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The Story of Goldilocks and Perioperative Blood Pressure: What is too high, too low or just right?

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In this issue of the British Journal of Anaesthesia Professor Venkatesan and colleagues using data from a large database, the United Kingdom Clinical Practice Research Datalink (CPRD) found a significant association between low preoperative blood pressure (BP) values and increased postoperative mortality, but only in an elderly population of patients. (1) The risk thresholds started at a preoperative systolic BP 119 mmHg and diastolic BP 63 mmHg compared to a reference BP 120 mmHg. Elevated diastolic, but not systolic BP, was also associated with increased mortality in the entire cohort of patients. These BP readings are considered within the normal, in fact optimal, ranges of acceptable BP for long term control. Readers should not be surprised that elevated BP was associated with adverse outcomes. However, the findings that only elevated diastolic readings, not systolic hypertension, and "low", (though the adjective "lower" would likely be more descriptive of the actual findings) BP are associated with mortality are novel findings. The findings regarding low BP add weight to a growing body of observational data suggesting intraoperative hypotension is associated with adverse outcome. This paper challenges us to perhaps be as concerned about low BP readings as we are about elevated BP in the preoperative as well as the intraoperative period.

Historically, healthcare providers and patients have focused on the harm associated with preoperative hypertension. Elevated BP on the day of surgery remains one of the most frequent reasons for cancellation of surgery.(2) A history of hypertension is quite common in the surgical population. Hypertension affects 1 billion individuals worldwide and increases with age.(3) Up to 25% of adults, 50% of people aged 60 to 69 years old, and 75% of patients more than 70 years old have hypertension.(4) Individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension.(5)

The duration and severity of hypertension correlates with subsequent end-organ damage, morbidity, and mortality in the non-operative period. Elevated BP has been identified as the leading cause (out of 67

studied) of death and disability.(6) Ischemic heart disease is the most common form of organ damage associated with hypertension. Each incremental increase of systolic BP of 20 mmHg or diastolic BP of 10 mmHg above 115/75 doubles the lifetime risk for cardiovascular disease in individuals 40 to 70 years old.(7) Diastolic BP is a more potent cardiovascular risk factor than systolic BP until age 50; thereafter, systolic BP is more important.(8) Other end-organ manifestations of hypertension are heart failure, renal insufficiency, and cerebrovascular disease. Adequate treatment of hypertension reduces the risk of myocardial infarction by up to 25%, stroke by as much as 40%, and heart failure up to 64%.(9) The Systolic Blood Pressure Intervention Trial (SPRINT) trial showed that lowering systolic BP to <120 mmHg, as compared with the standard goal of <140 mmHg, resulted in significantly lower rates of cardiovascular deaths and events, heart failure and death from any cause. Hypotension, syncope, electrolyte abnormalities, acute kidney injury and renal failure occurred more frequently in the intensive treatment group than in the standard-treatment group.(10) The Joint National Committee (JNC 7) for the Management of High Blood Pressure commission even defined a SBP 120-139 mmHg and/or DBP 80-89 mmHg as prehypertension.(11) There is no definitive evidence of increased risk of aggressive treatment unless DBP is lowered to <55 or 60 mmHg.(12) It is striking that the weight of evidence in the non-surgical setting points to elevated systolic BP as a cause for concern in the over 50s whereas the data from Venkatesan and colleagues point to diastolic hypertension being associated with significant risk. There is not an immediately obvious biological explanation for this but it does suggest that the mechanism of harms attributable to hypertension is different in the perioperative and community settings. After scores of randomized controlled trials optimal targets for adequate long-term control of blood pressure remain undetermined and, what constitutes acceptable, much less ideal blood pressure in patients having elective surgery is far from settled. Venkatesan's work provides us with some interesting new findings while at the same time challenging the need to further explore the all too common dilemma of how best to prepare the hypertensive patient anticipating anaesthesia.

The landmark study by Prys-Roberts which called attention to the association of hypertension with adverse outcomes with anesthesia was published in this same journal almost 50 years ago.(13) But, the literature has been mixed with subsequent studies failing to show that elevated BPs on the day of surgery are associated with significantly higher rates of adverse outcomes.(14, 15) We know that patients treated for hypertension, especially with certain classes of drugs, have higher rates of perioperative hypotension and adverse events.(16, 17)

Anaesthetists often only have access to BP readings taken immediately before surgery and these numbers are notoriously elevated due to missed doses of medications, anxiety, pain or perhaps hunger and thirst from fasting. The risks of anaesthesia in patients with elevated preoperative blood pressure have long been debated. It may be argued that BP measurements from the primary care physician's offices should be considered "the baseline."(2) Whatever values are used almost universally the focus has been on inadequate control of blood pressures, not on those patients with normal to low-normal BP.

Symptomatic hypotension has long been recognized by anaesthetists as dangerous. Preoperative hypotension in patients who are bleeding, critically ill or severely dehydrated raises appropriate clinical concern. Intraoperative hypotension is associated with higher rates of death, stroke, kidney and myocardial injury.(18-20) However, mild-moderate low blood pressures measured in the outpatient setting in community dwelling, non-critically ill individuals in line with the values shown to be associated with harm in this study do not cause alarm and deserve further investigation.

