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Manuel R. G. Carrapato, Teresa Andrade & Teresa Caldeira

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Hypotension in small preterms: what does it mean?

Manuel R G Carrapato [1,2]; Teresa Andrade[1]; Teresa Caldeira[1]

[1] São Sebastião Hospital, Santa Maria Feira, Portugal
[2] University Fernando Pessoa, Porto, Portugal

Correspondence to: rcarra@ufp.edu.pt

Abstract

Small preterms often have low blood pressure readings in the first few days of life. However, what is hypotension in preterms? Should there be an aggressive approach to its management? What are the immediate and long-term side effects of powerful medications? Alternatively, could be accepted a low blood pressure instead?

Our data show that, despite extremely low gestational age (ELGA) / extremely low birth weight (ELBW) neonates, almost half of these tiny babies have neither low MAP readings nor clinical signs of impaired perfusion. Yet, many of them are, variously treated or not, depending on individual decisions, rather than on sound evidence. We suggest should it be required to treat persistent hypotension, rather than treating just a low MAP recording, to address the whole issue of hypotension in the overall picture of clinical settings. Assess organ dysfunction caused by low output and use the least aggressive measures, preferably within written protocols, tailored to the given unit, but equally, sufficiently flexible to individual babies. Furthermore, allow for "permissive hypotension" especially if transient, in the absence of clinical signs of hypoperfusion, with normal SVC flow, normal cardiac output and normal brain scanning with normal cerebral doppler flows.

Whether treating hypotension, by whichever definition, "*per se*", will make any difference to both, immediate and late outcomes, in the end, treating remains open to questioning and calls for careful follow-up of these very susceptible preterms.

Introduction

Small preterms, whether sick or not, often have low blood pressure readings in the first few days of life. However, what is hypotension in preterms? A given numeric figure based on gestational and/or postnatal age, on centile charts for birth weight (1,2) or, on the contrary, is hypotension a clinical picture of impaired capillary refill time, low urine output, metabolic acidosis and so forth, regardless of a mean arterial pressure (MAP) reading (3)? What is the role of maternal/pregnancy related disorders and peripartum events upon neonatal circulation and haemodynamics? What might it be the influence of the mode of delivery and resuscitation on persistent fetal circulation and transient neonatal adaptation? Is low blood pressure a cause or a consequence of neonatal performance, will it matter in terms of outcome and what will it be the influence of treatment? Should there be an aggressive approach to its management? What are the immediate and long-term side effects of powerful medications? Alternatively, could be accepted a low blood pressure instead? (4)

All these questions become even more crucial when dealing with ELGA/ELBW, sometimes on the verge of viability. In fact, whilst some studies have shown an unfavorable outcome related to low MAP, from

increased mortality to severe neuro-sensorial and psychomotor developmental impairments (5), others have reported a good overall outcome in spite of a "permissive" low MAP (6).

Our data shows that, almost half of these tiny babies have neither low MAP readings nor clinical signs of impaired perfusion. However, many of them are, variously treated or not, depending on individual decisions, rather than on sound evidence.

The aim of this paper is to equate hypotension definition - MAP readings *versus* clinical features of poor perfusion - with medical decisions. In addition, whether there has been any changes in clinical practice over the years.

Methodology

Retrospective study of data collected from files of all live births with gestational age (GA) between $23^{0/7}$ and $31^{6/7}$ weeks, over 2 different periods: years 2000-2004 and 2008-2012. The exclusion criteria were neonates with major malformations, inborns transferred elsewhere or who died before 72 hours of life, outborns admitted after 72 hours of life and twins.

Maternal underlying and pregnancy related disorders included gestational diabetes mellitus (GDM), chronic hypertension (CHTN) or pregnancy-induced hypertension (PIH), prolonged rupture of membranes (PRM), previous prolonged rupture of membranes (PPRM), clinical chorioamnionitis, fetal growth restriction (FGR), use of antenatal corticosteroids (ANCS) and mode of delivery. PRM stand for rupture of membranes for over 18 hours and PPRM for prolonged rupture of membranes for more than 18 hours before the onset of labor. Clinical chorioamnionitis criteria included abdominal pain, fever, leukocytosis and fetal tachycardia.

