Manuscript Details

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Title	Current trends in vasopressor use to the operating room : a pharmaco-epidemiologic study in French teaching and military hospitals Evolution des consommations de vasopresseurs au bloc opératoire : étude pharmaco-épidémiologique multicentrique dans les centres hospitalo-universitaires et hôpitaux d'instruction des armées français
Short title	Current trends in vasopressor use to the operating room in French hospitals Evolution des consommations de vasopresseurs au bloc opératoire dans les hôpitaux français
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Abstract

Objectives Phenylephrine, ephedrine and norepinephrine are the vasopressors most commonly used in the operating room to treat anaesthesia-induced hypotension. Two new diluted forms of phenylephrine were released in 2011 (500µg /10ml and 500µg /5ml). We initiated a study to evaluate trends in the use of vasopressors in the operating room in French hospitals over the period 2011-2014. Methods We conducted a longitudinal, retrospective, observational study between 2011 and 2014 in French teaching and military hospitals. A questionnaire was sent in February 2015 to hospital pharmacists of each centre to retrospectively collect the consumption of each type of vasopressor. Yearly numbers of vasopressor ampoules were divided by the yearly numbers of anaesthetics recorded. For each vasopressor, we calculated the number of ampoules per 100 anaesthetics recorded (/100A). Results Thirty-two hospitals (82%) completed the questionnaire. One hundred per cent of hospitals had registered the diluted form of phenylephrine (61% had chosen the dilution 500µg /10ml), whereas concentrated ampoules were available in 68% of hospitals. Over the period, an exponential increase in the use of diluted phenylephrine was observed (from 1.0 ampoule /100A in 2012 to 31.7 in 2014), the use of ephedrine remained stable (26 ampoules and 17 pre-filled syringe/100A), and use of norepinephrine trended upwards (from 6.7 to 8.2 ampoules/100A). Conclusions The use of diluted phenylephrine has exponentially increased without reducing consumption of other vasopressors. This trend might be secondary to practice changes in hypotension treatment following the release of French guidelines in 2013 related to fluid management, the restriction of indications of hydroxylethyl-starch solutions in 2013, and a better knowledge of the benefit of blood pressure optimization to reduce postoperative morbidity. Objectifs L'éphédrine, la phényléphrine et la noradrénaline sont des agents vasopresseurs couramment utilisés au bloc opératoire pour traiter les hypotensions. Suite au référencement de la PHE diluée (50 ou 100µg/ml) en 2011, nous avons initié cette étude afin d'évaluer l'utilisation des agents vasopresseurs au sein des centres hospitalo-universitaires et des hôpitaux d'instructions des armées français sur la période 2011-2014. Méthodes Nous avons réalisé une étude observationnelle, rétrospective, longitudinale entre 2011 et 2014 dans les hôpitaux français. Un questionnaire a été adressé en février 2015 aux pharmaciens de chaque établissement pour collecter la consommation annuelle de chaque vasopresseur. Le nombre d'ampoules annuellement consommées était divisé par le nombre annuel d'anesthésies. Pour chaque vasopresseur, nous avons calculé le nombre d'ampoules consommées pour 100 anesthésies (/100A). Résultats Trente-deux hôpitaux (82%) ont répondu à notre enquête. Cent pour cent des hôpitaux ont référencé la phényléphrine sous forme diluée, alors que 68% utilisaient la forme concentrée. Au cours de la période, une consommation exponentielle de phényléphrine diluée est observée (de 1.0 ampoule /100A en 2012 à 31.7 en 2014). La consommation d'éphédrine est stable (26 ampoules et 17 seringues pré-remplies /100A), et la consommation de noradrénaline augmente légèrement (de 6.7 à 8.2 ampoules/100A). Conclusions La consommation de phényléphrine diluée est exponentielle sans réduire la consommation des autres vasopresseurs. Cette évolution peut s'expliquer par les recommandations de la Société Française d'Anesthésie-Réanimation sur le remplissage vasculaire, la restriction d'utilisation des hydroxyéthylamidons depuis fin 2013 et la littérature récente sur les méfaits de l'hypotension artérielle peropératoire.

