An Automated Medical Device for Ultimate ABO Compatibility Test at the Patient's Bedside

Towards the Automation of Point-of-care Transfusion Safety

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Abstract: In blood transfusion, accidents still occur because of ABO mismatch between donor and patient's blood. These errors, sometimes lethal, are principally due to wrong identification of patient and/or blood product or to human errors. The best way to avoid these errors is to perform an ultimate ABO compatibility test at the patient's bedside immediately prior to transfusion. Ideally, this test should be performed automatically, without human interpretation and with minimum blood exposure for nurses. This ideal and ultimate method is not yet employed because of the lack of suitable device. In this paper, we propose a system that may fulfil the above mentioned requirements. It is based on selective blood capture on biochip surfaces in a device which automatically drives the different fluids, performs optical detection of captured red cells and finally interprets the optical reading in terms of ABO compatibility. So far, our device achieved blood compatibility test with 99.3 % sensitivity and 97.9 % specificity.

1 INTRODUCTION

In the field of blood transfusion, in all countries, a concordance verification test is performed at the patient's bedside (concordance regarding the patient's identity and various elements that had allowed the blood product delivery). In most countries, a laboratory cross-match test is performed before the concordance test. However, it becomes useless when an error occurs after the delivery (the wrong blood bag to the wrong patient, the most frequent case). In very few countries (in France for example), a second blood compatibility test is performed at the patient's bedside.

In countries where a unique test is performed at the patient's bedside and for which the hemo-vigilance is reliable, the ratio of adverse effects due to ABO incompatibility approaches 1/40000 red cell concentrate (RCC). This was the case in France before 2003 when only ABO compatibility was tested. This is still the case in some countries where only the concordance test is considered. After 2003 in France, the use of both concordance and ABO tests at the patient's bedside reduced the adverse effects to about 1/600000 (in those very few cases, concordance test had been omitted).

Based on these data, most countries are seeking a second test at the patient's bedside in order to reduce their number of ABO errors. However, the ABO test cards used in France rely on delicate manual operation and require a long and specific training. Therefore, they appear difficult to be rapidly employed worldwide. Furthermore, the compatibility card still requires a human interpretation of the agglutination test. Although iso-group compatibility does not require difficult interpretation of the agglutination test, non iso-group compatibility is still subject to interpretation errors. Indeed, the use of the current card is relatively difficult and is the source of several errors as illustrated later.

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All these facts highlight the need for a point-of-care device able to automatically perform an ultimate compatibility test with minimum manipulation and without human interpretation. This becomes urgent when considering the increase of blood product distributed during the last decade. For example in France an increase of the RCC delivery of almost 24% has been observed between 2000 and 2011 (EFS, 2012). In 2011, more than 2.3 millions of RCC where distributed (ANSM, 2012).

Several methods have been proposed for blood typing. They are mainly based on gel agglutination (Cid, 2006 – Langston, 1999). SPR (Malomgre, 2009 – Quinn, 2000 – Quinn, 1997) and Surface Plasmon Resonance imaging (SPRi) (Berthier, 2011 – Boozer, 2006 – Campbell, 2007 – Mansuy-Schlick, 2006) techniques can also be used. However, these studies demonstrate the possibility to detect captured cells with commercial laboratory apparatuses. Therefore, a direct translation to the patient's bedside may be difficult because the entire device used should be re-thought for point-of-care use.

Recently, long-range surface plasmon-polaritons to detect red blood cells (RBC) selectively captured by the surface chemistry was demonstrated (Krupin, 2014). However, because packed RBC must be diluted in a buffer of controlled refractive index, translation of the device to clinical use is still challenging.

Techniques based on image processing on plate test have been reported (Ferraz, 2010 – Ferraz, 2013). In this case, image processing is used to objectively observe and interpret red cell agglutination obtained manually. Issues concerning blood and antibodies manipulation still exist.

Spectroscopic methods have also been reported (Ramasubramanian, 2008 and 2009). However, the use of an optical spectrometer to measure absorption of diluted red cells may be difficult in clinical practice.

In fact, although these new devices are able to realize blood typing by objectively reading agglutination, they still require hard translational research work before to be installed in the patient's room.

In this paper, we present a mobile device meant to address the above mentioned issues. The main idea is to replace the four reaction zones of the manual compatibility card with four IgMs grafted biochips (two for the patient and two for the RCC) inspired from Surface Plasmon Resonance (SPR) and SPRi biochips. Hemagglutination is therefore replaced by red cell capture. The detection of capture red cells does not rely on SPR anymore. A simple optical absorption technique is used. Biochips are inserted in a mobile reader/actuator that drives the fluids (blood, RCC and physiological serum) and performs the optical reading and final interpretation.

Overall, research actions to set-up what we named SmarTTransfuser include four main steps. The first series of test consisted in studying the IgMs grafting and red cell capture using SPR and SPRi methods with homemade biochips. This has been previously reported (Charrière, 2011 and 2012) and will be briefly mentioned.