Neonatal data contemplated gender, GA, birth weight (BW), short-term morbidities including respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), peri-intraventricular hemorrhage (PIVH ≥ grade 3), necrotizing enterocolitis (NEC, Bell´s >2b), early onset sepsis (EOS), anemia and hypovolemic shock. Outcome at discharge included mortality, length of stay, bronchopulmonary dysplasia (BPD) defined as need for supplementary oxygen for more than 28 days and staging assessed at 36 weeks post menstrual age or at discharge, retinopathy of prematurity (ROP grade 2-3), periventricular leukomalacia (PVL).

Definition of numerical hypotension referred to MAP (mmHg) lower than GA; clinical features of hypotension included the presence of two or more signs of end organ dysfunction (cold skin, pallor/peripheral cyanosis, capillary refill time > 3 seconds, decreased urinary output, metabolic acidosis) within the first 72 hours of age, recorded at 12 hours intervals. Medical management of hypotension consisted of volume expansion with normal saline bolus, inotropes or corticosteroids, in isolation or in association.

Statistical analysis was performed using SPSS version 19© (SPSS Inc., Chicago, IL, USA). The t test was used for continuous variables, and the χ 2 test was used for categorical variables. Significance was taken at *P* value < 0.05.

Results

Following the exclusion criteria, out of 261 live births of GA between $23^{0/7}$ and $31^{6/7}$ weeks, our study population was reduced to 164 singleton neonates: 82 babies in the first period (2000-2004) and 82 in the second period (2008-2012). There were no significant differences between the two period groups, regarding either GA (28.96 ± 2.09 vs 28.04 ± 2.12 wks) or BW (1259.40 ± 384.16 vs 1105.12 ± 360.04 grams). Therefore, the whole population was grouped as one single cohort (GA 28.50 ± 2.15 wks; BW 1182.26 ± 379.13 grams).

Maternal data showed that 39 women (24%) presented with high blood pressure: 82.1% with CHTN and 17.9% with PIH. Antibiotics for threatened preterm labor, were given to 54 (33%) of women, with or without PRM/ PPRM; clinical chorioamnionitis was recorded in 15.2% of cases and FGR was diagnosed in 15.9% of fetus. ANCS, either betamethasone or dexamethasone, were prescribed to 83% of women. Overall, 60.4% of the deliveries were by caesarean section, especially with increasing gestational age (65 % at over 28 weeks GA) whether due to maternal reasons (71.1%) or to fetal distress (28.9%). Active resuscitation was

required in 68.3% of liveborns and 63.4% received exogenous surfactant, none prophylactically and 18.1% using INSURE method: INtubation SURfactant Extubation.

Neonatal demographics revealed a non-significant preponderance of males over females (55.6 % vs 44.4%) and an even distribution of GA and BW between sexes. Hypotension, according to MAP < GA, was recorded in 49/164 (29.9%) and showed to be independent of GA but significantly influenced by BW (1074 ± 331 vs 1229 ± 390 grams, respectively for hypotensive and normotensive neonates; $p < 0.05$). Clinical features of hypotension were present in 58/164 (35.4%) of neonates and were significantly correlated to both GA (27.7 ± 2.3 vs 28.9 ± 2.0 wks; $p<0.05$) and BW (1093 ± 349g vs 1231 ± 388 grams, $p<0.05$), respectively for clinical hypotensive and normotensive patients. As a whole 50.6% of the population had neither low MAP readings nor clinical features of hypotension. Twenty-three (14%) of babies, although with low MAPs, revealed no clinical manifestations, whilst 32 (19.5%) of neonates presented with clinical signs of hypoperfusion albeit with normal MAP readings. All in all, only 26 (15.9%) of babies had both, low MAPs and clinical features of hypotension (Table 1).

We found that pregnancy related disorders ranging from maternal hypertension to FGR and chorioamnionitis had no significant influence either on neonatal blood pressure recordings or on clinical features of hypotension. Nevertheless, babies born to mothers with chorioamnionitis, whether treated with antibiotics or not, showed a trend to clinical hypoperfusion, regardless of MAP readings. ANCS played no role, one way or the other, on blood pressure or on end-organ perfusion.