Keywords	Vasoconstrictor Agents, pharmacoepidemiology, phenylephrine, ephedrine, norepinephrine agents vasopresseurs, pharmacoépidémiologie, phényléphrine, éphédrine, noradrénaline
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Introduction

Arterial hypotension occurs frequently during anaesthesia with an incidence that varies between 5 to 99%[1], this requires treatment in two third of cases. Some anaesthetic agents inhibit the release of catecholamine from sympathetic neurons while others create arterial and venous vasodilation, or have myocardial action. In cases of neuraxial anaesthetics (spinal or epidural), the extension of the sympathetic blockade generates hypotension by a reduction of cardiac preload. The achievement of hemodynamic stability is recommended during intra-operatory period in order to reduce the risk of postoperative complications, particularly after major surgeries or among patients with comorbidities.[2, 3]

Recent studies have demonstrated that intraoperative hypotension can induce severe adverse effects such as acute kidney injury or myocardial injury, this risk increasing with the duration of hypotension [3]. In the delivery room, maternal blood pressure must be controlled during spinal anaesthesia in order to preserve foetal vitality. [4]

Among vasopressors available in French hospitals, phenylephrine, ephedrine and norepinephrine are the most commonly used. In 2011, two new forms of diluted phenylephrine were released (500µg/10ml and 500µg/5ml). In order to avoid medication errors by confusion, French heath regulatory authorities decided in 2013 to withdraw the marketing authorisation of concentrated phenylephrine (5mg/1ml).

In this context, we measured the use of vasopressors in order to examine current trends in anaesthetic management of hypotension in the operative room.

We hypothesised that diluted phenylephrine would become increasingly used while reducing the usage of other vasopressors.

Materials et methods

We conducted a longitudinal retrospective observational study between 2011 and 2014 in French university hospitals (*Centres Hospitaliers Universitaires* - CHU) and military hospitals (*Hôpitaux d'Instruction des Armées* - HIA) in order to collect consumption data for the three major sympathomimetic agents (phenylephrine, ephedrine and norepinephrine) within operative rooms. We included the 30 existing CHUs and nine existing HIAs (a total of 39 hospitals).

In February 2015, we emailed the hospital pharmacists of each centre a questionnaire. In the questionnaire, we listed the commercially available formulations of vasopressors in the French market: concentrated ampoule of ephedrine (30mg/1ml), diluted ampoule of ephedrine (30mg/10ml), prefilled syringe (PFS) of ephedrine (30mg/10ml), concentrated ampoule of phenylephrine (5mg/1ml), diluted ampoule of phenylephrine (500μg/10ml and 500μg/5ml), and ampoule of norepinephrine (8mg/4ml and 16mg/8ml).

The pharmacist was asked to complete the questionnaire with the yearly number of ampoule and PFS delivered by hospital pharmacies to operating rooms (i.e. excluding drug dispensing to critical care units) over the period 2011-2014. Email reminders were sent to non-responders. In the event of nonresponse, an email was sent to the Head of department of anaesthesia-critical care unit to obtain data.

In cases where responders had stated that they were not able to identify drug delivery to operating rooms only, the centres were excluded from final analysis because clinical management for hemodynamic stability differs between operating rooms and critical care units.

To facilitate data analysis, we categorised vasopressor forms into 5 groups: ephedrine ampoule of 30mg (diluted or concentrated); ephedrine PFS of 30mg; phenylephrine concentrated ampoule of 5mg; phenylephrine diluted ampoule of 500 μg (5 or 10ml) and norepinephrine ampoule of 8 mg. In cases where responders stated the delivery of norepinephrine ampoules of 16mg, we converted the number into ampoules of 8mg (one ampoule of 16mg = 2 ampoules of 8mg).

In order to address the possibility that the largest hospitals were likely to have larger drug consumption, we divided the yearly number of ampoules or PFS by the yearly number of anaesthetics in each centre. The latter was extracted from the French Medical Information System (*programme de médicalisation des systèmes d'information* [PMSI]). The PMSI is a national database in which activity data from French hospitals (both public and private) are prospectively collected, including the number of recorded anaesthetics. Hence, we expressed

the use of vasopressors as a number of ampoule / PFS per 100 anaesthetics (abv: /100A). We first analysed the annual frequency of vasopressors use across all hospitals, and then we analysed data individually for each hospital depending on their category (CHU/HIA). We used descriptive statistics throughout.