The second set of experiments consisted in translating the SPR biochip to biochips inserted into cartridges and to detect the capture of red cells in these half-bulk conditions together with the correlation between the number of captured cells and optical reading (article in press).

The third part of the experiments is the subject of the current publication. It consists in using a large number of whole blood (WB) and RCC samples to test the automated fluid flow control, optical reading and software interpretation of the ABO compatibility result. The goal is to determine sensitivity and specificity of the device together with the blood group concordance between what is expected and what the device reads. We also studied the performance of the device according to the age of RCC.

The last part of the work will consist in inserting the mobile device directly into the transfusion line and to test the fluid flows and device compatibility in a clinical-like situation before to envisage clinical trials. This will be reported later.

In what follows, we present the general SmarTTransfuser concept. We then briefly recall biochips fabrication and testing using SPR and SPRi techniques. In section 4, we will present the SmarTTransfuser device before to present the experimental studies and corresponding results. Then, a conclusion and future work will be proposed.

2 GENERAL CONCEPT

2.1 Current Card Test Technique and Sources of Errors

Figure 1 shows the principle of current ABO compatibility cards.

The principle consists in hydrating four reactive zones. Two for the patient are coated with anti-A

and anti-B IgMs, the same for the RCC. Blood is sampled from the patient using a special needle. The blood drop must be carefully deposited on the patient's corresponding collection area. The same holds for RCC aliquot. Once both bloods are deposited in corresponding areas, the four antibody zones must be hydrated using physiological serum. Doing this, cross-contamination between antibodies of different nature must be avoided.

One spatula is used to transfer the right quantity of patient's blood to its corresponding anti-A zone. The right blood volume must be taken at the first attempt. A new spatula must be used for each of the four blood transfers to avoid cross-contamination.

After this, the card is slightly shaken until a possible hemagglutination is observed.

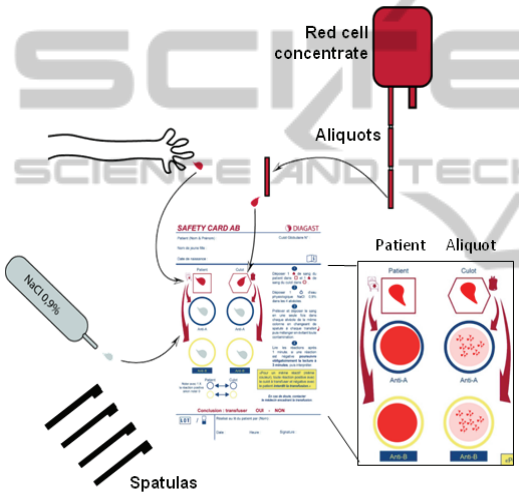

Figure 1: Current ABO compatibility cards.

Finally, the compatibility rules are applied to interpret the results: for the same antibody zones, positive reaction on RCC reaction zone and negative on patient reaction zone forbids transfusion. By interpreting the card, nurses decide if transfusion is allowed or not. This method is the source of various errors.

- Manipulation errors: cross contamination while transferring bloods or hydrating antibodies.
- Reading errors: hemagglutination may be difficult to observe, especially with patients requiring transfusion.
- Interpretation errors.
- Risk of blood exposure when sampling patient's blood.

Recently, cards a bit easier to use have been proposed (ABTEST CARD®), but manipulation, blood exposure and interpretation issues remains.

2.2 Concept of SmarTTransfuser

The general SmarTTransfuser concept is depicted in figure 2. This concept is currently protected by two patents (Pazart, 2011-1 and 2011-2).

As previously mentioned, two biochips are used to test the patient's blood. One is grafted with anti-A IgMs the other one with anti-B IgMs. These two biochips are inserted into a mobile cartridge. Another similar cartridge is used to test the RCC. The "patient" cartridge is connected to the patient's arm. Patient's venous return is used to fill the cartridge in order to minimise risks of blood exposure. The "RCC" cartridge is connected to the RCC.

Both cartridges are inserted into a mobile reader/actuator. It is used to drive the fluids into the cartridges (the measurement sequence will be described later) and to perform the optical reading. Embarked software is used to control ABO compatibility. If bloods are compatible, the security valve is opened and transfusion can be done. Conversely, if bloods are not compatible, physicians can either refuse the transfusion or force the security valve to transfuse anyway (this may happen in extreme cases).

