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Journal of Cardiovascular Medicine and Surgery

July - December 2015
Volume 1 Number 2

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Original Article

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - Dcecmber 2015

Impact of Perioperative Pentoxifylline Treatment on Cardiopulmonary Bypass Induced Inflammatory Response: A Randomized Controlled Trial

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Abstract

Background: The frequent occurrence of bypass induced systemic inflammation after coronary artery bypass grafting (CABG) is a major concern for scientists. Various attempts in attenuating the inflammation have been tried. Recently few studies showed that pentoxifylline (PTF) treatment reduces inflammation from cardiopulmonary bypass (CPB). The perioperative use of PTF on inflammatory response was estimated by measuring biomarkers of inflammation. *Objectives:* To evaluate the effect of PTF on biomarker of inflammation in patients undergoing CABG using CPB. *Methods:* Sixty patients age between 40-65 years scheduled for CABG surgery using CPB were included in the study. The study group was administered PTF (Group I) 400 mg twice daily orally from the day of admission to 6th day after surgery. Whereas the control group was not administered PTF (Group II). Blood samples were collected perioperatively at 4 points of time; before induction of anaesthesia, after 1h of termination of CPB, 24h after surgery and 6thpost-operative day for interleukin-6 (IL6) and C- reactive protein (CRP) as inflammatory markers. The data was analyzed and P<0.05 was considered significant. *Results:* The IL-6 and CRP values were similarbefore induction of anaesthesia (p= 0.473 and p=0.315) between two groups. The PTF treated group had lesser rise in the level of IL-6 (51.38±30.04 vs 119.74±103.86. p<0.017; 69.70±23.60 vs 135.72±88.19, p<0.002; 12.11±5.65 vs 40.20±30.58; p< 0.000) and CRP (6.04±2.88 vs 8.83±2.9, p< 0.000; 158.79±42.37 vs 223.87±93.00, p<0.004; 92.70±33.07 vs 184.52±117.82, p< 0.000) compared to control group patients after 1h of termination of CPB, 24h after surgery and 6thpost-operative day. *Conclusions:* Pentoxifylline attenuates rise in level of IL6 and CRP due to cardiac surgery. Hence perioperative treatment of pentoxifylline will reduce inflammatory reaction in patients undergoing CABG with CPB.

Keywords: Coronary Artery Bypass Grafting; Cardiopulmonary Bypass; C- Reactive Protein; Interleukin-6; Pentoxifylline.

Introduction

Incidences of postoperative myocardial, pulmonary, renal, hepatic and neurocognitive dysfunctions are reported with coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). [1] The major mechanism is systemic inflammatory response syndrome (SIRS) induced by CPB. Systemic inflammatory response syndrome leads to increased length of hospital stay, morbidity and mortality of the patients. [1, 2]

Many methods were tested to reduce the SIRS after CABG. The improvements in biomaterials, pharmacological, anaesthetic and surgical managements are continuously surfacing. [3] The complete reduction of SIRS from CPB is yet not

achieved. New effective pharmacological agents are needed to overcome the morbidities. Recently few studies show that pentoxifylline (PTF) administration reduces inflammation from CPB[4, 5]. Pentoxifylline with blood viscosity lowering and immunomodulatory property improves microcirculation and oxygenation of brain[6, 7]. Interleukin 6 (IL6) and highsensitivity (HS)-CRP are established markers for detecting inflammation[8].

The aim and objective of the study was to evaluate the effect of PTF on biomarkers of inflammation in patients undergoing CABG under CPB in a prospective randomized controlled trial.

Methods

Study Design

The prospective randomized controlled trial conducted in a tertiary care hospital. The study was conducted after ethical approval from the institutional ethics committee and written informed consent from all patients to participate in the study. The participants were free to withdraw at any time.

Patient Selection

Eightyfive patients for elective CABG under CPB were eligible for the study. Twenty five patients were excluded after implementing allselection criteria. Remaining 60 patients were divided into 2 groups using a computer generated randomized list. Groups 1(n =30) received pentoxifylline (PTF) 400 mg twice daily orally from the day of admission to 6th day after surgery. Whereas the control group was not administered PTF (Group 2). Patients with neurological, kidney disease, liver disease, emergency surgery, recent myocardial infarction, redo-surgery, coagulation disorder, use of anti-inflammatory drugs and uncontrolled diabetes mellitus were excluded from the study.

Sample Calculation and Statistical Analysis

The sample size for the study was calculated based on the result of IL-6 values incontrol group 234±63 versus 99±43pg/ml in PTF group by Otani S et al[7]. Taking 5% as level of significance and 80% power, the estimated sample size of 30 in each group would be sufficientfor a two tailed study.

Statistical analysis was performed using STATA 11.2,Texas; USA was used for data analysis. Data was presented as mean and standard deviation (SD), percentage and frequency unless otherwise indicated. Demographic details, illness variables, anaesthesia and surgical details were recorded using a semi-structured proforma. All the quantitative baseline variables were compared using t-test or Mann Whitney, McNamara test between the two groups, whereas all the categorized variables will be compared using Chi-square or Fisher's exact test while change in groups was seen by paired t test or Wilcoxon Signed ranks or McNamara test as applicable. P value less than (<) 0.05 were considered significant results.

Anesthesia Technique

All patients were kept fasting 6 to 8 h for solid food and 3 to 4 h for liquid before surgery. They were premedicated with oral diazepam 5mg night before and on morning of surgery. All patients received injection morphine 0.1mg/kg and promethazine 0.5mg/kg intramuscular on the day of surgery 45 minutes prior to shifting operation room. Induction of anesthesia consisted of fentanyl, thiopentone sodium and rocuronium. Maintenance of anesthesia included intermittent doses of midazolam, fentanyl, pancuronium and oxygen in air and isoflurane. Monitoring included continuous 5 lead ECG, invasive arterial blood pressure, central venous pressure, pulmonary capillary wedge pressure (PCWP), transesophageal echocardiography, end tidal carbon dioxide, SpO_2, temperature, hourly urine output, intermittent arterial blood gases, electrolytes and blood glucose.

Surgical Technique and Cardiopulmonary Bypass

Standard mid-sternotomy, saphenous vein graft and left internal mammary artery graft harvestation were used. Coronary artery bypass with CPB involved heparin 400IU/kg, ascending aortic and two stage venous cannulation in the right atrium, a standard circuit primed with 1.5 liters of ringer's solution, 0.5mg/kg of mannitol and 5000IU of heparin, membrane oxygenator, non-pulsatile flow with perfusion 2.2 to 2.4L/min/m^2 with hypothermia up to 32^{0}C. The mean perfusion pressure was maintained in the range of 70-90mmHg. Cardiac asystole was achieved with multiple dose cold St. Thomas cardioplegia solution after application of aortic cross clamp. Hematocrit was maintained around 25% during CPB. Patients rewarmed to 36^{0}C and heparin was neutralized with protamine sulfate. All operations were performed by the same surgical team. The physicians working in the operating room and the ICU were blinded to treatment protocols. Duration of CPB, number of vessels grafted, any perioperative

use of blood, blood products, inotropes and use of IABP were noted. The decision for extubation and discharge in the ICU was made according to hospital protocol.

Blood Sampling

Blood samples were collected before induction of anaesthesia (T_1), after 1 hr. of termination of CPB (T_2), 24 h after surgery (T_3) and 6thpost-operative day (T_4) for estimation of IL6 and HS-CRP as a serologic marker of inflammation. The estimation of IL6 and HS-CRP were performed with ELISA immunoassay technique by a person blinded to the study.

Other Parameters

Any major cardiovascular, pulmonary, renal and neurological complications related to the procedure were recorded and those patients were excluded. Time of discharge from ICU and hospital were recorded.

Results

All 60 patients, 30 patients in study or pentoxifylline group (group 1) and 30 patients in control group (group 2) completed the study and qualified for statistical analysis. The mean age of the control group (58.1±6.7) was slightly higher than the study group (56.4±7.7) however the difference was not statistically significant. Higher percentages of patients were male in both the groups, (Table 1). Group 2 patients had more number of patients with diabetes ($p<0.03$).

The levels of IL-6 between group-1 and group-2 had significant difference except at the base line time T_1 (Table 2, Figure 1). The results from IL6 levels proved that the control group patients had higher inflammation in comparison to PTF treated group.

The levels of CRP between group-1 and Group-2 had significant difference except at the base line time T_1 (Table 3, Figure2). The results from CRP levels proved that the control group patients had higher inflammation in comparison to PTF treated group.

Table 1: Demographic data

Parameters	Group 1(Study) n=30	Group2(Control) n=30	P value
Age (mean±SD)	56.4±7.7	58.1±6.7	0.36
Weight	69.6±10.3	64.6±8.1	0.04
Gender			
Male	26 (86.7%)	27 (90%)	0.89
Female	4 (13.3%)	3 (10%)	0.54
Diabetes mellitus	6 (20%)	14 (46.6%)	0.03*
CPB time	48.6±11.1	47.38±14.5	0.66
Number of grafts	3.2±0.6	3.18±0.6	0.6
No of PRBC used	2.3±0.9	2.2±0.7	0.5
ICU discharge time (hours)	28.2±4.9	32.4±7.0	0.01*
Hospital discharge time (days)	7.9±0.7	8.0±0.8	0.82
IABP and high inotropes support	7 (23.3%)	7 (23.3%)	1

Abbreviations: CPB- Cardiopulmonary Bypass, ICU- Intensive Care Unit, IABP- Intra aortic Balloon Pump, PRBC- Packed Red Blood Cells, SD- Standard Deviation.

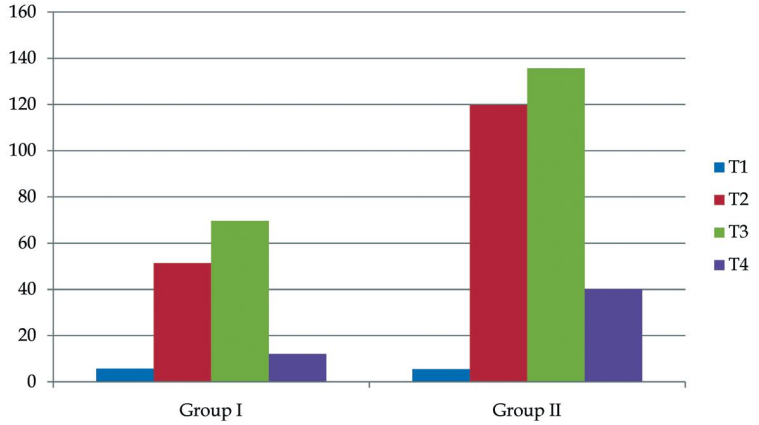

Fig. 1: Chart diagram showing the levels of IL-6 (pg/mL) between two groups at four time points

Table 2: Levels of IL-6 (pg/ml) at different time points of both groups

Time points	Group-1 (n=30)	Group-2 (n=30)	P value
T1	5.76±7.58	5.55±8.00	0.473
T2	51.38±30.04	119.74±103.86	0.017
T3	69.70±23.60	135.72±88.19	0.002
T4	12.11±5.65	40.20±30.58	0.000

Table 3: Levels of CRP (mg/L) at different time points of both groups

Time points	Group-1 (n=30)	Group-2 (n=30)	P value
T1	1.93±2.13	2.68±2.96	0.315
T2	6.04±2.88	8.83±2.91	0.000
T3	158.79±42.37	223.87±93.00	0.004
T4	92.70±33.07	184.52±117.82	0.000

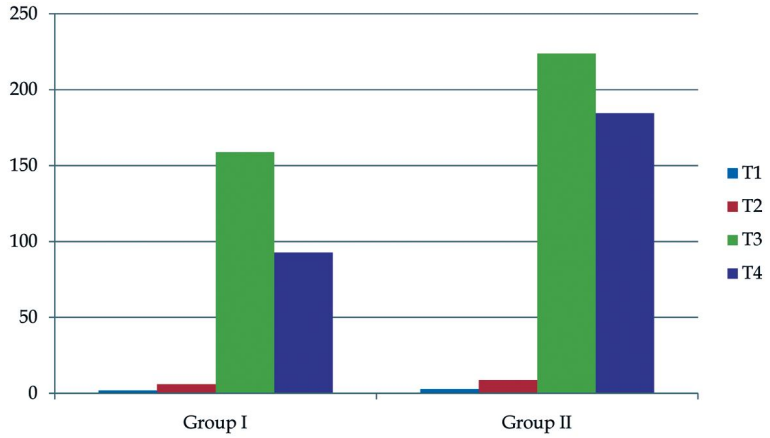

Fig. 2: Chart diagram showing the levels of HS-CRP (mg/L) between two groups at four time points

Discussion

The present study determined that perioperative PTF was effective in reducing the rise in level of inflammatory markers like IL6 and CRP in patients of CABG surgery with CPB. The reduction in inflammation was manifested by early discharge of patients from ICU. The levels of CRP and IL-6 were increased in both the groups from base line time. But the PTF treated group had markedly low rise of the biomarkers than control group patients in the subsequent periods of 1h after termination of CPB, 24h after surgery and 6thpost-operative day.The study also showed that the pro-inflammatory markers level continued to be high even after 6 days after cardiac surgery.

Pentoxifylline is methyl xanthine derivative with phosphodiesterase inhibiting property[6]. It releases the intracellular signaling molecules mainly the cyclic adenosine monophosphate (c-AMP)[7]. The accumulation of c-AMP prevents the release of inflammatory cytokines like tumor necrosis factor alpha (TNFá), IL-6 and CRP. Pentoxifylline has the vasodilatory and rheological property in blood[6]. This improves the microcirculation, reduction in inflammation and immune modulation during cardiac surgery under hypothermic CPB[7,9]. Pentoxifylline also prevents endothelial injury produced due to systemic inflammatory response[10]. All the mechanism of PTF helped in reducing the levels of inflammatory markers in PTF group patients.