Results

Participating centres

Of the 39 CHUs and HIAs, 32 (82%) participated and completed the questionnaire (72% of CHU / 28% of HIA). We excluded four hospitals because data contained intensive care unit data (n=3) or because of incomplete answers (n=1), leading to an analysis set of 28 (72%) centres (21 CHU/ 7 HIA).

Raw data on vasopressor consumption and anaesthetics (general, neuraxial or troncular) are summarised in Table 1.

Overall data

The four-year evolution of the number of delivered vasopressors per 100A is shown in Figure 1. Before the marketing authorisation of diluted phenylephrine (<2011), concentrated phenylephrine ampoules were registered in 68% of hospitals (14 CHU/5 HIA) although consumption was limited (average of 5.6 ampoules/100A). Diluted phenylephrine became progressively available over the period and was finally registered in 100% of hospitals by the end of 2014. Seventeen centres (61%) had chosen the dilution 500µg/10ml, nine (32%) had registered the dilution 500µg/5ml, and two (7%) had both dilutions. The use of diluted phenylephrine increased exponentially during the observation period (1.0 ampoule/100A in 2012, 12.3 in 2013 and 31.7 in 2014). Following the withdrawal of its marketing authorisation, consumption of concentrated phenylephrine became null. The use of ephedrine remained stable over time for both ampoule and PFS (on average 26.3 ampoules/100A and 16.9PFS/100A). The consumption of norepinephrine slightly increased from 6.7 ampoules/100A in 2011 to 8.2 in 2014.

Individual data

Trends in vasopressor consumption in CHUs and HIAs are shown in Figures 2a and 2b, respectively.

Among CHUs, 67% had registered the concentrated form of phenylephrine in 2011 with an average of 2.9 ampoules/100A although large disparities were observed (range, 0 to 9.2 ampoules/100A).

Ninety per cent of CHUs had registered the diluted form phenylephrine from 2013, and 100% from 2014, the strength at 500µg/10ml being chosen in 81% of cases. In 2014, the average

consumption of diluted phenylephrine was 15.7 ampoules/100A though with great variation between hospitals (range, 1.1 to 32.0 ampoules/100A).

In 2011, ephedrine was available in PFS form in 12 centres (57%) and exclusively used in 19% of cases. Eight centres (38%) had registered ephedrine both as PFS and ampoules (either diluted or concentrated).

Between 2011 and 2014, one hospital switched from ephedrine PFS to ephedrine diluted ampoule. Two hospitals started using PFS, one in an exclusive manner (in replacement to concentrated ephedrine) and the other in association with diluted ephedrine ampoule. In the latter, the use of PFS was limited.

Consumption of ephedrine in PFS slightly increased from 12.7PFS/100A in 2011 to 14.6/100A in 2014. Hospitals that had been using ephedrine ampoules had a stable consumption over time (in average 29.7 ampoules/100A).

The average consumption of norepinephrine was 7.8 ampoules/100A in 2011, then increased gradually over time (8.5 in 2012, 8.8 in 2013, and 9.7 ampoules/100A in 2014). Large disparities were observed in 2014 between hospitals (range, 0.8 to 22.2 ampoules/100A).

In two centres (9.5%), the use of norepinephrine decreased. Moreover, these centres had a high consumption of ephedrine (around 60 ampoules or PFS/100A).

Among HIAs, five (71%) registered concentrated phenylephrine in 2011. The average consumption was 13.8 ampoules/100A with large differences between hospitals (range, 0 to 45.2 ampoules/100A).

One hundred per cent of HIAs had registered diluted phenylephrine from 2013, the diluted form 500µg/5ml being chosen in 75% of cases. In 2014, the average consumption of diluted phenylephrine was 79.4 ampoules/100A, still with large disparities between centres (range, 23.4 to 144.8 ampoules/100A).

Seventy-one per cent of HIA (5 hospitals) had registered ephedrine PFS. Two centres (29%) had initially registered both ephedrine ampoules and PFS and progressively turned to increasingly exclusive consumption of ephedrine PFS.

