Chapter

Cardiac Arrest Following Central Neuraxial Block

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Abstract

Central neuraxial blocks (CNB) are used worldwide in anesthesia practice. They are safe, however, not devoid of untoward complications. Cardiac arrest (CA) is one of the major devastating complications. The anesthesiologists are concerned about CA as it can occur unexpectedly and suddenly even in a young ASA grade I patient, undergoing elective surgery, at any time during and after administration of CNB in spite of continuous vigilance. A better understanding of the physiology of CNB, availability of monitoring devices, and safer local anesthetic drugs contribute to reduced mortality, yet cases of CA are reported even recently. These case reports provide information relevant to particular incidents and may be inadequate to provide comprehensive information to explain the overall clinically important aspects related to CA following CNB. This chapter would provide a summary and analysis of the current recommendations about etiology, predisposing factors, preventive measures, and various measures tried for the treatment of cardiac arrest, although the exact etiology and predisposing factors are still not known. The comprehensive information would be helpful for anesthesiologists during day-to-day practice and to increase the safety of patients undergoing CNB. Proper patient selection, pre-/co-loading of fluids, the modifying technique of CNB as per patient's need, early use of epinephrine during bradycardia refractory to atropine, continuous monitoring, vigilance during intra- and postoperative period would help in prevention, early detection, and prompt treatment of CA. Challenges faced by anesthesiologists during CNB practice and newer modalities used for the treatment of refractory CA are also discussed. The mystery of sudden unexpected CA is yet to be solved and research in this direction is warranted. Electronic medical record keeping and reporting untoward incidence to the national board will also help to improve patient safety in the future.

Keywords: anesthesia, epidural; anesthesia, spinal; anesthetic technique, central neuraxial block; complications, bradycardia, cardiac arrest, hypotension

1. Introduction

Central neural blocks (CNB) are commonly used in the perioperative period and are an integral part of anesthetic practice because of well-known reasons [1]. The low rate of complications is one of the reasons for their popularity particularly in regions with the limited health care resources.

The techniques are considered safe but major adverse events such as neurological complications and cardiac arrest (CA) are reported at times, and the techniques are not without risks [1, 2]. It is evident from reports of studies that cardiac arrest following CNB is not rare [3–6]. CA under CNB is a major concern as it is reported in ASA grade I young patients, undergoing elective surgery, and can occur suddenly without warning signs [4, 7]. CA following spinal anesthesia is reported since 1940, yet the exact etiology is not known [1, 8]. Even though the outcome of patients developing CA has improved in the last two decades, the possibility of tragic events does exist despite adequate and timely resuscitation [9]. These case reports provide information relevant to particular incidents and may be inadequate to provide comprehensive information to explain the overall clinically important aspects related to CA following CNB. This chapter would provide a comprehensive view of etiology, predisposing factors, preventive measures, and treatment of cardiac arrest. The information would help to increase patient safety during spinal and epidural anesthesia. The anesthesiologists can make use of this information for proper selection of patients, preoperative optimization of patients, modifying anesthetic technique as well as monitoring as per patient need, to implement measures to prevent severe bradycardia, hypotension, use of different modalities during refractory cardiac arrest and for postoperative care of patients receiving CNB. The importance of vigilance and monitoring during intraoperative as well as in the postoperative period is reinforced as unexpected CA can occur at any time [2, 10]. The chapter would also make the anesthesiologists aware of where the research stands on this critical issue of CNB and in what direction future research is needed.

This chapter is intended to serve as a pragmatic review for use in daily anesthesia practice of CNB (spinal, epidural, and combined spinal-epidural) in adult patients. The manuscript is structured in a way that may help the anesthesiologists to quickly find the most important information about CA relating to the current information and underlying evidence. We did not carry out a systematic literature review. To present a holistic overview of this clinically important subject, a comprehensive literature search was performed in January–April 2022 in MEDLINE, PubMed, and Google Scholar to retrieve articles pertaining to a cardiac arrest related to CNB. The keywords used in various combinations included "Central neuraxial blocks and cardiac arrest"; spinal anesthesia and cardiac arrest; epidural anesthesia and cardiac arrest; local anesthesia systemic toxicity; hypotension and spinal anesthesia. A systematic review would result in a larger and more detailed manuscript that could be difficult to use as a quick clinical reference, even though it would decrease the probability of excluding relevant publications [11].

Incidence of cardiac arrest: The exact incidence of CA is not known [1]. The real incidence of CA related to CNB is heterogeneous and has a wide range from 0.07 to 49 per 10,000 patients [2, 4, 5, 10, 12]. In 2002, the incidence of CA following CNB was 10:10,000 [13]. A better understanding of physiological changes following CNB, availability of safer local anesthetic drugs, and improved monitoring have contributed to the reduction in the incidence of CNB [14]. However, even recent reports confirm that CA under spinal anesthesia is not rare [5, 8, 10].

In 2002, the incidence of CA following spinal anesthesia was more as compared to that following epidural, 2.5/10,000 and 0–0.5/10000, respectively [15, 16]. Incremental doses and slower onset of epidural contribute to a lower incidence of CA as compared with spinal anesthesia [3]. However, Cook et al. observed a higher incidence of permanent neurological damage including death following epidural and combined spinal epidural than spinal, 18.2 and 2.8 per 100,000, respectively [2].

Biboulet et al. reported that the incidence of CA was more following spinal than general anesthesia [17]. However, according to the majority of investigators, the incidence is more during general anesthesia [8, 14, 18]. It may be because the more complicated surgeries and high-risk patients are conducted under general anesthesia.

2. Etiology

The real etiology of CA is still not known, even though CA following spinal was reported in 1940. Etiology of CA following spinal and epidural is multifactorial. Due to inconsistent reporting, risk factors leading to bradycardia and CA under spinal anesthesia remain uncertain and contradictory [19]. Etiology of CA is summarized in **Table 1**.

1. **Respiratory etiology**: In 1988, Caplan postulated after analysis of 14 cases, that CA during spinal anesthesia was related to hypoxemia secondary to excessive sedation and/or sensory level above the T4 segment [7]. However, peak block height had the weakest correlation to bradycardia and there were no changes in tidal volume and the diaphragmatic function was unaffected by mid-thoracic levels of the spinal blockade [20]. As the pulse-oximeter was available, several authors reported that hypoxia was not the primary cause of CA and many of the patients did not receive sedative drugs [9, 21].

