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Anesthesia Management for Carotid Endarterectomy: Review Article

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Abstract

Atherosclerotic carotid artery disease is responsible from 20% to 25% of ischemic stroke events. Open carotid surgery and stent insertion are two main types of treatment procedures. Carotid endarterectomy (CEA) can be performed under general anaesthesia, regional anaesthesia (interscalen block, cervical plexus block either by landmark technique or by US guidance), combination of general and regional anaesthesia, regional anaesthesia with combination of periferic block. The aim of all anesthetic techniques is to prevent pain during the three painful periods (1. Skin incision, 2. Insertion of a retromandibular retractor, 3. Perivascular preparation) during CEA). All techniques have their own advantages and disadvantages. But there is no certain data about which one is superior to other. There

is no consensus on anaesthetic choice for CEA. At present regional anaesthesia versus general anaesthesia for patients undergoing CEA is still debate topic. Improvements in medical therapy, use of cerebral monitoring, better timing for surgery after ischemic events, better surgical techniques, increased use of ultrasound for regional anaesthesia improve procedural outcomes. Despite these improvements, anaesthesia management is still deciding according to surgeon and anaesthesiologist preferences, the patient's satisfaction and the conditions in the hospitals where we work.

Keywords: Carotid endarterectomy, anaesthesia techniques, general anaesthesia, cervical plexus block, local anaesthesia

Introduction

Atherosclerotic carotid artery disease, which leads to cerebrovascular diseases by embolization of atheromatous material or thrombotic occlusion, responsible from 20%

to 25% of ischemic stroke events⁽¹⁻⁴⁾. Open carotid surgery and stent insertion are two main types of treatment procedures⁽⁵⁾. Carotid endarterectomy (CEA) was first reported at St. Mary's Hospital, London, in 1954^(1,6) and



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since 1970, CEA accepted as the best treatment option in patients who has high grade carotid artery stenosis⁽⁷⁾. While CEA is accepted as “gold standart” in symptomatic patients with stenosis >70%; there is still a controversy in management of asymptomatic patients^(2,3,5,8,9). Stent insertion for carotid stenosis was first reported by Kerber et al. in 1980, approximately 30 years after the CEA⁽⁶⁾. Two main types of techniques are used in CEA: ventrojugular approach (the standart surgical technique) and retrojugular approach (improve patient tolerance and facilitate the surgical procedure)⁽⁵⁾. CEA is a preventive surgery and useful in symptomatic patients if the operation can be done within two weeks. On the other hand, patients undergoing CEA have so many comorbidities and prone to intraoperative hemodynamic fluctuations^(6,10,11-13). Although anaesthesiologists have a very limited time to optimize the patient, they should also select the most appropriate method for anaesthesia management^(10,14).

CEA can be performed under general anaesthesia, regional anaesthesia [interscalen block, cervical plexus block either by landmark technique or by ultrasound (US) guidance], combination of general and regional anaesthesia, regional anaesthesia with combination of periferic block^(8,10). The aim of all anesthetic techniques is to prevent pain during the three painful periodss (1. Skin incision, 2. Insertion of a retromandibular retractor, 3. Perivascular preparation) during CEA⁽¹⁵⁾. All techniques have their own advantages and disadvantages. But there is no certain data about which one is superior to other^(8-10,16-18). Radak et al. conducted a study to answer the question “Should the guidelines now be updated for CEA?”. They reported that improves after CEA procedures can be explained by improvements in medical therapy, more appropriate timing of CEA, the use of local anaesthesia and the se of preoperative cerebral monitoring and as well as improves in surgical techniques⁽⁶⁾.

The General versus Local Anaesthesia which is the only large randomized control study comparing general anaesthesia (GA) and regional anaesthesia (RA) (Landmark guided superficial cervical plexus block

or deep cervical plexus block) for CEA, conclude that there is no difference in myocardial infarction (MI), death and stroke when comparing GA with RA. On the contrary shunt requirement was 50% in GA group, 14% in RA group⁽¹⁹⁾. Moulakakis et al.⁽²⁰⁾ advocate to perform a study, compared CEA under RA without shunting, even if patients manifest neurological symptoms, compared with CEA under GA without shunting, answer the question: “The role of shunting in prevention of stroke.”

NSQIP (National Surgical Quality Improvement Program) study compared 30-day postoperative MI, stroke, and mortality between CEA under RA or local anaesthesia (LA) and CEA under GA. NSQIP study analysis suggests that CEA under GA has an increased risk of postoperative MI. They prefer patients to undergo CEA either by RA or LA, who have risk for postoperative MI⁽⁴⁾.

Malik et al. demonstrated that the use of RA versus GA in CEA is associated with decreased risk of postoperative pneumonia and reduced need for perioperative blood transfusions⁽¹⁸⁾. Markovic et al. reported that type of anaesthesia does not affect the outcome of surgical treatment of CEA but regional techniques are related with fewer respiratory complications, later requirement for first postoperative analgesic and awake patient after surgery (who can continue oral therapy earlier)⁽²¹⁾. Lobo et al. reviewed their 10 year practice of GA and locoregional anaesthesia for CEA. They showed that the number of studies about impact of anaesthesia type (evaluating delirium, cognitive impairment and quality of life after surgery) is very small. This indicates a need for randomized studies⁽²²⁾.

Cross-clemp intolerance (CCI) is a rare event during CEA. Hypertension and symptomatic carotid stenosis were independent and significant risk factors for CCI. Recently, in selective patients, carotis artery stending (CAS) has been used as alternative treatment for CEA who developed CCI during CEA. If patient has risk factors for CCI, GA is more suitable option as anaesthetic method because of risk for shunting or conversion to CAS⁽²³⁾. On the other hand, Dellaretti et

al. demonstrated that locoregional anaesthesia is a safe method for identifying patients with CCI and the mean degree of contralateral carotid stenosis was associated with CCI⁽²⁴⁾. Several CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) showed that CAS was associated with a significantly higher risk of stroke, CEA is associated with higher incidence of MI. In other CREST study performed by Hye et al. reported that risk of periprocedural MI was similar in patients undergoing CEA under RA and those undergoing CAS. But the risk was doubled in CEA under GA compared to the patients undergoing CAS⁽²⁵⁾. Hofer et al. assessed early sympathetic activity during CEA in ultrason guided-intermediate cervical plexus block with GA. Although, United States-Information and Communications Policy Bureau (US-ICPB) is a feasible, effective and safe form of RA for CEA; it induces temporary intraoperative hypertension and increase the stress hormone levels⁽²⁶⁾.

Anaesthesia methods for carotid endarterectomy:

1. General anaesthesia: GA is still the most preferred anaesthetic technique for CEA^(1,27).

Advantages of GA are:

- Control of ventilation (Tight control of arterial carbon dioxide concentration)^(1,3, 9,14,28)
- Cerebral protection afforded by volatile anaesthesia (especially during the cross-clamp)^(1,2,9,10,25,29)
- Airway security (Anaesthetist preference)^(1,7,9,10,28)
- Excellent and comfortable operation conditions (especially in patients with high carotid bifurcation)^(3,7,10,25,29)
- Prevent myocardial ischemia⁽¹⁰⁾
- Less stressful than a regional procedure^(3,25)
- Prevent patients from coughing and straining⁽¹⁰⁾
- Possibility of inducing hypothermia if required⁽⁹⁾

Disadvantages of GA are:

- GA necessitates shunt insertion more commonly than RA techniques^(3,7,30)
- Requires brain monitoring (stump pressure,

somatosensory evoked potential, transcranial Doppler, EEG and near-infrared spectroscopy, jugular venous oxygen, cerebral oximetry)^(3,7,9,14,30). These methods shows poor sensitivity and specificity according to awake patient, in terms of requirement for shunt placement^(9,11).

- Anaesthetic-induced circulatory depression is associated with labile blood pressure⁽³⁾ and necessitates greater vasopressor support (to ensure adequate cerebral perfusion pressure during carotid cross-clamping)^(3,7)

- Higher incidence in postoperative neurocognitive dysfunction^(7,27,28)

⇒ **Only general anaesthesia:** General anaesthesia can be performed by intubation (preferred) or by laryngeal mask airway (in difficult airway circumstance) for CEA^(7,10). General anaesthesia can be managed using inhaled or total intravenous agents Cerebral metabolic rate reductions are similar with propofol and halogenated volatile agents but cerebral blood flow is lower with propofol than halogenated volatile agent⁽²⁷⁾.

Kuzkov et al. reported that sevoflurane (induction and maintenance of anaesthesia with sevoflurane) is better than propofol (Total intravenous anaesthesia with propofol) to improve early postoperative cognitive dysfunction⁽³¹⁾. Wang et al. results offers low-dose sevoflurane with propofol in patients undergoing CEA reduces the incidence of myocardial injury in symptomatic patients after CEA⁽³²⁾.

Tsujikawa et al. reported that low-dose dexmedetomidine improves hemodynamic stability during the emergence and the recovery phases of general anaesthesia in patients undergoing CEA, in their randomized double-blind placebo-control trial⁽²⁹⁾.

⇒ **General anaesthesia with superficial cervical plexus block:** Addition of superficial-CPB to general anaesthesia provides lower VAS scores at discharge from the postoperative care unit⁽⁵⁾.

⇒ **Combined general anaesthesia with regional anaesthesia:** Recent studies reported that the quality of block should be evaluated according to the “patient

satisfaction”. So new trend is combination of RA with GA⁽⁹⁾.

⇒ **General anaesthesia with cooperative patient:**

It is like “wake-up” test performed during neurosurgical surgeries^(1,9). Anaesthesia is induced and maintained with propofol and remifentanyl. Before clamping, doses of drugs are reduced until patient obey the verbal comments⁽¹⁾. It was first used by Baldinelli during CEA⁽⁹⁾. The first pilot study, performed by Luchetti, reported that it guaranteed more stable hemodynamic conditions, better patient comfort and more effective analgesia as compared to superficial cervical plexus block alone during CEA⁽³³⁾. Then Bevilacqua defined a new technique: “Cooperative Patient General Anaesthesia” (Co.PA.Ge.A.), which is similar to Luchetti technique. In this technique, LA is injected to the anterior border of sternocleidomastoid muscle, instead of superficial cervical plexus block. In these three studies remifentanyl was used as opioid in general anaesthesia application and demonstrated as safe and with low rate of conversion to GA⁽⁹⁾.

Regional anaesthesia: “Right dose of the right drug placed in the right place” is a sentence that describes the “gold standart” in every nerve block^(1,9).

Advantages of regional anaesthesia are:

- Awake patient is the gold standart cerebral function monitoring^(1,3,9,11,12,14,17,28,34)
- Reduce cardiac and respiratory related morbidity^(1,3,30,34),
- Lower shunt insertion rate^(1,3,9,16,25,30),
- Shorten hospital stay^(1,3,14,17,25,27,34),
- Lower cost^(1,3,25, 27),
- Improves outcomes after surgery (better postoperative analgesia, reduce blood loss, lower risk of tromboembolic events)^(1,14,25),
 - Safer⁽¹⁾,
 - Safe method to identify the patients at risk for cross-clamp intolerance^(1,3,12),
 - Hemodynamic stability^(9,10,12,17,25,28),

- Preserved cerebral autoregulation^(3,10,28,30),
- Reduce vasopressor requirement⁽²⁸⁾,
- Reduces operative time⁽²⁵⁾,
- Disadvantages of regional anaesthesia are:
 - Needs patient collaboration^(3,7,28),
 - Procedural complications (diaphragmatic and vocal cord paralysis, neural injuries, epidural, subaracnoid or intravascular injection of local anaesthetics)⁽⁷⁾,
 - Urgent conversion of regional anaesthesia into general anaesthesia^(7,9,35),
 - Anxiety during the operation^(9,35).

⇒ **Cervical epidural block:** For CEA an epidural catheter is sited at C6-C7 level and a dilue LA solution is injected (exp: 0.25% bupivacaine)⁽¹⁴⁾. It provides suitable operation conditions but associated with major anesthetic complications (dural tap, epidural hematoma, direct spinal cord damage)^(10,14). But conversion to general anaesthesia is higher because of higher technical failure rate and higher rate of life-threatening complications^(5,14,36,37). Hakl et al. compared cervical epidural block and cervical plexus block (superficial and deep blocks) for failure rate and the frequency of anaesthesia related complications. Although both methods were acceptable for CEA, anaesthesia related complications are lower with CPB. Failure rates were similar between the groups⁽³⁷⁾.

⇒ **Posterior cervical paravertebral block:** Single injection, at C4 level, using nerve stimulator for blocking C2-4 dermatomes is another anaesthetic technique for CEA. By this technique, accidental vascular injury or injection is low⁽¹⁴⁾.

Cervical plexus block (CPB): CPB is commonly accepted RA technique for CEA⁽¹⁶⁾. Cervical plexus formed by anterior rami of four upper servical spinal nerves. It has two branches. 1. Superficial branches: provides cutaneous innervations to the head and anterolateral neck; 2. Deep branches: innervates muscles of the anterior neck, the anterior and middle scalen and the diaphragm^(5,10,14). Carotid surgery requires blockade of C2-C3-C4 cervical nerves^(5,11,38). Cervical fascia

classified as superficial and deep fascia. Deep cervical fascia has three layers: Superficial layer (investing layer), middle layer and deep layer⁽³⁹⁾. Figure 1 is showing the sides of injection for CPBS⁽³⁴⁾. Regional anaesthesia can be performed by landmark technique or Ultrasound (US) guidance⁽¹⁾. There is a difficulty in classifying the CPBs when landmark technique is used. Because exact location of the needle cannot be known. If needle perforates the investing layer of the neck, this block should be termed as “intermediate block” instead of “superficial block”. CPBs can be performed more thoroughly and safely by US-guidance⁽³⁹⁾. US guidance during performing the block, permits direct visualization of nerve and other structures^(1,9,17,38,39), observation of the needle and LA spreading during injection^(9,17,38,39), increases the efficiency (faster onset and longer duration) and success rate, lower puncture related complications (avoidance of accidental vascular puncture), reduces LA dose (prevents tissue swallowing)^(3,7,9-11,15,17,38-41). Disadvantages of CPB are palsy of the vagus nerve (which causes hoarseness, difficulty in swallowing, respiratory distress and are not clinically significant), conversion to general anaesthesia because of block related complications or inadequate analgesia⁽¹⁾. One of the major complication of RA is

the need for urgent conversion to GA especially with cervical epidural block and deep servical block^(1,3,8,10). Indications for conversion from RA to GA are both surgery (loss of consciousness at carotid clamping, shunt related complications) and anaesthesia (block failure, pain and restlessness, claustrophobia, systemic toxicity of LA, airway obstruction, accidental subarachnoid injection, diaphragmatic or vocal cord paralysis causing respiratory distress) related⁽⁸⁾. Pandit et al conducted a study to assess the complication rates associated with superficial (or intermediate) and deep (or combined deep plus superficial/intermediate)⁽³⁴⁾. They conclude that superficial/intermediate block is safer than any method that employs a deep injection. The main reason to convert GA with deep cervical plexus block (DCPB)/deep combined CPB is direct complication of the block. Blocks combined with SCPB provides better analgesia. Pasin et al. reported that RA is the first-choice in their center⁽⁸⁾. In their practice, CEA under RA is safe and associated with very low rate of conversion to GA. The exact concentration and volume of LA for nerve blocks is still debated⁽⁹⁾. The block that was performed with lower dose LA under US-guidance is effective as that LA has to surround the entire nerve, “Doughnut sign”, for

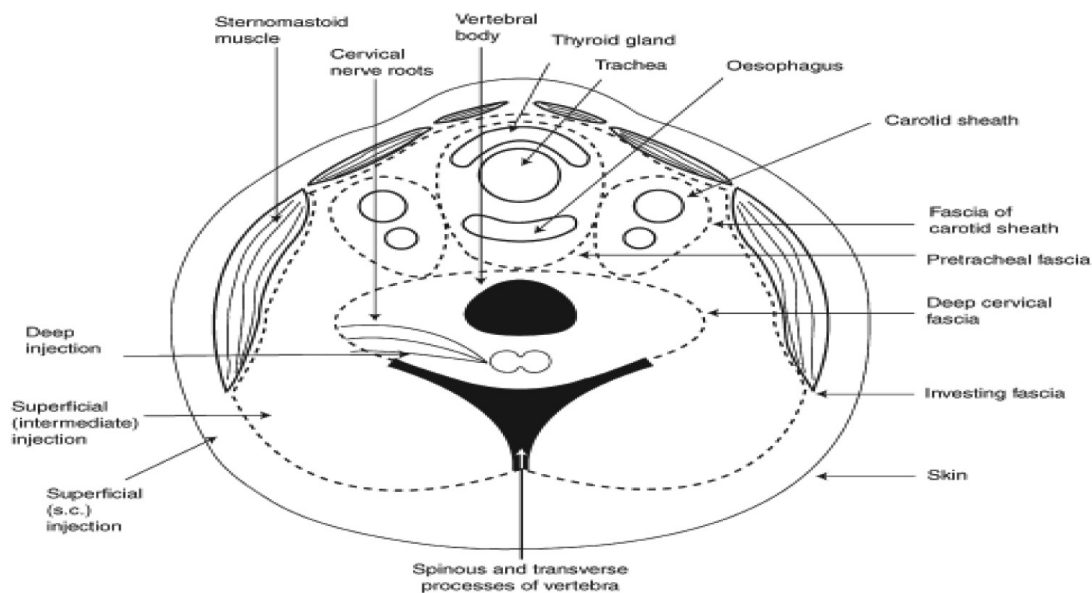


Figure 1. Cross-section of the neck at the C4 level, showing the sites of the injection of the deep, intermediate and superficial blocks

successful block⁽⁹⁾. Clinicians may prefer one block to another but there is no consensus which one is the best⁽³⁴⁾.

a. Superficial cervical plexus block (SCPB):

Local anaesthetic is administered to posterior border of sternocleidomastoid muscle, superficial to the investing layer of deep cervical fascia^(1,10,14,34,41,42). It is a simple subcutaneous injection with an easy technique as described by Murphy and Scott^(9,34,35,41). SCPB can be performed under traditional or US-guidance technique. Nevertheless, the success rate of the techniques, onset time and total anaesthesia related times are similar^(9,14). The advantages US-guided technique over landmark technique are visualize the spread of LA and avoid accidental puncture of structures⁽¹⁴⁾. While large volumes (20-30 mL) of LA are used for SCPB by landmark technique; lower volumes (10-15 mL) of LA are used for SCPB by US-guidance⁽²⁶⁾. It only provides analgesia, not paralyze the muscles^(9,10,14). According to Hariharan et al. experience, when SCPB is used alone, there is an increased need for supplementation of LA infiltration, especially during the dissection of the distal portion of ICA⁽⁴³⁾.