Ephedrine ampoules consumption decreased gradually between 2011 and 2014, from 20.0 ampoules/100A in 2011 to 12.8 ampoules/100A in 2014. The same trend was observed for ephedrine as PFS, which= decreased from 33.7 PFS/100A in 2011 to 27.0 PFS/100A in 2014.

The average consumption of norepinephrine was 3.5 ampoules/100A in 2011. A transitory reduction of norepinephrine use was observed in 2012 (2.3 ampoules/100A) since in 2013 the consumption increased (3.7 ampoules/100A in 2014).

Discussion

Our aim was to evaluate trends in medical practices following the release of a new form of phenylephrine more relevant to anaesthetic use, as a bolus of 50 to 100µg are often administered to patients.

We found an overall increase in vasopressor consumption in the operation room, and an exponential use of diluted phenylephrine since its marketing authorisation.

The former presentation of concentrated phenylephrine (5mg/1ml) had to be diluted to 100µg/ml and had to be used within four hours. This might explain the relatively limited consumption of concentrated phenylephrine in 2011, which was registered in only 68% of centres.

Following its commercialization, 100% of hospitals registered the diluted form of phenylephrine in the operating room. Interestingly, no decrease in use of other vasopressors was subsequently observed. Conversely, a trend toward more frequent use of norepinephrine was observed.

The large variations in the use of vasopressors suggest heterogeneous practices among CHUs and HIAs. From 2011, HIAs used phenylephrine more frequently compared to CHUs, and this difference rose notably when diluted phenylephrine became available.

In 2011, 39,878 ampoules of concentrated phenylephrine had been delivered to operating rooms which is not negligible compared to the 183,493 ampoules of diluted phenylephrine dispensed in 2014. However, due to inadequate presentation, only a small proportion of phenylephrine concentrated ampoules was administered to the patient. Hence, the amount of phenylephrine that was used in 2011 is probably overrated by the count of concentrated ampoule.

When phenylephrine infusion is administered, several ampoules are given in the same intervention to maintain blood pressure. Our data provide an overall estimate of phenylephrine consumption but they do not accurately provide the exact amount of diluted phenylephrine needed per intervention.

This observational study also demonstrates trends with respect to use of other vasopressors that can be used in the operating room. While ephedrine was initially released as concentrated ampoules (30mg/1mL), diluted ephedrine has been progressively available in the French market since the 2000s, firstly as PFS from 2003, then in ampoules from 2007. The main advantage of diluted ephedrine is its practicality compared to concentrated ephedrine as it does not necessitate any further dilution before administration. Hence, it prevents dilution errors.

Surprisingly, 36% of centres still have concentrated ephedrine in addition to diluted ephedrine (ampoule or PFS) on their formulary. Overall, ephedrine consumption was relatively stable over time, the only changes being the registered form within centres. In CHUs, the use of PFS of ephedrine increased notably while in HIAs, increased consumption of diluted phenylephrine was associated with a decrease of ephedrine consumption (both ampoule and PFS). Ephedrine PFS can potentially improve safety of drug preparation and save nursing time [5]. However, only 61% of hospitals reported its use. This is likely to be due to the additional cost of PFS compared to ampoules [6, 7].

The use of norepinephrine increased between 2011 and 2014, with an average consumption of 8.2 ampoules per 100 anaesthetics in 2014. The exponential increase in the use of phenylephrine was not associated with a decrease of other vasopressors.

There is no universal definition for arterial hypotension. While hypotension may be defined as a blood pressure inferior to a threshold, some consider hypotension as a decrease of pressure from a baseline value[1]. Similarly, some define hypotension by mean arterial pressure whereas others define it by systolic arterial pressure. Lastly, some authors define intraoperative hypotension with a minimal duration of 5 or 10 min [1].

Perioperative hypotension is an independent risk factor of cardiovascular and cerebrovascular morbidity. [8-10]

Anaesthesia-induced hypotension is partially limited by three pathways of regulation: the sympathetic nervous system, the renin angiotensin system (RAS), and the vasopressin system.