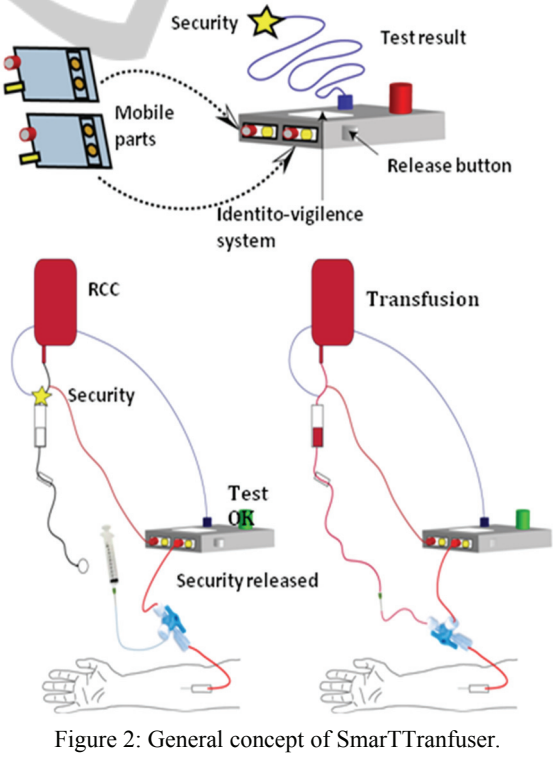

Figure 2: General concept of SmarTTranfuser.

3 BIOCHIP FABRICATION AND TESTING

Here, we briefly recall the fabrication and testing of biochips using SPR and SPRi techniques we presented before (Charrière 2011 and 2012).

3.1 Chemical Functionalization and SPR Experiments

Homemade chromium/gold biochips were chemically functionalized as follows. The chemical functionalization was obtained using a mixture of 11-mercapto-1-undecanol (11-MUOH) and 16-mercapto-1-hexadecanoic acid (16-MHA) (purchased from Sigma–Aldrich). The mixture of 11-MUOH/16-MHA (97/3 by mole) at 1mM in absolute ethanol was sonicated for 10 min using an Elma sonicator (power 90W, frequency 50/60 Hz). Surfaces were rinsed by ethanol and ultra-pure water and electrostatic preconcentration test was realized with the Biacore™ 2000 apparatus at 25 °C at a rate of 2 µL/min. Different immobilization pHs were tested and the optimal pH conditions for promoting functionalized antibody/surface interactions were established. For each antibody, the best interaction was obtained with pH 4.65.

Then, the carboxyl groups were activated using 240 µL of N-hydroxysuccinimide (NHS) at 10 mM and 1-Ethyl-3-(3-dimethylaminopropyl) carbodi-imide (EDC) at 48 mM (Amine Coupling Kit from Biacore AB, Uppsala, Sweden) and incubated for 30 min at RT. Surfaces were rinsed by ultra-pure water. This procedure prepares the chips for the immobilization step.

The antibodies used were IgM anti-A or IgM anti-B (DIAGAST, provided by the French Blood Transfusion Center, Besançon). The running buffer was saline phosphate buffer (PBS, 100 mM at pH=7.4 with NaCl 50 mM). For each antibody, the surface was nearly saturated after the first injection, showing that our grafting conditions are optimized. The grafting rate reaches 1500 IgMs/µm^2 on average, which could potentially involve 100 000 antibodies for each captured red blood cell.

3.2 Red Cell Capture using SPR Imaging

The biochip preparation was performed as described above. Four spots of IgMs antibodies were grafted onto the surface. Antibodies anti-A or anti-B were diluted (1/10) in acetate buffer (0.1 mg/mL, pH=4.5) and 2 spots of each specie (2 µL/spot) were deposited on each surface and incubated for 1 hour at room temperature in a humid chamber. Then a blocking agent (Rat Serum Albumine 40 µg/mL, pH=5.2) was used to passivate the surface by incubation at room temperature for 30 min. Incubation in ethanolamine (0.2 M) was then used to target the free NHS entities in order to desactivate the surface. Finally, the biochips were rinsed with ultra pure water and used for SPRi experiments. They were performed using a SPRi-Plex imager (Horiba Scientific, France) equipped with a 660 nm wavelength LED and a CCD camera.

Erythrocytes are captured according to the compatibility rules: red cells from A group are captured on the anti-A biochip only. B group red cells are captured only on anti-B biochips. AB red cells are captured on both anti-A and anti-B biochips while O red cells are not captured at all.

Figure 3 shows SPRi images obtained with this technique. This illustrates the ability of the biochips to efficiently and selectively capture red blood cells

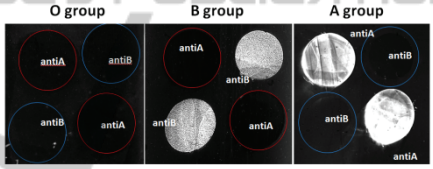

Figure 3: Selective capture of RBC using SPR imaging.

4 DESCRIPTION OF THE DEVICE

Schematic views of the device are shown in figure 4.