2. Cardiocirculatory etiology (Reduction in preload and blockade of cardio-accelerator fibers):

   The most likely etiology of CA during spinal/epidural anesthesia is mainly peripheral vasodilatation and reduction of preload resulting from sympathetic blockade. The level of sympathetic blockade extends two to six dermatomes

Spinal anesthesia	**Epidural anesthesia**
Reduction in preload and blockade of cardio-accelerator fibers)	Reduction in preload. Cardio-accelerator fibers are blocked in thoracic epidural
Parasympathetic over activity	Parasympathetic over activity
Intrinsic cardiac reflexes	Intrinsic cardiac reflexes
Inhibition of catecholamine release	Inhibition of catecholamine release
Inherent vagotonia	Inherent vagotonia
Sudden bradycardia & cardiac arrest	Sudden bradycardia & cardiac arrest
Myocardial ischemia	Myocardial ischemia
Total spinal following repeat spinal anesthesia	Accidental total spinal
	LAST* due to intravascular injection or overdose toxicity while using mixture of local anesthetics
	Absorbed local anesthetic can add to bradycardia

**LAST—Local anesthetic systemic toxicity.*

Table 1.
Causes of cardiac arrest.

above the sensory blockade [3, 22]. Cardio-accelerator fibers (T1-T4) can be blocked when a sensory level is at T4 and their blockade produces negative chronotropic, inotropic, and dromotropic effects. Nevertheless, it is not uncommon to see high-sensory blockade levels without hemodynamic changes, particularly in young patients. Reduction in right atrial pressure is likely in 36% of the patients, when the level block is less than T4 dermatome and in 53% of patients when it is above that [13, 23]. Anesthesiologists generally test the level initially till the desired level is achieved for surgical procedure. Higher levels achieved subsequently (due to patient position, baricity, type of local anesthetic, and other factors) may remain unnoticed.

3. Exacerbation of the parasympathetic nervous system

Sympathetic blockade results in significant bradycardia and even asystole. The final pathway is the absolute or relative increase in activity of the parasympathetic nervous system [23]. CA is more common in young individuals as they have a greater vagal tone. The parasympathetic response following spinal anesthesia, traction on viscera, pain, etc., is further exaggerated in these patients [3]. Cardiac arrest during needle insertion is reported particularly in the anxious patients [6]. CA was preceded by bradycardia in many studies [9, 16].

4. Intrinsic cardiac reflexes

A decrease in preload may initiate reflexes leading to severe bradycardia [24] (**Figure 1**).

a. Reflexes involving the pacemaker stretch: The rate of firing of cells of the pacemaker within the myocardium is proportional to the degree of stretch. Decreased venous return to the right atrium results in the decreased stretch and a slower heart rate.

b. The reflex from low-pressure baroreceptors in the right atrium and vena cava.

c. Reflexes arise from inhibitory mechano-receptors in the left ventricle. Decrease in ventricular volume would normally decrease receptor activity leading to tachycardia. However, a rapid decrease in left ventricular volume may trigger a paradoxical increase in the activity of these receptors, which could be due to forceful ventricular contraction around an almost empty chamber. This reflex slowing should allow time for a more complete filling of the heart [25].

Ecoffey et al. studied the effect of sympathetic blockade with echocardiography in unpremeditated volunteers and observed that two out of eight volunteers developed bradycardia and hypotension along with a reduction in left ventricular diameter, with epidural anesthetic levels of T8 and T9. Changes reverted by head-down positioning and rapid infusion of I.V. fluids. The increased levels of human pancreatic polypeptide, a marker of parasympathetic function, associated with these episodes of bradycardia suggest vagal activation. Bradycardia due to an increase in vasopressin levels without changes in catecholamine levels is observed after the head-up tilt in the presence of sympathetic blockade [26]. Pregnant patients undergoing spinal

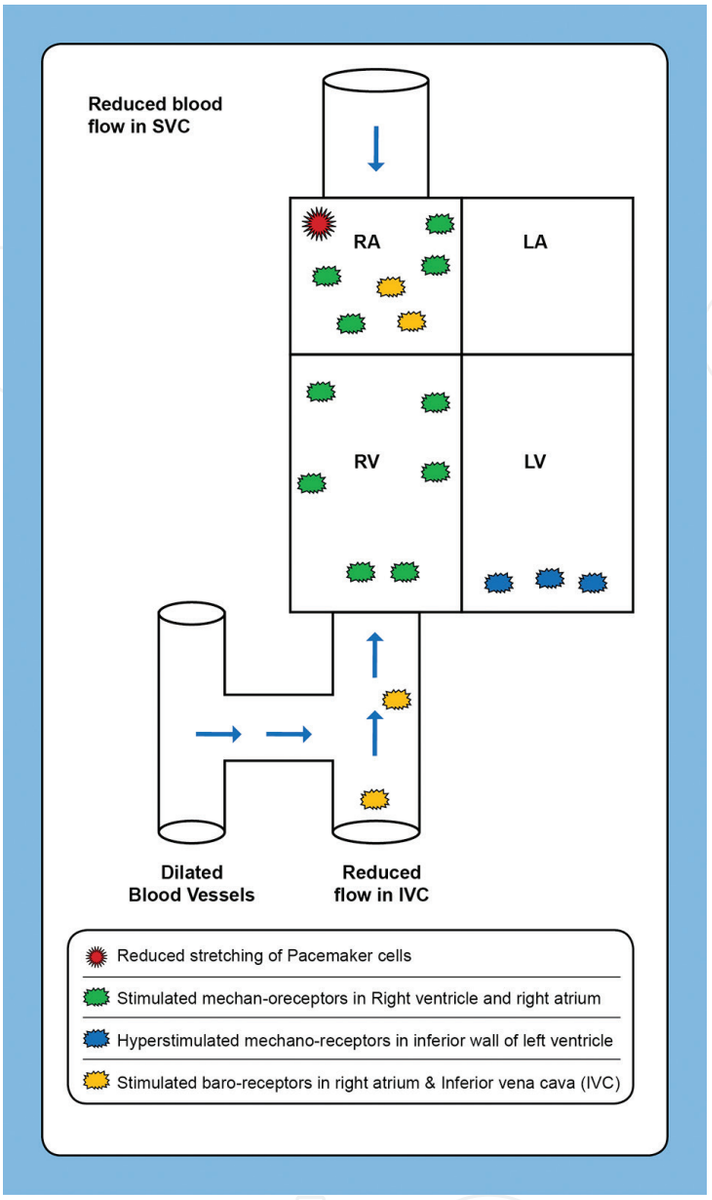

Figure 1.
Receptors in heart responsible for cardiac arrest following CNB.

anesthesia are at increased risk for hypotension and bradycardia due to aortocaval compression and a higher level of spinal block [27].

5. **Inhibition of** catecholamine **release:** Suprarenal glands are innervated from nerve fibers emerging between T8 and L1. There is inhibition of catecholamine release during the spinal.