Anaesthesiologists also have several means to prevent the onset of hypotension or to reduce its duration: the volemia optimization, the reduction of anaesthetic drug usage for an optimal level of sedation, and the injection of vasopressor drugs. Hypotension occurs more frequently in the operating room due to aging, and incidence of diseases like high blood pressure. [11, 12]

The high blood pressure-induced physiopathology (whether treated or not) is responsible for substantial haemodynamic changes secondary to anaesthesia induction. This is due to idiopathic deregulation of blood pressure, reduction of vessel compliance, or diastolic dysfunction of left ventricle. Treatments for high blood pressure can also modify haemodynamic stability. Diuretics generate hypovolemia while others treatments inhibit the autonomic adaptation system.

When patients have coronary heart disease, the use of phenylephrine is relevant to treat hypotension. Phenylephrine has only alpha-adrenergic agonist activity, as opposed to

ephedrine which has chronotropic and inotropic effects by beta-adrenergic receptor stimulation.

When patients are under angiotensin-converting enzyme inhibitors (ACEIs) or antagonists of the receptor of angiotensin II (AIIRAs), hypotension is more frequent and severe. In this case, the first-line treatment is fluid resuscitation, then ephedrine. This vasopressor is more adapted than phenylephrine as a result of its alpha and beta-adrenergic effect.

Refractory hypotensions are particularly frequent in patients with long-term ACEIs or AIIRAs treatment. A bolus of terlipressin (long-acting synthetic analog of vasopressin) generates a significant vasoconstriction, and notably has a quick and prolonged effect on blood pressure. [13] However, terlipressin leads to a reduction of cardiac output by reflex mechanism, and some authors have described a decrease of gut mucosal perfusion with terlipressin [14].

Hypotension is also deeper with epidural anaesthesia, especially with thoracic position. In this situation, phenylephrine seems more effective than ephedrine. [15]

Due to potential interactions with anaesthesia drugs, ACEIs/AIIRA must be discontinued before surgery except in cases where patient have an important dyspnoea or a left ventricular failure [16].

Recent data suggest that norepinephrine infusion is of use in high-risk patients to maintain blood pressure. By its adrenergic effects, norepinephrine increases systemic vascular resistance without adverse effects on oxygenation and perfusion in the intestinal tract. A trial [17] is currently ongoing to analyse the incidence of postoperative organ failure and to compare the management of intraoperative arterial hypotension by norepinephrine versus ephedrine.

The increase use of vasopressors may partially be explained by the release in 2013 of French guidelines for perioperative haemodynamic optimization. [18]

For high-risk patients, fluid management needs to be performed by titration, and has to be continued until stroke volume stops to increase (measured by oesophageal Doppler) or by monitoring dynamic parameters. This strategy based on cardiac output measurement reduces postoperative morbidity compared with the empirical strategy based on clinical parameters (blood pressure, heart rate).

With these recommendations, the administration of vasopressors such as norepinephrine is earlier in case of intraoperative hypotension, if a fluid challenge is not efficient to increase cardiac output.

These guidelines also insist on the treatment of maternal hypotension related to spinal anaesthesia for C-section. The management of such hypotension must be systematically associated a volume replacement with vasopressors. Phenylephrine is recommended as first agent to increase the venous return and with a limited placental transfer. [19, 20]

The association of ephedrine and phenylephrine has the advantage of avoiding maternal bradycardia. Some studies showed that norepinephrine could also avoid this reflex bradycardia. [21]

In November 2013, the European Medicines Agency decided to restrict the use of hydroxylethyl-starch solutions (HES) to the treatment of haemorrhagic shock when crystalloids are insufficient.

This restriction on HES might also have contributed to the observed increase of vasopressors.

This study has several limitations. First, we selected CHUs and HIAs and consequently we excluded private and secondary hospitals. However, one can assume that medical practices should be similar in those centres.

Second, the duration of the observation period may be considered as too limited to accurately evaluate the changes in anaesthesiology practices. Since the time to registration for new drug on the formulary can significantly vary between hospitals, diluted phenylephrine has not been available simultaneously in the selected hospitals. Some hospitals were able to register diluted phenylephrine from 2013 whereas others used it from 2014. Although our study highlighted marked changes in practices since 2011, the situation on vasopressors use cannot be considered to have stabilised as of the end of 2014. Hence, an extended follow-up study could be beneficial in the next few years to confirm these trends seen in the current study.