Interleukin-6 and CRP are markers of tissue inflammation and complement activation[11]. The levels of IL6 and CRP are high in control group compared to PTF treated group. This suggested that PTF had anti-inflammatory effect. The anti-inflammatory effect of PTFis supported by the study of Otani S et al with the evidence of reduction in IL-6 level[7]. In a similar study with single dose administration of PTF by Heinze Het al detected a marked reduction in the level of inflammatory marker like TNF-á.[12]Tsang GMK et al detected insignificant reduction of IL-6 in PTF treated patients in comparison to placebo therapy in patients undergoing CPB for CABG[10].

The time of ICU discharge was short in PTF group compared to control group. The reason is the anti-inflammatory effect of PTF producing less pulmonary dysfunction related to CPB. Reduced inflammation might have facilitated for less tissue edema, early

extubation, and early stabilization of cardiac function in PTF group. This is supported by the study of Otani S et al and Heinze H et al [7, 12]. Otani S et al detected reduced respiratory index and better pulmonary function in PTF treated patients. Heinze H et al detected lower ventilation time and high dependence unit stay in cardiac surgical patients treated with PTF.Tsang GMK et al in a study found that PTF reduced endothelial injury and lung permeability as well as dysfunction [10].

Limitations**:** The present study had not included elderly patients of age more than 65 year. Patients were only coronary artery disease with less co-existing diseases. The patients were small in number; a larger population will strengthen the finding.

To conclude the perioperative pentoxifylline treatment reduces inflammation markers like interleukin-6 and C-reactive protein in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass support. Further study with enrollment of large number of patients will establish .the findings of the present study.

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Review Article

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

PCSK 9 Inhibtors: New Era in Dyslipidemia Management

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Abstract

Low-density lipoprotein cholesterol (LDL-C) is the most important risk factor for developing coronary artery disease (CAD) as evidenced in landmark INTERHEART study. PCSK9 inhibition offers a novel therapeutic mechanism for lowering low-density lipoprotein cholesterol (LDL-C) levels.PCSK9 is a serine protease that binds the LDL receptor (LDL-R) and acts as a chaperone for endocytosis and shuttling the PCSK9-LDLR complex to lysosomes for degradation. *In the absence of PCSK9 the LDLR-LDL-C complex dissociates and LDL-R is recycled back to the cell surface.* Humanized monoclonal antibodies against PCSK 9 (*evolocumab, alirocumab, bocolicumab*) have been developed which increase LDL-R by 2-fold and lower LDL-C by up to 75 percent with no significant side effects, with the exception of injection site reactions. These novel agents play a pomising role in filling the therapeutic gap in *statin intolerant, difficult dyslipidemics and familial hypercholesterolemic patients*. When combined with statins they bring out a better cardiovascular outcome with a stable and target lipid profile.

Keywords: PCSK9 Inhibitor; Coronary Artery Disease; Low-Density Lipoprotein Cholesterol; Cardiovascular; Dyslipidemia; Statin.

Introduction

Today's dyslipidemia management revolves around the statin world. Statins although display penopoly of cardiovascular benefits through pleiotropic actions, controversy that emerged about statins include statin induced DM, statin hepatomyopathy and intolerance; those led the science emerge with those PCSK 9 inhibitors with better edge than of statins. Familial hypercholesterolemia was a big challenge to the lipidogists in achieving the goal with statin therapy but these golden drugs made the path mistfree. French people were dying of PCSK 9 mutation (F216L, R 218S) induced malignant hypercholesterolemia and accelerated early CAD where statins were not being able to achieve the lipid goal [1, 2]. Mean LDL-C level was more than 200mg/dl in those patients with PCSK 9 mutations [3]. This novel molecule was discovered in 2003 and it exhibited its promising antilipidemic efficacy in 2009 in patients with familial hypercholesterolemia. PCSK 9 mutation was associated with early onset myocardial infarction with an odds ratio of 0.40[4] while loss of function PCSK 9 mutations leads to drastically low level of LDL C in the range of 15-20mg/dl. The discovery of PCSK 9 inhibitors was a miraculous achievement in treating difficult dyslipiemics including the patients with familial hypercholesterolemia.

PCSK 9

The discovery of *proprotein convertase subtilisin/kexin* Type 9 (PCSK9) has opened the possibility for effective and adjunctive therapy for those who are not optimized with statins, who are intolerant and have little alternatives. It was initially identified as neural apoptosis-regulated convertase-1 (NARC-1). PCSK9 is processed in the endoplasmic reticulum where it undergoes cleavage producing a prodomain and catalytic subunit. In the extracellular space, PCSK9 binds to LDL receptor via its catalytic subunit while its C-terminal subunit acts as a chaperone for

endocytosis and shuttling the PCSK9-LDLR-LDL complex to lysosomes for degradation. In the absence of PCSK9, LDLR-LDL complex dissociates and LDLR is recycled back to the cell surface[5].

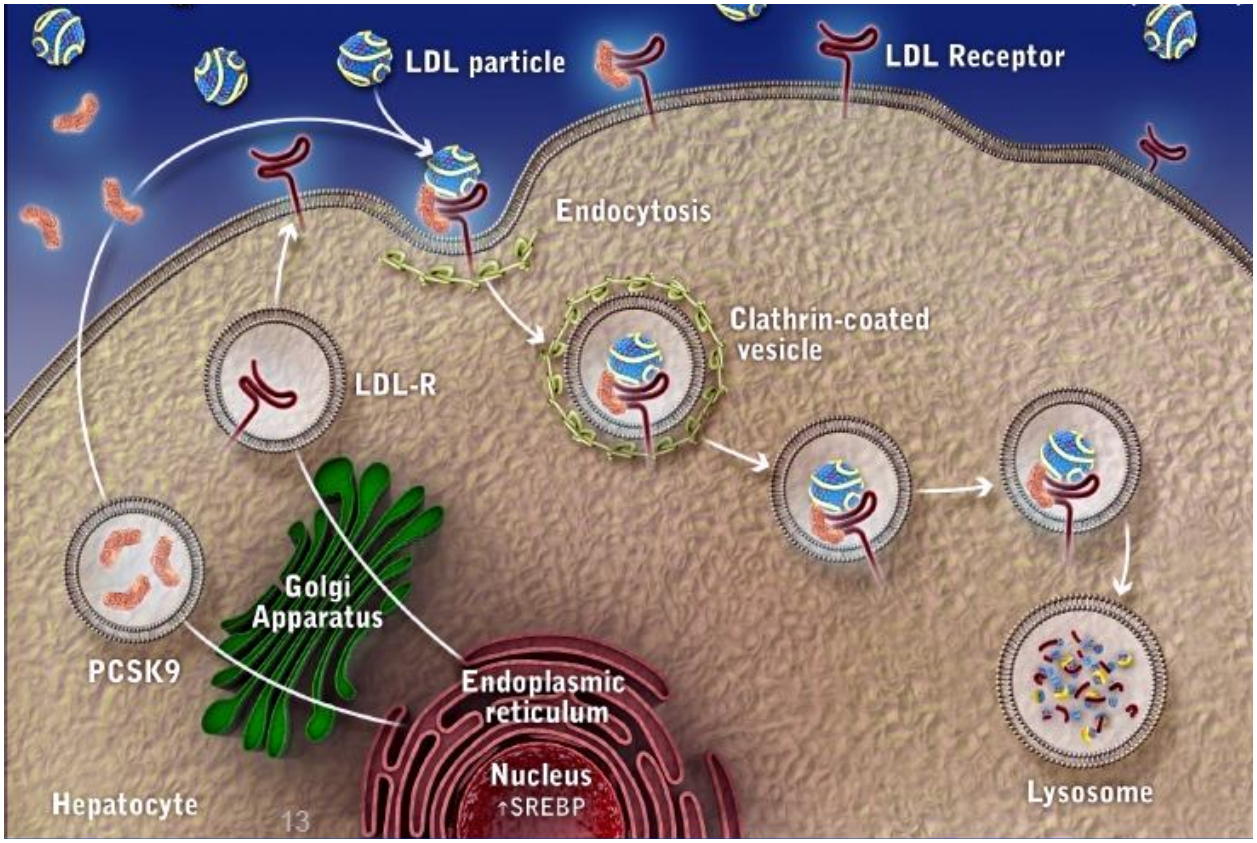

Fig. 1: PCSK 9 aiding in LDL receptor internalization

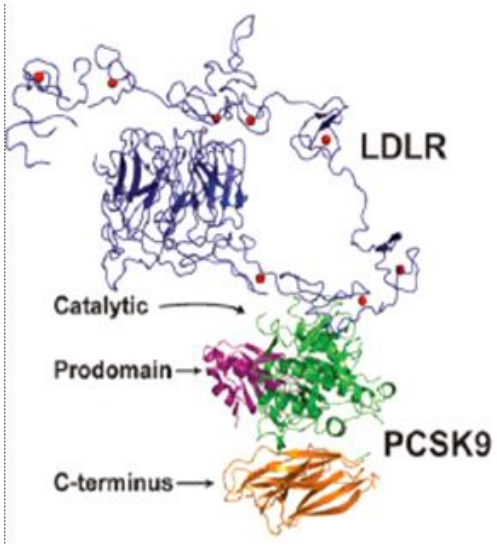

Fig. 2: PCSK 9 and LDL receptor interaction

The PCSK9 gene is located on chromosome 1p32 and its expression is regulated by intracellular cholesterol via SREBP-2[6]. Synthesis of PCSK9 occurs mostly in the liver, small intestine and kidney. Low intracellular levels of cholesterol stimulate the synthesis of LDL-R and PCSK9 to maintain intracellular delivery of cholesterol. *In the setting of statin, fibrate and ezetimibe use, PCSK9 expression is up-regulated due to low intracellular cholesterol levels* [7]. Thus, *PCSK9 inhibition is additive to statin therapy and play a synergistic role in lipid-lowering effect.*

Familial Hypercholesterolemia and Pcsk 9

Heterozygous FH is an autosomal dominant genetic disorder with an estimated prevalence between 1 / 200and 1 / 500 in the general population It is estimated that PCSK9 mutations represent 1% to 2% of all familial hypercholesterolaemia (FH) cases. Mutations of the PCSK9 gene are the third cause of FH, after mutations in the LDL receptor or apolipoprotein B (ApoB) genes.

Pcsk 9 Inhibitors

Approach to reduce PCSK 9 interaction with LDL receptor includes inhibition by monoclonal antibodies and *adnectins* and reduces PCSK 9 synthesis by *antisensen* RNA. Monoclonal antibodies evolved from mouse monoclonal antibody to chimeric, humanized and human monoclonal antibody in due course of time.

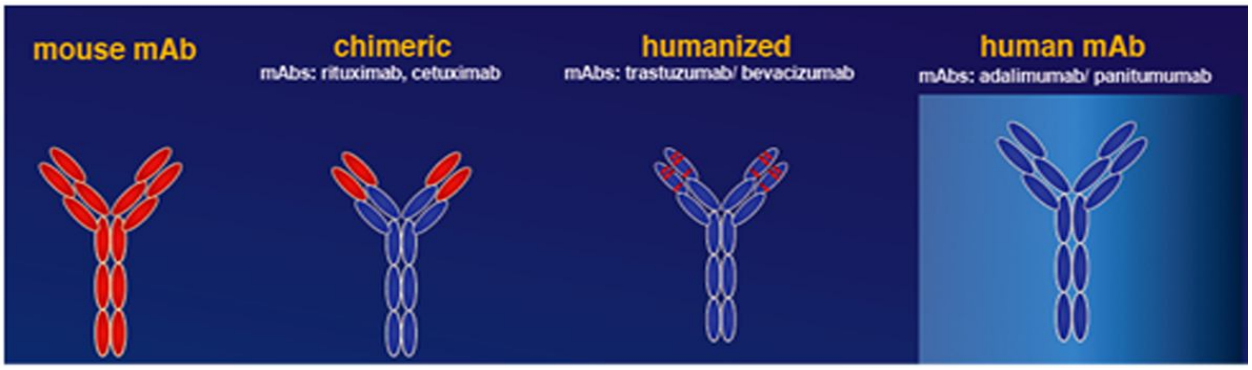

Fig. 3: Evolution of monoclonal antibody

Monoclonal Antibodies

In 2009, the first successful development of monoclonal antibody against PCSK9 was developed by Chan et al [8]. The fully human monoclonal antibody (mAB) binds to both the catalytic and prodomain sites preventing PCSK9 binding to LDL-R. Monoclonal AB increase LDL receptor levels by 1.7-2.2-fold and had synergistic effects when administered concomitantly with statin.

Alirocumab

Alirocumab shows dose-dependent LDL-C lowering effects. In the phase II clinical trial evaluating the use of alirocumab in the background of atorvastatin in subjects with LDL-C e 100 mg, arilocumab decreased LDL-C by as much as 72 % with *150 mg administered every two weeks*[9]. With significant reduction in apolipoprotein B (apoB), non-high density lipoprotein cholesterol (non-HDL-C) and lipoprotein (a) [Lp(a)][10]. Alirocumab is well-tolerated and effective in FH (68 % reduction in LDL-C compared with 11 % in the placebo group)[11]. In the ODYSSEY program presented in European Society of Cardiology (ESC) congress, alirocumab was shown to decrease LDL-C levels by 61 % compared to placebo and also lowered CV risk after one year therapy (HR 0.46, CI 0.26-0.82, p = <0.01) (*ESC Barcelona Spain 2014*).

