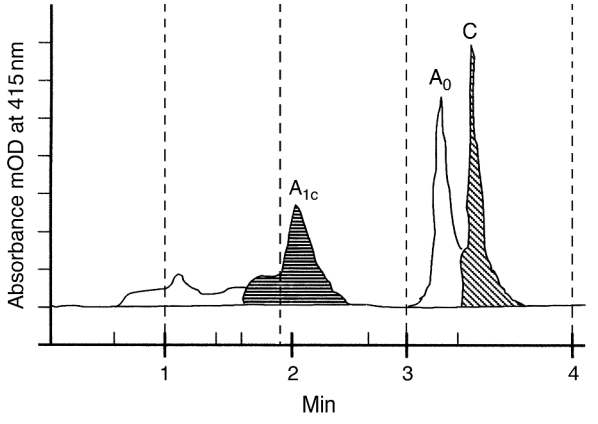

Figure 1. *Hb peaks on chromatography. For ease of presentation, sensitivity of HbA_{1c} peak hase been adjusted to 2 mOD units, and HbA_0 (A_1 and A_2) and HbC to 42 mOD units per unit scale.*

In the past 12 months, at the Western Infirmary Glasgow there have been four other incidences of unsuspected haemoglobinopathy discovered during Hb_{1c} screening. This suggests that biochemistry departments may already be undertaking *en passant* haemoglobinopathy screening during HPLC measurements of HbA_{1c}. Given the prevalence of diabetes, this may be a major diagnostic route where population haemoglobinopathy screening is not routinely undertaken. A recent publication[1] drew the attention of haematologists to the usefulness of HPLC haemoglobinopathy screening in detecting unsuspected diabetes mellitus. We wish to draw the attention of biochemists to the reverse, i.e. unsuspected haemoglobinopathy uncovered during HBA_{1c} analysis.

Acknowledgement

We are grateful to Dr Richard Soutar of Haematology, Western Infirmary Glasgow, where haemoglobinopathy screening was undertaken.

Reference

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Computer simulation analysis and relocating a phlebotomy department

We read with interest the article on the effectiveness of simulation analysis on the relocation and reorganization of a phlebotomy department in our hospital.[1] The relocation took place in May 2002 and we can now report on how effective the recommendations have proved to be.

The long waiting times have not been reduced despite the simulation-based layout of the new department. The location of the reception desk has caused queues to form along a hospital corridor and further reduced patient privacy. The pneumatic tube sample transport system has proved very effective and reduced the distance staff have to walk by 250 m. The patient callboard was not implemented because many patients need help in moving to the cubicle and it would therefore not prove advantageous. The double reception desk was implemented, but not staffed, because it would cause patients to overflow to the waiting room.

Validation of the simulation model was made during one working day and it did not reflect the fluctuation in patient numbers seen throughout the day, between days and over the year. Variability in patient numbers was a factor considered in the model but not the degree of variation, which we have seen in practice. We conclude that the authors have not provided convincing evidence that simulation is a particularly effective design tool, that the use of a fixed number of staff throughout the day is not effective and that flexibility

in staffing numbers remains the most potent mechanism to address bottlenecks and waiting times.

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Reference

1 Groothuis S, Goldschmidt HMJ, Drupsteen EJ, de Vries JCM, Hasman A, van Merode GG. Application of computer simulation to assess the effects of relocating a hospital phlebotomy department. *Ann Clin Biochem* 2002; **39**: 261–72

Authors' reply

In their letter, Dr Oosterhuis and Dr van den Berg describe the current situation in St Elisabeth's hospital. They report long waiting times, a patient callboard that was not implemented and a second workspace at the reception desk which was constructed but not staffed.

In our study, we described the new location and the procedures as they were designed at the beginning of the year 2000. We simulated this situation as it was designed, along with some small modifications based on a validated simulation model. We assumed that patients needed assistance to go to the cubicle in 50% of the cases. Not implementing a callboard means that 100% of the patients need to be guided to the cubicles. Using the simulation model, it is possible to study the effects of this change. Since the management intended to use a callboard there was no reason to model a situation without a callboard, which is a proven approach in other hospitals.

The authors state that the second workplace has not been used. We predicted a higher average turn-around time (TAT) when used (situation C) then when not (situation D) (*see* Table 4 in original published article). Not using a second workplace will create longer waiting lines in the hospital corridor. Experience at other public places is that those waiting like to be informed and preferably wait in a seating area rather than having to stand. The number of seats in the waiting room (26) was calculated based on the peak load and included four chairs for disabled and a playing corner for children.

Dr Oosterhuis and Dr van den Berg state that we did not take into account variations in the arrival of patients within a single day, between days and during a year. During our study we measured the arrivals of patients and their TATs and, according to the employees of the phlebotomy department, the number of patients and their arrival time represented an average working day.

By using arrival patterns, the number of patients arriving within a time slot will vary in the different replications. We studied the effects of an increase in the number of patients per day assuming the arrival pattern stays the same. The results were presented in Figure 8 in the original published article.