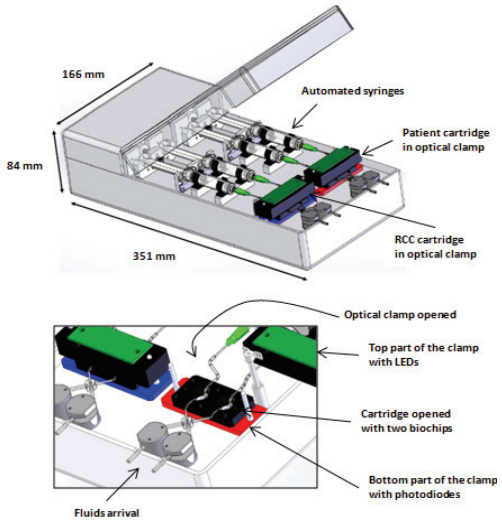

Figure 4: Views of the device.

The heart of the device consists of two cartridges, one used to test the patient's blood, the other for the RCC. Both of them contain two IgMs grafted biochips, one with anti-A, the other with anti-B antibodies. When blood (either WB or RCC) is applied to the biochips, antigen-antibody recognition occurs.

These microfluidic cartridges are placed into an optical clamp that consists of blue LEDs and photodetectors. Each biochip can then be interrogated with its own LED/Detector pair. Red cells trapped onto the biochip absorb light. The detection principle consists in measuring the transmission before red cells are driven onto the chip, when physiological serum fills the circuitry, (reference measurement) and after red cell/surface interaction followed by washing with physiological serum (final measurement). This is illustrated in figure 5. The optical reading is therefore an absorbance measurement given by:

$$\text{absorbance} = (\text{reference-final})/\text{reference} \quad (1)$$

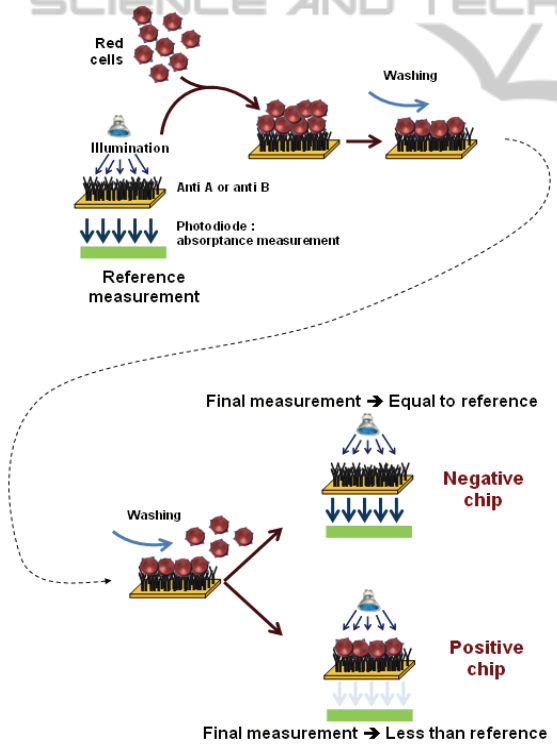

Figure 5: Optical detection principle.

In what follows, positive chips are defined as chips that have captured red cells, regardless of the blood group. Conversely, negative chips correspond to chip where no capture occurred.

Fluids (blood, RCC and physiological serum) are driven by means of automated syringes controlled *via* dedicated software. This software also drives the optical measurement, human-machine interface and USB connection to a PC for data recording and processing.

Figure 6 shows an example of signal recording corresponding to both positive (red curve) and negative (blue curve) chips.

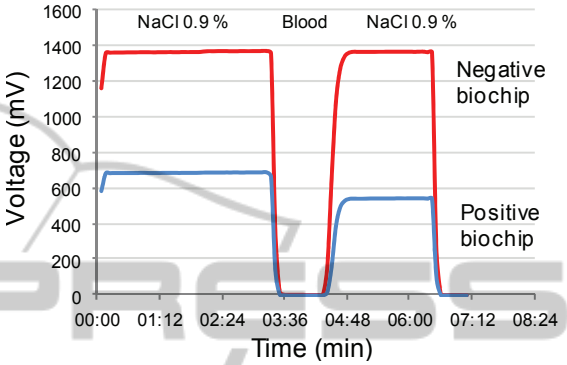

Figure 6: Example of recorded signal.

5 EXPERIMENTAL TESTING

The device was tested using 148 blood aliquots. This represents 296 biochips and therefore 148 cartridges. Blood comes from both RCC and WB. Samples were provided by the French Blood Agency in accordance with the ethic rules and with informed consent obtained from donors.

Among these 296 chips, 4 are not taken into account because errors occurred while assembling the cartridges. The goal of this paper is to present de behaviour of the device and not the ability to correctly fabricate cartridges. Perfect fabrication of cartridges will be the responsibility of the company who eventually will fabricate the device according to their own quality control policy.