The association of elevated DBP with worse outcomes in this study is consistent with what we know about diastolic blood pressures and cardiovascular risk in the community setting.(21) But, the finding of perioperative risk associated with BP measurements considered normal, and in fact optimal when

recorded in non-surgical patients, is a surprising new concept. JNC 7 recommended treating BP to targets <140/90 mmHg to decrease cardiovascular complications. In patients with hypertension and diabetes or renal disease, the BP goal was <130/80 mmHg. The SPRINT trial as noted suggested that even these targets may be too lenient. The findings are plausible from a physiological perspective. Within the limits of autoregulation the systemic circulation is a constant pressure variable flow system which maintains a stable mean arterial pressure (MAP) in the system with blood flow through tissues regulated at arteriolar level. Flow becomes pressure dependent when the systemic pressure falls below the limit of autoregulation. MAP is a function of diastolic pressure. Should an already low DBP be further reduced by anaesthesia the MAP may be outside the limits of autoregulation and organ perfusion may be compromised.(22) The challenge for the anaesthetist is to identify a limit below which the blood pressure should not be allowed to fall. An analysis of a very large perioperative clinical database reported that even short periods of a MAP <55 mmHg was associated with an increase in biomarker detected renal and cardiac injury.(23) The lower limit of cerebral autoregulation in cardiac surgery patients has been shown to range between 40 and 90 mmHg.(24) It has been proposed that monitoring cerebral autoregulation thresholds might be used to guide individual therapy, but this is complex and expensive to implement on a large scale.(25)

The most recent (2014) report of The JNC 8significantly backed off previously recommended treatment targets for hypertension.(26) Their recommendations based on evidence from randomized controlled trials support treatment for long term benefits of hypertension to targeted thresholds of <150/90 mmHg for patients aged 60 years and older and a diastolic goal of <90 mmHg for those 30-59 years old. These guidelines were met with some controversy as not stringent enough.

Useful insights on associations between perioperative BP management and outcomes have been gained from studies using Anaesthesia Information Management Systems.(19) Such systems

have yet to be widely implemented in the United Kingdom. However, the UK has considerable strength in the area of electronic patient records in primary and community care. Computerized records are the norm in this setting and large anonymized databases such as ResearchOne and the Clinical Practice Research Datalink (CPRD) are available for research. CPRD is jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is a regularly updated database of de-identified primary care health care records from general practitioners from 674 practices caring for over 11.3 million patients in the United Kingdom (England, Wales, Scotland and Northern Ireland) as of mid-2013. This is approximately 7% of the UK population. Patients in the database are representative of the UK population in terms of age, sex and ethnicity. (27) CPRD includes data from routine clinical practice on demographics, symptoms, tests, diagnoses, treatments, and referrals to specialty care. Established in London in 1987, it is one of the largest databases of longitudinal medical records from primary care in the world. If a practitioner opts into the system all patients under his/her care are included unless they individually request not to be. Data are collected by practices and typically uploaded to the CPRD secure servers monthly. Quality of some data is monitored by CPRD internal processes and the Quality and Outcomes Framework in the UK.

The research strengths of the CPRD data includes the large number of patients, the wide representation of the population, long-term follow-up, and data quality. The January 2014 dataset contained 79 million person-years of follow-up. Epidemiological associations can be reviewed and estimated with a high level of statistical precision. The vast numbers of patients and data are particularly important when studying relatively rare occurrences such as mortality during anesthesia. The quality of the data varies because it is entered by clinical staff during routine patient care, not for the purpose of research. Validation of the

CPRD has shown high positive predictive value of diagnoses. Comparisons with other UK data sources indicate that the data are robust.(28) Weaknesses of this database include the inconsistency of data for individual patients over time and among patients. One must presume that if a condition is not noted the patient does not have that diagnosis but this may be failure to document. There is the lack of uniform, standardized definitions for diagnoses. There is also wide variation in the use codes within primary care databases which is then translated into research databases such as CPRD. Primary care data systems generally use Read codes. (29) These have a complex structure and any one of a number of codes may be used to describe a given condition. A study to develop an electronic frailty index used 1,574 codes to capture 36 conditions or deficits considered components of frailty. The identification of codes in the study by Venkatesan and colleagues was well described and consistent with accepted methods and the authors themselves note possibility of missing data impacting on their results. This work provides valuable epidemiological data and makes a robust case for further studies with prospective data collection.

The findings of Venkatesan and colleagues are clinically important. They add to the weight of evidence that the anaesthetist should be concerned about the potential risks associated with low blood pressure. However, this study does not provide information to direct clinical care. In older patients undergoing major surgery where the baseline risk associated with anaesthesia and surgery is significant the relatively small adjusted odds ratio of 1.37 associated with a DBP 60 mmHg in patients aged over 65 years may represent an important increase in absolute risk. The iHypE study, a UK wide study of the prevalance of intraoperative hypotension and its association with cardiac injury, renal injury and death, has completed its data collection phase. If this large study with prospective BP data collection also shows an association between low BP and adverse outcome there will be a strong case for a large interventional study of targeted BP control in non-cardiac surgery. Whilst this will be costly, the potential for substantial reductions in morbidity and mortality in the non-cardiac surgery population will more than justify the

investiment. In the meantime, the data from Venkatesan and colleagues suggests that the anaesthetist should make a pragmatic judgement as to the best estimate of the patient's baseline BP and generally aim to maintain the DBP >65 mmHg. The results of this study and secondary analyses of the VISION study suggest that vasoactive drugs such as angiotensin converting enzyme inhibitors and angiotesion II receptor blocking agents should be withheld immediately before surgery in elderly patients.(16) If more evidence is required to guide optimal clinical management of diastolic hypotension, then the position with regard to diastolic hypertension is even less clear. Where there is a plausible mechanism for the association between hypotension and adverse outcome, the causal pathway for hypertension is not readily evident. The iHypE study is unlikely to add information in this case, as it examines only intraoperative hypotension. At present it is possible to give only unsatisfactory advice, suggesting that the anaesthetist should aim at the "Goldilocks" range for intraoperative blood pressure and avoid excursions in either direction. This is too vague to be very helpful, but the work of Venkatesan and colleagues brings the important message that future studies of perioperative blood pressure control needs to collect data on and examine the impact of a wide range of blood pressure.

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