In conclusion, Dr Oosterhuis and Dr van den Berg describe a situation that is different to the one we simulated, and it is therefore invalid to apply our conclusions to it.

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Rheumatoid factor can interfere with cystatin C measurement

We read with interest Dr Newman's excellent and comprehensive review on cystatin C.[1] We agree with his general conclusion that cystatin C assays are robust in the presence of commonly encountered interferents, and this is a significant advantage of cystatin C measurement over serum creatinine. We recently reported the analytical performance of a particle- enhanced rate nephelometric immunoassay (PENIA) for serum cystatin C.[2] This assay used reagents supplied by Dako Ltd (Ely, UK, catalogue no. K 0071), that had originally been designed for use in a particle-enhanced turbidimetric immunoassay (PETIA) format. Our adaption of these reagents to a rate nephelometric system (Immage™ analyser, Beckman-Coulter Ltd., High Wycombe, UK) produced an assay with within-batch imprecision $< 4\%$ and relative freedom from interference due to haemolysis, lipaemia and icterus. Further clinical and research experience with this assay caused us to evaluate the effects of rheumatoid factor (RF).

Measurement of cystatin C in five clear serum samples containing RF (1270, 1540, 1820, 2330, 3070 kIU/L) demonstrated concentrations (median

2·60, range 1·07–3·56 mg/L, reference range 0·57–1·05 mg/L) in excess of those we would have predicted given the level of renal function (serum creatinine concentration $< 85\ \mu$mol/L in all cases). Dilution (1:9) of the manufacturer's highest calibrator (12·3 mg/L) in these serum samples demonstrated mean recovery of cystatin C of 123% (range 109–136%). This compared to 102% (range 97–103%) in five serum samples with RF < 33 kIU/L (P=0·009) and 99·4% (range 93–104%) in five serum samples containing paraproteins (IgGκ 17·6 g/L, IgMλ 8·1 g/L, IgMκ 21·6 g/L, IgMκ 19·9 g/L, IgGκ 11·6 g/L). There was no relationship between RF concentration and percentage recovery (r=0·02), although the sample size was too small to draw conclusions in this respect.

Our results infer that cystatin C concentrations may be falsely elevated in serum samples containing high concentrations of RF. Cystatin C assays have generally been reported to be resistant to interference from RF,[1] including the current reagents when used in PETIA mode,[3,4] although it should be noted that lower concentrations of RF were studied (300–1000 kIU/L). Additionally, the sample fraction used in our PENIA assay (3·9%) is twice that utilized by Newman *et al.*[4] and 10-fold higher than in the PENIA assay of Finney *et al.*[5] Our observations confirm the continuing need for vigilance in the application of immunoassays for clinical purposes.[6]

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Serum angiotensin-converting enzyme assays should be ubiquitously available

Dr Muller provided a very useful and interesting *Personal view* on analysis of serum angiotensin-converting enzyme (SACE, EC 3.4.15.1) activity.[1] It was suggested that, because of the problems of genetic polymorphism, poor analytical performance, lack of national external quality assessment and diverse reference intervals, these assays should perhaps be the province of specialist laboratories able to offer genotyping.

SACE is however, not only useful in the monitoring, and possibly diagnosis, of sarcoidosis. Recently, we have examined the role of SACE activity assays in the monitoring of adherence to the very widely prescribed ACE inhibitor (ACEI) drugs. ACEIs are the most successful drugs in the treatment of chronic heart failure (CHF). However, non-adherence is common in CHF patients and has dire consequences. Patients with CHF tend to be elderly and on multiple drugs, both of which contribute to non-adherence. It is notoriously difficult to assess adherence and an objective measure of adherence to ACEI therapy would be very clinically beneficial.

In a clinical trial setting, we showed that SACE activity was an excellent marker of the recent ingestion of an ACEI and discriminated readily between drug and placebo.[2] We then assessed compliance with ACEIs by measuring SACE activity in CHF patients while collecting data on whether and when prescriptions for ACEIs were redeemed at community pharmacies: we showed that a low SACE activity was indicative of adherence and a high SACE activity gave high predictive accuracy that the patient was less than 100% adherent.[3] Moreover, when we randomized 39 patients with CHF to regimens of ACEI non-adherence, ACEI adherence, or two versions of partial adherence, then again SACE activity assays distinguished full adherence from all other forms of adherence. We also followed 32 patients for 1 year using monthly visits by a research nurse and showed that there was large inter-individual and intra-individual adherence to ACEI treatment and that non-adherence could be detected by SACE activity assays.[5] Even when patients have very high SACE activity, this is suppressible with ACEI treatment, and the SACE falls to low activity, allowing monitoring of adherence even in such individuals.[6]

We have therefore shown that adherence to ACEI therapy can be monitored using simple, inexpensive, and easy to automate SACE activity assays. For this reason we believe that the assay should be available in all laboratories.

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