Research article

Laboratory Automation and Sensitive Analytes - National Study from Clinical Biochemistry Departments in Denmark

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Increased laboratory automation (LA) is becoming a necessity for high throughput centralized laboratories, however, LA provides new pre-analytical challenges. Prolonged air exposure may cause spurious analytical results for sensitive analytes when the de-capped open blood tubes are transported on assembly lines for prolonged periods and at different temperatures. This study maps LA systems in Denmark and investigates if sensitive analytes and LA is an issue of concern in Danish laboratories.

To nationally map LA and LA procedures for two sensitive analytes, blood alcohol and total carbon dioxide, a questionnaire was sent to all clinical biochemistry departments in Denmark (n=36 with inhouse analysis). Three departments were selected for further short interviews in 2020. In total, 86% (31/36) responded. Of respondents, 84% (26/31) had implemented LA: 65% with total laboratory automation and 35% with partial. When LA operated smoothly in the 26 laboratories, the median transport time was 5 minutes (range 2-90) from de-capping of blood tubes to blood analysis. Local laboratory guidelines on open tube stability of the analytes varied considerably: Blood alcohol 60 (0-300) minutes, and total carbon dioxide 60 (0-360) minutes. Consequently, some laboratories still handled sensitive analytes manually off the LA assembly line. This study demonstrated a diversity in how laboratories manage sensitive analytes and LA. This may jeopardize analytical results and patient safety, and evidence-based stability studies, international guidelines and LA technical adaptions are warranted for sensitive analytes to adopt to the contemporary LA setting.

Key words: Preanalytical; laboratory automation; blood alcohol; carbon dioxide; un-stoppered; de-capped; sensitive analytes.

Introduction

Implementation of laboratory automation (LA) has become a prerequisite in the contemporary clinical biochemistry laboratory to increase analytical capacity and efficiency.[1-6] The LA systems are often built with a separate tube decapper function; blood samples are transported in open tubes on the assembly line before reaching the analytical instruments.[5-7] However, prolonged air exposure to blood

Accepted: April 9, 2022

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samples may cause spurious analytical measurements for sensitive analytes.[8,9] Transporting the open tubes at increased temperatures, during technical downtime or within larger LA systems may jeopardize patient safety. Some blood analytes may be more vulnerable than others, for instance, blood alcohol and total carbon dioxide are suspected to be sensitive due to the volatile nature of the substances.[8,9]

Guidelines and thorough studies concerning the stability of sensitive analytes in open tubes have not previously been described. This may result in lack of standardization for the LA pre-analytical handling of sensitive analytes. To investigate if sensitive analytes and LA is an issue of concern in the laboratories, this study mapped local laboratory stability guidelines and how laboratories handled blood alcohol and total carbon dioxide in LA. In addition, the differences in LA systems and the open tube transportation time was also reviewed. A survey was created and distributed to all clinical biochemistry laboratory departments in Denmark supported by short qualitative interviews.

Materials and methods

In April 2020, a questionnaire was distributed to all clinical biochemistry departments with inhouse analysis in Denmark. The questionnaire focused on whether the department had LA or not; type; time from de-capping to start of analysis; local guidelines regarding the stability of the blood alcohol and total carbon dioxide analytes in open tubes. Three departments representing dissimilar answers in the questionnaire were interviewed in May 2020. Informants signed a written consent before the audio recorded short semi-structured telephone interview. The interview included: 1) LA system and de-capping procedure and 2) blood alcohol and total carbon dioxide stability in open tubes. Interviews were completed and transcribed in Danish. GraphPad Prism 8.4.3 (GraphPad Software, USA) illustrated data. Fisher's exact test was applied to two-group comparisons, $\alpha = 0.05$. Ethical approval was not required according to the Danish ethical committees.[10]

Results

In total, 86% (31/36) of the departments responded to the questionnaire.