SCPB is associated with lower complication rates⁽¹⁰⁾. Complications related with SCPB are hematoma, infection, local anesthetic toxicity and inadvertent intravascular injection⁽¹⁾.

b. Intermediate cervical plexus block (ICPB): In 2003 Pandit et al. in 2004, Telford and Stoneham defined “intermediate-CPB” as the injection of LA between the superficial and deep cervical fascia^(9,14,38,39,42,44). Local anaesthetic is administered under the investing layer of the deep fascia and superficial to the prevertebral fascia^(1,10,34). ICPB can be performed by landmark (loss of resistance or pop technique) or US-guided technique^(38,42). Choquet first described US-guided ICPB⁽⁹⁾. US-guided ICPB can be performed anterior or posterior approach. Up to date, only one study described the technique of US-ICPB for CEA by using anterior approach. Authors reported that anterior approach is easy to perform than posterior approach^(38, 39,42). Complications of ICPB are similar with SCPB^(1,42). The authors showed that the deep cervical

fascia is permeable^(9,42). It means that ICPB is safer than deep-CPB^(9,42), paralyzes the muscles like deep cervical plexus block^(1,9,14,42) but it doesn't associated with serious complications like deep cervical plexus block^(9,10,14,42). Theoretically, expectation from ICPB is to reduce the complications related with DCPB^(14,38).

Leblanc et al. reported that ICPB by US-guidance was safe (even in patients receiving antitrombotic agents), simple to perform, provide effective anaesthesia (with real-time neurological assessment and adequate haemodynamic stability) for CEA⁽¹²⁾.

Barone et al. reported that ICPB by landmark technique is feasible, effective and safe for CEA with low perioperative and postoperative complication rates⁽⁴⁴⁾.

c. Deep cervical plexus block (DCPB): Local anaesthetic is administered under deep cervical fascia to cervical transverse process^(1,14) either by one single injection or multiple injection (three separate injections)^(10,14,16,34,42). The number of injections does not influence LA absorption as reflected by the Cmax and Tmax. Single injection technique can cause less pain during block and may be associated less systemic absorption of LA⁽⁴⁵⁾; but there is no relationship between the number of injections and overall block efficacy⁽¹⁴⁾. DCPB can be performed by landmark or US-guided technique⁽⁹⁾. There are two approach for US guided technique: vertebral artery loop which can be easily identified by US, represents an accurate landmark for C2 transvers process^(9,14) or the longus capitis can be identified as a landmark⁽⁹⁾. It provides exact analgesia but it is technically difficult and associated with serious complications (epidural, subarachnoid, subdural or vertebral arter injection, seizures, recurrent laryngeal nerve palsy, phrenic nerve palsy, large neck hematoma, Horner's syndrome, higher conversion rate to GA^(1,3,5,9,10,14,17,44). By the introduction of US-guidance technique, the DCPB has become a relatively safe and simple procedure⁽⁴²⁾.

While performing a deep CPB increasing number of injection from 1 to 3, increasing the injected volume from from 10 to 40 mL, observing a paresthesia, using

neurostimulation or US guidance would not confer any clinically advantage over superficial CPB alone⁽⁵⁾.

C1. Continous deep cervical plexus block: This block is considered in high risk cases in which the procedure is expected to prolong⁽¹⁴⁾.

⇒ **Combined block:** Combined blocks appears as equally efficacious as SCPB⁽¹⁴⁾.

a. Superficial and deep cervical block: If locoregional anaesthesia is choiced for CEA, combined superficial and deep CPB is preferred⁽⁴⁴⁾. Although some authors demonstrated that combined superficial and deep CPB is more effective in producing muscle relaxation; others demonstrated that CEA can be successfully performed under S-CPB alone or combined block^(9,14). Muscle relaxation with DCPB has not been shown to be important clinically⁽⁴²⁾. Kavaklı et al. compared combined block (US-guided superficial and deep CPB) with US-ICPB for CEA⁽³⁸⁾. Based on their result, combined block requires less analgesic requirement, provides lower VAS scores and higher patient satisfaction than US-ICPB.

b. Intermediate and deep cervical block: Another form of combined block^(14,34).

c. US-guided ICPB combined with carotid sheath infiltration: Madro et al. compare infiltration anaesthesia with US-guided ICPB combined with carotid sheath infiltration for CEA. They reported that combined block improves patient and surgeon comfort, safer, relatively simple, easy to master, requires little time to perform⁽³⁶⁾.

⇒ **US-guided carotid sheath block:** Injection of LA to the carotid artery by US-guidance, the place of the operation, called as carotid sheath block instead of cervical plexus block by Casutt et al^(11,17,41). But Martusevicius et al. named the block as “locoregional anaesthesia” and Rössel et al. named the block as “perivascular regional anaesthesia”. All authors reported that US-guided carotid sheath block can be performed rapidly, sufficient for surgery, lower supplemental LA during surgery and an alternative approach with lower complication rate^(9,11,17).

⇒ **US-guided high interscalene plexus block:** High-resolution US-guided (17.5-MHz device) high interscalene plexus block for CEA was first reported by Roessel et al. Although they reported that they were not encountered with complications, the small study group (n=14) does not allow meaningful conclusion regarding safety of the procedure⁽⁴⁶⁾.

⇒ **Regional anaesthesia with combination of peripheric block:** Performing peripheral blocks with US-guidance reduce incidence of LA toxicity compared to peripheral blocks that were performed without US-guidance⁽³⁸⁾. Combining S-CPB with fascial nerve block may reduce the pain associated with prolonged use of retractor at the cephalic end of the incision⁽⁹⁾. Seidel et al. combined US-guided ICPB with new subplatysmal injection technique for peripheral fascial nerve block⁽¹⁵⁾. They reported that US-guided block is feasible, associated with high success rates, especially during initial skin incision. In another study, Seidel et al. combined US-guided ICPB with perivascular LA infiltration; but they reported no clinical benefits of an additional periarterial LA infiltration⁽⁴⁰⁾. Blocking mandibular division of trigeminal nerve by intraoral approach, alleviate the submandibular and dental pain which does not respond to administration of LA. It may be useful in patients with high carotid bifurcation or where atheromatous plaque extends cranially in the internal carotid artery^(14,47). Ozturk et al. compared the effect of combining CPB (US-guided SPCB and DCPB) with mandibular block for CEA. They reported that combining CPB with mandibular block provides better intraoperative pain control (lower intraoperative VAS scores, reduces intraoperative supplemental LA needs and intravenous analgesic requirement) and greater patient satisfaction than cervical plexus alone⁽⁴⁷⁾.

⇒ **Awake test under regional anaesthesia with sedation:** Anxiety, uncomfortable neck position, traction pain are the problems that we encounter when we use RA alone for CEA^(28,47). Sedation can be administered as supplement to regional blocks to overcome these limitations. Sedative agents have been used are: opioids (remifentanyl,

fentanyl), alfa-2-agonists (clonidine, dexmedetomidine), propofol^(3,5,14), midazolam⁽⁵⁾, historically, butyrophenones (droperidol, haloperidol)^(3,14) or with their combinations (midazolam-fentanyl)⁽⁵⁾. “Awake test” is the most reliable method for detecting hypoperfusion⁽²⁸⁾. Studies in literature that compare RA with sedation with dexmedetomidine versus conventional sedation (fentanyl, remifentanyl or midazolam), prefers dexmedetomidine as sedative agent for CEA with RA. Because dexmedetomidine is a selective alpha-2 adrenoreceptor agonist with sedative, analgesic and anesthetic sparing effects. It does not suppress the respiratory function, maintains hemodynamic stability and patients can be awakened easily after cessation of its use^(14,28,29).

2. Local anaesthesia: Local anaesthesia can be performed by two technique: Simple layer by layer to approach or four step approach (intradermal injection parallel to the anterior border of sternocleidomastoid muscle, subplatysmal injection, identification and individual infiltration of the cervical nerves and topical carotid anaesthesia)^(5,14).

Bhattathiri et al. studied effect of awake CEA under local anaesthesia with sedation on peri-operative blood pressure⁽¹³⁾. Their study showed that local anaesthesia maintains a stable blood pressure during and immediately after CEA.

Choice of local anaesthetic and adjuvants

Other issue is LA choice for RA. Lidocaine, mepivacaine, bupivacaine, ropivacaine, levobupivacaine are suitable agents for RA^(1,5,48). If a mixture of LA is used, the total amount should be carefully predetermined as their toxicity is additive. Where bupivacaine offers the longest time, the mepivacaine the shortest time for first analgesic requirement⁽⁵⁾.

Cristallı et al. used ropivacaine versus levobupivacaine for cervical plexus block (deep and superficial block by anatomic landmark) to compare arterial blood pressure and incidence of hypotension. That reported ropivacaine as a first drug choice for CPB⁽⁴⁸⁾.

Adjuvants may be added to LA to enhance the block efficiency⁽⁹⁾. Epinephrine can be added to LA solution^(1,5). While epinephrine 1/200,000 (5 mcg/mL) increase the heart rate 15%, epinephrine 1/300,000 (3.75 mcg/mL or 2 mcg/kg) not⁽⁵⁾. Clonidine, alpha-2 receptor agonist, induce direct peripheral effects on action potentials or nerve fibres, can be added as adjuvant to LA. It decreases onset time, decreases intraoperative LA and analgesic requirement^(5,9,14). Fentanyl (50 mcg) accepted as an analgesic adjuvant to LA. Increase the quality and duration of the cervical block, decrease sedation requirement during CEA and delay the first analgesic requirement after operation⁽¹⁴⁾. Sindjelic et al. combined 10 mL bupivacaine 0.5% and 4 mL lidocaine 2% with the addition of either fentanyl 1 mL or saline placebo for deep cervical plexus block. They reported that addition of fentanyl to LA mixture enhanced the quality and duration of CPB⁽⁴⁹⁾.

Conclusion

There is no consensus on anaesthetic choice for CEA. At present RA versus GA for patients undergoing CEA is still debate topic. Improvements in medical therapy, use of cerebral monitoring, better timing for surgery after ischemic events, better surgical techniques, increased use of ultrasound for regional anaesthesia improve procedural outcomes. Despite all, anaesthesia method should be decided by considering the personal preferences of the surgeons and anesthesiologists, the patient’s satisfaction and the conditions in the hospitals where we work.

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Ethics

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Management of Prosthesis-patient Mismatch After Aortic Valve Replacement

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Abstract

Valve prostheses have played an important role in the past four decades in the management of patients with valvular heart disease. Many of the devices have been used for valve replacement and they have introduced new clinical problems. One of these problems is prosthesis-patient mismatch (PPM) which is associated with increased mid- and long-term mortality after surgical aortic valve replacement (AVR) and transcatheter aortic valve implantation. The aim of this study was to systematically review the literature on the importance,

prevention and feasibility of PPM in AVR and percutaneous-AVR. The articles about PPM published between 2003-2018 were analyzed. The results of surgical and transcatheter methods were discussed together to prevent PPM.

Keywords: Surgical aortic valve replacement, percutaneous aortic valve replacement, prosthesis-patient mismatch, valvular heart disease, transcatheter aortic valve implantation

Introduction

Prosthesis-patient mismatch (PPM) was first described in 1978 by Rahimtoola as an effective prosthetic valve area is smaller than a normal human valve area⁽¹⁾. PPM results in an abnormally high postoperative transvalvular

gradient⁽²⁾. Increased transvalvular gradient causes structural deformation of the prosthesis with calcific degeneration, thrombosis, pannus, or endocarditis⁽³⁾.

Effective orifice area (EOA), cross-sectional area of the trans-prosthetic blood flow jet, is easily measured



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with Doppler echocardiography. Indexed EOA (EOAI) which is gained by dividing patients' EOA to the body surface area [EOAI=EOA/body surface area (BSA)] is optimal parameter to determine PPM⁽⁴⁾. An EOAI <0.85 is now considered the threshold for PPM. If this value is between 0.65 and 0.85, it is classified as moderate PPM and if it is below 0.65 it is classified as severe PPM⁽¹⁾.

After surgical aortic valve replacement, prevalence of moderate and severe PPM was reported as 20-70% and 2-11%, respectively⁽⁵⁾. It has been shown that PPM following AVR has some negative effects on left ventricular (LV) mass regression, recovery of LV systolic function, functional class, quality of life and bioprosthetic valve durability. While left ventricular mass regression was 23% in patients with EOAI >0.8 cm²/m², it was reported as 4.5% in patients with an EOAI <0.8 cm²/m²⁽⁴⁾. Furthermore, PPM also is associated with increased rates of perioperative and long term morbidity and mortality. Late congestive heart failure, bleeding complications caused by abnormalities of the von-Willebrand factor and early structural valve deterioration might develop related to the PPM⁽⁶⁾.

There are two theories for the development of PPM: Decreased size of the aortic annulus due to calcification and fibrosis and relative obstruction of the structural support of the prosthesis⁽⁷⁾. Preoperative risk factors for the development of PPM are old age, smaller prosthesis, valvular stenosis, increased BSA and body mass index⁽⁴⁾.

Transcatheter aortic valve implantation (TAVI), which is used in the treatment of severe aortic stenosis, has been increasingly used in recent years and it has comparable results in the patients with moderate surgical risk compared to surgical AVR^(8,9). In the literature there is restricted information about PPM after the TAVI procedure. In this article, we have analyzed a systematic review of the incidence, predictive approaches and outcomes of PPM in a comprehensive and quantitative way to be valid for both methods.

Materials and Methods

In this review, we analyzed English-language literature for reported PPM and aortic valve replacement by PubMed[®] search using the terms of "aortic valve replacement, PPM and EOA". We reviewed published original articles about "PPM and AVR between 2003-2018". Reference lists of original articles were also included. Case reports and congress presentations were not included.

Results

There were almost 50 studies about PPM in the literature. The study included 42 eligible studies after extracting the overlapping articles. PPM is a strong and independent predictor of short-term mortality in the patients who had undergone AVR. The mortality rates in non-significant, moderate and severe PPM were reported as 3%, 6% and 26%, respectively. Compared to non-significant PPM, severe PPM 11-fold increases the mortality risk⁽¹⁰⁾.

Impact of PPM is more important in early term mortality rather than the late term mortality since left ventricle is more vulnerable during the early postoperative period. Operative mortality was increased 1-2% with PPM⁽¹¹⁾. In the patients with poor left ventricular function, increased afterload does not well tolerated⁽⁴⁾. The mortality rate of PPM in the patients with preoperative left ventricular ejection fraction (LVEF) below 40% is 77 times higher than the patients with normal LVEF (Figure 1)⁽¹⁰⁾.

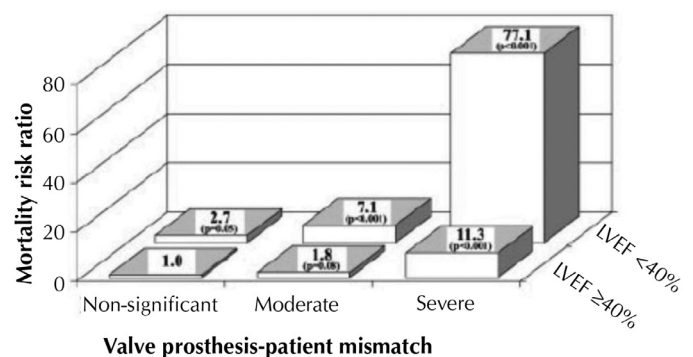


Figure 1. Mortality risk of patients according to the prosthesis-patient mismatch and ejection fraction⁽¹⁰⁾
LVEF: Left ventricle ejection fraction

The impact of PPM on late term survival is still controversial. Several recent studies confirm that PPM is independent risk factor for reduced late survival, where as others report the opposite. Head et al. found that there was a statistically significant increase in all-cause and cardiac-related mortality in moderate and severe PPM in the long-term with the evaluation of more 27,000 patient and 133,000 patient years (Table 1)⁽¹²⁾. Similarly EOA <0.75 cm²/m² is reported a risk factor for mortality after 12 years follow-up of the 2,500 patients⁽¹³⁾. Twelve years survival of minimal, moderate and severe PPM was reported as 77%, 63% and 47%, respectively⁽⁴⁾.

In the evaluation of 312 patients with stress echocardiography at postoperative six month, Bleiziffer et al. found that exercise capacity was significantly decreased in patients with PPM⁽¹⁴⁾. In addition it was clearly demonstrated that structural valve deterioration was more prominent in the patient with PPM and started two or three years after the surgery⁽¹⁵⁾.

How can we prevent the development of PPM?