Therefore, only 292 biochips were tested. Remember that 2 biochips are required to test 1 sample. For two samples, inversions of the anti-A and anti-B biochips were made. Although the biochips behave correctly and are taken into account for biochip testing, the corresponding samples were not taken into account for compatibility testing. At the end, 142 samples were tested for compatibility.

The repartition of samples in terms of RCC, WB and blood group is given in table 1.

Table 1: Number of samples used in this study.

Group	A	B	AB	O
RCC	19	25	14	20
WB	17	13	20	14

In what follows, we present results concerning the ability of the biochip to correctly capture red blood cells regardless of the age of the blood, the correlation between the red cell density on the chip and the optical reading, the ability of the software to interpret the result obtained from the optical reading and the correlation between the tested blood group and the blood group detected by the device.

5.1 Biochip Efficiency

Here, 292 biochips were tested. Figure 7 shows the absorbance measured as a function of positive and negative biochips for both RCC and WB. Positive and negative biochips correspond to the 4 blood group.

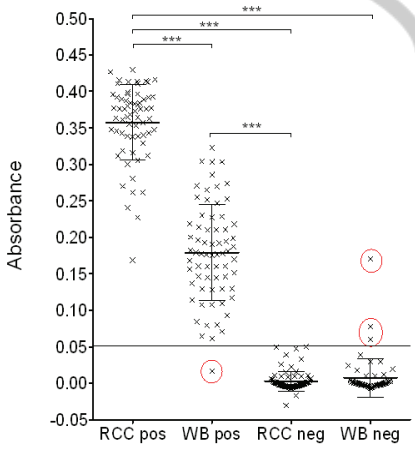

Figure 7: Absorbance versus positive or negative biochips. Mean ± SD. Kruskal-Wallis test followed by Dunn's multiple comparison tests. *** $p < 0.001$. Negative values are due to a slight drift of the electronics (also visible in figure 9).

There is a strong difference between positive and negative biochips. No statistical variation of the absorbance was observed in negative biochips (0.003 ± 0.001 for RCC neg and 0.007 ± 0.02 for WB neg). Conversely, significant difference is observed in positive biochips (0.36 ± 0.006 for RCC pos and 0.18 ± 0.008 for WB pos). This result may be related to the large difference of erythrocytes number in samples ($4.3x10^9 \pm 10^8$ RBC/mL for RCC and 10^9 C/mL for WB).

The best absorbance threshold to discriminate between positive and negative biochip was set to 0.05 (minimization of mis-assignments). In this way, only 4 errors occurred (red circles in the figure). One biochip represents a false negative. For it, not enough red cells were captured although the biochip should have been positive. Indeed, red cell capture is not homogenous on the surface, probably due to an antibodies graft problem. This means that 1 patient of group O was detected as A. Three other biochips were false positive. For them a strong non-specific retention of red cells was recorded due to washing problem. This means that 1 patient of group O was detected as A, 2 patients B detected as AB and 1 patient AB detected as A.

As seen in figure 8, this positive and negative determination is obtained for A and B groups for both RCC (0.38 ± 0.008 for RCC group A anti-A and 0.0035 ± 0.003 for RCC group A anti-B; 0.003 ± 0.004 for RCC group B ant-A and 0.35 ± 0.008 for RCC group B anti-B) and WB (0.16 ± 0.014 for WB group A anti-A and 0.001 ± 0.002 for WB anti-B; 0.024 ± 0.013 for WB group B anti-A and 0.17 ± 0.018 for WB group B anti-B). As expected, no difference is observed between anti-A and anti-B biochips for AB and O groups for both WB and RCC.).

Results given in figures 7 and 8 are in good agreement with measurements made during the second set of experiments described in the introduction.

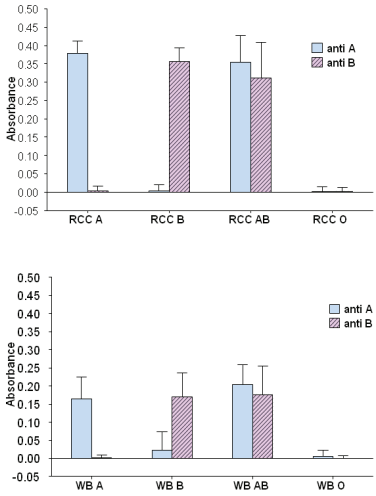

Figure 8: Absorbance versus blood group. . It shows the absorbance as a function of the blood groups for both RCC and whole blood. For each kind of sample, absorbance of both anti-A and anti-B biochips are given. Mean ± SD. Kruskal-Wallis test followed by Dunn's multiple comparison tests. *** $p < 0.001$.

From these results, sensitivity and specificity of the device can be calculated. For this, we consider the following definitions.

- True positive chip (TP): red cells are present on biochips when it should
- False positive chip (FP): red cells are present on biochips when it should not.
- A true negative chip (TN) does not capture cells when it should not.
- A false negative chip (FN) does not capture cells when it should.