Evolocumab

Evolocumab, a full human monoclonal antibody, is administered subcutaneously either as every two weeks or every four weeks dosing regimen. GAUSS study evaluated the efficacy and safety of evolocumab in patients with statin intolerance with significant reduction in LDL-C compared to placebo (41%) [12]. When administered to subjects who are already taking statin, administration of evolocumab further decreased LDL-C by *63–75 %* compared to placebo in subjects with heterozygous FH [13]. Evolocumab also decreased Lp(a). In a small study by Stein et al., the effect of evolocumab was studied in both LDL-R negative subjects and LDL-R defective patients. Evolocumab significantly reduced LDL-C by 26 % in only the LDL-R defective subjects. In a 12-week phase III clinical trial, evolocumab with moderate or high-intensity statin showed significant reduction in LDL-C (up to 75 % reduction)[14]. Also in another 12-week phase III study evaluating evolocumab use in subjects with intolerance to statin, those treated with evolocumab had significant reduction of LDL-C compared to ezetimibe (53–56 % vs 37–39 % p< 0.001). Patients those were previously enrolled in prior phase II studies (GAUSS, RUTHERFORD, LAPLACE-TIMI 57, and MENDEL) were evaluated in the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) trial. This study showed that *subjects who continued to take evolocumab for the duration of the year on a monthly dosing regimen, maintained decreased LDL-C levels, whereas those that discontinued the study drug resumed their baseline levels* [15]. In the LAPLACE-TIMI 57 phase II trial, the mean LDL-C concentration reduction was dose-dependent, and ranging from 41.8% to 66.1% every two weeks, and from 41.8% to 50.3% every four weeks. In the MENDEL trial, evolocumab in 406 patients with hypercholesterolaemia and statin intolerance significantly reduced LDL-C concentrations with the maximal effect for the regimen of 140 mg every two weeks (–51%).

In the RUTHERFORD trial, 167 patients with heterozygous familial hypercholesterolemia and uncontrolled LDLC (e 2.6 mmol/l) with statin and evolocumab achieved substantial reduction in LDL-C (43% for 350 mg and 55% for 420 mg) on top of intensive statin use. Recently, the DESCARTES trial, including 901 patients with a range of cardiovascular risks treated with diet ,atorvastatin 80 mg plus ezetimibe once a day were randomised to 420 mg evolocumab or placebo every four weeks. At 52 weeks, evolocumab significantly reduced LDL-C

levels with all previous described regimens (from 48.5% to 61.6%), as well as apo B, non-high-density lipoprotein cholesterol and lipoprotein. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza and back pain.

Bococizumab

The monoclonal antibody bococizumab has undergone phase I clinical trial and shown that single and escalating intravenous and subcutaneous dose significantly lowered LDL-C by as much as 54 % with 150 mg Q2 week regimen without significant adverse effects[16].

Other Targets for Pcsk9 Inhibition

Direct inhibition of PCSK9 can be attained using small mimetic peptides called *adnectins*. Mimetic peptides of the PCSK9 binding domain for LDL have been shown to decrease LDL-R degradation[17]. Another approach in PCSK9 inhibition is gene silencing techniques. Antisense RNAs (siRNA) are also being developed to target PCSK9 mRNA. Natural inhibitors, such as annexin A2, a protein expressed in many tissues, inhibit PCSK9 and increase LDL-R.[18] *Berberine,* a natural occurring plant alkaloid has been shown to also decrease PCSK9 mRNA expression and increase LDL-R *in vitro* and animal studies.[19]

Monoclonal Antibody Dose and Ldl-C Reduction

All monoclonal antibodies produce dose dependent LDL-C reduction ranging from 48-85% as depicted in the following table.

Pcsk 9 and Cariovascular Outcome

Metaanalytic cardiovascular benefits of PCSK 9 inhibitors are depicted below providing the message that PCSK 9 inhibitors are associated with a better CV outcome.

Table 1: Dose dependent LDL-C reduction with monoclonal antibody

Monoclonal Antibodies	Reduction of LDL-C from Baseline
Alirocumab	
150 mg every two weeks	66–72 %
300 mg every four weeks	43–48 %
Evolocumab	
140 mg every two weeks	51–76 %
420 mg every four weeks	48–71 %
Bococizumab	
150 mg every two weeks	33 % (0.5 mg/kg) – 85 % (18 mg/kg)
300 mg every four weeks	Mean reduction 53 mg/dL
	Mean reduction 45 mg/dL

low-density lipoprotein cholesterol

Table 2: PCSK 9 inhibitors and CV outcome

Outcome	OR (95% CI)	P	I^2	N	Events PCSK9 group (%)	Events control group (%)
All-cause mortality	0.45 (0.23-0.86)	0.015	0%	10,159	19 (0.3%)	21 (0.5%)
CVD Mortality	0.50 (0.23-1.10)	0.084	0%	10,159	12 (0.2%)	13 (0.3%)
MI	0.49 (0.26-0.93)	0.030	0%	5,195	19 (0.6%)	19 (1.0%)

Phase Iii Study and Monoclonal Antibody

Adverse Events

Serious adverse events from monoclonal antibodies targeting PCSK9 are rare. *The most common adverse reactions are local injection site reactions* (erythema, pruritis, discoloration, haematoma, swelling). In the GAUSS trial, myalgias were the most common adverse event but had low incidence overall [20]. Alirocumab had similar adverse reactions between placebo and treatment groups in its phase II trials. In a dose escalating study of alirocumab, one of 152 subjects receiving a dose of alirocumab developed *cutaneous leukocytoclastic vasculitis* that was successfully treated with prednisone[21]. For evolocumab, the most common treatment related adverse reaction was not only injection site reaction (pain), but also headache [22].

Table 3: Phase III study with monoclonal antibodies

Monoclonal Antibody	Name of Phase III	Population
Evolocumab	MENDEL-2	Subjects with hypercholesterolaemia, Framingham Risk score < 10%, monotherapy
		Statin-intolerant subjects, compared to ezetimibe
	GAUSS-2	Subjects with hypercholesterolaemia, statin intolerance, ezetimibe controlled
	LAPLACE-2	Subjects treated with evolocumab on high or low dose statin
	FOURIER	Evaluating cardiovascular outcomes in subjects with hypercholesterolaemia and elevated risk cardiovascular risk
Alirocumab	ODYSSEY	Global Phase III program
	COMBO-I	subjects treated with maximally tolerated statin therapy
	CHOICE I	Alirocumab administered every four weeks compared with placebo
	CHOICE II	Alirocumab as monotherapy compared to other non-statin lipid lowering therapies
	LONG TERM	Alirocumab use in the background of lipid lowering therapies and long term safety and efficacy
	OUTCOMES	Alirocumab effects in cardiovascular outcomes in subjects with acute coronary syndrome
Rocolicumab	SPIRE-1	CV outcomes in subjects with high risk and LDL-C ≤ 70 but ≤ 100 mg dL
	SPIRE-2	CV outcomes in subjects with high risk and LDL-C ≥ 100 mg dL
	SPIRE-IS	Subjects who are intolerant to statin
	SPIRE-HR	Subjects with high or very high risk for CV events
	SPIRE-LL	Subjects with primary hyperlipidaemia at high or very high risk

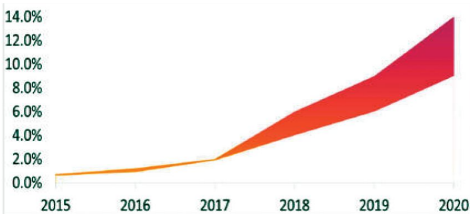

Fig. 4: Projected PCSK 9 inhibitors among Statin users (National Cooperative USA)

Conclusion

Although statins have revolutionized lipid therapy, there remains a significant residual risk among statin intolerant, inadequately controlled and patients with familial hypercholesterolemia that can be further targeted. Statin-induced myopathy may represent up to 10 % of treated patients in a primary care setting. PCSK9 inhibitors have successfully shown to rescue these situations with significant reduction in LDL-C, non-HDL-C and Lp(a). As an add on therapy to statins, those acting *synergistically* with statins will bring out significant reduction in LDL-C with better cardiovascular outcome in near future.

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Review Article

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Microvascular Angina-An Enigma

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Abstract

Prognosis of patients with Microvascular angina is not as benign as is considered despite normal coronaries. It contributes to increased suffering, health care costs and may have role in long term increased cardiovascular risk. There is increasing consensus about underlying coronary microvasculature abnormality with or without other risk factors. A lot more research and clinical work is required to develope effective and optimum treatment to alleviate the symptoms and improve microvascular function. In this review we have discussed the prevalence, pathophysiology and available investigative and treatment modalities and present limitations and need of further studies and research about coronary microvascular dysfunction.

Keywords: Angina; CFR; Coronary; Microvascular; Syndrome X.

As coronary angiography (CAG) became widely practiced since 1960s, many patients have undergone CAG because of angina on exertion with clinical diagnosis of coronary artery disease (CAD). It is seen that not all patients with clinical suspicion of CAD had obstruction of coronary arteries. Up to 40% of patients undergoing CAG fall into this category[1], having normal or near normal coronary arteries at angiography and no evidence of coronary vasospasm. As many as 50% to 65% of these patients with chest pain without obstructive CAD are believed to have coronary microvascular dysfunction (CMD), also known as microvascular angina [2-5]. CMD is defined as impaired vasodilatation of arterioles, leading to an inadequate increase in blood flow from rest to stress. The term "Microvascular Angina" (MVA) was coined by Cannon and Epstein [6]. They thought that dysfunction of small intramural prearteriolar coronary arteries is central to the pathogenesis, hence used the term. The term "cardiac syndrome X" is used for patients with anginal chest pain and ST-segment depression or perfusion abnormality during stress despite normal coronary arteriogram. The cardiac Syndrome X is characterized by angina predominantly on excretion, a positive electrocardiogram (ECG) response to exercise testing, normal coronary arteries at angiography and absence of epicardial coronary artery spasm and of known causes of microvascular dysfunction such as left ventricular hypertrophy, systemic hypertension, and valvular heart disease. Often the term microvascular angina and cardiac syndrome X are used interchangeably however microvascular angina is an identifiable pathophysiological mechanism whereas there is no universal mechanism described for cardiac syndrome X. The lack of definitive evidence of ischemia in some patients with syndrome X has focused attention on alternative nonischemic causes of cardiac-related pain, including a decreased threshold for pain perception—the so-called sensitive heart syndrome [7]. So it is prudent to use the term microvascular angina instead of syndrome X to avoid ambiguity. Irrespective of the definition used (whether exercise-induced ischemic changes are present in the ECG or not), patients with angina with normal coronary angiograms show a distinct female preponderance [8,9]. Even after correcting for body surface area, women have smaller coronary arteries. This can seriously affect symptoms from anything that reduces diameter such as stenosis or endothelial dysfunction. Most women with diagnosis of

microvascular dysfunction have estrogen deficient state i.e. PCOS or post menopausal women. But how estrogen affect the microvasculature is still speculative. In WISE study [10], 42% of women with anginal chest pain in the absence of obstructive CAD had coronary microvascular dysfunction.

Pathophysiology

The mechanisms proposed include endothelial cell and smooth muscle dysfunction i.e. microvascular dysfunction, diffuse atherosclerosis, platelet dysfunction, inflammation local or systemic, estrogen deficiency and abnormal pain perception. Involvement of coronary arterioles with diameter less than 500 M sparing epicardial arteries is responsible for reduction of myocardial perfusion and clinical spectrum in microvascular angina. The impaired vasodilatation of arterioles with inadequate blood flow in response to stress causes structural and functional changes to myocardium and angina. Even in the absence of atherosclerosis and vasospastic disease, coronary microvascular dysfunction (CMD) can lead to transient myocardial ischaemia as in patients with coronary artery disease (CAD), cardiomyopathy (CMP) or in Takotsubo syndrome and there may be overlap of atherosclerosis, vasospasm and microvascular dysfunction in significant proportion of patients.

Camici and Crea [11]divided coronary microvacsular dysfunction into 4 types depending on presence or absence of obstructive CAD (type 1 and type 2 respectively), involvement of myocardium (Type 3) and whether iatrogenic (type 4). Microvascular angina can also be classified as primary or secondary where primary microvascular angina is diagnosis of exclusion while secondary form occurring in association with specific cardiac or systemic diseases with cardiac involvement. Microvascular angina can also be classified on the basis of clinical presentation as stable or unstable with stable form related to effort while unstable form occurring at rest or on minimal exertion or increasing type of angina.

Risk factors for microvascular angina include gender, aging, hypertension, diabetes, obesity, insulin resistance, early menopause, smoking, lipid abnormalities and chronic inflammation resulting in endothelial dysfunction, smooth muscle dysfunction and vascular remodeling. Abnormal endothelium dependent and non-endothelium-dependent microvascular dilatation results in decreased myocardial perfusion, ischaemia and angina. Systemic lupus erythematosus and rheumatoid arthritis are characterized by an inverse correlation between coronary flow reserve (CFR) and C-reactive protein concentrations suggesting that chronic inflammation may contribute to microvascular abnormalities. Disorders of nitric oxide metabolism, dysregulation of numerous mediators including inflammatory cytokines, estrogen, or adrenergic receptors, and alterations in the expression or production of local vasoactive substances such as angiotensin II and endothelin are other plausible mechanisms contributing to microvascular dysfunction.

Assessment and Diagnosis

It is important to rule out other causes of chest pain like gastroesophageal reflux disease, musculoskeletal pain, pericardia or pleural involvement and psychogenic and functional involvement. Diagnosis of primary MVA also requires the exclusion of significant lesion of epicardial coronary arteries on angiography and ruling out coronary spasm or other abnormalities like bridging before labeling as primary microvascular angina.