After calculating the patient’s body surface area (BSA), we can multiply by 0.85 cm²/m² to calculate the minimum EOA required to avoid PPM using the appropriate prosthesis. Bioprosthesis have smaller EOA than the mechanical prosthesis⁽⁷⁾. It should be kept in mind while deciding valve prosthesis especially in the patients with small aortic annulus. EOAs of different types of prostheses are shown at Figure 2⁽¹⁶⁾. Trifecta valve has 10-

fold lower risk for the development of PPM⁽¹⁷⁾. If there is a risk of moderate to severe PPM, it is an option to implant prosthesis with a larger EOA (mechanical, prosthetic, homograft) or to perform aortic root enlargement to place larger valve prosthesis. Aortic root enlargement procedures increase the operative mortality 3.5-7%⁽¹¹⁾. Although increased surgical risks, root enlargement has excellent results in the follow-up period. According to some authors root enlargement does not increase the rates of 30-day mortality, stroke, reoperation for bleeding or myocardial infarction. In the evaluation of 114 patients, it was concluded that aortic root enlargement might be performed with minimal additional risk to prevent PPM in the patients with small aortic root. In a study the operational risk of aortic valve replacement with or

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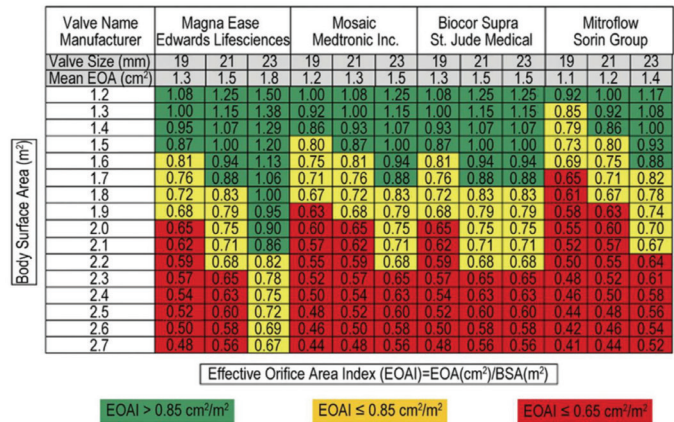


Figure 2. Effective orifice area of different valve prosthesis⁽¹⁶⁾
EOA: Esophageal obturator airway, BSA: Body surface area

Table 1. Results of studies about prosthesis-patient mismatch

Study	n	PPM incidence	Surgical method	Short term results	Long term results	Conclusion
Blais et al.	1266	38% moderate or severe	AVR	Mortality: Severe PPM 26% Moderate PPM 6%		Independent risk factor of short term mortality
Head et al.	27186	44.2%	AVR		In severe PPM HR increased to 6.5	Increased all-cause and cardiac-related mortality in long term
Bleiziffer et al.	312	34.3%	AVR		Reduced exercise capacity	Reduced exercise capacity
Flemeng et al.	648	49% Moderate 4% Severe	AVR			Independent risk factor for SVD

AVR: Aortic valve replacement, HR: Hazard ratio, PPM: Prosthesis-patient mismatch, SVD: Structural valve deterioration, n: Number of the patients

without root dilatation was investigated in 2,300 patients to protect from PPM. Finally, it was found that aortic root enlargement itself did not increase the risk of surgery, but was mostly performed among high-risk patients⁽¹⁸⁾. In conclusion recent new generation prosthesis decreased requirement of aortic root enlargement procedures with better hemodynamics. In the comparison of 339 patients with Trifecta valve and 963 patients with other bioprosthesis the PPM rates was found extremely low in the patients with Trifecta prosthesis. All differences; EOA, EOAI and mean transaortic gradients were statistically significant lower with Trifecta bioprosthesis⁽¹⁷⁾.

Can TAVR be an alternative to avoid PPM?

Some recent studies have reported that TAVI is superior to surgical AVR to provide valve hemodynamics in a subset of patients with small aortic annulus⁽¹⁹⁾. After TAVI procedure in the patients with severe aortic stenosis and small aortic annulus hemodynamic and clinical results were found to be acceptable and severe PPM was observed in only 6% of the patients⁽¹⁹⁾. In other study the rate of the moderate and severe PPM of TAVI procedure was reported as 31% and 9%, respectively. And, 5-year survival rates were similar between the patients with PPM and without PPM⁽²⁰⁾. However, improvement of the functional status was 98.5% without PPM and 63%

with PPM⁽²¹⁾. In the comparison of the hemodynamic performance of TAVI and surgical AVR; TAVI was found to have superior hemodynamic performance in terms of prevention severe PPM and to decrease transprosthetic gradient. In this study rate of PPM was 11% for TAVI, 26% for stented AVR, 28% for stentless AVR⁽²²⁾.

Similarly in the PARTNER study, that comparing the rate of PPM between the TAVI and surgical AVR and evaluating effect of PPM on LV hypertrophy and mortality regression, PPM was more common after surgical AVR (Table 2)⁽¹³⁾.

What about sutureless valves?

Sutureless valves easily replaced with minimally invasive approach. It gives opportunity to extract calcified tissue, but has disadvantages of requirement of cardiopulmonary bypass. Sutureless valves have advantages in geriatric patients, especially those with small aortic annulus compared to conventional biological valves in the short and mid term⁽²³⁾. These valve prosthesis are also ideal for patients with excessive calcification.

Conclusion

Surgery is still the gold standard for the treatment of aortic stenosis. Surgical treatment of aortic valve

Table 2. Results of studies comparing transaortic valve implantation and aortic valve replacement*

Study	n	Surgical method	Aortic root size	Prosthesis	PPM (%)	Conclusion
Kalavrouziotis et al.	35	TAVI	<20 mm	23 mm Edwards Saphien	Severe 6%	Good postoperative valve hemodynamics in high risk patients with AS and small annulus
Clavel et al.	50	TAVI	Mean 20.1 mm	Crible Edwards/ Edwards Saphien	7 (<20 mm) 14 (>20 mm)	Lower transvalvular gradient and severe PPM with TAVI
	50	AVR-SL		Medtronic	36 (<20 mm) 18 (>20 mm)	
	50	AVR-ST		Edwards	29 (<20 mm) 25 (>20 mm)	
Pibarot et al.	270	AVR	<20 mm		19 severe	Higher severe PPM with AVR in high risk patients and severe AS
	304	TAVI-RCT			33.7 severe	
	1637	TAVI-NRCA				

AS: Aort stenosis, AVR: Aortic valve replacement, AVR-SL: Aortic valve replacement-stentless, AVR-ST: Aortic valve replacement-stented, TAVI: Transaortic valve implantation, RCT: Randomized controlled trial, PPM: Prosthesis-patient mismatch, n: Number of the patients, NRCA: Non-randomized continued access

might be performed both by conventional surgery and percutaneously with lower perioperative mortality and morbidity rates. After the surgery, quality of life improves in patients of all ages accept surgical with lower operative risk.

Transprosthetic gradient and EOA is important to relief the symptoms and improve functional capacity after the surgery. To indicate optimal surgical procedure and prosthesis is important to improve postoperative outcome and patients' satisfaction. The most important complication after AVR is PPM. PPM is a widespread and modifiable risk factor that causes poor hemodynamic functions in postoperative period, less recovery of ventricular functions, more cardiac events and lower survival. The EOAI foreseen to avoid PPM must be systematically calculated. In this description EOAI is indicator of the effective valve area. Pibarot and Dumesnil declared three steps to reduce the PPM after the aortic valve surgery: Calculating BSA, determining the minimum ($0.85 \text{ cm}^2/\text{m}^2$) EOA to provide the minimum required EOAI, selecting the appropriate prosthesis⁽¹³⁾. Decision of EOAI is changes according to patient's clinical condition and expectation from the surgery. While moderate PPM might be acceptable in elderly and sedentary patients with normal EF, avoiding of PPM is important in the young and active patients⁽⁴⁾.

The prevalence of severe PPM tends to decrease in the last decade due to awareness and recognition of PPM, more widespread implementation of preventive strategies, improved design and hemodynamic performance of new generation prostheses. In patients who are expected to develop PPM, alternative options should be considered in the light of the patient's general clinical status. In the last decade, several tissue heart model valves have been introduced in line with the developing technology. Thrombogenicity and valve destruction risk is decreased with new generated bioprosthetic valves with improved hemodynamic performance. The Trifecta aortic valve, developed as a new generation bioprosthesis, decreased the incidence

of PPM by approximately 10 times compared to other bioprostheses. PPM is almost eliminated in patients with aortic annulus 21 mm or greater with this new generation valve⁽¹⁷⁾.

Percutaneous AVR is a good alternative in the patients with comorbid factors. After the TAVI procedure patients had larger EOAI than the patients with surgical AVR⁽²²⁾. This result is encouraging to perform TAVI procedure in high-risk patients.

PPM is associated with increased postoperative morbidity and mortality during the aortic valve replacement. Management of the surgical procedure is important to avoid PPM. Evaluating of the patient's clinical condition and determining optimum prosthesis improve postoperative outcomes.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.D., Concept: E.D., Design: E.D., Data Collection or Processing: İ.D., Analysis or Interpretation: E.D., İ.D., M.U., Literature Search: E.D., İ.D., M.U., Writing: E.D., İ.D., M.U.

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Is There A Correlation Between Left Atrium Diameter and NT-ProBNP Levels in Resistant Hypertension?

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Abstract

Objectives: Resistant hypertension (RHT) defines uncontrolled blood pressure despite appropriate treatment and identifies a high-risk population, which may benefit from different diagnostic and therapeutic approaches. This study has investigated the relationship between left atrial diameter (LAD) and N-terminal pro-brain type natriuretic peptide (NT-proBNP) levels in true RHT patients with sinus rhythm.

Materials and Methods: The outpatient data of Kemalpaşa State Hospital's cardiology clinic has been reviewed retrospectively. The patients with RHT are included but patients with secondary hypertension, pseudo-RHT, atrial fibrillation and left ventricle ejection fraction <50% are excluded from analysis. Age and gender specific cut-off levels have been used for NT-proBNP.

Results: Among 74 true RHT patients, 48 were female.

The mean age was 61.9±11.2 years. Mean LAD was 40.9±4.0 mm and mean NT-proBNP was 330.3±394.9 pg/mL. Larger LAD was correlated to higher levels of NT-proBNP ($r=0.451$, $p<0.001$). Even after controlling for age, gender, heart rate, systolic and diastolic blood pressures, partial correlation was continued between LAD and NT-proBNP ($r=0.234$, $d.f=67$, $p<0,05$).

Conclusion: The current study showed that larger LAD is related to higher levels of NT-proBNP in RHT, which may allow us to use simple echocardiographic parameter to diagnose high-risk patients and hypervolemia instead of NT-proBNP, an expensive biomarker. Because of single-center results and limited number of patients, further studies are needed.

Keywords: Resistant hypertension, NT-proBNP, left atrial diameter



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Introduction

Resistant hypertension (RHT) is defined as failure to achieve blood pressure goals under recommended treatment strategy in adherent patients. RHT definition requires that the recommended treatment strategy contains appropriate lifestyle and optimal or best tolerated doses of at least three drugs with the condition that at least one being diuretic⁽¹⁾. While the underlying mechanism of RHT is poorly understood, it is known that the patients with RHT are at higher risk of target organ damage and cardiovascular events⁽²⁾.

Left atrial (LA) enlargement is a common finding in hypertension and considered closely related to the diastolic dysfunction of left ventricle. LA enlargement is also crucial in atrial fibrillation (AF), which carries high risk for stroke and mortality⁽³⁾. According to the Framingham study, a 5 mm increase in LA diameter (LAD) led to a 39% increase in the AF-incidence⁽⁴⁾.

Natriuretic peptides involve volume homeostasis and cardiac remodeling and excite attention for risk stratification in various clinical scenarios. According to Framingham Offspring Study, brain natriuretic peptide (BNP) level above 80th percentile was associated with increased risk for major cardiovascular events, including heart failure and mortality⁽⁵⁾. Masugata et al. reported that as an echocardiographic parameter, LAD correlates best with BNP in well-treated hypertensive patients⁽⁶⁾. Such as BNP, N-terminal pro brain natriuretic peptide (NT-proBNP) is also a predictor of mortality in hypertension and in secondary prevention. It is shown that NT-proBNP correlates with left ventricular mass index⁽⁷⁾.

In the present study, we aimed to investigate the correlation between LAD and NT-proBNP in RHT population and searched for the answer if LAD, a basic echocardiographic parameter, could be used instead of NT-proBNP, an expensive biomarker, to identify the highest risk patients in the high-risk population of RHT.

Materials and Methods

The outpatient data of Kemalpaşa State Hospital is screened retrospectively through the hospital communication system (HCS), Probel. System records, which contain data about patient demographics, laboratory and imaging records, prescription and adherence information of patients, who applied to the cardiology outpatient clinic between January and September 2015, are reviewed. Data of 1057 hypertensive patients older than 18 years in both genders is screened retrospectively. RHT is defined as 1) lack of blood pressure (BP) control despite three drugs, one diuretic or 2) need for more than three drugs (four or more) to control BP in adherent patient, in whom secondary hypertension (HT) and white-coat HT are excluded. To avoid any misevaluation, patients with moderate to severe valvular disease, systolic heart failure as left ventricle ejection fraction (LVEF) <50% and AF are excluded. Also patients with a creatine level of >1.5 mg/dL are excluded because this level of creatine is considered as a manifestation of chronic kidney disease. After applying all the criteria, 74 patients with RHT on sinus rhythm are included to analyze.

All data is collected through the HCS according to the International statistical classification of diseases and related health problems. Patient's demographics, such as age, gender, patient's complaint at application, accompanying illness, systolic and diastolic BP in the office is obtained from the patient's application page. For ECG and echocardiographic parameters such as LVEF, left ventricle hypertrophy (LVH), left ventricle diastolic dysfunction (LVDD), LAD and diameter of ascendant aorta, imaging studies are used. Blood and urine biochemistry, fasting glucose, renal and liver function tests, lipid panel, thyroid function tests, NT-proBNP, microalbuminuria, are collected from laboratory studies. Medication and adherence are controlled through the www.medeczane.gov.tr, if the patients refilling their pills appropriately.

NT-proBNP measurement is made with Cobas® system and the Elecsys proBNP II assay; Roche Diagnostics GmbH. Reference ranges for NT-proBNP are defined

according to prospectus information in 97.5th percentile, which differ with age and gender. Reference values are given in the Table 1.

Statistical Analysis

In the statistical analysis, all continuous measures are expressed as mean ± standart deviation. Frequencies and percentages are reported for categorical variables. Statistical analyses are performed with the IBM SPSS Statistics 22 software package. Associations between variables are tested by Pearson’s correlation (Pearson’s coefficient of correlation “r”). A p value <0.05 is considered statistically significant.

Compliance with ethical standards

The present study is designed as a retrospective archive screening study. For this study, no external funding is received. All authors declare no conflict of interest. Ethic approval for the study is obtained from the Clinical Research Ethical Board of Ege University School of Medicine on 22.11.2016 with the number 16-10.1/3. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

After screening outpatient data and applying the inclusion criteria, 74 patients are defined as true RHT on sinus rhythm. Exercise intolerance and fatigue were the

most frequent complaints according to the application reports. Among 74 patients, 48 (64.9%) were female and 26 (35.1%) were male. The mean age was 61.76±11.27 years. All the 74 patients were receiving adequate doses of a renin-angiotensin system blocker, either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, plus a diuretic. The third pill was a beta-blocker in 21 patients and a calcium antagonist in 12 patients. The remaining 41 patients needed more than three drugs. Type 2 diabetes mellitus was present in 25 patients. None of the diabetic patients were taking high doses of glitazones, which is known as a specific factor for hypervolemia, and only two patients were receiving intensive insulin treatment.

Mean systolic and diastolic blood pressures were 172.55±20.21 and 93.31±13.74 mmHg. Patient’s imaging studies are reviewed for echocardiographic parameters. All the 74 RHT patients had LVH and LVDD. LVEF, ascendant aorta width and LAD were 57.36±2.89%, 35.41±3.73 mm and 40.96±4.09 respectively. The mean NT-proBNP level was 330.30±394.96 pg/mL. All the remaining demographics are given in the Table 2.

Table 2. Demographics for RHT patients on sinus rhythm

RHT patients on sinus rhythm (n=74, 48 female and 26 male)	
Age (years)	61.76±11.27
Heart rate (bpm)	72.74±11.87
Systolic BP (mmHg)	172.55±20.21
Diastolic BP (mmHg)	93.31±13.74
NT-proBNP (pg/mL)	330.30±394.96
LAD (mm)	40.96±4.09
LVEF (%)	57.36±2.89
Ascendant Aorta (mm)	35.41±3.73
Fasting glucose (mg/dL)	120.31±44.31
Urea (mg/dL)	35.54±13.10
Creatinin (mg/dL)	0.96±0.21
Potassium (mmol/L)	4.34±0.46
Low density lipoprotein (mg/dL)	114.37±36.94
Triglyceride (mg/dL)	165.19±70.84
C-reactive protein (mg/dL)	5.06±4.91

RHT: Resistant hypertension, BP: Blood pressure, LAD: Left anterior diameter, LVEF: Left ventricular ejection fraction
Demographics are given as arithmetic mean ± standart deviation

Table 1. Age and gender specific cut-off levels of NT-proBNP

Age	NT-proBNP for male	NT-proBNP for female
18-44 years	<85.8 pg/mL	<130 pg/mL
45-54 years	<125 pg/mL	<249 pg/mL
55-64 years	<210 pg/mL	<287 pg/mL
65-74 years	<376 pg/mL	<301 pg/mL
>75 years	<486 pg/mL	<738 pg/mL

NT-proBNP: N-terminal pro b-type natriuretic peptide,
Reference ranges for NT-proBNP are defined according to prospectus information in 97.5th percentile, which differ with age and gender

After group demographics, the relationship between LAD and NT-proBNP is investigated and Pearson's correlation analysis is performed (Table 3). Between LAD and NT-proBNP, a pairwise correlation ($r=0.451$, $p<0.001$) is found. After controlling for age, gender, heart rate, systolic and diastolic BP, a partial correlation ($r=0.234$, $d.f=67$, $p=0.049$) is still remained. The correlation between age and NT-proBNP is already known. Therefore cut-off values based on NT-proBNP are qualified by age. Also in the present study, this relationship is well observed. There was a pairwise correlation between age and NT-proBNP ($r=0.670$, $p<0.001$) and the correlation still remained after controlling for gender, heart rate, systolic and diastolic BP ($r=0.590$, $d.f=67$, $p<0.001$). At last, the correlation between LAD and age is investigated. At first glance, there was a pairwise correlation between LAD and age ($r=0.469$, $p<0.001$) but after controlling for gender, heart rate, NT-proBNP, systolic and diastolic BP, the partial correlation is disappeared ($r=0.175$, $d.f=67$, $p=0.151$). This suggests that the correlation between LAD and NT-proBNP is not a spurious relationship driven by age, gender, heart rate or blood pressure.