6. **Inherent vagotonia and autonomic hyper reflexia:** 7% of the population has a sympathetic and parasympathetic imbalance. "Vagotonia" describes the clinical situation of resting bradycardia, atrioventricular (AV) block, or complete AV dissociation [28]. Patients may have a history of fainting attacks at the site of blood. Any tendency to bradycardia that might otherwise have been more benign, transient, or possibly unnoticed may be exaggerated in vagotonic patients [19]. In

addition, anxiety or viscous traction, in such individuals, can produce severe bradycardia or atrioventricular heart blocks [3, 29]. A small postural change includes placing legs in the holder, and turning the patient to the left lateral or prone position and CA was reported even after the surgical procedure was over. It is difficult to explain these situations based only on preload changes. Maybe they are due to reflex phenomena similar to those of autonomic dysfunction or hyperreflexia described in patients with a spinal cord section. One should be vigilant during the change of posture of the patient receiving spinal anesthesia [30].

Paradoxically young patients and athletes are frequently classified as low-risk ones, have increased vagal tone, and appear to be at risk of developing severe bradycardia. The highly competitive athlete, in addition, may have "athletic heart syndrome". Its features include sinus bradycardia, sinus dysrhythmias, first-degree and Mobitz type I blockades, and alterations in repolarization. Occasionally, CA has been described during the spinal anesthesia in athletes [31, 32]. Jordi et al. observed the development of first-degree AV block progressing to asystole in patients undergoing spinal anesthesia with the sensory blockade at the T3 dermatome [23]. Retrospective analysis of postoperative holter monitoring indicated persistent first-degree block for six hours after anesthesia. Development of a first-degree block can be a warning sign for the development of asystole. However, the difficulty in diagnosing first-degree block using a cardioscope limits the applicability of this finding [4].

7. **Total spinal following repeat spinal anesthesia:** Total spinal can be there due to a high dose of local anesthetic if due precautions are not taken. If not detected and treated in time, the patient may develop cardiac arrest [33].

8. **Sudden bradycardia & cardiac arrest**: These complications may develop despite vigilance and satisfactory resuscitation, which is yet a mystery. It is observed in young patients undergoing minor surgery. These situations are often attributed as the consequence of mismanagement of the spinal technique and not to an intrinsic risk of the technique itself [32]. Detailed analysis of the hemodynamics in the minute or two leading up to bradycardia or asystole during CNB is a time frame in which intervention is needed to prevent calamities.

Causes of Cardiac arrest following epidural block:

Cardiac arrest can occur during epidural anesthesia [6, 21, 34, 35] due to causes similar to that following spinal anesthesia. In addition, unintentional "total spinal" anesthesia, and local anesthetic systemic toxicity (LAST) are common causes of CA during an epidural block. Absorbed local anesthetic from vascular epidural space can add to bradycardia. Occasional severe toxicity and deaths are reported. While using a mixture of local anesthetics, one should not use maximum doses of two local anesthetics in the belief that their toxicities are independent [36]. Heavy intravenous sedation with drugs such as midazolam can mask early signs of LAST, particularly convulsions. Among all, bupivacaine is considered to be 4–16 times more cardiotoxic than lignocaine. The use of ropivacaine and levobupivacaine may help reduce cardiotoxicity due to stereo-selective binding of sodium and potassium channels resulting in less affinity and strength of inhibitory effect [37]. Jacobson concluded that reduction in preload leading to an increase in vagal activity is responsible for arrest rather than blockade of cardiac accelerator nerves from the study on healthy volunteers receiving

epidural [25]. Development of third-degree heart block is reported following thoracic epidural block in a patient having preoperative first-degree heart block [38]. Even though there is a segmental block during epidural, partial sympathetic block can be there in lower segments resulting in preload reduction [39].

A combined spinal-epidural technique (CSEA) may be preferable to a continuous epidural technique as is associated with a lower failure rate, better pain scores, and patient satisfaction. Epidural top-ups of local anesthetic should be given in small incremental doses [40].

Causes of early-onset CA may be vasovagal during needle prick, hypovolemia, compromised cardiovascular status, posture-related changes, and accidental intravascular/intrathecal injection during an epidural block, etc. Late-onset CA may be due to blood loss, myocardial infarction, and delayed spread of local anesthetic after spinal anesthesia, surgical stimulus like traction on mysentry, cementing, posture change, tourniquet release, and use of vasodilators such as nitroglycerine or sodium nitroprusside during total hip replacement, etc.

3. Predisposing factors for cardiac arrest

Although the development of CA during spinal anesthesia is considered as the final step of a spectrum of manifestations that starts with bradycardia, establishing an association among factors related to its development can help identify patients at-risk to develop CA during spinal block [3].

Risk factors for severe bradycardia: Pollard has suggested the risk factors as shown in **Table 2** [3].

According to Carpenter, the level of the block had the weakest correlation with the development of bradycardia [20]. The presence of two or more listed factors in **Table 2** may place these patients at high risk for bradycardia and cardiac arrest under spinal anesthesia [3]. Due to inconsistent reporting, the risk factor associated with the occurrence of bradycardia and cardiac arrest under spinal anesthesia remains uncertain and contradictory [19].

Patients with a background of vagal dominance, and with a history of vasovagal syncope, may be predisposed to severe bradycardia and even cardiac arrest following spinal anesthesia [10]. I.V. supplementary drugs such as fentanyl, dexmeditomidine, droperidol, beta-blockers, and ondansetron [41–45] can be predisposing factors due to alpha- or beta-receptor blocking effect.

Sr. No.	Criteria
1	Age < 50 years
2	Baseline heart rate < 60/minute
3	ASA physical status grade I and II
4	Use of beta-blockers
5	Sensory-level blockade above T6 dermatome
6	Prolonged P-R interval

J. B. Pollard [3].

Table 2.
Risk factors for bradycardia during central neuraxial block.

Sr. No.	Criteria
1	Hypovolemia
2	Preoperative hypertension
3	High sensory nerve block height
4	Age older than 40 years
5	Orthopedic surgery
6	Combined general and spinal anesthesia
7	Chronic alcohol consumption
8	Elevated body mass index
9	Emergency surgery
10	Pregnancy > 20 weeks gestation

Adrian Chin and André van Zundert [40].

Table 3.
Risk factors for hyotension during central neuraxial block.

Risk factors for hypotension: These include hypovolemia, age > 40 to 50 years, emergency surgery, obesity, chronic alcohol consumption, and chronic hypertension, aortocaval compression after 20 weeks of gestation, and alkalinization or excessive doses of local anesthetic (**Table 3**) [7, 22, 46, 47].