Though it is not feasible to image coronary microcirculation directly or catheterize resistance vessels, there are noninvasive and invasive methods to assess coronary microcirculation. In fact, indirect parameters such as myocardial perfusion and perfusion reserve provide an index of microvascular function. Until now percutaneous angiography has been the traditional invasive method to assess micro circulation using blush score, use of flow wire and calculation of CFR. Now with advancement in science and technology we are able to assess microvascular function non invasively with modalities like myocardial contrast study in conjunction with trans thoracic echo, cardiac magnetic resonance imaging(CMR) and PET scan. PET scan is valuable in measuring absolute myocardial perfusion and perfusion reserve to assess microvascular dysfunction. In one of the recent analysis [12] Marinescu et al proposed a definition of CMD, as CFR or myocardial perfusion reserve (MPR) <2.5 using PET, CMR, intracoronary (IC) Doppler wire, or thermodilution methods in the presence of angina or symptom equivalent, exclusion of epicardial CAD with stenosis 50% or no evaluation of CAD and absence of known structural heart disease or heart failure.

Treatment

Treatment for microvascular angina is mainly directed at risk factor reduction, symptomatic and

targeting coronary microvasculature to improve myocardial perfusion. Non pharmacological measures are equally important in improving endothelial dysfunction and improving coronary microcirculation like Smoking cessation, weight loss, Mediterranean diet and physical exercise. Strict glycaemic control also reduces microvascular disease to a greater extent. Treatment with quinapril an angiotensin convertase enzyme inhibitor (ACEI) was shown to improve CFR by Pauly et al in a double-blind placebo-controlled trial where as kaski et al and motz et found improved stress test parameters in their studies. Statins due to their pleotropic action including anti-inflammatory and antioxidative action may help in improving endothelial function and microvascular tone. Metformin by reducing Insulin resistance can improve microvascular dysfunction and needs large scale trials. Despite inconsistent response to Beta-blockers in patients with microvascular angina they are the first line treatment and more effective in reducing exercise related symptoms and anginal episodes. Nebivolol causes release of nitric oxide at endothelial level and improves coronary flow reserve in addition to its beta blocking property and needs large scale studies in patients with microvascular angina. Due to conflicting results from various studies and unproven role calcium antagonists are used as add on or second line therapy. Oral Nitrates have no proven action at micro vasculature and doubtful role in isolated microvascular dysfunction with sublingual nitroglycerin reducing angina in less than 50% of patients with micro vascular angina.

Newer Drugs and Other Treatment Modalities

Nicorandil causes arterial vasodilatation by opening potassium channel and improves myocardial perfusion. Many trial have shown improved TIMI score in primary percutaneous coronary intervention (PCI) and improving no reflow with use of parenteral nikorandil. Despite symptomatic benefit, due to fewer studies of nikorandil in patients with microvascular angina large scale trials are warranted before its routine use in these subsets. Trimetazidine is a 3-ketoacyl coenzyme A thiolase inhibitor decreasing free fatty acis(FFA) oxidation and has favorable impact in patients with primary stable MVA in terms of reducing anginal episodes and improving effort tolerance as seen in small studies and needs further evaluation. Ivabradine is funny channel inhibitor acting on sinus node and improves symptoms in patient with microvascular angina through unknown mechanism. Ranolazine is late sodium current inhibitor, may improve diastolic function and was shown to have beneficial effects in patients with primary stable MVA though it has no direct effect on endothelial function or coronary flow. Sildenafil causes endothelium-dependent dilatation of arterioles and vascular smooth muscle relaxation by inhibition of the breakdown of cyclic guanosine monophosphate. One of the studies had statistically significant improvement in coronary flow in patient's of microvascular angina with CFR less than 2.5 but no benefit if baseline CFR was >2.5. Aminophylline is adenosine receptor antagonist increasing exercise-induced chest pain threshold and has favourable impact to reduce angina by redistribution of coronary flow. Imipramine is serotonin and noradrenalin uptake inhibitor reducing visceral pain and may be tried in patients symptomatic for angina despite optimum medications. However its side effect profile may limit its widespread use. By altering central pain processing in cerebral cortex and improving tone of coronary microvasculature through local spinal circuits spinal cord stimulation may have positive impact and can be tried as last resort. Trans cutaneous electrical nerve stimulation has shown to reduce symptoms in some patients with refractory micro vascular angina.

According to ESC guidelines beta blockers, aspirin and statins are first line therapy while Calcium channel blockers are second line as alternative to β blockers in patients not tolerating or responding to β blockers.

Future

Routine use of CFR or MPR with a cutoff 1.5 and 2.5 seems to help stratify patients with CFR or MPR >2.5 ruling out CMD while a CFR <1.5 affirming CMD. According to Suwaidi et al [13] value of <1.5 is suggestive of endothelial-dependent dilation and <2.5 for endothelial-independent dilation in patients with angina but normal coronaries. There is need of validation of imaging techniques with large randomized trial in various ethnic groups over widespread geography in patients with chest pain without obstructive CAD. Also large studies are required with newer agents.

Conclusion

Even though patients with normal coronaries have better prognosis as compared to those with obstructive CAD, those with proven microvascular

angina and microvascular dysfunction are associated with poorer prognosis and can result in significant morbidity and contribute even to mortality. At present the treatment for microvascular dysfunction is mainly directed at reduction and treatment of risk factors and use of current day antianginals. Large scale randomised trials with newer promising agents are required to expand the armamentarium against microvascular angina.

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Review Article

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

hsCRP, A Risk Factor Behind Atherosclerosis

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Abstract

Novel risk factors are emerging behind the genesis of atherosclerosis in today's era of moleculogy. High sensitive CRP is one of the frontiers in this field besides homocysteine, fibrinogen and Lp (a). We report a case of premenopausal lady without conventional risk factors with malignant manifestations of atherosclerosis having only elevated hsCRP to explain the scenario. Being a biomarker behind inflammatory vascular stress, it stands out a promising molecule in today's atherobiology. Exercise and statins can bring down this inflammatory insult, resulting in a healthy vascular tree.

Keywords: hsCRP; Atherobiology; Atherosclerosis; LMCA; ECG.; Novel; Atherosclerosis; Cardiovascular.

Introduction

We report a case of 39 year old premenopausal lady presenting to the Cardiology OPD of AIIMS, Bhubaneswar with effort dyspnea NYHA class III with rest angina, dysphagia and dull abdominal pain. She was thin built (36kg),nondiabetic and nonhypertensive. She denied any history of familial coronary artery disease. Physical examination was unremarkable except presence of mild cardiomegaly with presence of LVS_4. ECG revealed old anterior wall myocardial infarction with ST elevation in aVR more than V_1 suggestive of LMCA lesion as depicted below. Serum chemistries including blood glucose, lipid panel, renal profile were within normal limit.

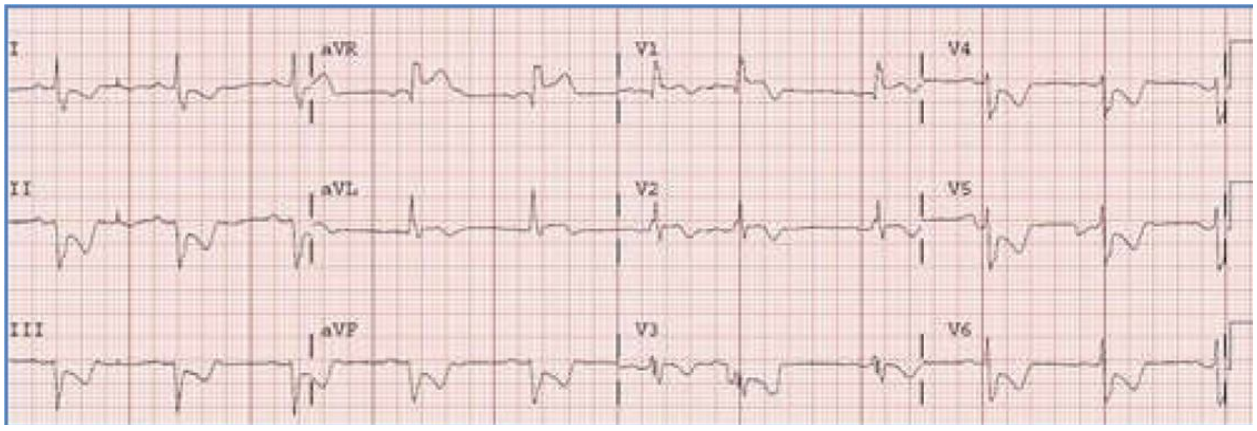

Fig. 1: ECG showing LMCA occlusion

We carried out further biomarker analysis including hsCRP, plasma fibrinogen, serum homocysteine and Lp (a) which were as follows: ***3.9 mg/L***, 130mg/dl, 10 µmol/L and 10 mg/dl respectively. Cardiac Troponin I was negative and NT PRO BNP was elevated modestly i.e. 550 pg/ml.

Chest roentgenogram revealed cardiomegaly with aneurysmal dilation of aortic arch with wall calcification. Echocardiography revealed dilated left ventricle with RWMA in LAD territory with severe LV systolic dysfunction with hugely dilated descending aorta in PLAX view. Aortic arch interrogation in suprasternal echo window revealed a thin retrograde dissection flap freely hanging in the arch with a very small and short false lumen. We ruled out cardiovascular syphilis by doing VDRL in view of giant arch aneurysm.

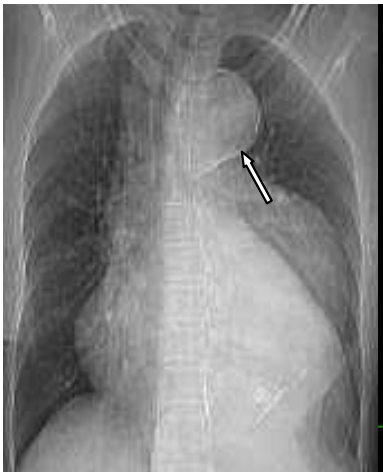

Fig. 2: X-ray showing cardiomegaly with aneurymal arch

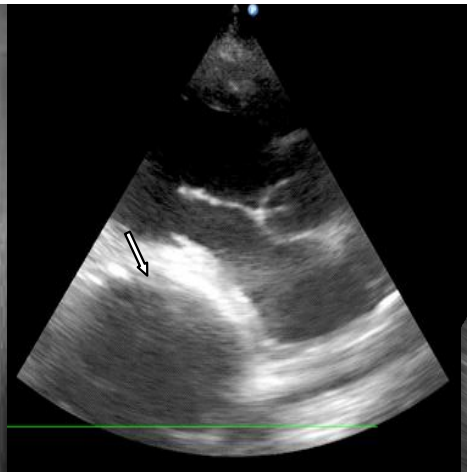

Fig. 3: Echocardiography showing hugely dilated aorta in PLAX view

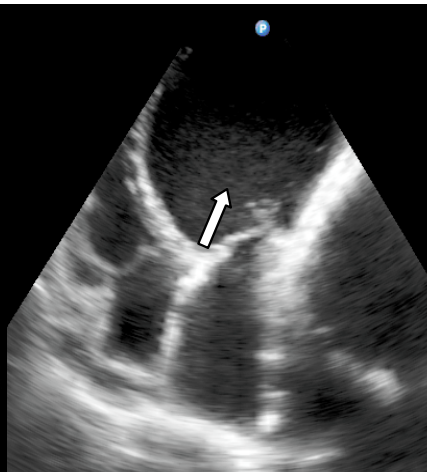

Fig. 4: Hugely dilated LV in A_4CH view

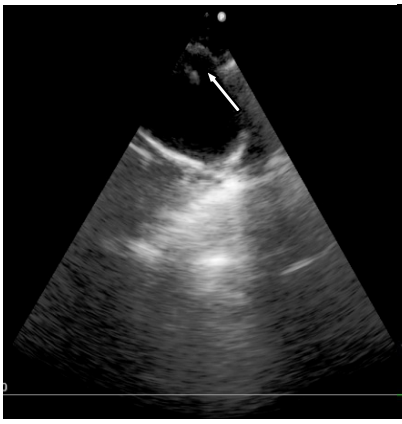

Fig. 5: Echocardiography showing small false lumen

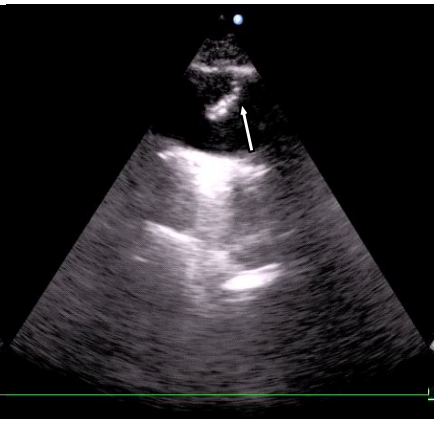

Fig. 6: Thin hanging dissection flap

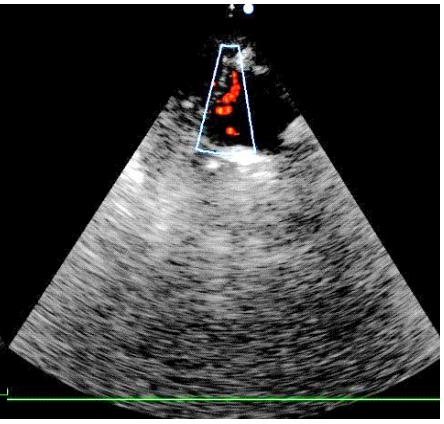

Fig. 7: Retrograde flow in false lumen

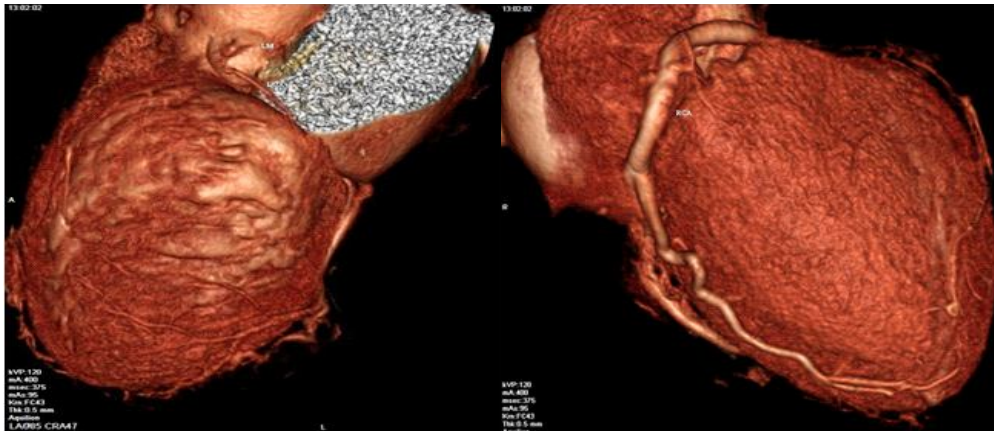

Fig. 8: CT CAG revealing near total occlusion of LMCA with thinned out and diseased LCX with distal LAD being filled by collaterals