Discussion

RHT defines a specific population among hypertensive patients. True RHT prevalence is considered less than 10% of all-treated hypertensive patients, but RHT patients carry a higher risk for hypertension mediated organ damage, chronic kidney disease and early

cardiovascular events⁽¹⁾. Daugherty et al. demonstrated that RHT is associated with an increased risk of adverse cardiovascular outcomes, even after multivariable adjustment⁽⁸⁾. It is very important to make the risk stratification for identifying the highest risk patients who may benefit from specific diagnostic and therapeutic approaches. Gaddam et al. reported patients with RHT have higher levels of natriuretic peptide levels compared to controls⁽²⁾, but there is evidence that not all the RHT patients have high levels of NT-proBNP⁽⁹⁾, which leads to the question if NT-proBNP may be used in risk stratification beyond its volume-overload meaning also in the RHT population. Apart from its role in the diagnosis of heart failure, NT-proBNP is related to cardiac remodeling and is a predictor of mortality in hypertension⁽⁷⁾, so it has become even more popular in detecting the high-risk patients for cardiovascular conditions. There are several studies, which confirmed the relationship between NT-proBNP and LAD in hypertensive patients^(3,6,10). Recently, Courand et al. has demonstrated that NT-proBNP mirrors the damaging effects of high BP on target organs in hypertensive patients and NT-proBNP level increases with the increasing number of target organs involved⁽⁷⁾. Because of the number of true RHT patients are relatively low, RHT patients are not studied widely in this condition. The present study has investigated if LAD, a simple echocardiographic parameter, is correlated with NT-proBNP, an integrative marker of high clinical interest. When established further this relationship can be used to predict high risk patients among the adherent RHT patients on the appropriate therapy. There was a significant pairwise correlation between LAD and NT-proBNP ($r=0.451$, $p<0.001$) in the RHT group and the partial correlation still remained statistically significant after controlling for other risk factors like age, gender, heart rate, systolic and diastolic BP, which are known for interference. This study suggests that LAD and NT-proBNP correlate positively, so larger LAD is related to higher NT-proBNP levels, even after controlling for other interacting factors. This finding may be used to predict the patients with high NT-proBNP levels, which

Table 3. Pairwise and partial correlations between NT-proBNP, LAD and age

		LAD (mm)	Age
NT-proBNP	Pairwise	0.451 ($p<0.001$)	0.670 ($p<0.001$)
	Partial	0.234, ($p=0.049$) ^a	0.590 ($p<0.001$) ^b
LAD (mm)	Pairwise	-	0.469 ($p<0.001$)
	Partial	-	0.175 ($p=0.151$) ^c

NT-proBNP: N-terminal pro b-type natriuretic peptide, LAD: Left atrial diameter

Pairwise correlation coefficients are Pearson's *r*

^aControlling for Age, Gender, HR, SBP, DBP

^bControlling for LA, Gender, HR, SBP, DBP

^cControlling for BNP, Gender, HR, SBP, DBP

is an indicator for high cardiovascular and mortality risk, by using LAD. There was also a pairwise correlation between age and NT-proBNP ($r=0.670$, $p<0.001$) and even after controlling all other related factors, a powerful and significant correlation ($r=0.590$, $d.f=67$, $p<0.001$) remain, which is very important in the studies involve NT-proBNP to take age specific cut-off levels instead of common cut-off's to avoid misvaluation. Another interesting finding of this study is the relation between LAD and age. While a powerful pairwise correlation between LAD and age was detected consistent with some previous studies^(11,12), the correlation disappears after controlling for other effecting factors, such as gender, NT-proBNP, heart rate, systolic and diastolic BP. This finding is consistent with the findings of some more recent studies that normal ageing does not increase LA size⁽³⁾.

Limitations of the study

The most important limitation of the study is its retrospective single-center design. The sample size is another important limiting factor. Because of the low prevalence of true RHT, despite of retrospective screening data of 1057 hypertensive patients only 74 true RHT patients on sinus rhythm were identified. A larger dataset with perhaps data from multiple centers can allow for more advanced tests. This study used office-based BP measurement, but ambulatory BP measurement could be more accurate. Also medications and treatment adherence are controlled through the health insurance system, but there is always a chance that some patients have refilled their prescriptions and not taken pills regularly. Despite these limitations, these study presents analyses performed on the real-world patient data and can help inform practitioners about their diagnostic and treatment decisions.

Conclusion

The present study suggests, in RHT patients, larger LADs are related to higher levels of NT-proBNP and the correlation is still consistent even after controlling other

factors, which may influence this relation. This may allow us to use a simple echocardiographic parameter to predict not only the volume status of the patient but also identify the high-risk patients.

Ethics

Ethics Committee Approval: Ethic approval for the study is obtained from the Clinical Research Ethical Board of Ege University School of Medicine on 22.11.2016 with the number 16-10.1/3.

Informed Consent: Informed consent was not obtained due to the study is retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ.T., Concept: E.İ.T., Design: E.İ.T., Data Collection or Processing: E.İ.T., E.Ş., Analysis or Interpretation: E.İ.T., E.Ş., Literature Search: E.İ.T., Writing: E.İ.T., E.Ş.

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The Relationship Between Physical Activity Status and Dietary Habits with the Risk of Cardiovascular Diseases

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Abstract

Objectives: This study designed to evaluate the relationship between physical activity status and dietary habits with the risk of cardiovascular diseases (CVD).

Materials and Methods: In this cross-sectional study 207 medical students (107 female, 100 male) aged 15-25 years were recruited. Physical activity level and dietary habits assessed by Arab teens lifestyle study questionnaire. Risk of CVD was determined by Framingham, ASSIGN and British National Formulary scoring systems.

Results: In the present study the incidence of CVD was higher in males than females. Female spending more time in sedentary behaviour than male. The incidence of

different CVD was higher in male and female that spending more time in sedentary behaviour. Sedentary time, sugary drinks, French fries, potato chips intake were positively correlated with CVD. Eating fresh fruits, energy drinks and dairy products negatively correlated with CVD.

Conclusion: The risk of CVD is higher among male and increase in both sex with physical inactivity and sedentary life style. Sedentary behaviours regarded as independent risk factors for CVD. High sugary diet increases the incidence of CVD and dairy products decrease the incidence of CVD.

Keywords: Cardiovascular diseases, sedentary behaviour, dietary habits



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Introduction

Recommendation from many recent studies have documented that lifestyle modification in adolescents and young adults are necessary because of the increased tendency of various adverse health outcomes not otherwise typical for their age, including hypertension, dyslipidemia, and metabolic syndromes⁽¹⁾.

It is now well recognised that a physically active lifestyle is associated with decreased cardiovascular diseases (CVD) risk⁽²⁾. One of the mechanisms for decreased CVD risk with increasing physical activity is through the action of physical activity on established CVD risk factors, such as levels of blood pressure or lipids⁽³⁾.

Excessive energy intake and sedentary lifestyle in young adults can be associated with the increased prevalence of dyslipidemia, obesity, and CVD⁽⁴⁾. Particularly, sedentary lifestyle (e.g., watching TV) is associated with unhealthy snacking patterns, including low intake of fruits and vegetables and overconsumption of energy and fat^(4,5). Because the level of physical activity influences on physical condition, health status, and quality of life, it is important to undertake physical activity of different intensities until the age of 25-30 to maximize the development of motor skills and physical fitness^(6,7).

An important time to examine factors associated with CVD risk among adolescents and young adults is during the college years. College students engage in several high risk behaviours associated with CVD development including cigarette smoking, alcohol abuse, physical inactivity, and low fruit and vegetable consumption^(8,9). Weight gain is also common among college students⁽¹⁰⁾ with the frequency and magnitude of weight gain the possibility of gaining weight is greater among male than female⁽¹¹⁾.

Students also perceive that it is acceptable to engage in unhealthy behaviours during their college years, which may be a barrier to incorporating CVD preventive behaviours⁽⁸⁾. Because CVD risk behaviours such as

physical inactivity, obesity, and smoking increase during the transition from adolescence to emerging adulthood⁽¹²⁾. It is critical to have a greater understanding of perceptions related to CVD risk among emerging adults in college.

Materials and Methods

Observational cross-section study was conducted in Faculty of Medicine, Omdurman Ahlia University, Sudan. Two hundred and seven students (100 male, 107 female) aged 15 to 25 years were participated in this study. Participant with hypertension, diabetes, CVD and those taking lipid lowering drugs was excluded. All students signed a written consent form. Basic anthropometrical measurements including body weight and height were measured; weight was measured by body-weight measuring machine (measurement precision 0.1 kg, SECA device), height was measured using a flexible measuring tape (measurement precision 0.1 cm)

Assessment of Physical Activity Status and Dietary Habits

Physical activity and dietary habits were assessed by using Arab Teens Lifestyle Study (ATLS) questionnaire⁽¹³⁾. The physical-activity part of the questionnaire intended to collect information on frequency, duration, and intensity of a variety of light-, moderate-, and vigorous intensity physical activities during a typical week and across different activity domains (transport, house hold, fitness, and sports activities). Metabolic equivalent (MET) values were attributed to the physical activities based on the compendium of physical activity and the compendium of physical activity for youth. Physical activity levels were then classified into two categories (active or inactive) based on a cut-off value for total METs-min/week of below or 1,680 MET-min/week. These cut-offs were employed as a score of 1,680 METs-min/week is equivalent to 60 minutes of moderate-intensity daily physical activity (60 minutes 3-7 days 3-4 METs 51,680 METs-min/week), and a score of 2,520 METs-min/week is equivalent to 60 minutes of moderate-to vigorous- intensity daily physical activity (60 minutes 3-7 days 3-6 METs 52,520 METs-min/

week). Sedentary behaviours were then assessed by asking how much time in a typical day was spent watching TV, playing video games, and using the computer and internet. To classify total screen time, the “American Academy of Pediatrics” guidelines of a maximum of 2 h/day was employed.

The dietary habit section of the questionnaire covered healthy and unhealthy dietary behaviours and asked how many times in a typical week the participants consumed breakfast, vegetables (cooked and uncooked), fruit, milk and dairy products, sugar-sweetened drinks including soft beverages, donuts and cakes, candy and chocolate, energy drinks and fast foods. Possible responses ranged from zero intake (never) to a maximum intake of 7 days/week (every day). Participants were then classified into two categories based on the frequency of their intake for each respective food (41 days/week, <4 days/week).

Assessment of the Incidence for CVD

For assessment of the risk for CVD three CVD scoring systems were used which are Framingham, ASSIGN, and British National Formulary. The variables required for risk calculation by these scoring systems include time in years over which risk is calculated, age of the subjects, sex of the subjects, number of cigarettes smoked per day, smoking status, family history of premature cardiovascular disease, presence of diabetes, presence of left ventricular hypertrophy on ECG, Scottish index of multiple deprivations (usually 20) Systolic blood pressure in mmHg, total cholesterol in mmol/L and high density lipoprotein total cholesterol (HDL-C) in mmol/L.

Venous blood was collected in the morning after an overnight fast of 12 hours. The total cholesterol and HDL-C were measured by using spectrophotometer by kits from Bio-system Company Costa Brava, 30, Barcelona (Spain). Blood pressure was measured by sphygmomanometer.

Statistical Analysis

Data was analysed by using PASW for Windows® version 24.0 software (formerly SPSS Statistics Inc. Chicago, Illinois). Our data was normally distributed.

Results were presented as mean ± standard deviations for all variables. Student t-test was used to compared between two groups. Pearson correlation was used to correlate between CVD and other variables. P<0.05 was considered significant difference.

Results

Among 207 participants included in the study, 107 of them (51.7%) were female, 100 (48.3%) were male. Regarding physical activity 20 (18.7%) of female and 39 (39%) of male regarded as physically active. As shown in Table 1, age, weight, height and the sum of MET which represent the physical activity were statistically significantly higher in male than females (p≤0.05). Results presented in Table 2, showed that the risk of CVD according

Table 1. Anthropometric characteristics and activity status of the study population according to genders

Variables	Male (n=100) Mean ± SD	Female (n=107) Mean ± SD	P value
Age (year)	19.50±1.58	19.07±1.10	0.002
Weight (kg)	67.04±13.88	60.57±13.23	0.001
Height (m)	1.72±0.64	1.59±0.06	0.000
Sum of MET	1775.08±1841	1158.3±1272	0.005
Sedentary time (h/d)	1.86±0.35	1.88±0.33	0.695

Sum of MET: Sum of metabolic equivalent, n: Number of the patients, SD: Standard deviation

Table 2. Comparison of the different CVD between male and female

Variables	Male (n=100) Mean ± SD	Female (n=107) Mean ± SD	P value
CVD - Framingham	0.296±0.52	1.00±8.83	0.424
CHD	0.507±0.91	0.774±8.01	0.440
MI	0.212±0.54	0.598±6.19	0.534
Stroke	0.040±0.03	0.018±0.01	0.000
Risk of Death from CHD	0.002±0.02	0.591±6.11	0.337
Risk of Death from CVD	1.204±1.30	1.317±8.67	0.939
CVD - BNF	0.546±0.92	0.792±8.01	0.762
CVD - ASSIGN	1.727±1.09	0.599±0.42	0.000
Systolic BP	119.47±9.34	111.93±7.71	0.000
Diastolic BP	74.81±6.99	71.80±7.39	0.003

CVD: Cardiovascular diseases, CHD: Coronary heart disease, MI: Myocardial infarction, BNF: British National Formulary, BP: Blood pressure, n: Number of the patients, SD: Standard deviation

to ASSIGN criteria, stroke according to Framingham criteria, systolic blood pressure and diastolic blood pressure were statistically significantly higher in male than females ($p \leq 0.05$). As shown in Table 3, only risk of death from coronary heart disease was significantly higher in the inactive male ($p \leq 0.05$). Regarding time spending

Table 3. The risk of death from CHD among active and inactive males

Variable	Gender	Activity	n	Mean \pm SD	p value
Risk of Death from CHD	Male	Inactive	61	0.0036 \pm 0.01	0.007
		Active	39	0.0005 \pm 0.00	

CHD: Coronary heart disease, SD: Standard deviation, n: Number of the patients

Table 4. Comparison of different CVD in relation to time spending in sedentary behaviour according to gender

Variable	Gender	Sedentary time	n	Mean \pm SD	P value
MI	Male	High	86	0.239 \pm 0.57	0.04
		Low	14	0.046 \pm 0.08	
CVD -Framingham	Male	High	86	0.326 \pm 0.55	0.04
		Low	14	0.118 \pm 0.12	
CVD -ASSIGN	Male	High	86	1.792 \pm 1.14	0.032
		Low	14	1.332 \pm 0.61	
CVD -ASSIGN	Female	High	94	0.567 \pm 0.39	0.39
		Low	13	0.831 \pm 0.58	

CVD: Cardiovascular diseases, MI: Myocardial infarction, n: Number of the patients, SD: Standard deviation

Table 5. Correlation of CVD with the sedentary activity in males

Variable	Gender	Correlation	Time spending on computer per day	Watching TV or videos per week end
Death from CVD	Male	Pearson Correlation Sig. (2-tailed)	0.212* 0.034	0.233* 0.020
Systolic BP	Male	Pearson Correlation Sig. (2-tailed)		0.215* 0.032
Diastolic BP	Male	Pearson Correlation Sig. (2-tailed)		0.195* 0.052

CVD: Cardiovascular diseases, BP: Blood pressure, Sig: Significance test

Table 6. Correlation of CVD with the sedentary activity in females

Variable	Gender	Correlation	Watching TV or videos per day
Stroke	Female	Pearson Correlation Sig. (2-tailed)	-0.237* 0.014
CVD-ASSIGN	Female	Pearson Correlation Sig. (2-tailed)	-0.209* 0.032

CVD: Cardiovascular diseases, Sig: Significance test

in sedentary activity results presented in Table 4, showed that the risk of myocardial infarction, CVD according to Framingham criteria is statistically significantly higher in high sedentary male. Risk for development of CVD according to ASSIGN criteria is statistically significant higher in high sedentary male and female ($p \leq 0.05$). Regarding correlation of cardiovascular diseases with the time spending in different types of sedentary activity in male results presented in Table 5, showed that the risk of death from CVD statistically significantly positively correlated with time spend on the computer and/or internet per day and watching TV and/or DVD per weekend. Systolic blood pressure and diastolic blood pressure were statistically significantly positively correlated with the watching TV and/or DVD per weekend ($p \leq 0.05$). While in female results presented in Table 6, showed that the incidence of CVD according to ASSIGN criteria and stroke according to Framingham is statistically significantly negatively correlated with time spending in watch TV and/or videos per day ($p \leq 0.05$). Regarding the correlation of CVD with dietary habits, male results that presented in Table 7, showed that the incidence of CVD according to SSIGN criteria statistically significantly positively correlated with eating fresh fruit. Systolic blood pressure

significantly negatively correlated with drinking energy drinks. Diastolic blood pressure statistically significantly positively correlated with sugar drink and negatively correlated with eating fresh fruit. While the female results that presented in Table 8, showed that systolic blood pressure statistically significantly negatively correlate with eating diary product. Diastolic blood pressure statistically significantly negatively correlated with eating French fries or potato chips, sweet and chocolate ($p \leq 0.05$).