CA observed shortly after CNB is due to excessive doses of local anesthetic in the previously hypovolemic patient. Preoperative fasting, dehydration, diuretics and vasodilator drugs for hypertension are common causes. Incidence of CA is more during orthopedic surgeries like hip surgery. Blood loss during surgery, cementing, or postural changes also contribute to CA [16, 48]. The level of sensory blockade in elderly patients is usually higher than that of young adults with the same dose of local anesthetic. According to Biboulet et al. [14], doses as low as 5 mg of bupivacaine, hyper- or isobaric, can cause a sensorial blockade reaching up to T2-T4 [17]. Overdose of local anesthetic using the subarachnoid route is a known cause of CA in elderly patients. It is recommended that the level of the blockade should be limited to T6 and hemodynamic reserves should be evaluated perioperatively to prevent untoward events. [48]

When SA is administered by surgeons and non-anesthetist health care providers, the incidence of CA was more [49]. This is due to lack of monitoring, delay in detection, and treatment of complications by non-qualified health care professionals. Lozts et al. postulated that hyperbaric solutions can have delayed cephalad spread even after minutes post-injection and it can take more than 40–60 minutes to fix finally [50]. Obstetric patients have more sympathetic activity so a lower incidence of CA is expected [2, 3]. Adekola et al. observed more cardiac arrests (7.3/10000) in pregnant mothers as compared with non-obstetric patients, however postmortem reports revealed that the causes were not related to spinal anaesthesia [12].

4. Prevention of severe bradycardia, hypotension, and cardiac arrest

Final pathway for the development of severe bradycardia and CA is parasympathetic over activity. Specific strategies to anticipate and prevent vagal predominance

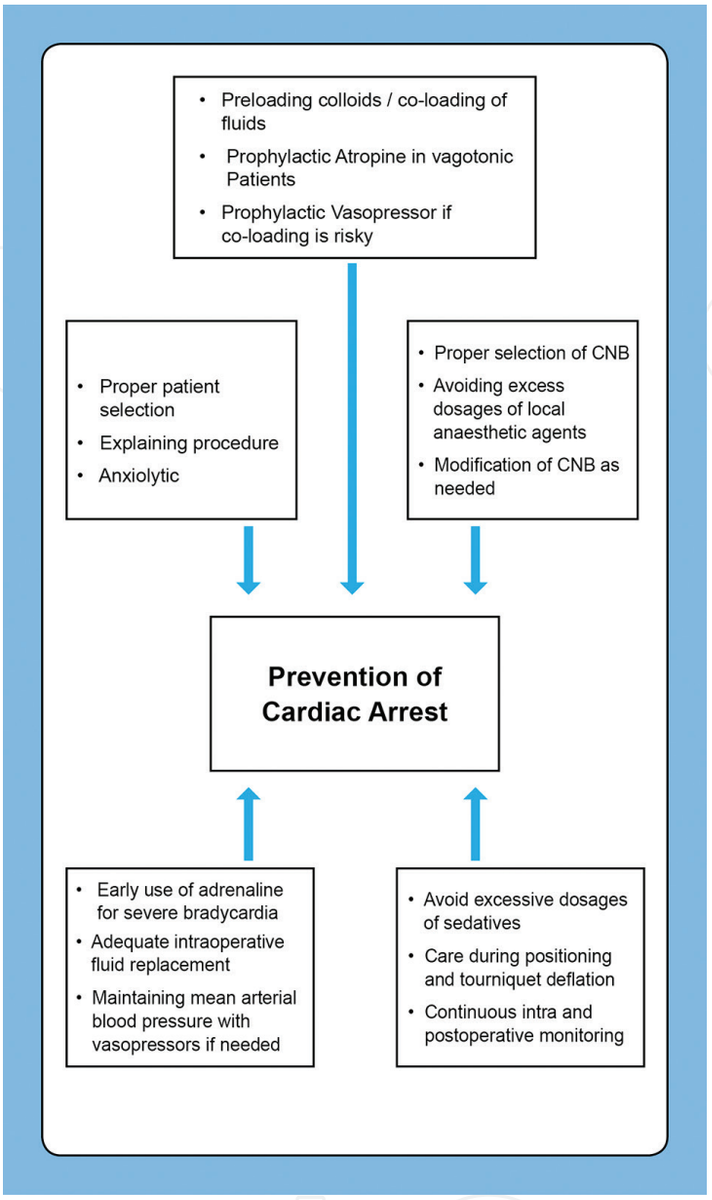

Figure 2.
Prevention of cardiac arrest.

form the mainstay in the management of severe bradycardia and CA under spinal anesthesia (**Figure 2**).

A. Prevention:

a. **Appropriate patient selection:** When two or more risk factors are present **(Table 2)** and when significant intraoperative blood loss or use of vasodilators such as sodium nitroprusside or nitroglycerine is anticipated, one should reconsider the choice of spinal anesthesia [3].

b. **Explaining the procedure to the patient during pre-anesthetic checkup:**

This will help to reduce anxiety and fear, which can trigger severe bradycardia. Anxiolytic like oral hydroxyzine in the apprehensive patients, atropine pre-

medication in the selected patients (vagotonic), application of local anesthetic cream or infiltration before insertion of the needle, administration of CNB in the lateral position, etc., can help to reduce incidence of sudden bradycardia during needle insertion [51].

c. **Prophylactic atropine premedication:**

Routine premedication with atropine is not recommended and does not reduce the incidence of bradycardia and hypotension [52]. Bradycardia of different grades is observed during CNB (mild<60, moderate <50, severe </ min). Clinically significant bradycardia occurs in 10 to 15 percent of spinal anesthetics [53]. The incidence of bradycardia with epidural anesthesia depends on the level and extent of the block. It may be considered in elderly patients having bradycardia and those with the history suggestive of vagotonic symptoms (0.5 mg immediately after spinal anesthesia) [54]. Prophylactic administration of I.V. atropine after spinal did not prevent a decline in blood pressure in parturients even though heart rate was more at 15 and 20th min [55]. I.V. atropine prevented bradycardia when dexmeditomidine sedation was administered but there was increase in the blood pressure so should be used carefully [56]. Epinephrine should be administered in the presence of refractory bradycardia. Early administration of 0.2–0.3 mg adrenaline or drip 0.15 mcg/kg/minute prevents cardiac arrest and subsequent morbidity [3, 40].

d. **Modification in CNB technique:** Hemodynamic consequences can be reduced a) by administering a low dose of local anesthetic with the additive [57], using unilateral spinal anesthesia for lower limb surgery [58] by titrating the required level by using continuous spinal anesthesia [59]. This can reduce the extent of sympathetic block. Care should be executed for local anesthetic toxicity while using a mixture of local anesthetics and epidural dosages when combined spinal epidural anesthesia is administered.

e. **Maintaining adequate preload and prevention of hypotension**: Uncorrected hypovolemia increases the risk of hypotension with the onset of CNB and is an absolute contraindication for spinal anesthesia. Risk factors for hypotension include hypovolemia, age > 40 to 50 years, emergency surgvery, obesity, chronic alcohol consumption, pregnant patient with gestational period of more than 20 weeks, and chronic hypertension (**Table 3**) [40]. In vagotonic patients particularly when blood loss is expected during surgery, preload maintenance is essential [3]. Unfortunately, this is not routinely followed [3, 29]. Preloading with colloids or co-loading with colloids or crystalloids administered within 5–10 minutes is effective [60, 61]. Co-loading should be practiced carefully in patients with preeclampsia.