Fig. 9: A normal RCA

Fig. 10: CT Aortic angiogram revealing aortic arch and descending aorta aneurysm

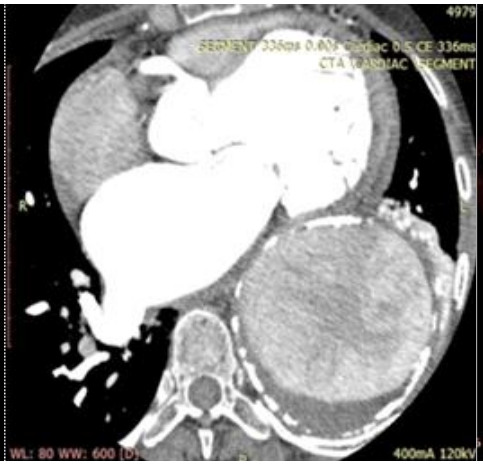

Fig. 11: Intraluminal thrombus with calcification in arch aneurysm

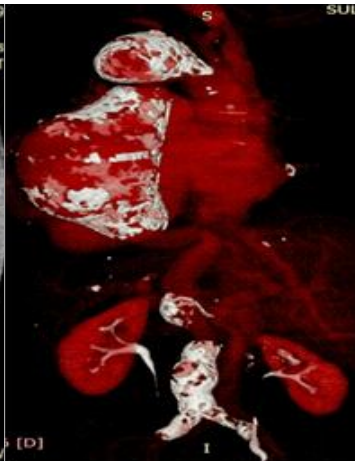

Fig. 12: Infrarenal and suprarenal aortic aneurysm with left renal artery stenosis with renal atrophy

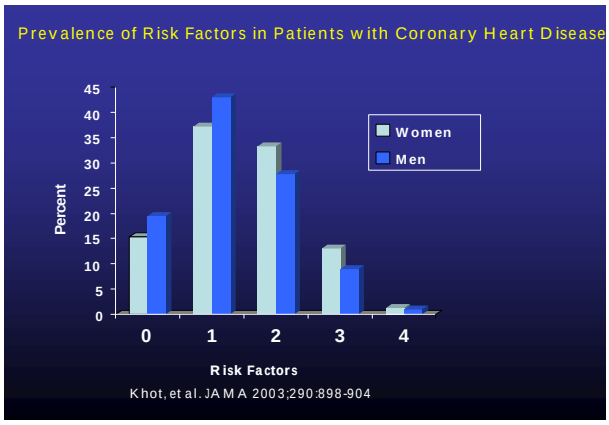

Fig. 13: CHD and no conventional risk factors

Coronary CT angiography revealed near total occlusion of LMCA with trickled flow into thinned out and diseased LCX with no flow in proximal LAD and distal LAD partly being filled by growing collaterals from normal RCA.

We performed CT angiography of thoracic and abdominal aorta to delineate the extent of vascular atherosclerosis as Carotid Doppler revealed minimal atherosclerotic changes without significant obstruction. Aortic angiogram revealed huge aortic arch and descending aorta aneurysm with intraluminal thrombus and wall calcification with aneurysmal involvement of suprarenal and infrarenal aorta with significant left renal artery stenosis and left renal atrophy. The aforesaid patient revealed atherosclerosis in most malignant form in form of significant coronary artery disease with LMCA lesion with significant LV systolic dysfunction, aortic arch aneurysm with intraluminal thrombus and wall calcification with a thin hanging retrograde dissection flap, infra and suprarenal aortic aneurysm with left renal artery stenosis with atrophic left kidney. We advised the patient to undergo immediate CABG with surgical resection of arch aneurysm with graft repair. Although endovascular aneurysm repair (EVAR) was an immediate option, as the patient was ideal candidate for CABG, we opted for surgical correction of aneurysm besides CABG. We did not think for left renal artery stenting as DTPA renogram did not dictate about the benefit of renal intervention in non functioning left kidney. Post procedure patient was on ant ischemic and antiplatelets and was uneventful. Patient's dyspnea now has abated to moderate extent and doing fare now. We were amazed to see such a malignant and myriad manifestation of atherosclerosis where conventional risk factors were absent and out of the novel risk factors only hsCRP was elevated to a higher level of 3 mg/L. Although recent literature clearly describes hs CRP as a novel risk factor, our case was a golden witness to this hypothesis. Although hsCRP is not a mandatory routine in screening atherosclerosis, our case dictates not to forget to do an hsCRP before leaving a patient with atherosclerotic cardiovascular disease. Only exercise and statin as evidenced in JUPITER trial can bring down this hsCRP, we can say no to these malignant manifestations of atherosclerosis by using these two simple weapons.

Discussion

Despite the popular myth that only about 50% of patients with CHD have traditional risk factors, the data from Khot and colleagues which looked at risk factor prevalence in 122,458 patients enrolled in 14 major clinical trials of CHD during the prior decade revealed that relatively few had more than two risk

factors, *only about 15% of women and 20% of men had no traditional risk factors.* Nonetheless, given the likelihood that non-traditional risk factors may play a significant role in cardiovascular disease,modern atherobiology identified four major risk factors i.e. hsCRP, fibrinogen, homocysteine and Lp(a) which opened doors to both risk prediction and therapeutic option. MRFIT trial [1] was one of the earliest study to delineate the role of hsCRP behind genesis of cardiovascular disease, subsequently it was included in *Reynolds risk score* [2] as one of the cardiovascular risk factor in defining population at risk. hs CRP otherwise known as *poor man's risk factor* [3] explains the scenario when a village farmer lands in large myocardial infarction without any prior harbor of conventional risk factors and it is only vascular inflammation that ignites the vascular milieu to have florid atherosclerosis [4]. Our case was unique as this woman in premenopausal age without conventional risk factors had only hsCRP elevated to a higher level to explain this myriad manifestation of atherosclerosis. hsCRP plays a vital role behind genesis of atherosclerosis in Indian population [5,6]. ACC/AHA recommends hsCRP screening as Class IIa recommendation for primary prevention in intermediate risk patients (10-20% 10-year CHD risk) to help direct further evaluation, treatment and in patients with stable CAD or ACS, as an independent marker of recurrent events, including death, MI and restenosis following PCI [7]. If level > 10 mg/L, test should be repeated and patient examined for sources of infection or inflammation. ACC/AHA classify risk as follows:

Low	:	< 1 mg/L
Average	:	1.0 – 3.0 mg/L
High	:	> 3.0 mg/L

Our case is a standing appraisal of the established role of hsCRP behind genesis of atherosclerosis and its penopoly of complications. In our patient hsCRP was elevated i.e 3.9 mg/L which falls in high risk category. Patient was advised high dose atrovastatin 80mg to address the nonaddressed vascular tree with regular morning walk for 30 minutes a day with yogic therapy. Studies are underway to know the cause behind this vascular inflammation, may be the real life stress a contributing factor. hsCRP in today's era stands out as a promising cardiovascular risk factor [8, 9,10], well taken care by exercise and statins.

Conclusion

Our case is an unique witness to the fact that hsCRP is a promising novel risk factor behind CAD. The aforesaid patient had the most malignant manifestations of atherosclerosis in form of giant atherosclerotic aortic aneurysm with dissection and intraluminal thrombus, severe CAD, atherosclerotic renal artery stenosis with renal atrophy, only explained by raised hsCRP level. Taking care of this novel risk factor will bring out a new era in the therapeutic horizon of atherosclerosis.

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Review Article

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Exercise-Based Cardiac Rehabilitation: An Overview of Science from Systematic Reviews and Meta-Analyses to Guide Clinical Practice

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Abstract

This review article aimed to enlighten evidence-informed researchers and clinicians with a descriptive overview of systematic reviews and meta-analyses on exercises for cardiac rehabilitation from PubMed. Exercise-based cardiac rehabilitation (EBCR) includes either exercise training administered alone or exercise training in addition to psychosocial, risk factor management and / or educational interventions and was considered a Class I indication [i.e., useful and effective] for patients with coronary heart disease.There were six systematic reviews that measured risk factors, clinical and quality of life outcomes following exercise training in cardiac rehabilitation; and five other systematic reviews included one each on high-intensity interval training, resistance training, aerobic training, Chinese Qiqong exercise and physical activity prescription. Overall, there is high-level evidence suggesting exercises as per earlier evidence-based recommendations.

Keywords: Exercise Therapy; Exercise-Based Cardiac Rehabilitation; Exercise Prescription; Exercise Training; Cardiovascular Rehabilitation.

This review article aimed to enlighten evidence-informed researchers and clinicians with a descriptive overview of systematic reviews and meta-analyses on exercises for cardiac rehabilitation from PubMed.

Effects on Risk Factors and outcomes

Lawler et al [1] performed a meta-analysis of 34 randomized controlled trials (RCTs) from MEDLINE and found that exercise-based CR was associated with a lower risk of reinfarction, cardiac mortality, and all-cause mortality, with favorable effects also on cardiovascular risk factors, including smoking, blood pressure, body weight, and lipid profile.

Oldridge [2] performed an overview of six meta-analyses which included a total of 71 randomized clinical trials on 13,824 patientsand clearly demonstratedbeneficial clinical outcomes (reduced all-cause and cardiac mortality, nonfatal reinfarction and reduced hospitalization rates) and positive changes in modifiable risk factors (total cholesterol, triglycerides and systolic blood pressure).

Isaksenet al [3] reviewed nine studies on 1889 patients with implantable cardioverter defibrillators (ICDs) for exercise training (ET) in cardiac rehabilitation outcomes. ET was safe and was not associated with increased risk of shock. ET also improved aerobic capacity in ICD patients, while effects on anxiety, depression and quality of life are unknown (Isaksenet al, 2011).

Heranet al [4]studied the effectiveness of exercise-based cardiac rehabilitation (exercise training given alone or in combination with psychosocial or educational interventions) on mortality, morbidity and health-related quality of life of patients with coronary heart disease (CHD) by performing a systematic review which identified 47 studies randomising 10,794 patients to exercise-based cardiac rehabilitation or usual care. Exercise-based cardiac rehabilitation was effective in reducing total and cardiovascular mortality (in medium to longer term studies) and hospital admissions (in shorter term studies) but not in preventing total MI or revascularisation (CABG or PTCA). In seven out of 10 trials there was evidence of a significantly higher

level of quality of life with exercise-based cardiac rehabilitation compared to usual care.

Puetzet al [5] performed a meta-analytical reviewof 36 studies consisting of 4765 subjects and found that cardiac rehabilitation exercise programs were associated with increases in energy and decreases in fatigue. Exercise-based cardiac rehabilitation programs also had larger effects on feelings of energy and fatigue compared with anxiety and depression.

Self-Efficacy and Adherence

Woodgateand Brawley [6] systematically reviewed41 CR studiesthat measured self-regulatory efficacy for actions that facilitate adherence. The authors found that most studies examined self-efficacy during the intensive center-based phase of CR, with little attention to long-term maintenance. The authors provided recommendations for CR literature as follows; "examining (a) self-efficacy as a major rehabilitation outcome, (b) measurement of self-regulatory efficacy for behavior change, (c) suspected moderators of self-efficacy (i.e. gender, age), and (d) self-efficacy relative to maintenance."

Interval Training

Guiraudet al[7] performed a non-systematic review of studies on High-intensity interval training (HIIT) in patients with coronary artery disease (CAD) and heart failure (HF), as well as in persons with high cardiovascular risk. To summarize, HIIT appears safe and better tolerated by patients than moderate-intensity continuous exercise (MICE). HIIT gives rise to many short- and long-term central and peripheral adaptations in these populations. In stable and selected patients, it induces substantial clinical improvements, superior to those achieved by MICE, including beneficial effects on several important prognostic factors (peak oxygen uptake, ventricular function, endothelial function), as well as improving quality of life. HIIT appears to be a safe and effective alternative for the rehabilitation of patients with CAD and HF. It may also assist in improving adherence to exercise training.

Resistance Training

The German Federation for Cardiovascular Prevention and Rehabilitation provided recommendations for resistance training in CR which explained the potential risk of increased blood pressure during resistance training, and other factors such asmagnitude of the isometric component, the load intensity, the amount of muscle mass involved as well as the number of repetitions and / or the load duration influence the BP responses. The authors recommendedlow-intensity resistance training [40-60% maximum voluntary contraction (MVC)] with 15-20 repetitions, since it produced only modest elevations in blood pressuresimilar to those seen during moderate endurance training [8].