Discussion

The present study revealed that most our college students were physically inactive and spending their time in sedentary activities, These findings concur with a number of previous studies^(8,9). Moreover, our results indicated that development of CVD diseases was higher in male than female, this in accordance with the investigators that suggest the lifetime risk for developing CVD is higher among men than women⁽¹⁴⁾ across most age groups⁽¹⁵⁾. Emerging adult males, those 18-25 years of age,⁽¹⁶⁾ may be particularly at risk for engaging in CVD risk behaviours due to greater independence, less parental monitoring, and financial instability. Cardiovascular risk factors established during adolescence and emerging

adulthood have been shown to extend into later adulthood,⁽¹⁷⁾ increasing the risk for CVD. In the current study we observed that the risk of CVD was higher in physically inactive male than physically active ones. Furthermore, the risk of CVD was higher in the high sedentary male and female. These finding agree with the recommendation for ideal cardiovascular health that adopted by the American Heart Association which included lifestyle-related recommendations for physical activity and dietary behaviours, not smoking, and a body mass index less than 25 kg/m²⁽¹⁸⁾.

In the current study it is clear that sedentary behaviour is independent risk factor for different type of CVD and its risk factors in male and females, this finding agree with a number of previous studies that conclude prolonged sedentarism is regarded as independent risk factor for CVD independent of physical activity and other potentially confounding factors^(19,20). Moreover regarding physical inactivity pattern that potentially affect the CVD, our finding showed that the time spending on the computer and/or internet per day and watching TV was significantly associated with the CVD and its associated risk factors in male and females, these findings are in accordance with a research that reported TV watching appear to be separate

Table 7. Correlation of CVD with the dietary habits in males

Variable	Gender	Correlation	Eating fresh fruit	Taking energy drinks	Sugary drink
CVD-ASSIGN	Male	Pearson Correlation Sig. (2-tailed)	0.195 0.05		
Systolic BP	Male	Pearson Correlation Sig. (2-tailed)		-0.215* 0.032	
Diastolic BP	Male	Pearson Correlation Sig. (2-tailed)	-0.250* 0.012		0.226* 0.024

CVD: Cardiovascular diseases, BP: Blood pressure, Sig: Significance test

Table 8. Correlation of CVD with the dietary habits in females

Variable	Gender	Correlation	Eating diary product	Eating French fries or potato chips	Eating sweets or chocolate
Systolic BP	Female	Pearson Correlation Sig. (2-tailed)	224* 0.020		
Diastolic BP	Female	Pearson Correlation Sig. (2-tailed)		-0.190 0.050	-0.205* 0.034

CVD: Cardiovascular diseases, BP: Blood pressure, Sig: Significance test

entities and is independently associated with cardio-metabolic risk^(21,22).

Regarding association between dietary habits and CVD we observed that in males, the sugary drinks increases the diastolic blood pressure, eating French fries and/or potato chips decreases diastolic blood pressure. While in females the dairy products significantly decrease systolic blood pressure, eating French fries and/or potato chips, sweets and/or chocolates decreases the diastolic blood pressure.

Furthermore, present study found that high consumption of fruit, increases the risk for development of CVD according to ASSIGN this might be due to intake of high sugary fruit juices with fast food.

Study Limitations

This study is limited in the term of calculation of incidence of cardiovascular diseases because we used cross-sectional study that is suitable to our study population.

Conclusion

The risk of cardiovascular diseases is higher among male and increases in both sex with physical inactivity and sedentary life style. Sedentary behaviours regarded as independent risk factors for cardiovascular diseases. High sugary diet increases the incidence of cardiovascular diseases and dairy products decrease the incidence of cardiovascular diseases.

Ethics

Ethics Committee Approval: This study approved by ethical committee of the faculty of medicine International Africa University (number 27-2017)

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.A.O., Z.M.A., Design: A.A.O., Z.M.A., Data Collection or Processing: A.A.O., Z.M.A.,

Analysis or Interpretation: A.A.O., Z.M.A., Literature Search: A.A.O., Z.M.A., Writing: A.A.O., Z.M.A.

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Cardiopulmonary Bypass Management Using High-volume Continuous Hemofiltration in Patients with Comorbidities

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Abstract

Objectives: To evaluate the effectiveness of hemofiltration during longstanding cardiopulmonary bypass (CPB) in patients with comorbidities.

Materials and Methods: Prospective randomized clinical trial included 38 male patients with ex-pecting duration of CPB >120 minutes due to comorbid pathology. Standard anesthesia protocol was carried out. Study includes two groups: first group (controlled, n=20) included standard CPB, 2nd group (analyzed, n=18) included perfusion with high-volume hemofiltration using polyionic buffered solution 80 mL/min during all CPB time. Hemofiltration has been also supported by ultra-filtration for hydro-balance maintenance at the level of 8-10 mL/kg. Laboratory tests, respiratory and renal complications, drainage blood loss,

hemostasis disorders, requiring hemostatics and blood transfusion, intensive care unit (ICU) and in-hospital were evaluated. Nonparametric methods-Mann-Whitney U test for independent samples and Wilcoxon signed-rank test for dependent samples were used.

Results: IL-6 level in 2nd group was significantly lower (p=0.0017) and did not exceed 7.4 pg/mL. C-RP, metalloproteinase and procalcitonin levels were lower too, but not statistically significant. Lactate level in analyzed group was in reference range, while in control group after perfusion it in-creased to 8.3±4.2 mmol/L. Renal dysfunction, requiring dialysis, was diagnosed in six (20,7%) patients from controlled group vs two patients (6.1%) from analyzed group. Respiratory insufficiency



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developed in three patients (10.3%) only in controlled group. In-hospital stay was significantly lower in analyzed group and so was the ICU length. Polyorganic insufficiency syndrome occurred in three patients (10.3%) from the controlled group.

Conclusion: High-volume hemofiltration using polyionic

buffered solution for longstanding CPB reduces damaging effects of traditional roller pump and reduces risks of organic dysfunction in postoperative period.

Keywords: Cardiopulmonary bypass, hemofiltration, systemic inflammatory response

Introduction

Despite the development of new technologies and cardiopulmonary bypass (CPB) techniques, its negative effects still remain significant⁽¹⁾. Systemic inflammatory response makes serious contribution to the pathophysiology and it depends on surgical trauma, blood and artificial surfaces interactions during extracorporeal circulation, ischemia/reperfusion, endotoxemia and etc⁽²⁾. At the same time, number of patients with organic dysfunction due to comorbidities is increasing every year. That is why preventing of inflammatory response during CPB can lower postoperative complications. For example, invention of centrifugal pumps influenced a lot CPB management in cardiac surgery. Recent studies are showing advantages of using centrifugal pumps over roller pumps⁽³⁾. But the conclusions are still controversial, since these studies included only operations with perfusion duration less than 90 minutes. The magnitude of complement activation is proportional to the duration of CPB⁽⁴⁾. There are several ways to reduce the inflammatory response, such as ultrafiltration, plasmfiltration, hemosorption (with polymethyl methacrylate). All of them have proven their effectiveness, but still there is a lack of data in using these methods. Also Rabie Soliman et al. in his research discovered that hemofiltration can cause lactate level in serum⁽⁵⁾. Currently, there are no guidelines to the CPB management during surgeries with different perfusion time. Correlation between mediators of inflammatory response level during and after CPB and the incidence of organic insufficiency is not evaluated in any studies.

Materials and Methods

Prospective randomized clinical trial with 38 male patients included with CPB duration over 120 minutes during concomitant heart surgery. Inclusion criteria: patients with coronary artery disease and/or heart valve disease with the history of atrial fibrillation and comorbidities (chronic pyelonephritis, chronic obstructive pulmonary disease, diabetes mellitus), requiring coronary artery bypass grafting (CABG) surgery and/or valve surgery and “maze” procedure. Patients who underwent urgent surgery were excluded from the trial. The study was approved by the local ethic committee; informed consent was signed by all patients. Standard anesthesia protocol was carried out. Study includes two groups: First group (controlled, n=20) included standard CPB, 2nd group (analyzed, n=18) included perfusion with high-volume hemofiltration using polyionic buffered solution 80 mL/min during all CPB time. Hemofiltration has been also supported by ultrafiltration for hydro-balance maintenance at the level of 8-10 mL/kg. For the study we are using Maquet hemoconcentrators with priming volume 65 mL and membrane surface 0.7 m² and as a substitute solution MultiBic bicarbonate buffer solution with potassium concentration 4 mmol/L was used. Hemofiltration ends after weaning from CPB.

Statistical Analysis

Main clinical data, such as age, weight, CPB duration and others were comparable in both groups (Table 1). Envelope randomization was carried out. Laboratory tests (WBC, Hb, Plt, IL-6, IL-10, lactate, procalcitonin,

C-RP) were evaluated, as well as respiratory and renal complications, drainage blood loss, hemostasis disorders, requiring hemostatics and blood transfusion, ICU and in-hospital.

All operations included in this study in both groups were concomitant, such as coronary artery bypass surgery with the valve repair or replacement and atrial fibrillation surgery, and all of them required long CPB and cross-clamping time (Table 2). Data in both groups was comparable. All results presented as mean value \pm standard deviation (σ). To evaluate the diversity significance between all parameters Student's t-test was used. P-level <0.05 was considered as significant.

Results

IL-6 level was significantly lower in analyzed group ($p=0.0017$) and did not exceed 7.4 picogram per mL, while

IL-10 level was comparable in both groups (Table 3). Also procalcitonin, C-RP levels were lower, but not statistically relevant. Lactate level remained normal, while in control group it has been increased to 8.3 ± 4.2 mmol/L after perfusion. Transfusion rate were the same in both groups, but patients from analyzed group didn't require any hemostatic therapy. There was no need in inotropic and vasopressor medications in the analyzed group by the end of the first postoperative day, all patients were extubated in first postoperative hours. Renal dysfunction, requiring dialysis, was diagnosed in 6 (20.7%) patients from controlled group vs. two patients (6.1%) from analyzed group. Respiratory insufficiency developed in three patients (10.3%) only in controlled group. In-hospital stay was significantly lower in analyzed group and so was the ICU length. Polyorganic insufficiency syndrome occurred in three patients (10.3%) from the controlled group.

Discussion

The use of CPB in major cardiac surgery initiates an acute inflammatory response that is complex, unpredictable and can cause significant morbidity and mortality, especially during long-standing procedures. Pathophysiology of CPB negative effects can be summarized as generalized inflammatory response,

Table 1. Clinical data

	Control group (n=20)	HVH group (n=18)
Age, years	69.3 \pm 11.3	72.1 \pm 12.7
Weight, kg	74.9 \pm 9.4	71.9 \pm 12.6
HF (NYHA class), n (%):	20 (100)	18 (100)
II	11 (55)	10 (55.6)
III	9 (45)	8 (44.4)
Comorbidities:		
Renal failure (RIFLE), n (%)	6 (30)	5 (27.8)
R	2 (10)	2 (11.1)
I	3 (15)	2 (11.1)
F	1 (5)	1 (5.55)
Respiratory failure, n (%) (A.G.Dembo chronic respiratory insufficiency classification ⁽⁶⁾)	8 (40)	7 (38.9)
I	2 (10)	1 (5.6)
II	4 (20)	4 (22.2)
III	2 (10)	2 (11.1)
Diabetes mellitus, n (%)*	8 (40)	7 (38.9)
EuroSCORE 2, %	4.3	3.7

HVH: High-volume hospital, HF: Heart failure, NYHA: New York Heart Association, n: Number of the patients

Table 2. Operative data

	Control group (n=20)	HVH group (n=18)
CABG + MV replacement + RFA, n (%)	6 (30)	5 (27.8)
CABG + MV repair + RFA n (%)	7 (35)	9 (50)
CABG + MV replacement + LV aneurysm repair + RFA n (%)	1 (5)	1 (5.5)
AV and MV replacement + RFA n (%)	4 (20)	1 (5.5)
AV replacement + CABG + RFA n (%)	2 (10)	2 (11.1)
CPB duration, min	182 \pm 44	176 \pm 52
Cross-clamp time, min	145 \pm 27	142 \pm 39
Surgery duration, min	330 \pm 56	340 \pm 60
Intraoperative blood loss, mL	725 \pm 55	730 \pm 65

HVH: High-volume hospital, CABG: Coronary artery bypass grafting, MV: Mitral Valve, RFA: Radiofrequency ablation, LV: Left ventricular, AV: Atrioventricular, CPB: Cardiopulmonary bypass, n: Number of the patients

ischemia-reperfusion injury, endotoxemia, and operative trauma. Also the longer cardiopulmonary bypass was, the more expressed inflammatory response was⁽⁷⁾. At the same time, number of patients with organic dysfunction is increasing every year, as well as CPB duration during complex concomitant surgery. That is why techniques to minimize the negative effects of inflammatory response during CPB, allowing to reduce or remove alterative factors during perfusion, remain relevant⁽⁸⁾.

In our study main inflammatory response markers, that are always associated with long-standing CPB, were significantly lower, such as IL-6, IL-10 and others. Moreover, there were lower complication rate, less ICU and in-hospital stay, lower blood transfusion rate and there was no need in vasopressor and cardiotoxic therapy in hemofiltration group. Most of the known approaches to reduce the CPB alterative effect are using minimally invasive extracorporeal circulation,

improving of the circuit biocompatibility, using of centrifugal pumps⁽⁹⁻¹¹⁾. But these techniques have their disadvantages too: absence of venous reservoir can increase the risk of air embolism. Also membranes in new oxygenators have better biocompatibility, but prevent blood saturation with isoflurane, so it is impossible to use inhalational anesthetics and their better protective effect on myocardium, which limits the use of this technology. High-volume continuous hemofiltration with standard roller pump CPB, that we offer, as we assume, doesn't have these disadvantages. Modified techniques of blood ultrafiltration^(12,13), hemosorption and apheresis^(14,15) removes small amount of liquid, that don't let us to accomplish clinical and laboratory evaluation of inflammatory mediators through the semipermeable membrane of hemofilter, leading to indifferent elimination of both inflammatory and antipyretic mediators. And the cost price of these procedures often exceed operations'

Table 3. Main laboratory data in early postoperative period

Parameter	Before CPB		24 h after surgery		p
	HVH group, n=18	Control group, n=20	HVH group n=18	Control group, n=20	
Oxygenation index	342±64	376±88	406±96	269±55	0.01
Creatinine, µmol/L	107±30	89±28	88±36	288±55	0.01
Carbamide, mmol/L	4.9±2.1	6.08±3.3	5.92±2.4	15.7±5.1	0.01
Diuresis, mL/h	135±55	150±70	85±15	35±15	0.01
AST, un/L	37±9	24±15	66±28	188±32	0.01
ALT, un/L	62±22	49±31	71±21	106±18	0.02
Lactate, mmol/L	0.8±0.4	0.8±0.5	3.0±2.1	8.3±4.2	0.015
IL-6, pg/mL	7.4±3.1	6.2±3.9	5.9±1.5	19.7±3.9	<0.01
IL-10, pg/mL	8.2±2.9	7.4±4.1	11.4±2.9	12.6±3.3	0.27
Procalcitonin, ng/mL	1.4±0.6	1.1±0.7	1.25±0.5	2.1±0.3	0.09
CR-P, mg/L	9.8±3.3	7.9±5.1	15.6±6.6	22.9±8.1	0.045
WBC, x10 ⁹	7.2±4.3	7.89±2.9	13.1±6.4	17.9±4.2	0.06
Drainage blood loss, mL	-	-	270±50	310±70	0.07
Ventilation time, min	-	-	205±70	530±120	0.01
Dopamine, µg/kg/min	2.9±0.5	2.2±0.5	0	3.3±0.5	-
Noradrenaline, µg/kg/min	0.03±0.01	0.03±0.01	0	0.05±0.05	-
ICU stay, hours	-	-	18.9±6.1	41.3±18.3	0.019
In-hospital stay, days	-	-	11.9±3.3	19.9±4.5	0.035

CPB: Cardiopulmonary bypass, HVH: High-volume hospital, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, C-RP: C-Reactive protein test, WBC: White blood cell, ICU: Intensive care unit, n: Number of the patients

cost. Moreover, roller pump, used in these techniques initiates inflammatory response by itself and damages blood cells. In our study usage of polyionic buffer solution with hydro-balance maintenance at level 8-10 mL/kg during long-standing CPB lowers these disadvantages. This study shows promising results in patients undergoing concomitant surgery with long cross-clamping time, but final results can be interpreted only after the full trial will be held.

Ethics

Ethics Committee Approval: This study was approved by A.V.Vishnevsky National Medical Research Center of Surgery local committee (approval no:23).

Informed Consent: All patients have signed informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.P., A.R., E.M., Concept: G.P., Design: G.P., Data Collection or Processing: V.C., E.M., Analysis or Interpretation: V.P., G.P., A.R., E.M., Literature Search: V.C., G.E., Writing: G.E.

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The Protective Role of Resveratrol on Diabetic Cardiomyopathy in Streptozocin Induced Diabetic Rats

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Abstract

Objectives: We aimed to investigate the effect of resveratrol on diabetic cardiomyopathy in streptozocin-induced diabetic rats.