Change from supine to prone or Trendelenburg/lithotomy to supine posture, tourniquet release, intra-operative blood loss, and use of vasodilators can produce preload changes and need preload correction in anticipation. The position should be resumed if hypotension/bradycardia is observed. 30 centimeter leg elevation increases the venous return and is useful in settings with resource constraints [62].

10–15 degrees left lateral tilt is beneficial in parturient to reduce aortocaval compression reducing preload. Unfortunately, adequacy of preload is difficult to assess clinically. Assessment of inferior vena cava diameter and left ventricular volume by using non-invasive techniques such as ultrasonography (USG) and transthoracic echocardiography can be useful but may not prevent CA [63, 64].

Invasive blood pressure monitoring can help to increase safety in critical patients [65]. Bradycardia may be an early manifestation of reduction in preload and atropine or vasopressor may be needed to treat vagal manifestation and only fluid administration may not be sufficient. Administration of atropine 0.4–0.6 mg is recommended to prevent cardiac arrest.

f. **Vasopressors**: Vasopressors with different modes of action are tried for the prevention and treatment of hypotension in elderly and obstetric patients, particularly when pre- or co-loading is risky as in patients of preeclampsia (**Table 4**).

Ephedrine, phenylephrine, or noradrenaline can be used for prophylaxis. Ephedrine produces tachycardia and is to be avoided in patients where tachycardia is undesirable as in patients with aortic stenosis. It produces tachyphylaxis when used in repeated doses, and hence is administered as intermittent boluses and not as an infusion. Phenylephrine (alpha-agonist) has duration of action of up to 20 minutes. Noradrenaline increases cardiac output due to its alpha-agonist action and additional weak beta-agonist effect. About 8 mg ondansetron blocks Bezold Jarisch reflex activated by serotonin and is used to limit hypotension. Further evidence is awaited for routine use of ondansetron [66–70].

g. **Continuous vigilance throughout the procedure:** Blood loss, altered consciousness, and signs of vagal over activity such as nausea, sweating, bradycardia, change of posture, traction on viscera, and vital parameters are essential throughout the procedure as well as in the postoperative period also. Awareness about delayed CA is necessary [32].

5. Treatment of bradycardia and hypotension

Treatment of bradycardia: Mild bradycardia (<60/min) should be treated in patients with risk factors (3). It is enough to have intra-operative hypotension with bradycardia (<50/min) to rapidly administer atropine plus a vasoconstrictor (e.g., ephedrine). Treatment of moderate and severe bradycardia with hypotension must be quick, intensive, and multimodal. According to Tarkilla et al., atropine is recommended for bradycardia as glycopyrrolate is ineffective [46]. Alexander has suggested that atropine (0.5 mg) or glycopyrrolate (0.2 to o.4 mg) and ephedrine (5 to 10 mg) I.V. can be used for the treatment of bradycardia with hypotension [71]. It does not seem to be wise to administer just one of these drugs and then wait for the result [3, 32]. Pollard recommended a stepwise approach of administering atropine (0.4–0.6 mg), ephedrine (25–50 mg), and epinephrine (0.2–0.3 mg) for the treatment of moderate bradycardia. If there is no improvement after atropine and vasoconstrictors, intravenous epinephrine must be administered without any delay, as recommended by the SOS ALR group in France [74]. Head low position (careful before 30 minutes after spinal) [75] and fluid administration should

	Drug	Receptors	Effects	Dose	Undesirable effects
1	Ephedrine [66]	Alpha- and beta-adrenoreceptors	Maintains arterial pressure by increasing cardiac output and heart rate (beta 1 receptor)	Prophylaxis:10 mg after spinal anesthesia Treatment: rescue dose 5 mg	Weak alpha-activity
2	Mephenteramine [67]	Alpha- and beta-adrenoreceptors	Increases CO and SBP	Treatment of hypotension 5 mg bolus, 2.5 mg/ min infusion	Less significant increase in peripheral resistance
3	Phenylephrine [66, 68]	Alpha-adrenergic agonist causes release of norepinephrine	Increases SVR and MAP *via* arteriolar vasoconstriction resulting in increased CO	Prophylaxis:100 microgram after spinal anesthesia Treatment: rescue dose 50 microgram	Reflex bradycardia
4	Norepinephrine [69]	Potent alpha-agonist and weak beta-agonist	Increase in HR and CO	Prophylaxis: Infusion of 0.07–0.08 mcg/kg/min, Treatment : rescue dose 8 mcg bolus	Bradycardia, weak beta-agonist
5	Theoadrenaline (norepinephrine & theophylline) [70, 71]	Beta 1 adrenoreceptor stimulation, partial agonist at alpha 1 receptor	Increased ionotropic activity Release of nor adrenaline from nerve endings and increased SV, CO	(Ampoule containing cafedrine 200mg/ theoadrenaline 10mg) slow IV 1 ml/min for the treatment of hypotension	Further data awaited
6	Ondansetron [72, 73]	5-HT3 receptors	Inhibits BJR by blocking serotonin binding to 5-HT3 receptors in left ventricle leading to increased BP and HR	4–8mg, 5 min prior to spinal anesthesia	Further data awaited

CS—Cesarean section, CO—cardiac output, SBP—systolic blood pressure, SVR—systemic vascular resistance, MAP—mean arterial pressure, mcg—microgram, BP—blood pressure, HR—heart rate, SV—Stroke volume, IV—intravenous, BJR—Bezold Jarisch reflex. [Number in bracket indicates reference number].