Now, sensitivity is defined as the probability to record a positive test with positive biochips. It is given by:

$$\text{sensitivity} = TP / (TP+FN) \quad (2)$$

In the same manner, the specificity is defined as the probability to record a negative test with negative biochips. It is given by:

$$\text{specificity} = TN / (TN+FP) \quad (3)$$

Table 2 presents the sensitivity and specificity of biochips in terms of grafted antibodies for both RCC and WB. Almost all sensitivities are 100%, except for anti-B biochips (97%) used with WB (false negative described earlier). It is the same for specificities: all biochips are 100% specific, except the anti-A biochips used with WB (3 false positives described previously).

Table 2: System performance in terms of biochips.

	RCC		WB	
	Anti-A	Anti-B	Anti-A	Anti-B
Number of Biochips	82	78	68	64
Expected positives	36	39	39	33
Recorded positives	36	39	39	32
Sensitivity	**100%**	**100%**	**100%**	**97%**
Expected negatives	46	39	29	31
Recorded negatives	46	39	26	31
Specificity	**100%**	**100%**	**89.7%**	**100%**

Table 3 presents the same parameters regardless of the blood type and for the entire device. At the end, specificity of the device is 99.3% and specificity is 97.9%. Improving fabrication of the cartridges would probably resolve these mis-assignments and improved sensitivity and specificity.

Table 3: Performance in terms of antibodies and for the entire device.

	RCC + WB		Entire device
	Anti-A	Anti-B	
Number of Biochips	150	146	292
Expected positives	75	72	147
Recorded positives	75	71	146
Sensitivity	**100%**	**98.6%**	**99.3%**
Expected negatives	75	70	145
Recorded negatives	72	70	142
Specificity	**96%**	**100%**	**97.9%**

Biochips performance was also tested as a function of the age of the blood donation. In this case, only RCC were considered because WB is meant to be fresh. For this test we used:

- 30 positive biochips with 6 to 8 days old donations.
- 31 negative biochips with 6 to 8 days old.
- 29 positive with 43 to 44 days old.
- 40 negative with 43 to 44 days old.

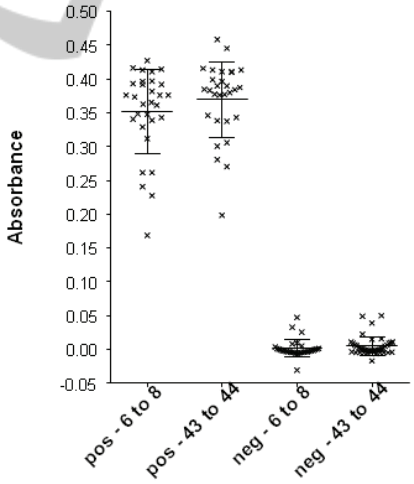

Figure 9: Efficiency versus age in terms of positive/negative.

Figure 9 shows the absorbance obtained in terms of positivity/negativity while figure 10 refers to blood groups. No difference was observed between all kinds of positive biochips: 0.35 ± 0.011 for 6 to 8 days old RCC and 0.37 ± 0.01 for 43 to 4 days old RCC. The same is observed between negative biochips: 0.001 ± 0.002 for 6 to 8 days old RCC and 0.005 ± 0.002 for 43 to 44 days old RCC. Statistical

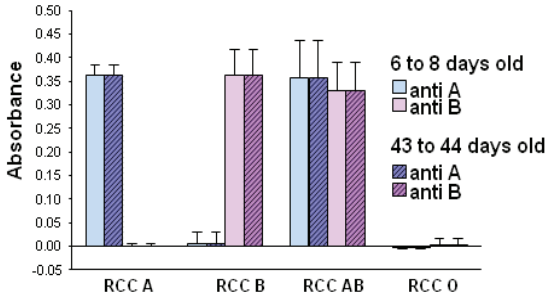

Figure 10: Efficiency versus age in terms of blood groups.

analysis: Kruskal-Wallis test followed by Dunn's multiple comparison test.

It is quite clear that the age of the blood donation does not impact biochips performances.

5.2 Correlation Between Red Cell Concentration and Optical Reading

After each test, cartridges are dismounted and biochips are observed with a microscope. Pictures of five random zones of the chips are taken and the number of red cells in each zone is counted using ImageJ software. Figure 11 shows pictures of red cells trapped on the biochip surface for both positive and negative biochips.

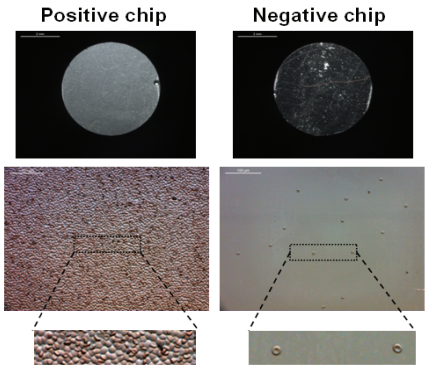

Figure 11: Pictures of red cells capture for both positive and negative biochips.