Materials and Methods: Rats were injected with streptozocin to establish diabetes model. After four weeks, heart tissues were collected for histopathological examination and immunoexpression of nitric oxide synthases-2 (NOS-2) and transforming growth factor-β1 (TGF-β1). Lipid peroxidation was evaluated.

Results: In diabetic rats, cardiac muscle cell thickness (hypertrophy), TGF-β1 and NOS-2 expression were increased significantly when compared to control group. Administration of resveratrol in diabetic rats causes a

significant reduction both in cardiac muscle cell thickness, TGF-β1 and NOS-2 expression in these rats.

Blood glucose levels were significantly increased in diabetic rats expectedly, but there was no important difference between diabetic rats and resveratrol administrated diabetic rats in terms of blood glucose levels.

Conclusion: We showed protective effects of resveratrol on dilated cardiomyopathy on diabetic rats by reducing oxidative stress. As the prevalence of diabetes mellitus is increasing, resveratrol supplementation could help preventing diabetic cardiomyopathy.

Keywords: Resveratrol, diabetic cardiomyopathy, type 2 diabetes mellitus



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Introduction

Diabetic cardiomyopathy (DCM) is a clinical entity diagnosed when ventricular dysfunction occurs after excluding coronary atherosclerosis and hypertension⁽¹⁾. The mechanism leading to DCM is not clear yet but myocardial hypertrophy and fibrosis have been shown to be the major pathogenesis of DCM⁽²⁾. Activation of reactive oxygen species (ROS) linked pathways play a major role in the pathogenesis of myocardial hypertrophy and fibrosis⁽²⁾.

Malondialdehyde (MDA) is a three-carbon low molecular weight aldehyde produced from free radical species of poly unsaturated fatty acids reflecting the degree of lipid peroxidation⁽³⁾. Transforming growth factor- β 1 (TGF- β 1) is a multifunctional cytokine regulating cell proliferation and extracellular matrix production which leads to fibrosis in tissues and organs when produced excessively⁽⁴⁾. Nitric oxide synthases-2 (NOS-2) is absent in healthy states, rather it's expressed under inflammatory conditions⁽⁵⁾.

Resveratrol is a polyphenol mainly found in grape skin and seeds⁽⁶⁾. Resveratrol has a wide range of protective effect on ageing, inflammation and glycation⁽⁷⁾. In this study, we evaluated the protective role of resveratrol on streptozocin-induced diabetic rats.

Materials and Methods

Animals

Male Sprague Dawley albino mature rats at eight weeks, weighing 200-220 g, were used in the experiments. The animals had access to food and water ad libitum. The animals were housed under a temperature-controlled environment (22-24°C) with light/dark cycles of 12:12 hours. Experimental procedures were approved by the Committee for Animal Research of Celal Bayar University. All animal studies are strictly conformed to the animal experiment guidelines of the Committee for Human Care.

Experimental protocol

Diabetes was induced by intraperitoneal (i.p.) injection of streptozocin (STZ, Sigma-Aldrich, Inc.; Saint Louis,

MO, USA) (60 mg/kg in 0.9% NaCl, adjusted to a pH 4.0 with 0.2 M sodium citrate) for 14 rats. Remaining rats without streptozocin injection were selected as control group (n=6). Diabetes was verified as blood glucose levels of 250 mg/dL and higher after 24 hours by evaluating blood glucose levels with the use of glucose oxidase reagent strips (Boehringer-Mannheim, Indianapolis). Diabetic rats were randomly divided into two groups; diabetes group treated with 1 mL/kg saline (Diabetes) (n=6), and diabetes group treated with 10 mg/kg/day resveratrol (Sigma Aldrich), (Diabetes + resveratrol) (n=6) was administrated by i.p. for four weeks.

The animals were euthanized and blood samples were collected by cardiac puncture. Removal of the heart was performed for histopathological examination.

Histopathological examination of heart tissue

All animals were anesthetized by an i.p. of ketamin (40 mg/kg, (40 mg/kg, Alfamine[®], Ege Vet, Alfasan International B.V., Holland)/xylazine (4 mg/kg, Alfazyne[®], Ege Vet, Alfasan International B.V., Holland) and formaldehyde was used for histological and immunohistochemical studies. Formalin-fixed hearts cut into 5 μ m sections were stained with hematoxylin and eosin (H&E). All sections were photographed with Olympus C-5050 digital camera mounted on Olympus BX51 microscope.

Computerized image analysis system was used to assess morphological analysis. Heart muscle cell hypertrophy degree was examined by light microscopy. Thickness of muscle cells was calculated from the cross-sectional image. Muscle fiber was measured by image analysis software (Image- Pro Express 1.4.5, Media Cybernetics, Inc. USA). Average of 50 cardiac muscle cell from each animal was used for analysis.

NOS-2, TGF- β 1 immunoexpression

For immunohistochemistry, sections were incubated in primary antibodies (TGF- β 1, NOS-2 Bioss, Inc.; 1/100) for 24 h at 4°C. Histostain-Plus Bulk kit (Bioss, Inc) against rabbit IgG was used to detect

antibody, and the final product was visualized by 3.3' diaminobenzidine (DAB). All sections were washed in PBS and photographed with an Olympus C-5050 digital camera mounted on Olympus BX51 microscope.

Measurement of plasma TGF-β

Plasma TGF-β were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kit (Biosciences). TGF-β levels were expressed as pg/mL.

Evaluation of lipid peroxidation

Malondialdehyde (MDA) levels as thiobarbituric acid reactive substance (TBARS) was measured for the evaluation of lipid peroxidation. MDA levels were expressed as nM and tetraethoxypropane was used for calibration.

Statistical Analysis

Non-parametric (Mann-Whitney U) test was used to assess all quantitative data. Between-group differences were assessed by Student's t-test. All data are shown as mean values ± standard error of the mean. P values of <0.05 were regarded as statistically significant. All analyses were performed using SPSS v.21.0 for Windows (SPSS, Inc., Chicago, Illinois, USA).

Results

In diabetic rats, cardiac muscle cell thickness (hypertrophy), TGF-β1 and NOS-2 expression were increased significantly when compared to control group (Figure 1 and 2). Administration of resveratrol in diabetic

rats causes a significant reduction both in cardiac muscle cell thickness, TGF-β1 and NOS-2 expression in these rats (Table 1).

Diabetic rats had significantly higher levels of blood glucose levels but there was no significant difference between diabetic rats and resveratrol administrated diabetic rats in terms of blood glucose levels (Table 1). Plasma levels of TGF-β1 and MDA were significantly elevated in diabetic rats and resveratrol administration caused significant reduction (Table 2).

Discussion

In this present study, resveratrol reduced oxidative stress and myocardial hypertrophy in streptozocin-induced diabetic rats. Diabetes mellitus is a condition defined by elevations on blood glucose levels leading to deaths mostly from cardiovascular causes⁽⁸⁾. Hyperglycemia and insulin resistance contributes to impaired mitochondrial calcium handling and oxidative stress leading to cardiac hypertrophy and fibrosis⁽⁹⁾.

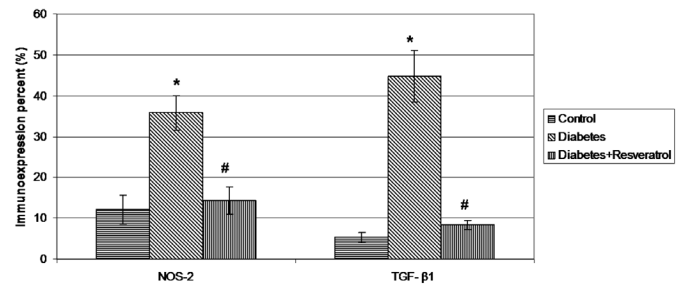


Figure 2. Immunoeexpression percent of NOS-2 and TGF-β1
**p*<0.05 Control group compared diabetes
#*p*<0.01 Diabetes group compared diabetes+resveratrol

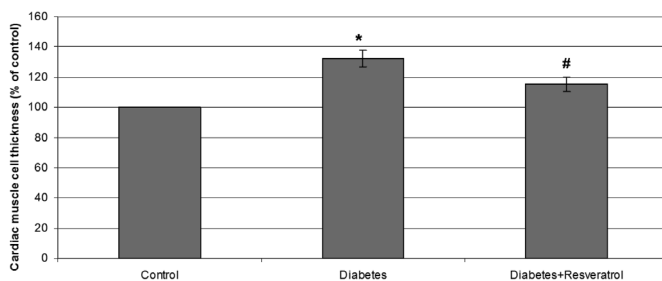


Figure 1. Cardiac muscle cell thickness in rats
**p*<0.001 Control group compared diabetes
#*p*<0.05 Diabetes group compared diabetes+resveratrol

Table 1. Cardiac muscle cell thickness, TGF- β1 and NOS-2 immunoeexpression and blood glucose levels of rats

	Control	Diabetes	Diabetes and resveratrol
Cardiac muscle cell thickness (% of control)	100	132.3±5.6	115.2±4.8
Immunoeexpression NOS-2 percent (%)	12.1±3.5	35.8±4.2	14.3±3.4
Immunoeexpression TGF-β1 percent (%)	5.3±1.2	44.7±6.3	8.4±1.1
Blood glucose (mg/dL)	103.2±7.2	482.3±30.4	468.4±18.5

NOS-2: Nitric oxide synthases -2, TGF- β1: Transforming growth factor-b1

The role of resveratrol on blood glucose levels is conflicting. Lekli et al. showed that resveratrol reduces the blood glucose levels on diabetic rats⁽¹⁰⁾. However, some other studies suggested that resveratrol has no effect on blood glucose levels^(11,12). In our study, blood glucose levels were decreased, but this change was non-significant compared to diabetic rats who did not receive resveratrol treatment. These conflicting results in studies may suggest that the protective role of resveratrol on DCM is not related to improved hyperglycemia.

Cardiac fibrosis has a major role in the pathogenesis of DCM. TGF- β 1 is a regulator cytokine for cell proliferation and excessive production of TGF- β 1 leads to tissue fibrosis⁽¹³⁾. TGF- β 1 has been showed to be overexpressed in DCM^(14,15). Zhang et al. investigated the role of microRNA-155 on myocardial fibrosis induced by diabetes in mice and showed that myocardial fibrosis was regulated via TGF- β 1-Smad 2 signaling pathway⁽¹⁶⁾. Resveratrol had been shown to reduce pulmonary fibrosis in rats⁽¹⁷⁾. In our study, the level of TGF- β 1 was upregulated in diabetic rats as shown in previous studies, and administration of resveratrol reduced the level of TGF- β 1.

Oxidative stress is defined as an imbalance between generation of ROS and the antioxidant defense. Oxidative stress plays an important role in the process of diabetic complications⁽¹⁸⁾. Mitochondrial oxidative stress and ROS generation had been shown to be elevated in diabetic rats contributing to myocardial hypertrophy and fibrosis⁽¹⁹⁾.

Table 2. Plasma levels of TGF- β 1 and MDA

	TGF-Beta (pg/mL)	MDA (nM)
Normal Control (group 1)	10.2 \pm 2.8	94.2 \pm 11.4
Diabetes (saline treatment) (group 2)	43.5 \pm 5.1*	402.8 \pm 32.5*
Diabetic rat (resveratrol treatment) (group 3)	19.7 \pm 2.9#	286.1 \pm 22.3##

TGF- β 1: Transforming growth factor- β 1, MDA: Malondialdehyde
 * $p < 0.000$, saline treatment diabetic rats compared control group
 # $p < 0.001$, resveratrol treatment diabetic rats compared saline treatment diabetic rats
 ## $p < 0.0001$, resveratrol treatment diabetic rats compared saline treatment diabetic rats

Resveratrol is a well-confirmed antioxidant inhibiting excessive ROS production and lipid peroxidation⁽²⁰⁾. MDA, final product of polyunsaturated fatty acid peroxidation, is indirectly reflecting the degree of cell damage. Fang et al. had shown increased expression of antioxidant enzymes and reduced MDA levels in diabetic mice treated with resveratrol⁽¹¹⁾. In our study, the level of MDA was significantly increased as shown in previous studies, but administration of resveratrol reduced the level of MDA.

Nitric oxide synthases (NOS) mediates the synthesis of nitric oxide (NO), a short-living free radical that is an important mediator for cardiac contractility and vasodilatation⁽²¹⁾. NOS-2 isoform, known as induced NOS, is expressed only under unhealthy conditions contributing to endothelial dysfunction⁽²¹⁾. NOS-2 level was found to be elevated in cardiomyocytes in myocarditis, dilated cardiomyopathy⁽²²⁾. Mungro et al. showed that cardiomyocyte overexpression of NOS-2 resulted in peroxynitrite generation, heart block and sudden death⁽⁵⁾. In our study, the level of NOS-2 was significantly increased. Administration of resveratrol reduced the level of NOS-2.

Study Limitations

As a limitation of our study, streptozocin induced diabetes mellitus may cause atherosclerotic heart disease, we didn't perform coronary artery histopathological examination. We may have missed atherosclerosis.

Conclusion

In conclusion, we demonstrated protective effects of resveratrol on dilated cardiomyopathy on diabetic rats by reducing oxidative stress. As the prevalence of DM is increasing, resveratrol supplementation could help preventing diabetic cardiomyopathy.

Ethics

Ethics Committee Approval: Experimental procedures were approved by the Committee for Animal Research of Celal Bayar University. All animal studies are

strictly conformed to the animal experiment guidelines of the Committee for Human Care.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.E., T.Ç., G.Y., Concept: İ.P.C., O.E., Design: İ.P.C., O.E., U.A., Data Collection or Processing: İ.P.C., O.E., Analysis or Interpretation: İ.P.C., O.E., Literature Search: İ.P.C., Writing: İ.P.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of the Relationship Between Resting Heart Rate and Endocan, Thrombomodulin Levels in Healthy Adults

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Abstract

Objectives: Resting heart rate (RHR) is a physiological parameter that has been reported to be associated with endothelial dysfunction. Endocan and thrombomodulin are mediators released from endothelium, which are determined to increase in blood with endothelial damage. We aimed to investigate the relationship between RHR and these biomarkers.

Materials and Methods: Sixty-eight healthy volunteers (28 females; mean age: 44.2±6.3 years) were included in the study. Subjects divided into two groups according to heart rate quartiles: lower two quartiles as group 1 (n=35,) and upper two quartiles as group 2 (n=33). Endocan and thrombomodulin levels in blood of the individuals were

measured.

Results: Clinical features and laboratory findings were similar in both groups ($p>0.05$ for all variables). Mean RHRs were 70.9±4.9 in group 1 and 84.8±4.3 in group 2. No statistically significant difference was found in endocan and thrombomodulin levels in both groups ($p>0.05$ for all variables). No significant correlation was detected between RHR and these molecules.

Conclusion: RHR was not associated with endothelium derived biomarkers endocan and thrombomodulin.

Keywords: Resting heart rate, endothelial dysfunction, biomarker, endocan, thrombomodulin



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Introduction

Resting heart rate (RHR) is an indicator of the autonomic nervous system balance and its increase shows that this balance is impaired in favor of sympathetic system. In epidemiological studies, increased heart rate was found to be associated with poor prognosis in cardiovascular diseases (CVD), especially in coronary artery disease (CAD), independent of other known cardiovascular risk factors⁽¹⁻³⁾. Although the underlying mechanism is not fully understood, it has been reported in experimental and clinical studies that the increase in RHR accused of endothelial dysfunction with increased sympathetic activity and mechanical stress on the vessel wall which led to atherosclerosis⁽⁴⁻⁷⁾.

A healthy endothelium is essential in the regulation of vascular tone, platelet adhesion, inflammation, fibrinolysis and vascular proliferation. In doing so, the endothelium secretes a variety of mediators, primarily nitric oxide. Thrombomodulin (sTM) and endocan are two of these released from the endothelium and shown to be associated with endothelial dysfunction⁽⁸⁻¹¹⁾.

Based on the studies showing the relationship between RHR and endothelial dysfunction^(6,7), in healthy adults we aimed to investigate the relationship between RHR and endocan, sTM which is thought to play a role in endothelial dysfunction.

Materials and Methods

A total of 68 healthy volunteers whose age were between 18 and 65 years were consecutively enrolled in the study. All individuals were included in the study after a detailed medical evaluation including clinical history, physical examination, routine laboratory panel, electrocardiography (ECG) and echocardiography. Hypertension, diabetes mellitus, CAD, significant valvular heart disease, heart failure (left ventricular ejection fraction <40%), inflammatory diseases (acute or chronic), smoking, use of any medical drugs which have an impact on heart rate and hepatic, thyroid and renal disorders were the exclusion criteria. Twenty-four hours of Holter monitoring with Promedic HECG-12 Holter

management system including Ambulatory ECG Systems software running under Microsoft Windows was applied to all cases. All patients were advised to avoid activities that could increase heart rate, such as smoking and drinking coffee during the holter recording. RHR was calculated by the mean of the three lowest heart rates obtained from day time (09:00 a.m.-10:00 p.m.) recordings by two blinded cardiologists. Nighttime heart rate was excluded due to concerns regarding the influence of diurnal variation⁽¹²⁾. Subjects were grouped according to quartiles of RHR as per most previous heart rate studies⁽¹³⁾. Subjects with lower two quartiles heart rate between 60-78 beat/min were included in group 1 and subjects with upper two quartiles heart rate between 79-96 beat/min were included in group 2. Informed consent was obtained from all participants and the study was approved by Harran University Ethics Committee with project number 74059997.0510.01.04/107.