Automation in Denmark

Laboratories with automated assembly lines and choice of LA system in Denmark are shown in Figure 1. The questionnaire included the open-ended question "*How long does it take to transport a blood sample on the automated assembly line from de-capping to analysis on a day when everything runs smoothly?*" and Table 1 shows the LA median open tube time and the difference within the same manufacturer of the LA system. Table 1 also shows if tubes for blood alcohol and total carbon dioxide measurements were chosen to be transported on or off the assembly line. There were no differences between sensitive analytes for this choice (Table 1, $p>0.9$). There were no differences in reported stability time between blood alcohol and total carbon dioxide (Table 2, $p>0.9$).

Bispebjerg and Frederiksberg Hospital, Copenhagen (BF Copenhagen) started to operate a total LA system in January 2020, but a specialized biomedical laboratory scientist (BLS) expressed concerns about flow related difficulties and having manual steps for *e.g.* sensitive analytes: "... this was not expected with implementing total LA."

Blood alcohol and automation

When measuring blood alcohol, tubes were not always transported on the automated assembly lines in Danish laboratories, Table 1. BF Copenhagen initially transported the open tubes on the assembly line. However, samples continuously exceeded the 30 minutes stability warned by the alarm system. Even by drawing blood into a separate tube at phlebotomy for alcohol measurement only, the time issue was still not resolved. This resulted in blood alcohol testing in separate tubes and handled manually off the assembly line. The BLS from Zealand

University Hospital Roskilde (ZUH Roskilde) reported samples were centrifuged in the TLA system and sorted to the output station still capped from where they were manually handled for analysis to avoid evaporation.

There was an interlaboratory variation in local guidelines for the stability of blood alcohol in open tubes, Table 2.