Table 4.
Vasopressors used for prevention and treatment of spinal/epidural anesthesia-induced hypotension.

also be done simultaneously as bradycardia may be the manifestation of reduced preload. The possibility of cephalad spread of hyperbaric local anesthetic and hemodynamic effects must be anticipated. When the level of the sensory block is higher than or at T6, there can be pooling of 20% circulating blood volume in the hepato-splanchnic region and this volume can be mobilized by the use of vasopressors [76]. A transcutaneous pacemaker should be used if bradycardia is not responding [77].

Treatment of hypotension: Incidence of hypotension during spinal is 47% [47]. Systolic blood pressure less than 80% of the baseline value should be treated [68]. Mean arterial pressure should be targeted more than systolic blood pressure. When the same level of dermatomal block is achieved following epidural and spinal anesthesia, the incidence of hypotension is similar, although the onset of hypotension may be slower with epidural anesthesia [3].

20 degrees head low position, co-loading with colloids or crystalloids (around 1000 ml) and vasopressors are used for treatment. Ephedrine is used when there is bradycardia and hypotension [66]. Phenylephrine 100 mcg is used for the treatment of hypotension (100 mcg bolus or 10 mg ampoule in 100 ml saline—100 mcg/ml, i.e., 1 ml/min drip-rate). Phenylephrine can reduce the level of spinal and produce hypertensive crises when administered with atropine [40]. Reflex bradycardia due to hypertension usually limits hypertensive crises. Noradrenaline can also be used instead of phenylephrine with less risk of bradycardia. A combination of caffedrine (covalently linked norephedrine and theophylline) having an inotropic effect and theodrenaline (covalently linked noradrenaline and theophylline) having vasoconstricting effect is used in Germany. The combination has early-onset and long-lasting hypertensive effects [70, 71]. Additional evidence is awaited (**Table 4**).

Treatment of cardiac arrest: Vasodilatation during spinal anesthesia can make resuscitation refractory [3]. Epinephrine is to be administered after CA to maintain coronary perfusion pressure of 15–20 mm of Hg. Rosenberg has recommended 0.01–0.1 mg/kg adrenaline for the treatment of refractory bradycardia but once CA develops one mg of adrenaline must be administered. Spinal anesthesia blocks nerves going to the adrenal glands. Their suppression results in a reduction in circulating levels of noradrenaline and adrenaline during the stress of CA and is an important reason for refractory CA [78]. Adrenaline is not having a vagolytic effect and its use does not preclude the use of other drugs [1]. Veno-arterial ECMO can be used if ROSC is not restored. It may be difficult to find out the cause of cardiac arrest. 12 lead ECG, Troponin test, S. tryptase and 2D Echo would be helpful to diagnose myocardial infarction, anaphylaxis, embolism and hypovolemia. Veno-arterial ECMO may be helpful during this period [79].

After the restoration of circulation, myocardial stunning may need vasopressor support for prolonged period. Refractory cardiac failure may need to leave ventricular assist device [27].

Summary of treatment of bradycardia and cardiac arrest:

1. Mild-to-moderate bradycardia (heart rate – 60/min)—stepwise escalation of therapy.

    a. Atropine 0.4–0.6 mg, IV, b. Ephedrine 25–50 mg, c. Epinephrine 0.2–0.3 mg.

2. Severe bradycardia or cardiac arrest—as shown in the algorithm (**Figure 3**).

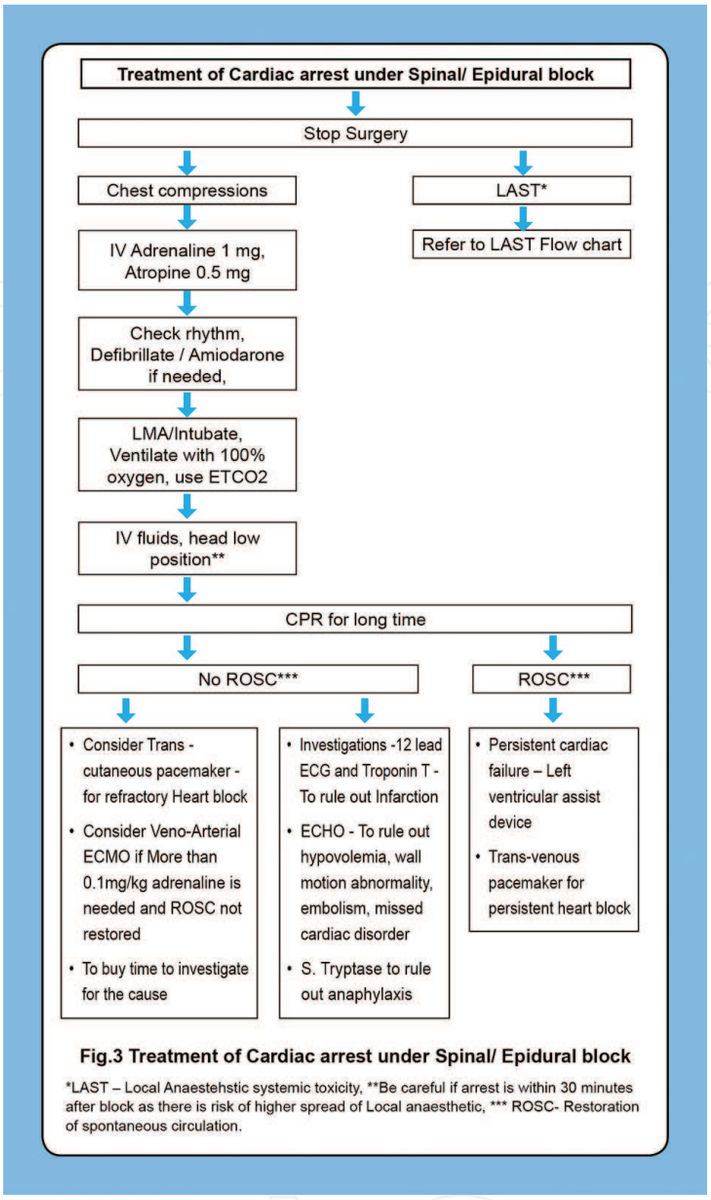

Figure 3.
*Treatment of cardiac arrest under spinal/epidural block. *LAST—Local anesthetic systemic toxicity, **Be careful if arrest is within 30 minutes after block as there is risk of higher spread of local anesthetic. ***ROSC—Restoration of spontaneous circulation.*

Reposition the patient and stop surgical stimulus.

Treatment of local anesthetic systemic toxicity (LAST):

LAST needs a special mention. Seizures should be suppressed immediately to reduce oxygen consumption, and prevent hypoxia and hypercarbia. Administration of a benzodiazepine (midazolam 1 to 2 mg I.V.) is preferred. If ventilation is inadequate, suxamethonium is administered and the airway is secured. The management of ventricular arrhythmias and CA as a result of LAST is different than other CA scenarios and may require prolonged effort [50]. Amiodarone and defibrillation are used for the treatment of ventricular fibrillation. Lignocaine should not be used. Based on animal studies, the bolus dose of epinephrine is to be reduced to ≤1 mcg/kg IV to avoid arrhythmogenic effects. The optimal dose of epinephrine is unknown.