The percentage of surface occupied by red cells is then calculated by averaging measurements in all zones. Figure 12 shows the correlation between the percentage of red cells captured on the biochips and the absorbance measured for both RCC and WB.

Again, results given in figure 12 are in good agreement with measurements made during the second set of experiments described in the introduction.

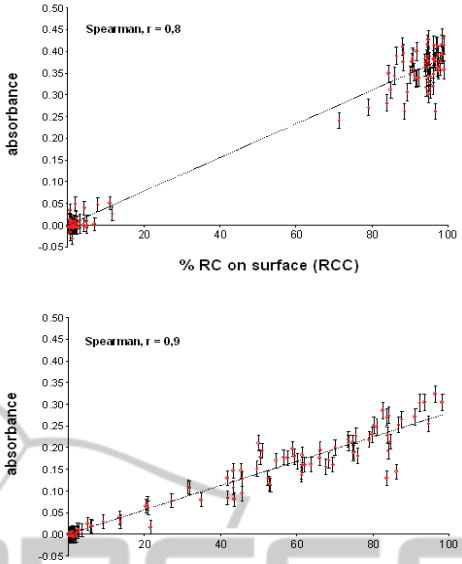

Figure 12: Correlation between percentage of captured cells and optical reading.

5.3 Compatibility Interpretation

For this, 74 compatibility tests were performed. In all cases the software delivered the right compatibility information, perfectly coherent with what happened at the biochip surface.

Of course, we mentioned cases where mis-assignments occurred. However, this part of the test concerns the fact that the device delivers the right information from the result of the optical measurement.

For example, with sample SO11 (WB of group O), a strong non-specific RCC retention has been observed on the anti-A biochip, with an absorbance of 0.06 corresponding to a percentage of red cells of 21% on the biochip surface. This "patient" was considered A group. When testing the compatibility with B group RCC, the device concluded that the transfusion should not be allowed. Therefore the optical reading and the interpretation software work properly.

This highlights the fact that mis-assignments principally come from biochips dysfunctions.

5.4 Concordance Tests

The last experiment concerned the ability of the device to correctly identify blood groups. Among 142 concordance tests performed 4 mis-assignments occurred. The concordance performance is therefore 97% as detailed in table 4.

Table 4: Detail of the concordance test (m-a: mis-assignment).

Group		A	B	AB	O
RCC	N° of tests	19	25	14	20
	Concordance %	**100**	**100**	**100**	**100**
WB	N° of tests	17	13	20	14
	Concordance %	**100**	**84.6** 2 m-a	**95** 1 m-a	**94.4** 1 m-a
		All groups			
RCC + WB	N° of test	142			
	Concordance %	**97** 4 m-a			

Mis-assignments reported here correspond to those already mentioned in section 5.1.

6 CONCLUSIONS

In this paper, we presented a new device able to semi-automatically perform an ultimate ABO compatibility test. It is based on biochips grafted with anti-A and anti-B antibodies. They are inserted into disposable cartridges and placed into a mobile and re-usable reader/actuator. The latter includes embarked software that drives and controls the fluid flows, performs the optical detection of captured red cells and interpret the result in terms of ABO compatibility.

In the current study, 292 biochips were tested. The device exhibits sensitivity and specificity equal to 99.3% and 97.9% respectively. We still need to fully understand why 4 mis-assignments occurred during these tests. However, for the 3 false positives, washing was imperfect, probably due to a slight motor dysfunction. For false negative biochips, IgMs were probably not optimally grafted which may explain the non-uniform red cells capture. Optical reading and software interpretation are not to be blamed. However, just after these 4 false results have been observed, the same samples used with new biochip were re-tested. This time, everything worked correctly and no mis-assignment was observed.

Future work will consist in inserting the device in the transfusion line and to control that RCC and patient's blood are correctly driven onto the biochips. Previous experiments (not shown here) already demonstrated the efficient use of patient's venous return in order to sample patient's blood with minimum blood exposure risks.

To conclude, we believe that the SmarTTransfuser concept may help enhancing blood transfusion safety, not only in countries where a double ultimate test is already performed, but also in countries where only one test is considered. Furthermore, such a device is meant to drastically reduce non-compatibility accidents in countries where the whole transfusion process (blood donation, conservation, delivery and transfusion) is not yet fully satisfactory.

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REFERENCES

ANSM, 2012 and 2014. Rapport d'activité hémovigilance. http://ansm.sante.fr/Mediatheque/Publications/Bilans-Rapports-d-activite-Bilans-et-rapports-d-activite#folder_26762.

Berthier, A., Elie-Caille, C., Lesniewska, E., Delage-Mourroux, R., Boireau, W., 2011. Label-free sensing and atomic force spectroscopy for the characterization of protein-DNA and protein-protein interactions: application to estrogen receptors, J. Mol. Recognit. JMR. 24, p.429–435.