Our results may be considered as valid among French hospitals but cannot be generalised to other countries where the availability of vasopressor drugs may differ to those used in France.

Lastly, we used the amount of ampoules/PFS dispensed by hospital pharmacies to operating rooms to estimate the changes on practices for the management of hypotension. This method is not optimal to accurately determine the real dose of drugs administered during surgeries. However, it can be considered as a good indicator in trends on anaesthesiology practices [22].

Conclusion

Since its marketing authorisation in 2012, diluted phenylephrine has been registered in 100% of French teaching and military hospitals and its use increased exponentially in the operating room while the consumption of other vasopressors remained stable. The overall increase of

vasopressors use in French hospitals may be explained by changes in medical practices secondary to clearer evidence that the optimization of blood pressure and volume status in per operative period reduces post-operative morbidity.

In most cases, intraoperative hypotension is treated by fluid administration and vasopressors. In some specific situations, transfusion or positive inotropic drug (like dobutamine) could be useful.

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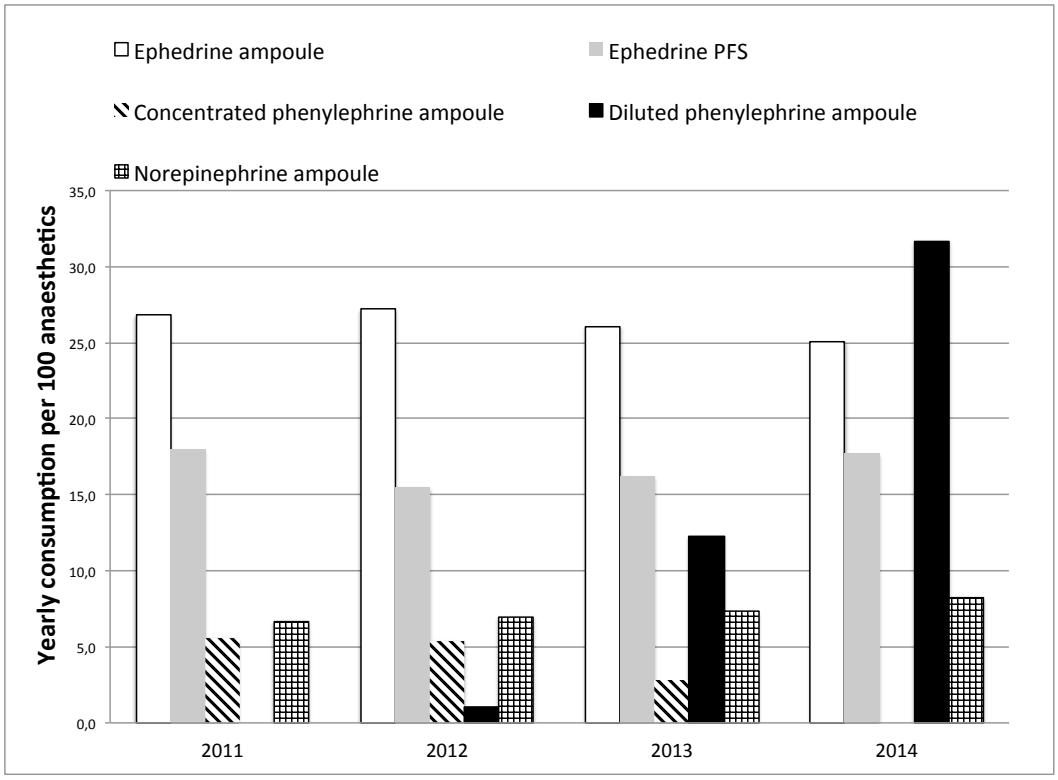
Figure 1
National trends in vasopressor use per 100 anaesthetics during the period 2011-2014

Evolution nationale des consommations en vasopresseurs pour 100 anesthésies sur la période 2011-2014.