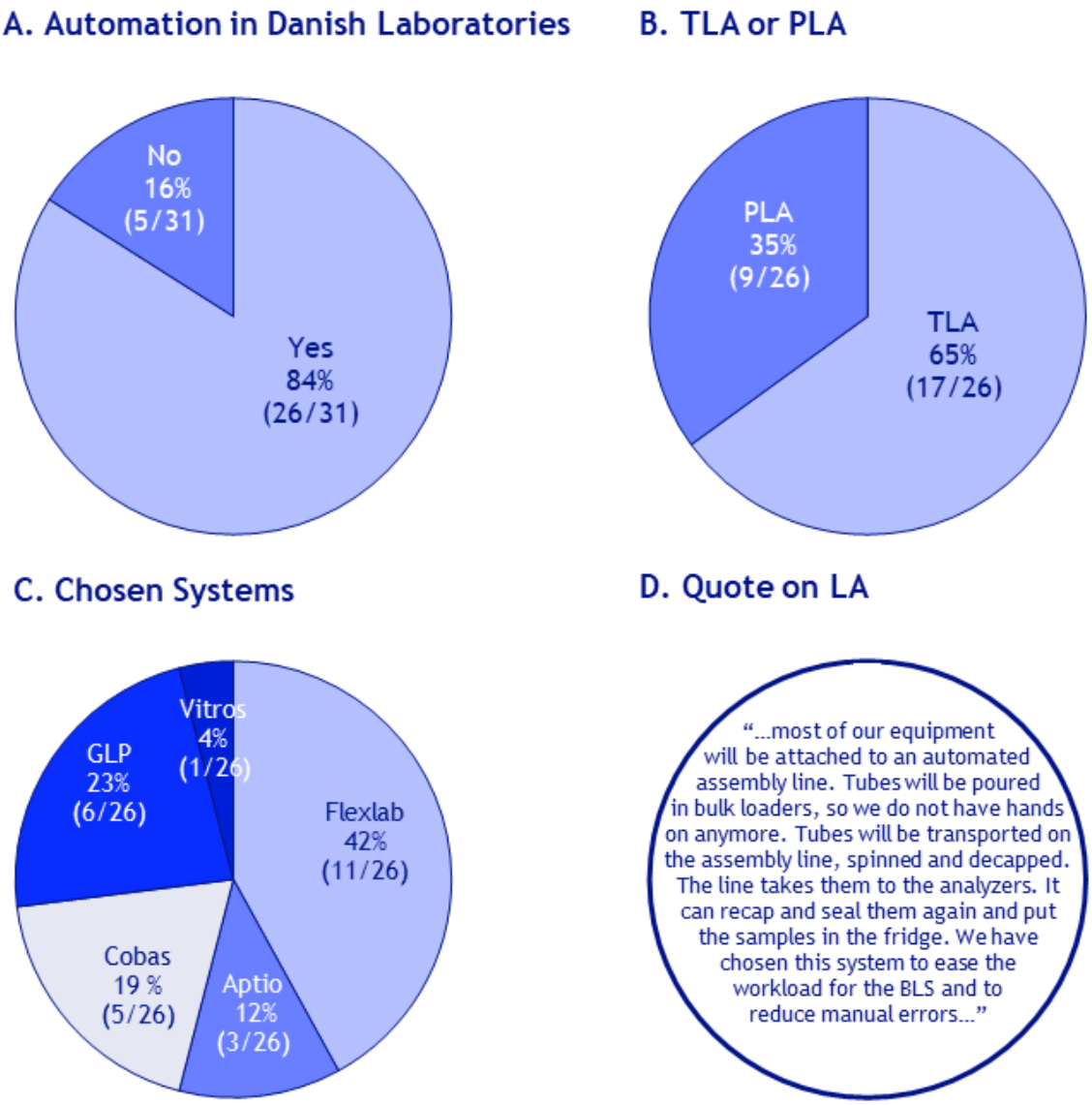

Figure 1: Laboratory Automation (LA) in Denmark in year 2020.

A: Laboratories with and without LA among departments with in-house analysis.

B: Distribution of total laboratory automation (TLA) and partial laboratory automation (PLA) among laboratories with LA.

C: Distribution of laboratories choice of type of LA systems. Note Aptio is based on the Flexlab system from Inpeco, but with a Siemens instrumental collaboration.

D: Quote from a biomedical laboratory scientist (BLS) from Regional Herning Hospital who elaborated benefits of their awaited new LA system and the decapping function.

Abbreviations: Aptio = Aptio Automation (Siemens Healthineers, Germany & Inpeco SA, Switzerland). Cobas = Cobas Connection Modules (Roche Diagnostics, Switzerland). Flexlab = Flexlab Automation (Inpeco SA, Switzerland). GLP = GLP Systems (Abbott Laboratories, USA - IL). Vitros = VITROS Automation Solutions (Ortho Clinical Diagnostics, USA - NJ).

Table 1: The reported laboratory automation (LA) system at clinical biochemistry departments in the Danish health care system (n = 26). The table shows open tube transportation time on assembly lines (i.e. time from de-capping tubes to analysis). The table also shows whether the laboratories measure blood alcohol/total carbon dioxide or not; and if they use the assembly line or not.

LA system	N	Minutes from de-capping to analysis,median [range]	Transport type	Blood Alcohol			Total Carbon Dioxide		
				On assembly line (%)	Off assembly line (%)	Do not analyze (n)	On assembly line (%)	Off assembly line (%)	Do not analyze (n)
Aptio	4	10 [4-60]	Individual	75 (3/4)	25 (1/4)	0	100 (4/4)	0 (0/4)	0
Cobas	5	60 [5-90]	Racks of 5 samples	60 (3/5)	40 (2/5)	0	60 (3/5)	0 (0/5)	2
Flexlab	10	5 [2-30]	Individual	90 (9/10)	0 (0/10)	1	60 (6/10)	0 (0/10)	4
GLP	6*	3.5 [2-15]	Individual	67 (4/6)	33 (2/6)	0	0 (0/6)	50 (3/6)	3
VITROS	1	20 [-]	Individual	0 (0/1)	100 (1/1)	0	0 (0/1)	0 (0/1)	1
Total	26	5 [2-90]	-	76 (19/25)	24 (6/25)	1	81 (13/16)	19 (3/16)	10

No difference between sensitive analytes in use of assembly line or not, p>0.9.
*) Medan [range] based on four answers, as two respondents did not specify their time range from decapping to analysis.
Aptio = Aptio Automation (Siemens Healthineers, Germany & Inpeco SA, Switzerland); Cobas = Cobas Connection Modules (Roche Diagnostics, Switzerland); Flexlab = Flexlab Automation (Inpeco SA, Switzerland); GLP = GLP Systems (Abbott Laboratories, USA - IL); VITROS = VITROS Automation Solutions (Ortho Clinical Diagnostics, USA - NJ).