C-section strongly correlated to low MAP readings ($p<0$, 05), but not to clinical features of hypoperfusion. However, neonates delivered by C-section were considerably smaller than those delivered vaginally were (1127. 03±371 vs 1266.38 ±377. 37 grams; $p<0$. 05).

Of the 112 babies resuscitated 46 (41.1%) presented with clinically significant hypotension ($p<0.05$) although they were also the smallest (1095.36±365.17 vs 1369, 44±341.85 grams; $p<0.05$) and the more immature neonates (27.95±2.13 vs 29.69±1.64 wks; $p<0.05$), respectively for resuscitated and not resuscitated babies. However, of the 58 babies with clinical features of hypotension (Table 1), 79% had been subjected to resuscitation, a statistically significant result ($p<0.05$).

INSURE was only started in the latter part of study (2008-2012) and therefore was only performed in 19 babies, a very small sample for analysis. However, in other babies with similar demographics and indications, but not subject to INSURE, there appeared to be a tendency, albeit not significant, to hypotension either numerical or clinical.

Invasive mechanical ventilation (IMV) was required in 97 (59.1%) babies, similarly distributed between the two study periods (47 vs 50). IMV was significantly related ($p<0.05$) to both GA and BW (27.60 ± 2.07 vs 29.81 ± 1.49 wks GA and 1030.72 ± 331.45 vs 1401.66 ± 335.54 grams BW, respectively for IMV and non IMV); 46 (47.4%) of those ventilated, presented with clinical signs of poor perfusion ($p<0.05$), with or without low MAP.

Of the early neonatal morbidities, RDS, sepsis and anemia were all associated with clinical hypotension ($p<0.05$), regardless of MAP recordings; however, they were also the more immature and smaller babies ($p<0.05$). PIVH and PDA was observed in those same babies of lower GA and BW ($p<0.05$), regardless of MAP readings or hypoperfusion.

Table 2 reveals that almost 60% (97/164) of the whole population were variously treated for hypotension either with volume load (N=4), vasopressor inotropes (N=66) or a combination of both strategies (N=27). Overall, only 25.8% of the treated patients presented with both clinical features of hypotension and low MAP readings (Table 1) whilst 33% of those treated presented none of those changes. Conversely, close to one quarter of babies with the same clinical criteria of hypotension and low MAP readings received no treatment (Table 2).

At discharge, the overall mortality of this high-risk study group was a conservative 5.6% (9/162). As for the morbidities, only periventricular leukomalacia (PVL) was significantly related to clinical hypotension ($p<0.05$), with or without low MAP readings, but not to numerical blood pressure in isolation. However, these were also the most ELGA and ELBW infants ($p<0.05$). None of the other morbidities usually occurring in this population (BPD; NEC; ROP) were related to low blood pressure, whether as a numerical reading or as clinical hypotension. Furthermore, treating hypotension made no significant contribution to outcome at discharge.