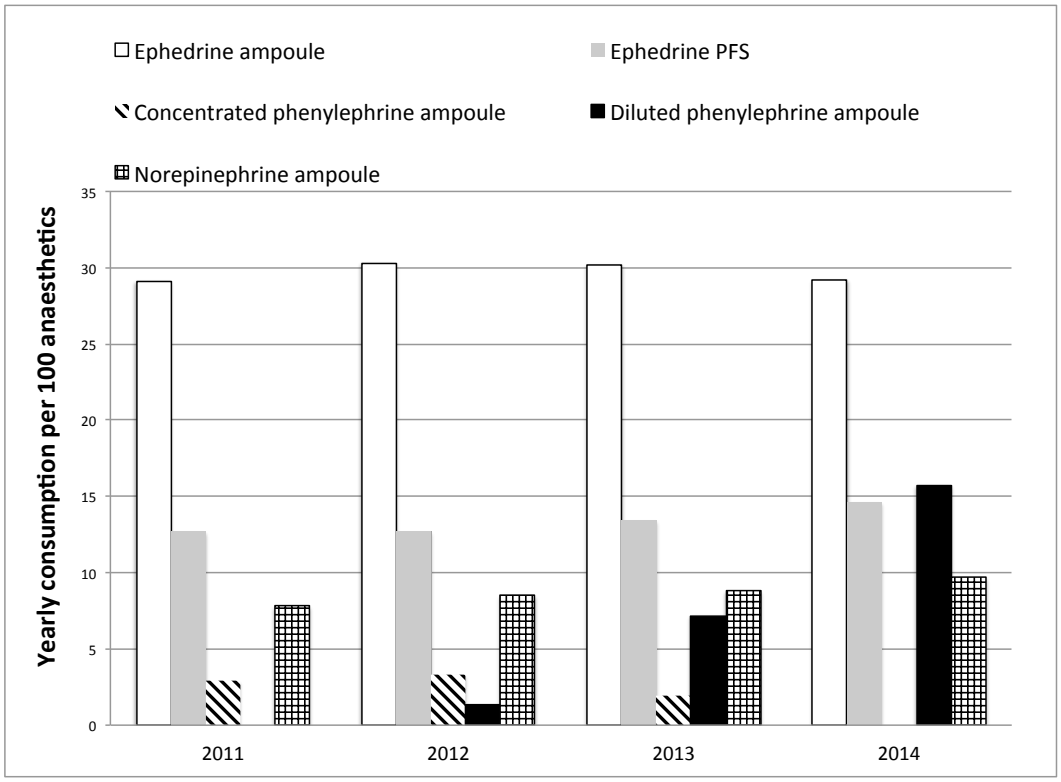
PFS : prefilled syringe

Figure 2

Trends in vasopressor use per 100 anaesthetics in CHU (a) and HIA (b)

Evolution des consommations en vasopresseurs pour 100 anesthésies dans les CHU (a) et dans les HIA (b)

