Development of a novel technology from clinical research

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MetroDoloris

I. Research and development

General anaesthesia results from the administration of drugs whose combined effects produce unconsciousness, analgesia and myorelax- ation in order to make painful surgical procedures possible. Neuro- muscular blocking agents have long been monitored, and monitoring the effects of hypnotic drugs thanks to EEG monitors has been largely validated in the last decade, leading to lower cumulative doses and lesser undesirable effects.
Monitoring analgesia however is not yet common practice, and its beneficial impact on patients still needs to be demonstrated. Heart rate variability (HRV) analysis has long been shown to provide an insight into the autonomous nervous system (ANS), in particular in the sympathetic and parasympathetic (pS) tones [1]. We made the hypothesis that hemodynamic reactivity during general anaesthesia could be predicted by measuring the reactions of the ANS to nociception with the help of HRV analysis.
While classically HRV has been measured by the Fourier transform, some authors showed that wavelet transform was a better tool for non stationary signal analysis and provided simultaneously information about any spectral alteration and the precise time when it occurred [2]. Using normalised and high frequency filtered RR series, we developed an original graphical measurement (AUCmin and AUCtot) of the respiratory influence on the RR series: this provided the basis for reactivity prediction because the respiratory influence on the RR series tends to diminish when pS tone decreases (Fig. 1).

I.2 Mock up and preliminary clinical trial?

We recorded ECG during general anaesthesia in 49 patients under- going surgery, 19 of them presented with hemodynamic reactivity defined by a 20 % increase in heart rate or systolic blood pressure. Post hoc analysis of the RR series showed that the normalised high frequency spectral content decreased significantly up to 10 min before reactivity [3]. There was a good correlation with AUCmin and AUCtot, which provided the basis for the Analgesia Nociception Index (ANI) computation [4].
Two patent deposits were decided: one for an online RR series filtering, one for ANI's computation.

II. Prototype and bio-incubation

Using the preliminary clinical results, a prototype of a bedside monitor was built at the Cic-It 807 of the University Hospital of Lille. After safety checks, it showed that online RR series computation and ANI measurements were possible, and made sense with the way anaesthesia and surgery were conducted.
The project came then to the Bio-incubator Eurasante´, on the same campus as the University Hospital. Its aim is to make technology transfer possible and to help the founders of a start-up company to raise funds. The project won a national contest which brought 32 k€ to help launch the start-up. A first market survey was completed, and the future CEO started working on the project. Competitors were identified, and a first business model was discussed.

III. Start-up creation

Reliability in the intellectual property is key to finding funds for an innovative company. An anteriority research was conducted by an independent consultant, as well as a second market survey.
The first market survey showed that there was a potential market of 80 M€ in Europe. The second survey aimed more specifically at other European countries, showed an even bigger potential market with 32 000 monitors, and potentially 7.2 M patients/year benefiting from the monitor.
Negotiations with the University Hospital lasted almost 2 years for the licensing of the two patents, which was exclusive and worldwide and included internal future R&D. MetroDolorisTM was born in June 2010. The company soon won several awards and credits. Fund raising from the founders, business angels and venture capital totalled 1.1 M€.
A first batch of monitors was CE marked in order to enable clinical studies to start in several university hospitals. This V1 monitor has to be plugged on the analog ECG output of a classical (or multipa- rameter) anaesthesia monitor in order to get the signal.

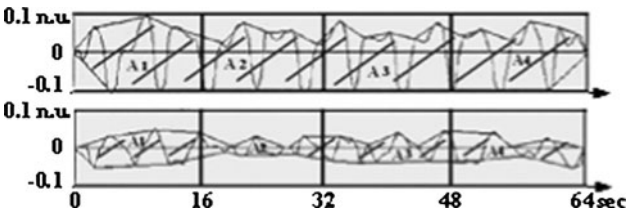

Fig. 1 Normalized and filtered RR series during general anaesthesia. A1, A2, A3 and A4 are the areas measuring the respiratory influence in the RR series; upper panel: adequate analgesia; lower panel: light analgesia leading to reactivity

Marketing included the creation of a website, scientific communications, radio and TV communications. France is covered by two sales reps, while business agreements have been signed with several other European countries. The feedback from users and key opinion leaders has led to the development of a V2 monitor, working on a battery and able to get the ECG signal directly on the patient. Future developments include ambulatory monitoring of chronic pain patients, a specific monitor for detecting pain in neonates and foetal monitoring during labour. References

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