Discussion

The approach to hypotension in the V/ELBW and/or ELGA and its management demands a thorough understanding of the hemodynamic processes involved in the transitional adaptation at birth, ranging from foramen ovale and ductal shunting to the sudden systemic and pulmonary vascular resistance changes in addition to the physiological myocardial immaturity typical of this population (3). Our study revealed that, LBW per se influences MAP recordings whilst clinical features of hypoperfusion both related to LBW as well as lower GA. However, regardless of V/ELBW and/or ELGA, at least half of these babies presented neither clinical features of hypotension nor low MAP recordings, a fact of paramount importance in everyday practice and, furthermore, although some of these tiny preterms (14%) had low MAPs, nevertheless, they did not show any signs of peripheral/end-organ hypoperfusion (table1). It can be argued that MAP<GA is not a good indicator of adequate systemic blood flow, especially, if estimated by oscillometry (4). That may be true as, moreover, close to 20% of these neonates presented with clinical signs of hypotension in spite of normal MAPs rendering a given blood pressure reading in isolation an unreliable feature of hypotension. Unfortunately, in everyday settings it is, frequently, the only available tool. Other parameters ought to be added to evaluate, not just BP by whichever method, but also any repercussions upon organ function and oxygen delivery to tissues. Cardiac output and superior vena cava flow (normal > 41 ml/kg/min) assessments by echocardiography have made their way into clinical practice over the last few years (7). Blood pressure may remain within normal ranges while cardiac output is already significantly impaired. A strong association has been shown between persistently low left ventricular output (LVO) in the first 24 hours and higher mortality in preterm infants (8). However, LVO has its limitations due to left-to-right shunting occurring during the first 72 hours of life; right ventricular output (RVO) may be a surrogate estimate of systemic cardiac output in the absence of a significant interatrial shunting across the patent oval foramen (9). Cardiac biochemical markers (troponins and NT Pro BNP) although a good indicator of cardiac dysfunction in term neonates (10), besides requiring invasive measurement, their reference ranges are insufficiently documented in sick preterms undergoing serious adaptation from intra-uterine life, subjected to all sorts of medical interventions and, therefore, rendering them a poor option in these context. Other methods, like near-infrared spectroscopy (NIRS) providing a clear picture of the brain's perfusion and oxygenation, are still a matter for research and far from clinical widespread use (3,11).

We chose to study data from two different periods (2000-04 and 2008-12) to see whether changes in the overall clinical management of these tiny babies had any impact on blood pressure and it´s management. As perceived by our available data, blood pressure assessment and interventions remained very much the same in both periods of time - mostly empiric. In later years, following an individual tailored stabilization at birth in pursuit of the *"golden hour"* (12,13), these babies are being nursed in a less aggressive fashion towards a more conservative approach mostly with non-invasive ventilation, reduced O2 supplements and severe BPD, length of stay, etc. Whether these changes in management will also have an effect on neonatal hypotension deserves an update to this study (2013-17) to complement this paper.

Retrospective studies have many drawbacks, but at least they have the merit to set in motion the opportunity for reflexion. What are the potential implications of intra-uterine events upon neonatal blood pressure and are we overlooking their role in the full spectrum of cardiovascular adaptation to extra-uterine life? Our data, on attempting to correlate neonatal hypotension to common pregnancy related disorders of PIH and FGR found no definite associations, quite likely, due to the study design. Several researchers have identified ANCS as playing a direct role on the cardiovascular changes following birth (14). In our study, after all the confounding data were excluded, ANCS did not affect blood pressure simply because most of our population (83%) were the recipients of antenatal steroids. Chorioamnionitis, whether treated or not, did appear to show a trend towards clinical hypotension, pointing to the relevance of the fetal inflammatory response persisting into post-natal life. Caesarean section was statistically associated with hypotension, whether clinical or with low MAP readings as well as resuscitation at birth leading to clinical features of end-organ dysfunction. Findings such as maternal infection, caesarean section and resuscitation may be related, eventually, to the developing of neonatal hypotension and they ought to be taken into consideration in clinical practice. However, it is not possible from this study to, firmly establish, the impact of each factor individually or in association and these are some of the pitfalls of retrospective data analysis.

Neonatal demographics per se, may play a role in the observed transitional low blood pressure of these tiny babies, often, in the lower limit of viability (15). Indeed, whilst BW alone may influence low MAP recordings, either the BW or the GA may significantly influence clinical features of end-organ perfusion, being the smallest and the most immature of them the most affected. Clinical signs of impaired perfusion, regardless of MAP findings, were significantly present with some of the common early neonatal morbidities of RDS, sepsis and anemia but, quite likely, as a consequence rather than a cause. Symptomatic PDA with hemodynamic changes and PIVH with impaired cerebral perfusion showed no correlation with, either clinical hypotension and/or low MAPs, supporting the assumption that the observed transient hypotension is a consequence and not, necessarily, the cause of the morbidities.