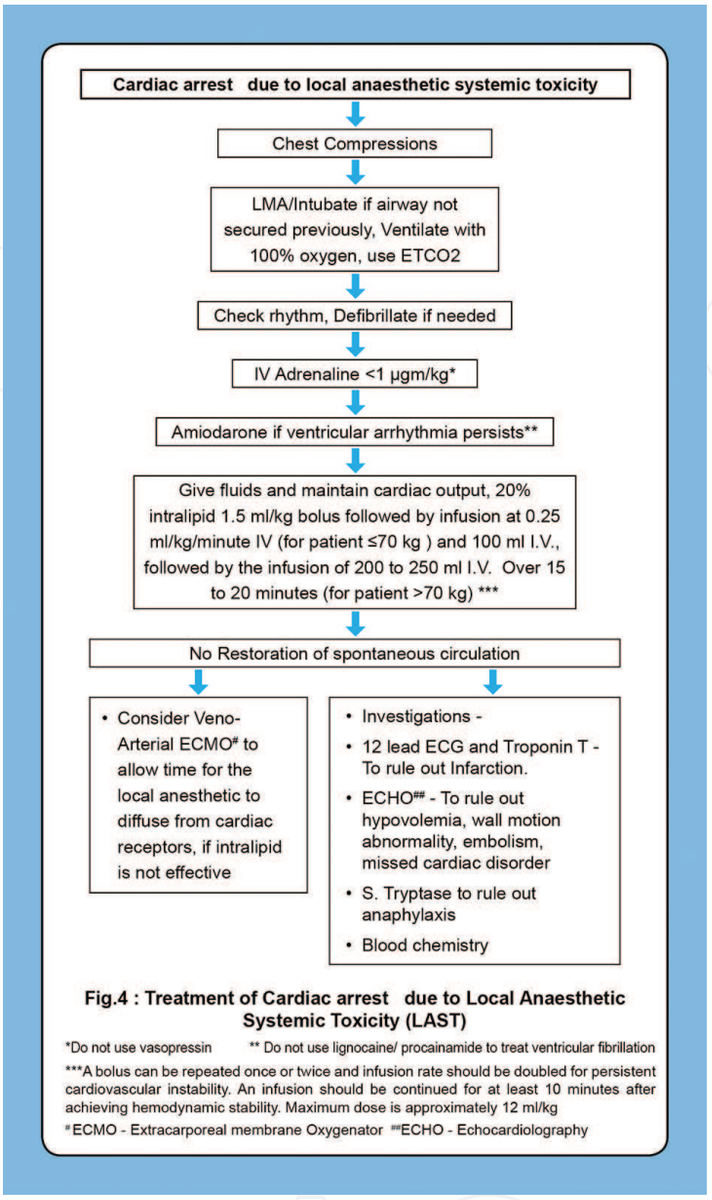

Figure 4.
*Treatment of cardiac arrest due to local anesthetic systemic toxicity (LAST). *Do not use vasopressin. **Do not use lignocaine/procainamide to treat ventricular fibrillation. *** A bolus can be repeated once or twice and infusion rate should be doubled for persistent cardiovascular instability. An infusion should be continued for at least 10 minutes after achieving hemodynamic stability. Maximum dose is approximately 12 ml/kg. #ECMO—Extracarporeal membrane oxygenator, ##ECHO—echocardiography.*

Vasopressin should not be used as it can lead to pulmonary hemorrhage. Administer 20% lipid emulsion along with advanced cardiac life support or when neurotoxicity is evident. 1.5 mL/kg bolus followed by infusion at 0.25 ml/kg/minute IV (for patient≤70 kg) and 100 ml I.V., followed by the infusion of 200 to 250 ml I.V. over 15 to 20 minutes (for patient >70 kg). A bolus can be repeated once or twice and the infusion rate should be doubled for persistent cardiovascular instability. An infusion should be continued for at least 10 minutes after achieving hemodynamic stability. The maximum dose is approximately 12 ml/kg. Lipid emulsion improves cardiac conduction, contractility, and coronary perfusion by drawing the lipid-soluble local anesthetic out of the cardiac tissue (**Figure 4**).

Propofol should not be used as a substitute for 20 percent intralipid. Cardiopulmonary bypass may be necessary to allow time for the local anesthetic to diffuse from cardiac receptors if advanced cardiac life support and intralipid emulsion are not effective and may be lifesaving [37].

Evolution in the knowledge of the pathophysiology of CNB, better availability of monitoring devices, safer local anesthetic agents and treatment, and now the outcome in the last two decades are better. Institution of timely treatment leads to recovery of patients without any sequelae [1].

Unfortunately, the fact remains that despite timely treatment death may result [9].

CNB is used frequently all over the world and the number of patients developing CA is reported in the current literature. The detailed analysis of these cases will help to prevent catastrophes in the future.

6. When to anticipate cardiac arrest?

Unexpected CA may be observed in ASA grade I patients during spinal anesthesia [1]. Although the common belief is that CA usually occurs within the first 20–30 minutes, [32]; however, this is not true. Cardiac arrest has been reported within 12 to 72 minutes of spinal anesthesia and 180 min after epidural due to the residual sympathetic block [2, 5, 20, 35]. Lesser et al., while using automatic record keeping systems, observed that the mean interval to develop unexpected CA after the administration of spinal anesthesia was 58 minutes [53]. This finding is worrisome since after a short duration of surgical procedures, the situation can arise in the postoperative recovery room or ward when the situation might be worse. Close monitoring should be continued in the postoperative period [21].

Sudden bradycardia and CA may develop in a patient under vigilance with normal vital parameters. It is yet a mystery. Brown et al. reported sudden loss of consciousness and CA during patient chatting with the anesthesiologist [76]. These situations are often attributed as the consequence of mismanagement of the spinal technique and not due to an intrinsic risk of the technique itself [32].

Vigilance will not prevent the episodes of catastrophe but will help to provide timely treatment effectively and uneventful recovery of the patient.