Aerobic Exercise Training

The European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation published a joint position statement on aerobic exercise prescription in cardiac rehabilitation [9] which provided information regarding the identification of different exercise intensity domains, the methods of direct and indirect determination of exercise intensity for both continuous and interval aerobic training, the effects of the use of different exercise protocols on exercise intensity prescription and the indications for recommended exercise training prescription in specific cardiac patients' groups. A shift from a 'range-based' to a 'threshold-based' aerobic exercise intensity prescription, combined with thorough clinical evaluation and exercise-related risk assessment,was recommended to maximize the benefits obtained by the use of aerobic exercise training in cardiac rehabilitation.

Chinese Qigong Exercise

Chan et al [10] did a systematic review of 6 RCTs and one CCT on a total of 540 patients to assess evidence for Chinese qigong exercise for atrial fibrillation, coronary artery disease, myocardial infarct, valve replacement, and ischemic heart disease. The evidence suggested that Chinese qigong exercise was an optimal option for patients with chronic heart diseases.

Physical Activity Prescription

Chase [11] reviewed 14 intervention studies to maintain or increase physical activity (PA) after CR using cognitive and / or behavioral strategies. The cognitive interventions were self-efficacy enhancement measures, barrier management, and problem solving. Behavioral interventions were self-monitoring, prompting, goal setting, and feedback. Inconsistent findings were reported in cognitive intervention studies, whereas positive findings were reported by behavioral studies and studies that used combinations of interventions.

There were six systematic reviews that measured risk factors, clinical and quality of life outcomes following exercise training in cardiac rehabilitation; and five other systematic reviews included one each on high-intensity interval training, resistance training, aerobic training, Chinese Qiqong exercise and physical activity prescription. Overall, there is high-level evidence suggesting exercises as per earlier evidence-based recommendations.

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Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Compression of Right Atrium and Superior Vena Cava from Anterior Mediastinal Teratoma

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Abstract

The occurrence of anterior mediastinal teratoma is very rare. Compression of right atrium and superior vena cava by tumor produces challenges to cardiac anaesthetist and surgeon during surgical excision. We present the perioperative management for surgical removal of a giant anterior mediastinal teratoma compressing the right atrium and superior vena cava.

Keywords: Anterior Mediastinal Tumor; Teratoma; Superior Vena Cava; Right Atrium; Transesophageal Echocardiography.

Introduction

Patient with mediastinal tumor can be challenging to manage in the perioperative period. Many casesrelatedto mediastinal masses have been reported [1]. A careful stepwise preoperative evaluation of thoracic structures and induction of anesthesia is mandatory. In high risk patients with a mediastinal mass related signs, symptoms or radiologic findings such as severe postural symptoms, stridor, cyanosis, tracheal compression or with associated bronchial compression, pericardial effusion or superior vena cava syndrome is essential [2]. Mediastinal tumors in some occasion may compress the superior vena cava (SVC), cardiac chambers, pulmonary artery and vein. SVC compression will lead to superior vena cava syndrome. Induction of anaesthesia may produce hypotension, cardiac arrest and arrhythmia. During surgery chance of bleeding, air embolism and massive blood loss and injury to other vital structures may happen. Necessity of one lung ventilation and cardiopulmonary bypass are needed in some occasion[3]. Intermediate risk patients who have mild to moderate tracheal compression are also assessed and perioperative care should be planned for airway security.

We present the perioperative management of a case of anterior mediastinal teratoma compressing the SVC and right atrium (RA).

Case History

A 33-year-old previously healthy female 64 kg weight presented with a small swelling in the right anterior upper chest. Thepresence of anterior mediastinal tumor wasconfirmedafter a chest radiograph during routine evaluation for tonsillectomy surgery. She had no signs or symptoms related to mass such as cough,chest pain,venous congestion, hoarseness of voice, syncope, dysphagia, dyspnoea; or noisy breathing at rest or exertion, in the supine position or during sleep.

Her contrast enhanced computed tomography (CECT) scan,detected amass of (9 cm ×5 cm × 14 cm) in the right anterior tomiddle mediastinum, compressing the right superior vena cavaand right atrium but did not show any airway compromise. The chest X-ray showed a mass on the upper half of the right lung field without tracheal compression.

A median sternotomy and surgical excision of the mediastinal mass was planned. The anaesthesiologist and the cardia surgeonagreed to perform stepwise inductionof anesthesia without

initiation of CPB because the patient did not show any preoperative airway compromise related to the anterior mediastinal mass.

The patient was transferred to the operating roomafter premedication with morphine 6mg, promethazine 20mg and 0.2 mg glycopyrrolate. Routine anaestheticmonitoring was applied. Induction was achieved with an initialdose of 80 mg propofol.The patient's spontaneous mask ventilation was maintained without any respiratory difficulties. Rocuronium 50mg was administered to achieve tracheal intubation. A size 7.5mm cuffed endotracheal tube was placed easily via direct laryngoscopy demonstrating a Cormack-Lehane grade I view. Left radial arterial catheter was placed to monitor invasive blood pressure and arterial blood gas analysis. Fiberopticbronchoscope (FB) (PortaView-LFTM, Olympus Medical Systems Corp., Tokyo, Japan) revealed no compression of the trachea or both main bronchi. Bilateral breathing sounds and bilateral chest expansionwere also confirmed and 4 mg of vecuronium was administered. Sevoflurane and fentanyl were used to maintainanesthesia. A central venous catheter was placed in the femoral vein without difficulty.

The transesophageal echocardiography revealed the tumor adhered to SVC and RA with significant compression. (Figure 1 and 2) On median sternotomy, a round mass with a smoothmargin was found located in the right anterior to middle mediastinum and was compressing the carina, superior vena cava, and right atrium. The mass was totallyremoved with minimal blood loss (figure 3). Postoperative TEE revealed no compression of RA and SVC (Figure 4) End-tidal carbon dioxide and peak inspiratory pressure remained within the normal range and ventilation was kept stable through surgery. FB was performed after excision of tumor to assess airway patency. At the end of the operation, the patient was extubateduneventfully. She did not show any difficulties of breathing in the post-anesthesia care unit. No injuries on the tracheaand bronchus caused by the mediastinal mass. The histopathological diagnosis confirmed the mass as a mature cystic teratoma with normal thymus tissue and no immature cells.

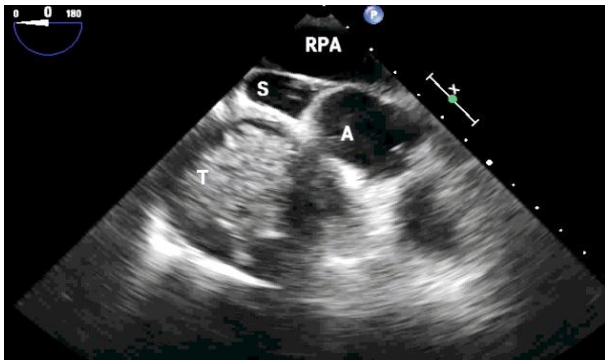

Fig. 1: Transesophageal echocardiography upper esophageal view showing the tumor adjacent to superior vena cava (S) , aorta (A) and right atrium. Abbreviations-S= superior vena cava, A= aorta, T= teratoma and RPA= right pulmonary artery

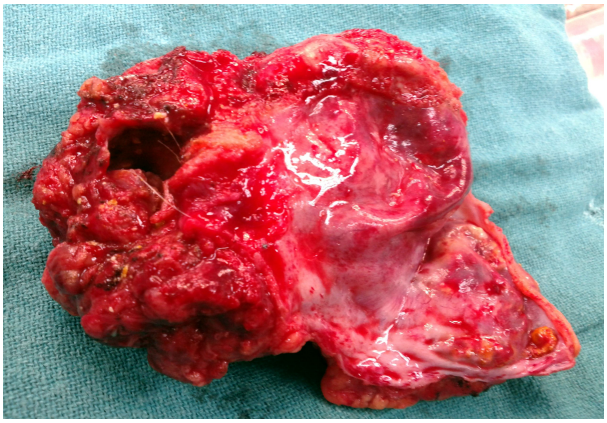

Fig. 3: Teratoma mass after excision with the hair inside the cavity

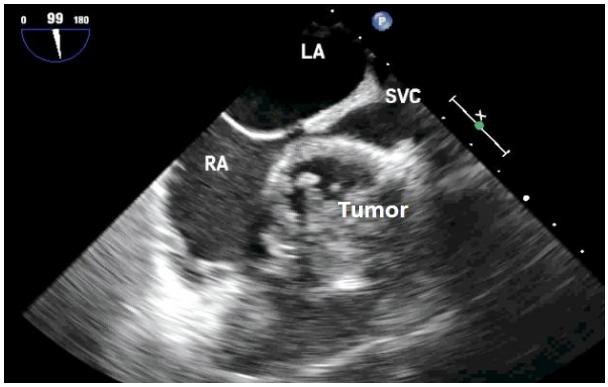

Fig. 2: Transesophageal echocardiography mid-esophageal bicaval view showing the tumor compressing both right atrium (RA) and SVC. Abbreviations-SVC= superior vena cava, LA= left atrium, and RA= right atrium

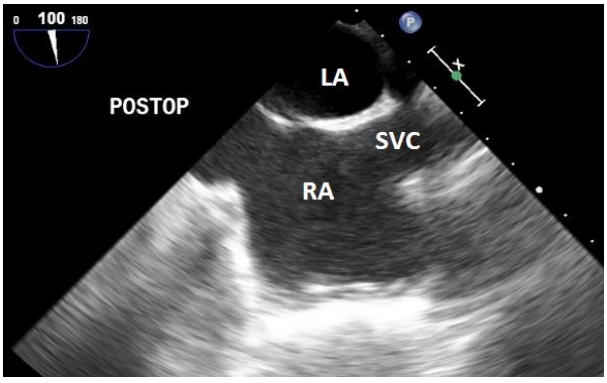

Fig. 4: Transesophageal Echocardiography mid-esophageal bicaval view showing no compression to SVC and RA after the removal of teratoma. Abbreviations- SVC= superior vena cava, LA= left atrium, and RA= right atrium

Discussion

Anterior mediastinal tumors are a group of rare tumors presenting in all age groups [1]. These tumors can be benign or malignant. The tumors create compression to adjacent structures like lungs, trachea, bronchus, great vessels and heart. Compression to SVC and RA is rarely seen like our patient. The tumor like teratoma as in our case again is very rare.

Perioperative management of patients with anterior mediastinal masses is very complicated. Clinicians should look for any symptoms such as cough, dyspnoea on exertion, chest pain, fatigue, or vocal cord paralysis [2,3]. A careful evaluation of the size and the location of the mass are important for predicting the physiological effects it will have on surrounding mediastinal and other thoracic structures [6]. Based on this information, an anaesthetic plan should be formulated prior to induction of anesthesia. This is, however, particularly the case in intermediate to high riskpatients with a mediastinal mass related signs, symptoms, and radiologic findings [2, 3]. In contrast, low risk patients such as our patient tolerated general anesthesia with tracheal intubation. Our patient did not have any signs and symptoms related to the mediastinal mass and the CT scan showed that the airway was intact; thus, stepwise induction with propofol and rocuronium was performed. Fiberoptic bronchoscope revealed that airway patency was maintained after tracheal intubation; therefore, vecuronium was given. Femoral vein catheterization was performed in our case for the reason that the tumour was compressing right SVC, so injury or surgical intervention around it might have cut of the drug administration, fluid therapy and monitoring of central venous pressure.The compression of SVC by the tumor and thrombus invasion into the lumen might present as superior vena cava syndrome [4, 5]. Superior vena cava syndrome consists of facial edema, dilatation of veins in the neck and head, facial swelling, upper limb edema and cyanosis. The early removal of tumor is necessary to relieve the problems.

Double lumen tube (DLT) intubation was not our first choice because our patient had a low risk of airwaycompromises and DLT intubation causes more frequentcomplications such as sore throat, hoarseness, vocal cordsinjuries, and tracheobronchial injuries [2]. To use a DLT, several limitations should be considered. First, use of a DLT is an option for some patients with masses externally compressing the carina or bronchus; it is not an option, however, for patients with intrinsic airway tumors. Second,the nature of the mass may also influence the successful insertion of a DLT. Solid mass may bedifficult to move. In this case, CT scans indicated that themass was not so hard. Third, a DLT cannot be a possiblesolution to maintain airway patency if the main bronchusis entirely collapsed. Fourth, because the right main bronchus is shorter than theleft main bronchus, it may be much more difficult to placea DLT in a patient with compression of the right main bronchus. Lastly, this procedure is not for patients with hemodynamiccompression can be assessed by TEE.

Intraoperative transesophageal echocardiography (TEE) plays a great role in detecting the level and extent of compression. It will also guide to assess the hemodynamic alterations during manipulation of the tumor and diagnose the air embolism quickly. The post-surgery successful relieve of the vascular and cardiac compression.

Vascular injury and opening of cardiac chambers is the dreaded complications during the surgical removal. The chance of massive bleeding, arrhythmia, air embolism and hypotension due to sudden blood loss is the common happening during surgery. All the precautions related to these complications should be adopted[1].

In conclusion, the management of anterior mediastinal teratoma needs a complete preoperative evaluation to assess the compression of structures. All the precautionary measures for bleeding, accidental opening of cardiac or vascular chambers and airway complications are to be followed throughout surgery. Transesophageal echocardiography plays a big role to guide the surgical removal of tumor and hemodynamic monitoring.