Boozer, C., Kim, G., Cong, S., Guan, H., Londergan, T., 2006. Looking towards label-free biomolecular interaction analysis in a high-throughput format: a review of new surface plasmon resonance technologies, Curr. Opin. Biotechnol. 17, p. 400–405.

Campbell, C., Kim, G., 2007. SPR microscopy and its applications to high-throughput analyses of biomolecular binding events and their kinetics, Biomaterials. 28, p. 2380–2392.

Charrière, K., Guerrini-Chapuis, J.S., Wacogne, B., Elie-Caille, C., Pieralli, C., Pazart, L., Morel, P., Boireau, W., 2011. SmartTransfuser: a lab-on-chip system for enhancing transfusion security", 2nd International Conference on Bio-sensing Technology, Amsterdam, The Nederlands.

Charrière, K., Guerrini-Chapuis, J.S., Wacogne, B., Elie-Caille, C., Pieralli, C., Pazart, L., Morel, P., Boireau, W., 2012. SmarTTransfuser - A Biochip System for the Final ABO Compatibility Test, in: SciTePress - Science and and Technology Publications, Vilamoura, p. 257-262.

Cid, J., Nogués, N., Montero, R., Hurtado, M., Briega, A., Parra, R., 2006. Comparison of three microtube column agglutination systems for antibody screening:

DG Gel, DiaMed-ID and Ortho BioVue, Transfus. Med. Oxf. Engl. 16 p. 131–136.

EFS, 2012 and 2013. Rapport d'activité 2012, (2013). http://www.dondusang.net/rewrite/article/5592/l-efs/publications/feuilletez-en-ligne-le-rapport-d-activite-2012-de-l-efs.htm?idRubrique=790.

Ferraz, A., Carvalho, V., Soares, F., 2010. Development of a Human Blood Type Detection Automatic System, in: B. Jakoby, M.J. Vellekoop (Eds.), Eurosensors Xxiv Conf., Elsevier Science Bv, p. 496–499.

Ferraz,, A., Carvalho, V., 2013. A Prototype for Blood Typing Based on Image Processing, in: SENSORDEVICES 2013 Fourth Int. Conf. Sens. Device Technol. Appl., p. 139–144.

Houngkamhang, N., Vongsakulyanon, A., Peungthum, P., Sudprasert, K., Kitpoka, P., Kunakorn, M., et al., 2013. ABO Blood-Typing Using an Antibody Array Technique Based on Surface Plasmon Resonance Imaging, Sensors, 13 p. 11913–11922.

Krupin, O., Wang, C., Berini, P., 2014. Selective capture of human red blood cells based on blood group using long-range surface plasmon waveguides, Biosens. Bioelectron. 53, p. 117–122.

Langston, M.M., Procter, J.L., Cipolone, K.M., Stroncek, D.F., 1999. Evaluation of the gel system for ABO grouping and D typing, Transfusion (Paris), 39, p. 300–305.

Malomgre, W., Neumeister, B., 2009. Recent and future trends in blood group typing, Anal Bioanal Chem., 393, p. 1443–1451.

Mansuy-Schlick, V., Delage-Mourroux, R., Jouvenot, M., Boireau, W., 2006. Strategy of macromolecular grafting onto a gold substrate dedicated to protein–protein interaction measurements, Biosens. Bioelectron., 21, p. 1830–1837.

Quinn, J.G., O'Neill, S., Doyle, A., McAtamney, C., Diamond, D., MacCraith, B.D. et al., 2000. Development and Application of Surface Plasmon Resonance-Based Biosensors for the Detection of Cell–Ligand Interactions, Anal. Biochem., 281, p. 135–143.

Quinn, J.G., O'Kennedy, R., Smyth, M., Moulds, J., Frame, T., 1997. Detection of blood group antigens utilising immobilised antibodies and surface plasmon resonance, J. Immunol. Methods., 206, p. 87–96.

Ramasubramanian, M., Anthony, S., Lambert, J., 2008. Simplified spectrophotometric method for the detection of red blood cell agglutination, Appl. Opt., 47, p. 4094–4105.

Ramasubramanian, M.K., Alexander, S.P., 2009. An integrated fiberoptic–microfluidic device for agglutination detection and blood typing, Biomed. Microdevices, 11, p. 217–229.

Steiner, G., 2004. Surface plasmon resonance imaging, Anal. Bioanal. Chem., 379, p. 328–331.

Pazart, L., Wacogne, B., Pieralli, C., Boireau, W., Morel, P.,2011. Device for taking a sample of a body fluid and method for implementing same, WO 2011055029.

Pazart, L., Wacogne, B., Pieralli, C., Boireau, W., Morel, P., 2011. Secure perfusion system. WO 2011055031.