Consequences of cardiac arrest during central neural block:

Despite well-conducted CPR efforts, high mortality rates (26%) were observed in two French reviews by AUROY et al. [15, 16]. Reports during 2001 revealed that 89% of patients had neurological damage or death [30]. The use of atropine with vasopressors resulting in successful resuscitation with minimal or no neurological damage is reported later on in many studies [9, 29, 53]. Caplan pointed out that those patients in whom epinephrine was used after 8 minutes of CA had a worse prognosis [7]. Ayuroy et al. reported that epinephrine was used in less than half of the patients with severe bradycardia and the mortality rate was 25% [48]. If the patient develops CA, prolonged resuscitation efforts may be needed, especially if a high sympathetic blockade is present and also for the treatment of LAST [32, 37].

Evolution in the knowledge of the pathophysiology of CNB, better availability of monitoring devices, safer local anesthetic agents and early treatment, and now the outcome have improved a lot in the last two decades [5, 6, 8]. After restoration of circulation, myocardial stunning may need vasopressor support or left ventricular assist device for refractory cardiac failure [27].

Patient with CA within 20 minutes after spinal has a better prognosis than delayed CA (more than 40 minutes), in which resuscitation is difficult due to blood loss during surgery, postural changes, and surgical procedures like cementing [16]. One should believe and intervene immediately if any detectable abnormalities are seen. Disbelief and insecurity are common patterns in this situation and may influence the outcome [32]. Therefore, the knowledge of the physiologic changes caused by CNB and its complications, proper patient selection, respecting the contraindications of the procedure, adequate monitoring, and constant vigilance are important deciding factors for outcome [8].

Anesthesiologists would face medicolegal problems following such incidents. It is necessary to maintain the proper documentation (preferably electronic medical record systems) of the preoperative status of patients, discussion during informed consent, details of technique, monitoring, perioperative events, consultation, and treatment. Anesthesiologists may be called upon long after the event and proper records will be very helpful to defend. Electronic medical record systems, reporting the adverse events to the national board, and finding out risk factors in a specific group of patients will help to improve patient safety in the future.

7. Discussion

Anesthesiologists are facing problems as well as challenges and have raised queries long ago about unexpected cardiac arrest during CNB which are yet to be answered. Future research is needed in these directions [32].

When CNB is administered, physiological changes are almost always present. It is not clear why do some individuals have these severe complications while the majority of others do not? Efforts to identify the definitive risk population in the preoperative period are needed. Hypovolemia is difficult to diagnose as well as assess clinically during perioperative period and therefore to treat up to the mark. Perioperative treatment of hypovolemia is essential, although it might not be the key factor in preventing hemodynamic instability during CNB [63]. It seems additional knowledge regarding the effect of reduced venous return, vasodilatation, and several reflexes mediated by intrinsic and/or neural mechanisms is needed. Are we missing any links?

We still do not understand what the definitive cause of sudden onset CA is during CNB when vital parameters in immediate pre-arrest period are normal. What happens during the period immediately preceding the cardiac arrest? Is automatic record keeping the answer? Unfortunately, information about this is inadequate and not provided by authors even while reporting an account of their cases recorded by automated anesthesia record keepers [53]. Finding out this information would be difficult without continuous invasive arterial blood pressure monitoring [32]. We need to find out whether this mystery can be solved by using advanced noninvasive hemodynamic monitors such as echocardiography, biomedical impedance, and inferior vena cava dimensions during the perioperative period.

One more dilemma is regarding the dosages of atropine. Whether we should use a higher dose of Atropine (1 mg) to treat bradycardia during CNB as recommended treating other bradyarrhythmias as per AHA 2020 guidelines? Should we use atropine during treatment of cardiac arrest following spinal anesthesia as there is no parasympatholytic action to adrenaline [1]. Atropine is not included in the treatment of asystole as per AHA 2019 guidelines [80].

Are cardiac arrests reported long after spinal/epidural anesthesia has been administered, really due to the anesthetic technique? How to establish the cause

effect relationship is a real challenge. CA is reported in postoperative period as late as 72 minutes after epidural anesthesia [5, 20]. What is the adequate timing for sending the patient back to the ward? Guidelines are not uniform and definitive. Is it enough to wait till the recovery of motor and sensory blocks? Sympathetic block outlasts motor block. Is it justified to send the patient inward when he is moving lower limbs or should we wait till the patient voids urine spontaneously? We have to find out user-friendly device to assess sympathetic block.

8. Summary and conclusions

Without any question, central neuraxial blocks are safe and are indispensable techniques in the practice of modern anesthesia. However, safety should not be taken for granted. Although the development of bradycardia is predictable, one should not forget that the possibility of acute evolution to CA is real. The severity of CA increases because ASA grade I young patients may be affected by undergoing elective surgeries unexpectedly.

The definitive etiology of CA following CNB is still not known and seems to be multifactorial. Sympathetic blockade producing a reduction in preload seems to be the founding stone and parasympathetic over activity, the final common pathway of the etiology of CA. Abrupt changes in patient position, intraoperative blood loss, use of vasodilators, release of tourniquet, etc., can trigger the effects resulting from reduced preload contributing to CA, particularly in elderly patients. Patients treated with beta-blockers, the "vagotonic" patients, and patients undergoing hip surgery are more likely to develop CA. Proper selection of patients and type of anesthesia, and adequate monitoring and constant vigilance are essential for early diagnosis, treatment, and successful outcome following CA. CNB technique has to be modified (unilateral spinal, CSE, or continuous spinal) along with invasive monitoring if these blocks are be administered in critical patients having compromised cardiac function. Atropine premedication would be useful in vagotonic patients. Preloading with colloids or co-loading with colloids or crystalloids, vasopressors, head low position may be helpful in preventing and treating hypotension. Early use of adrenaline for treating severe bradycardia, if atropine is not effective reduces the chances of CA and increases the chances of successful revival without subsequent morbidity. A better understanding of the physiologic changes caused by CNB and its complications, availability of safe local anesthetic drugs, and monitoring devices contribute to a successful outcome after CA and complete recovery of the patient. Sympathetic blockade causes significant vasodilatation, which might make CPR difficult, and long-duration CPR may be necessary. Effective and aggressive treatment is necessary to improve the prognosis following CA. ECMO, left ventricular assist device, non-invasive monitors such as abdominal USG (for the size of inferior vena cava), and echocardiography can be useful diagnostic tools if cardiac failure is persistent or CA is refractory. A high index of suspicion and respecting the contraindications of the spinal and epidural block are equally important. Continuous vigilance during and after the procedure till complete recovery after spinal and epidural is essential as unexpected CA can occur at any time during this period.

Electronic medical records and a national registry of cases of CA following central neuraxial block will enable to conduct the research and better understanding of risk factors and etiology of unexpected CA. With the popularity of spinal anesthesia and the reported frequency of these arrests, the potential impact of these interventions on further improving the safety of spinal anesthesia could be substantial.

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