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Case Report

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Persistent Left Superior Vena Cava

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Abstract

Persistent left superior vena cava can be incidental, accidental, descriptive and investigative when the left anterior cardinal veins not obliterated. Dilated coronary sinus in the absence elevated right sided filling presence, coronary sinus opacification after right arm anticubital vein injection are the trinity for left sided superior vena cava. A case of persistent left superior vena cava in a 10 year girl with a normal right superior vena cava and a persistent bridging vein brachiocephalic vein leads to formation of superior vena cava duplication.

Keywords: Coronary Sinus; Echocardiography; Computed Tompgraphy; Vena Cava.

Introduction

Haemodynamically insignificant persistent left superior vena cava has 923 citation in the literature. It has an incidence of 0.3% to 0.5% of general population representing one in every 200 to 325 people and a prevalence of 6.1%. 4.3-11% of patients with congenital heart diseases. 15% patients catheterized for congenital heart disease have a PLSVC. PLSVC when present travels lateral to the aortic arch at an orthogonal angle, then travels inferiorly between the left atrial appendage and the left upper pulmonary vein where the ligament of Marshall (fibrosed Left SVC) should be. PLSVC has two types of connection to the heart. Either it drains into the right atrium via coronary sinus (90%), or it drains into the left atrium creating a right to left shunt of small magnitude(10%).

PLSVC is a venous anomaly of the thorax. It was first described by LECHAT in 1787. It may have variable communications to right superior vena cava or no communication with the RSVC i.e the innominate vein may be absent. The normal RSVC may be absent in 0.09 – 0.13% cases.

It is often suspected when, on echo there is a dilated coronary sinus with rapid blood flow, difficulty in reaching convenient pacing site when pacing leads are inserted from left side and rhythm disturbance due to SA node dysfunction or AV block. Bartram et al noticed 46% of congenital heart anomalies like ASD (16%), endocardial cushion defect (11%) and Tetralogy of Fallot (9%) associated with this defect. In 80-90% of cases a coexistent right superior vena cava is present which is usually smaller than normal. In less than 10% of cases persistent LSVC with unroofed coronary sinus drains into the left atrium or in a pulmonary vein leading to predisposition of cyanosis, paradoxical embolism and brain abscess. Higher incidence of conduction anomaly can occur with this malformation along with other congenital anomalies. PLSVC, with an aberrant right superior vena cava or absent / small left brachiocephalic vein (65%) and absent superior vena cava (10%) is frequently diagnosed incidentally during pacemaker implantation or central venous catheter insertion. PLSVC with absent RSVC interfere with the use of retrograde cardioplegia. Cannulation in a case of PLSVC can create disadvantages during an atrial septal defect repair [1-4].

Case Report

A 10 year old female presented with progressive shortness of breath and palpitation. She denied any syncopal attacks, chest pain or limb swelling. On examination a widely split second heart sound and a systolic murmur was noted. Her electrocardiogram was normal. Echocardiogram revealed a dilated coronary sinus of 25mm. Agitated saline injection into left antecubital vein showed dilated coronary sinus filled first then emptied into the right atrium. Cardiac computed tomography was performed and revealed a persistent Left SVC draining into the dilated coronary sinus. There was a small connecting vein between the right and left superior vena cavae. (The arterial saturation of the patient was 95% on room air. The anomalous vena cava was seen descending vertically along the left superior mediastinum and continued caudally posterior to the left atrial appendage and left atrium and anterior to left superior pulmonary vein and then entered the coronary sinus (vide images). Anterior posterior and oblique three dimension volume rendered images from a contrast enhanced computed tomographic scan demonstrated left SVC draining into the coronary sinus.

Discussion

X-Ray of the chest with a prior left sided central venous catheter placement is symbolic of persistent left SVC. It shows the catheter course from left subclavian/jugular vein to PLSVC then on left of Aortic arch to area of coronary sinus. A blood gas study compatible with venous/arterial blood may be useful to differentiate whether the catheter tip is in Coronary sinus/RA or into the LA, respectively. Apart from that obese patient, short neck, vasculopathy can be suggestive of PLSVC.

Associated finding with persistent LSVC are genetic (VACTERL, CHARGE and OPITZ G/BBB Syndrome), chromosomal (Trisomi 21, TURNER and microdiletion 22 q11.2), increased nucheal translucency, oesophageal atresia, cardiac heterotaxy, Tetralogy of Fallot, coarctation of aorta,

Modified, Adjusted Diagram of the Left superior Vena Cava

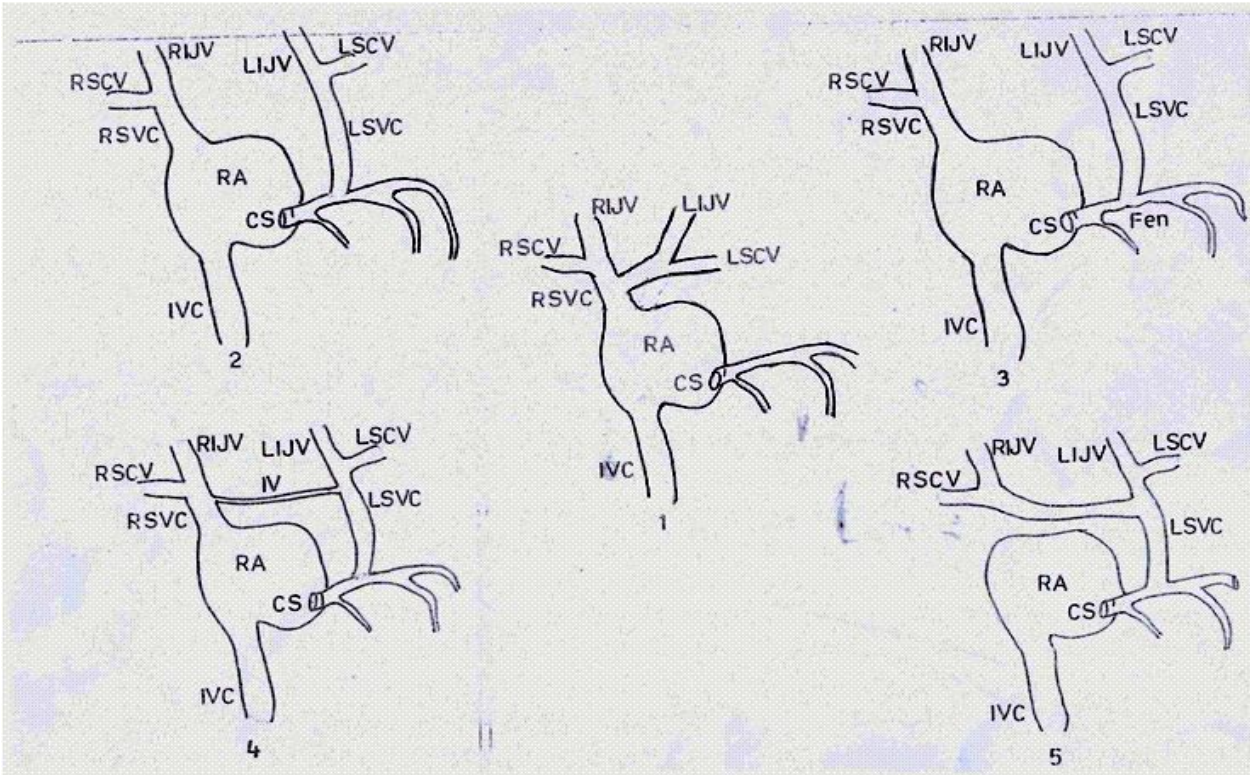

Fig. 1: Normal Figure: Coronary Sinus, Draining into Right Atrium, No Left Superior Vena Cava. **Fig. 2:** Persistent Left SVC draining through dilated Coronary Sinus into Right Atrium. **Fig. 3:** Persistent Left SVC draining through Fenestrated Coronary Sinus, No Left Brachiochephalic vein. **Fig. 4:** Persistent Left SVC connected to Right Superior Vena Cava by Innominate Vein and also to Coronary Sinus. **Fig. 5:** Persistent Left SVC draining into Right Atrium through Coronary Sinus. No Right Superior Vena Cava. Right Innominate vein joins to Left SVC through Left Innominate Vein. This is isolated Left Superior Vena Cava

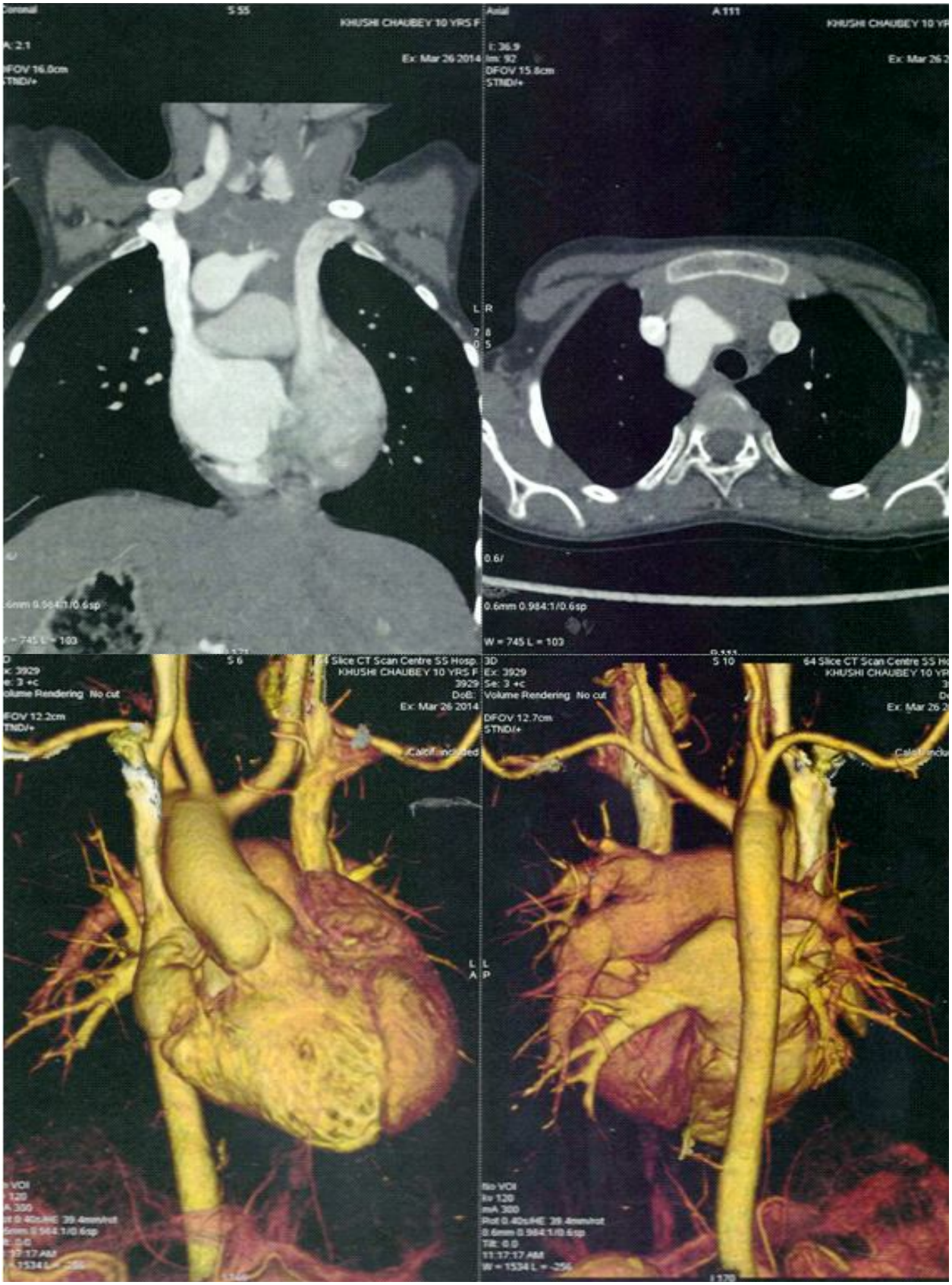

Fig. 1 A,B,C,D: Contrast enhanced CT images coronal (A), Axial (B) showing right and left superior vena cava but no innominate vein (C, D). Left superior vena cava is draining into coronary sinus

VSD, double aortic arch [5,8], bicuspid aortic valve and cortriatrium. Dextrocardia with tga, bilateral SVC and left atrial isomerism [11].

Persistent Left SVC is diagnosed indirectly by a recognition of a dilated coronary sinus in parasternal long axis view during echocardiography. It appears like a circular structure in the atrioventricular groove, located anterior to the posterior pericardium. In four chamber view with posterior angulation coronary sinus can be viewed in long axis passing behind the left atrium towards the right side. Contrast echocardiography from the left antecubital vein shows coronary sinus opacification with contrast and dilated coronary sinus in absence of elevated right atrial filling pressure, and, lastly normal sequence of opacification after right arm antecubital vein injection. In PLSVC the coronary sinus has oval shape with eccentricity index < 0.8 but symmetric distension of the vessel suggests elevated right atrial pressure. The echocardiographic findings [5] in left SVC are

1. Dilated coronary sinus in the absence of the elevated right side filling pressures.
2. Normal sequence of opacification after right arm antecubital vein injection of agitated saline.
3. Coronary sinus opacification by bubble study before the right atrium when injected in the left arm.
4. Presence of bilateral superior vena cava.
5. In 10% cases Right superior vena cava is smaller or absent.

Course and Tributaries of PLSVC

A. PLSVC Draining in Left Atrium (Unroofed Coronary Sinus)

1. Starts at junction of left subclavian and left internal jugular vein
2. Passes lateral to the aortic arch
3. Receives left superior intercostal vein
4. Courses anterior to the left hilum of lung.
5. Joined by hemiazygos vein
6. Passes between the left superior pulmonary vein posteriorly and the left atrial appendage anteriorly to become coronary sinus.
7. Opens into LA or some pulmonary vein.