All biochemical and hematologic values were on the day of sample collection following a fasting period of 12 hours. The Abbott Diagnostics C8000i auto-analyzer (Abbott, Wiesbaden, Germany) was used to determine all biochemical panels. Blood samples were collected into plain tubes and serum was separated after centrifugation at 1,500 g for 10 minutes and stored at -80°C for analysis of sTM and endocan. Both serum endocan and sTM levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit with high sensitivity and specificity for detecting human endocan (Cusabio Bioscience Inc, Wuhan, China). The minimum detectable concentrations of endocan and TM were 0.039 ng/mL and 7.8 pg/mL, respectively. The intra-and inter-assay coefficients of variation were less than 8% and 10%, respectively, for both biomarkers^(8,9).

Statistical Analysis

SPSS for Windows software (ver. 22.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A Shapiro-Wilks test was applied to assess the normality of the distributions of continuous variables. For comparison, the independent samples t-test or Mann-Whitney U test

were used where appropriate. The results were presented mean ± standard deviation or median (minimum-maximum). Pearson’s correlation analysis was performed for normally distributed variables. P value <0.05 was considered to indicate statistical significance.

Results

Demographic, clinical and laboratory data of the study sample were given in Table 1. A total of 68 individuals with mean age 44.2±6.3 years were enrolled in this study. Group 1 consisted of 35 patients (21 men) with mean age 44.9±7.1 years and group 2 consisted of 33 subjects (19 men) with mean age 43.3±7.7. With respect to age, gender, body mass index (BMI), lipid panel, creatinine, fasting glucose, high-sensitive C-reactive protein (hsCRP) and hemoglobin levels there were not any significant difference between groups. Normally distributed RHR values of the study population are shown in Figure 1. Mean RHR values were 70.9±4.9 in group 1 and 84.8±4.3 in group 2.

Table 1. Baseline demographic, clinical and laboratory characteristics of the study population

	Group 1 (n=35)	Group 2 (n=33)	P value
RHR (beats/min)	70.9±4.9	84.8±4.3	< 0.001
Age, years	44.9±7.1	43.3±7.7	0.24
SBP (mmHg)	121±7	122±6	0.67
DBP (mmHg)	78±5	79±4	0.76
Female, n (%)	14 (40)	14 (42)	0.79
BMI, kg/m ²	25.9±2.8	25.3±1.7	0.56
Total cholesterol, mg/dL	185(133-270)	190 (84-256)	0.52
LDL, mg/dL	104±29	109±21	0.66
HDL, mg/dL	35.4±6.2	34.7±7.3	0.75
Triglyceride,mg/dL	195 (85-317)	181 (75-303)	0.69
Fasting glucose, mg/dL	87 (72-105)	89 (79-103)	0.84
Creatinine, mg/dL	0.77±0.12	0.80±0.17	0.35
Hemoglobin, g/dL	15.5 (13.1-16.8)	15.2 (13.4-17)	0.74
hsCRP, mg/dL	0.46±0.21	0.44±0.23	0.56

RHR: Resting heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure BMI: Body mass index, HDL: High-density lipoprotein, hsCRP: high sensitive C-reactive protein, LDL: Low-density lipoprotein, n: Number of the patients

Values are expressed as mean ± standard deviation

There was not any significant difference in endocan and sTM concentration between groups as shown in Figure 2 (p=0.23 and p=0.81 respectively). In correlation analysis, no significant association was found between RHR and endocan, sTM (Table 2).

Discussion

RHR is a simple non-invasive physiological parameter of autonomic dysfunction which was reported to be a strong predictor of adverse cardiovascular events and all-cause mortality both in healthy individuals and population with CVD in epidemiologic studies^(1-3,14). In some studies, although heart rate was suggested to be associated with CVD independent of other known risk factors, others claimed that this relationship was dependent to confounding risk factors^(3,15,16). Moreover, RHR has been found to be associated with sudden cardiac death and cardiovascular risk factors such as diabetes, hypertension, dyslipidemia and obesity⁽¹⁷⁻¹⁹⁾.

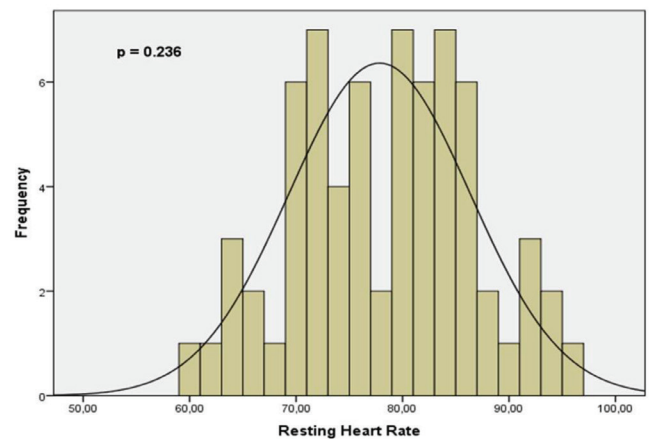


Figure 1. Histogram of the resting heart rate distribution of the study population

Table 2. Correlation between resting heart rate and other parameters

	Coefficient*	p
Age	-0.245	0.33
BMI	0.354	0.24
Thrombomodulin	0.261	0.19
Endocan	0.378	0.21
hsCRP	-0.215	0.42

BMI: Body mass index, hsCRP: High sensitive C-reactive protein

*From Pearson’s correlation analysis

Previous studies have presented strong evidence proving the association between increased RHR and many stages of atherosclerosis, such as endothelial dysfunction, CAD severity, and even plaque rupture^(5,6). An increase in RHR increases the frequency and strength of the mechanical load applied to the arterial wall. Relatively shortening of the duration of diastole as a result of the increase in heart rate causes increase in the time spent in systole which prolong the exposure of arterial endothelium to the systolic low and oscillatory shear

stress. Furthermore, increase in frequency of periodically change in arterial geometry due to high heart rate promotes the power of tensile and shear stress on the vascular wall. All these changes induce structural changes in vascular endothelium which promotes vascular stiffening and then atherosclerosis⁽⁵⁾.

In a study conducted in a multiethnic population with 6484 participants, RHR was associated with increased arterial stiffness, which is an indicator of endothelial dysfunction⁽²⁰⁾. Moreover, both in animal studies and in human studies, the beneficial effects of decreased heart rate on endothelial function have been demonstrated^(4,6,7). Endocan and TM are two molecules released from endothelium that have been shown to be associated with endothelial dysfunction in previous studies⁽⁸⁻¹¹⁾. In our study, we tried to evaluate the relationship between RHR and endothelial function by investigating whether there is a relationship between these endothelium derived molecule levels and RHR in healthy participants. Our study groups were homogeneous according to their demographic, clinical and laboratory characteristics. In our work, we did not detect any difference in both sTM and endocan levels in patients grouped due to their heart rates (Figure 2). Unlike previous studies mentioned, we did not find any relationship between RHR and these biomarkers which are thought to have role in endothelial dysfunction. We also did not detect any relationship between RHR and age, gender and BMI. Although previous studies have shown a positive correlation between the hsCRP concentration^(13,21), which is an indicator of inflammation, and RHR, we did not find any relationship in our study.

Observational design and relatively small sample may be the reasons of our study's inability to detect significant correlations. Single time measurement of biomarkers could not clearly reflect the long-term state of subjects. We did not also measure nitric oxide level, which is considered to be the primary biomarker in demonstrating endothelial functions. Lack of evaluating heart rate variability, psychiatric disorders and social background

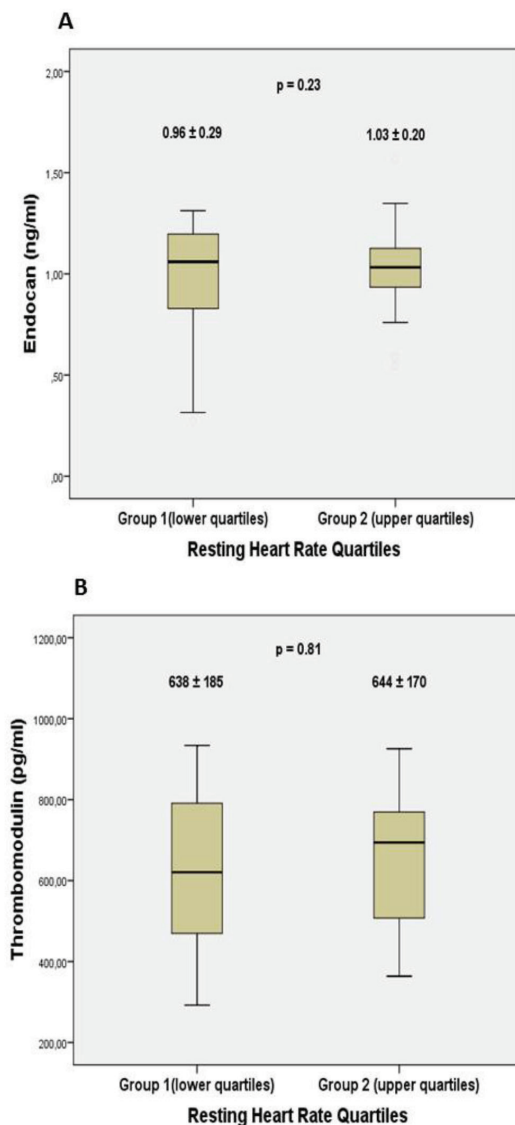


Figure 2. (A) Endocan, (B) thrombomodulin levels of the study population grouped by heart rate quartiles

variables such as economic and education status are the other limitations of our study.

Our study results presented that RHR was not associated neither with endothelium derived biomarkers sTM and endocan nor with age, gender and BMI. Further large prospective studies with large sample size are required to its clinical utility.

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Ethics

Ethics Committee Approval: This study was approved by Harran University Ethics Committee with project number 7405997.0510.01.04/107.

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Financial Disclosure: All support for this study came from institutional and departmental resources.

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A Huge True Axillobrachial Aneurysm Following Arteriovenous Fistula Ligation

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Abstract

Aneurysmal degeneration of the upper limb arteries is a rare entity. We discuss the clinical characteristics, surgical options for a huge true axillobrachial artery aneurysm following arteriovenous fistula closure after renal transplantation. The underlying pathogenesis of the true axillobrachial artery aneurysm remains unclear. The current theory is that the adaptive arterial wall enlargement is secondary to the increased flow in the inflow artery.

Immunosuppressive therapy and corticosteroids contribute to the aneurysmal formation. Surgical treatment including aneurysmal excision, bypass with autogenous or prosthetic grafts are the primary therapeutic options.

We believe that this case will be inspiring and helpful to the cardiovascular surgeons during their daily practice.

Keywords: Aneurysm, axillobrachial aneurysm, vascular access, hemodialysis, arteriovenous fistula

Introduction

Aneurysmal degeneration of the upper limb arteries is a rare entity⁽¹⁾. A true aneurysm formation that is proximal to the inflow artery after closing an

arteriovenous fistula (AVF) is a rare complication⁽²⁾, and the underlying pathogenesis of a true axillobrachial artery aneurysm (TABA) remains unclear⁽³⁾. The current theory is that the adaptive arterial wall enlargement is secondary to the increased flow in the inflow artery⁽³⁾, and



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immunosuppressive therapy and corticosteroids contribute to aneurysm formation⁽²⁾. Surgical treatment, including excision and bypass, is the primary therapeutic option⁽¹⁾. The surgeons must be careful to identify patients with a TABA in order to provide the required surgery in time.

This paper explains our surgical approach to the treatment of a TABA that occurs after AVF ligation following successful renal transplantation (RTx).

Case Report

A 63-year-old female with complaints of increasing pain, swelling, and paresthesia in her left arm was admitted to the clinic. The patient had a 30-year history of chronic renal failure, and the left brachiocephalic AVF was used for hemodialysis without any revision. She underwent successful RTx in 2008. The AVF was ligated at the level of the anastomosis with a single surgical tie in 2009. No additional information was available regarding the procedure because the operation was performed at another hospital. For this reason, there is no information about the diameter of the brachial artery or whether or not duplex ultrasonography (DUS) was performed during ligation. She received immunosuppressive therapy for nine years. During the long postoperative period, the swelling in the left arm of the patient expanded gradually. The patient was admitted to several hospitals, but she was not received due to the high surgical risk.

On physical examination, paresthesia, muscle weakness, and a huge pulsatile mass were detected in the left upper limb (Figure 1A). There were ischemic changes and weakened distal pulses in her left hand.

The DUS showed a true aneurysm of 7 cm in diameter originating from the left axillobrachial artery. The aneurysm extended to the brachial artery bifurcation and was highly tortuous. The aneurysm examination was performed using DUS because CT angiography (CTA) was not available.

The decision for surgical repair was made because of the excessive dilatation of the aneurysm. The patient underwent the operation under elective conditions.

In the operation, a left subclavicular incision was made, and the left subclavian artery was controlled. A longitudinal incision was made in the aneurysm, the aneurysmal mass was exposed (Figure 1B), and the distal arteries were clamped. A saphenous vein graft was harvested. The aneurysm was extended from the axilla to the forearm. We preferred a composite graft in order to prevent the potential risk of a kink in the prosthetic graft at the elbow level and to avoid diameter incompatibility in the axillary region. The composite graft interposition was performed before the aneurysmal sac resection to avoid a long ischemia time (Figure 2A). The total arterial occlusion time was 26 minutes. The median nerve was carefully dissected from the aneurysmal wall. After the aneurysm was removed, the reversed vein graft was resized to fit its anatomical trace. Finally, the enlarged skin flap was removed. The operation was completed without complications. The postoperative follow-up was uneventful (Figure 2B). At two years follow-up, there were no ischemic or neurologic events in the left upper extremity and the graft was patent.

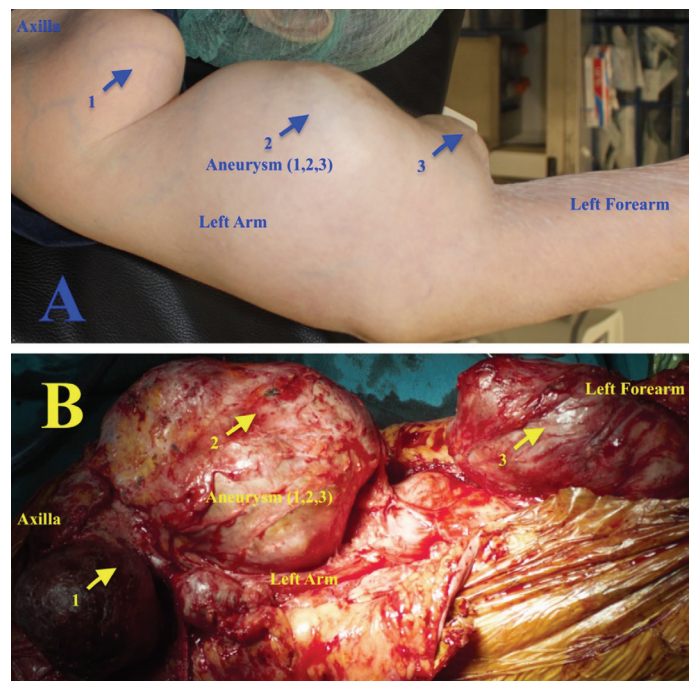


Figure 1. Preoperative view of the left arm (A) and intraoperative view of the aneurysmal exploration (B)

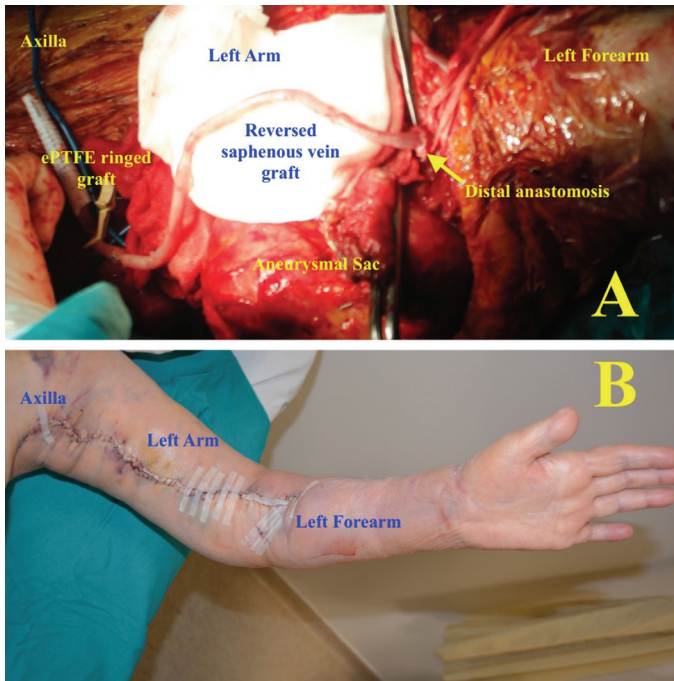


Figure 2. The revascularization procedure: (A) and postoperative day#3 view of the left arm (B)

Discussion

Aneurysm formation is a serious complication of vascular access. The surgical approach for treating a huge TABA requires the use of a combination of experiences in most cases. The decision to attempt a surgical reconstruction in the case of a huge TABA can be a nightmare for a surgeon due to the possible complications⁽⁴⁾.

Axillobrachial aneurysms are rare entities and may occur for many reasons, including multiple vascular traumas, vasculitis, and endocarditis⁽⁵⁾. A TABA is a very rare condition⁽⁴⁾. It is difficult to detect progression in a TABA because of its unknown nature. Duplex imaging is a simple method for following the enlargement of the brachial artery over time⁽³⁾. However, we could not get sufficient information about the previous imaging results and follow-up because the patient underwent follow-up in another hospital. Although other true peripheral aneurysms are seen as synchronous with each other at certain times, there is no relation between TABAs and other peripheral aneurysms⁽¹⁾. This suggests that TABAs have a different pathogenesis.