As to the management of these very preterm neonates, we found no sustained approach towards treatment requirements, other than the clinician subjective evaluation of the particular situation, rather than on hard-core evidence. In our study 16.5% of babies with low MAP alone were treated for hypotension (Table 2), even though, there is no evidence that treating a given numeric figure (MAP's <GA) translates into a better outcome. Additionally, one third of those subjected to treatment showed neither clinical signs of hypoperfusion nor low MAP readings. It is a matter for concern that some of these babies may be unnecessarily treated, perhaps, not always, with the most appropriated interventions and with very powerful drugs (16, 17,18). Our data shows that close to 60% (97/164) of V/ELBW preterms were variously treated for hypotension, either with volume load, inotropes or a combination of all these strategies. Although hypovolemia is a rare cause of low BP in tiny preterms, similarly to many other studies normal saline bolus was our first option to increasing cardiac output and BP through the Frank-Starling effect (1, 6, 19). As for inotropic medication, we also used dopamine and dobutamine, often in association and in increasing doses (from 5 up to 20 µg/kg/min), in spite of the potential risks of end organ vasoconstriction, particularly concerning cerebral blood flow (15, 20). However, our data was quite reassuring in this regard from both, the clinical point of view and from brain scanning and Doppler assessment, in line with published studies (19), supporting the thesis of no correlation between cerebral blood flow and blood pressure because of cerebral blood flow autoregulation remaining intact in these V/ELBW infants (21, 22). Adrenaline/epinephrine and/or steroids, for refractory hypotension were not required.

From our study and, although these observations and comments are based on retrospective data, the question is raised for written protocols within each unit to avoid personal interventions based on individual empirical appreciations. Of paramount importance, it must be taken into account the normal transient fall in BP on the first hours of postnatal life, without any clinical implications, followed by the physiological rise over the subsequent 24 hours and, therefore, avoiding unnecessary treatment. Furthermore, available data from many other studies have been put forward that a "permissive" approach to BP, in the absence of clinical repercussions, may be quite safe and without any of the serious side effects of anti-hypotensive interventions (15).

At discharge, the overall mortality of this high-risk study group was a conservative 5.6% (9/164 patients). Of the morbidities, only periventricular hemorrhage / leukomalacia were significantly correlated to clinical hypotension ($p<0.05$) but not to low MAP. Otherwise, none of the other major morbidities usually occurring in this population, were related to low blood pressure, whether as a numerical reading or as clinical symptoms of impaired perfusion and organ failure. Furthermore, treating hypotension, from load replacement to vasopressors and inotropes, or a combination of all, made no significant contribution to outcome at discharge.

In summary and in spite of a potentially high risk group for low blood pressure, we would suggest to pay particular attention to the physiological changes of immediate haemodynamics adaptation to extra-uterine life and to pre-natal and intrapartum events which may add to the equation of transient low MAPs without clinical implications. Should it be required to treat persistent hypotension, rather than treating just a low MAP recording, address the whole issue of hypotension in the overall picture of clinical settings. Assess organ dysfunction caused by low output and use the least aggressive measures, preferably within written protocols, tailored to the given unit, but equally, sufficiently flexible to individual babies. Furthermore, allow for "permissive hypotension" especially if transient, in the absence of clinical signs of hypoperfusion with normal SVC flow (> 41 ml/Kg/min), normal cardiac output (>150 ml /min/kg) and normal brain scanning with normal cerebral doppler flows.

Whether treating hypotension (by whichever definition used), "*per se*", will make any difference to both immediate and late outcomes in the end, treating remains open to questioning, and deserves careful follow-up of these very susceptible preterms.

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		Clinical features	
		Normotension 106 (64.6%)	**Hypotension** 58 (35.4%)
MAP	**Normal** 115 (70.1%)	83 (50.6%)	32 (19.5%)
	Low 49 (29.9%)	23 (14%)	26 (15.9%)

Table 1. MAP according to GA versus clinical features of systemic hypoperfusion. (N=164)

	Normal MAP & normal perfusion	**Low MAP**	**Hypoperfusion**	**Low MAP & hypoperfusion**
No Treatment (N=65)	76.9%	10.8%	10.8%	1.5%
Treatment (N=97)	33%	16.5%	24.7%	25.8%

Table 2. Treated preterms according to MAP versus presence of clinical features of systemic hypoperfusion (p<0, 05).