B. PLSVC Draining into Right Atrium

1. Starts at junction of the left subclavian vein and left internal jugular.
2. Passes lateral to aortic arch
3. Receives the left superior intercostal vein
4. Courses anterior to the left hilum of lung.
5. Joined by hemiazygos vein
6. Crosses posterior wall of the left atrium and midline obliquely.
7. Receives great cardiac vein to become coronary sinus (usual).

Contrast enhanced computed tomography is the most easy and accurate imaging modality to diagnose and confirm the exact anatomy of PLSVC. It not only demonstrates the PLSVC, gives its exact course, size, drainage site but shows the anatomy, size and tributaries of RSVC. Other imaging modalities are contrast venography, cardiovascular magnetic resonance and foetal echocardiography showing coronary sinus enlargement and abnormal three vessel view. A venogram via the right internal jugular vein or the subclavian vein can show the absence of right superior vena cava and the brachiocephalic vein joining with the PLSVC that drained into the right atrium through the dilated coronary sinus [1,2]. Clinical problems associated with persistent Left SVC are rhythm disturbances, inability to insert central venous catheters, inability to insert transvenous pacing leads through the left internal jugular or left subclavian veins, and delivery of retrograde cardioplegia. The existence of acute angle between the coronary sinus and the tricuspid valve in persistent LSVC calls for long (85 cm) active fixation with wide loop technique during pacemaker implantation. Pacing through the tributaries of the coronary sinus in a patient with LSVC has been reported. Failure to drain the left superior vena cava during cardiopulmonary bypass could result in inadequate venous return to the pump, excessive blood return to the operative filed, unnecessary rewarning of the heart and residual intracardiac shunt due to poor visibility. A PLSVC needs drainage by a separate cannula. Either a tricaval cannulation is done or usual bicaval cannulation and a third cannula or suction for coronary sinus is used in right sided open heart surgical procedures. Delivery of retrograde cardioplegia is not feasible because of inability to obtain tight seal by the balloon of cardioplegia catheter, inadequate cardioplegia solution delivery to the myocardium and lastly fear of cerebral congestion. During PA catheterization a lack of progression of normal right heart waveform occurred in presence of high cardiac output when a pulmonary artery catheter (PAC) was incorrectly placed into the coronary sinus, is reported.

The embryological development of systemic and pulmonary veins is complex and subject to considerable variation. During normal development, the anterior cardinal veins, which drain the head, neck and arms unite with the posterior cardinal vein in the very early embryonic stage and enter the heart as the right and left horns of sinus venosus. With the exception that the cardinal veins of both i.e., right and left side drain into the right atrium, the cardinal venous system is bilaterally symmetrical at this stage. Most of the left sided cardinal system disappears leaving only the coronary sinus and a remnant of obliterated LSVC known as the ligament of Marshall. Simple failure of obliteration of the left anterior cardinal vein results in the persistence of LSVC[10]. Other variations are absence of RSVC (0.36%), drainage into LA with variable communications, creating a right to left shunt, absence of bridging innominate vein between PLSVC and Right SVC. The genetic culprit may be genes for left to right signalling [5-7].

When the right ventricle appears dilated and volume loaded with an apparently intact atrial septum on a conventional transthoracic echo view, it may be needed to look for a sinus venosus atrial septal defect. Diagnosis of PLSVC is usually incidental during retrograde cardiophegia in cardiac surgery, left subclavian vein cannulation for monitoring or therapeutic purposes, device implantation or cardiovascular imaging but transthoracic contrast echocardiography is the method of choice [9].

Abbreviations and ACRONYMS

RA	:	Right Atrium
LA	:	Left Atrium
CS	:	Coronary Sinus
LSVC	:	Left Superior Vena Cava
RSVC	:	Right Superior Vena Cava
PLSVC	:	Persistent Left Superior Vena Cava
IVC	:	Inferior Vena Cava
RIJV	:	Right Internal Jugular Vein
LIJV	:	Left Internal Jugular Vein
IV	:	Innominate Vein (Brachiocephalic Vein)
LSCV	:	Left Subclavian Vein
RSCV	:	Right Subclavian Vein
MDCT	:	Multi Detector CT Scan
TGA	:	Transposition of Great Arteries
VACTERL	:	Syndromic Anomalies of **V**ertebrae, **A**nus, **C**ardiac, **T**rachea, **E**sophagus, **R**enals - Radial, and **L**imb
CHARGE	:	**C**oloboma of eye, **H**eart defects, **A**tresia of nasal Choanae, **R**etardation of growth, **G**enital and urinary abnormalities, **E**ar abnormalities.

Conclusion

Persistent superior vena cava connection to the coronary sinus is often incidental but an important finding which helps in planning safe invasive procedures [11,12].

Recognition of persistent left superior vena cava with embryological variants is essential for physicians. These variations can be detected by a radiological picture of the heart showing straight borders on both sides and a broad pedicle. MDCT cardiac angiography is very useful to confirm the presence or absence of PLSVC. It shows the clear anatomy and sizes of both SVCs and also shows the bridging innominate vein. On transthoracic Echocardiography with Doppler, the large size of the coronary sinus with its ostium and unusually excessive venous drainage through it indicates the presence of a persistent left superior vena cava, draining into the coronary sinus. In the ICU setting when central line is in place through the left sided veins a skiagram of the chest along with a blood gas study compatible with venous blood may be enough to make the diagnosis of persistent left superior vena cava; others are Transesophageal echocardiography, MRI. Preoperative knowledge about PLSVC and other anatomical variants are necessary for the surgeon for planning of surgery for congenital cardiac lesions.

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Short Communication

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Exercises in Essential Hypertension: Is it Really Essential to Exercise?

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Abstract

This short communication paper intended to provide a descriptive evidence summary on efficacy studies of exercises in essential hypertension through a PubMed-based search for systematic reviews and / or meta-analyses. There were high quality evidence for aerobic exercise, device-guided breathing exercise, Tai Chi exercise, with an evidence-based recommendation and American college of sports medicine endorsing a position statement, all of which favored use of exercises as a safe and effective treatment modality.

Keywords: Cardiovascular Rehabilitation; Hypertension; Blood Pressure; Exercise Rehabilitation.

This short communication paper intended to provide a descriptive evidence summary on efficacy studies of exercises in essential hypertension through a PubMed-based search for systematic reviews and / or meta-analyses.

Aerobic Exercise

An individually tailored short-duration low intensity aerobic exercise (moderate intensity (40% to <60% of VO2 Reserve), for 30 minutes or more of continuous or accumulated physical activity per day) had immediate antihypertensive effect [1].

Hameret al [2]did a systematic review of 15 randomised controlled trials (RCTs) on the effect of acute aerobic exercise on blood pressure (BP) responses to psychosocial stress.Ten RCTs demonstrated significant dose-dependent reductions in post-exercise stress related BP responses compared with control.The minimum exercise dose to show a significant effect was 30 min duration at 50% VO2max intensity.

Device-Guided Breathing Exercise

Mahtaniet al [3]studied efefcts of device-guided breathing (DGB)on blood pressure (BP) by systematically reviewed eight trials consisting of 494 adult patients. The device produced reductions in SBP by 3.67 mmHg and decreased DBP by 2.51 mmHg, with no overall effects observed on heart rate or quality of life using the device.

Tai Chi Exercise

Yehet al [4] did a systematic review of 26 studies (9 randomized controlled trials, 13 nonrandomized studies, and 4 observational studies) on the effect of tai chi exercise on blood pressure (BP) in patients with and without cardiovascular conditions. Majority of studies reported reductions in BP with tai chi (3-32 mm Hg systolic and 2-18 mm Hg diastolic BP reductions).

Evidence-Based Recommendations

Gordon et al [5] provided recommendations based upon a recent meta-analysis of 25 longitudinal aerobic training studies, in which the average sample-size-weighted reductions in resting systolic and diastolic blood pressures were 10.8mm Hg and

8.2mm Hg, respectively. Aerobic exercise prescription should adhere to5 basic principles: the type of exercise to be performed, and the frequency, intensity and duration of exercise training. Aerobic exercise training performed at an intensity 60 to 85% of maximal heart rate and duration and frequency modulated to achieve a weekly energy expenditure of between 14 and 20 kcal/kg of bodyweight is considered to be beneficial.

Position Statement

American College of Sports Medicine published a position stand which is as follows; "Exercise programs that primarily involve endurance activities prevent the development of HTN and lower blood pressure (BP) in adults with normal BP and those with HTN. The proposed mechanisms for the BP lowering effects of exercise include neurohumoral (decreased catecholamines), vascular (decreased peripheral resistance), and structural adaptations (improved insulin sensitivity, and alterations in vasodilators and vasoconstrictors). Individuals with stable controlled HTN and no CVD or renal complications may participate in an exercise program or competitive athletics, and it is reasonable for the majority of patients to begin moderate intensity exercise (40-<60% VO2R) such as walking. Drugs such as angiotensin converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers in case of ACE inhibitor intolerance) and calcium channel blockers are currently recommended for recreational exercisers and athletes who have HTN. Exercise remains a cornerstone therapy for the primary prevention, treatment, and control of HTN in adults while the optimal training frequency, intensity, time, and type (FITT) need to be better defined to optimize the BP lowering capacities of exercise, particularly in children, women, older adults, and certain ethnic groups. Frequency: on most, preferably all, days of the week. Intensity: moderate-intensity (40-<60% VO2R). Time: > or = 30 min of continuous or accumulated physical activity per day. Type: primarily endurance physical activity supplemented by resistance exercise" [6].

There were high quality evidence for aerobic exercise, device-guided breathing exercise, Tai Chi exercise, with an evidence-based recommendation and American college of sports medicine endorsing a position statement, all of which favored use of exercises as a safe and effective treatment modality.

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Short Communication

Journal of Cardiovascular Medicine and Surgery
Volume 1 Number 2, July - December 2015

Effects of Therapeutic Exercise on Quality of Life in People with Cardiovascular Disorders-An Integrative Overview of Systematic Reviews

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Abstract

This article is aimed to inform the readers on the role of exercise therapy in improving quality of life of people with cardiovascular disorders by providing an integrative overview of systematic reviews. There were two systematic reviews on stroke, three on chronic heart failure and two on intermittent claudication found in our search of PubMed database, and most of them reported improvements in physical functioning and bodily pain components of health-related quality of life (HrQoL) in people who were administered supervised aerobic exercise training. This throws light on need for future studies addressing non-operative and pre-/post-operative rehabilitation using exercise and its effect on HrQoL in this population.

Keywords: Health-Related Quality of Life; Cardiovascular Disorders; Cardiovascular Rehabilitation.

This article is aimed to inform the readers on the role of exercise therapy in improving quality of life of people with cardiovascular disorders by providing an integrative overview of systematic reviews.

Stroke

Chen and Rimmer [1] searched MEDLINE, Cumulated Index to Nursing and Allied Health Literature, EMBASE, and SportsDiscus databases and found 9 RCTs on 426 stroke survivors of which eight studies were rated as good quality. There was evidence that exercise can have a small to medium effect on HRQOL outcomes at post-intervention but not at follow-up after exercise was terminated.

Pang et al [2] searched major electronic databases to identify randomized controlled studies and found 25 trials that fulfilled the selection criteria, of which 8 were level 1 studies. "There was strong evidence that aerobic exercise (40-50% HRR progressing to 60-80%) conducted 20-40 min and 3-5 days per week was beneficial for enhancing aerobic fitness, walking speed and walking endurance in people who have had mild to moderate stroke and are deemed to have low cardiovascular risk with exercise after proper screening assessments (grade A recommendation)."

Chronic Heart Failure

Chien et al [3] identified 10 randomised controlled trials with 648 participants of New York Heart Association Class II or III of chronic heart failure. The exercise programs ranged from 6 weeks to 9 months at low to moderate intensity (40-70% of maximum heart rate or heart rate at 70% peak VO2. Home-based exercise increased 6-min walking distance by 41 m and peak VO2 by 2.71 ml/kg/min more than usual activity.

Pan et al [4] searched PubMed and EMBASE databases and found four randomized controlled trials (RCTs) (n = 242) met the inclusion criteria. Tai Chi significantly improved QoL. Tai Chi was not associated with a significant reduction in N-terminal pro brain natriuretic peptide, systolic blood pressure, diastolic blood pressure, improved 6 min walking distance, or peak oxygen uptake.

Van Tol et al [5] included 35 randomised controlled trials in their meta-analysis and found benficial effects of exercise for diastolic blood

pressure and end-diastolic volume. During maximal exercise, significant effects were found for systolic blood pressure, heart rate, cardiac output, peak oxygen uptake, anaerobic threshold and 6-min walking test.

Intermittent Claudication

Guidon and McGee [6] identified 23 studies including five randomized controlled trials in their systematic review. Eleven studies reported beneficial effects on the SF-36 Physical Functioning scale, and others reported positive effects on the scales of Bodily Pain, Role-Physical, Vitality, General Health and the Physical Component Score. Disease-specific measures demonstrated greater improvements across a range of QoL domains.

Spronk et al [7] found five studies (202 patients) in the exercise group, and three studies (470 patients), in the angioplasty group in their systematic review and found that ankle-brachial index was improved in the angioplasty group but not in the exercise group. "Quality of life in terms of physical functioning and bodily pain improved in the exercise group.

There were two systematic reviews on stroke, three on chronic heart failure and two on intermittent claudication found in our search of PubMed database, and most of them reported improvements in physical functioning and bodily pain components of health-related quality of life (HrQoL)in people who were administered supervised aerobic exercise training. This throws light on need for future studies addressing non-operative and pre-/post-operative rehabilitation using exercise and its effect on HrQoL in this population.

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Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540-7.

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Corporate (collective) author

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Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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