2a



2 b

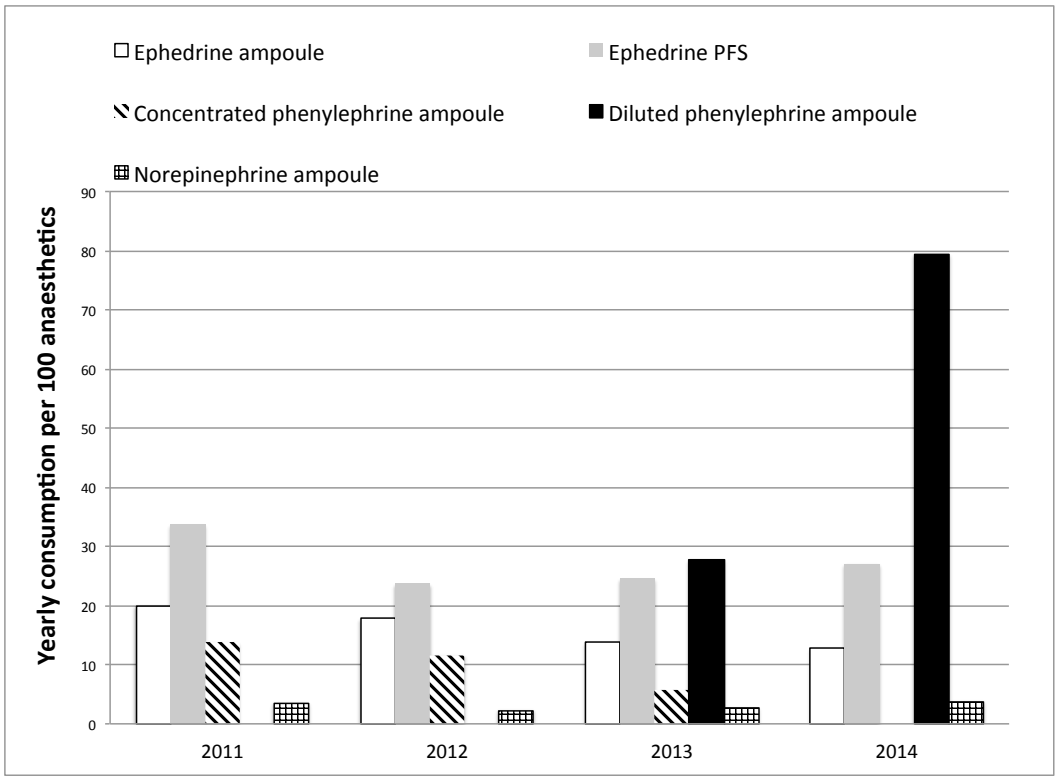


Table 1

Yearly consumption of vasopressor and yearly numbers of anaesthetic for the 28-responding hospitals.

Consommation annuelle de vasopresseurs et nombre annuel d'anesthésie dans les 28 hôpitaux répondeurs.

YEAR	2011	2012	2013	2014
Ephedrine ampoules (n)	235,250	248,430	252,183	244,756
Ephedrine PFS (n)	134,941	137,946	144,139	160,352
Concentrated phenylephrine ampoules (n)	39,878	45,610	22,716	24
Diluted phenylephrine ampoules (n)	0	7,760	83,151	183,493
Norepinephrine ampoules (n)	77,974	90,717	91,764	101,476
Anaesthetics (n)	956,891	976,023	990,140	1,009,571

PFS : prefilled syringe

Table 2: Four-year number of units of vasopressors per 100 anaesthetics.

Consommation en vasopresseur pour 100 anesthésies sur les 4 années 2011-2014

	2011			2012			2013			2014		
Ephedrine ampoules (n/100A)	**26.8 ± 25.0**	*18.9*	*(0 -71.9)*	**27.2 ± 24.6**	*23.4*	*(0 – 63.6)*	**26.1 ± 25.1**	*24.3*	*(0 – 64.8)*	**25.1 ± 25.7**	*17.8*	*(0 – 67.0)*
Ephedrine PFS (n/100A)	**18.0 ± 25.0**	*4.4*	*(0 – 102.4)*	**15.5 ± 18.9**	*6.8*	*(0 – 64.1)*	**16.2 ± 18.1**	*10.9*	*(0 – 63.7)*	**17.7 ± 19.0**	*16.7*	*(0 -72.5)*
Concentrated phenylephrine ampoules (n/100A)	**5.6 ± 9.3**	*2.4*	*(0 – 45.2)*	**5.4 ± 6.9**	*3.4*	*(0 – 27.0)*	**2.8 ± 2.9**	*2.5*	*(0 – 9.2)*	**0**	*0*	-
Diluted phenylephrine ampoules (n/100A)	**0**	*0*	-	**1.0 ± 5.1**	*0*	*(0 – 26.8)*	**12.3 ± 15.9**	*5.5*	*(0 – 67.7)*	**31.7 ± 35.3**	*18.9*	*(1.1 – 143.8)*
Norepinephrine ampoules (n/100A)	**6.7 ± 5.0**	*5.8*	*(1.3 – 21.7)*	**7.0 ± 5.4**	*5.9*	*(1.3 – 23.0)*	**7.3 ± 5.5**	*5.9*	*(0.9 – 21.6)*	**8.2 ± 5.4**	*6.2*	*(0.8 – 22.2)*

PFS: prefilled syringe

In bold type: mean ± standard deviation; in italic type: median; in parentheses: minimum – maximum.