Table 2: Danish clinical biochemistry department's reported open tube stability on blood alcohol and total carbon dioxide according to their laboratory local guideline. The stability according to the LA system of the laboratory is also shown. Of the 26 laboratories with LA, 96% (25/26) measured blood alcohol, but only 62% (16/26) measured total carbon dioxide.

After decapping: Reported stability in minutes*	Blood Alcohol (n=25 laboratories)		Total Carbon Dioxide (n=16 laboratories)	
	%	Laboratory LA System	%	Laboratory LA System
0-30	32	Aptio, Flexlab, GLP	31	Aptio, GLP
31-60	20	Flexlab, Vitros	31	Cobas, Flexlab,GLP
61-90	0	-	0	-
> 90	28	Cobas, Flexlab, GLP	19	Flexlab
Not established	20	Flexlab, Cobas, GLP	19	Flexlab, Cobas

No difference between blood alcohol and total carbon dioxide reported stability time guidelines (p>0.9).
*) Median (range) for reported stability of blood alcohol was 60 min (0-300 min), and for total carbon dioxide it was 60 min (0-360 min).
LA = laboratory automation; Aptio = Aptio Automation (Siemens Healthineers, Germany & Inpeco SA, Switzerland); Cobas = Cobas Connection Modules (Roche Diagnostics, Switzerland); Flexlab = Flexlab Automation (Inpeco SA, Switzerland); GLP = GLP Systems (Abbott Laboratories, USA - IL); Vitros = VITROS Automation Solutions (Ortho Clinical Diagnostics, USA - NJ).

Total carbon dioxide and automation

When measuring total carbon dioxide, not all laboratories transported the blood tubes on the LA assembly line, Table 1. The majority of the laboratories, 62 % (10/16), had an open tube stability guideline of one hour or less, Table 2, which also shows an interlaboratory variation in local guidelines.

According to the BLS from Regional Hospital, Herning (RH Herning), open tubes for total carbon dioxide measurements were transported on a partial LA system, which would warn if a test result and stability was about to be exceeded. The laboratory stress-tested the system regularly for turnaround time during peak periods. ZUH Roskilde claimed that staff, once every hour, ensured measurement did not expire by checking if test results were available. If no results were available, the staff would manually take the

open tubes off the assembly line to ensure the sample was properly analyzed to avoid evaporation.

Discussion

Even though LA systems significantly improve capacity and efficiency, and reduce human errors, the systems possess pre-analytical challenges that laboratories must address.[11] This includes sensitive analytes transported on assembly lines in open tubes, which may evaporate or otherwise react to prolonged air exposure at various temperatures.[1-4] It was observed that local open tube stability guidelines varied greatly from 0 to 300 minutes for blood alcohol and 0 to 360 minutes for total carbon dioxide among different laboratories. Two previous studies addressed the open tube concern for blood alcohol and total carbon dioxide analytes and suggested that analytical measurements are acceptable when analyzed within 120 minutes after de-capping.[8,9] Nielsen *et al*. suggested that the majority of common analytes (20 of 23 analytes) were not sensitive to de-capping and plasma evaporation with a stability of 6 hours or more at room temperature. The study did not include blood alcohol and carbon dioxide.[12] In practice and without downtime, this study demonstrated that open tubes in general were transported on assembly lines for a median five minutes (after automated de-capping and until analysis), however, some Danish laboratories reported up to 90 minutes transportation time. Many laboratories avoided the problem by handling the tubes for sensitive analytes manually and off the assembly lines. This again confirms preanalytical issues are handled differently among laboratories, sometimes even despite international guidelines exists, like procedures of blood tube order of draw.[13]

De-capped open blood tubes transported on automated assembly lines may be a new preanalytical LA based challenge and could jeopardize the quality of analytical results and patient safety. For quality assurance and standardization of stability guidelines, this study suggests that there is a requirement for evidence-based temperature and time stability studies on sensitive analytes in open tubes. LA manufactures may also assist in solving this preanalytical issue with certain LA adaptions.

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