Many cases in the literature suggest a relation between TABAs and AVFs⁽³⁻⁵⁾. While some studies correlate this relationship to AVF creation⁽³⁾, some also correlate it to AVF closure^(4,5). Currently, the pathogenesis is explained by the fact that the shear forces arising from the increased flow in the arterial lumen cause the dilation of the arterial wall⁽³⁾. Even if the AVF is completely closed, this process cannot be stopped, and a permanent arteriomegaly will develop⁽⁶⁾. According to Eugster's results, the aneurysm formation in the brachial artery following AVF creation is time-dependent. He also argues that high flow through the AVF is the main trigger for aneurysm formation⁽⁶⁾. We cannot explain the pathophysiological process from a single patient, and we cannot provide a histopathological sample for the aneurysm because of the inadequate infrastructure. As in our case, RTx and immunosuppressive drugs may be related to the progression of a true aneurysm⁽²⁾. Investigations have shown that TABAs are more commonly observed in transplant patients than in non-transplant patients⁽⁶⁾. The use of post-transplant immunosuppressive agents and corticosteroids also contributes to the progression of the aneurysm⁽²⁾.

TABAs have clinical findings similar to other peripheral aneurysms. Most of the cases are asymptomatic. Clinical manifestations include pain, ischemic changes, and neurological findings due to local compression⁽⁵⁾. In our case, there was pain, ischemia, paresthesia, and muscle weakness.

The physical examination should include both neurological examination and vascular examination⁽⁵⁾. DUS is the first step in diagnosis and is highly reliable⁽⁵⁾. CTA may be used in selected cases, particularly when planning an operation⁽⁵⁾. We performed the preoperative examinations using DUS because CTA was not available. However, we believe that DUS is sufficient for pre- and post-operative follow-up.

The main option in TABA treatment is surgery^(2,4,5). In very rare cases, such as with vasculitis, medical treatment may be tried as the first management⁽¹⁾. However, if the aneurysm is large, surgery is the primary option⁽⁴⁾. In most studies, surgery is recommended when the artery

diameter is 1.5 to 2 times larger than normal⁽¹⁾. We support this view, but most surgeons are reluctant to operate on huge aneurysms⁽¹⁾. Our patient required the operation very early, but she did not accept because of its high risk. Surgical interventions usually include excision, ligation, and bypass grafting. Venous patches may also be used in anatomically suitable cases⁽¹⁻⁶⁾.

Because of the huge size of the aneurysm, we performed a different surgical technique, as detailed above. Because the subclavian artery was dilated and the aneurysm extended under the elbow, there was a graft mismatch risk. For this reason, we preferred to use a composite graft. In similar cases, the saphenous vein has been used as a conduit⁽¹⁻⁶⁾. Prosthetic grafts or other native veins have been used in a few cases⁽⁴⁾.

Currently, endovascular interventions are feasible with suitable true aneurysms and pseudoaneurysms associated with vascular-access procedures, but they are not convenient with huge TABAs^(1,4).

Conclusion

We believe that proximal arterial control is useful for reducing the risk of bleeding in cases of huge aneurysms and that complications can be minimized using an autogenous and non-autogenous graft combination in difficult cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case

report and accompanying images. A copy of this consent is available upon request.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O., U.Ö., Concept: A.O., U.Ö., Design: A.O., Data Collection or Processing: A.O., U.Ö., Analysis or Interpretation: A.O., Literature Search: A.O., Writing: A.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Pulmonary Artery Aneurysm Causing Left Main Coronary Artery Disease

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Abstract

Pulmonary artery aneurysm is a rare clinical condition but may lead to serious complications such as pulmonary artery dissection, rupture and compression of left main coronary artery. The relation between the pulmonary artery and the adjacent structures should be considered after the diagnosis of the aneurysm. Surgery is suggested in the patients with increased diameter of the pulmonary artery or symptoms caused by the compression to the neighborhood tissues. In this case, we are reporting a 52-year-old female patient with

pulmonary artery aneurysm causing the compression of left main coronary artery and presenting with chest pain. Owing to the successful surgical correction of the aneurysm, the compression of the left main coronary artery was removed. Relief of the coronary artery from the compression might be enough to improve symptoms in the patients with pulmonary artery aneurysm.

Keywords: Aneurysm, dissection, left main coronary artery, pulmonary artery

Introduction

Pulmonary artery aneurysm (PAA) is a rare clinical condition, which might be developed congenitally or acquired⁽¹⁾. Main pulmonary artery diameter over 43.4 mm in males and 40.4 mm in females or 1.5 times wider than normal values is defined as PAA⁽²⁾. Congenital cardiac diseases, connective tissue diseases, vasculitis,

endocarditis, infection, pulmonary hypertension, neoplasia, trauma, pulmonary cardiac disease, pulmonary artery dissection, pulmonary embolism, arteriovenous fistula and idiopathic causes were reported in the etiology of the PAA⁽³⁾.

PAA has no specific symptoms. PAA might cause compression on neighboring structures by getting



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wider and patients might be symptomatic due to the compression⁽⁴⁾. Cough, dyspnea, hoarseness, pulmonary artery fistulization to trachea, hemoptysis and chest pain might develop according to the compressed tissue. In this case we are presenting successful surgical treatment of PAA that referred with chest pain and dyspnea.

Case Report

A 52-year-old patient referred to our clinic with the complaints of chest pain and dyspnea. The functional capacity of the patient was New York Heart Association (NYHA) class 3 and vital findings were normal. In the chest radiography, cardiothoracic ratio had minimally increased (0.55) and pulmonary artery shadow was pronounced. Pulmonary artery was enlarged with the diameter of 54 mm. in the transthoracic echocardiography (TTE). Also, there were 12 mm. secundum type atrial septal defect, mild tricuspid and pulmonary valve regurgitation. Left main coronary artery (LMCA) disease caused by the compression of the PAA was diagnosed in the coronary angiography (Figure 1). Mean pulmonary artery pressure was 32 mmHg. Computed tomography revealed main PAA with the diameter of 56 mm. That extending to the

right and left pulmonary arterial branches and compressed on LMCA.

After the median sternotomy and pericardiectomy expansion in pulmonary artery and its branches was noted. Standard cardiopulmonary bypass (CPB) was maintained with aortic and bicaval venous cannulation. Aneurysmatic pulmonary artery was exposed. Pulmonary arteriotomy was done. Pulmonary valve had a normal anatomic structure, then aneurysmatic pulmonary artery was extracted. Graft interposition of 32 mm Dacron graft for the main pulmonary artery and 28 mm Dacron graft for pulmonary arterial branches was done with 4-0 prolene stitches. Atrial septal defect was repaired with pericardial patch. Operation was ended after termination of the CPB. Aortic cross clamp time was 111 minutes and total perfusion time was 136 minutes. The patient was extubated on postoperative seventh hour. There was mild tricuspid valve regurgitation and low pulmonary arterial hypertension in the postoperative second day control TTE. Control angiography was performed at postoperative 5th day and it was observed that the stenosis caused by the external compression on LMCA had completely disappeared (Figure 2). The patient was discharged from the hospital on postoperative seventh day. Postoperative functional capacity of the patient was observed as NYHA class 1 in follow-up period.



Figure 1A. Left main coronary artery stenosis due to compression of the pulmonary artery aneurysm

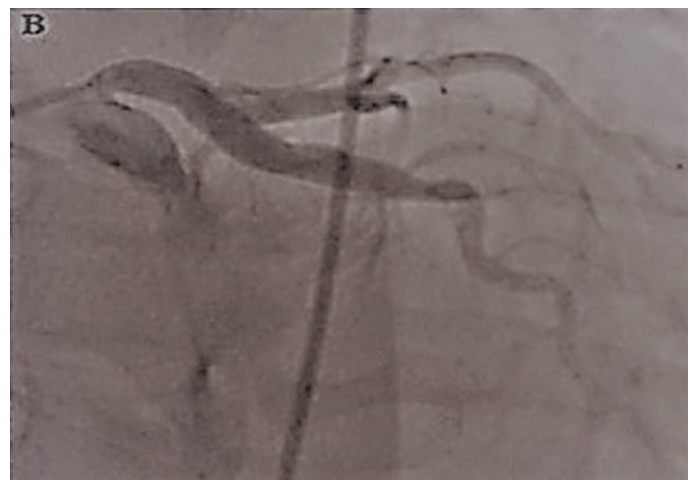


Figure 1B. View of the left main coronary artery after removal of the compression

Informed consent form was obtained from the patient.

Discussion

PAA involving main pulmonary artery together with its branches are rare as in our case and it was reported with rate of 11% of all PAAs⁽⁵⁾. External compression of the coronary arteries might be presented as coronary arterial disease. In this clinic condition relief of compression might be enough for the treatment rather than the coronary artery bypass grafting. In our case we diagnosed external compression of the PAA to the LMCA in the detailed examination. There is no need to coronary artery bypass grafting after decompression of the PAA.

Although there is no exact mechanism of the etiology, cystic medial degeneration of the media layer of pulmonary artery or prostaglandin E receptors might play role for the development of the PAA⁽⁶⁾. In the surgical indication of the PAA, there is not any consensus yet. However, pulmonary arterial dissection of PAA with the diameter of 60x55 mm was reported in the literature⁽⁷⁾. Compression to the LMCA, higher than 55 mm pulmonary artery diameter is suggested for surgical intervention⁽⁸⁾.

Different techniques such as pericardial patchplasty, aneurysmorrhaphy, plication and graft interposition are among surgical strategies⁽⁹⁾. Plication is a fast and easy technique to apply, but recurrence might develop after this surgical procedure. Graft interposition decreases the recurrence risk with the advantages of extraction of the native vessel wall⁽¹⁰⁾. In our patient we performed graft interposition to the main pulmonary artery and its branches. There was not any complication in the perioperative period and postoperative follow-up.

PAA might be kept in mind in the differential diagnosis of the non-specific complaints such as dyspnea, chest pain, cough and hoarseness. In the patients with compressed coronary arteries it might presented as coronary artery disease. Surgical treatment of the PAA might be enough in the complications caused by the compression syndrome.

Ethics

Informed Consent: Informed consent form was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ö., N.T., Concept: B.Ö., Design: B.Ö., Data Collection or Processing: B.Ö., Analysis or Interpretation: B.Ö., N.T., Literature Search: N.T., Writing: B.Ö., N.T.

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How Old is Too Old? Observing A Centenarian After Primary PCI

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Abstract

Very elderly and frailty are two common risk factors for patients in the setting of acute myocardial infarction and its outcomes. Due to their exclusion from clinical research, follow-up data is inadequate in patients at their nineties and in centenarians. Timely performed percutaneous coronary intervention is the treatment of choice for acute myocardial infarction in very elderly. Unfortunately, patients in their

late “90s or in nonagenarians, physicians or patients” relatives usually reject this approach for its invasive nature, multiple comorbidities, lack of larger meta-analysis and misbelief related fear. This report contains a history 98-year-old female presented within the first hour of an acute myocardial infarction and her two years’ follow-up.

Keywords: Acute coronary syndrome, elderly, centenarian

Introduction

Advanced age is an important risk factor for patients with acute coronary syndromes⁽¹⁾. As population aged, centenarians or oldest old patients in the other term, became quite common in daily routine practice. Because of widely available modern catheter laboratory facilities, improved device technology and increased experience in interventional cardiology, primary percutaneous coronary intervention become the therapy of choice in very elderly with ST-segment elevation myocardial infarction⁽²⁾.

Despite of reported complications, both radial and femoral approach can be performed successfully in these ages. On the other hand, regardless of all improvements for this safe and proven treatment option, patient’s invasive procedure related fear, and their relative’s opinion in these settings are the major barrier for timely performed percutaneous coronary interventions^(1,3).

Case report

A 98-year-old female was referred to our emergency room within 30 minutes of continuous chest pain and



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rapidly progressive dyspnea. Sinus bradycardia (39 bpm) and hypotension (85/55 mmHg) were noted at admission. Her electrocardiogram's showed signs of acute inferior and right ventricular myocardial infarction (Figure 1A-B). No pulmonary crackles and other physical examination abnormalities were observed. Echocardiography showed mild right ventricular dilatation, inferior wall akinesia, moderate mitral insufficiency, and 45% left ventricular ejection fraction (LVEF). Immediately after 300 mg acetylsalicylic acid, 600 mg clopidogrel and 5000 IU unfractionated heparin load, a transvenous pacemaker was implanted and a coronary angiography was performed

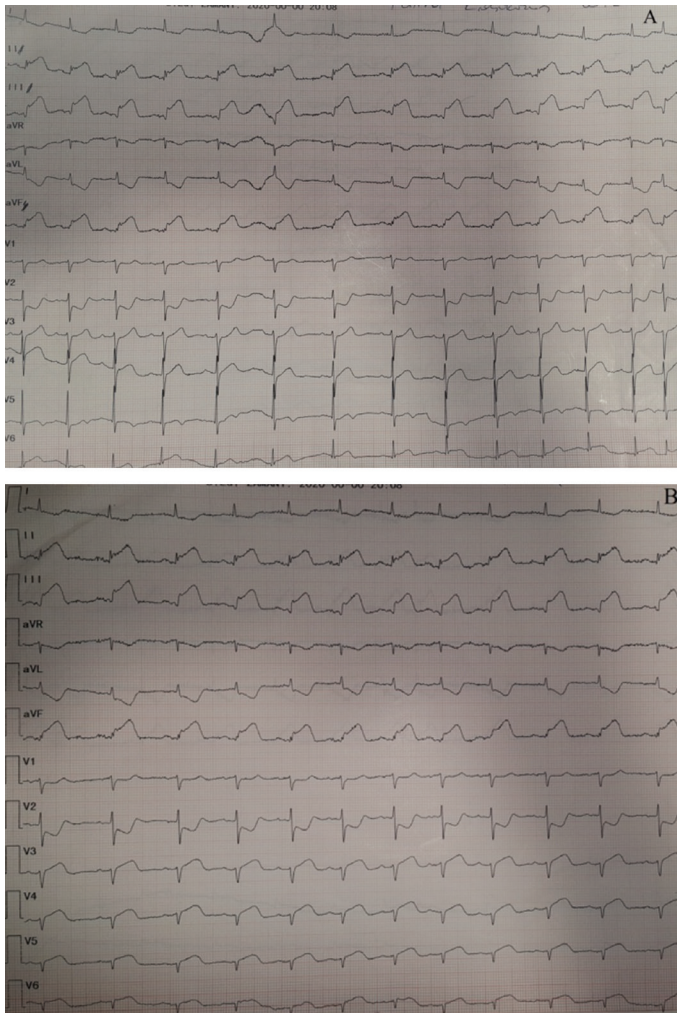


Figure 1. (A-B) Admission ECGs show an acute inferior and right ventricular myocardial infarction (A: left precordial leads, B: right precordial leads)

(Figure 2). At the same session, a drug eluting stent was implanted for proximal right coronary artery occlusion, and medical management decision made for borderline contra-lateral coronary lesions (Figure 2). She was complication free in-hospital course. The pacemaker removed on the second day and she discharged on the sixth day of hospital admission. In two-year follow-up at her 100 years of age; the patient was event-free, physically and mentally well with 54% LVEF, a mild mitral regurgitation, and slight increase in kidney function tests. Her medical treatment was optimized and invited for regular clinical visits.

Discussion

People at their nineties (nonagenarians) are rapid growing proportions of patients treated with primary percutaneous coronary interventions in current clinical practice. Also, age-related physiological changes, disease progression, and frailty increase both potential benefits of mechanical revascularization and procedure-related adverse outcomes (e.g. access site bleeding and thrombotic

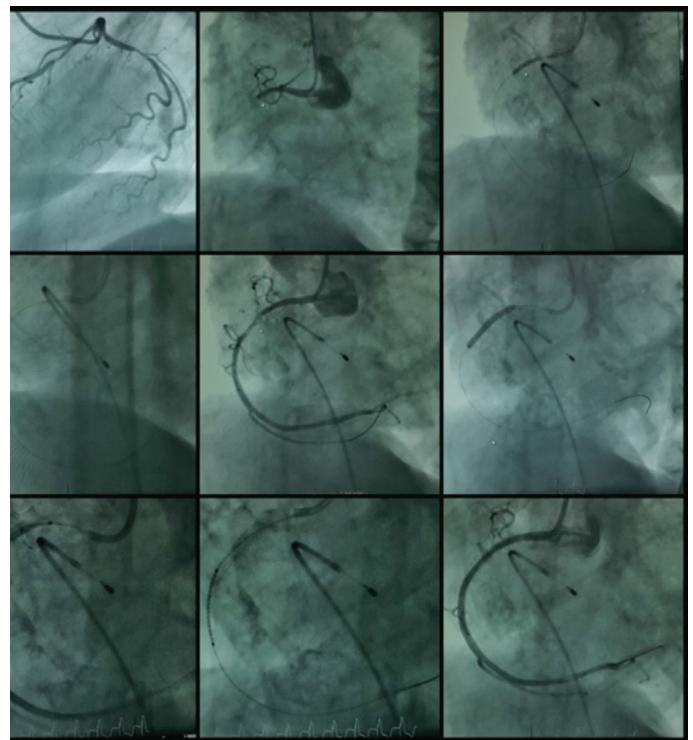


Figure 2. Coronary Angiography shows the lesions and stent implantation

complications). We would like to stress it out that, timely invasive treatment in very elderly is better in acute setting in terms of short- and long-term outcomes. Including more patients at these ages to future randomized trials will help to improve our clinical experience in acute setting, broad current knowledge on this population, and might address advanced age-related problems in follow-up care. In this case report, we summarized our daily practice as performing coronary intervention in urgent settings in patients >90 years old along with mid to long term follow-up is safe but rare in the current literature.

Ethics

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Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.K., Concept: Ç.K., C.Z., Design: Ç.K., C.Z., Data Collection or

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Conflict of Interest: No conflict of interest was declared by the authors.

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